Supplement B

The chemistry of

acid derivatives

Volume 2

Supplement B: The Chemistry of Acid Derivatives, Vol. 2
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—COOH(R); —$CONH_2$; —COHal

Supplement B
The chemistry of
acid derivatives

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Edited by

SAUL PATAI

The Hebrew University, Jerusalem

1992

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Foreword

Among the original volumes in *The Chemistry of Functional Groups* series, three dealt with acid derivatives, namely *The Chemistry of Carboxylic Acids and Esters* (1969), *The Chemistry of Amides* (1970), and *The Chemistry of Acyl Halides* (1972). By the end of the seventies, it became obvious that several new subjects relevant to acid derivatives had to be considered and reviewed, in addition to important developments in the subjects already dealt with in the above mentioned three main volumes. Hence a supplementary volume, entitled *Supplement B. The chemistry of acid derivatives* was planned and printed in 1979.

The passing of another decade caused the repeat of the above process, and thus we present now a second volume of *Supplement B.* This again includes several subjects which have not been treated at all in the Functional Groups series, as well as subjects which have been dealt with but in which important recent developments justified the publication of a new review.

As always, it is one of the pleasures of the editor to be able to assemble a wide international group of authors. In the present volume, this group includes authors from three continents and from fifteen countries.

The editor would be very grateful to readers who would draw his attention to mistakes or omissions in the present volume as well as in all other volumes of the series.

Jerusalem
April 1992

SAUL PATAI

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adquately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES—as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically

labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E and F). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff members of the publisher also rendered me invaluable aid. My sincere thanks are due to all of them, especially to Professor Zvi Rappoport who, for many years, shares the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, Israel

SAUL PATAI

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List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt
Fc	ferrocene
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_5)
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital

i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-choloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Pip	piperidyl($C_5H_{10}N$)
Ph	phenyl
ppm	parts per million
Pr	propyl (also *i*-Pr or Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_4N)
R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TMEDA	tetramethylethylene diamine
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition. Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

General and theoretical

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I. INTRODUCTION

This chapter is concerned with a theoretical description of acid derivatives, especially amides. The usual cliches about how there has been tremendous progress in treating this class of compounds (in its wider sense, as will be described subsequently) are particularly appropriate here. These recent advances are the result of the development of new methodologies and theoretical treatments that can be applied to experimentally interesting systems. On the other hand, the carboxylic acids and derivative amides have a pervasive presence in biochemical systems and a dominating influence on their physiological activities. The combination of high interest and importance coupled with improving theoretical capabilities place quantum chemical research on these types of compounds in the forefront of scientific activity.

The last review of theoretical applications to the acid derivative-type systems in the 'Functional Groups' series appeared over 12 years ago[1] and included an extensive description of basic *ab initio* theoretical methods on the Hartree–Fock (HF) self-consistent-field (SCF) level. These theoretical models were relatively novel at that time. In the interim, the HF methods (restricted-RHF and unrestricted-UHF) have become familiar and relatively routine in their application[2] using standard computer programs[3,4]. As an example, we refer the reader to recent extensive and systematic *ab initio* studies of sulphinic[5] and sulphonic[6] acid/derivative systems. The great strides made in applying theory in the past twenty years can be gauged by comparing these descriptions with the electronic structure chapter in the original amide volume in this series[7].

This review will therefore concentrate on the more recent and significant theoretical developments and their applications to the acid/amide systems, with occasional emphasis

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on biological associations. Only the most necessary theoretical background will be given. For more details the reader is referred to monographs and references devoted to these subjects. The choice of topics is selective rather than comprehensive and probably reflects the authors' biases and interests. This will also explain why much of the work described, both published and, as yet, unpublished, involves the authors in various collaborative efforts.

The topics covered in this review include hydrogen bonding, active sites and amide hydrolysis, reaction field methods and metal ion–acid/amide complexes. A theme that runs as a thread connecting most of these subjects is not only a common concern with the carboxylic acid/amide functional groups, but also the changes in their relative stabilities and reactivities that are caused by interaction with other such groups, solvent, metal ions, etc.

II. HYDROGEN BONDS

Carboxylic acids and amides are the major components of the most common amino acids in proteins. The hydrogen bond (H-bond) involving the N—H···O=C and O—H···O=C units plays a crucial role in determining structures and properties of proteins. Other types of hydrogen bonds[8] are important to the structure and properties of nucleic acids and the activities of enzymes. Water as a solvent competes with these inter-unit interactions for hydrogen bonding sites[9] and thereby influences the structure and conformational properties of proteins. These properties and the effect of solvent are best treated from a theoretical point of view by dynamical simulation methods[10,11]. However, all such model calculations are based on interaction potentials derived from experimental data and electronic structure calculations[12–17]. Although interactions in condensed phase systems depend on more factors than are present in simple binary complexes, the potential functions are usually taken to be pairwise additive. More sophisticated methods add induced polarization terms to account for cooperative effects[18,19]. These have been studied specifically with *ab initio* models for some simple hydrogen bonded systems such as the hydrogen halides[19].

The hydrogen bonded interactions of pairs of molecules or fragments can be studied theoretically both for comparison with experimental gas-phase studies using microwave and infrared spectroscopy and as models or components of more complicated systems. For example, the cyclic structure of the water–formamide complex has been predicted theoretically[20] and observed experimentally[21]. Of greater interest in this regard is the interaction of water with glycine which is the simplest amino acid and combines the carboxyl and amino functional groups in the same molecule. Thus the exclusive or simultaneous use of the carboxyl and amino groups in hydrogen bonding can be studied. Glycine has three low-energy conformers of which two have been observed in microwave spectroscopy[22]. It is therefore of interest to explore which of the conformations of isolated glycine gives the strongest binding interaction with a water molecule and how these interactions affect the bare glycine geometry.

Such a study has been carried out using *ab initio* geometry gradient optimization techniques on several cyclic 1:1 glycine–water complexes[23], with the water molecule spanning the carbonyl and amino or hydroxyl groups through a pair of hydrogen bonds. The calculations were carried out with the 1s core electrons on the carbon, nitrogen and oxygen atoms replaced by accurate compact effective potentials (CEP)[24]. The accompanying double-zeta (DZ) valence electron basis consists of four gaussian-type functions for the valence sp shell with shared exponents, split 3/1. The smallest exponent gaussian is split off as a separate basis function. This type basis set is denoted CEP-31G, by analogy to the standard 6-31G basis sets of Pople and coworkers[2]. The accuracy of

the CEP has been determined by comparison with corresponding all-electron (AE) basis set calculations[25,26] and experiment[26,27]. Generally, the use of a CEP for the passive core electrons not only makes the calculations more efficient, especially for heavier atoms, but also, in conjunction with reasonably large valence electron basis sets, minimizes the basis set superposition error (BSSE)[20]. The major contribution to BSSE usually comes from an inadequate representation of the high-energy core electrons in each monomer* with the AE basis set. The use of other monomer valence basis functions in the complex to correct for this (and other) deficiencies usually leads to spuriously large binding energies[28], called BSSE.

The valence DZ basis set was augmented by polarization functions on all the atoms; d-type on carbon, nitrogen, oxygen and p-type on the hydrogen atoms, to give the CEP-31G** basis set. Splitting the valence atomic orbital basis set 3/1 provides radial flexibility and the higher angular momentum functions on each atom add angular polarization capability, allowing the atom better to adjust to its molecular environment. The geometry optimizations for the monomers and complexes were carried out at the RHF level for these closed-shell systems. However, this theoretical model is known to have certain deficiencies. By analogy with the classical molecular hydrogen case[29] the HF method overestimates ionic terms in the calculated molecular wave function and, in multi-electron systems, also underestimates the instantaneous or dynamical correlation between as well as among electron pairs. These sources of error are typically lumped together and are collectively known as correlation energy error. Even in hydrogen bonds, and especially for the strong hydrogen bond, these errors could be significant as the heavy atom–hydrogen atom bond is stretched as in a proton transfer curve. Higher-level theoretical models (post-Hartree–Fock methods) of either the variational [multi-configuration SCF (MCSCF)[30] and configuration interaction (CI)[31]] or perturbation [Moeller–Plesset to *n*th order (MPn)[2]] type can correct these deficiencies to different degrees depending on the seriousness and type of error and the extent to which the higher-level methods are applied.

MP2 is the simplest post-HF method and is expected to be adequate for the type of bonding systems discussed here. The calculated RHF–SCF results were tested at the MP2 level in order to probe the effect of correlation on the relative energies of the lowest-energy glycine–water complexes and, at the same time, to evaluate the importance of correlation on the equilibrium H-bond length. The RHF gradient optimized geometries and relative energies of the complexes are shown in Figure 1 The geometric conformers of glycine are labelled according to their monomer structures, I, II and III. In structure I (as in I-A) the C—OH bond is *trans* to C-amine across the C—C bond, while in II and III they are *cis* to each other. Monomer structures II and III differ from each other in the relative orientations of the O—H and N—H bonds. The RHF (MP2) calculated relative energies of monomer structures I, II and III are 0(0), 3.0 and 2.0(1.7) kcal mol^{-1}, respectively.

Five stable 1:1 water–glycine complexes were explored, as shown in Figure 1. In absolute energy terms the RHF relative stabilities (in parentheses) are I-A(0), III-A(1.4), I-B(2.3), II-D(6.3) and I-C(both 6.4), in kcal mol^{-1}. One-dimensional optimization of the O(water)···H—O bond at the MP2 level reduces the relative stability of III-A to 1.2 kcal mol^{-1} while reducing the hydrogen bond length by ~0.1 Å. Ignoring the calculated stability differences between the various glycine monomers, however, gives the following RHF binding energies (each relative to its own monomer conformation asymptotes): III-A(9.0) > I-A(8.6) > II-D(5.3) > I-B(5.4), I-C(2.2), in kcal mol^{-1}. MP2 optimization increases these stabilities to 11.5 and 11.0 kcal mol^{-1} for III-A and I-A, respectively.

* We use the term 'monomer' for any of the constituent single molecules of a complex.

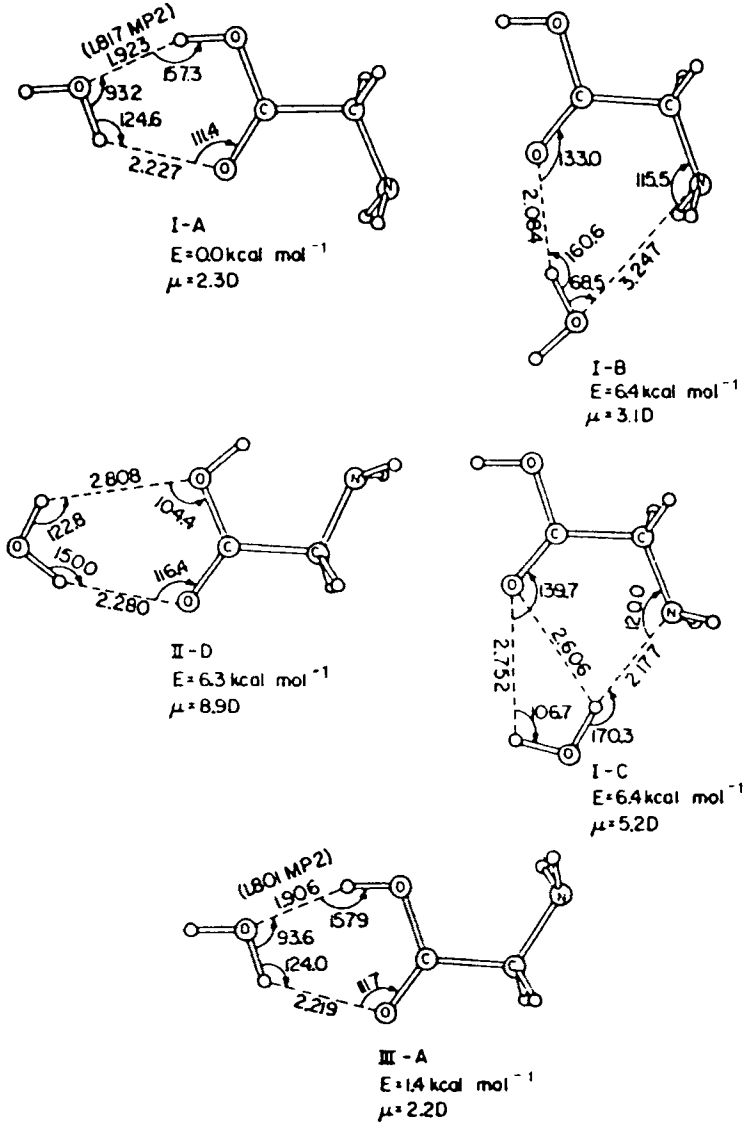

FIGURE 1. Stable cyclic hydrogen-bonded structures for the glycine–water complex including their relative energy (E) and dipole moments (μ). Numbers in parentheses were obtained from correlated calculations at the MP2 level. E(I-B) is actually 3.2 kcal/mole

Thus, both on the RHF and MP2 levels glycine structure III is more stabilized by water than the lower-energy monomer conformation I, although not enough to reverse the absolute stability ordering of the monomers[23].

The hydrogen bonds formed between the regular (not zwitterionic) glycine structures and a water molecule, whether cyclic or linear, are termed weak hydrogen bonds because

of their low (2–11 kcal mol^{-1}) binding energy range and relatively long (>2.7 Å) O···O or O···N internuclear distances. In these systems hydrogen bonding is a relatively weak perturbation and structural/energetic changes in the monomer are expected to be small, as is found for both the glycine–water[23] and formamide–water[20] complexes.

However, hydrogen bonds in cationic $(A—H\cdots B)^+$ or anionic $(A—H\cdots B)^-$ systems involving strong acids (A) and bases (B) are known to have particularly short A···B distances, large binding energies and unusual spectroscopic properties[32–34]. Recently, a particularly large enthalpy of dissociation in the gas phase of 36.8 kcal mol^{-1} [35,36] has been measured by Meot-Ner for the biformate anion. This binding energy value is considered to be unexpectedly large, even for strong acid–base hydrogen-bonded anionic systems, requiring perhaps some unusual structural feature for its explanation[36]. For example, the H-bond enthalpy of the biacetate anion has been determined to be 29.3[36]–30.0[37] kcal mol^{-1}, some 7 kcal mol^{-1} less than for the biformate anion. By comparison, the methanol–methoxide binding energy is only ~3 kcal mol^{-1} smaller than that of the water–hydroxide system[38]. Thus, the experimentally determined dissociation energy for the biformate anion is unusually large.

Although the [HCOOH + $HCOO^-$] enthalpy of dissociation was measured in the gas phase[36] most structural information on these type systems comes from condensed phase studies where the crystal structure, matrix or solvent can affect the H-bond energy, geometry and characteristic properties. Recent IR[39] and NMR[40] studies of such hydrogen-bonded systems in both solution and the solid state have also indicated a not insignificant role for solvent and crystal effects in determining H-bond properties. The biformate anion has the possibility of both symmetric and (as will be explained subsequently) asymmetric locations of the bridging hydrogen atom. Thus, aside from external perturbational effects, the intrinsic energy profile (single or double minimum) for proton transfer between the formate anion fragments is relevant to the interpretation of the gas-phase results. In this regard, a recent *ab initio* study of the analogous $H(OH)_2^-$ system predicted an asymmetric (double minimum) hydrogen bond structure on the

TABLE 1. Optimized geometric parameters and energies for formic acid–formate anion dimer[a]

Symmetry	O—H bond distance	Total energy (a.u)		H-bond energy[f] (kcal mol^{-1})	
		RHF	MP2[d]	RHF	MP2
C_{2h}(II)	1.1954[b]	−75.582638	−76.491222	21.7	29.2
C_{2h}(I)	1.1393[c]	−75.584400	−76.491428		
	1.1893[b]	−75.587358	−76.495628	24.7	31.9
	1.2393[c]	−75.584954	−76.494643		
C_s[e]	1.0498	−75.585053	−76.490757	23.2	28.9
	1.5971	−75.593965	−76.496669	28.8	32.6
	1.450	−75.592907	−76.497348	28.1	33.0

[a] All geometry optimizations are at the RHF level.
[b] Complete gradient optimizations in C_{2h} symmetry.
[c] Frozen distance; all other geometric parameters taken from the complete gradient optimization for that structure.
[d] At the RHF optimization geometry.
[e] See Figure 2.
[f] Relative to optimized (*syn*)formic acid + formate anion.

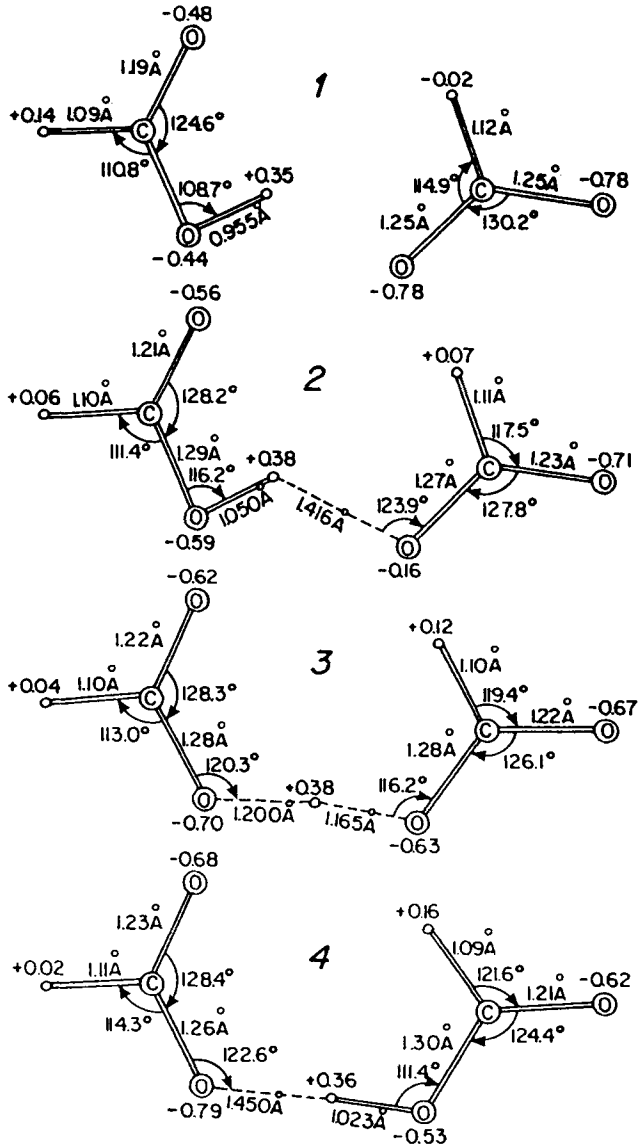

FIGURE 2. Snapshot sequence of RHF gradient optimized parameters as a function of one of the O—H distances for the asymmetric formic acid and-formate anion complex. The numbers on the atoms are the Mulliken atomic charges. Structures 1 and 7 are for the dissociated fragments

RHF/6-31G** level which changed to a symmetric (single minimum) energy curve for proton transfer when correlation was included[41]. Here the asymmetric structure could be an artificial symmetry broken result of the HF method[42]. Thus, the level of theoretical treatment necessary for the accurate description of the strong hydrogen bond requires further study.

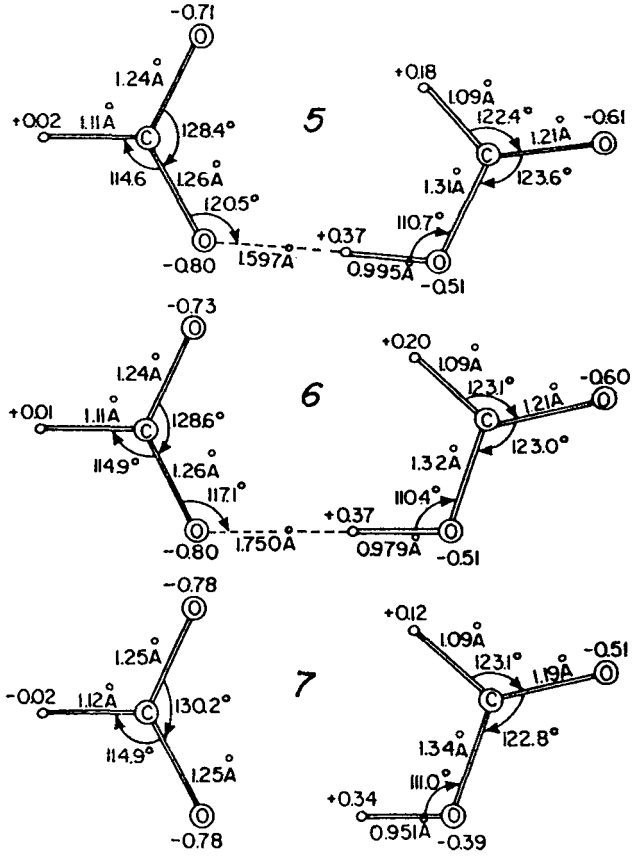

FIGURE 2. (*continued*)

Recent *ab initio* calculations have addressed these questions about the strong hydrogen bond in the biformate anion[43–45]. In the most extensive of these studies[45], geometry optimization was carried out on the RHF level with the CEP-31G* basis set[23,26], adding a p-type polarization function on the bridging hydrogen atom only. In order to describe better the extra negative charge that is expected to concentrate on the more electronegative oxygen atoms, a set of single gaussian diffuse sp orbitals was also added to each of the four oxygen atoms (only). MP2 calculations were then carried out at each of the RHF optimized geometries (MP2//RHF).

Experimentally, a large number of different bicarboxylic acid crystal structures are known[30,31,46–50]. Aside from crystallographic effects, the different structures are based on combinations involving actual or incipient (formate anions before proton transfer) formic acid monomers that are either in the *syn* (O—H tilting towards C=O) or *anti* (O—H tilting towards C—H) conformation. Thus the possible biformate anion combinations are symmetric *syn–syn* or *anti–anti*, and asymmetric *syn–(anti)*, *anti–(syn)*, *syn–(syn)* or *anti–(anti)*, where the parentheses indicate the conformation of the formate ion relative to the H-bond. The latter two asymmetric possibilities are induced by environmental effects. This aspect has been studied by Lunell and collaborators[44].

The relative energies of the symmetric [C_{2h}(II)] *syn–syn* and [C_{2h}(I)] *anti–anti*

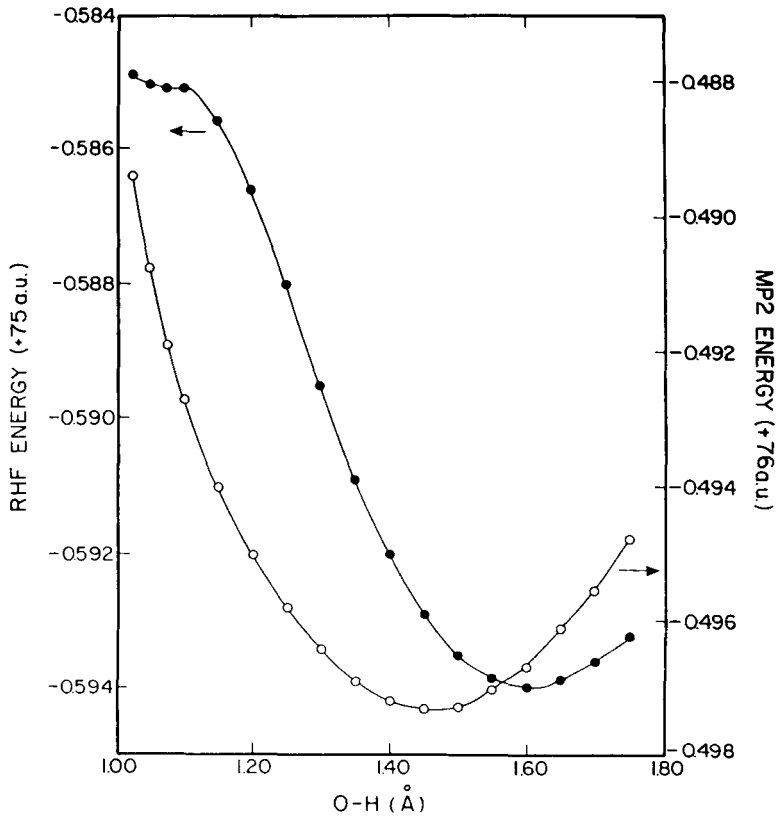

FIGURE 3. RHF (left side scale) and MP2 (right side scale) energies as a function of O—H distance in the asymmetric formic acid–formate anion complex

combinations, and asymmetric (C_s) *syn*-(*anti*) and (*syn*)-*anti* dimers are presented in Table 1. A snapshot sequence of selected points in the proton transfer process for the *syn*–(*anti*) to the (*syn*)–*anti* combination is shown in Figure 2 and the energetics of the transfer is drawn in Figure 3. It should be noted that the *syn* form of formic acid is more stable than the *anti* form[45] in the CEP-DZ + polarization + diffuse basis set by 5.8(RHF) or 5.4(MP2//RHF) kcal mol^{-1} [51]. Thus, ostensibly, the biformate dimer that has the 'most' *syn* character would be expected to be most stable.

The calculated results displayed in Table 1 show this not to be generally true. In the C_{2h} symmetric dimers the *syn–syn* combination (II) is calculated less stable than *anti–anti* (I) by 3.0(RHF) or 2.7(MP2//RHF) kcal mol^{-1}. Both conformations have been observed in crystal structure[46,47]. However, the asymmetric (*syn*)–*anti* combination is calculated to have the largest dimer binding energy at 28.8(RHF) or 32.6(MP2//RHF) kcal mol^{-1} at a H-bond distance of 1.597 Å (structure 5 in Figure 2). The proton transfer energy profile curve [*syn*–(*anti*) → (*syn*)–*anti*] has a double minimum-like shape at the RHF level. However, only a single minimum is found at $R \sim 1.45$ Å (structure 4, Figure 2) with a binding energy of 33.0 kcal mol^{-1} when calculated by the MP2//RHF method. It is this structure that is identified with the gas-phase experiment that finds a dissociation energy of 36.8 kcal mol^{-1} for the biformate anion[35,36].

One feature that emerges in stepping across the increasing C—O···H—O distance in Figure 2, going *syn–(anti)* → *(syn)–anti*, is the decreasing C—O···H—C distance. This attractive hydrogen-bond interaction seems to enhance the stability of the biformate anion. A qualitative estimate of its contribution to the overall H-bond energy is obtained by rotating one of the monomers about the O···H···O axis by 90°, maintaining all other geometric parameters unchanged. At the RHF energy minimum (R = 1.597 Å) the total energy rises by 2.1(RHF) or 1.8(MP2//RHF) kcal mol^{-1} upon twisting while at the approximate MP2 minimum ($R \sim 1.45$ Å) the energy difference is 2.4(RHF) or 2.1(MP2//RHF) kcal mol^{-1}. Thus there is a clear indication of an intermolecular stabilizing interaction involving the C—H and C=O groups, which is not possible in the biacetate anion, and which contributes to the special stabilization of the *(syn)–anti* biformate anion in the gas phase. Such type hydrogen bonds involving alkyne[52,53], alkene[54] and even alkane[55,56] C—H bonds with strong bases (such as C=O and S=O) have been noted before[57].

This H-bond interaction involving the C—H group is apparently less attractive in the *syn–(anti)* conformation (structure 2 in Figure 2) because of less favourable electrostatic interactions that arise from the charge distribution differences between the two conformer combinations. This can be seen from the atom charges tabulated in Figure 2 and comparing structure 5 to structure 2. In general, an energy decomposition analysis of the formic acid–formate anion dimer attributes[45] the difference in stabilities between the *(syn)–anti* and *syn–(anti)* forms to a combination of electrostatic and exchange repulsion interactions[58,59].

A particularly interesting discussion of proton transfer in hydrogen bonded systems involving the carboxylate group has been given by Cybulski and Scheiner[60] who emphasize the angular features of the H-bond. In the context of a large molecule such as an enzyme the protein environment can affect the relative basicities of the fragments from an electrostatic potential point of view. The orientation of the hydrogen bond can also be changed by dynamical adjustments in the structure of the enzyme in the vicinity of the active site. Thus, given the small energy differences found, for example, for the different conformations of the formic acid–formate anion system and their sensitivity to environmental effects, it is clear that the equilibrium position in such hydrogen bonds can be easily shifted from one base to another by relatively small changes in the enzyme structure. This sensitivity could be the basis for both proton relay shifts[61] and final step regeneration of the native enzyme after a catalytic cycle.

III. ACTIVE SITES AND AMIDE HYDROLYSIS

Aspartic proteinases are a class of enzymes that hydrolyse (digest) peptide bonds (C—N)[62–64]. Proteinase is also active in the life cycle of the AIDS virus[65]. Three-dimensional X-ray studies[65–67] show a consistently similar picture of the active site. The centre of the site generally contains two aspartic (asp) residues with carboxylate groups facing, in a nearly planar arrangement. A solvent water (or hydroxide anion or hydronium cation) is found in proximity to a pair of the carboxylate oxygen atoms in a bridging position between the two asp residues. Since the proton positions are not determined by crystallography, the precise ionization (charge) of each of these groups is not known. The heavy atom distances, however, are consistent with a carboxylic acid–solvent–carboxylate anion type configuration (a catalytic triad) with an additional bridging hydrogen bond directly between an asp in the acid form and an asp anion to form an approximately cyclic structure. The catalytic mechanism thus divides into two parts; the local structure of the active site and the hydrolysis reaction.

Several research groups[68–70] have modelled the aspartyl residues at the active site by formic acid/formate anion groups. Although the enzyme structure restricts the possible

conformations around the active site, certain degrees of freedom remain, such as the location of the hydrogen atoms (i.e. degree of ionization of each group and solvent), geometric conformation, and exact location and nature of the solvent molecule located within or near the cavity between the asp residues. Hadzi and coworkers[69,70] have carried out a series of *ab initio* calculations on the equilibrium structure and energetics of such model systems using modest size (STO-3G and 4-31G) basis sets. These calculations have also been carried out[71] using the standard RHF/6-31G* theoretical model/basis set[2-4] which should give more reliable results. The objective of such studies is to obtain structural information about the active site which is not available from experiment and an estimate of energy differences between the various structures. These 'gas phase' results should be viewed only as the first step or iteration towards including more solvent and more of the enzyme to the extent that is needed to accurately describe the reaction mechanism.

The gradient optimized structure for the commonly accepted model of the active site is shown in Figure 4. The geometric parameters displayed are for the (constrained) planar geometry (I-P) but both the constrained and unconstrained (non-planar, I-NP) geometries were separately optimized. The energies are tabulated in Table 2. The non-planar structure is 1.2 kcal mol^{-1} more stable than the planar conformation. Actually, a lower-energy planar structure (II-P, Figure 5) has been located which, as noted by Hadzi's group[69], corresponds approximately to the positions of the heavy atoms (Asp32 and Asp215) and to the solvent oxygen atom in endothiopepsin[72]. Structure II-P is 1.4 kcal mol^{-1} more stable than I-P, both in their respective geometry optimized forms. The source of the preferred stability of II-P relative to I-P is not clear and may even be an artificial result of the RHF method which prefers localized structures[42] where possible. Given the small (1–2 kcal mol^{-1}) energy differences involved, localizing the charge on the doubly hydrogen bonded oxygen atom (Figure 5), as the Mulliken atomic changes show[71], would enhance the electrostatic interaction that stabilizes the hydrogen bond.

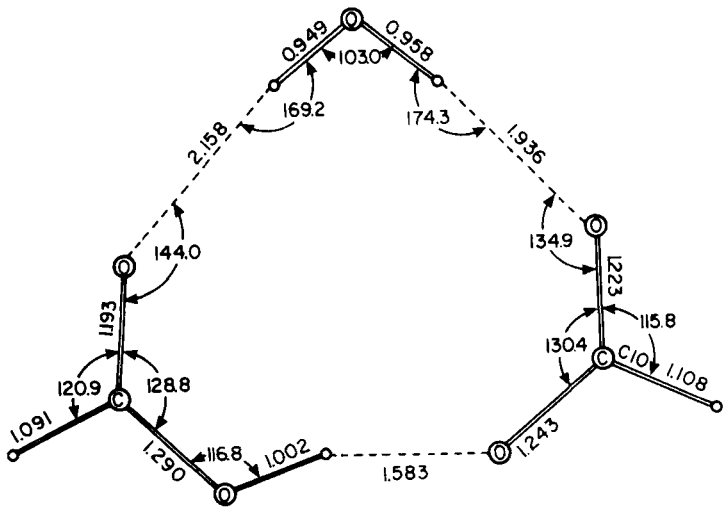

FIGURE 4. Formate–water formic, structure I-P. Bond lengths in Å, bond angles in degrees

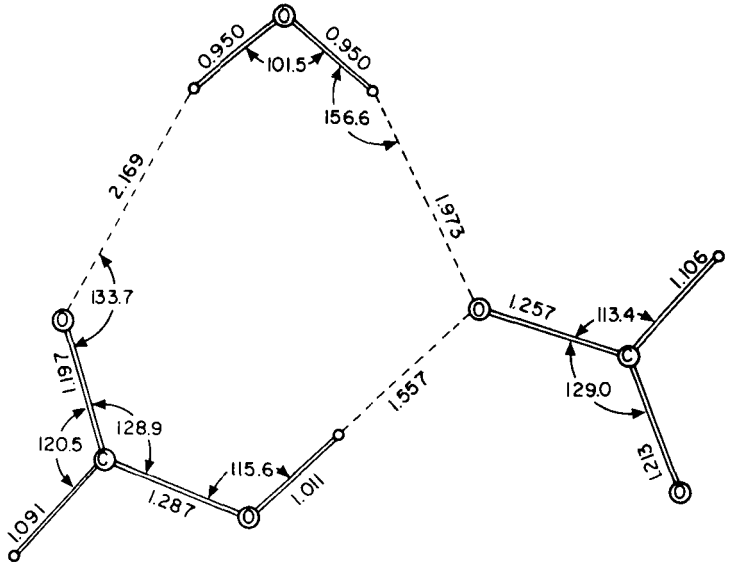

FIGURE 5. Formate water–formic, structure II-P. Bond lengths in Å, bond angles in degrees

An alternative structure for the active site[73] interposes a solvent water molecule directly between the aspartyl residues. Such a geometric conformation has also been RHF/6-31G* gradient optimized both in planar (III-P, Figure 6) and non-planar (III-NP) forms. The already cyclic water–formate anion complex is found to pivot on the (formic)O—H···O(water) bond axis and rotate away from the carbonyl oxygen atom on the formic acid to give the large O3···H7 distance of ~3.90 Å in both the planar and non-planar geometries, for what might have been expected to be a normal hydrogen bond interaction. This apparently repulsive motion wouldn't be allowed by the constraints of the aspartyl proteinase protein structure and, therefore, structure III must be considered improbable for energy reasons. As seen from Table 2, structure III-P (Figure 6) is calculated 3.4 kcal mol^{-1} higher in energy than II-P and, as noted, with the constraints of the active site it will be even less favoured energetically.

All attempts to optimize the neutral formic acid–hydroxide–formic acid structure without geometry constraints led to a spontaneous (no barrier) transfer of a proton from one of the formic acids to the hydroxide anion. Energetically (Table 2), in this valence

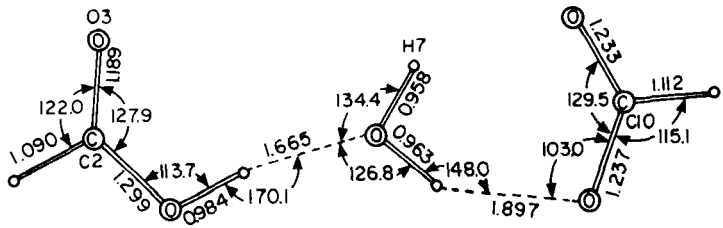

FIGURE 6. Formate water–formic, structure III-P. Bond lengths in Å, bond angles in degrees

TABLE 2. Energies of fragments and molecules in the formic–water–formate systems[a]

Molecule/structure	Energy[b]
H_2O	−76.010747
H_3O^+	−76.289338
OH^-	−75.326599
HCOOH	−188.762309
$HC(OH)_2^+$	−189.056532
$HCOO^-$	−188.182626
I-NP	−453.023549
I-P[c]	−453.021662
II-P[d]	−453.023950
III-NP	−453.019609
III-P[e]	−453.018514
IV-P[f]	−453.000121
V-NP[g]	−452.998753
VI-NP[h]	−453.573487
VI-P	−453.573171

[a] See text for basis set. All energies are for RHF optimized structures.
[b] In a.u.
[c] Figure 4. P = planar, NP = non-planar
[d] Figure 5.
[e] Figure 6.
[f] Figure 7.
[g] Figure 8.
[h] Figure 9.

basis set, the hydroxide anion is calculated to have a higher proton affinity than the formate anion by 65.5 kcal mol^{-1} and the proton migration in this model system is unhindered by a barrier. Imposing the appropriate symmetry constraints on the geometry in order to force the hydroxide bridge leads to the O—H···O(water)···H—O hydrogen bond system shown in Figure 7 (structure IV in Table 2). Energetically, this structure is 14.9 kcal mol^{-1} higher than II-P and hardly seems likely to fit the real active site. It also looks more like formate–hydronium–formate, although the bridging protons are almost symmetrically centred. Asymptotically (Table 2), even without diffuse basis functions for the anions, the hydroxide anion form is favoured by 123 kcal mol^{-1}. Unconstrained (non-planarity) geometry optimization gives the true symmetric formate–hydronium–formate configuration (V-NP, Figure 8) which separates even more charge than the previous structure and allows a closer approach of the oppositely charged fragments. This structure is (Table 2) 15.8 kcal mol^{-1} less stable than II-P, although electrostatic environmental effects could preferentially stabilize the latter more ionic conformation.

Other questions of interest about the aspartyl proteinase model systems involve the barriers to proton transfer (formic → formate) between asps in structure I-P (Figure 4) and in a possible formate–hydronium–formic model. Due to the much higher proton affinity of the formate anion relative to water, the more stable conformer in the latter case must be the formic–water–formic (VI-P, Figure 9) structure, in agreement with Hadzi[69]. The hydronium cation structure might be of special importance to the peptide acidic hydrolysis mechanism, the first step of which could be protonation of the carbonyl oxygen atom or the amine group[62,63,72,73]. The proton transfer barriers provide relevant

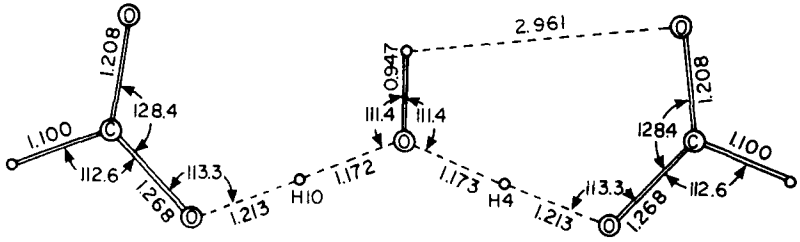

FIGURE 7. Formic-hydroxide–formic, structure IV-P. Bond lengths in Å, bond angles in degrees

information about the possibility of closed cycle proton shuttle mechanisms in the hydrolysis reaction which can induce the reaction and/or restore the native enzyme. A more detailed report on these results and modelling the active site in aspartyl proteinases will be given elsewhere[71].

Various mechanisms have been proposed for the (cleavage) hydrolysis of the peptide (C—N) bond by proteinases[62–64,72,73]. This problem can be crudely modelled by a formamide molecule representing the substrate and exploring the reaction mechanism for the acid/base catalysed hydrolysis of formamide[70]. Since the proteinases function in a naturally acidic environment (in the stomach, for example) many of the proposed mechanisms for the hydrolysis reaction involve, as a first step, protonation of the substrate at the carbonyl oxygen[62,64,72]. Subsequent steps involve the attack of water or hydroxide anion on the protonated formamide, protonation of the NH_2 group either from the surroundings (with concerted proton shifts, as necessary) or from an adjacent hydroxide group, and, finally, cleavage of the C—N bond. The concerted attack of a hydronium cation directly on formamide to form the protonated amine-*gem*-diol is considered unlikely. Other mechanisms[63,73] begin with an OH^- (generated from a polarized solvent water molecule) attacking the carbonyl carbon atom, followed by protonation at the amine nitrogen and cleavage of the C—N bond. All mechanisms invoke networks of hydrogen bonds to assist the reaction process and it is assumed that the scissile peptide bond is strained in its native form.

Model calculations on formamide + water for the hydrolysis process, such as will be described here, can only serve as indicators of the structure and energetics of the reaction path. A full understanding of the reaction mechanism requires fitting the substrate into

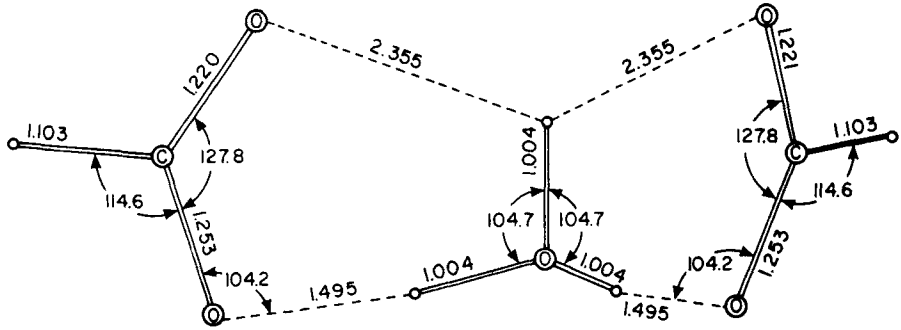

FIGURE 8. Formic–hydronium–formic, structure V-NP. Bond lengths in Å, bond angles in degrees

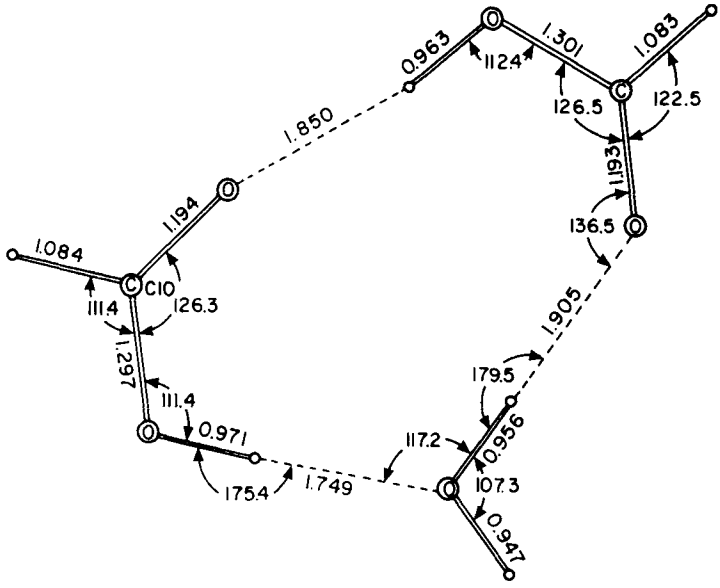

FIGURE 9. Formic–water–formic, structure VI-P. Bond lengths in Å, bond angles in degrees

the enzymatic site using realistic models of the enzyme and substrate, including solvent, and calculating the free energy profile for the reaction pathway[74,75]. It should be noted that amide hydrolysis via an aminodihydroxymethane adduct complex, $CH(OH)_2NH_2$, by addition of water to formamide, or to the O-protonated species is an active area of research in physical organic chemistry[76,77].

Some preliminary *ab initio* calculational results are now available[78]. Because almost all mechanisms postulate the initial generation of a tetrahedral carbon atom on the peptide, we have examined the addition complex that arises from both the attack of water on formamide across the carbonyl bond to form $CH(OH)_2NH_2$ (WF) and the attack of water on O-protonated formamide across the C—N bond to form $CH(OH)_2NH_3^+$ (WPF). The concerted addition reactions that exothermically produce both adducts pass through their respective transition states[79], which will not be discussed here. On the other hand, the hydroxide anion adds to formamide exothermically at the carbonyl carbon atom without a barrier[80,81]. This latter adduct complex requires a larger basis set representation than was used here for WF and WPF because of the diffuse functions needed to describe the anion.

Ab initio CAS-MCSCF calculations were carried out on the WF and WPF adduct complexes with unconstrained gradient optimization of the geometries[3]. In both cases the standard 6-31G* basis set was used, giving 70 basis functions for WF and 72 basis functions for WPF. Both adduct complexes have 34 electrons occupying 17 MOs which were divided into a passive space and an active space. The 24 electrons assigned to the passive space MOs were constrained to be doubly occupied in all the CAS configurations but were SCF optimized along with the active space MOs. In WF the passive MOs represent the 1s atomic orbitals on carbon, nitrogen and oxygen, two sets of lone pair electrons on each oxygen atom, the C—H and two N—H bonds, and the nitrogen atom lone pair of electrons. In WPF the list of doubly occupied MOs is exactly the same

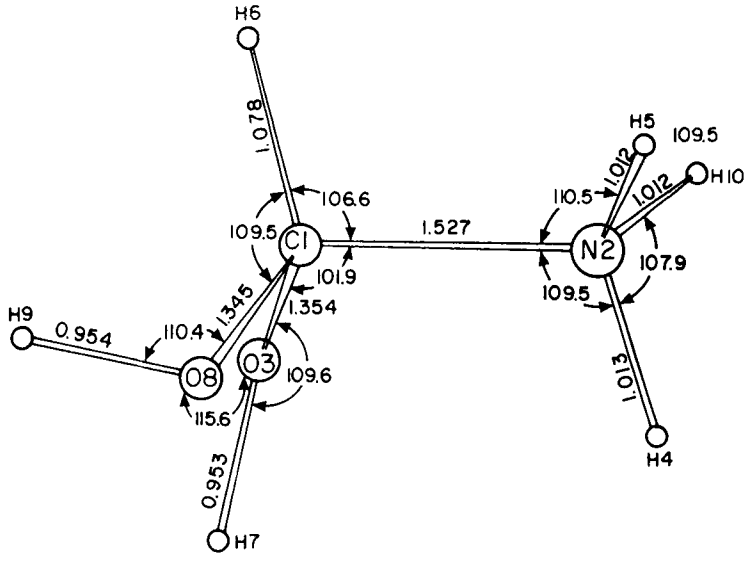

FIGURE 10. Water + O-protonated formamide (WPF). CAS-MCSCF geometry. Energy (RHF) = −245.293932 a.u. Energy (CAS) = −245.410693 a.u. Bond lengths in Å, bond angles in degrees

except that the O8—H9 bond pair (see Figure 10) replaces the N atom lone pair. The active space consists of 10 electrons distributed among ten MOs arranged as five bonding–antibonding pairs of MOs. For WF (see Figures 11 and 12) the bonds described are C1—N2, C1—O3, C1—O8, O2—H7 and O8—H9. For WPF O8—H9 enters the passive space and is replaced in the active space by the additional N2—H10 bond. All possible distributions of the 10 electrons in the ten MOs were taken into account to all excitation levels (CAS) to give 19,404 configurations for the spin singlet electronic ground state. The geometries were gradient optimized separately for the single configuration RHF (17 doubly occupied MOs) and CAS models (12 doubly occupied and 10 variably occupied MOs). The final WPF(CAS), WF(RHF) and WF(CAS) geometries are shown in Figures 10, 11 and 12, respectively. Mulliken and Lowdin[82] atomic charges are listed in Table 3.

The steroelectronic effects which differentiate between the fifteen possible staggered conformations of aminodihydroxymethane (WF) have been discussed[77]. Clearly the conformer preference in the enzyme reaction mechanism cannot be addressed in the isolated formamide + water adduct complex. This preliminary report mainly restricts itself to general observations on the calculated geometric and electronic structures and to commenting on the effect of correlation in the form of the CAS-MCSCF method. A comparison of equilibrium bond lengths between Figure 11 (RHF) and Figure 12 (CAS) for the WF adduct complex reveals the expected increase in equilibrium internuclear distance for those bonds that were correlated. Thus, the O—H bond increases in length by ~0.02 Å, C—O by ~0.03 Å and C—N also by ~0.02 Å due to partial occupancy of the corresponding antibonding MOs. The uncorrelated bonds (N—H and C—H) are affected by an order-of-magnitude smaller change in equilibrium distance.

The most outstanding feature of the two WF structures (RHF and CAS) is the non-planarity (rotation–pyramidalization) of the amide linkage (C—NH—R, with

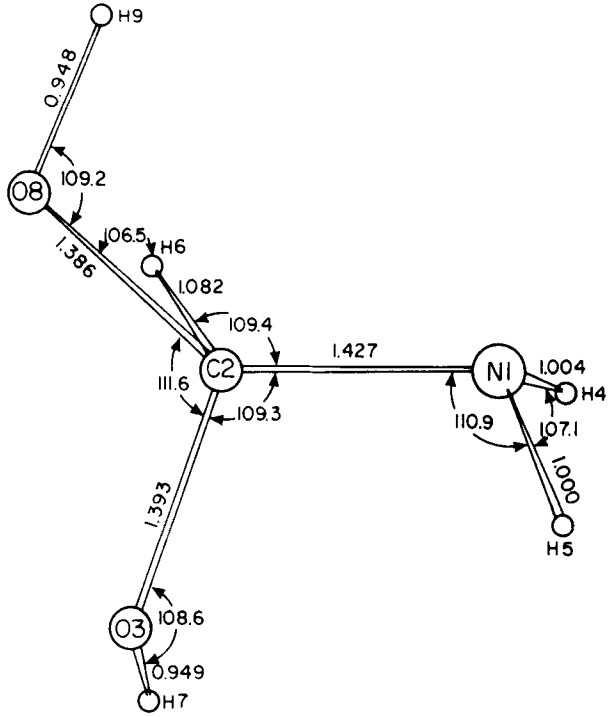

FIGURE 11. Water + formamide (WF). RHF geometry. Energy = −244.936289 a.u. Bond lengths in Å, bond angles in degrees

R = H here) which has been found previously[77,83]. The C—N bond length also increases substantially from its RHF/6-31G* optimized value in formamide of 1.349 Å[78] to 1.427 Å (RHF) and 1.449 Å (CAS). The calculated distortion about the nitrogen atom relative to planar formamide confirms the hypothesis that the presence of such structural features in the substrate peptides will enhance the hydrolysis reaction by reducing that part of the transition state barrier (to the formation of the adduct complex) that can be attributed to such changes about the nitrogen atom[84]. The twisted, non-planar amine structure in the peptide linkage leaves open the possibility of initial N-protonation in the actual enzyme reaction[85,86]. Although N-protonation is highly unfavourable in the gas phase relative to O-protonation[78], it has been claimed that solvents selectively stabilize N-protonation[87]. In all, except for the conformational change affecting mainly H9 (a rotation of ~68° in the H9–O8–O1–H2 dihedral angle) in WF(CAS) relative to WF(RHF), the generation of the CAS structure seems hardly worth the effort. Of course, in tracing the reaction mechanism path from reactants through transition state to products, the flexibility in the bond making/breaking description afforded by the CAS method will be crucially important for an accurate description of homolytically broken or strained (diradical) bonds.

The aminodihydroxymethane adduct complex (WF) can also be formed by a non-concerted process in two stages; protonation of the carbonyl oxygen atom followed by nucleophilic attack by OH^- at the carbon centre. Similarly, the WPF adduct complex can be viewed as the result of protonation at NH_2 followed by water addition across

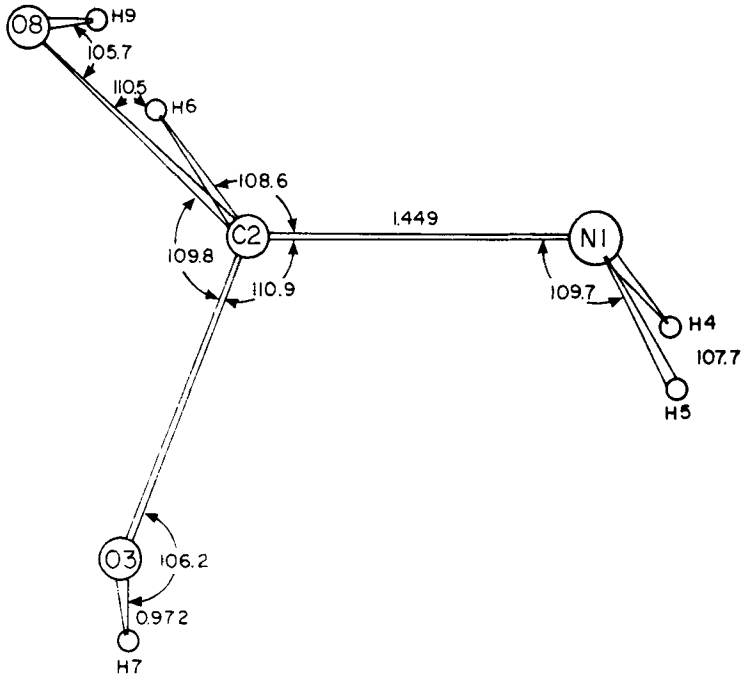

FIGURE 12. Water + formamide (WF) CAS-MCSF geometry. Energy = −245.063053 a.u. Bond lengths in Å, bond angles in degrees

TABLE 3. Calculated atomic charges for WF and WPF

	WPF[a]			WF[b]		
	RHF	CAS		RHF	CAS	
	Mulliken		CAS Lowdin	Mulliken		CAS Lowdin
C1	0.5652	0.5121	0.2133	0.6043	0.5577	0.1867
N2	−0.8507	−0.7899	−0.3562	−0.8671	−0.8418	−0.5869
O3	−0.7084	−0.6625	−0.4466	−0.7469	−0.6934	−0.4934
H4	0.4680	0.4693	0.3540	0.3501	0.3519	0.2791
H5	0.4755	0.4765	0.3550	0.3571	0.3487	0.2781
H6	0.2563	0.2585	0.1842	0.1553	0.1443	0.1211
H7	0.5100	0.4745	0.3952	0.4469	0.4162	0.3546
O8	−0.6788	−0.6682	−0.4424	−0.7498	−0.7026	−0.4969
H9	0.4916	0.4899	0.4004	0.4502	0.4190	0.3375
H10	0.4713	0.4399	0.3432			

[a] Water + O-protonated formamide adduct complex. See caption to Figure 10 and text.
[b] Water + formamide adduct complex. See captions to Figures 11 and 12, and text.

the C=O bond. In the gas phase, of course, protonation at oxygen followed by addition across the C—N bond is favoured. The WPF(CAS) geometric structure is shown in Figure 10. Unlike what was found for WF, there are hardly any conformational differences for WPF between the CAS and RHF optimized structures. Therefore, only the CAS structure is shown. Again, all the correlated bonds increase by 0.02–0.03 Å (RHF → CAS) while the dihedral angles are hardy affected. The Mulliken calculated atomic charges show a large part of the net unit positive charge on the NH_3 fragment both in RHF (+0.564) and CAS(+0.596). The Lowdin (CAS) charge on NH_3 is even larger at +0.696 electrons. The C—N bond length in WPF jumps to 1.527 (RHF) and 1.548 Å (CAS) from 1.427 and 1.449 Å in WF, respectively. This large increase reflects the bonding between tetrahedral carbon and nitrogen atoms in WPF which increases the C–N distance to pure single bond character and length. The calculated proton affinities of WPF are 224.4 (RHF) and 218.1 (CAS) kcal mol^{-1}. For comparison, the (RHF) calculated proton affinity of formic acid (Table 2) is 184.6 kcal mol^{-1}. The calculated high stability of WPF even in the gas phase argues against this complex being able to play a significant role in the hydrolysis of the peptide linkage. A more detailed analysis of these and other related results will be presented elsewhere[78].

IV. REACTION FIELD METHODS

The electronic structure description of molecules and their properties in chemical and biochemical systems by *ab initio* methods is currently undergoing continued improvement and extension. For large systems the molecule size that can be treated using standard[2–4] SCF methods and their extensions to include the correlation energy error, where necessary, is constantly increasing as the result of improved methodology[88] and computer technology[89]. Since spatial interaction energies are typically the starting point even for dynamical studies, and these are, in some way, always based on time-independent quantum-mechanical calculations, the continued importance of the electronic structure description is assured.

However, it is difficult to imagine the RHF method ever being applied to a complete protein or enzyme with accompanying solvating species and ions, as are found in biological systems. It is not even clear that such a calculation would be necessary or even useful from a thermodynamic point of view. It is also not at all clear that such a calculation is even required in order to solve most chemical problems. If the desired property is well localized to a manageably sized quantum mechanically (QM) treated portion of the biomolecule, the rest of the system could be regarded as a perturbation on the QM site and treated by simpler methods appropriate to the weak interaction regime.

Based on perturbation theory with overlap[90] it is possible to decompose the weak interactions in the Hartree–Fock approximation between closed-shell molecules into electrostatic, exchange–repulsion, polarization and charge-transfer components. The accuracy of such an expansion, of course, depends on the degree of overlap and becomes increasingly unreliable as penetration of the interacting fragment charge clouds increases. Within this limitation, the individual contributions to the total interaction energy can be evaluated *ab initio* using frozen-fragment, reduced variational space calculations[58]. The formal theoretical basis for such a separation is found in McWeeny's theory for separable electron pairs[91], although its practical application to large systems is difficult[92,93]. The interaction terms are therefore replaced by effective potentials which represent the interaction of the QM system with the environment or solvent. These terms are incorporated into the Fock Hamiltonian and become part of the SCF equations for the QM part.

This self-consistent reaction field approach was pioneered and developed by the groups of Tapia[94], Warshel[95] and van Duijnen[96] in their original and subsequent papers. These investigators differ from each other in their treatment of the QM part and representation of the electrostatic, exchange–repulsion and polarization terms. All these methods ignore charge transfer and therefore their validity is restricted by this limitation. Other investigators have also tried to account for charge transfer effects[97,98]. Exchange repulsion has been treated in different ways as a van-der-Waals interaction[95], a calibrated (from *ab initio* work) parameterized potential term[98], within the local charge density approximation[97] or ignored[94,96,99]. A repulsive potential is essential for any geometry optimization procedure or relative motion between the QM part and the surrounding which generate the potential interaction terms. Correlation or dispersion effects, neglected in the Hartree–Fock approximation, are sometimes added but weak bonding or non-bonding interactions shouldn't be affected by this term which should be additive to the others[100]. The polarization term has been variously handled as atom-centred polarizabilities with induced dipoles[95,98] or as a parametric scalar quantity[86]. Finally, the purely electrostatic potential is represented as point dipoles[94], point charges[95,97] or as a multi-centre multi-polar expansion[98,101-104].

Generally, these treatments have introduced phenomenological parameters or approximations to the exact interaction terms that have ruled out a systematic understanding of the error incurred or the hierarchy of approximations introduced. Thus improvements in the computational scheme within the framework of the given model are difficult to formulate.

Recently, a new formulation of the reaction field method has been developed[105]. This approach is designed to simultaneously maximize accuracy and computational efficiency while defining the error incurred at each level of approximation for each term. As usual, the total system is divided into a QM part and an environment consisting of one or more well-defined fragments whose mutual interaction can be treated classically. In this version, the fragments are not bonded to the QM part. The environment introduces new one-electron potential operator terms into the *ab initio* calculation of the quantum mechanical species of interest, which represent the interaction of the fragments with the QM part.

The new one-electron Fock Hamiltonian operator (F^{Q}) is used to solve for the doubly occupied molecular orbitals (ϕ_i) and orbital energies (ε_i) of the closed-shell QM part in the presence of a number of fragments (S),

$$F^{Q}\phi_i^{Q} = \varepsilon_i\phi_i^{Q} \tag{1}$$

where equation 1 is solved in the usual self-consistent way[106], and

$$F^{Q} = F_o^{Q} + (V_S^{ES} + V_S^{XR}) \tag{2}$$

Here, F_o^{Q} is the ordinary Fock operator for the isolated (no environment) QM part, V_S^{ES} is a one-electron representation of the electrostatic potential of the molecular charge density of S, and V_S^{XR} is a one-electron effective repulsive potential representing the exchange orthogonality interaction with S. The total energy of the QM system is given by equation 5 where,

$$E'_Q = \langle\phi_i|h^{Q} + F^{Q}|\phi_i\rangle \tag{3}$$

$$E_Q^{POL} = \langle\psi|V_S^{POL}|\psi\rangle \tag{4}$$

$$E_Q = E'_Q + E_Q^{POL} \tag{5}$$

Equation 3, which does not include the polarization potential term V_S^{POL}, is the basis for the variational procedure that gives equation 1 in the usual manner[2]. With the form

of the polarization potential used here (see later), where the interaction term is a function of the charge density (ψ is the total wave function for QM), incorporation of the total polarization energy (equation 4) directly into the variational equations (1) poses severe formal and practical problems, as discussed by Sanhueza and coworkers[107]. Therefore, the total polarization energy (E_Q^{POL}) is treated as a first-order perturbation correction in the total energy (E'_Q, equation 3) obtained in the usual SCF manner using equation 1[2]. Of course, the electric field of the QM part also interacts with, and polarizes, the environmental fragments (S). This latter effect can be represented as an appropriate collection of induced dipole moments in S and their interaction with the QM part added in an iterative manner to the solution of the Hartree–Fock equation 1. We will not explore this point further here.

Thus, the total reaction field contribution is a sum of electrostatic, exchange repulsion and polarization interactions. The electrostatic potential of S, V_S^{ES} in equation 2, is represented by a modified form of the relatively compact distributed multipolar expansion proposed originally by Stone[108] which has been shown to be superior to other distributed monopole (point changes)[95–97,109] and multi-pole expansions[98,101–104,110,111], whether centred at the atoms, bonds or localized MO centroids[112]. The single centre expansion has been shown to be inadequate and even divergent[113].

Stone's method[108] is suited to the basis set expansion methods generally used in *ab initio* electronic structure work. The procedure consists of assigning each product of primitive gaussian basis functions to one of a small set of pre-determined expansion centres. Each product of gaussian functions naturally defines a new gaussian function on a centre lying somewhere along the line joining the origins of the two original gaussian functions[114]. These origins are typically taken as the nuclear centres and, therefore, a natural choice of expansion centres is the nuclei themselves (the one-centre atomic terms fall naturally on them) and the internuclear (bond) midpoints. This is Stone's recommended choice[108]. Each product gaussian is then assigned to the expansion point nearest to the product gaussian centre. The total electron density can then be expressed as a sum of overlap charge density terms originating from each expansion site. Those product gaussians that fall exactly on one of the expansion sites are represented by the direct multipole expansion of that overlap charge density which gives a finite number of terms. It can be shown that for a pair of product functions with angular momentum quantum numbers l and l' the highest multi-pole moment will be of rank $L = l + l'$. Those product gaussian centres that do not coincide with one of the distributed sites are expanded about the nearest site (nuclear centre or bond midpoint) as a new origin in terms of the moments of the off-centre product distribution. This expansion is not finite but, as expected, is found to be rapidly convergent for the choice of distributed sites taken as the nuclei and the bond midpoints. At each of the chosen sites all the contributions from the different (on-site and off-site) products at a given multi-pole level (L) are summed.

Tests[105] on a number of molecules have shown the off-site expansion to be well converged already at the quadrupole level, accurate at the octupole level, and to give a very good representation of the molecular charge distribution. These tests compare the calculated electrostatic potential using the exact charge distribution with the distributed multi-pole representation. The individual multi-pole terms (including the monopole charge) are found to be basis set dependent, as are the individual components of the Mulliken population[115], but the over-all accuracy is good. However, in calculating electrostatic interactions the multi-polar expansion under-estimates attractive interactions (or over-estimates repulsions). This is attributed to the absence of penetration effects with the point source distributed multi-pole expansion which are present in the electrostatic interaction between real charge distributions, even if they are frozen. The

net effect of such charge cloud penetration is an attractive (stabilizing) interaction[116] in the overlap region. Since these characteristics are similar to those of the repulsion potential (see later) but with the opposite sign, it is possible to absorb penetration effects into the repulsive potential in its formulation and evaluation.

An alternative possibility is to multiply the distributed multi-polar terms by a screening function[117,118] of the form

$$1 - b \exp[-a(r - r_c)^2] \tag{6}$$

where r_c is the expansion centre, for ease of integral evaluation (see later). The attractive penetration term is clearly seen here. The a and b parameters in equation 6 are obtained by fitting the exact molecular electrostatic potential specifically in the atomic valence region using the distributed multi-polar expansion with the screening function. A common set of screening function parameters is applied to all the multi-polar terms at a given expansion centre but a separate set of parameters is allowed for each centre. This procedure gives an improved molecular electrostatic potential which is reflected in the interaction energies[105].

The electrostatic potential due to the distributed multi-poles enters the QM Fock operator (equation 2) and the appropriate one-electron matrix element integrals over gaussian basis functions need to be evaluated. The analytical forms of these operator terms can be simply expressed as the potential ($\sim 1/r$) for monopoles, electron field for the dipoles and field gradient for the quadrupole terms[119]. The necessary integral formulae are typically already coded in the standard electronic structure codes[3] or are readily constructed and added[120]. The screening function in the above (equation 6) form just adds another multiplicative gaussian term, which is easily absorbed into the gaussian charge distribution products.

The classical polarization energy for a point charge source in a uniform external electric field is given by the interaction between the induced dipole at the point source and the electric field[119]. The induced dipole itself is also proportional to the field where the proportionality constant is the polarizability tensor. For a scalar polarizability of molecule or fragment S (α_S) the corresponding QM operator can be taken as

$$T_S^{POL} = -\tfrac{1}{2}\alpha_S \mathbf{f}_S \cdot \mathbf{f}_S \tag{7}$$

where $\mathbf{f}_S$ is the electric field at S. Again, as in the case of the charge distribution, a more accurate description of the polarizability interaction is obtained by using multi-centre (λ) distributed polarizabilities. In our case, the external field is produced by the electrons (k) and the nuclei (n) of the QM part,

$$V_S^{POL} = -\tfrac{1}{2} \sum_{\lambda(S)} \alpha_\lambda^S \mathbf{f}_\lambda^S \cdot \mathbf{f}_\lambda^S \tag{8}$$

where

$$\mathbf{f}_\lambda^S = \sum_k \mathbf{r}_{k\lambda}/r_{k\lambda}^3 - \sum_n Z_n \mathbf{R}_{n\lambda}/R_{n\lambda}^3 \tag{9}$$

and α_λ^S is the dipole polarizability at centre λ in fragment S. Clearly, the polarizabilities by component on the different centres must sum to the total polarizability of S.

This formulation has been successfully used to calculate core polarization (correlation) in valence configuration interaction calculations and its *ab initio* application stems from that source[121]. Actually, $\mathbf{f}_\lambda^S$ in equation 9 is multiplied by a damping or cut-off function of the form

$$C_{k\lambda} = [1 - \exp(-\gamma_\lambda r_{k\lambda}^2)] \tag{10}$$

which serves an important function. Substituting equation 9 into equation 8 and applying equation 4 gives three contributing terms to E_Q^{POL}; electron–electron, electron–nuclear and nuclear–nuclear. The electron–electron terms have both diagonal and off-diagonal components. Although the latter is a two-electron integral, its factored form makes use of only one-electron gaussian basis function integrals over the $r_{k\lambda}/r_{k\lambda}^3$ operators. However, the diagonal electron–electron interaction involves effective $1/r_{k\lambda}^4$ type operators whose matrix elements (integrals over all space) are divergent because of the zero at the origin. The cut-off function (giving operators of the type $C_{k\lambda}^2/r_{k\lambda}^4$ prevents electron penetration to the origin of λ and avoids divergence of the integrals. Again, the analytic form of $C_{k\lambda}$ (equation 10) does not complicate the integral evaluation. These integrals over the effective $1/r^4$ type operators are conveniently evaluated using the integral transform,

$$1/r^m = A \int_0^\infty u^{(m-1)} \exp(-r^2u^2)\mathrm{d}u \tag{11}$$

and their appropriate derivatives[122].

There remains now the choice of distributed polarization centres and the method for determining the values of the centre polarizabilities α_λ^S in equation 8. Stone[123] has proposed a multi-centre polarization model which, however, suffers from practical application problems[124]. A distributed model of molecular electric dipole polarizabilities has recently been developed as an effective and practical alternative[125]. The method is similar to that of Maestro and Moccia[126] who proposed writing the coupled-perturbed Hartree–Fock (CPHF)[127] dipole polarizability of a closed-shell molecule as a sum of contributions from localized molecular orbitals (LMO) obtained using the Boys localization method[128]. An equivalent but simpler method of obtaining the desired localized polarizabilities uses finite electric-field calculations on S. A full discussion of the method and applications, including transferability, has been published[125]. The result is a full set of polarizability tensors, $\alpha_{\lambda,rs}$ ($r, s = x, y, z$) located at the centroids of each LMO of molecule S. The individual scalar dipole polarizabilities α_λ^S in equation 8 are then constructed from these tensors.

The last component of the reaction field Fock operator for the QM part is the exchange repulsion V_S^{XR} term in equation 2 which is expressed as a repulsive effective potential (REP). This repulsion causes charge densities in the region of overlap-interaction to be smaller than the sum of the superimposed charge densities for the unperturbed systems. Of course, owing to normalization requirements charge density increases elsewhere in the system. The effective fragment potentials described here for the environment are, necessarily, for the undeformed electron distribution and this deformation depletion in the interaction region of the QM part of the over-all system must be induced by a REP (V_S^{XR}). Apparently, the largest component of V_S^{XR} is a reduction in the nuclear(QM)–electronic(S) potential energy which, of course, cannot be balanced by a corresponding decrease in the point charge nuclear–nuclear interactions[129]. These exchange–repulsion interactions are the most difficult to model because, unlike the electrostatic and polarization terms, V_S^{XR} is primarily a quantum-mechanical effect and has no clear classical analogue.

Two types of REP have been considered. The first is a sum of purely one-centre (k) functions of the form

$$\mathrm{REP} = \sum_k (C_k/r^n)\exp(-\beta_k r^2) \tag{12}$$

with $n = 0$ and/or $n = 1$. These potential functions, which interact with the QM electrons (only), are centred either at the nuclei or at the LMO centroids of S. Integral evaluation

over gaussian basis functions for the special $n = 1$ case has been described previously[130]. The values of the parameters C_k and β_k are determined by fitting the exact (*ab initio*) interaction energy between two fragments assuming that one is the QM part and the other is S. Representing S are the electrostatic and polarization terms described previously and the residual interaction energy is attributed to V_S^{XR}. The values of C_k and β_k are then chosen so as to exactly reproduce the interaction energy for various relative orientations and distances between the two fragments. Although the equation 11 representation of REP is simple and the method of its determination straightforward, the resulting V_S^{XR} suffers from poor transferability. For example, determining C_k and β_k from argon–water interactions gives poor binding energies for water(QM)–water(S) and formamide(QM)–water(S) systems[131].

A second method of modelling REP is the two-centre approach where the contribution of the exchange repulsion to the total interaction energy is given as the sum of two half calculations:

$$E_{QS}^{XR} = \langle QM | V_S^{XR} | QM \rangle + \langle S | V_{QM}^{XR} | S \rangle \tag{13}$$

The first term gives the V_S^{XR} potential operator term in equation 2 and the second term is a constant structure-factor addition to the total energy (equation 5) after the SCF calculation has converged. Quantities V_S^{XR} and V_{QM}^{XR} are derived individually using an argon atom probe[132] with the analytical REP form and method of generation as described for the one-centre repulsive potential. In this approach the effective potential representation of the QM charge distribution is also required. Tests on water-formamide, and for the water and formamide dimers using a REP representation (equation 11) with more than a single term per centre k have been carried out. Both transferability and the exchange repulsion energies *per se* are much improved compared to the one-centre approach[131].

Altogether, the terms described here combined to give an effective fragment potential (EFP). The methods outlined here enable the EFP to be generated without great effort and used straightforwardly. A number of test calculations[105,131] on hydrogen-bonded dimers and trimers, where different fragments are alternately considered to be the QM part, show that the EFP model works reasonably well. Comparison here is made with *ab initio* reduced variational space calculations which define the partitioning of the interaction energy in the same manner as the reaction field method[58].

In addition, the simple QM–S model can be extended in several directions.

(1) Methods for replacing fragments that are directly chemically bonded to the QM part by an EFP need to be developed. Singh and Kollman[133] have discussed one possible approach A formulation based on frozen LMO is now being tested[134].

(2) In line with almost all other current *ab initio* methods, the geometric optimization of the QM part for a fixed EFP can be implemented. This requires only small modifications of existing integral evaluation programs[131].

(3) The fragment(S)–fragment(S′) interaction energy needs to be developed. This term converts the reaction field framework for determining the electronic structure of a QM system under the influence of a discrete perturbing environment(S) into a quantum analog of a molecular mechanical method which may allow full geometry optimization. Since S–S′ distances are expected to be large, simplifications in the interaction terms will be possible.

(4) The QM + discrete environment can be surrounded (or, more accurately, permeated) by a dielectric continuum of varying complexity and detail of description to represent solvent, for example. This approach has been developed by Rashin[135] and is readily combined with the EFP-reaction field method described here[134].

The *ab initio* reaction field method with the effective fragment potential has a very promising future which must be proven with specific examples. Although only methods

have been described here, enough application and comparison calculations have been carried out already to justify the optimism expressed in this article. These will be reported on subsequently[105,131,134].

V. METAL ION–ACID/AMIDE COMPLEXES

The coordination of metal cations to proteins[136] and nucleic acids[137], for example, is ubiquitous in biological systems. Although the metal ions are usually doubly charged (M^{2+}) other ligands or solvent molecules such as water are attracted and attach themselves to such a high electrostatic potential and polarizing source as a dication so that the charge is effectively reduced[138]. Coordinated metal ions affect hydrogen bonding properties[139] and the detailed structure/reactions of DNA[140], together with their constituent sugar and phosphate units[8]. On the other hand, the interaction of single or multiple ligands with bare cations in the gas phase has also become a very active area of experimental research due to great strides and innovations in mass spectrometry instrumentation[141–145]. The determination of accurate binding energies[146] by these experimental methods and their variation with the nature of the metal ion, ligand and number of substituents can give insight into the nature of the metal–ligand bonding.

So far, however, these experiments do not give direct information on the structure of such complexes. Of particular interest in the latter regard is the preferred site attachment of the metal ion in cases where the ligand can offer multiple coordination and conformational possibilities for complexation. Recent high-quality *ab initio* electronic structure calculations have begun to address these questions for the binding of simple, single-site ligands[147–153]. Optical absorption and fluorescence experiments on metal ion–ligand complexes in the gas phase are now being reported[154,155]. Finally, it should be noted that simple molecules such as carboxylates and formamidates have long been known as effective and strong bridging ligands in binuclear transition metal complexes[156,157].

Recent gas-phase studies and accompanying *ab initio* calculations for metal-fragment ions that are electrostatically bound (M^+—X) have been reported for X = rare gas atoms, small molecules (like water and CO) and saturated hydrocarbons[143–154,158,159]. The interaction between M^+ and X can also lead to direct chemical bonding attachment, as well as elimination and insertion reactions. In this latter case the metal ion interposes itself between two bonded atoms (such as C—H or C—C) or, in unsaturated systems, for example, breaks a π bond to form two metal-fragment σ bonds in a three-membered ring geometry. However, the focus in this study is on the electrostatic-type interactions as was discussed long ago for the Ag^+–ethylene system[160], where the perturbation of the ligand geometry and electronic structure is relatively small and no new bonds are formed.

Because of the great interest and focus on amides and carboxylic acids, as described above, a survey set of *ab initio* electronic structure calculations has been carried out here on a series of 1:1 M^+—X fragment combinations where $M^+ = Ni^+$, Pt^+, Cu^+, Au^+, Zn^+ and Hg^+, and X = formamide, formic acid, glycine, the formamidate and formate anions, and the glycine zwitterion (but not all combinations)[161]. Properties of interest include preferred binding site locations and orientations, metal–ligand binding energies and equilibrium bond distances, changes in ligand geometric structure, comparison to protonation structures and proton affinities, and metal ion electronic configurations (especially for Ni^+ and Pt^+) in the complexes. In this latter regard, the three column groups of metal ions represent very different bonding opportunities: open (d) d^9s^0 shell (Ni^+, Pt^+), closed $d^{10}s^0$ shell (Cu^+, Au^+) and open (s) $d^{10}s^1$ shell (Zn^+, Hg^+). This survey study allows a comparison of the electronic and geometric properties among them, as well as a comparison of first-row and third-row transition metal ion bonding.

The details of the calculations are as follows. The geometries of the M^+—X complexes were gradient optimized at the RHF (closed-shell) or unrestricted HF (UHF, open-shell) levels[4]. At each HF calculated equilibrium geometry a single point calculation was also carried out of the appropriate MP2 type (RMP2 or UMP2). Therefore, all quoted MP2 calculated quantities imply MP2//HF. Full BSSE corrections were applied to both the HF and MP2 energies using the Boys' counterpoise method[28] for all the complexes except for those involving anionic or zwitterionic ligands, and the protonated species. This correction typically reduced the calculated binding energy by about 5% at the HF level and ~10% at the MP2 level. Since the counterpoise method is considered to give a reasonably good estimate, but, at most, an upper limit to the true BSSE[162], the relatively small adjustment to the HF binding energy is encouraging. The larger MP2 level corrections probably reflect the large correlation energy error in the occupied d electrons of the metal ions[163] which are using the off-centre ligand basis functions for this purpose in the expanded virtual space of the combined $M^+ - X$ complex. The calculated $\langle S^2 \rangle$ value at the UHF optimized geometries for the spin doublet states were all in the 0.752–0.766 range (exact value, 0.75) except for certain of the Pt^+ complexes where the spin-squared expectation value ranged as high as 0.832 (with formate).

Ab initio relativistic compact effective potentials (RCEP) were used for all the transition metal atoms. These have been generated for K to Rn (except for the Lanthanides)[164] by a method similar to that used for the first two rows of the Periodic Table[23], but based on relativistic atomic orbitals[165]. Some applications involving the transition metal atoms using the RCEPs have been reported[8,138,140,166]. The use of relativistic CEPs has been shown to be particularly important for the Pt atom[167]. The RCEP used here do not include the ns^2np^6 subshell ($n = 3$ for first-row and $n = 5$ for third-row metals) in the effective core potential. These semi-core electrons, so called because they physically occupy the same (radial) space as the valence *n*d electrons but don't participate in chemical bonding, are explicitly considered in the valence space and appropriately represented by basis functions. The need for such a partitioning has recently been documented[168]. The gaussian function basis set on each metal atom is $I^{sp}J^d$ (the sp are shared-exponent) contracted to $4^{sp}3^d$ to describe the *n*s, *n*p, *n*d, $(n + 1)$s and $(n - 1)$p atomic orbitals[164]. For the first-row transition metal atoms $I = 8$ and $J = 6$, while for the third-row, $I = 7$ and $J = 5$. The semi-core and valence sp subshells are described by double sets of contracted basis functions while the valence *n*d electrons have triple-zeta (TZ) representation. The importance of the TZ split for the open d-shell systems has been discussed[169]. The carbon, nitrogen and oxygen atom basis sets are the valence and polarization CEP-211G* set, split from the CEP-31G* basis described in a previous paper[24]. The combined $M^+ + X$ basis set is designated TZP. All calculations reported here were carried out with this basis unless otherwise indicated. For those calculations involving the anionic (formate and formamidate) ligands an additional single gaussian diffuse sp-type basis function (with an exponent equal to one-half the smallest exponent in the valence sp basis) was added to the nitrogen and oxygen atoms only to give the TZP + basis. In each case, the standard[3,4] $(4^s)/[2^s]$ representation of the hydrogen atom was used. Only the five spherical harmonic components of the d-type basis functions were included in the calculations.

The calculated binding energies, referenced to their own asymptotes at large metal ion–ligand distance, are displayed in Table 4. All the cation-formamide structures are for attachment at the carbonyl oxygen atom in the molecular plane (σ complexes). Although the geometry optimizations were run in C_1 symmetry, only a limited attempt was made to locate other minimum energy structures either in, or out of, the molecular plane. The cations were usually pre-positioned near or between the electronegative atoms as initial structures for the geometry optimizations. These comments are generally appropriate for all the M^+—X calculations reported here. Mulliken populations for the

TABLE 4. Calculated bond dissociation energies for M^+—X[a]

X		M^+	Ni^+	Cu^+	Zn^+	Pt^+	Au^+	Hg^+	H^+
Formamide	HF	49.2	46.0	47.5	43.5	38.9	34.0	209	
	MP2	54.2	51.6	49.1	50.6	44.9	37.1	202	
syn-Formic acid	HF	37.2			32.7			181	
	MP2	41.0			37.5			172	
anti-Formic acid	HF	43.4			37.9			187	
	MP2	47.3			43.4			178	
Glycine I	HF	64.9	59.8		61.9	50.8		222[b] 208[c]	
	MP2	75.5	69.9		76.7	62.2		219[b] 201[c]	
Glycine II	HF	52.6	49.5		49.0	43.3		211[d]	
	MP2	58.1	55.4		55.9	50.0		202[d]	
Formate anion	HF	167.0[e]			164.7[e]			354	
	MP2	179.4[e]			180.3[e]			342	
Formamidate anion	HF	178.1[e]			181.2[e]			381	
	MP2	192.6[e]			196.6[e]			372	
Glycine zwitterion	HF	76.2	72.4		74.4	66.4		249	
	MP2	82.9	80.0		81.4	73.8		238	

[a] In kcal mol^{-1}.
[b] N-protonated (Figure 28), relative to conformer I (Figure 29).
[c] O-protonated (Figure 27), relative to conformer I (Figure 29).
[d] O-protonated (Figure 27), relative to conformer II (Figure 30).
[e] In the TZV + basis set.

metal ion *n*d, $(n-1)$s and $(n-1)$p atomic orbitals in the various complexes (summed over their multiple-zeta representations) are shown in Table 5.

The geometry optimized M^+-formamide complexes for $M^+ = Ni^+$, Cu^+, Zn^+, Pt^+, Au^+, Hg^+ and H^+ are shown in Figures 13–15. The gradient optimized isolated formamide molecule is shown in Figure 16 for comparison purposes. The optimum M^+–oxygen atom distance (R) in Figure 13 is seen to be in the 1.97–2.01 Å range for all three of the first-row transition metal ions studied here. These distances are shorter than the reported HF calculated M^+–water equilibrium bond length[170] and are comparable to the correlation MCPF calculated[148] M^+–water distances for these metal ions. The higher dipole moment and polarizability of formamide relative to water are expected to enhance the interaction and shorten the metal–ligand equilibrium separation for these primarily electrostatically bound complexes. The dipole moment in formamide lies roughly parallel with the C=O bond, with a tilt towards the aliphatic hydrogen atom[7]. The metal ions in Figures 13 and 14 are seen to be approximately aligned with the formamide dipole-moment direction for maximum charge–dipole interaction. Although diffuse basis functions are generally needed for an accurate description of molecular polarizability[171] the metal ion–ligand interactions here are dominated by local interactions (see later) for which the valence basis set appears to be adequate[161].

The third-row transition metal ions (Figure 14) have equilibrium R values that are 0.13, 0.23 and 0.36 Å longer than their first-row counterparts, respectively, for the Ni, Cu and Zn columns in the Periodic Table. Such a differential increase in calculated M^+–ligand bond distances has also been found for the CO ligand between the first- and second-row metal ions[172] in the Ni and Cu columns. This differential increase in R could be an indication of a degree of covalent bonding in the third-row transition metal ion adduct complexes, not present in the first row, and of the decreasing importance of such covalency in going from the d^9 to the d^{10} configuration in the third row[173]. However, covalency implies delocalization of charge and the numbers in Table 5,

TABLE 5. Metal Mulliken atomic orbital populations

X	M^+	*n*d	(*n* + 1)s	(*n* + 1)p
Formamide	Ni^+	9.02	0.06	0.07
	Cu^+	9.99	0.01	0.08
	Zn^+	10.01	0.97	0.21
	Pt^+	9.02	0.10	0.06
	Au^+	9.94	0.14	0.06
	Hg^+	9.99	1.01	0.11
syn-Formic acid	Ni^+	9.02	0.05	0.06
	Pt^+	9.02	0.08	0.05
anti-Formic acid	Ni^+	9.02	0.06	0.06
	Pt^+	9.01	0.09	0.06
Glycine I-C	Ni^+	8.99	0.13	0.10
	Cu^+	10.01	0.21	0.10
	Pt^+	8.96	0.22	0.09
	Au^+	9.94	0.18	0.08
Glycine II-D	Ni^+	9.02	0.07	0.07
	Cu^+	10.00	0.01	0.07
	Pt^+	9.01	0.11	0.06
	Au^+	9.94	0.15	0.05
Formate anion	Ni^+	9.02	0.24	0.16
	Pt^+	9.00	0.34	0.15
Formamidate anion	Ni^+	9.01	0.25	0.17
	Pt^+	8.98	0.37	0.10
Glycine zwitterion	Ni^+	9.02	0.11	0.11
	Cu^+	10.01	0.13	0.09
	Pt^+	9.01	0.07	0.07
	Au^+	9.93	0.21	0.07

although consistent with these trends, show only small variations in atomic orbital populations compared with the differential charges on *R*. The relatively large (+0.13 Å) increase in the calculated *R* value for Hg^+ relative to Au^+ could be connected with its larger effective radius due to the addition of the outer s sub-shell electron, although a corresponding increase in *R* for Zn^+ in the first row is not found.

The differences in *R* values between Figures 13 and 14 are roughly consistent with the calculated bond dissociation energies (BDE) in Table 4. Thus, for the first-row metal ions, the BDE don't vary much going $Ni^+ \rightarrow Cu^+ \rightarrow Zn^+$ (HF and MP2). For the third-row metals both HF and MP2 values decrease steadily in going $Pt^+ \rightarrow Au^+ \rightarrow Hg^+$, while being generally smaller in magnitude. The different *R* value and BDE trends between first- and third-row metal ions for $d^{10} \rightarrow d^{10}s^1$ show that outer-shell s–p hybridization is more efficient in Zn^+ than in Hg^+, which is confirmed by the atomic orbital populations in Table 5.

The calculated protonation energy (PE) of formamide [209 (RHF) or 202 (MP2) kcal mol^{-1}][161] at the oxygen atom is, of course, much larger than the metal ion affinities (Table 4) due to the closer approach distance and the much larger polarizing capability of the proton[136]. The protonated adducts are also expected to be more covalently bound (more delocalized) than the metal ion complexes. This is reflected in the much smaller $C{=}O{-}H^+$ angle (Figure 15) than for $C{=}O{-}M^+$ (Figures 13 and 14). The experimental proton affinity of formamide, reported[174] at 199 kcal mol^{-1}, is slightly smaller

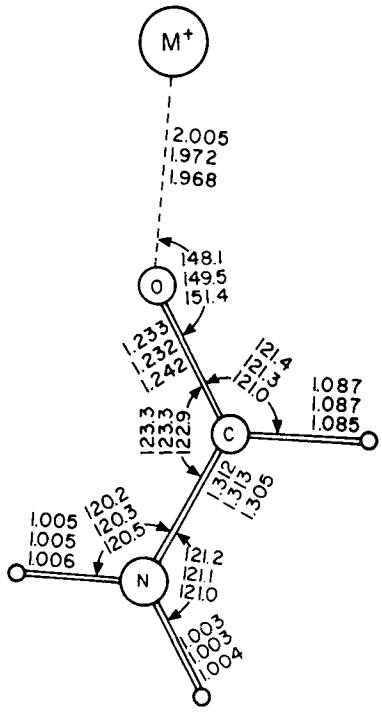

FIGURE 13. Metal ion formamide, metal = Ni (top number), Cu and Zn. Bond-lengths in Å, bond angles in degrees

than the calculated values, which are uncorrected for the zero point, vibrational temperature, translational and rotational energy differences, and conversion to enthalpy. These adjustments to the theoretical numbers are necessary for comparison to experiment[2] and will reduce the calculated value by about 3–4% but still leave it close to the experimental value.

The changes in the formamide monomer ligand geometry upon metal ion complexation compared to simple protonation are seen by comparing Figures 13–16. As expected, the C=O bond length increases in the order monomer → complexed → protonated, reflecting the strength of binding and the degree of perturbation of the local ligand structure. The C—N bond, however, decreases in length in the same order, 1.35 Å → 1.31 Å → 1.28 Å, indicating a strengthening of the C—N bond which is usually attributed to increased π bonding. Further evidence from more such systems is necessary to determine if this is a general trend and, if so, to explain the phenomenon. Metal ions are known to enhance or inhibit the hydrolysis of the amide bond depending on structural factors[175]. It has been proposed[176] that it is actually π complexation at the nitrogen atom, for example, that enhances the reaction rate preferably compared to σ complexation. This suggestion would be consistent with the decreased C—N bond length found here for σ complexation of the metal ions since enhanced hydrolysis rates would be expected to correlate with a weakening of the C—N bond.

The ground states of the $M^+ = Ni^+$, Zn^+, Pt^+ and Hg^+ ion formamide complexes are $^2A'$ in C_S symmetry with the singly occupied d orbital in Ni^+ and Pt^+ facing the

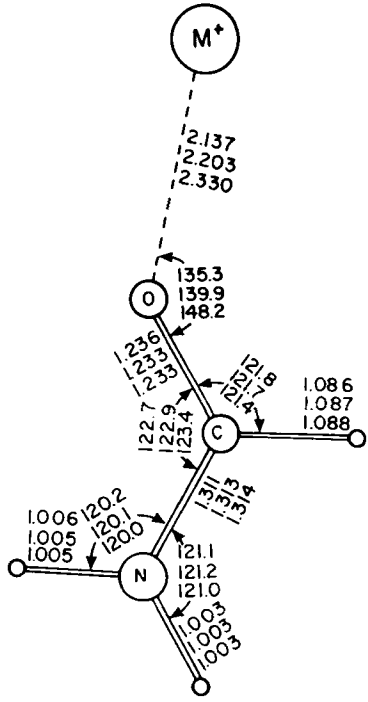

FIGURE 14. Metal ion–formamide, metal = Pt (top number), Au and Hg. Bond lengths in Å, bond angles in degrees

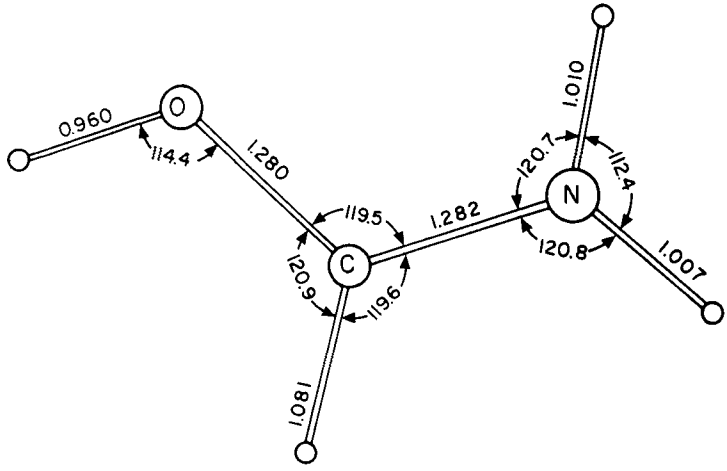

FIGURE 15. O-Protonated formamide. Bond lengths in Å, bond angles in degrees

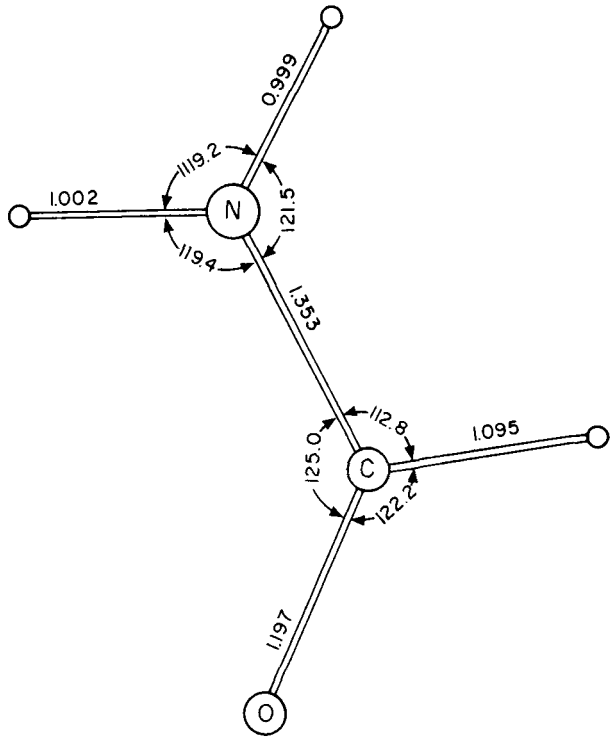

FIGURE 16. Formamide. Bond lengths in Å, bond angles in degrees

carbonyl oxygen atom. This arrangement, which minimizes electron repulsion, has also been found for X = H_2O and CO[148,149,170]. The $(n + 1)$p orbital populations (Table 5) for $M^+ = Zn^+$ and Hg^+ are also larger than for the formally $(n + 1)s^0$ configuration metal ions because of the need to hybridize the more diffuse (relative to *n*d) valence $(n - 1)$s electron away from the direction of the ligand. Such s–p mixing minimizes repulsion with X and allows a closer approach of the ion to the ligand for enhanced ion–dipole binding[177]. As noted, the $(n + 1)$p orbital population is larger for Zn^+ than for Hg^+, indicating the greater effectiveness of the former ion in removing the $(n + 1)$s electron from the bonding region. This might explain the differential increase in R in comparing Zn^+ with Hg^+ noted above.

The monomers, metal cation (Ni^+ and Pt^+) complexes and protonated structures are shown in Figures 17–22 for formic acid in both its *syn* and *anti* forms. The conformer differences have been discussed above[45,51]. The *syn* geometry is the more stable of the two in the monomer but the *anti* conformer has the possibility of the cation interacting with two oxygen atoms. Table 4 confirms the expected greater bond dissociation energy (relative to its own asymptotes) of the *anti* metal ion complex structure by 5–6 kcal mol^{-1}, at both the HF and MP2 levels. Since in this basis set the monomer *syn–anti* energy difference is 6.0(RHF) or 5.7(MP2) kcal mol^{-1} the *syn* and *anti* metal ion complex are about equally stable on an absolute BDE basis.

The calculated metal ion–formic acid binding energies are uniformly smaller than for formamide (for the same transition metal ion), although the *anti* conformer BDEs are

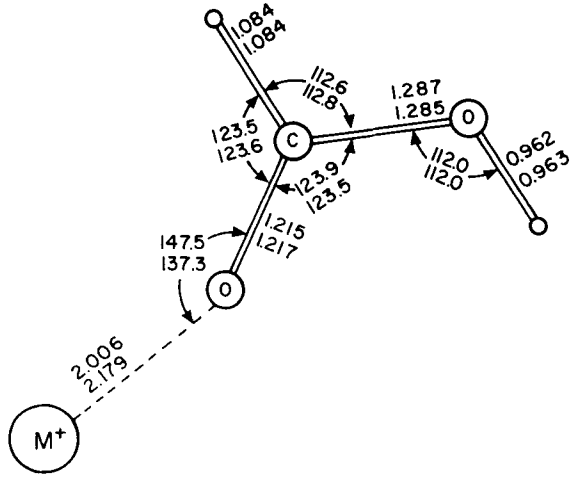

FIGURE 17. Metal ion–(*syn*)-formic acid; metal = Ni (top number) and Pt. Bond lengths in Å, bond angles in degrees

approaching those of formamide. The calculated monomer dipole moments (μ) here are: formamide ($\mu = 4.28D$), *syn* formic ($\mu = 1.68D$) and *anti* formic ($\mu = 4.52D$). Thus, both the calculated and experimental[178] dipole moments of *syn* formic acid are smaller than for formamide. The experimental dipole polarizability of HCOOH is also smaller than that of formamide[178], and this is expected to be true also for the *anti* conformer. The metal ions, which are oriented relative to the C=O bond similarly for both Ni^+ and Pt^+ (7°–10° differences), are aligned closely with the monomer dipole moments for both the *syn* and *anti* conformers. The latter complexes include an attraction of the metal ions to the hydroxyl oxygen atom, which is reflected in the smaller C=O—M^+ angles in the *anti* complexes (comparing Figures 17 and 18). In spite of the metal ions following the dipole-moment directions of the monomers, emphasizing the dominant charge–dipole nature of the interactions, the calculated BDE (*syn* → *anti*) are not proportional to the dipole-moment ratios of the monomers, probably reflecting the more local nature of the interaction.

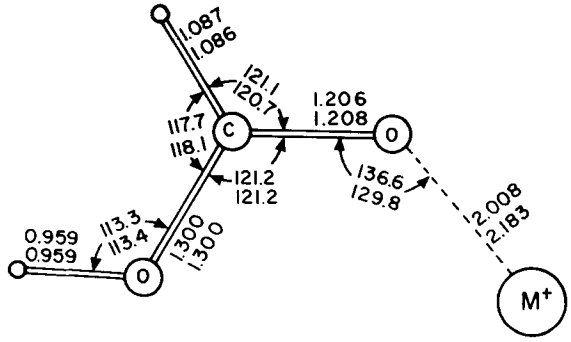

FIGURE 18. Metal ion–(*anti*)-formic acid; metal = Ni (top number) and Pt. Bond lengths in Å, bond angles in degrees

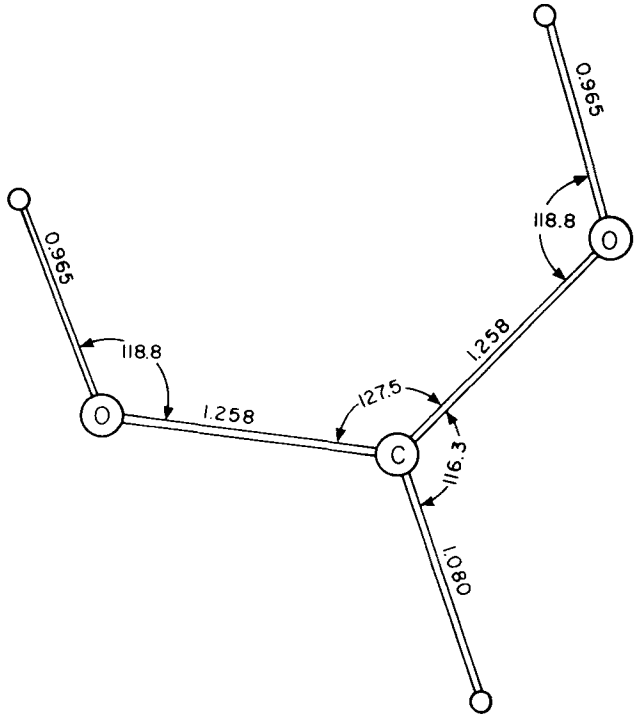

FIGURE 19. Protonated-(*syn*)-formic acid. Bond lengths in Å, bond angles in degrees

The metal–oxygen (O=C) equilibrium distances are very similar for the formic acid complexes, comparing *syn* (Figure 17) and *anti* (Figure 18) conformers for the same metal ion. The calculated protonation energies for the two conformers (Figures 20 and 21), *syn*-181 (HF) or 172 (MP2) and *anti*-187 (HF) or 178 MP2 kcal mol^{-1} [161], each relative to its own asymptotes (Table 4) are smaller for formic acid than for formamide, reflecting the 178.8 kcal mol^{-1} experimental value for the former[179] in comparison with 199.0 kcal mol^{-1} for formamide[174]. Although, unlike the metal ions, the protonated species are expected to have a certain degree of covalent binding (or greater delocalization of the positive charge), the proton in the lower energy protonated formic acid (Figure 20) sits approximately on the dipole-moment direction relative to both the *syn* and *anti* (precursor) structures.

As expected, the C=O bond length in formic acid is seen to increase uniformly from 1.19 Å (*syn*) or 1.18 Å (*anti*) in the monomers (Figures 21 and 22), to 1.22 Å (*syn*) or 1.21 Å (*anti*) complexed (Figures 17 and 18), to 1.26 Å (*syn*) or 1.25 Å and 1.26 Å (*anti*) protonated (Figures 19 and 20); the same trend as found for formamide. The C—OH bond length changes from (monomer) 1.32 Å (*syn*) or 1.33 Å (*anti*), to (complexed) 1.29 Å (*syn*) or 1.30 Å (*anti*), to (protonated) 1.26 Å (*syn*) or 1.25 Å (*anti*). The general trend here is for decreasing C—OH bond length upon cation attachment to the carbonyl oxygen atom, as was found for the C—N bond in formamide.

The glycine geometries studied here are shown in Figures 23–31. Referring back to Figure 1 in this review[23], the most favourable structures for metal ion complexation

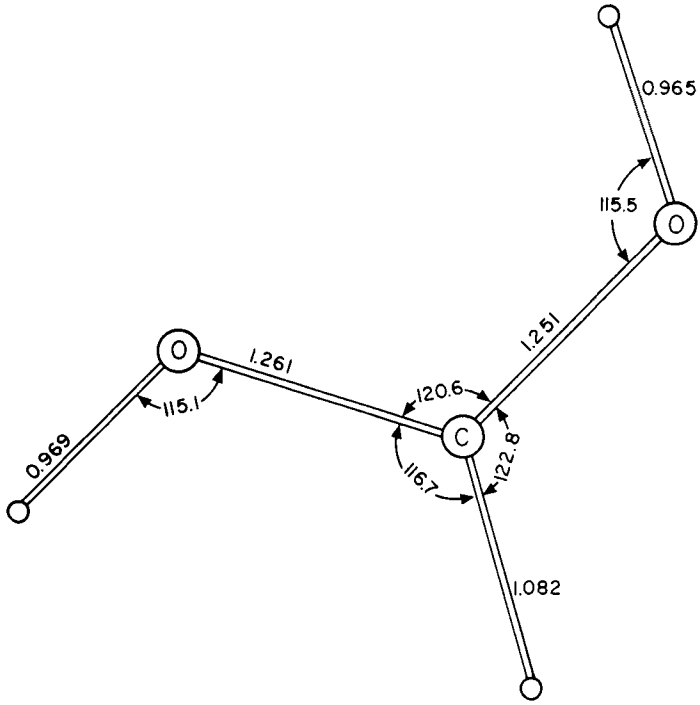

FIGURE 20. Protonated-(*anti*)-formic acid. Bond lengths in Å, bond angles in degrees

appear to be the ones labelled I-C and II-D in that figure because they allow a bidentate interaction of the ligand, with the carbonyl oxygen atom and with either the amine nitrogen or the hydroxyl oxygen. In the hydrogen-bonded systems with water[23] attachment at the carbonyl oxygen atom as one of the sites was found to be favoured energetically. The cyclic, double attachment is expected to be more stable than any linear, single site coordination. For the protonated species the shorter $H^+—X$ bond distance means that there are ostensibly two minimum energy structures for both the I-D and II-C geometries, each with the proton attached exclusively to one of the electronegative atoms. However, carbonyl protonated II-D is identical to carbonyl protonated I-C. In addition, an attempt to protonate the hydroxyl group in structure II led to the spontaneous migration of the hydroxyl proton to the amine group. Therefore, there are only two independent protonated structures (Figures 27 and 28).

The calculated BDEs for the $M^+ = Ni^+$, Cu^+, Pt^+ and Au^+ complexes are shown in Table 4. Glycine I (Figure 29) is the most stable monomer conformer[22,23] but in its native form it can be expected to offer only a single metal ion coordination site with an electronegative atom (O—H, O=C or NH_2) for a given structure because of steric repulsion with both the hydroxyl and amine hydrogen atoms. However, inversion of the hydrogen atoms at the amine centre and reoptimization of the geometry, which raises the energy of glycine I by 5.5 (RHF) or 5.4 (MP2) kcal mol^{-1} [161] but increases the dipole moment from 1.35*D* to 3.17*D*, allows the double cyclic interaction (I-C) shown in Figures 23 and 24. Glycine III (Figure 31), the next conformer in RHF energy ordering

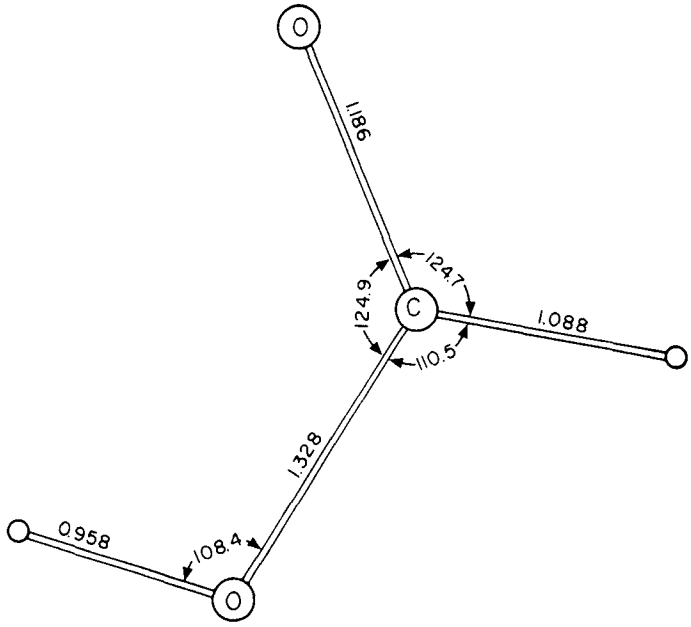

FIGURE 21. *Syn* formic acid. Bond lengths in Å, bond angles in degrees

[1.9 (RHF) or 1.6 (MP2) kcal mol^{-1} higher] again allows only a single interaction site at a time unless the amine group is inverted. The possible bidentate site then involves the hydroxyl and amine groups simultaneously. This combination was expected to be less bound than any bidentate coordination that involved the carbonyl oxygen atom and hasn't been explored. The lower dipole moment for III with the inverted amine group ($\mu = 2.45D$)[161] also argues for a weaker BDE. Conformer II (Figure 30), the highest RHF energy monomer form [3.1 (RHF) but only 1.5 (MP2) kcal mol^{-1} above I][161], with an impressive dipole moment of 6.07*D*, allows simultaneous metal ion interaction with the carbonyl and hydroxyl group oxygen atoms (structure II-D) similar to the *anti* formic acid complexes. These are shown in Figures 25 and 26.

As noted, inversion of the amino group in glycine I allows bidentate coordination and increases the ligand dipole moment to 3.17*D*, which should also enhance interaction with the metal ion. As judged from the calculated M^+–A (A = oxygen or nitrogen) equilibrium distances, the structures in Figures 23 and 24 seem to show that the metal ion interaction with the amine lone pair of electrons is equally as important as the interaction with the carbonyl oxygen atom. Thus, perhaps contrary to expectations, the metal ions are found to be almost equidistant from the nitrogen and oxygen atoms. It should also be noted that in this bridging position the metal ions lie far from the (inverted amine) monomer dipole moment axis direction, which is oriented almost parallel to the C=O axis but tilted towards the hydroxyl group. The II-D structures (Figures 25 and 26) show a similar picture. Here, both attachments are to A = oxygens but the monomer dipole moment axis ($\mu = 6.0D$)[161] bisects the O—C=O angle with a significant tilt towards the hydroxyl oxygen atom. The metal ion complexes defy this orientation and the M^+–oxygen distances are ~1 Å shorter to the carbonyl group than to the hydroxyl group for both the first- and third-row metal atoms. Thus, for both the I-C and II-D

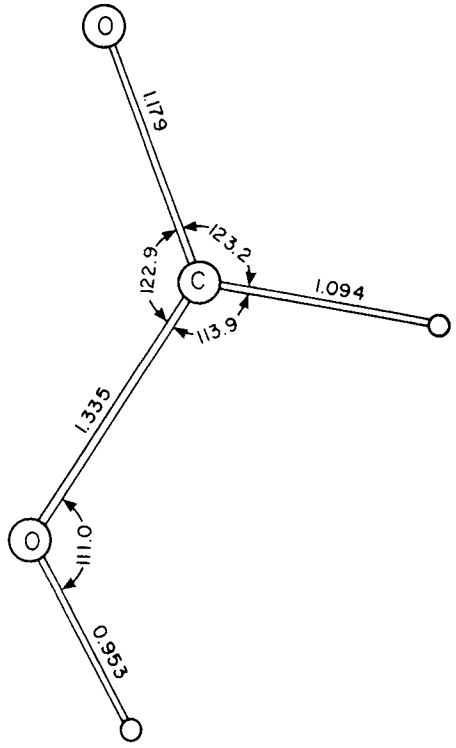

FIGURE 22. *Anti* formic acid. Bond lengths in Å, bond angles in degrees

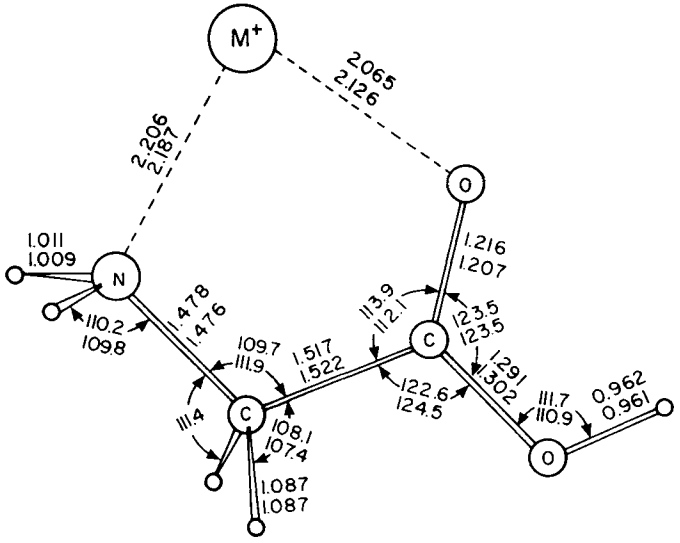

FIGURE 23. Metal ion–glycine (I-C), metal = Ni (top number) and Cu. Bond lengths in Å, bond angles in degrees

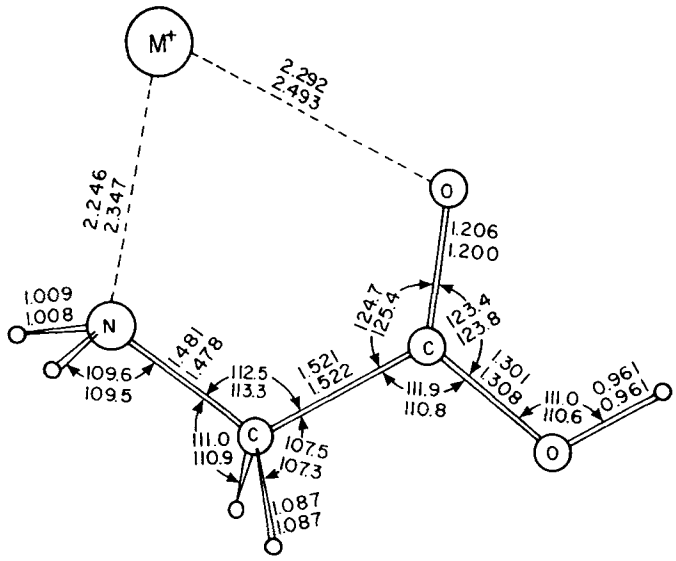

FIGURE 24. Metal ion–glycine (I-C), metal = Pt (top number) and Au. Bond lengths in Å, bond angles in degrees

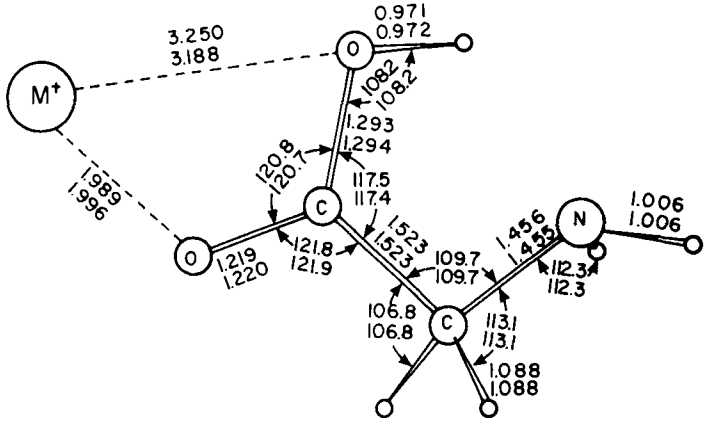

FIGURE 25. Metal ion–glycine (II-D), metal = Ni (top number) and Cu. Bond lengths in Å, bond angles in degrees

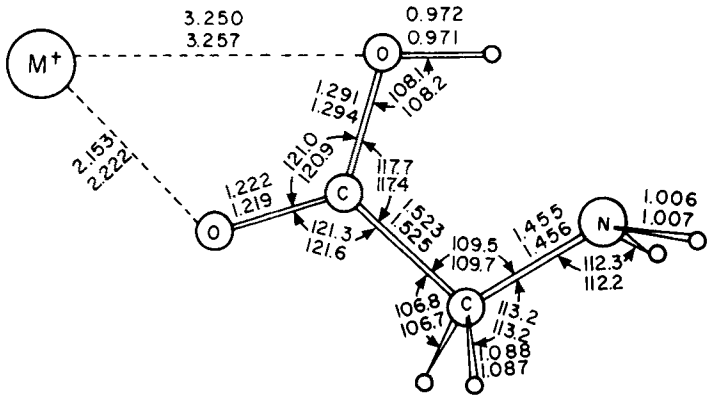

FIGURE 26. Metal ion–glycine (II-D), metal = Pt (top number) and Au. Bond lengths in Å, bond angles in degrees

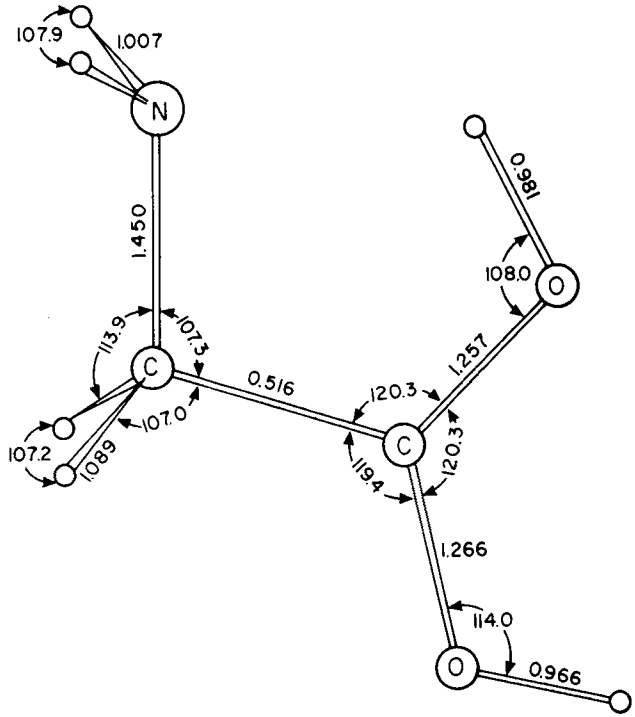

FIGURE 27. O-Protonated glycine I with inverted amine group. Same as O-protonated glycine II. Bond lengths in Å, bond angles in degrees

structures, it must be that local, and not overall molecular, dipole-moment forces dominate the interactions and determine the complex adduct geometries.

The binding energies in Table 4 show that the I-C structures (Figures 23 and 24) are generally more stable than II-D, which probably reflects the local dipole-moment differences in the monomers (with the inverted amine group in glycine I) and, perhaps, the greater polarizability of the amino group relative to hydroxyl. The changes in BDE going both across ($Ni^+ \rightarrow Cu^+$ and $Pt^+ \rightarrow Au^+$) and down ($Ni^+ \rightarrow Pt^+$ and $Cu^+ \rightarrow Au^+$) the Periodic Table are similar to those found for formamide. The M^+—A bond lengths for the third-row metal ions are generally consistent with these trends, where higher BDEs correlate with longer R values.

The protonated species are shown in Figures 27 and 28. The lower energy structure is N-protonated glycine I with the proton adding to the far side of the amino group. This conformer is 0.7 kcal mol^{-1} more stable than the I-C type structure with the inverted NH_2 group probably because of eclipsed interactions with the methylene hydrogen atoms. The (uncorrected) calculated proton affinity (relative to conformer I, Figure 29), 222 (RHF) or 219 (MP2) kcal mol^{-1} (Table 4), is close to the experimental value (213.0 kcal mol^{-1})[180]. The O-protonated structure (Figure 27) has PE = 208 (RHF) or 201 (MP2) kcal mol^{-1} relative to glycine I (Table 4). Comparing Figures 23 and 24, and 27–29 for all the I-C related structures, the expected trend in C=O bond length is followed in going monomer → complexed → protonated. Analogously, comparing Figures 25–27 and 30 (glycine II) for the II-D related structures shows the same increase in C=O distance upon complexation/protonation at this site. Cation attachment at the carbonyl oxygen draws electron density from the C=O bond and weakens it.

The (single) C—O bond adjacent to C=O, on the other hand, decreases in length upon metal ion complexation or protonation at C=O. This could be explained by the cation attachment making the carbonyl carbon atom more electronegative and drawing π electron density into the C—O bond from the hydroxyl oxygen atom which strengthens it by adding partial double bond character. This type of explanation is not appropriate to the C—C bond which is relatively unaffected by complexation/protonation (Figures 23–31). The C—N bond in length, on the other hand, is hardly affected (a small decrease) by cation coordination at remote (one bond removed) coordination sites (C=O and O—H). The decrease in bond length for a bond adjacent to (i.e. sharing

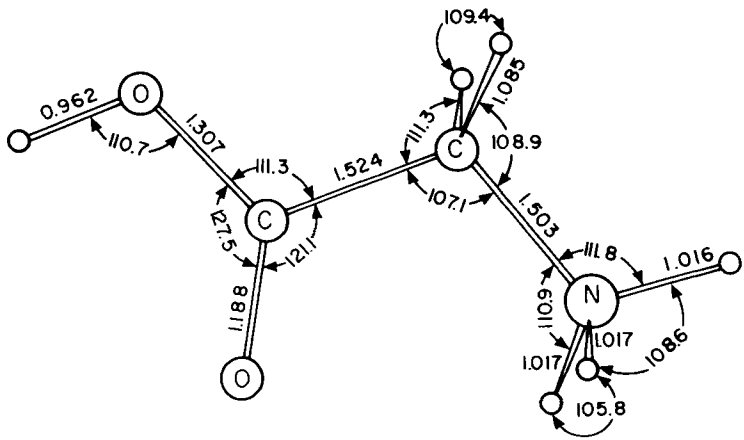

FIGURE 28. N-protonated glycine I. Bond lengths in Å, bond angles in degrees

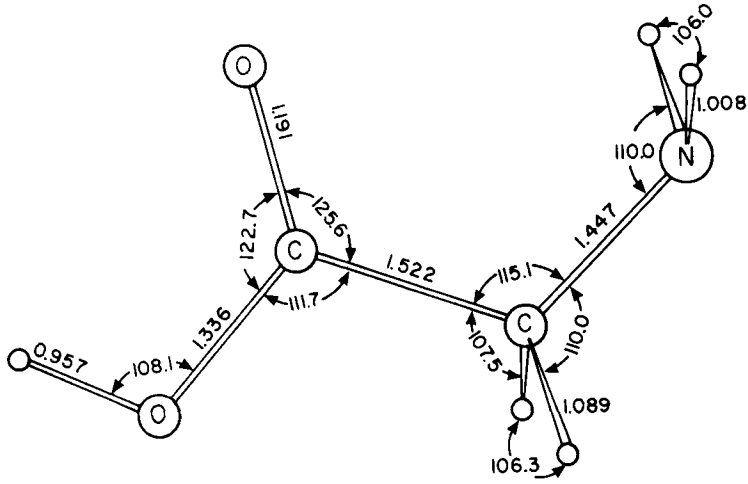

FIGURE 29. Glycine I. Bond lengths in Å, bond angles in degrees

a common atom with) a complexed/protonated site was commented upon for X = formamide (C—N) and is also found for X = formic acid (C—O). In each case of bond shortening the atom attached to the carbonyl carbon atom had lone pair electrons. For the I-C structures (Figures 23 and 24) and protonation at C=O (Figure 27) the C—O bond also shortens as in II-D, but the N—C bond lengthens for the complex because the bidentate attachment involves coordination of the metal ion at the nitrogen atom.

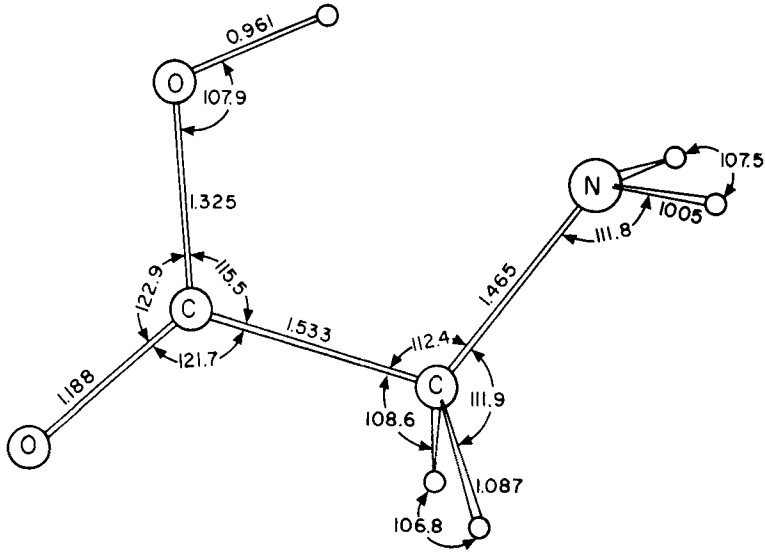

FIGURE 30. Glycine II. Bond lengths in Å, bond angles in degrees

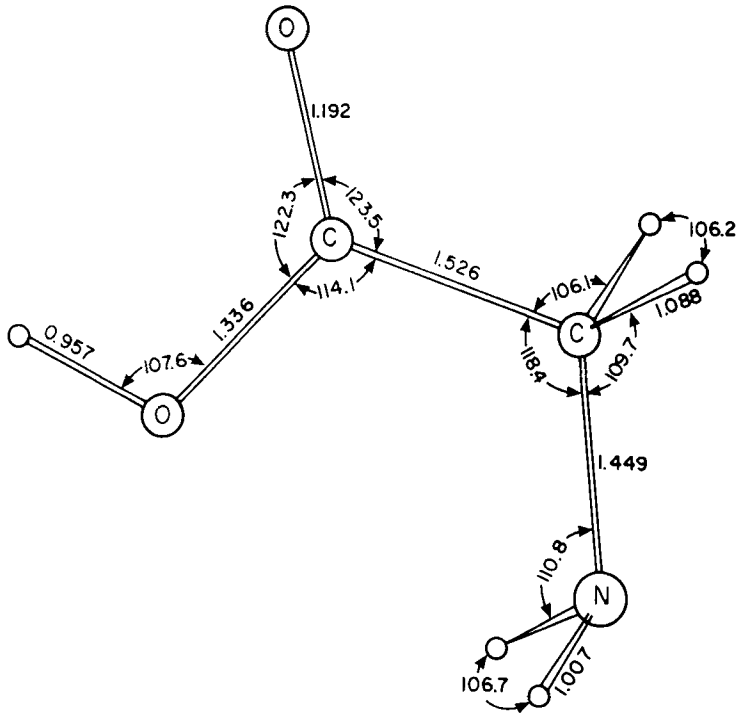

FIGURE 31. Glycine III. Bond lengths in Å, bond angles in degrees

Protonation at the carbonyl oxygen atom (Figure 27) changes C—N very little while protonation at $\underline{N}H_2$ (Figure 28) causes the C—N distance to increase as expected.

As noted before, another set of metal ion–glycine adduct complexes that can be considered is based on glycine III (Figure 31) with an inverted amine group. The geometry optimized N-inverted structure (III′) is only 4.0 (HF) or 4.3 (MP2) kcal mol^{-1} above III, but 2.7 (HF) or 4.4 (MP2) kcal mol^{-1} above glycine II (Figure 30) from which it can also be derived by rotation of the hydroxyl hydrogen atom to the carboxylate *syn* conformation. The dipole moment of III′ is 2.45*D* compared to 2.01*D* for III and 6.07*D* for II. However, local dipole-moment forces are expected to be dominant and these should be probed with metal ions. Such calculations are currently underway.

The formate anion is shown in Figure 32 and the geometric structures of the Ni^+– and Pt^+–formate complexes are given in Figure 33. Both formate and formamidate anion ligands and their metal complexes were calculated in the TZV + basis set. The corresponding *syn* formic acid and formamide were also re-optimized in this basis set for comparison purposes. Thus the (Table 4) proton affinity of the formate anion is calculated (uncorrected) at (HF) 354 or (MP2) 342 kcal mol^{-1} (Table 4), compared to the experimental value of 345 kcal mol^{-1} [181]. The *ab initio* calculation of acidities has recently been discussed[182].

A survey of the Cambridge Structural Database for the preferred site (one or two oxygen atoms) and conformational (*syn* or *anti*) attachment of metal ions to carboxylate groups in metal-containing proteins has recently been carried out[183]. Statistically speaking, it was found that monodentate attachment in the *syn* conformation is preferred, although the transition metal ions in this survey were all doubly charged. The constraints

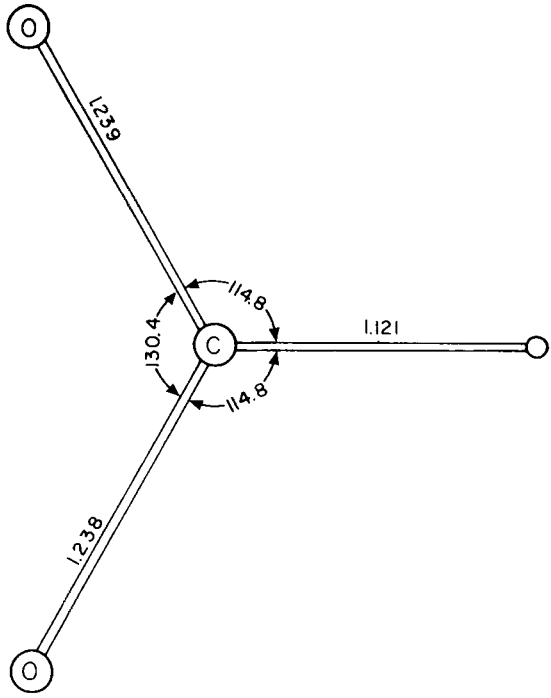

FIGURE 32. Formate anion. Bond lengths in Å, bond angles in degrees. TZV + basis

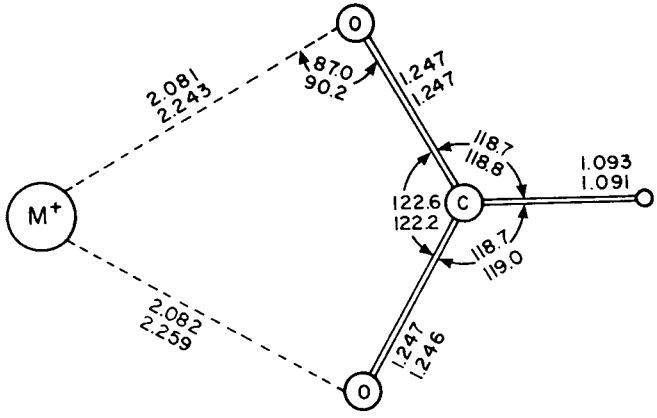

FIGURE 33. Metal ion–formate anion; metal = Ni (top number) and Pt. Bond lengths in Å, bond angles in degrees. TZV + basis

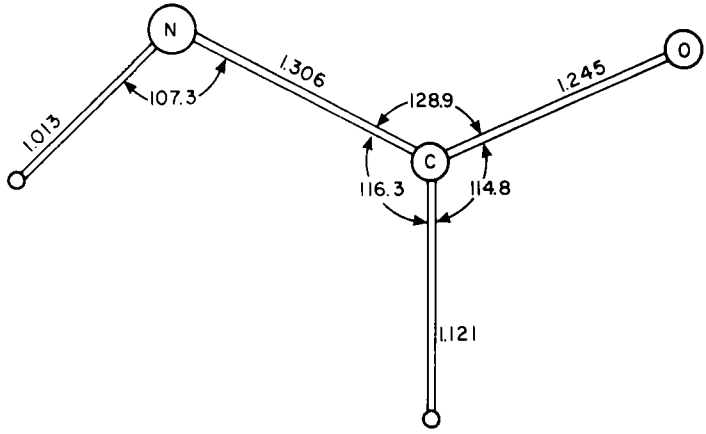

FIGURE 34. Formamidate anion. Bond lengths in Å, bond angles in degrees. TZV + basis

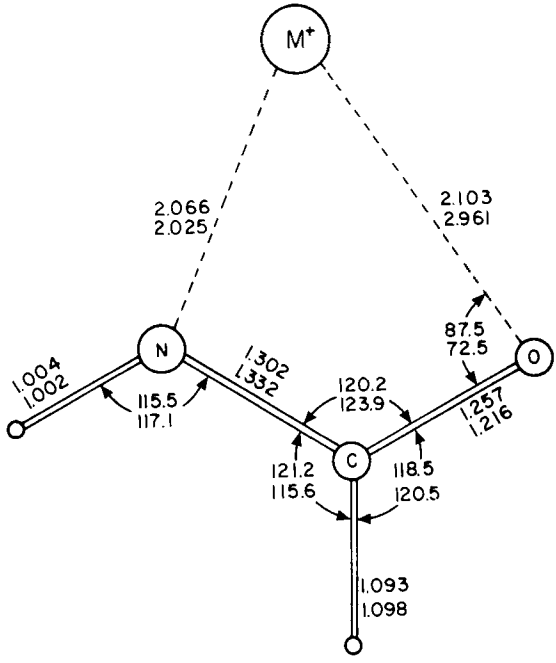

FIGURE 35. Metal ion–formamidate anion; metal = Ni (top number) and Pt. Bond lengths in Å, bond angles in degrees. TZV + basis

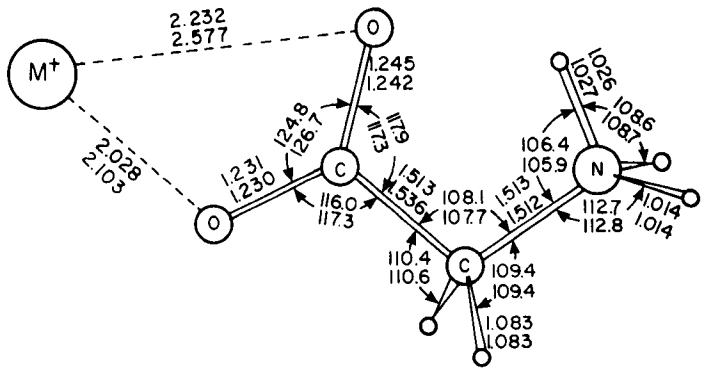

FIGURE 36. Metal ion–glycine zwitterion, metal–Ni (top number) and Cu. Bond lengths in Å, bond angles in degrees

and influence (see later) of the amino acid and protein structures are probably the dominant factors here. Gas-phase structures[154] involving the pure formate anion show the bidentate mode of binding to the same cation, while in binuclear metal complexes the carboxylate group typically bridges the two metal ions[156,157].

The gradient optimized M^+–formate geometries for $M^+ = Ni^+$ and Pt^+ show the symmetric bidentate structure (Figure 33). The calculated M^+—O bond distances, 2.07 Å and 2.24–2.26 Å (the spread is due to space polarization in the UHF) respectively, are reasonable. The metal ion affinities (Table 4) for Ni^+ [167 (HF) or 179 (MP2) kcal mol^{+1}] and Pt^+ [165 (HF) or 180 (MP2) kcal mol^{-1}] are smaller than the formate anion proton affinities and much larger than the metal ion–neutral monomer BDEs, as expected, and are larger than the corresponding alkali metal ion affinities[184]. The C—O bond length increases and the O—C—O bond angle decreases (to give a smaller bite angle) in going from the free anion (Figure 32) to the bidentate complex (Figure 33) with no surprises.

The geometric structures of the M^+–formamidate complexes, with $M^+ = Ni^+$ and Pt^+, are shown in Figure 35. The ligand anion is displayed in Figure 34 for reference. The proton affinity (Table 4) is calculated to be 381 (HF) or 372 (MP2) kcal mol^{-1} (uncorrected) compared to a quoted experimental enthalpy value of 360 kcal mol^{-1} [185]. The binding of the metal ions in the complex is bidentate, as has also been predicted for Ca^{2+} and Sr^{2+} coordination[155]. For Ni^+ the C=O bond length is increased and the C—N bond distance remains essentially unchanged upon complexation. The ligand geometry in Figure 35 is similar to that found in the first-row metal ion binuclear complexes with formamidate as a bridging ligand[157], although in the later case the C=O bond is observed to be even longer than calculated here. Compared to formamide itself (Figure 16) the C—N bond decreases in the formamidate ligand and the C=O distance increases. Both changes indicate a delocalization of the positive charge which strengthens the double-bond character of C—N and somewhat weakens C=O. The bond dissociation energies for the formamidate ligand are larger than for the formate anion which parallels the formamide/formic acid trends discussed above, probably for the same reasons.

For Pt^+ the optimized geometric parameters in Figure 35 (which is drawn more appropriate to the Ni^+ complex) show that the metal ion binds preferentially to the nitrogen atom, like the protonated form (formamide). This very different behaviour of Pt^+ relative to Ni^+ is just an extreme example of trends generally observed in these

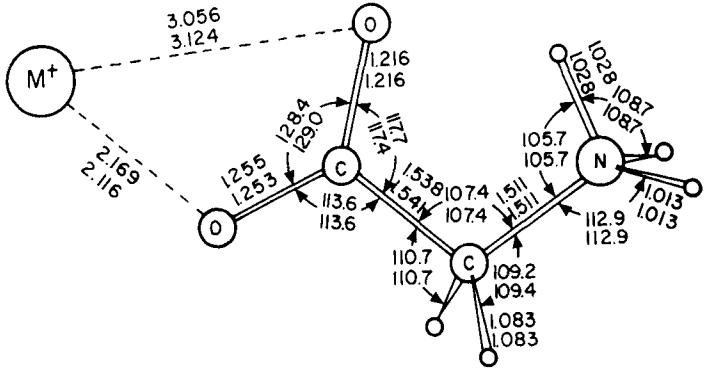

FIGURE 37. Metal ion–glycine zwitterion, metal = Pt (top number) and Au. Bond lengths in Å, bond angles in degrees

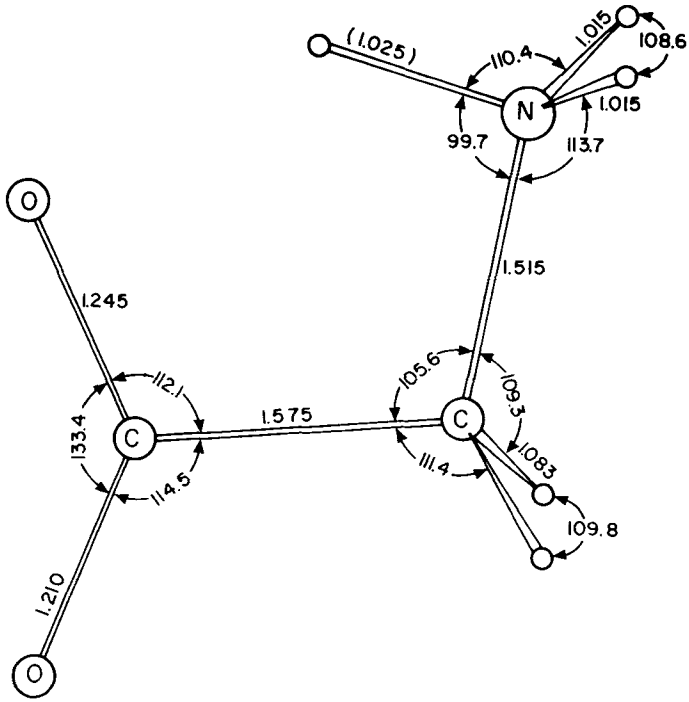

FIGURE 38. Glycine zwitterion. The N—H bond lengths were frozen. Bond lengths in Å, bond angles in degrees

metal ion complexes comparing first- and third-row metal ions, and requires further investigation.

The metal d-orbital populations (Table 5) show larger electron counts in the outer s and p atomic orbitals for the anionic ligands, compared with the corresponding neutral ligands, for a given metal ion. The delocalization (ligand anion → metal cation) is of the order of 44%. Caution must be exercised in interpreting this result because of the known deficiencies of the Mulliken population analysis for an extended basis set in anions[45].

The isolated glycine zwitterion ($^+NH_3CH_2CO_2^-$), with an in-plane N—H bond pointing at an oxygen atom, spontaneously (with no barrier) undergoes a proton migration to neutral glycine ($NH_2CH_2CO_2H$). One water molecule is insufficient to stabilize the isolated zwitterion[23]. As shown in Table 4, the monovalent transition metal ions stabilize the $^+NH_3CH_2CO_2^-$ zwitterion structure. The metal ion (Ni^+, Cu^+, Pt^+ and Au^+) coordinated zwitterions are shown in Figures 36 and 37. A constrained isolated zwitterion was optimized with the in-planar N—H bond tilting towards an oxygen atom (in C_s symmetry) frozen at a bond distance of 1.025 Å with the other N—H bonds set at 1.015 Å, for comparison purposes. The resulting structure is shown in Figure 38.

Metal binding to the zwitterion is, necessarily, by attachment to the carboxylate oxygen atoms. From Figures 36 and 37 we see that the metal ions face both oxygen atoms but in an asymmetric fashion, with the third-row metal ions showing essentially localized bonding to one of the oxygen atoms. Thus, the conformation is always *syn*, as was found in the general survey of metal ion–carboxylate groups[183]. The preferred oxygen atom is *trans* to the ammonium group across the C—C bond. Here, the direction axis of the dipole moment in the monomer (Figure 38) is also tilted towards the *trans* oxygen atom. The effect of metal ion complexation on the zwitterion is quantitatively different for the first-row transition metal ions (Ni^+ and Cu^+) which give only a 10–20% difference in the two M^+—O equilibrium bond distances, and the third-row cations (Pt^+ and Au^+) where the difference is in the 40–45% range. The inequivalence of the two C—O bonds is already present in the monomer (Figure 38) due to the proximity of the $-NH_3^+$ group to the *cis* oxygen atom.

The binding energies of the metal complexes with the glycine zwitterion are not easily calculated because, as noted in the conformation of Figure 38, the dissociated ligand has no stable existence. The binding energy, however, should be much larger than for any of the glycines themselves, even for cases where the metal ions are bound very asymmetrically to the carboxylate oxygen atoms, because of the large dipole moment ($\mu = 10.92D$) calculated for the structure in Figure 38. The $^+NH_3CH_2CO_2^-$ zwitterion can be protonated to give $^+NH_3CH_2CO_2H$, which is N-protonated glycine I (Figure 28). The calculated protonation energy is 249 (HF) or 237 (MP2) kcal mol^{-1} (Table 4), which is not much larger than the ordinary glycine protonation energies (Table 4). The energy difference between glycine I and the zwitterion is 27 (HF) or 19 (MP2) kcal mol^{-1}. At about 6 kcal mol^{-1} per water molecule[23], and assuming simple additivity, it would then probably take at least 4 water molecules to stabilize the bare zwitterion, if the water–water interactions are ignored.

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CHAPTER 2

Thermochemistry of carboxylic acids and derivatives

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I. INTRODUCTION

Thermochemical data for many carboxylic acids and their derivatives have been included in several comparatively recent compilations: *Thermochemistry of Organic and Organometallic Compounds* by Cox and Pilcher in 1970[1], *Sussex–NPL Computer Analysed Thermochemical Data: Organic and Organometallic Compounds* by Pedley and Rylance in 1977[2] and *Thermochemical Data of Organic Compounds* by Pedley, Naylor and Kirby in 1986[3]. Thermodynamic quantities over a range of temperatures were given for some of these compounds in *The Chemical Thermodynamics of Organic Compounds* by Stull, Westrum and Sinke in 1969[4].

So many enthalpies of formation of compounds in this category have been reported that there is a reasonable probability that if one requires the value for a particular compound, an experimental value exists or at least a value for a closely related compound from which it may seem simple to estimate the required value. The occasional user of these thermochemical data, however, does have the problem of deciding whether the information reported is reliable or not. For this reason, in this chapter the data are reviewed critically in an attempt to sort out those values which can be accepted as being within the stated limits of experimental uncertainty away from those which are not acceptable. The most important criterion of acceptability is the quality of the experimental work, discussed in Section II. Secondly, one can examine whether the reported enthalpies of formation correlate with other properties, and in particular whether they are understandable when related to the structure of the molecule. This latter approach leads to an analysis in terms of bond-energy schemes, discussed in Section III before analyses of the thermochemical data. If an experimental value disagrees with that expected from bond-energy calculations, then the attitude that the experimental value is immediately suspect must be resisted for it would imply that our understanding of the relations between structure and energy content are complete, and this is not so. However, some large discrepancies between observed and calculated enthalpies of formation do occur, and when there is no obvious or sensible explanation it is reasonable to regard the experimental value with suspicion. Using the most acceptable results to establish parameters for a bond-energy scheme does lead to confidence in estimated values.

II. EXPERIMENTAL METHODS

The most important method for determining enthalpies of formation of organic compounds is measurement of enthalpies of combustion. The experimental methods have been described[5]; essentially the result depends on (a) measurement of an energy quantity by a calorimetric method, and (b) measurement of the amount of chemical reaction to be ascribed to the energy quantity. Calorimetric techniques have been so well developed that incorrect results arising from error in measuring the energy quantity are extremely improbable. The quality of the final result rests mainly on the chemical part of the investigation, in particular the purity of the sample and tests to establish completeness of combustion. Various methods for evaluating purities have been used, e.g. from melting temperature as a function of the fraction of sample melted, spectroscopic and gas chromatographic methods and chemical analyses. If samples purified by different methods are measured with agreement, this may be regarded as a satisfactory criterion for adequate purity. Completeness of combustion can be established by testing for the presence of carbon monoxide, but more commonly by measuring the total amount of carbon dioxide produced. If the final result is based on the carbon dioxide formed, this has the advantage of reducing error due to non-combustible impurities such as water.

As an example, there have been four reports of the enthalpy of combustion of

pentanoic acid. In 1936, Schjånberg[6] measured two samples and gave the mean value $-(2833.4 \pm 1.3)$ kJ mol^{-1}; in 1954, Hancock and coworkers[7] reported $-(2850.1 \pm 5.9)$ kJ mol^{-1} but gave no information on the purity of the sample or on completeness of combustion; in 1964, Lebedeva[8] gave $-(2836.5 \pm 0.7)$ kJ mol^{-1} for a sample of 99.9% purity and with CO_2 recovery > 99.97%; in 1965 Adriaanse and collaborators[9] gave $-(2838.0 \pm 0.6)$ kJ mol^{-1} for a sample of 99.85% purity and made tests to establish completeness of combustion. As these last two results agree closely we accept the mean value and would also favourably consider other results by these authors, whereas the result of Hancock's group does not appear to be acceptable and we would approach other results by these authors with caution. The early result by Schjånberg, where attention was paid to the purity of the sample, is much closer to the accepted value than that of Hancock and coworkers.

For compounds containing S, F, Cl and Br, rotating-bomb methods are now employed[5], and earlier measurements made using static-bomb calorimeters are unlikely to be acceptable. As rotating-bomb calorimeters are much less common than the conventional static-bomb type, they tend to be operated by the more experienced investigators in this field and hence the results are generally reliable.

Although combustion calorimetry dominates, reaction-solution calorimetry plays an important subsidiary role, and because enthalpies of reaction in solution tend to be of an order of magnitude smaller than those of combustion, requirements for purity of samples are not as stringent. Usually a series of measurements have to be combined to obtain the desired result, e.g. to derive the standard enthalpy of hydrolysis of ethyl ethanoate Wadsö[10] measured

$$CH_3CO_2C_2H_5(l) + H_2O\,(NaOH\ soln.) \longrightarrow [CH_3CO_2H + C_2H_5OH]\,(NaOH\ soln.)\quad \Delta_1H = -44.27 \pm 0.08\ kJ\ mol^{-1}$$

$$C_2H_5OH(l) + NaOH\,(soln.) \longrightarrow C_2H_5OH\,(NaOH\ soln.)\quad \Delta_2H = -0.21 \pm 0.02\ kJ\ mol^{-1}$$

$$CH_3CO_2H(l) + NaOH\,(soln.) \longrightarrow CH_3CO_2H\,(NaOH\ soln.)\quad \Delta_3H = -48.58 \pm 0.21\ kJ\ mol^{-1}$$

$$H_2O(l) + NaOH\,(soln.) \longrightarrow H_2O\,(NaOH\ soln.)\quad \Delta_4H = -0.79 \pm 0.04\ kJ\ mol^{-1}$$

Then for

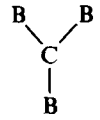
$$CH_3CO_2C_2H_5(l) + H_2O(l) \longrightarrow C_2H_5OH(l) + CH_3CO_2H(l)$$
$$\Delta_rH^\circ = \Delta_1H - \Delta_2H - \Delta_3H + \Delta_4H = 3.73 \pm 0.25\ kJ\ mol^{-1}$$

The required enthalpy of reaction is small but results from the combination of larger enthalpies of reaction, hence it is necessary that these have been measured carefully. Enthalpies of hydrolysis are of importance in deriving the enthalpies of formation of esters, thioesters, anhydrides and acyl halides, and enthalpies of hydrogenation have been used to derive enthalpies of formation of unsaturated acids and esters. Enthalpies of reaction in solution give the difference in enthalpies of formation of reactants and products, hence to derive a particular enthalpy of formation the values for the other participants must be known, and these are generally obtained by combustion calorimetry.

Studies of chemical equilibrium have played such a minor role in this area, and in most cases they have yielded results in agreement with subsequent calorimetric measurements, that the reader is directed to Reference 4 for discussion of the reliability of these methods.

III. BOND-ENERGY SCHEMES

About 1960, three different bond-energy schemes were introduced, each of which took account of interactions between neighbouring bonds. The Allen scheme[11] in addition to bond-energy parameters introduced interaction terms,

Γ_{ABC} for A—B—C and Δ^{C}_{BBB} for 

The Laidler scheme[12] used different values for (C—H) bond energies depending on whether the (C—H) bond was present in a primary group $-CH_3$, secondary group $-CH_2-$ or a tertiary group $>CH-$. The group scheme of Benson and Buss[13] postulates that two-centred redistribution reactions should be thermoneutral, i.e. $\Delta_r H^\circ_m = 0$ for reactions of the type

$$X-Y-Y^1-X + Z-Y-Y^1-Z \longrightarrow X-Y-Y^1-Z + Z-Y-Y^1-X$$

and this implies the assumption that the energy associated with a particular bond is constant provided the nearest neighbours of the bond are the same, leading to partition of the enthalpy of formation into values for groups. It has been shown that these three schemes are equivalent[1], and if the parameters in each are chosen in accordance with the equivalence relations, the schemes will yield identical values.

We choose here the Benson and Buss group scheme[13] and use their symbolism. A group is defined as a polyvalent atom together with its ligands, e.g. $[\mathbf{C}-(C)(H)_3]$ represents the $-CH_3$ group, $[\mathbf{C}-(C)_2(H)_2]$ the $-CH_2-$ group, $[\mathbf{C}-(C)_3(H)]$ the $>CH-$ group and $[\mathbf{C}-(C)_4]$ the $>C<$ group. It is convenient to treat some polyatomic combinations as entities, e.g. (CO); and where only a value for a combination of groups can be unambiguously derived, e.g. for carboxylic acids $[(\mathbf{CO})-(C)(O)] + [\mathbf{O}-(CO)(H)]$ can be obtained from the enthalpies of formation, an assumed value can be assigned to one group to make easy the listing of group values, e.g. we may place $[(\mathbf{CO})-(C)(O)] = [(\mathbf{CO})-(C)(H)]$. Although such assigned values are arbitrary, they must not be changed because of the other values dependent on them. The group parameters used to correlate and estimate $\Delta_f H^\circ_m(g)$ values are given in Table 1.

As the group scheme allows only for interactions between neighbouring bonds, longer-range interactions or energy effects which are a property of the whole molecule must be considered as additional terms; in general

$$\Delta_f H^\circ_m(g) = \sum \text{Group parameters} - \sum \text{Strain energies} - \sum \text{Stabilization energies}$$

There are several causes of strain energy:

(a) The *gauche* configuration of n-butane is less stable than the *trans* configuration by *ca* 2.1 kJ mol^{-1} [14], and in highly branched alkyl chains, the presence of some *gauche* 1,4 configurations is inevitable. The simplest approach, adopted by both Allen[11] and Benson and Buss[13], is to assume the destabilizing effect of *gauche* 1,4 interactions to be constant, for which we give the value 2.33 kJ mol^{-1}. This produces a satisfactory outcome except for very crowded situations such as

TABLE 1. Group parameters for estimation of $\Delta_f H^\circ_m(g)$ in kJ mol^{-1} [a]

[C—(C)(H)$_3$]	−41.90	[C—(Cl)(C$_2$)(H)]	−55.90
[C—(C)$_2$(H$_2$)]	−20.68	[C—(CO)(N)(H)$_2$]	−21.00
[C—(C)$_3$(H)]	−7.85	[C—(CO)(N)(H)(C)]	−9.00
[C—(C)$_4$]	−0.51	[C—(CO)(Cl)$_2$(H)]	−52.30
[C$_d$—(C$_d$)(H)$_2$]	+26.02	[C—(CO)(Cl)(H)$_2$]	−45.98
[C$_d$—(C$_d$)(C)(H)]	+36.19	[C—(CO)(Cl)(C)(H)]	−96.80
[C$_d$—(C$_d$)(C)$_2$]	+40.79	[C—(CO)(Cl)$_3$]	−50.00
[C$_t$—(C$_t$)(H)]	+113.68	[C—(CO)$_2$(H)$_2$]	−25.66
[C$_t$—(C$_t$)(C)]	+114.68	[C—(CS)(H)$_3$]	−41.90
		[C—(S)(C)(H)$_2$]	+124.91
[(CO)—(O)(H)]	−123.90	[C—(S)(C)$_2$(H)]	+139.56
[(CO)—(O)(C)]	−135.53	[C—(S)(C)$_3$]	+154.26
[(CO)—(O)(C$_b$)]	−130.96		
[(CO)—(C)(N)]	−135.53	[O—(CO)(H)]	−254.90
[(CO)—(C)$_2$]	−132.47	[O—(CO)(C)]	−189.19
[(CO)—(C)(S)]	−147.45	[O—(CO)$_2$]	−218.60
[C—(CO)(H)$_3$]	−41.90	[N—(C)(H)$_2$]	+19.33
[C—(CO)(C)(H)$_2$]	−21.42	[N—(C)$_2$(H)]	+66.90
[C—(CO)(C)$_2$(H)]	−3.10	[N—(C)$_3$]	+103.30
[C—(CO)(C)$_3$]	+11.97	[N—(CO)(H)$_2$]	−60.16
[C—(CO)(C$_d$)(H)$_2$]	+21.26	[N—(CO)(C)(H)]	−18.27
[C$_d$—(CO)(C$_d$)(H)]	+31.33	[N—(CO)(C)$_2$]	+33.13
[C—(O)(H)$_3$]	−41.90	[N—(CO)$_2$(C)]	−9.44
[C—(O)(C)(H)$_2$]	−33.47	[N—(CO)$_3$]	−17.81
[C—(O)(C)$_2$(H)]	−29.41	[N—(CS)(H)$_2$]	+19.33
[C—(O)(C)$_3$]	−27.87	[N—(CS)(C)$_2$]	+103.30
[C—(N)(H)$_3$]	−41.90		
[C—(N)(C)(H)$_2$]	−26.94	[(CS)—(N)(S)]	−215.73
[C—(N)(C)$_2$(H)]	−18.16	[(CS)—(N)(C)]	−215.73
[C—(N)(C)$_3$]	−13.64	[S—(CS)(H)]	+277.11
[C—(Cl)(C)(H)$_2$]	−66.86	[S—(CO)(H)]	+18.95
		[S—(CO)(C)]	−122.71

[a] C$_d$ denotes double bonded, C$_t$ triple bonded and C$_b$ aromatic.

where the calculated steric strain should be increased by 8.2 kJ mol^{-1} and

CC
CCCC
CC

where the increase should be 16.4 kJ mol^{-1}.

(b) In some alkyl groups, hydrogen atoms situated on 1,5 carbon atoms are forced into close proximity giving rise to even greater strain energies. In these cases the thermochemist derives the strain energy as the difference between the observed enthalpy of formation and that calculated for a strain-free structure and then judges whether the value is reasonable.

(c) Cyclic compounds may exhibit strain energies due to (i) enforced eclipsed configurations on neighbouring carbon atoms, (ii) close approach of hydrogen atoms across the ring and (iii) distortion of preferred bond lengths and bond angles. Again the thermochemist derives the strain energy from the observed enthalpy of formation. Considerable progress in the understanding of such strain energies is provided by molecular mechanics

TABLE 2. Cox scheme[16] parameters (C_6H_5A) for $\Delta_f H^\circ_m(g)$ of benzene derivatives in kJ mol^{-1}

A		A	
H	82.6 ± 0.7	NH_2	87.1 ± 1.0
CH_3	50.4 ± 0.6	NO_2	67.5 ± 0.6
C_2H_5	29.9 ± 1.1	F	−116.1 ± 1.4
i-C_3H_7	4.0 ± 1.0	Cl	52.0 ± 1.3
t-C_4H_9	−22.6 ± 1.2	Br	105.4 ± 4.1
OH	−96.4 ± 0.9	I	164.9 ± 5.9
OCH_3	−67.9 ± 0.9	CF_3	−599.1 ± 0.5
COOH	−295.4 ± 0.2	$COOC_6H_5$	−142.2 ± 2.2

calculations[15]: we will not consider the principles of these calculations here but will quote results when they are relevant.

Stabilization energies arise from several causes:

(a) π-delocalization energy is well known. The thermochemical derivation is beset with the problem of what are the appropriate values for the parameters in the unstabilized structure, and the derived π-delocalization energy depends on these values. Hence thermochemically derived delocalization or 'resonance' energies have this limitation affecting the significance of the absolute values. Theoretical *ab initio* calculations nowadays are made for many of these systems.

(b) Stabilization of some molecules can arise due to intramolecular hydrogen bonding.

π-delocalization is a feature of aromatic compounds. Cox[16] proposed an empirical scheme of a type similar to the group method to deal with these, in particular substituted benzene derivatives. If the transferability of bond energies holds, the increment in $\Delta_f H^\circ_m(g)$ for substitution of a particular group will be constant so that

$$\Delta_f H^\circ_m(C_6H_{6-a-b-}A_aB_{b--}, g) = a\Delta_f H^\circ_m(C_6H_5A, g) + b\Delta_f H^\circ_m(C_6H_5B, g) - (a + b + --- - 1)\Delta_f H^\circ_m(C_6H_6, g)$$

This simple procedure would give the same calculated value of $\Delta_f H^\circ_m(g)$ for all members of a set of positional isomers. The model was refined to take account of steric effects between adjacent substituted groups by:

(a) a correction of +4 kJ mol^{-1} for every pair of *ortho* substituents unless A and B are CH_3 or A is OH and B is CO_2H when no correction term is applied, and

(b) +4 kJ mol^{-1} additional to correction (a) for every set of three substituents oriented 1,2,3.

The basic terms for applying the Cox scheme are the values of $\Delta_f H^\circ_m(g)$ for monosubstituted benzenes and these are listed in Table 2.

IV. ALIPHATIC CARBOXYLIC ACIDS

A. Linear Alkyl Chain Carboxylic Acids

Two major investigations have been made on linear alkyl carboxylic acids. Lebedeva[8] measured the enthalpies of combustion of the series from formic to nonanoic acids, and hexadecanoic and octadecanoic acids. Adriaanse and coworkers[9] measured the series from pentanoic to eicosanoic acids, together with identification of the crystal forms and measurement of the enthalpies of melting. The results of these two investigations are in very good agreement and there are other measurements also in agreement, e.g. Sinke[17] for formic acid, Evans and Skinner[18] for acetic acid, Fenwick and collaborators[19] for

TABLE 3. Linear alkyl carboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta_f H^\circ_m$(l)	$\Delta^g_{cr,l} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
Formic		−425.1 ± 0.2	46.3 ± 0.3[21]	−378.8 ± 0.4	−378.8
Ethanoic		−484.3 ± 0.2	51.6 ± 1.5[21]	−432.7 ± 1.5	−432.3
Propionic		−510.7 ± 0.3	55.0 ± 2.0[21]	−455.7 ± 2.0	−454.0
Butanoic		−533.9 ± 0.6	58.0 ± 2.5[21]	−475.9 ± 2.6	−474.7
Pentanoic		−559.4 ± 0.7	62.4 ± 3.0[22]	−497.0 ± 3.1	−495.4
Hexanoic		−583.9 ± 1.6	73.2 ± 2.0[22]	−510.7 ± 2.6	−516.1
Heptanoic		−610.2 ± 1.5	72.0 ± 1.5[22]	−538.2 ± 2.1	−537.7
Octanoic		−636.0 ± 1.1	82.9 ± 1.0[22]	−553.1 ± 1.5	−557.4
Nonanoic		−659.7 ± 2.0	82.4 ± 0.4[23]	−577.3 ± 2.1	−578.1
Decanoic	−713.8 ± 1.0	−684.3 ± 1.5	118.9 ± 2.1[23]	−594.9 ± 2.3	−598.8
Undecanoic	−735.9 ± 1.0	−710.2 ± 1.5	121.3 ± 1.3[23]	−614.6 ± 2.0	−619.5
Dodecanoic	−774.6 ± 1.0	−737.9 ± 1.8	132.6 ± 1.7[23]	−642.0 ± 2.0	−640.1
Tridecanoic	−806.6 ± 1.4	−763.5 ± 2.2	146.4 ± 2.1[23]	−660.2 ± 2.5	−660.8
Tetradecanoic	−833.5 ± 1.5	−788.8 ± 2.2	139.7 ± 3.8[24]	−693.8 ± 4.1	−681.5
Pentadecanoic	−861.7 ± 1.6	−811.7 ± 2.5	162.8 ± 4.2[23]	−698.9 ± 4.5	−702.2
Hexadecanoic	−891.5 ± 1.7	−838.1 ± 2.2	154.4 ± 4.2[24]	−737.1 ± 4.5	−722.9
Heptadecanoic	−924.4 ± 1.8	−865.6 ± 2.9			−743.5
Octadecanoic	−947.7 ± 2.1	−884.7 ± 3.3	166.5 ± 4.2[24]	−781.2 ± 4.7	−764.2
Nonadecanoic	−984.1 ± 2.4	−916.4 ± 3.6	198.7 ± 3.4[24]	−785.4 ± 5.6	−784.9
Eicosanoic	−1012.1 ± 1.6	−940.0 ± 3.3	199.6 ± 7.5[24]	−812.4 ± 7.7	−805.6

hexanoic acid and Swain and coworkers[20] for tetradecanoic, hexadecanoic and octadecanoic acids. Table 3 lists the experimental values of $\Delta_f H^\circ_m$ for the crystalline, liquid and gaseous states together with values for the gaseous state calculated using the group scheme. The experimental values were chosen as the weighted mean values of those results produced in the best investigations.

The enthalpies of formation in the crystalline, liquid and gaseous states are plotted in Figure 1, and may be represented by the linear relations:

$$\Delta_f H^\circ_m(C_nH_{2n}O_2, \text{cr})/(\text{kJ mol}^{-1}) = -\{(414.7 \pm 0.9) + (29.64 \pm 0.07)n\}$$
$$n = 10\text{–}20$$

$$\Delta_f H^\circ_m(C_nH_{2n}O_2, \text{l})/(\text{kJ mol}^{-1}) = -\{(433.20 \pm 0.58) + (25.28 \pm 0.05)n\}$$
$$n = 2\text{–}20$$

$$\Delta_f H^\circ_m(C_nH_{2n}O_2, \text{g})/(\text{kJ mol}^{-1}) = -\{(391.14 \pm 1.05) + (20.55 \pm 0.15)n\}$$
$$n = 2\text{–}11$$

The (CH_2) increments are close to generally accepted values, e.g. for alkanes, the (CH_2) increment in the gaseous state is (20.68 ± 0.03) kJ mol^{-1}, and in the liquid state (25.66 ± 0.04) kJ mol^{-1}. It is apparent from the comparison of the experimental and calculated $\Delta_f H^\circ_m$(g) values in Table 3 and the curves in Figure 1 that the enthalpies of sublimation, particularly of the C_{14}, C_{16}, C_{18} and C_{20} acids, require re-examination.

B. Branched Alkyl Chain Carboxylic Acids

The few measurements on branched alkyl chain carboxylic acids are listed in Table 4. As the value for pentanoic acid by Hancock and coworkers[7] did not appear to be reliable, we would regard their values for its isomers with some suspicion. The value for

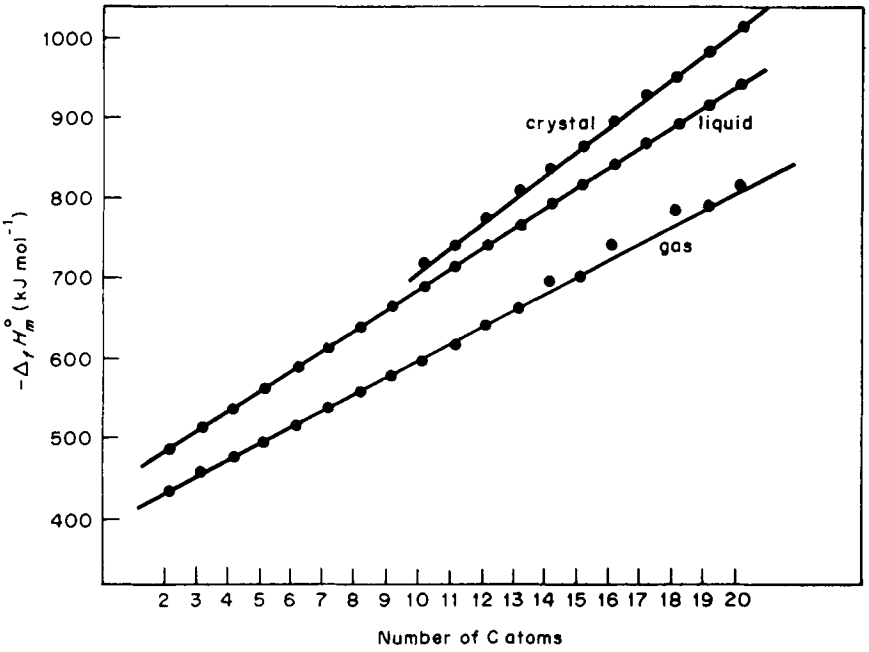


FIGURE 1. $\Delta_f H_m^\circ$ of linear alkane carboxylic acids versus chain length

2-ethylhexanoic acid is reliable. At present for this group of compounds it would seem that values calculated by the group scheme are to be preferred.

C. Unsaturated Monocarboxylic Acids

The reported enthalpies of formation of unsaturated monocarboxylic acids are given in Table 5 together with the enthalpies of hydrogenation to produce the saturated liquid products: those for the pentanoic acids were calculated from the enthalpies of combustion, the remainder were direct measurements. The enthalpies of vaporization or of sublimation of these compounds have not been measured, so it is not possible to evaluate these results using the group scheme. The enthalpies of hydrogenation, however, compare reasonably well with those for the corresponding hydrocarbons where the $—CO_2H$ group is replaced by $—CH_3$ as shown by the column of the differences given in Table 5. The final two differences are affected by the fact that, for these particular cases, the acids are crystalline.

TABLE 4. Branched alkyl chain carboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H_m^\circ(l)$	$\Delta_l^g H_m^\circ$	$\Delta_f H_m^\circ(g)$	Calc.
2-Methylbutanoic	-554.5 ± 5.9[7]			−495.7
3-Methylbutanoic	-561.6 ± 5.9[7]	57.5 ± 3.0[22]	-504.1 ± 66	−503.5
2,2-Dimethylpropanoic	-564.5 ± 5.9[7]	73.2 ± 3.0[22]	-491.3 ± 6.6	−504.2
2-Ethylhexanoic	-635.1 ± 1.8[25]	75.6 ± 0.4[25]	-559.5 ± 1.8	−560.9

TABLE 5. Unsaturated monocarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid		$\Delta_f H^\circ_m$	$\Delta_h H^\circ_m$	$\Delta(\Delta_h H^\circ_m)$
2-Propenoic	C=C—CO_2H (l)	−383.9 ± 0.9	−127.0 ± 0.8[26]	−2.3 ± 1.2
4-Pentenoic	C=CCCCO_2H (l)	−430.6 ± 2.5[6]	−128.8 ± 2.6	−3.2 ± 2.9
3-Pentenoic	CC=CCCO_2H (l)	−434.8 ± 2.1[6]	−124.6 ± 2.2	−9.6 ± 2.7
2-Pentenoic	CCC=CCO_2H (l)	−446.5 ± 2.1[6]	−112.9 ± 2.2	+2.1 ± 2.7
2-Propynoic	C≡CCO_2H (l)	−193.1 ± 2.9	−317.6 ± 2.9[27]	−28.0 ± 3.0
3-Butynoic	C≡CCCO_2H (cr)	−241.9 ± 1.0	−292.0 ± 0.8[28]	−1.2 ± 1.1
3-Pentynoic	C—C≡CCCO_2H (cr)	−292.3 ± 3.9	−267.1 ± 3.8[28]	4.2 ± 4.0

D. Halogen-substituted Monocarboxylic Acids

The reported enthalpies of formation of halogen-substituted monocarboxylic acids are given in Table 6. The value for trifluoroethanoic acid is from the work of Kolesov and collaborators[29,30] where two separate determinations by the combustion method gave closely agreeing results. 3-iodopropionic acid was studied by Roth[31] whilst testing the procedure for combustion of iodine compounds. The chloro acids were measured by Smith and coworkers[32] in a static bomb with a quartz wool lining saturated with arsenious oxide to reduce chlorine produced by the combustion to chloride: this technique was the forerunner of the rotating-bomb method and in general the results have proved to be reliable, albeit within comparatively large uncertainties. Smith's group also measured several chloro esters by the same method and a critical assessment of these results will be made later when considering enthalpies of esterification.

E. Amino-substituted Monocarboxylic Acids

The reported enthalpies of formation of amino-substituted monocarboxylic acids are given in Table 7. In cases where discrepant results have been reported, the values of Huffman and coworkers[34] and Skuratov and collaborators[40] have been preferred. There appears to be no reason to expect that optically active isomeric forms of a particular acid would have differing enthalpies of formation and for this reason, in particular, the reported values for *l*-alanine[38] and for dl-leucine[34] are suspect. The situation regarding enthalpies of sublimation is confused and there are some large discrepancies in some reported values; e.g. for glycine, Svec and Clyde gave 136.4 ± 0.4 kJ mol^{-1} [35] whereas

TABLE 6. Halogen-substituted monocarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr/l)	$\Delta^g_{cr,l} H^\circ_m$	$\Delta_f H^\circ_m$(g)
Trifluoroethanoic (l)	−1070.3 ± 1.5[29]	38.5 ± 0.8[30]	−1031.8 ± 1.7
Chloroethanoic (cr)	−510.5 ± 8.4[32]	75.3 ± 4.2[33]	−435.2 ± 9.4
Dichloroethanoic (l)	−496.3 ± 8.4[32]		
Trichloroethanoic (cr)	−503.3 ± 8.4[32]		
2-Chloropropionic (l)	−522.5 ± 8.4[32]		
3-Chloropropionic (cr)	−549.3 ± 8.4[32]		
2-Chlorobutanoic (l)	−575.5 ± 8.4[32]		
3-Chlorobutanoic (l)	−556.3 ± 8.4[32]		
4-Chlorobutanoic (l)	−566.3 ± 8.4[32]		
3-Iodopropionic (cr)	−460.0 ± 5.0[31]		

TABLE 7. Amino-substituted monocarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
Glycine	−528.5 ± 0.5[34]	136.4 ± 0.4[35]	−392.1 ± 0.6	−392.1
N-Methylglycine	−513.3 ± 0.3[36]	146.0 ± 1.0[37]	−367.3 ± 1.1	−386.4
l-Alanine	−604.0 ± 2.1[38]	138.1 ± 0.8[35]	−465.9 ± 2.3	−424.0
dl-Alanine	−563.6 ± 0.6[34]			−424.0
d-Alanine	−561.2 ± 0.6[39]			−424.0
4-Aminobutanoic	−577.9 ± 0.9[40]			−440.1
5-Aminopentanoic	−604.1 ± 0.9[40]			−460.8
l-Valine	−617.9 ± 0.6[41]	162.8 ± 0.8[35]	−455.1 ± 1.0	−471.8
l-Leucine	−637.4 ± 1.0[34]	150.6 ± 0.8[35]	−486.8 ± 1.3	−492.4
dl-Leucine	−640.6 ± 1.0[34]			−492.4
d-Leucine	−637.3 ± 1.0[34]			−492.4
l-Isoleucine	−637.9 ± 0.9[41]			−490.3
dl-Isoleucine	−635.3 ± 1.8[42]			−490.3
nor-Leucine	−639.1 ± 1.3[40]			−484.0
4-Aminohexanoic	−646.2 ± 1.3[40]			−494.0
5-Aminohexanoic	−643.3 ± 1.3[40]			−494.0
6-Aminohexanoic	−639.1 ± 1.3[40]			−481.5
7-Aminoheptanoic	−667.4 ± 1.3[43]			−502.2
9-Aminononanoic	−727.8 ± 1.7[40]			−543.5

Sabbah and Laffitte[36] report 153.2 ± 4.2 kJ mol^{-1}, and similarly for *l*-alanine the corresponding reported values were 138.1 ± 0.8 kJ mol^{-1} and 153.2 ± 4.2 kJ mol^{-1}, respectively. The values of Svec and Clyde were used in Table 7 as these authors examined more compounds and the results should be consistent. These enthalpies of sublimation are large because the zwitterion structures in the solid state lead to enhanced intermolecular attractions and these compounds have very low vapour pressures, making measurements difficult. Further measurements in this area are desirable. The calculated gaseous enthalpies of formation were based on the parameters given in Table 1, and when combined with the crystalline enthalpies of formation do lead to sensible trends in derived enthalpies of sublimation with respect to the size of the molecule. It is surprising that in view of their fundamental biological importance, the thermochemistry of amino acids has not attracted much more attention.

TABLE 8. Linear dicarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid		$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
Oxalic	$C_2H_2O_4$	−829.9 ± 0.9[44]	97.9 ± 2.1[45]	−732.0 ± 2.3	
Malonic	$C_3H_4O_4$	−891.0 ± 0.4[44]			
Succinic	$C_4H_6O_4$	−940.4 ± 0.2[46]	117.6 ± 3.3[47]	−822.8 ± 3.3	−823.7
Glutaric	$C_5H_8O_4$	−960.0 ± 1.2[44]			−844.4
Adipic	$C_6H_{10}O_4$	−993.7 ± 0.8[48]	129.3 ± 2.5[47]	−864.4 ± 2.6	−865.1
Pimelic	$C_7H_{12}O_4$	−1009.4 ± 1.2[48]			−885.7
Suberic	$C_8H_{14}O_4$	−1038.0 ± 1.5[48]	143.1 ± 3.8[47]	−894.9 ± 4.1	−906.4
Azelaic	$C_9H_{16}O_4$	−1054.3 ± 2.1[48]			−927.1
Sebacic	$C_{10}H_{18}O_4$	−1082.6 ± 2.1[48]			−947.8
Undecanedioic	$C_{11}H_{20}O_4$	−1099.4 ± 2.6[48]			−968.5
Dodecanedioic	$C_{12}H_{22}O_4$	−1130.0 ± 2.9[48]	153.1 ± 2.9[47]	−976.9 ± 4.1	−989.1
Tridecanedioic	$C_{13}H_{24}O_4$	−1148.3 ± 3.4[48]			−1009.8

TABLE 9. Alkyl-substituted succinic acids: quantities in kJ mol^{-1} at 298.15 K[49]

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta_f H^\circ_m$(g)(calc.)
Methylsuccinic	−958.2 ± 1.1	−847.3
Ethylsuccinic	−989.2 ± 1.5	−868.0
2,2-Dimethylsuccinic	−987.8 ± 1.4	−874.1
meso-2,3-Dimethylsuccinic	−977.5 ± 1.5	−870.9
rac-2,3-Dimethylsuccinic	−983.8 ± 1.5	−870.9
(−)-2,3-Dimethylsuccinic	−982.5 ± 1.5	−870.9
2,2-Diethylsuccinic	−1032.7 ± 2.2	−915.5
meso-2,3-Diethylsuccinic	−1019.2 ± 2.2	−912.3
rac-2,3-Diethylsuccinic	−1026.3 ± 2.2	−912.3
Trimethylsuccinic	−1000.8 ± 1.8	−897.7
Triethylsuccinic	−1066.3 ± 2.8	−959.7
Tetramethylsuccinic	−1012.4 ± 2.2	−924.5
Tetraethylsuccinic	−1096.5 ± 3.5	−1007.2

F. Dicarboxylic Acids

The reported enthalpies of formation of linear dicarboxylic acids are given in Table 8. The four values C2 to C5 derive from combustion measurements made in the modern period and the value for succinic acid has been so well established that this substance is recommended as a test material for combustion calorimetry[5]. The remaining measurements, C6 to C13, were made by Verkade's group[48] in 1926, and their values for the lower members of the series are in excellent agreement with the more recent determinations, but their values for the higher members for which the enthalpies of combustion become quite large, *ca* 7000 kJ mol^{-1}, would require confirmation.

The values for the alkyl-substituted succinic acids given in Table 9 result from one single publication by Verkade and Hartman[49] in 1933, and none of these compounds has been examined subsequently. The enthalpies of formation in the gaseous state calculated using the parameters in Table 1, when combined with the values for the crystalline state, lead to derived enthalpies of sublimation which seem to be of reasonable magnitudes though none has yet been measured. It would seem that these particular results are of good quality.

Table 10 lists the few measurements reported on unsaturated dicarboxylic acids. The values for maleic and fumaric acids require comment. It is to be expected that the

TABLE 10. Unsaturated dicarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)
cis-2-Butenedioic acid (maleic acid)	−786.5 ± 0.6[44]	110.0 ± 2.5[50]	−676.5 ± 2.6
trans-2-Butenedioic acid (fumaric acid)	−810.3 ± 0.6[44]	136.0 ± 6.3[50]	−674.3 ± 6.3
trans-2-Methyl-2-butenedioic acid (citraconic acid)	−824.4 ± 1.5[51]		
Methylenebutanedioic acid (itaconic acid)	−841.1 ± 0.6[51]		
2-Butynedioic acid (acetylenedicarboxylic acid)	−577.3 ± 4.6[28]		

TABLE 11. Hydroxy and polycarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid		$\Delta_f H^\circ_m$(cr)
l-Lactic acid (*l*-2-hydroxypropanoic acid)	$C_3H_6O_3$	-694.0 ± 1.0[52]
rac-Malic acid (*rac*-hydroxybutanedioic acid)	$C_4H_6O_5$	-1105.7 ± 0.6[44]
l-Malic acid	$C_4H_6O_5$	-1103.6 ± 4.2[44]
Citric acid (2-hydroxy-1,2,3-propanetricarboxylic acid)	$C_6H_8O_7$	-1543.8 ± 4.6[44]
Citric acid monohydrate	$C_6H_{10}O_8$	-1837.5 ± 0.5[53]
α-Ketoglutaric acid (2-oxopentanedioic acid)	$C_5H_6O_5$	-1026.2 ± 0.9[51]
trans-Aconitic acid (1,2,3-propenetricarboxylic acid)	$C_6H_6O_6$	-1232.7 ± 2.5[51]
cis-Aconitic acid	$C_6H_6O_6$	-1224.7 ± 7.5[51]

enthalpy of sublimation of fumaric acid would exceed that of maleic acid because the *trans*-isomer would pack more closely in the crystal. It is, however, somewhat surprising that the *cis* and *trans* isomers have the same enthalpies of formation in the gaseous state, and this suggests that the energy of the intramolecular hydrogen bond in maleic acid approximately cancels any destabilizing effects of dipole–dipole repulsion. From their chemical behaviour it is clear that fumaric acid is the more stable of the two isomers but this does not result from an intrinsically more stable molecule, rather from its greater enthalpy of sublimation.

Table 11 lists the few values available for aliphatic hydroxycarboxylic acids and polycarboxylic acids, all of which appear to be acceptable.

V. AROMATIC CARBOXYLIC ACIDS

A. Alkyl-substituted Benzoic Acids

The properties of benzoic acid are ideal for combustion calorimetry, hence its specific energy of combustion (as determined for particular samples by National Standardizing Laboratories) is used as a primary standard for the calibration of bomb calorimeters, and this substance has been subjected to more measurements than any other. Since the first accurate determination by Jessup and Green in 1934,[80] at least fifteen determinations of its specific energy of combustion have been reported, all made in electrically calibrated bomb calorimeters, with values ranging between the narrow limits of 26432 ± 3 J g^{-1} and 26436 ± 4 J g^{-1}. The generally accepted value for highly purified benzoic acid is 26434 ± 3 J g^{-1} under specified standardizing bomb conditions.

The enthalpies of formation of the complete series of methyl-substituted benzoic acids are given in Table 12, and of some other alkyl-substituted benzoic acids in Table 13. These values all derive from the work of Colomina and his colleagues in Madrid[54–66,108]. The compounds were purified carefully and various criteria for establishing purity were applied. The combustion results were based on the carbon dioxide produced and, in the few cases where the authors were not completely satisfied with the results, repeat measurements were made. The enthalpies of sublimation were derived from vapour pressures measured by the Knudsen method, and where possible the values corrected to 298.15 K. The series of results in Tables 12 and 13 constitute a major achievement and are an important contribution to the thermochemistry of aromatic compounds.

TABLE 12. Methyl-substituted benzoic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
Benzoic (BA)	−384.9 ± 0.2[1]	89.5 ± 0.1[54]	−295.4 ± 0.2	
2-Me-BA	−416.5 ± 1.5[55]	95.9 ± 0.1[56]	−320.6 ± 1.5	−323.6 ± 0.9
3-Me-BA	−424.9 ± 1.5[56]	97.0 ± 0.3[56]	−327.9 ± 1.4	−327.6 ± 0.9
4-Me-BA	−429.2 ± 1.5[55]	98.8 ± 0.3[56]	−330.4 ± 1.5	−327.6 ± 1.9
2,3-DiMe-BA	−450.4 ± 1.7[57]	104.6 ± 0.4[58]	−345.8 ± 1.7	−347.8 ± 1.9
2,4-DiMe-BA	−458.5 ± 1.7[57]	103.5 ± 0.3[58]	−355.0 ± 1.7	−355.8 ± 1.9
2,5-DiMe-BA	−456.1 ± 1.6[57]	105.0 ± 0.6[58]	−351.1 ± 1.7	−355.8 ± 1.9
2,6-DiMe-BA	−440.7 ± 1.7[57]	99.1 ± 0.2[58]	−341.6 ± 1.7	−347.8 ± 1.9
3,4-DiMe-BA	−468.8 ± 1.9[57]	106.4 ± 0.3[58]	−362.4 ± 1.9	−355.8 ± 1.9
3,5-DiMe-BA	−466.4 ± 1.7[57]	102.3 ± 0.3[58]	−364.5 ± 1.7	−359.8 ± 1.9
2,3,4-TriMe-BA	−486.8 ± 1.8[59]	109.3 ± 0.3[60]	−377.5 ± 1.8	−372.0 ± 2.8
2,3,5-TriMe-BA	−488.9 ± 1.8[59]	106.7 ± 0.3[60]	−382.2 ± 1.8	−380.0 ± 2.8
2,3,6-TriMe-BA	−475.8 ± 1.9[59]	104.4 ± 0.2[60]	−371.4 ± 1.9	−372.0 ± 2.8
2,4,5-TriMe-BA	−495.8 ± 2.0[59]	109.6 ± 0.5[60]	−386.2 ± 2.1	−384.0 ± 2.8
2,4,6-TriMeBA	−478.0 ± 1.9[59]	103.6 ± 0.3[60]	−374.4 ± 1.9	−380.0 ± 2.8
3,4,5-TriMe-BA	−501.1 ± 1.8[59]	111.0 ± 0.5[60]	−390.1 ± 1.9	−380.0 ± 2.8
2,3,4,5-TetraMe-BA	−514.6 ± 2.2[61]	115.9 ± 0.6[62]	−398.7 ± 2.3	−396.2 ± 3.7
2,3,4,6-TetraMe-BA	−507.8 ± 2.0[61]	109.7 ± 0.5[62]	−398.1 ± 2.1	−396.2 ± 3.7
2,3,5,6-TetraMe-BA	−506.2 ± 2.0[61]	106.1 ± 0.8[62]	−400.1 ± 2.2	−396.2 ± 3.7
PentaMe-BA	−536.3 ± 1.4[61]	113.4 ± 1.8[62]	−422.9 ± 2.9	−408.4 ± 4.6

Comparison of the derived enthalpies of formation in the gaseous state with values calculated using the Cox scheme shows that this scheme for these compounds fulfils the claim that the calculated values are reliable to within ±10 kJ mol^{-1} except for the heavily substituted compounds, and for these the deviations are not much larger. Some improvement might be possible by varying the parameters for interaction between neighbouring groups, i.e. depending on whether they were carboxyl or alkyl; however, that would subtract from the simplicity of the scheme. In Table 13, however, by comparing the observed and calculated enthalpies of formation in the gaseous state for 2-ethyl, 2-isopropyl and 2-butylbenzoic acids, the increase in steric hindrance between the adjacent alkyl and carboxyl groups consequent on the increasing size of the alkyl group is clearly apparent.

TABLE 13. Alkyl substituted benzoic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
2-Et-BA	−441.4 ± 1.5[63]	100.7 ± 0.4[63]	−340.7 ± 1.5	−344.1 ± 1.3
3-Et-BA	−445.9 ± 1.4[63]	99.1 ± 0.4[63]	−346.8 ± 1.4	−348.1 ± 1.3
4-Et-BA	−454.5 ± 1.9[64]	98.9 ± 0.2[64]	−355.6 ± 1.9	−348.1 ± 1.3
2-isoPr-BA	−460.2 ± 1.9[65]	101.0 ± 0.4[65]	−359.2 ± 1.9	−370.0 ± 1.2
3-isoPr-BA	−479.6 ± 1.9[65]	104.1 ± 0.3[65]	−375.5 ± 1.9	−374.0 ± 1.2
4-isoPr-BA	−483.8 ± 2.0[65]	101.1 ± 0.3[65]	−382.7 ± 2.0	−374.0 ± 1.2
2-terBu-BA	−476.2 ± 1.9[108]	100.1 ± 0.8[108]	−376.1 ± 2.1	−396.6 ± 1.4
3-terBu-BA	−504.3 ± 1.6[108]	103.5 ± 10[108]	−400.8 ± 1.9	−400.6 ± 1.4
4-terBu-BA	−502.9 ± 17[108]	104.4 ± 1.0[108]	−398.5 ± 2.0	−400.6 ± 1.4
3,5-diEt-BA	−511.9 ± 1.3[66]	104.1 ± 0.4[66]	−407.8 ± 1.4	−400.8 ± 2.8
3,5-diterBu-BA	−624.6 ± 1.6[66]	108.4 ± 0.5[66]	−516.2 ± 1.7	−505.8 ± 2.9

B. Substituted Benzoic Acids

Enthalpies of formation of other substituted benzoic acids are given in Tables 14 and 15, the latter restricted to halogen-substituted benzoic acids. From the comparison of the observed and calculated enthalpies of formation in the gaseous state, 2-hydroxybenzoic acid and 2-aminobenzoic acid show the effect of intramolecular hydrogen bonding, of about 24 kJ mol^{-1} and 10 kJ mol^{-1}, respectively. Intramolecular hydrogen bonding is not apparent for 2-methoxybenzoic acid, demonstrating that the carbonyl oxygen is that involved in the hydrogen bonding.

The enthalpies of formation of the halogen-substituted benzoic acids (Table 15), except for those involving iodine, were determined by rotating-bomb calorimetry. The values for 4-fluorobenzoic acid, 4-chlorobenzoic acid and 4-bromobenzoic acid have been very well established by several independent determinations and these compounds are

TABLE 14. Various substituted benzoic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
2-OH-BA	−589.7 ± 1.1[67]	95.7 ± 0.8[67]	−494.0 ± 1.4	−470.4 ± 1.2
3-OH-BA	−590.5 ± 1.0[67]			−474.4 ± 1.2
4-OH-BA	−594.5 ± 1.0[67]			−474.4 ± 1.2
2-NH_2-BA	−400.9 ± 0.9[68]	104.9 ± 1.0[69]	−296.0 ± 1.3	−286.9 ± 1.2
3-NH_2-BA	−411.6 ± 2.3[68]	128.0 ± 3.2[69]	−283.6 ± 3.9	−290.9 ± 1.2
4-NH_2-BA	−412.8 ± 1.0[68]	116.1 ± 3.7[69]	−296.7 ± 3.8	−290.9 ± 1.2
2-NO_2-BA	−398.5 ± 0.7[70]			−306.5 ± 0.9
3-NO_2-BA	−414.0 ± 0.5[70]			−310.5 ± 0.9
4-NO_2-BA	−426.9 ± 0.9[70]			−310.5 ± 0.9
2-MeO-BA	−538.5 ± 1.2[71]	104.7 ± 0.3[71]	−433.8 ± 1.2	−441.9 ± 1.2
3-MeO-BA	−553.5 ± 1.2[71]	107.5 ± 0.4[71]	−446.1 ± 1.3	−445.9 ± 1.2
4-MeO-BA	−561.7 ± 1.3[71]	109.8 ± 0.6[71]	−451.9 ± 1.4	−445.9 ± 1.2
2,3-DiMeO-BA	−737.0 ± 1.4[72]	116.6 ± 0.3[72]	−570.4 ± 1.5	−584.4 ± 2.3
2,4-DiMeO-BA	−712.2 ± 1.4[72]	123.4 ± 0.4[72]	−588.8 ± 1.5	−592.4 ± 2.3
2,6-DiMeO-BA	−693.8 ± 1.4[72]	121.7 ± 0.4[72]	−572.1 ± 1.5	−584.4 ± 2.3
3,4-DiMeO-BA	−714.0 ± 1.4[72]	129.8 ± 0.6[72]	−584.2 ± 1.5	−592.4 ± 2.3
3,5-DiMeO-BA	−724.0 ± 1.5[72]	127.1 ± 0.6[72]	−596.9 ± 1.6	−596.4 ± 2.3

TABLE 15. Halogen-substituted benzoic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
2-F-BA	−567.6 ± 1.5[73]			−490.1 ± 1.6
3-F-BA	−582.1 ± 0.8[73]			−494.1 ± 1.6
4-F-BA	−585.8 ± 0.7[74]	91.2 ± 1.3[75]	−494.6 ± 1.5	−494.1 ± 1.6
2-Cl-BA	−404.5 ± 0.8[76]	79.5 ± 3.3[50]	−325.0 ± 3.4	−322.0 ± 1.5
3-Cl-BA	−424.3 ± 1.6[76]	82.0 ± 3.3[50]	−342.3 ± 3.7	−326.0 ± 1.5
4-Cl-BA	−427.9 ± 0.8[76]	87.9 ± 3.3[50]	−340.0 ± 3.4	−326.0 ± 1.5
2-Br-BA	−368.3 ± 1.4[77]	110.9 ± 1.1[77]	−257.4 ± 1.8	−267.3 ± 3.2
3-Br-BA	−394.7 ± 1.2[77]	105.0 ± 1.1[77]	−289.7 ± 1.6	−271.3 ± 3.2
4-Br-BA	−379.6 ± 1.3[77]	107.6 ± 1.1[77]	−272.0 ± 1.7	−271.3 ± 3.2
2-I-BA	−302.3 ± 4.2[78]			−207.8 ± 6.0
3-I-BA	−316.9 ± 4.2[78]			−211.8 ± 6.0
4-I-BA	−316.1 ± 4.2[78]	87.9 ± 4.2[1]	−228.2 ± 5.9	−211.8 ± 6.0
Penta-F-BA	−1239.6 ± 1.9[75]	91.6 ± 4.2[75]	−1148.0 ± 4.6	−1288.9 ± 7.8
3-CF_3-BA	−1069.7 ± 1.2[79]			−977.1 ± 1.2

TABLE 16. Benzene polycarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid	$\Delta_f H_m^\circ(cr)$[81]	$\Delta_{cr}^g H_m^\circ$	$\Delta_f H_m^\circ(g)$	Calc.
1,2-Benzenedicarboxylic acid	−782.0 ± 0.6			(−669.4)
1,3-Benzenedicarboxylic acid	−803.0 ± 0.6	106.7 ± 2.1[82]	−696.3 ± 2.2	(−673.4)
1,4-Benzenedicarboxylic acid	−816.1 ± 0.6	98.2 ± 2.5[83]	−717.9 ± 2.6	(−673.4)
1,2,3-Benzenetricarboxylic acid	−1160.4 ± 0.9			(−1039.4)
1,2,4-Benzenetricarboxylic acid	−1179.2 ± 0.9			(−1047.4)
1,3,5-Benzenetricarboxylic acid	−1190.0 ± 1.0			(−1051.4)
1,2,3,4-Benzenetetracarboxylic acid	−1548.6 ± 0.9			(−1409.4)
1,2,3,5-Benzenetetracarboxylic acid	−1562.2 ± 1.0			(−1417.4)
1,2,4,5-Benzenetetracarboxylic acid	−1570.8 ± 1.0			(−1421.4)
Benzenepentacarboxylic acid	−1929.7 ± 1.3			(−1775.4)
Benzenehexacarboxylic acid	−2298.7 ± 1.3			(−2137.4)

recommended as secondary standards for combustion calorimetry. Deviations between the observed and calculated enthalpies of formation in the gaseous state are greater for these molecules than for the alkyl-substituted benzoic acids, and noteworthy is the deviation for pentafluorobenzoic acid, 141 kJ mol^{-1}. Deviations of this magnitude have been reported for heavily substituted fluorinated benzenes, e.g. for C_6HF_5 105.6 ± 9.6 kJ mol^{-1}, C_6F_6 155.1 ± 8.5 kJ mol^{-1}, and these have been ascribed to the effect of dipole–dipole repulsions between the adjacent (C—F) bonds[75].

The enthalpies of formation of the benzene polycarboxylic acids listed in Table 16 are from the work of Yukhno and Bikkulov[81], and their result for the benzenedicarboxylic acids are in excellent agreement with earlier measurements by Schwabe and Wagner[84] and Parks and coworkers[85] and Colomina's group[217], giving confidence in this complete series. Values for the gaseous state calculated by the Cox scheme are in parentheses because of the uncertainties arising from the interactions of adjacent carboxyl groups; steric repulsions could be partially balanced by intramolecular hydrogen-bonding attractions. The pattern shown by the calculated values, however, does parallel that of the enthalpies of formation in the crystalline state.

C. Miscellaneous Aromatic, Heterocyclic, Amino and Peroxycarboxylic Acids

Table 17 lists the remaining reported enthalpies of formation of miscellaneous carboxylic acids culled from the literature. For these the following comments are pertinent:

(a) Some of the values in Table 17 can be considered to be completely reliable, in particular those for the naphthalenecarboxylic acids and the naphthaleneacetic acids measured by Colomina and his colleagues[91,192]. The values for 3-pyridinecarboxylic acid and for hippuric acid are so well established that on several occasions these compounds have been proposed as suitable secondary standards for combustion calorimetry.

(b) For the compounds in Table 17, values have not been estimated for the gaseous state because for most of these compounds the complex structures preclude reasonable estimates.

(c) The large differences between the enthalpies of formation of the *dl*- and *d*-forms of proline and of threonine are not expected and this leads to a lack of confidence in these values for the amino acids. It would be sensible to regard the values for the amino acids in Table 17 as provisional and re-examination of most of these compounds is desirable.

TABLE 17. Miscellaneous aromatic, heterocyclic, amino and peroxycarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Acid		$\Delta_f H_m^\circ$(cr)	$\Delta_{cr}^g H_m^\circ$	$\Delta_f H_m^\circ$(g)
dl-α-Hydroxybenzeneacetic acid	$C_8H_8O_3$	-579.4 ± 0.9[86]		
l-α-Hydroxybenzeneacetic acid	$C_8H_8O_3$	-580.6 ± 0.9[86]		
2-Acetoxybenzoic acid	$C_9H_8O_4$	-815.6 ± 1.4[87]		
Phenylsuccinic acid	$C_{10}H_{10}O_4$	-841.0 ± 2.3[49]		
cis-Cyclohexane-1,2-dicarboxylic acid	$C_8H_{12}O_4$	-961.1 ± 7.5[88]		
trans-Cyclohexane-1,2-dicarboxylic acid	$C_8H_{12}O_4$	-970.7 ± 7.5[88]		
Adamantane-1-carboxylic acid	$C_{11}H_{16}O_2$	-643.1 ± 3.6[89]		
Adamantane-2-carboxylic acid	$C_{11}H_{16}O_2$	-627.2 ± 3.8[89]		
1,4-Dimethylcubane dicarboxylic acid	$C_{12}H_{12}O_4$	-219.0 ± 2.1[90]	118.9 ± 3.8[90]	-100.1 ± 4.3
1-Naphthalenecarboxylic acid	$C_{11}H_8O_2$	-333.5 ± 1.0[91]	110.4 ± 0.2[91]	-223.1 ± 1.0
2-Naphthalenecarboxylic acid	$C_{11}H_8O_2$	-346.1 ± 1.5[91]	113.6 ± 0.8[91]	-232.5 ± 1.7
1-Naphthaleneacetic acid	$C_{12}H_{10}O_2$	-359.2 ± 1.7[92]		
2-Naphthaleneacetic acid	$C_{12}H_{10}O_2$	-371.9 ± 1.9[92]		
3-Hydroxy-2-naphthalenecarboxylic acid	$C_{11}H_8O_3$	-547.8 ± 1.0[93]		
2-Furanecarboxylic acid	$C_5H_4O_3$	-498.4 ± 1.1[85]	108.4 ± 2.1[94]	-390.0 ± 2.3
3-(2-Furanyl)-2-propenoic acid	$C_7H_6O_3$	-459.0 ± 6.3[95]		
3-Pyridinecarboxylic acid	$C_6H_5O_2N$	-344.9 ± 0.9[96]	123.4 ± 1.2[97]	-221.5 ± 1.5
dl-Proline	$C_5H_9O_2N$	-524.2 ± 0.6[42]		
l-Proline	$C_5H_9O_2N$	-515.2 ± 0.3[37]	149.0 ± 4.0[37]	-366.2 ± 4.0
dl-Phenylalanine	$C_9H_{11}O_2N$	-460.6 ± 2.6[98]		
l-Phenylalanine	$C_9H_{11}O_2N$	-466.9 ± 0.9[99]	154.0 ± 0.8[35]	-312.9 ± 1.3
3-*N*-Phenyl-2-naphthalenecarboxylic acid	$C_{17}H_{13}O_2N$	-263.6 ± 2.2[93]		
l-Serine	$C_3H_7O_3N$	-732.7 ± 0.3[100]		
dl-Threonine	$C_4H_9O_3N$	-807.2 ± 0.9[38]		
l-Threonine	$C_4H_9O_3N$	-758.8 ± 0.5[42]		
1-Hydroxyl-*l*-proline	$C_5H_9O_3N$	-661.1 ± 1.8[42]		

N-Benzoylglycine (hippuric acid)	$C_9H_9O_3N$	-608.8 ± 1.6[101]
l-Tyrosine	$C_9H_{11}O_3N$	-685.1 ± 1.6[34]
l-Aspartic acid	$C_4H_7O_4N$	-973.3 ± 0.8[39]
l-Glutamic acid	$C_5H_9O_4N$	-1009.7 ± 0.8[41]
d-Glutamic acid	$C_5H_9O_4N$	-1005.2 ± 1.2[39]
dl-Ornithine	$C_5H_{12}O_2N_2$	-652.6 ± 1.8[42]
dl-Lysine	$C_6H_{14}O_2N_2$	-678.7 ± 1.5[42]
l-Tryptophan	$C_{11}H_{12}O_2N_2$	-415.3 ± 1.0[38]
l-Asparagine	$C_4H_8O_3N_2$	-789.4 ± 0.8[41]
N-Glycylglycine	$C_4H_8O_3N_2$	-747.7 ± 0.6[102]
l-Glutamine	$C_5H_{10}O_3N_2$	-826.4 ± 0.7[41]
N-*dl*-Analylglycine	$C_5H_{10}O_3N_2$	-777.8 ± 0.9[102]
N-Glycyl-*dl*-valine	$C_7H_{14}O_3N_2$	-835.0 ± 0.5[103]
N-*dl*-Leucylglycine	$C_8H_{16}O_3N_2$	-859.8 ± 1.3[102]
N-Glycyl-phenylalanine	$C_{11}H_{14}O_3N_2$	-684.4 ± 1.8[103]
N-Alanyl-phenylalanine	$C_{12}H_{16}O_3N_2$	-710.2 ± 0.6[103]
N-Valyl-phenylalanine	$C_{14}H_{20}O_3N_2$	-765.8 ± 1.6[103]
N-Hippuroylglycine	$C_{11}H_{12}O_4N_2$	-832.7 ± 1.5[105]
N-Seryl-serine	$C_6H_{12}O_5N_2$	-1177.7 ± 0.5[103]
Ethylene diamine tetra acetic acid	$C_{10}H_{16}O_8N_8$	-1759.4 ± 0.9[105]
N-(*N*-Glycyl-*dl*-phenylalanyl) alanine	$C_{14}H_{19}O_4N_3$	-926.8 ± 0.7[103]
Diethylene triamine penta acetic acid	$C_{14}H_{23}O_{10}N_3$	-2225.1 ± 1.0[105]
d-Arginine	$C_6H_{14}O_2N_4$	-623.5 ± 1.3[34]
l-Cysteine	$C_3H_7O_2NS$	-515.5 ± 2.1[106]
l-Cystine	$C_6H_{12}O_4N_2S_2$	-1032.7 ± 3.8[106]
Peroxydodecanoic acid	$C_{12}H_{24}O_3$	-680.3 ± 8.4[20]
Peroxytetradecanoic acid	$C_{14}H_{28}O_3$	-749.9 ± 9.6[20]
Peroxyhexadecanoic acid	$C_{16}H_{32}O_3$	-801.9 ± 9.2[20]
Peroxyoctadecanoic acid	$C_{18}H_{36}O_3$	-857.3 ± 11.3[20]
Perbenzoic acid	$C_7H_6O_3$	-367.0 ± 12.8[107]

(d) For the peroxyacids it can be deduced that for

$$RCO\cdot OOH(cr) \longrightarrow RCO_2H(cr) + \tfrac{1}{2}O_2(g)$$

when R is an aliphatic group, $\Delta_r H^\circ_m = -(89.5 \pm 9.0)$ kJ mol^{-1}, but for perbenzoic acid, $\Delta_r H^\circ_m = -(17.9 \pm 12.80$ kJ mol^{-1}, in accord with the fact that the peroxyaliphatic acids are more powerful oxidizing agents than peroxybenzoic acid.

VI. ESTERS

Thermochemical data for esters are extensive and, in view of the generally excellent results for the enthalpies of formation of carboxylic acids and of alcohols, it would seem that the most satisfactory method of determining the enthalpy of formation of an ester would be by measuring its enthalpy of hydrolysis. Surprisingly, very few calorimetric measurements of this type have been reported. There are values in kJ mol^{-1} for the hydrolysis of ethyl ethanoate (3.7 ± 0.3)[10], isopropyl ethanoate (2.3 ± 0.4)[10], n-butyl ethanoate (3.3 ± 0.4)[10], phenyl ethanoate $-(28.7 \pm 0.3)$[109] and 3-methylphenyl ethanoate $-(18.4 \pm 0.6)$[110]. For the majority of the remaining esters, the enthalpies of formation have been derived from enthalpies of combustion. Two criteria can be applied to assess the reliability of the results. When enthalpies of vaporization are available, the derived enthalpies of formation in the gaseous state can be compared with the values calculated using group parameters. In most cases experimental values of enthalpies of vaporization are not available but reasonable estimations can be made from the normal boiling points using equations developed from Trouton's Rule; e.g. Wadsö[114] proposed that for slightly associated or non-associated liquids,

$$\Delta_v H(298\ \text{K})/(\text{kJ mol}^{-1}) = 20.92 + 0.172(T_{bp}/\text{K} - 273)$$

and for associated liquids such as alcohols,

$$\Delta_v H(298\ \text{K})/(\text{kJ mol}^{-1}) = 25.10 + 0.230\,(T_{bp}/\text{K} - 273)$$

These equations, particularly the first, was used to estimate the enthalpies of vaporization of esters[1]. So many comparisons are possible between observed and estimated enthalpies of formation of esters that the group parameters are well established such that large discrepancies, certainly those greater than 10 kJ mol^{-1}, render the experimental values suspect.

Secondly, from the enthalpies of formation of the liquid esters and of the corresponding liquid carboxylic acids and alcohols, the enthalpy of hydrolysis of the ester according to

$$RCO_2R^1(l) + H_2O(l) \longrightarrow RCO_2H(l) + R^1OH(l)$$

can be derived and can be compared with any experimental determinations for esters of this particular type. Large discrepancies again mean that the experimental results should be regarded with suspicion, but in this comparison attention should be paid to both the enthalpies of formation of the ester and of the corresponding acid.

A. Alkyl Esters of Saturated Carboxylic Acids

Table 18 lists the results for the alkyl esters of saturated monocarboxylic acids: estimated enthalpies of vaporization are given in parentheses. The methyl esters of the linear carboxylic acids, methyl pentanoate to methyl pentadecanoate, are from the work of Adriaanse's group[9]. In Figure 2 are plotted the enthalpies of formation of these esters

TABLE 18. Alkyl esters of saturated mono carboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Ester	$\Delta_f H^\circ_m$(l)	$\Delta_l^g H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.	ΔH (hydrolysis)
Methyl formate	-386.1 ± 0.6[111]	28.6 ± 0.1[21]	-375.5 ± 0.6		7.7 ± 0.7
Methyl ethanoate	-445.8 ± 0.7[111]	32.5 ± 0.1[21]	-413.3 ± 0.7	-408.5	8.2 ± 0.8
Methyl pentanoate	-514.2 ± 0.7[9]	43.1 ± 0.1[112]	-471.1 ± 0.7	-471.3	1.5 ± 1.0
Methyl hexanoate	-540.2 ± 1.0[9]	48.0 ± 0.1[112]	-492.2 ± 1.0	-492.0	3.0 ± 1.9
Methyl heptanoate	-567.1 ± 0.9[9]	51.6 ± 0.5[112]	-515.5 ± 1.0	-512.7	3.6 ± 1.8
Methyl octanoate	-590.3 ± 0.9[9]	56.4 ± 0.5[112]	$-533\text{-}9 \pm 1.0$	-533.3	1.0 ± 1.5
Methyl nonanoate	-616.2 ± 1.5[9]	62.0 ± 0.4[112]	-554.2 ± 1.6	-554.0	3.2 ± 2.5
Methyl decanoate	-640.5 ± 1.8[9]	66.8 ± 0.6[112]	-573.7 ± 1.9	-574.7	2.9 ± 2.4
Methyl undecanoate	-665.2 ± 1.4[9]	71.4 ± 0.3[112]	-593.8 ± 1.4	-595.4	1.7 ± 2.1
Methyl dodecanoate	-693.0 ± 1.7[9]	77.2 ± 0.5[112]	-615.8 ± 1.8	-616.1	1.8 ± 2.5
Methyl tridecanoate	-717.9 ± 1.9[9]	82.7 ± 0.8[112]	-635.2 ± 2.1	-636.7	1.1 ± 2.9
Methyl tetradecanoate	-743.9 ± 2.2[9]	87.0 ± 0.9[112]	-656.9 ± 2.4	-657.4	1.8 ± 3.1
Methyl pentadecanoate	-771.0 ± 1.6[9]	93.5 ± 0.9[112]	-677.5 ± 1.8	-678.1	6.0 ± 3.0
Methyl 2-methylbutanoate	-534.3 ± 7.1[7]	[41.8 ± 1.2]	-492.5 ± 7.2	-476.4	26.5 ± 9.2
Methyl 3-methylbutanoate	-538.9 ± 7.1[7]	[41.0 ± 1.3]	-497.9 ± 7.2	-479.7	24.0 ± 9.2
Methyl 2,2-dimethylpropanoate	-530.0 ± 1.2[111]	38.8 ± 0.2[21]	-491.2 ± 1.3	-480.4	12.2 ± 6.0
Methyl 2,2,3-trimethylbutanoate	-506.4 ± 8.4[113]			-530.1	
Ethyl ethanoate	-479.8 ± 0.6[10]	35.7 ± 0.2[114]	-444.1 ± 0.6	-442.0	3.4 ± 0.7
Ethyl propionate	-502.7 ± 0.8[115]	39.1 ± 0.1[115]	-463.6 ± 0.8	-463.4	0.1 ± 0.9
Ethyl pentanoate	-553.0 ± 2.6[7]	[46.0 ± 1.3]	-507.0 ± 2.8	-504.8	18.5 ± 2.7
Ethyl 2-methylbutanoate	-566.8 ± 8.4[7]	[44.4 ± 1.3]	-522.4 ± 8.5	-509.9	20.2 ± 10.3
Ethyl 3-methylbutanoate	-570.9 ± 8.4[7]	[43.9 ± 1.3]	-527.0 ± 8.5	-513.2	17.2 ± 10.3
Ethyl 2,2-dimethylpropanoate	-577.2 ± 8.4[7]	41.3 ± 0.1[114]	-535.9 ± 8.4	-513.8	20.6 ± 10.3
Propyl pentanoate	-583.0 ± 1.3[6]	[49.4 ± 1.3]	-533.6 ± 1.8	-525.5	6.8 ± 1.6
iso-Propyl ethanoate	-518.9 ± 0.7[10]	37.2 ± 0.1[114]	-481.7 ± 0.7	-479.8	2.3 ± 0.4
iso-Propyl pentanoate	-592.2 ± 3.0[6]	[49.4 ± 1.3]	-542.8 ± 3.3	-542.6	0.5 ± 3.2
Butyl ethanoate	-529.2 ± 0.7[10]	43.9 ± 0.2[114]	-485.3 ± 0.8	-483.4	3.3 ± 0.3
Butyl pentanoate	-613.3 ± 1.7[6]	[53.1 ± 1.3]	-560.2 ± 2.1	-546.1	12.4 ± 1.9
Iso-Butyl pentanoate	-620.0 ± 3.4[6]	[51.5 ± 1.3]	-568.5 ± 3.6	-554.5	11.7 ± 3.5
sec-Butyl butanoate	-592.5 ± 3.8[116]	[47.3 ± 1.3]	-545.2 ± 4.0	-542.6	1.8 ± 4.0
sec-Butyl pentanoate	-624.2 ± 1.7[6]	[51.0 ± 1.3]	-573.2 ± 2.1	-563.3	8.0 ± 2.0
t-Butyl octanoate	-698.7 ± 12.6[20]			-645.0	-10.7 ± 13.0
t-Butyl decanoate	-752.8 ± 7.9[20]			-686.4	-4.9 ± 9.2
t-Butyl dodecanoate	-817.8 ± 12.1[20]			-727.7	6.5 ± 12.6
t-Butyl tetradecanoate	-862.7 ± 12.6[20]			-769.1	0.5 ± 13.0

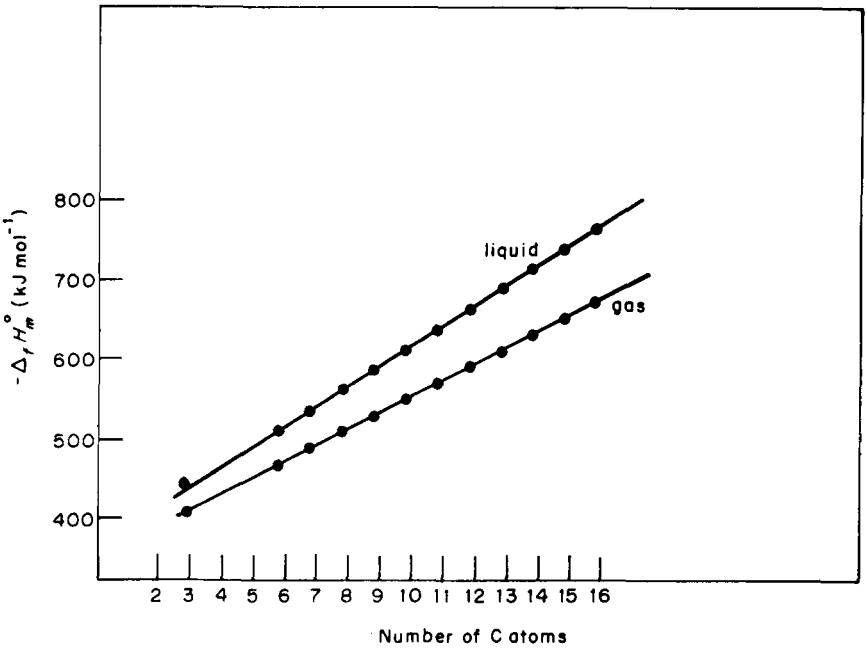


FIGURE 2. $\Delta_f H^\circ_m$ of methyl esters of linear alkane carboxylic acids versus chain length

in the liquid and gaseous states which may be represented by the linear relations

$$\Delta_f H^\circ_m(C_nH_{2n}O_2, l)/(kJ\ mol^{-1}) = -\{(361.2 \pm 1.0) - (25.51 \pm 0.08)n\}$$
$$\Delta_f H^\circ_m(C_nH_{2n}O_2, g)/(kJ\ mol^{-1} = -\{(348.7 \pm 1.1) - (20.55 \pm 0.10)n\}$$

The (CH_2) increments are close to the generally accepted values for alkanes, in the gaseous state (20.68 ± 0.03) and in the liquid state (25.66 ± 0.04) kJ mol^{-1}, and to those values previously derived for the linear carboxylic acids.

In considering the enthalpies of hydrolysis of the methyl esters of the linear carboxylic acids, the average value is (3.3 ± 1.3) kJ mol^{-1}, close to the enthalpies of hydrolysis of the ethyl esters as measured by Wadsö[10], a further demonstration of the excellence of the work of Adriaanse and coworkers[9].

The results of Hancock and collaborators[7] on the methyl and ethyl pentanoate isomers, however, fail both criteria, since comparison of observed and calculated enthalpies of formation in the gaseous state and the derived enthalpies of hydrolysis show large deviations from expected values. This is not surprising in view of the previous comments on the results for carboxylic acids by these authors.

Inspection of the values in Table 18 shows that the quality of these results is in general good, and the degree of fit between observed and calculated enthalpies of formation in the gaseous state can be so close that in unknown cases we can have confidence in values estimated using the group parameters of Table 1.

B. Unsaturated and Aromatic Esters

Table 19 lists thermochemical data for esters of unsaturated carboxylic acids and practically all these results are from measurements of enthalpies of combustion made

TABLE 19. Alkyl esters of unsaturated monocarboxylic acids: quantities in kJ mol^{-1} at 298.15 K

Ester	$\Delta_f H^\circ_m(l)$	$\Delta_l^g H^\circ_m$	$\Delta_f H^\circ_m(g)$	Calc.	ΔH (hydrolysis)
Methyl 2-propenoate	-362.2 ± 0.7[111]	29.2 ± 0.4[111]	-333.0 ± 0.8	−309.3	25.1 ± 1.2
Methyl *E*-2-butenoate	-382.9 ± 1.7[116]	[41.0 ± 1.3]	-341.9 ± 2.1	−341.0	
Methyl 2-methylene 3,3-dimethylbutanoate	-421.4 ± 8.4[113]				
Methyl *Z*-9-octadecenoate	-735.5 ± 11.7[117]	84.5 ± 4.2[118]	-651.0 ± 12.4		
Methyl *E*-9-octadecenoate	-737.0 ± 11.7[117]				
Methyl 2-hexynoate	-242.7 ± 5.1[28]				
Ethyl 4-pentenoate	-431.6 ± 2.1[6]	[46.0 ± 1.3]	-385.6 ± 2.5	−380.0	8.9 ± 3.3
Ethyl *Z*-3-pentenoate	-432.4 ± 3.3[119]	[44.8 ± 1.3]	-387.6 ± 3.5	−386.9	
Ethyl *E*-3-pentenoate	-437.0 ± 2.6[119]	[46.9 ± 1.3]	-390.1 ± 2.9	−390.9	10.1 ± 3.4
Ethyl *Z*-2-pentenoate	-440.8 ± 2.6[119]	[46.0 ± 1.3]	-394.8 ± 2.9	−391.2	
Ethyl *E*-2-pentenoate	-442.5 ± 3.3[119]	[48.1 ± 1.3]	-394.4 ± 3.5	−395.2	3.9 ± 3.9
Ethyl 2-methylene-3-butenoate	-338.2 ± 2.6[120]	[48.5 ± 1.3]	-289.7 ± 2.9		
Ethyl *Z*-9-octadecenoate	-775.8 ± 12.1[117]				
Ethyl *E*-9-octadecenoate	-773.2 ± 12.1[117]				
Ethyl 4-pentynoate	-281.7 ± 2.6[120]	[48.5 ± 1.3]	-233.2 ± 2.9	−213.8	
Ethyl 3-pentynoate	-287.6 ± 2.6[120]	[49.8 ± 1.3]	-237.8 ± 2.9	−234.2	3.2 ± 4.7
Ethyl 2-pentynoate	-301.8 ± 2.1[120]	[51.5 ± 1.3]	-250.3 ± 2.5		
Propyl *E*-2-butenoate	-433.3 ± 2.6[121]	[48.1 ± 1.3]	-395.2 ± 2.8	−395.2	
Propyl 4-pentenoate	-447.3 ± 3.0[6]	[49.4 ± 1.3]	-397.9 ± 3.3	−400.7	-16.0 ± 3.7
Propyl *E*-3-pentenoate	-454.4 ± 3.0[6]	[50.2 ± 1.3]	-404.2 ± 3.3	−411.6	2.8 ± 3.8
Propyl *E*-2-pentenoate	-464.9 ± 33.4[6]	[51.9 ± 1.3]	-413.0 ± 3.6	−415.8	1.6 ± 4.0
Propyl *Z*-9-octadecenoate	-792.3 ± 13.0[117]				
Propyl *E*-9-octadecenoate	-798.6 ± 13.0[117]				

(continued overleaf)

TABLE 19. *(continued)*

Ester	$\Delta_f H^\circ_m$(l)	$\Delta_l^g H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.	ΔH (hydrolysis)
Isopropyl *E*-2 butenoate	−457.1 ± 2.6[121]	[46.0 ± 1.3]	−411.1 ± 2.9	−412.3	
Isopropyl 4-pentenoate	−464.5 ± 1.7[6]	[47.3 ± 1.3]	−417.2 ± 2.1	−417.8	−14.3 ± 3.1
Isopropyl *E*-3-pentenoate	−473.3 ± 2.1[6]	[48.1 ± 1.3]	−425.2 ± 2.5	−428.7	6.2 ± 3.0
Isopropyl *E*-2-pentenoate	−478.7 ± 3.4[6]	[49.4 ± 1.3]	−429.3 ± 3.0	−433.0	−0.1 ± 4.0
Butyl *E*-2-butenoate	−467.8 ± 3.0[121]	[51.9 ± 1.3]	−415.9 ± 3.2	−415.8	
Butyl 4-pentenoate	−479.9 ± 1.7[6]	[52.7 ± 1.3]	−427.2 ± 2.1	−421.3	7.8 ± 3.0
Butyl *E*-3-pentenoate	−486.6 ± 2.6[6]	[53.6 ± 1.3]	−433.0 ± 2.9	−432.3	10.3 ± 2.4
Butyl *E*-2-pentenoate	−495.0 ± 2.6[6]	[55.2 ± 1.3]	−439.8 ± 2.9	−436.5	7.0 ± 3.4
Butyl *Z*-9-octadecenoate	−816.9 ± 13.8[117]				
Butyl *E*-9-octadecenoate	−823.6 ± 13.8[117]				
Isobutyl *E*-2-butenoate	−474.0 ± 2.9[121]	[50.2 ± 1.3]	−423.8 ± 3.2	−424.2	
Isobutyl 4-pentenoate	−488.3 ± 3.3[6]	[51.4 ± 1.3]	−436.9 ± 3.5	−429.7	8.8 ± 4.2
Isobutyl *E*-3-pentenoate	−505.4 ± 2.5[6]	[52.3 ± 1.3]	−453.1 ± 2.8	−440.6	21.7 ± 33.4
Isobutyl *E*-2-pentenoate	−506.7 ± 2.5[6]	[53.6 ± 1.3]	−453.1 ± 2.8	−444.9	23.3 ± 3.4
sec-Butyl *E*-2-butenoate	−474.5 ± 17.7[121]	[49.4 ± 1.3]	−425.1 ± 2.1	−433.0	
sec-Butyl 4-pentenoate	−497.1 ± 1.7[6]	[50.6 ± 1.3]	−446.5 ± 2.1	−438.5	9.7 ± 3.1
sec-Butyl *E*-3-pentenoate	−502.9 ± 2.6[6]	[51.5 ± 1.3]	−451.4 ± 2.9	−449.4	11.3 ± 3.4
sec-Butyl *E*-2-pentenoate	−510.4 ± 2.1[6]	[52.7 ± 1.3]	−457.7 ± 2.5	−453.7	7.1 ± 3.1
Isopentyl *E*-2-butenoate	−500.7 ± 3.0[121]	[54.0 ± 1.3]	−446.7 ± 3.3	−462.3	
Bicyclo[1,1,0]butane-1-carboxylic acid methyl ester	−203.1 ± 0.6[111]	38.6 ± 0.4[111]	−164.5 ± 0.7		
Cyclobutanecarboxylic acid methyl ester	−395.0 ± 1.3[111]	39.7 ± 0.4[111]	−355.3 ± 1.4		

TABLE 20. Unsaturated and aromatic esters: quantities in kJ mol^{-1} at 298.15 K

Ester	$\Delta_f H_m^\circ$ (l or cr)	$\Delta_{l,cr}^{g} H_m^\circ$	$\Delta_f H_m^\circ$(g)
Vinyl ethanoate (l)	-350.5 ± 1.5[122]	34.8 ± 1.3[123]	-315.7 ± 0.8
Isopropenyl ethanoate (l)	-386.4 ± 1.0[110]		
Phenyl formate (l)	-268.7 ± 2.8[124]	52.9 ± 1.0[124]	-215.8 ± 3.0
Phenyl ethanoate (l)	-334.9 ± 0.9[109]	55.2 ± 0.8[125]	-279.7 ± 1.2
Methyl benzoate (l)	-343.5 ± 2.4[111]	55.6 ± 0.1[126]	-287.9 ± 2.4
3-Methylphenyl ethanoate (l)	-374.1 ± 0.9[110]	60.7 ± 2.1[127]	-313.4 ± 2.3
Phenyl benzoate (cr)	-241.4 ± 2.1[128]	99.0 ± 0.4[129]	-142.4 ± 2.2
2-Naphthyl benzoate (cr)	-184.8 ± 3.4[130]		
1,3-Dicarbomethoxybenzene (cr)	-730.9 ± 1.0[218]		
1,4-Dicarbomethoxybenzene (cr)	-732.6 ± 1.0[218]		
1,3,5-Tricarbomethoxybenzene (cr)	-1101.1 ± 1.2[218]		
1,2,4,5-Tetracarbomethoxybenzene (cr)	-1432.4 ± 1.2[218]		
Pentacarbomethoxybenzene (cr)	-1788.1 ± 1.6[218]		
Hexacarbomethoxybenzene (cr)	-2110.8 ± 1.9[218]		

in the 1930s by Schjånberg[6,116,119–121]. The overall high quality of these results is demonstrated by the fact that the average deviation between the observed and estimated gaseous enthalpies of formation is only 4 kJ mol^{-1} and only three of the compounds, methyl 2-propenoate, ethyl 4-pentynoate and isobutyl E-3-pentenoate, show deviations > 10 kJ mol^{-1}. This illustrates the point that it is attention to the chemistry of the combustion process and purity of samples that is of prime importance, the measurement of energy quantities being relatively straightforward, as Schjånberg's apparatus would have been comparatively primitive compared with modern equipment. For those esters where the gaseous enthalpy of formation differs from the group scheme calculation by < 10 kJ mol^{-1}, the average enthalpy of hydrolysis is (4.0 ± 3.8) kJ mol^{-1}, a value close to that for the esters of the saturated monocarboxylic acids.

Table 20 lists thermochemical data for some unsaturated and aromatic esters. The appropriate parameters for estimation of the gaseous enthalpies of formation are not available, but examination of the experimental measurements indicates that these results are of high quality.

C. CHO Esters

Table 21 lists thermochemical data for a variety of (CHO) esters. The results for the butanediol ethanoates were obtained from equilibrium studies which appear to have been carefully controlled; the remaining results are from enthalpies of combustion and appear to be of variable quality. For diallyl phthalate independent measurements were in agreement, but for the glycerol tetradecanoates and hexadecanoates independent determinations differed by as much as 45 kJ mol^{-1}: the more recently determined results were selected. So few of the appropriate group parameters are available for estimation of the gaseous enthalpies of formation and few enthalpies of vaporization are known such that comparison with values from the group scheme is not feasible. Most of the results in Table 21 should be treated with caution, but at present these are the only available experimental measurements for these compounds.

D. Halogen-substituted Esters

Table 22 lists thermochemical data for halogen-substituted esters, almost entirely chloroesters. Practically all these results come from the same source, in which combustions were made using a static bomb with arsenious oxide solution distributed on a

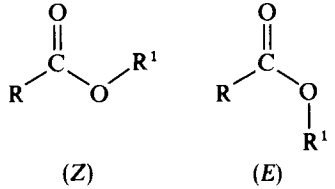
TABLE 21. Miscellaneous CHO esters: quantities in kJ mol^{-1} at 298.15 K

Ester		$\Delta_f H_m^\circ$(cr, l)	$\Delta^g_{cr,l} H_m^\circ$	$\Delta_f H_m^\circ$(g)
2,3-Butanediol monoethanoate (l)	$C_6H_{12}O_3$	-719.6 ± 3.6[131]		
Phenyl salicylate (cr)	$C_{13}H_{10}O_3$	-436.6 ± 4.6[132]	92.0 ± 4.2[123]	-344.6 ± 6.2
t-Butyl peroxydecanoate (l)	$C_{16}H_{32}O_3$	-738.3 ± 10.0[20]		
t-Butyl peroxytetradecanoate (l)	$C_{18}H_{36}O_3$	-795.8 ± 10.5[20]		
Glycerol 1-ethanoate (l)	$C_5H_{10}O_4$	-909.2 ± 3.7[133]		
Diethyl oxalate (l)	$C_6H_{10}O_4$	-805.5 ± 8.4[134]	63.5 ± 2.1[123]	-742.0 ± 8.7
2,3-Butanediol diethanoate (l)	$C_8H_{14}O_4$	-916.1 ± 3.3[131]		
Glycerol 1-benzoate (cr)	$C_{10}H_{12}O_4$	-777.3 ± 1.2[136]		
Glycerol 2-benzoate (cr)	$C_{10}H_{12}O_4$	-772.8 ± 1.2[136]		
Diethyl phthalate (l)	$C_{12}H_{14}O_4$	-776.6 ± 11.7[137]	88.3 ± 2.1[135]	-688.3 ± 11.9
Dimethyl *Z*-hexahydroisophthalate (l)	$C_{10}H_{16}O_4$	-846.5 ± 10.5[138]		
Dimethyl *E*-hexahydroisophthalate (l)	$C_{10}H_{16}O_4$	-854.5 ± 7.9[138]		
Diethyl *Z*-hexahydroisophthalate (l)	$C_{12}H_{20}O_4$	-933.7 ± 12.6[138]		
Diethyl *E*-hexahydroisophthalate (l)	$C_{12}H_{20}O_4$	-941.0 ± 12.6[138]		
Glycerol 1-decanoate (cr)	$C_{13}H_{26}O_4$	-1109.0 ± 1.3[136]		
Glycerol 2-decanoate (cr)	$C_{13}H_{26}O_4$	-1095.7 ± 2.0[136]		
Diallyl phthalate (l)	$C_{14}H_{14}O_4$	-551.5 ± 8.9[139]		
Glycerol 1-dodecanoate (cr)	$C_{15}H_{30}O_4$	-1160.9 ± 1.7[136]		
Glycerol 2-dedecanoate (cr)	$C_{15}H_{30}O_4$	-1152.6 ± 1.7[136]		
Dibutyl phthalate (l)	$C_{16}H_{22}O_4$	-842.6 ± 12.6[140]	91.6 ± 4.2[141]	-751.0 ± 13.3
Glycerol 1-tetradecanoate (cr)	$C_{17}H_{34}O_4$	-1222.6 ± 1.9[136]		
Glycerol 2-tetradecanoate (cr)	$C_{17}H_{34}O_4$	-1212.9 ± 1.9[136]		
Dipentyl phthalate (l)	$C_{18}H_{26}O_4$	-924.3 ± 13.4[140]	106.7 ± 4.2[142]	-817.6 ± 14.0
Di-iso-pentyl phthalate (l)	$C_{18}H_{26}O_4$	-941.0 ± 5.1[143]		
Glycerol 1-hexadecanoate (cr)	$C_{19}H_{38}O_4$	-1281.5 ± 2.2[136]		
Glycerol 2-hexadecanoate (cr)	$C_{19}H_{38}O_4$	-1268.7 ± 1.9[136]		
Diphenyl phthalate (cr)	$C_{20}H_{14}O_4$	-489.2 ± 9.2[143]		
Dicyclohexyl phthalate (cr)	$C_{20}H_{26}O_4$	-931.4 ± 10.9[143]		
Glycerol 1-octadecanoate (cr)	$C_{21}H_{42}O_4$	-1337.4 ± 19[136]		
Glycerol 2-octadecanoate (cr)	$C_{21}H_{42}O_4$	-1321.3 ± 2.4[136]		
Glycerol triethanoate (l)	$C_9H_{14}O_6$	-1330.8 ± 4.2[133]	82.0 ± 0.8[144]	-1248.8 ± 4.3
α-D-Glucose pentaethanoate	$C_{12}H_{24}O_{12}$	-2249.4 ± 1.7[145]		
β-D-Glucose pentaethanoate	$C_{12}H_{24}O_{12}$	-2232.6 ± 2.0[145]		

quartz fibre spiral to reduce any chlorine in the products to chloride; this method was the forerunner of the more accurate rotating-bomb technique. It is not to be expected that these results will be as precise as those for CHO compounds. In fact one-third of the values in Table 22 show deviations >10 kJ mol^{-1} between the observed and calculated gaseous enthalpies of formation, but the remaining two-thirds show very small deviations, an average of 2.2 kJ mol^{-1}; thus these results are somewhat erratic. Derivation of the enthalpies of hydrolysis of the liquid esters involves the enthalpies of formation of the corresponding chloroacids, also obtained from the same source. The enthalpies of hydrolysis suggest some trends; for the monochloroesters ΔH(hydrolysis) for 2-Cl esters appears to be 36 kJ mol^{-1}, for 3-Cl esters 17 kJ mol^{-1} and for 4-Cl esters 12 kJ mol^{-1}, appearing to show an effect depending on the position of the chlorine atom relative to the ester group. Surprisingly, however, for the dichloroethanoates the enthalpy of hydrolysis has fallen to 10 kJ mol^{-1}. Because of the large experimental uncertainties in the individual results, these differences in enthalpies of hydrolysis require confirmation and direct measurement of this quantity would be desirable and an interesting project.

VII. LACTONES AND LACTAMS

Several studies have been made of the energy difference between the *E* and *Z* conformations of esters, where the *E* conformation has a higher ground-state energy (i.e. is more stable) than the *Z* conformation but the energy differences found depend somewhat on



(*Z*) (*E*)

the structure of the ester and on the experimental methods used. For methyl formate, steric disfavouring of the *E* conformer will be a minimum: gas phase measurements indicate the energy difference to be 16.3 kJ mol^{-1} [155] or 19.9 kJ mol^{-1} [156]. In solution the energy difference appears to be smaller, 9.2 kJ mol^{-1} from studies of ^{13}C NMR spectra as functions of temperature in dimethylformamide[157]. A high-level *ab initio* computational study[158] on the rotational barrier in methyl formate suggested a (*Z* to *E*) energy difference of 23.4 kJ mol^{-1}. From comparative studies of the rates of alkaline hydrolysis of esters and lactones, Huisgen and Ott[159] estimated the (*Z* to *E*) energy difference to be 15.5 kJ mol^{-1}. This energy difference may be understood in terms of an increase in dipole–dipole repulsion in the *E* conformer; esters which adopt the *Z* conformation have dipole moments less than 7×10^{-30} C m whereas lactones, for which the *E* conformer is forced, have dipole moments of about 15×10^{-30} C m.

The energy difference between the *E* and *Z* forms will be reflected in the enthalpies of formation of lactones, together with the effects of ring strain. A conventional strain energy can be derived as the difference between the observed gaseous enthalpy of formation and that calculated using the group parameters from Table 1.

Table 23 lists the thermochemical results for lactones. The order of strain energies is unusual in that the six-membered ring compound, δ-valerolactone, is more highly strained than the five-membered ring compounds, γ-butyrolactone and γ-valerolactone.

TABLE 22. Halogen-substituted esters: quantities in kJ mol^{-1} at 298.15 K

Ester	$\Delta_f H^\circ_m(l)$	$\Delta^g_l H^\circ_m$	$\Delta_f H^\circ_m(g)$	Calc.	ΔH (hydrolysis)
Ethyl chloroformate	-505.2 ± 1.8[146]	46.7 ± 0.1[147]	-458.5 ± 1.8		
Propyl chloroethanoate	-515.8 ± 2.1[32]	[48.5 ± 4.2]	-467.3 ± 4.7	−466.8	
Butyl chloroethanoate	-538.4 ± 2.1[32]	[51.0 ± 4.2]	-487.4 ± 4.7	−487.4	
3-Methylbutyl chloroethanoate	-571.3 ± 8.4[32]	[54.8 ± 4.2]	-516.5 ± 9.4	−516.5	
Butyl 2-chloropropanoate	-571.9 ± 8.4[32]	[54.4 ± 4.2]	-517.5 ± 9.4	−580.2	7.7 ± 11.9
Isobutyl 2-chloropropanoate	-603.1 ± 8.4[32]	[53.6 ± 4.2]	-549.5 ± 9.4	−588.5	31.7 ± 11.9
Propyl 2-chlorobutanoate	-630.7 ± 8.4[32]	[52.3 ± 4.2]	-578.4 ± 9.4	−580.2	38.4 ± 11.9
3-Methylbutyl 2-chloropropanoate	-627.3 ± 8.4[32]	[52.3 ± 4.2]	-575.0 ± 9.4	−609.2	34.2 ± 11.9
Butyl 2-chlorobutanoate	-655.3 ± 8.4[32]	[52.7 ± 4.2]	-602.6 ± 9.4	−600.8	38.3 ± 11.9
Isobutyl 2-chlorobutanoate	-661.6 ± 8.4[32]	[52.3 ± 4.2]	-609.3 ± 9.4	−609.2	37.2 ± 11.9
3-Methylbutyl 2-chlorobutanoate	-684.0 ± 8.4[32]	[54.0 ± 4.2]	-630.0 ± 9.4	−629.9	37.9 ± 11.9
Propyl 3-chloropropanoate	-537.6 ± 8.4[32]	[51.9 ± 4.2]	-485.7 ± 9.4	−509.1	
Butyl 3-chloropropanoate	-557.9 ± 8.4[32]	[55.6 ± 4.2]	-502.3 ± 9.4	−529.7	
Isobutyl 3-chloropropanoate	-572.6 ± 8.4[32]	[55.2 ± 4.2]	-517.4 ± 9.4	−538.1	
Propyl 3-chlorobutanoate	-590.2 ± 8.4[32]	[52.3 ± 4.2]	-537.9 ± 9.4	−540.0	17.1 ± 11.9
3-Methylbutyl 3-chloropropanoate	-593.4 ± 8.4[32]	[54.0 ± 4.2]	-539.4 ± 9.4	−554.8	
Butyl 3-chlorobutanoate	-610.9 ± 8.4[32]	[53.1 ± 4.2]	-557.8 ± 9.4	−560.7	13.1 ± 11.9
Isobutyl 3-chlorobutanoate	-623.5 ± 8.4[32]	[52.3 ± 4.2]	-571.2 ± 9.4	−569.1	18.3 ± 11.9

3-Methylbutyl 3-chlorobutanoate	-644.3 ± 8.4[32]	[54.4 ± 4.2]	-589.9 ± 9.4	−585.7	17.4 ± 11.9
Ethyl 4-chlorobutanoate	-566.5 ± 8.4[32]	[52.7 ± 4.2]	-513.8 ± 9.4	−509.1	8.1 ± 11.9
Propyl 4-chlorobutanoate	-591.4 ± 8.4[32]	[53.6 ± 4.2]	-537.8 ± 9.4	−529.8	8.3 ± 11.9
Butyl 4-chlorobutanoate	-618.1 ± 8.4[32]	[54.4 ± 4.2]	-563.7 ± 9.4	−550.4	10.3 ± 11.9
Isobutyl 4-chlorobutanoate	-630.6 ± 8.4[32]	[54.0 ± 4.2]	-576.6 ± 9.4	−558.8	15.4 ± 11.9
3-Methylbutyl 4-chlorobutanoate	-656.4 ± 8.4[32]	[55.6 ± 4.2]	-600.8 ± 9.4	−579.5	19.5 ± 11.9
Butyl dichloroethanoate	-550.1 ± 8.4[32]	[52.3 ± 4.2]	-497.8 ± 9.4	−493.8	12.3 ± 11.9
Isobutyl dichloroethanoate	-553.8 ± 8.4[32]	[52.3 ± 4.2]	-501.5 ± 9.4	−502.1	8.6 ± 11.9
3-Methylbutyl dichloroethanoate	-575.0 ± 8.4[32]	[55.6 ± 4.2]	-519.4 ± 9.4	−522.8	8.1 ± 11.9
Allyl trichloroethanoate	-395.3 ± 8.4[32]	[52.3 ± 4.2]	-343.0 ± 9.4	−346.0	
Propyl trichloroethanoate	-513.0 ± 8.4[32]	[53.1 ± 4.2]	-459.9 ± 9.4	−470.8	
Isopropyl trichloroethanoate	-536.0 ± 8.4[32]	[51.9 ± 4.2]	-484.1 ± 9.4	−487.9	
Butyl trichloroethanoate	-545.8 ± 8.4[32]	[53.6 ± 4.2]	-492.2 ± 9.4	−491.5	
Isobutyl trichloroethanoate	-553.4 ± 8.4[32]	[53.1 ± 4.2]	-500.3 ± 9.4	−499.8	
3-Methylbutyl trichloroethanoate	-580.9 ± 8.4[32]	[57.7 ± 4.2]	-523.2 ± 9.4	−520.5	
Methyl pentafluoropropanoate	-1463.0 ± 1.8[148]	34.7 ± 2.1[148]	-1428.3 ± 2.8		
Dimethylhexafluoro-1,5-pentandioate	-1978.8 ± 4.3[148]	52.3 ± 4.2[148]	-192.5 ± 6.0		
Methyl 2-iodobenzoate (l)	-243.1 ± 4.2[78]				
Methyl 3-iodobenzoate (cr)	-278.3 ± 4.2[78]				
Methyl 4-iodobenzoate (cr)	-286.6 ± 4.2[78]				

TABLE 23. Lactones: quantities in kJ mol^{-1} at 298.15 K

Lactone	$\Delta_f H^\circ_m$(cr, l)	$\Delta^g_{cr,l} H^\circ_m$	$\Delta_f H^\circ_m$(g)	Strain energy
β-Propiolactone (l)	-329.9 ± 0.9[149]	47.0 ± 0.1[149]	-282.9 ± 0.9	96.7
γ-Butyrolactone (l)	-420.9 ± 0.7[150]	54.4 ± 0.4[150]	-366.5 ± 0.8	33.8
γ-Valerolactone (l)	-461.3 ± 1.0[150]	54.8 ± 0.4[150]	-406.5 ± 1.1	31.6
δ-Valerolactone (l)	-437.6 ± 0.8[150]	58.0 ± 0.4[150]	-379.6 ± 0.9	41.4
2-Oxabicyclo [2.2.2] Octane-3-one (cr)	-466.2 ± 1.6[151]	69.6 ± 2.1[151]	-396.6 ± 2.6	43.4

Strain energies in some cyclic compounds (including lactams, discussed later) are given in Table 24, from which it can be seen that lactones and lactams exhibit a different order of strain energies from other cyclic compounds.

The order of strain energies in lactones is in accord with chemical behaviour. The ease of cyclization of hydroxycarboxylic acids to 5-ring lactones is greater than to their 6-ring counterparts[160]; also, δ-valerolactone undergoes reversible polymerization at room temperature whereas γ-butyrolactone does not[161], and this is consistent with a higher strain energy in the former.

Molecular mechanics calculations by Allinger and coworkers[162,163] predicted strain energies in γ-butyrolactone of 42 kJ mol^{-1}, and for δ-valerolactone they placed the half-chair form 2.3 kJ mol^{-1} more stable than the boat form with a total strain of about 20 kJ mol^{-1}. These calculations show that the strain arises from the following:

(a) Conjugation in the carboxylate segment [—C—O—C(=O)—C—] enforces a preference for coplanarity in this 5-atom unit distorting the rest of the molecule, and this distortion appears to cause a greater strain-energy effect in the 6-ring than in the 5-ring.

(b) The (Z–E) energy difference in the ester linkage also affects the calculated strain energy because the group parameters were derived from the enthalpies of formation of esters in the Z conformation.

Table 25 lists the thermochemical results for lactams, all derived from careful combustion studies by Skuratov and collaborators[153,154]. The derived strain energies are much smaller than the values for the corresponding lactones, but this may be a consequence of the fact that the appropriate group parameters were derived from the gaseous enthalpy of formation of a single compound, n-butyl acetamide[164]. Nevertheless, these strain energies also indicate that the six-membered ring in 2-piperidone is more highly strained than the five-membered ring in 2-pyrrolidone, and this can be ascribed to the introduction of the segment [—C—NH—C(=O)—C—] for which the preferred conformation is planar resulting in greater distortion in the 6-ring than in the 5-ring.

TABLE 24. Conventional strain energies in cyclic compounds: kJ mol^{-1} at 298.15 K

Ring size	Lactone	Lactam	Cycloalkane	Cyclic ether	Cyclic ketone
4	96.7		110.7	106.6	94.6
5	32.7	4.6	26.5	23.5	24.3
6	41.4	10.3	0.1	4.9	11.0
7		17.1	26.5		10.5

TABLE 25. Lactams: quantities in kJ mol^{-1} at 298.15 K

Lactam	$\Delta_f H^\circ_m$(cr, l)	$\Delta^g_{cr,l} H^\circ_m$	$\Delta_f H^\circ_m$	Strain energy
2-Pyrroliodone (l)	−286.2 ± 0.5[153]	69.1 ± 0.5[150]	−217.1 ± 0.7	4.6
2-Piperidone (cr)	−306.6 ± 0.5[153]	74.5 ± 2.1[152]	−232.1 ± 2.2	10.3
ε-Caprolactam (cr)	−329.3 ± 0.9[153]	83.3 ± 0.4[152]	−246.0 ± 1.0	17.1
N-Methylpyrrolidone (l)	−262.3 ± 0.8[154]			
N-Methylcaprolactam (l)	−306.7 ± 0.8[154]			
5-Methylcaprolactam (cr)	−364.0 ± 1.3[153]			
7-Methylcaprolactam (cr)	−362.3 ± 1.3[153]			
ε-Enantholactam (cr)	−348.5 ± 1.3[153]			
N-Methylenantholactam (l)	−325.5 ± 1.3[154]			

VIII. ACID ANHYDRIDES

Enthalpies of formation of acid anhydrides are listed in Table 26. The enthalpies of formation of the first three of the non-cyclic anhydrides, acetic, propionic and trimethylacetic, were derived from enthalpies of hydrolysis[165,167] but the values for the aromatic compounds were derived from combustion measurements and these values require confirmation.

TABLE 26. Acid anhydrides: quantities in kJ mol^{-1} at 298.15 K

Acid anhydride	$\Delta_f H^\circ_m$(cr, l)	$\Delta^g_{cr,l} H^\circ_m$	$\Delta_f H^\circ_m$(g)
Acetic anhydride (l)	−624.3 ± 0.4[165]	50.8 ± 1.3[166]	−573.5 ± 1.4
Propionic anhydride (l)	−679.1 ± 0.8[167]	52.6 ± 2.1[123]	−626.5 ± 2.2
Trimethylacetic anhydride (l)	−779.9 ± 6.3[167]		
Benzoic anhydride (cr)	−431.0 ± 7.1[168]	96.7 ± 4.2[123]	−334.3 ± 8.2
Orthotoluic anhydride (cr)	−533.5 ± 7.9[168]		
Paratoluic anhydride (cr)	−520.9 ± 7.9[168]		
Cinnamic anhydride (cr)	−347.7 ± 8.4[168]		
Maleic anhydride (cr)	−469.9 ± 0.6[44]	71.5 ± 5.0[169]	−398.4 ± 5.0
Succinic anhydride (cr)	−608.6 ± 0.7[170]	80.7 ± 1.6[170]	−527.9 ± 1.7
Glutaric anhydride (cr)	−618.5 ± 0.9[170]	86.1 ± 1.6[170]	−532.4 ± 1.8
Methylmaleic anhydride (l)	−504.5 ± 1.6[167]	57.3 ± 2.1[123]	−447.2 ± 2.6
Methylsuccinic anhydride (l)	−617.5 ± 1.2[167]		
Dimethylmaleic anhydride (cr)	−581.6 ± 2.5[171]		
1,1-Dimethylsuccinic anhydride (l)	−645.5 ± 2.5[167]	63.8 ± 2.1[123]	−581.7 ± 3.3
cis-1,2-Dimethylsuccinic anhydride (cr)	−658.0 ± 1.5[49]		
trans-1,2-Dimethylsuccinic anhydride (cr)	−669.0 ± 1.5[167]		
Ethylsuccinic anhydride (l)	−642.4 ± 1.8[49]		
Trimethylsuccinic anhydride (cr)	−688.4 ± 1.8[49]	74.1 ± 4.2[166]	−614.3 ± 4.6
Tetramethylsuccinic anhydride (cr)	−691.9 ± 2.3[167]		
1,1-Diethylsuccinic anhydride (cr)	−688.8 ± 2.1[49]		
cis-1,2-Dimethylsuccinic anhydride (cr)	−658.0 ± 1.5[49]		
trans-1,2-Dimethylsuccinic anhydride (cr)	−669.0 ± 1.5[167]		
Ethylsuccinic anhydride (l)	−642.4 ± 1.8[49]		
Trimethylsuccinic anhydride (cr)	−688.4 ± 1.8[49]	74.1 ± 4.2[166]	−614.3 ± 4.6
Tetramethylsuccinic anhydride (cr)	−691.9 ± 2.3[167]		
trans-1,2-Diphenylsuccinic anhydride (cr)	−419.9 ± 3.9[49]		
Phthalic anhydride (cr)	−460.1 ± 1.9[172]		
Pyromelitic dianhydride (cr)	−925.1 ± 0.7[217]		

For the cyclic anhydrides there is excellent agreement between those values obtained by Conn and coworkers[167] by hydrolysis and values from combustion measurements; for maleic anhydride by Wilhoit and Shiao[44] and by Parks and collaborators[172] for succinic anhydride by Yang Meng-Yan and Pilcher[170], and for methylsuccinic anhydride and *trans*-1,2-dimethylsuccinic anhydride by Verkade and Hartman[49], hence we have confidence in these values and in the additional values obtained by combustion by the same authors.

Unfortunately, for only a few of these compounds is it possible to derive enthalpies of formation in the gaseous state, but for these, strain energies can be derived by applying the group parameters in Table 1. For maleic anhydride and methylmaleic anhydride, strain energies of 28.6 kJ mol^{-1} and 11.7 kJ mol^{-1}, respectively, were derived. For succinic anhydride and glutaric anhydride the strain energies are 4.6 kJ mol^{-1} and 20.8 kJ mol^{-1}, respectively. This behaviour is similar to that observed for lactones; the six-membered ring of glutaric anhydride is more highly strained than the five-membered ring of succinic anhydride. This may be ascribed to the introduction into the ring of the segment [C—C(=O)—O—C(=O)—C] for which the preferred conformation is planar, which produces greater distortion in the 6-ring than in the 5-ring.

IX. AMIDES

Enthalpies of formation of amides are listed in Table 27, which includes simple primary amides, $RCONH_2$, diamides, *N*-alkylamides, $RCONHR^1$ and $RCONR^1R^2$, *N*-acetylamides and cyclic imides.

The gaseous enthalpies of formation of the linear primary amides, $C_nH_{2n-1}CONH_2$, with the exception of pentanamide, agree closely with values calculated using the group parameters in Table 1. Except for ethanamide, the enthalpies of formation of these gaseous amides can be represented by

$$\Delta_f H^\circ_m[H—(CH_2)_nCONH_2, g]/(\text{kJ mol}^{-1}) = -(217.1 \pm 1.6) - n(20.97 \pm 0.34)$$

and to within the limits of uncertainty, the $—CH_2—$ increment agrees with the value found for alkanes and for carboxylic acids. By comparison of the enthalpies of formation of these gaseous primary amides with those of the corresponding carboxylic acids, the enthalpy of formation of a primary amide can be reasonably estimated by applying an increment of +193.1 kJ mol^{-1} to that of the corresponding carboxylic acid, and it is to be

Gaseous redistribution reaction	$\Delta_r H^\circ_m$/(kJ mol^{-1})
$\begin{matrix}CO_2H\\|\\CO_2H\end{matrix} + CH_3CH_3 \longrightarrow 2CH_3CO_2H$	-58.1 ± 5.8
$\begin{matrix}CO_2H\\|\\CONH_2\end{matrix} + CH_3CH_3 \longrightarrow \begin{matrix}CH_3CO_2H\\+\\CH_3CONH_2\end{matrix}$	-35.0 ± 2.8
$\begin{matrix}CONH_2\\|\\CONH_2\end{matrix} + CH_3CH_3 \longrightarrow 2CH_3CONH_2$	-5.7 ± 2.1
$\begin{matrix}CSNH_2\\|\\CSNH_2\end{matrix} + CH_3CH_3 \longrightarrow 2CH_3CSNH_2$	$+26.2 \pm 2.9$
$\begin{matrix}CH_2OH\\|\\CH_2OH\end{matrix} + CH_3CH_3 \longrightarrow 2CH_3CH_2OH$	0.9 ± 2.0

TABLE 27. Amides: quantities in kJ mol^{-1} at 198.15 K

Amide	$\Delta_f H_m^{\circ}$(cr, l)	$\Delta^g_{cr,l} H_m^{\circ}$	$\Delta_f H_m^{\circ}$(g)	Calc.
Ethanamide (cr)	−317.0 ± 0.8[173]	78.7 ± 0.3[174]	−238.3 ± 0.9	−237.6
Propanamide (cr)	−338.2 ± 0.5[173]	79.3 ± 0.3[175]	−258.9 ± 0.6	−259.0
Butanamide (cr)	−365.5 ± 0.8[173]	86.4 ± 0.4[175]	−279.1 ± 0.9	−279.7
Pentanamide (cr)	−379.5 ± 1.1[93]	89.3 ± 0.4[175]	−290.2 ± 1.2	−300.4
Hexanamide (cr)	−423.0 ± 0.5[176]	98.7 ± 1.7[176]	−324.3 ± 1.8	−321.1
Octanamide (cr)	−473.2 ± 0.9[93]	110.5 ± 2.9[175]	−362.7 ± 3.0	−362.4
2-Hexynamide (cr)	−117.9 ± 3.4[28]			
Benzamide (cr)	−202.6 ± 1.1[177]	101.7 ± 0.5[209]	−100.9 ± 1.2	
Oxamic acid (cr)	−661.2 ± 0.8[178]	108.9 ± 2.1[45]	−552.3 ± 2.2	
Oxamide (cr)	−504.4 ± 0.5[178]	117.3 ± 1.2[179]	−387.1 ± 1.3	
Malonic diamide (cr)	−546.1 ± 1.5[180]			−417.0
Succinic diamide (cr)	−581.2 ± 2.1[143]			−434.2
Tartramide (cr)	−1193.5 ± 5.9[143]			
N-Butylethanamide (l)	−380.9 ± 1.6[164]	75.0 ± 0.5[181]	−305.9 ± 1.7	−305.9
N-Butylpentanamide (cr)	−465.1 ± 1.7[43]			−368.7
N-Phenylethanamide (cr)	−209.6 ± 1.5[164]	80.8 ± 0.8[175]	−128.8 ± 1.7	
N,*N*-Dimethylformamide (l)	−239.3 ± 1.3[182]	46.9 ± 1.0[183]	−192.4 ± 1.6	
N,*N*-Dimethylethanamide (l)	−278.3 ± 1.5[182]	50.2 ± 1.0[183]	−228.1 ± 1.8	−228.1
N-Ethyl-*N*-methylpropanamide (l)	−336.0 ± 0.5[154]			−274.1
N,*N*-Diphenylethanamide (cr)	−42.9 ± 7.1[133]			
N-Phenyl-*N*-cyclohexylethanamide (cr)	−300.0 ± 15.9[133]			
N-Acetylimidazole (cr)	−119.6 ± 3.6[164]			
N-Acetyltetrazole (cr)	81.5 ± 1.3[164]			
N-Acetylhydrazobenzene (cr)	−11.2 ± 11.1[184]			
N-Acetylbenzidine (cr)	−160.6 ± 10.6[184]			
N-Acetyl-*N*-butylethanamide (l)	−538.9 ± 1.7[174]	64.4 ± 0.4	−474.5 ± 1.8	−474.5
N-Acetyl-*N*-phenylethanamide (cr)	−362.6 ± 1.6[174]	90.0 ± 0.8	−272.6 ± 1.8	
N,*N*-Diphenylacetoethanamide (cr)	−227.9 ± 8.4[133]			
N,*N*-Diacetylethanamide (l)	−610.5 ± 1.0[186]	60.4 ± 0.1	−550.1 ± 1.0	−550.1
N,*N*-Diacetylhydrazobenzene (cr)	−188.4 ± 4.6[184]			
N,*N*-Diacetylbenzidine	−472.5 ± 5.9[184]			
Methylethylmaleimide (cr)	−469.7 ± 3.8[187]			
Succinimide (cr)	−459.1 ± 0.3[188]	83.6 ± 1.5[170]	−375.5 ± 1.5	
Glutarimide (cr)	−487.7 ± 0.8[170]	94.1 ± 1.6[170]	−393.6 ± 1.8	

expected that the same increment would be applicable to those primary amides with branched alkyl groups.

Consideration of the enthalpies of the gaseous redistribution reactions listed on page 80 at 298.15 K lead to the following conclusions:

(a) When carbonyl groups are adjacent as in oxalic acid, the effect of dipole-dipole repulsion overwhelms any stabilization effects such as π-delocalization. The polar carbonyl groups are mainly responsible; the repulsion between OH groups as in ethylene glycol appears to be negligible.

(b) In oxamic acid and oxamide there appears to be additional stabilization due to intramolecular hydrogen bonding between the NH_2 group and the carbonyl group on the adjacent carbon atom. From the crystal structure of oxamide[189], the appropriate N---O distance is 0.275 nm, ideal for hydrogen bonding. The hydrogen bond energy is the same in both molecules as shown by the enthalpy change of the gaseous reaction:

$$\begin{array}{l} CO_2H \\ | \\ CO_2H \end{array} + \begin{array}{l} CONH_2 \\ | \\ CONH_2 \end{array} \longrightarrow 2 \begin{array}{l} CO_2H \\ | \\ CONH_2 \end{array} \qquad \Delta_r H^\circ_m = (6.1 \pm 6.7)\ \text{kJ mol}^{-1}$$

(c) In dithioxamide, polar repulsion is very much reduced but the N---S distance across the central (C—C) bond is calculated to be 0.292 nm[190], ideal for intramolecular hydrogen bonding.

These results fall into an expected pattern, but it is quite unrealistic to expect that such compounds could be included in a simple bond-energy scheme.

Unfortunately, for the *N*-alkylamides very few enthalpies of vaporization are available so that a thorough test of the results by using a bond-energy scheme is not possible. The few gaseous enthalpies of formation that have been determined were used to derive some of the parameters given in Table 1, but have not been applied to a range of compounds.

In considering the cyclic imides, succinimide and glutarimide, the appropriate group parameters are not available for calculation of strain energies. However, if it be assumed that the difference in $\Delta_f H^\circ_m(g)$ for strain-free five- and six-membered rings is due to the insertion of $-CH_2-$ group between two $-CH_2-$ groups for which $\Delta(\Delta_f H^\circ_m(g))/(\text{kJ mol}^{-1}) = -(20.6 \pm 0.1)$, then S(glutarimide)—S(succinimide) = (2.5 ± 2.3) kJ mol^{-1}. The six-membered ring of glutarimide is more strained, albeit slightly, than the five-membered ring of succinimide; and this is the same order of strain energies observed in lactones and cyclic anhydrides, and presumably results from the same cause. The presence in the ring of a structural group [—C—C(=O)—NH—C(=O)—C—] for which the preferred conformation is planar results in a greater distortion of the six-membered ring than of the five-membered ring.

X. ACYL HALIDES

The enthalpies of formation of acyl halides are listed in Table 28. The majority of these values were derived from enthalpies of hydrolysis and consideration of the experimental work done in this area leads us to conclude that the results are reliable. For acetyl chloride, bromide and iodide there is exact agreement between the results of Devore and O'Neal[192] and earlier measurements by Carson and Skinner[191] and Pritchard and Skinner[199]. There are insufficient values to make derivation of group scheme parameters useful, however, some interrelations amongst the gaseous enthalpies of formation can

be derived to demonstrate consistency in these results. The enthalpies of hydrogenation of the gaseous chloroacetyl chlorides can be derived:

	$\Delta_r H_m^\circ$/(kJ mol^{-1})
$CH_2ClCOCl + H_2 \longrightarrow CH_3COCl + HCl$	-98.1 ± 8.8
$CHCl_2COCl + H_2 \longrightarrow CH_2ClCOCl + HCl$	-96.5 ± 12.3
$CCl_3COCl + H_2 \longrightarrow CHCl_2COCl + HCl$	-93.9 ± 12.3

and these enthalpies of hydrogenation agree to within the limits of experimental error, showing that these enthalpies of formation provide a consistent set.

By considering the enthalpies of the gaseous reactions,

$$C_6H_5COX + CH_4 \longrightarrow CH_3COX + C_6H_6$$

$\Delta_r H_m^\circ$/(kJ mol^{-1}) for X = Cl is (8.8 ± 4.3), for X = Br (9.7 ± 6.4) and for X = I (14.6 ± 5.3); the agreement of these values to within the limits of experimental uncertainty shows that the enthalpies of formation of the benzoyl halides are consistent with those of the acetyl halides.

The dissociation enthalpies of the (C–halogen) bonds in the acetyl halides can be derived, requiring $\Delta_f H_m^\circ(CH_3CO,g)$/(kJ mol^{-1}) $= -(24.3 \pm 1.6)$[200] and the enthalpies of formation of the gaseous halogen atoms[1]. For CH_3COX, D(C—X)/(kJ mol^{-1}) for X = F is (497.2 ± 3.7), for X = Cl (348.4 ± 1.7), for X = Br (293.6 ± 1.7) and X = I (213.0 ± 2.0). These dissociation enthalpies are a linear relation with bond lengths as shown in Figure 3; the bond lengths were taken from Reference 201. Such a relation is not surprising, as the nature of the bonding of the halogen to carbon will be similar in all cases.

TABLE 28. Acyl halides: quantities in kJ mol^{-1} at 298.15 K

Acyl halide	$\Delta_f H_m^\circ$(l)	$\Delta_f^g H_m^\circ$	$\Delta_f H_m^\circ$(g)
Acetyl fluoride	-467.2 ± 2.6[191]	[25.1 ± 2.1]	-442.1 ± 3.3
Acetyl chloride	-275.2 ± 0.5[192]	23.8 ± 0.2[192]	-251.4 ± 0.5
Acetyl bromide	-225.6 ± 0.3[192]	29.6 ± 0.3[192]	-196.0 ± 0.4
Acetyl iodide	-165.2 ± 1.1[192]	34.7 ± 0.5[192]	-130.5 ± 1.2
Chloroacetyl chloride	-284.5 ± 8.4[193]	[38.9 ± 2.1]	-245.6 ± 8.7
Dichloroacetyl chloride	-280.7 ± 8.4[193]	[39.3 ± 2.1]	-241.4 ± 8.7
Trichloroacetyl chloride	-280.8 ± 8.4[193]	[41.0 ± 2.1]	-239.8 ± 8.7
Benzoyl chloride	-158.0 ± 0.5[194]	[54.8 ± 4.2]	-103.2 ± 4.2
Benzoyl bromide	-107.3 ± 0.5[194]	[58.6 ± 6.3]	-48.7 ± 6.3
Benzoyl iodide	-50.0 ± 8.1	[61.9 ± 6.3]	11.9 ± 5.1[195]
Oxalyl chloride	-376.6 ± 4.7[196]	[31.8 ± 4.2]	-335.8 ± 6.3
2-Chlorobenzoyl chloride	-171.3 ± 0.8[197]		
3-Chlorobenzoyl chloride	-189.7 ± 1.6[197]		
4-Chlorobenzoyl chloride	-191.7 ± 1.1[197]		
1,3-Benzenedicarbonyl dichloride (cr)	-367.5 ± 4.2[198]		
1,4-Benzenedicarbonyl dichloride (cr)	-384.6 ± 4.2[198]		

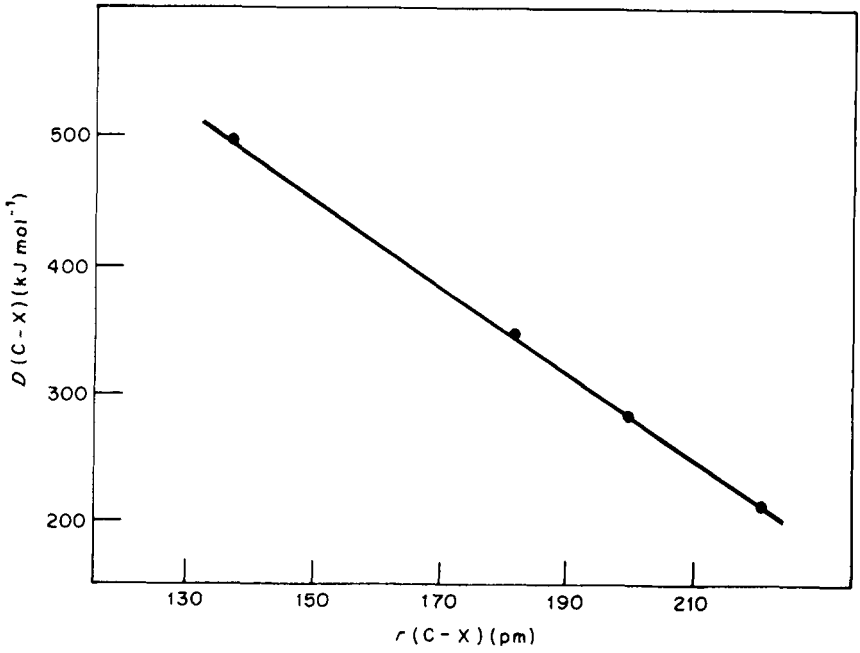


FIGURE 3. D(C—X) in acyl halides versus r(C—X)

XI. THIO DERIVATIVES

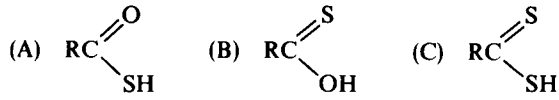
A. Thiol Acids and Esters

The enthalpies of formation of thiol acids and esters are listed in Table 29. Practically all these values were derived from enthalpies of hydrolysis, measured very carefully, except for the dithioacids which were derived from enthalpies of combustion measured

TABLE 29. Thiol acids and esters: quantities in kJ mol^{-1} at 298.15 K

	$\Delta_f H^\circ_m$(l)	$\Delta^g_l H^\circ_m$	$\Delta_f H^\circ_m$(g)	Calc.
Thiolethanoic acid	−216.9 ± 1.1[202]	[46.5 ± 4.0]	−170.4 ± 4.1	−170.4
Ethyl thiolethanoate	−268.2 ± 0.8[185]	40.0 ± 0.4[114]	−228.2 ± 0.9	−229.1
n-Propyl thiolethanoate	−294.5 ± 0.9[185]	44.1 ± 0.4[114]	−250.4 ± 1.0	−249.7
Isopropyl thiolethanoate	−298.6 ± 0.9[185]	42.3 ± 0.4[114]	−256.3 ± 1.0	−256.3
n-Butyl thiolethanoate	−318.7 ± 1.3[185]	48.1 ± 0.4[114]	−270.6 ± 1.4	−270.4
t-Butyl thiolethanoate	−326.5 ± 1.1[185]	43.0 ± 0.4	−283.5 ± 1.2	−283.5
Phenyl thiolethanoate	−122.4 ± 1.0[203]			
2-Thiolpropionic acid	−468.4 ± 3.4[204]			−416.5
Dithioadipic acid (cr)	−429.3 ± 2.5[205]			−341.2
Dithiosuberic acid	−418.8 ± 2.5[205]			−382.6
Dithioazelaic acid (cr)	−486.2 ± 2.5[205]			−403.2
Dithiosebacic acid (cr)	−518.8 ± 2.5[205]			−423.9

by rotating-bomb calorimetry. In principle there are three possible structures for thio derivatives of carboxylic acids and esters:



Although dithioacids C exist, there are no thermochemical data for such compounds when R is an alkyl group; there are data for the dithiocarbamic acids when R is $-NR_2^1$. Thiol acids and esters have structure A and not B, and for esters the relative stability of these structures can be demonstrated by a simple but crude estimate. From a comparison of the enthalpies of formation of amides and thioamides (Section XI,B), the increment in $\Delta_f H_m^\circ(g)$ for changing (C=O) to (C=S) is derived as (249.9 ± 2.3) kJ mol^{-1}. Approximately the same value is obtained from $\Delta_f H_m^\circ(CO_2, g)/(kJ\ mol^{-1}) = -(393.51 \pm 0.13)$[1] and $\Delta_f H_m^\circ(CS_{2,g})/(kJ\ mol^{-1}) = (117.3 \pm 0.8)$[1], giving for this same increment (255.4 ± 0.9) kJ mol^{-1}. By applying this increment to the enthalpy of ethyl ethanoate, then for the structure $CH_3C(=S)OC_2H_5$, $\Delta_f H_m^\circ(g)$ is estimated to be $-(194.2 \pm 2.4)$ kJ mol^{-1} whereas the actual value for ethyl thiolethanoate is $-(228.2 \pm 0.9)$ kJ mol^{-1}, thus showing the structure $CH_3C(=O)SC_2H_5$ to be about 34 kJ mol^{-1} more stable than $CH_3C(=S)OC_2H_5$.

From this point of view, however, the observed enthalpy of formation of thiolethanoic acid is difficult to understand, for by applying the above increment to the enthalpy of formation of ethanoic acid, $\Delta_f H_m^\circ(CH_3C(=S)OH, g)$ is then estimated to be $-(182.8 \pm 2.7)$ kJ mol^{-1} whereas the observed value for gaseous thiolethanoic acid is $-(170.4 \pm 4.1)$ kJ mol^{-1}; i.e. the observed value appears to be *ca* 12 kJ mol^{-1} less stable than that estimated for the structure $CH_3C(=S)OH$. The observed enthalpy of formation of thiolethanoic acid was derived from measurements of its enthalpy of hydrolysis[206] and from its enthalpy of combustion by rotating-bomb calorimetry[202], the results being in agreement. Further work on thiolethanoic acid and other thiolcarboxylic acids would be desirable to clarify this situation.

The enthalpies of hydrolysis of the thiolethanoates according to

$$CH_3COSR(l) + H_2O(l) \longrightarrow CH_3CO_2H(l) + RSH(l)$$

in kJ mol^{-1} are for $R = C_2H_5$, $-(3.6 \pm 1.0)$; n-C_3H_7, $-(3.5 \pm 1.2)$; *i*-C_3H_7, $-(5.4 \pm 1.2)$; n-C_4H_9, $-(4.1 \pm 1.8)$; *t*-C_4H_9, $-(12.2 \pm 1.4)$. The slight increase in exothermicity for the *t*-butyl ester is presumably due to the release of some steric strain in the ester on hydrolysis.

The agreement between the observed and calculated gaseous enthalpies of formation is good, but there are only few results for this comparison to be made. The estimated gaseous enthalpies of formation of the dithioacids lead to reasonable values, *ca* 85 kJ mol^{-1} for the enthalpies of sublimation of the crystalline acids, but for the liquid dithiosuberic acid, the enthalpy of vapourization is deduced to be *ca* 36 kJ mol^{-1}, which would be too small.

B. Thioamides

The few available enthalpies of formation of thioamides are given in Table 30; all were measured by rotating-bomb calorimetry. Some group parameters were derived from these given in Table 1; they may be applied to estimating enthalpies of formation of other thioamides.

The increment in $\Delta_f H_m^\circ(g)$ for changing (C=O) to (C=S), from ethanamide to thioethanamide is (251.0 ± 1.4) kJ mol^{-1} and from benzamide to thiobenzamide is

TABLE 30. Thioamides: quantities in kJ mol^{-1} at 298.15 K

Thioamide	$\Delta_f H^\circ_m$(cr)	$\Delta^g_{cr} H^\circ_m$	$\Delta_f H^\circ_m$(g)
Thioethanamide	-70.5 ± 1.2[207]	83.3 ± 0.3[207]	12.7 ± 1.2
Thiobenzamide	44.4 ± 1.5[208]	103.4 ± 2.2[208]	147.8 ± 2.7
N,N-Dimethylthiobenzamide	41.3 ± 1.9[208]	94.8 ± 2.0[208]	136.1 ± 2.8
N,N-Dimethylthiobenzamide	-10.3 ± 2.1[208]	91.4 ± 3.2[208]	81.1 ± 3.8

(248.7 ± 3.0) kJ mol^{-1}, in agreement. Application of the average value of this increment, (249.9 ± 1.5) kJ mol^{-1}, may provide the simplest basis for the estimation of the gaseous enthalpy of formation of primary thioamides from those of primary amides.

The difference between the enthalpies of formation of gaseous dimethylamine and diethylamine is $-(53.3 \pm 1.40)$ kJ mol^{-1} [3], and the corresponding difference for *N,N*-dimethylthiobenzamide and *N,N*-diethylthiobenzamide is $-(55.0 \pm 4.7)$ kJ mol^{-1}, in good agreement.

C. Dithiocarbamic Acids

Dithiocarbamic acids of the form R_2NCS_2H contain the sulphur analogue of the carboxylic acid group. These compounds are so unstable in the solid state that direct thermochemical measurements would not be feasible. Their enthalpies of formation in the gaseous state, however, have been determined by an indirect procedure. The enthalpies of formation of some crystalline dialkylammoniumdialkyldithiocarbamates, $R_2NH_2S_2CNR_2$, were measured by Ribeiro da Silva, Reis and Pilcher[210] using rotating-bomb calorimetry and reaction-solution calorimetry with results in agreement. Sublimation of these compounds was shown to proceed by decomposition according to

$$R_2NH_2S_2CNR_2(cr) \longrightarrow R_2NH(g) + HS_2CNR_2(g)$$

because the enthalpy of sublimation determined by a direct calorimetric measurement was approximately twice that determined from the variation of vapour pressure with temperature and applying the Clausius–Clapeyron equation[211]. Consequently, from the enthalpies of formation of the crystalline dialkylammoniumdialkyldithiocarbamates, their enthalpies of decomposition and the enthalpies of formation of the gaseous amines, the enthalpies of formation of the gaseous dithiocarbamic acids were derived as shown in Table 31. Comparison with values calculated using group parameters from Table 1 shows a large steric hindrance in di-isopropyldithiocarbamic acid. For alkanes derived by replacing the $[HS_2CN\diagup\diagdown]$... by $[CH_3CH\diagup\diagdown]$, the steric strain energies in these corresponding alkanes according to Skinner[216] are for R = Et, 4.0; n-Pr, 4.0; *i*-Pr, 17.4;

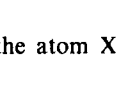
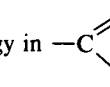
TABLE 31. Dialkyldithiocarbamic acids (HS_2CNR_2): quantities in kJ mol^{-1} at 298.15 K

R	$\Delta_f H^\circ_m$(cr) $R_2NH_2S_2CNR_2$	$\Delta_{dec.} H^\circ_m$	$\Delta_f H^\circ_m$(g) R_2NH	$\Delta_f H^\circ_m$(g) HS_2CNR_2	Calc.
Et	-249.2 ± 2.2	209.9 ± 2.8	-72.5 ± 1.2	33.2 ± 3.8	30.0
n-Pr	-353.2 ± 1.3	221.9 ± 3.6	-116.1 ± 0.5	-15.2 ± 3.9	-11.4
i-Pr	-349.6 ± 1.3	187.7 ± 1.0	-144.0 ± 0.5	-17.9 ± 1.7	-39.2
i-Bu	-463.8 ± 1.4	217.0 ± 1.8	-179.2 ± 0.7	-67.6 ± 2.4	-72.5

i-Bu, 2.8 kJ mol^{-1}. Hence the enthalpies of formation of $R_2NCS_2H(g)$ do fall into an expected pattern.

XII. RESONANCE ENERGIES IN ACYL DERIVATIVES

It is well known that a consequence of π-electron delocalization in benzene is that the enthalpy of formation of gaseous benzene is lower than that estimated for a Kekulé structure: the difference is known variously as the π-delocalization energy, π-stabilization energy, or it may however be called by the original term, resonance energy. Although the enthalpy of formation of benzene is a definite quantity, the enthalpy of formation of a Kekulé structure depends on the assumptions made in its calculation, i.e. what are the appropriate values to use for the bond energies in a Kekulé structure. The ambiguities in these procedures cannot be definitely resolved so that the value of the empirical resonance energy depends primarily on the assumptions made in calculating the enthalpy of formation of a Kekulé or localized structure. It is generally accepted that the empirical resonance energy of benzene is *ca* 150 kJ mol^{-1} as derived from the difference in the enthalpies of hydrogenation of benzene and of three cyclohexene molecules.

In carboxylic acids and acyl derivatives the π-electrons of the carbonyl bond can interact with the lone pair electrons in the atom X in  , and the consequent delocalization should also lead to a 'resonance energy' so that the question arises as to the most reasonable way to calculate this quantity and what is its magnitude. The group parameters in Table 1 account for the interactions of neighbouring bonds and hence automatically include the resonance energy in  .

Simple bond enthalpies are required and these are derived from the enthalpy of atomization of a molecule, $\Delta_a H$, i.e. the enthalpy change for

$$\text{Compound (gas)} \longrightarrow \text{Atoms (ground state, gas)}$$

$$\Delta_a H = \Sigma \Delta_f H^\circ_m \text{ (atoms, gas)} - \Delta_f H^\circ_m \text{ (compound, gas)}$$

The enthalpies of formation of the gaseous atoms that were used, in kJ mol^{-1}, are: C, 716.67 ± 0.44; H, 218.00 ± 0.01; O, 249.17 ± 0.10; N, 472.68 ± 0.40; S, 276.98 ± 0.25; F, 79.39 ± 0.30; Cl, 121.30 ± 0.01; Br, 111.86 ± 0.12; I, 106.76 ± 0.04. In general,

$$\Delta_a H = \Sigma \text{ bond enthalpies} - \text{strain energy} + \text{stabilization energy}$$

To derive bond enthalpies we select those molecules for which it is reasonable to assume absence of strain energy and of stabilization energy. As far as possible we select molecules in which the bonds are each in an environment close to that in the molecule under consideration, however this can never be completely achieved because if the matching of environments were exact, then the molecule from which the bond enthalpy was being derived would also exhibit π-electron delocalization. As the prime purpose of deriving 'resonance energies' is a qualitative one, to demonstrate the energy effect of electron delocalization, the simplest procedures, consistent with reasonableness, are the best to use.

The only molecule containing (C=S) not subject to interactions from other groups is thioformaldehyde for which, from mass spectroscopic electron impact measurements[212], $\Delta_f H^\circ_m(g)/(\text{kJ mol}^{-1}) = (100 \pm 11)$, and to maintain reasonable comparison, E(C=O) was derived from the enthalpy of formation of formaldehyde. The bond enthalpies are listed in Table 32 together with the 'resonance energies' for selected acyl

TABLE 32. Resonance energies in acyl derivatives

Bond enthalpies/(kJ mol^{-1})

E(C—C) 358.46	E(C_b—C) 371.21	E(C—N) 303.84	E(C—I) 229.51
E(C—H)$_p$ 411.26	E(C_6H_5-) 5104.53	E(N—H) 382.37	E(C=S) 514.85
E(C—H)$_s$ 407.40	E(C=O) 695.61	E(C—F) 457.94	E(C—S) 293.98
E(C—H)$_t$ 404.30	E(C—O) 353.50	E(C—Cl) 344.17	E(S—H) 360.48
E(C_b—H) 420.61	E(O—H) 451.68	E(C—Br) 286.82	

Resonance energies/(kJ mol^{-1})

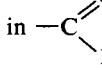
	$\Delta_f H^\circ_m$(g)	$\Delta_a H$(obs.)	$\Delta_a H$(calc.)	R.E.
HCOOH	−378.8 ± 0.4	2029.8	1905.1	124.7
CH_3COOH	−432.7 ± 1.5	3236.4	3093.0	143.5
$HCOOCH_3$	−357.5 ± 0.6	3161.2	3040.7	120.5
CH_3COOCH_3	−413.7 ± 0.7	4369.7	4228.6	141.1
$(CH_3CO)_2O$	−573.5 ± 1.4	5495.7	5282.7	213.0
CH_3CONH_2	−238.3 ± 0.9	3483.5	3356.4	127.1
CH_3COF	−442.1 ± 3.3	2858.0	2745.8	112.2
CH_3COCl	−251.4 ± 0.5	2709.2	2632.0	77.2
CH_3COBr	−196.0 ± 0.4	2644.4	2574.7	69.7
CH_3COI	−130.5 ± 1.2	2573.8	2517.4	56.4
CH_3COSH	−170.4 ± 4.1	3001.9	2942.3	59.6
$CH_3COSC_2H_5$	−228.2 ± 0.9	5365.0	5282.9	82.1
C_6H_5COOH	−295.4 ± 0.2	7103.9	6976.5	127.4
$C_6H_5CONH_2$	−100.9 ± 1.2	7365.4	7239.9	125.5
C_6H_5COCl	−103.2 ± 4.2	6578.1	6515.5	62.6
C_6H_5COBr	−48.7 ± 6.3	6516.4	6458.2	58.2
C_6H_5COI	11.9 ± 5.1	6450.7	6400.9	49.8
CH_3CSNH_2	12.7 ± 1.2	3260.3	3175.7	84.6
$C_6H_5CSNH_2$	103.4 ± 2.2	7144.6	7059.2	85.4
$(C_2H_5)NCSSH$	33.2 ± 3.8	6974.8	6894.9	79.9
$(NH_2)_2CO$	−245.6 ± 2.1	3028.8	2832.8	196.0
$(NH_2)_2CS$	22.9 ± 1.6	2788.1	2652.0	136.1

compounds. (C—H) bonds have been distinguished depending on whether they are primary (C—H)$_p$ in —CH_3, secondary (C—H)$_s$ in —CH_2—, tertiary (C—H)$_t$ in >CH—, aromatic (C_b—H) in C_6H_5—H. The value for E(C_6H_5—) was derived from the enthalpy of formation of benzene and includes the resonance energy of benzene, so that the resonance energies given for the aromatic acyl derivatives do not include that of the phenyl group.

The resonance energies of acyl derivatives show that:

(a) Resonance energies in acyl derivatives are of a similar order of magnitude to those in benzene derivatives, yet π-electron delocalization in benzene derivatives has always received much more attention than that in acyl derivatives. This lack of attention is surprising in view of the great importance of acyl derivatives in carboxylic acids, amino acids and peptides in biological chemistry.

(b) The order of the resonance energies in , for OH > NH_2 > F > Cl > Br > I = SH, seems sensible.

(c) The resonance energy in is much less than in  , quite in accord with chemical behaviour.

(d) Urea[104] and thiourea[106] were included in Table 32 and these show that where there are two sets of lone pair electrons able to interact with the π-electrons of the (C=O) or (C=S) bond, as is to be expected, the resonance energy is enhanced.

Thus viewing the thermochemistry of acyl derivatives from the point of view of their 'resonance energies', the results do fall into an expected and satisfying pattern.

XIII. DISSOCIATION ENTHALPIES IN ACYL DERIVATIVES

The dissociation enthalpy of the (C—X) bond in an acyl derivative is defined as $\Delta_f H^\circ_m$ for the process

$$RCOX(g) \longrightarrow RCO(g) + X(g)$$

and some values for acetyl derivatives are given in Table 33 together with corresponding values for $D(CH_3—X)$. $D(C—X)$ for ethanoic acid and ethanamide are both greater than $D(C—X)$ in the corresponding methyl derivatives, whereas for X = Cl the values are equal and for the remaining derivatives, X = Br, I, and SH, $D(C—X)$ in the acetyl derivative is smaller than in the corresponding methyl compound.

TABLE 33. Dissociation enthalpies in acyl derivatives: quantities in kJ mol^{-1}

CH_3COX	$\Delta_f H^\circ_m(X)$	$D(CH_3CO—X)$	$D(CH_3—X)$
CH_3COOH	33.9 ± 1.0[213]	442.3 ± 2.4	387.0 ± 1.2
CH_3CONH_2	182 ± 2[214]	396.0 ± 2.7	351.3 ± 2.1
CH_3COF	79.4 ± 0.3[213]	497.2 ± 3.7	
CH_3COCl	121.3 ± 0.1[213]	348.4 ± 1.7	349.5 ± 0.8
CH_3COBr	111.9 ± 0.1[213]	283.6 ± 1.7	293.7 ± 1.3
CH_3COI	106.8 ± 0.1[213]	213.0 ± 2.0	238.4 ± 1.4
CH_3COSH	146.4 ± 1.3[215]	292.5 ± 4.6	315.6 ± 1.6

A simple explanation can also provide a demonstration of the effects of resonance energies in these molecules. If the resonance energy in the molecule RCOX is greater than that in the radical RCO·, and apart from this the (C—X) bonds were the same in RCOX and RX, then we would expect $D(RCO—X) > D(CH_3—X)$, whereas if the reverse applied then the opposite order of dissociation enthalpies would be observed. Since the two dissociation enthalpies are approximately equal for CH_3COCl and CH_3Cl, this suggests that the resonance energy in the radical $CH_3CO·$ would be the same as that in CH_3COCl, i.e. 77 kJ mol^{-1}. $D(C—H)$ in acetaldehyde is 359.8 ± 2.5 kJ mol^{-1} and $D(CH_3—H)$ is 438.7 ± 0.6 kJ mol^{-1} [200]; and if the difference is ascribed to the resonance energy of the $CH_3CO·$ radical, then this gives 79 kJ mol^{-1} for the resonance energy in $CH_3CO·$, consistent with the previous interpretation.

Although this very simple explanation satisfactorily accounts for the observed results and in essence encompasses the main factor involved, it must be regarded as an approximation to the truth and a complete explanation would require detailed theoretical calculations.

XIV. CONCLUSIONS

One can generally conclude that the thermochemistry of carboxylic acids and their derivatives is extensive and interesting. It is somewhat surprising that a critical examination of the results reveals only a small fraction of the total reported work, certainly less

than five per cent, to be of doubtful quality and this in spite of the fact that a significant portion of the work was done about half a century ago. The overall high quality of the work gives great credit to those who have carried it out.

There are sufficient data for the derivation of the parameters in the group scheme to be made with confidence, hence this scheme will be useful for the prediction of unknown enthalpies of formation in the gaseous state. To estimate for the liquid or solid state requires guessing the enthalpies of vaporization or sublimation, but fortunately these are generally not large quantities and reasonable estimates are possible by comparison with values given in the tables for similar molecules. It is to be expected that in the future, refinements of molecular mechanics methods and *ab initio* calculations will make these methods more useful for the estimation of unknown enthalpies of formation.

Two areas of general interest in the thermochemistry of carboxylic acids and derivatives would benefit from further attention: these are halogen substituted compounds and amino acids and peptides. It would appear that application of thermochemical measurements to compounds of importance in biology and biochemistry has not received the attention this important topic merits. It is to be expected that future advances in this general area will be focussed on compounds of biological significance.

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CHAPTER 3

Chiroptical properties of acid derivatives

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I. INTRODUCTION

Chiroptical properties, and in particular circular dichroism (CD) spectroscopy, have been extremely useful in the elucidation of the configurational relations among naturally occurring substances. A considerable portion of these efforts have been directed to carboxylic acids and their simple derivatives, such as esters, lactones, amides, lactams, and their thio analogues.

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After a period of intense activity following the introduction of good commercial CD spectrometers some 30 years ago, the interest in CD spectra of carboxylic acid derivatives has gradually waned in the last decade. This may be a natural consequence of a certain 'saturation' on the level of sector rules, leading one reviewer to consider the field of carbonyl CD to be virtually complete with respect to data-gathering and empirical interpretation[1]. However, there are signs that a revitalization of this field, and of CD studies in general, is to be expected, and some of the factors responsible for this may be:

1. Synchrotron radiation and new commercial instruments allow measurements to shorter wavelengths than earlier, to 140 nm or lower with synchrotron radiation, to 170 nm with standard instruments[2].

2. Methods for theoretical calculations of rotational strengths have been considerably improved[3].

3. The almost explosive development of enantiomer separations by chromatography on chiral stationary phases has made a wide selection of optically active model compounds easily available[4,5].

4. While the rationalization of CD spectra of flexible molecules earlier encountered considerable difficulties, the increasing perfection of empirical force-field[6,7] and quantum-chemical (AM1[8], *ab initio*[9]) calculations of conformer geometries and conformational energies has placed work in this field on a safer basis.

The introduction to the CD field is facilitated by the publication of excellent reviews[10–12] and monographs[13–15]. A special issue of a journal gives a good picture of the state of the art in 1988[16].

The literature on chiroptical properties of carboxylic acids and their derivatives was reviewed up to 1977 in this series[17]. The present review will deal with works published up to 1990 with a few from 1991. It is not intended to be exhaustive but rather to focus on some important developments. Only studies in which the electronic transitions of carboxyl or modified carboxyl groups play an important role will be included. Proteins and peptides except for dipeptides will not be treated, nor will the important field of vibrational CD spectroscopy.

The electronic properties of the unconjugated carboxylic acid and modified carboxyl groups have been treated in previous volumes of this series[18,19]. Only one transition is observed in the near-UV region, the $n \rightarrow \pi^*$ transition of the C=O group, which appears in the wavelength range 205–225 nm for carboxylic acids, esters and amides. It is an electrically forbidden transition, weak in isotropic spectra but often with substantial intensity in CD spectra. At least two other bands appear in the vacuum-UV region, one of which is assigned to a $\pi \rightarrow \pi^*$ transition, falling in the range 175–200 nm. The other band, often in the neighbourhood of 170 nm, is variously assigned to a $n \rightarrow \sigma^*$ or a $n \rightarrow 3s$ Rydberg transition. In amides, conjugation between amino and carbonyl groups leads to a bathochromic shift of the $\pi \rightarrow \pi^*$ transition to the neighbourhood of 195 nm.

Spectroscopic studies of thione analogues of carbonyl compounds have a special interest in view of the similarities in electronic structure between the two classes of compounds. The differences in spectroscopic properties caused by exchange of oxygen for sulphur can be explained by the larger polarizability of sulphur and the smaller overlap between carbon and sulphur orbitals. Consequences of this are seen in UV spectra, which for simple thioamides display $n \rightarrow \pi^*$ bands near 350 nm, $\pi \rightarrow \pi^*$ bands near 270 nm and a third band above 200 nm. This band has been ascribed to a $n \rightarrow \sigma^*$ transition, but a recent *ab initio* random phase approximation (RPA) calculation[20] ascribes it to a transition from a lower sulphur n orbital with some C—S σ character (n_σ) to the lowest π^* orbital.

The interest in the spectroscopic properties of thiones has increased in recent time, partly as a result of the introduction of new efficient thionation reagents.

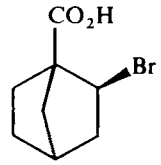
Pancoska *et al.*[21] have developed a mathematical technique, the modified factor

method, for resolution of CD spectra of a series of related chiral compounds into subspectra. The first subspectrum describes the common features of the spectra of the individual compounds, and the following subspectra, with positive or negative weight factors, the contributions due to structural variations and solvent effects. This technique may prove very helpful for analysis and interpretation of CD spectra, not least for flexible systems where several conformers are involved.

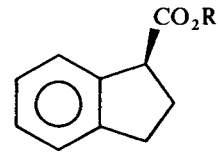
II. SIMPLE CARBOXYLIC ACID DERIVATIVES

A. Acids and Esters

The absolute configuration of (+)-2-*exo*-bromonorbornane-1-carboxylic acid (**1**) was established as (1*S*,2*S*) by X-ray structure analysis of the amide with (+)-(*R*)-phenylglycinol[22]. The diastereomeric amides formed from (+)-**1** were used for chromatographic resolution of **1**. The CD spectrum of (+)-**1** displays a $n \rightarrow \pi^*$ band at 215 nm ($\Delta\varepsilon = +1.10$). Under the assumption that the carboxylic carbonyl group eclipses the $C_{(1)}—C_{(7)}$ bond, the bromine atom is in a position similar to that in 3-bromocyclohexanone with axial bromine. Since bromine displays antioctant behaviour, chiroptical methodology leads to the same conclusion about the absolute configuration as the X-ray study.



(**1**)



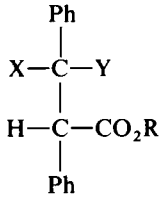
(**2a**) R = Me
(**2b**) R = H

The effect of homoconjugation on the CD spectra of α-arylcarboxylic acids and esters has been studied by two groups. Hansen *et al.*[23] have studied the solvent and temperature dependence of the CD spectrum of the methyl ester of (*S*)-indane-1-carboxylic acid (**2a**). Two bands with opposite signs observed in the range 220–235 nm were ascribed to slightly perturbed $n \rightarrow \pi^*$ transitions in two conformers. Both bands were observed in the spectrum in isopentane–methylcyclohexane at +60 °C, but on lowering the temperature, finally to −180 °C, the negative band disappeared and the positive band increased in intensity by a factor of 14. The differences in sign and intensity of the $n \rightarrow \pi^*$ bands of two conformers were discussed in terms of interaction between the benzene π orbitals and the n and π orbitals of the ester group. The form with negative $n \rightarrow \pi^*$ band dominates in methanol, the one with positive band in isooctane solution. The free acid, (*S*)-**2b**, shows a negative $n \rightarrow \pi^*$ band in both solvents, which is ascribed to dimer formation in isooctane, which favours the same rotamer as in methanol. Both rotamers, denoted I, (+), and II, (−), are assumed to have pseudoaxial carboxylic groups, with the C=O group eclipsing the $C_{(1)}—C_{(2)}$ bond in I and the $C_{(1)}—H$ bond in II.

In this connection, a dispute about the absolute configuration of **2b** was resolved. Already in 1956, Fredga[24] correlated (+)-**2b** with (−1)-(*R*)-2-phenylsuccinic acid. However, in 1979 Hansen *et al.*[25] pointed out that the assignment of (+)-**2b** to the (*R*) configuration was in contradiction to the assignment of the (*R*) configuration to (−)-1-methylindane[26], since this could be correlated with (−)-**2b**. Repetition of Fredga's work with circumvention of a possibly ambiguous step gave the same result, (+)-(*R*)-**2b**,

and the contradiction mentioned above was found to be due to an erroneous ORD spectrum of (−)-1-methylindane, which has in reality the (*S*) configuration[27].

Berova *et al.*[28] have studied similar chromophoric systems in 2,3-diphenylpropionic acid derivatives (**3**), where X and Y are hydrogen, amino or substituted amino groups, hydroxy or carboxy groups. Some mandelic acid derivatives were also included as simpler models. In compounds **3**, interaction between the aromatic ^1L_a[29] and higher-

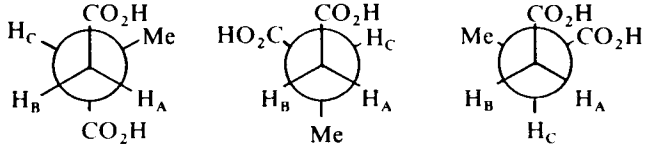


(**3**)

energy transitions may lead to strong CD absorption in the region around 220 nm, obscuring the $n \rightarrow \pi^*$ band of the carboxylic group. However, the $n \rightarrow \pi^*$ band, which may be quite strong due to homoconjugation to the 2-phenyl group, can be observed in the difference spectrum from **3** and the analogue, in which CO_2R is replaced by CH_2OH. This technique requires that the two compounds have the same conformations with respect to the phenyl groups. Direct observation of the $n \rightarrow \pi^*$ band was possible for a compound, for which the $n \rightarrow \pi^*$ and aromatic bands in the 220 nm region had opposite signs.

The sign and intensity of the $n \rightarrow \pi^*$ band depends on the relative orientation of the 2-phenyl and carboxyl groups. The effects of changing solvent and temperature were mostly moderate, indicating limited conformational mobility. The strongest effects were observed for mandelic acid derivatives, which can be expected to be more flexible than compounds **3**[30].

A strong conformation dependence of the CD spectrum is shown by 2-methylsuccinic acid (**4**)[31]. The pH dependence of the CD spectrum was studied by ^1H NMR spectroscopy. Two conformations, *anti* and *gauche*-(−), were considered, while *gauche*-(+) was expected to be too high in energy to be of interest. Analysis of the 360 MHz ^1H NMR



(**4**): *Anti* *Gauche*-(−) *Gauche*- (+)

spectra gave $J_{AC} = 10.1$ Hz and $J_{BC} = 5.0$ Hz at pH = 8.0 (dianion) and $J_{AC} = 5.3$ Hz and $J_{BC} = 9.1$ Hz at pH = 1.0 (diacid), and intermediate coupling constants at intermediate pH values. These results were interpreted to show that the dianion prefers the *anti* and the monoanion and diacid the *gauche*-(−) form. The CD spectrum of the (*S*)-acid showed a positive $n \rightarrow \pi^*$ band at high pH and a negative band at low pH, and bisignate curves at intermediate pH values (5–6). The authors discussed the possibility that the two bands are related to the two conformations, but they leave open the possibility of two kinds of transitions, $n_a \rightarrow \pi^*$ and $n_s \rightarrow \pi^*$ with opposite signs, the n_a and n_s states arising through interaction between the lone pair orbitals.

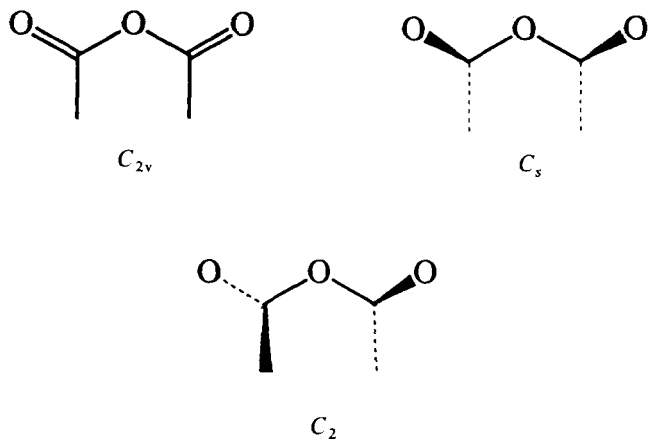


FIGURE 1. Conformations of the anhydride group in cyclic anhydrides

B. Cyclic Carboxylic Anhydrides and Imides

Snatzke and coworkers[32] have made a thorough theoretical and experimental analysis of the CD spectra of five- to seven-membered bicyclic anhydrides of known absolute configuration. Three conformations were considered for the O=C—O—C=O group: the achiral, planar C_{2v} form, the likewise achiral C_s form, in which the carbonyl oxygen atoms deviate in the same direction from the C—O—C plane, and the inherently chiral, twisted C_2 form (Figure 1). The analysis of the electronic transitions made use of CNDO[33] and *ab initio*[34] calculations and was based on the planar C_{2v} form, but it was expected to be valid also for moderately distorted forms. The MO diagram consists

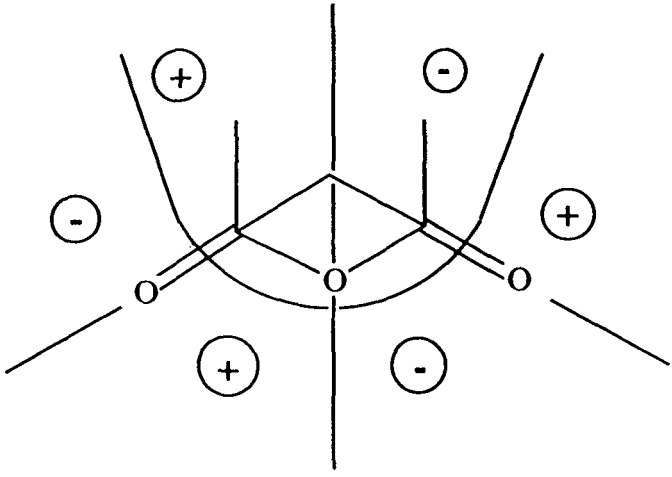
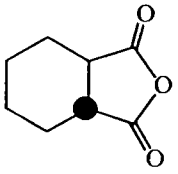


FIGURE 2. The 12-sector rule for n → π* transitions of cyclic anhydrides (upper sectors)[32]

of three bonding and two (π_4* and π_5*) antibonding π orbitals, and two lone pair orbitals (n_a and n_s), split by 0.8 eV by through-bond interaction[35]. The lowest excited state was described as mainly $n_a\pi_4$*, the following one as a low-energy combination of $n_s\pi_4$* and $n_a\pi_5$*, and the third as $\pi_3\pi_4$*. Experimentally, two weak ($|\Delta\varepsilon| < 2$) bands were observed, at 220 and 240 nm, of the same or opposite signs, and they were assigned to the two $n \rightarrow \pi^*$ type transitions discussed above. A 12-sector rule (Figure 2) was derived for the 240-nm band based on the calculated direction of the magnetic transition moment and the effect of static and/or dynamic perturbers to generate an induced electric transition moment in the same direction. A similar analysis led to a helicity rule for anhydrides of the C_2 form like *trans*-1,2-cyclohexanedicarboxylic anhydride (**5**). The 220-nm band should follow the same sector rule as the 240-nm band for planar anhydrides, but opposite signs for the two bands are predicted for C_2 anhydrides.



(**5**)

Sjöberg and Obenius[36] have studied a series of less rigid 2-alkylsuccinic anhydrides together with the *trans*-2,3-dimethyl analogue, all with known absolute configuration (*R* for primary and *S* for secondary 2-substituents). Most compounds showed two more or less well-resolved negative bands at 215 and 235 nm, the relative intensities of which varied with the solvent. This is in agreement with the sector rule discussed above, but two compounds deviated, the *trans*-2,3-dimethyl and the 2-cyclohexyl derivative, the first one showing a positive 215-nm band, and the second showing a weak negative couplet instead of the 235-nm band. Low-temperature spectra of the 2-ethyl and 2-isopropyl compounds in EPA showed bisignate spectra with opposite sign sequences at -185 °C. The authors give no final answer to the puzzles observed but they point out that equilibria between two twisted (C_2 type) conformations and solvation are important, but also that the spectra with two negative bands can in fact be generated by superposition of two Gaussians with opposite signs, a broad negative and a sharper positive band.

Polonski[37] has studied succinic anhydrides with alkyl, phenyl, hydroxy, alkoxy and ammonio substituents in 2(3) position. Empirical force-field calculations (MM2 with some new parameters) for some typical derivatives predicted moderately twisted conformations with pseudo-axial or pseudo-equatorial substituents. The 2-alkyl compounds were found to prefer the pseudo-equatorial and the 2-alkoxy compounds the pseudo-axial conformation.

Polonski rejected the 12-sector rule of Snatzke and coworkers[32] because it fails for some compounds, and instead proposed an octant rule (Figure 3), which should predict the signs for the 220- and 240-nm bands for both planar and twisted anhydrides, and which prescribes opposite signs for the two bands based on the opposite symmetries of the two transitions. The conformation of the ring (chiral second sphere)[10] is given greater weight than the orientation of the substituent (chiral third sphere). This rule gives generally correct results under the assumption that the quasi-axial form is favoured by bulky substituents and polar solvents.

Polonski[38] has also analysed the CD spectra of 3- and 3,5-substituted glutaric anhydrides (**6a,b**) and some bicyclic analogues (**7a,b**). The rigid compound **7a** with nearly

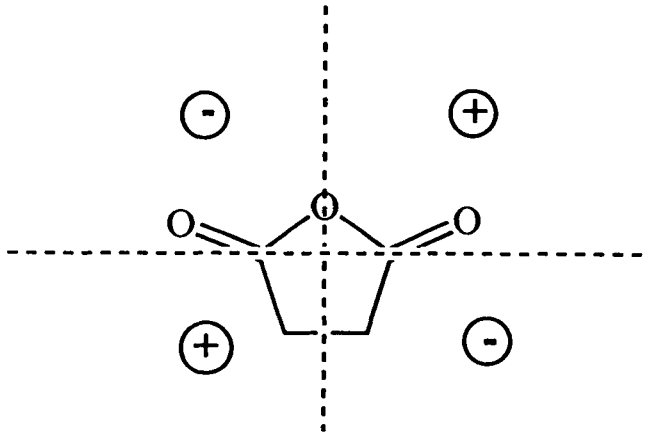
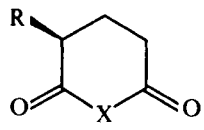
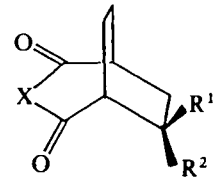


FIGURE 3. The octant-type sector rule (upper octants) for the lowest $n \rightarrow \pi^*$ transition of cyclic anhydrides and imides[37]

planar anhydride group gave a bisignate CD spectrum in agreement with the octant rule, whereas the isomer **7b** gave a broad positive maximum, indicating two weak bands of the same sign, less clearly explained by the octant rule. The monocyclic anhydrides **6a,b** were predicted by MM2 calculations to exist as mixtures of two sofa forms with C_{2v}-type anhydride groups and one twist-boat form with C_2-type anhydride group (Figure 4). The relative energies of these forms and their detailed geometries depend strongly on substituents and to some extent also on the solvent, which makes the application of the octant rule difficult.



(**6a**) R = Me, X = O
(**6b**) R = *t*-Bu, X = O
(**6c**) R = OH, X = NH
(**6d**) R = NH_3^+, X = NH
(**6e**) R = $NMeSO_2Me$, X = NH



(**7a**) R^1 = Me, R^2 = H, X = O
(**7b**) R^1 = H, R^2 = Me, X = O
(**7c**) R^1 = Me, R^2 = H, X = NH
(**7d**) R^1 = H, R^2 = Me X = NH

The electronic structure of the imide group is similar to that of the anhydride group, the UV and CD spectra of cyclic imides show two $n \rightarrow \pi^*$ type bands, the UV bands near 250 and 220 nm and the CD bands at slightly longer wavelengths. In the two works just discussed, Polonski[37,38] has also studied a number of cyclic imides, many of them analogues of the anhydrides. For the succinimides, the sign of short-wavelength $n \rightarrow \pi^*$ band was in general the same as for the related anhydride, but notable differences were observed. This was ascribed to conformational differences between the two classes of compounds.

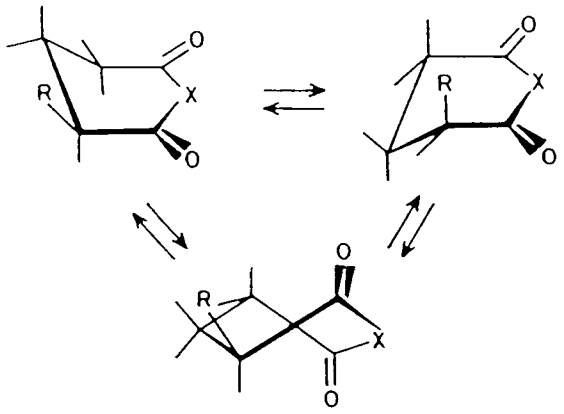


FIGURE 4. Conformations of glutaric anhydrides and glutarimides. Reproduced with permission from *J. Chem. Soc., Perkin Trans. 1*, 639 (1988)

For pairs of rigid bicyclic compounds, like **7a** and **7c** or **7b** and **7d**, the spectra are much more similar (Figure 5). Interesting information about the conformations of glutarimides was obtained from compounds **6c–e**. For **6c** and **6d** hydrogen bonding locks the twist-boat form with axial substituent, and the corresponding CD spectra show strong positive bands at 250 nm but very weak bands at 230 nm. For **6e** a sofa form dominates, leading to a bisignate CD spectrum. Analogues for which both forms are of importance may show a variety of spectra, also such with two bands of the same sign.

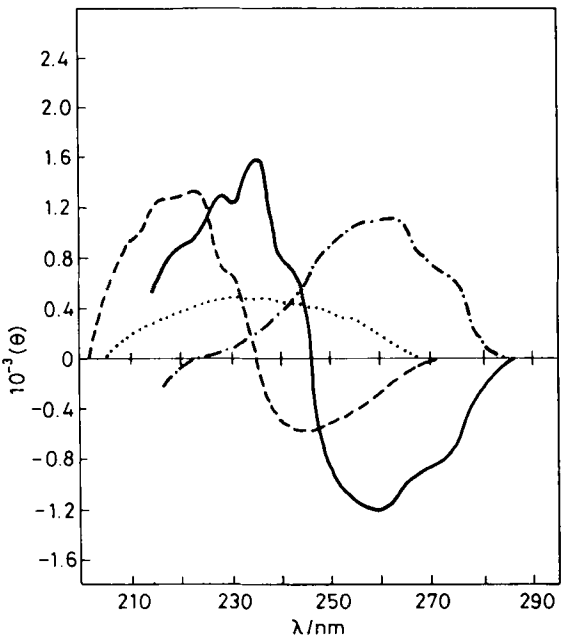


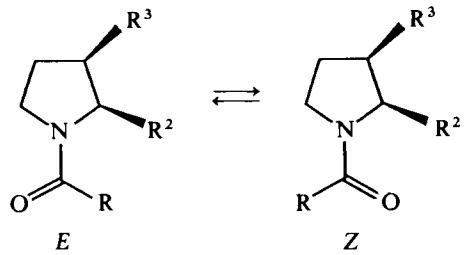
FIGURE 5. CD spectra of **7a** (- - - - -), **7b** (· · · · ·), **7c** (———) and **7d** (- · - · -) in cyclohexane–dioxane (4:1). Reproduced with permission from *J. Chem. Soc., Perkin Trans. 1*, 639 (1988)

To conclude, the problem of the CD spectra of cyclic anhydrides and imides is complicated by the conformational diversity of these compounds. This also makes it difficult to evaluate the respective merits of the 12-sector rule[32] and the octant rule[37]. The former rule is theoretically sound for the long-wavelength transition with proper reference to the nodal properties of the orbitals involved, while the 12-sector rule for the short-wavelength transition and the octant rule have more *ad hoc* character. For both rules the shape of the surfaces separating front and back sectors is a source of uncertainty.

III. AMIDES, LACTONES AND LACTAMS

A. Simple Amides

The effect of *E,Z* isomerism on CD spectra of 2- and 3-substituted *N*-acylpyrrolidines (**8**) has been studied by Ringdahl *et al.*[39]. According to ^{1}H NMR spectra the formyl derivative **8a** is predominantly *E*, and the acetyl derivative **8b** predominantly *Z*. On lowering the temperature, the intensity of the positive $n \rightarrow \pi^*$ band near 230 nm decreased for **8a** and increased for **8b**, which indicates that the rotational strength is weaker for the *E* than for the *Z* form. The pivaloyl compound **8d**, which is entirely *Z*,



E *Z*

(**8a**) R = R^3 = H, R^2 = Me
(**8b**) R = R^2 = Me, R^3 = H
(**8c**) R = R^3 = Me, R^2 = H
(**8d**) R = *t*-Bu, R^2 = Me, R^3 = H
(**8e**) R = Me, R^2 = Ph, R^3 = H
(**8f**) R = Me, R^2 = H, R^3 = Ph
(**8g**) R = *t*-Bu, R^2 = Ph, R^3 = H

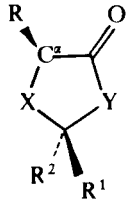
showed a stronger positive $n \rightarrow \pi^*$ band at ambient temperature, but at -196 °C it had changed to an even stronger negative band. This can hardly be ascribed to a change in the *E–Z* equilibrium but was discussed in terms of nonplanarity of the amide group.

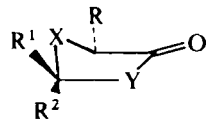
The phenyl-substituted compounds **8e–8g** displayed strong ^1L_a bands in the range 206–212 nm with negative sign as expected for coupling with the amide $\pi \rightarrow \pi^*$ transition in the *Z* form.

Cohen and Stevens[40] have extended an earlier work on $n \rightarrow \pi^*$ transitions in *N*-acetylglucosamines by calculation of the rotational strength as a function of the orientation of the 1- and 3-hydroxy groups, using the one-electron mechanism[41]. The results were used to rationalize solvent effects and may also be useful for interpretation of CD spectra of glycosaminoglycans.

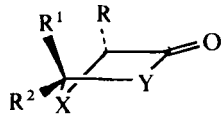
B. Lactones and Lactams

Polonski has published a series of papers[42–45] on the conformations and CD spectra of a series of similar five-membered lactones and lactams, containing a second heteroatom in the ring (**9–12**). The purpose of the study was to compare CD spectra of lactones and lactams with similar stereochemistry, derived from α-hydroxy- or α-aminocarboxylic acids with known stereochemistry (*S*). The stable conformations for these compounds are of envelope type with the $C_2—Y—CO—C^{\alpha}$ moiety in one plane and X above or below this plane. A higher-energy conformer with planar ring (B) was also considered for **9** and **10** on the basis of CNDO/2 calculations[42]. The envelope conformation can appear in two forms, with equatorial (E) and axial (A) C^{α}-substituent. As is seen later, the B form should probably be replaced by the A form. The E form is favoured for **9** and **10**, while bulky substituents on N_x in **11** and **12** cause A to be favoured, except when R^1 is bulky. Polar solvents increase the population of A when $X = NSO_2Me$ due to the increased bulk of the solvated sulphonyl group.



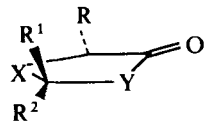


(E)



(A)

(**9**) X = Y = O
(**10**) X = O, Y = NR
(**11**) X = NR, Y = O
(**12**) X = Y = NR



(B)

The CD spectra of **9–12** display either one band, mostly on the short-wavelength side in the 200–250-nm range, or a relatively strong band on the short-wavelength side and a weaker band of opposite sign at longer wavelengths. Some typical CD spectra are shown in Table 1. The spectra were interpreted with aid of the sector rule for $n \rightarrow \pi^*$ transitions in lactones and lactams proposed by Weigang and coworkers[46]. This rule predicts a negative $n \rightarrow \pi^*$ band for the E form of **9a** provided that higher weight is given to a ring element than to a substituent in accordance with the hypothesis of chiral spheres by Snatzke[10], and a positive band for the B form. The two bands shown by **9a** in cyclohexane were thus ascribed to the presence of both E and B forms, while the latter was favoured in methanol. Bulky R^1 lead to dominance of the E form (**9b, 9c**), while a bulky R^2 group (**9d**) was assumed to favour the B form, in agreement with the observed signs.

The sector rule[46] requires opposite signs for the $n \rightarrow \pi^*$ band of lactones and lactams with the same stereochemistry. Thus, a positive band was predicted for the E form of **10** and a negative band for the B form. The E form was assumed to dominate in **10a**. The increased band intensity in methanol was ascribed to increased puckering of the E form in the polar solvent, while the decreased intensity for **10b** should reflect increased population of the form B due to destabilization of the E form by the bulky substituents.

In compounds **11** and **12** repulsion between the C^{α} substituent and the bulky X group was expected to favour the envelope form with axial R (A). The positive band at 216 nm in the spectrum of **11a** was assigned to the $n \rightarrow \pi^*$ transition in the A form, but the weak negative band at long wavelength was not assigned to the E form ($\Delta\varepsilon < 0$), since

TABLE 1. CD spectra of lactones and lactams **9**–**12**[42–45]

Compound	λ_{extr} nm ($\Delta\varepsilon$) in C_6H_{12}	Form[a]	λ_{extr} nm ($\Delta\varepsilon$) in MeOH	Form[a]
(**9a**) R = Me, $R^1 = R^2 = H$	206 (−0.06)	E		
	233 (+0.05)	B	224 (+0.18)	B
(**9b**) R = Me, $R^1 = R^2$ = Et	213 (−0.33)	E	213 (−0.20)	E
(**9c**) R = *i*-Pr, R^1 = *t*-Bu, R^2 = H	219 (−1.21)	E	219 (−1.09)	E
(**9d**) R = *i*-Pr, R^1 = H, R^2 = *t*-Bu	226 (+0.57)	B	223 (+0.62)	B
(**10a**) R = Me, $R^1 = R^2$ = H, Y = NMe	225 (+0.85)	E	219 (+1.28)	E
(**10b**) R = Me, $R^1 = R^2$ = Et, Y = NH	227 (+0.37)	E	220 (+0.70)	E
(**11a**) R = Me, $R^1 = R^2$ = H	216 (+1.06)	A	213.5 (+1.22)	A
X = NSO_2Me	255 ($-6 \cdot 10^{-4}$)	*E*	254 ($-1.8 \cdot 10^{-3}$)	E
(**11b**) R = R^1 = Me, R^2 = H	214 (+1.81)	A	212.5 (+1.96)	A
X = NSO_2Me				
(**12a**) R = Me, $R^1 = R^2$ = H	205 (+3.5)		205 (+4.5)	
X = NSO_2Me, Y = NMe	240 (−0.22)	A	235 (−0.13)	A
(**12b**) R = Me, $R^1 = R^2$ = Et	222 (+0.49)	E	216 (+2.2)	E
X = NSO_2Me, Y = NH				
(**12c**) R = *i*-Pr, $R^1 = R^2$ = H	235 (−0.65)	A	234 (−0.28)	A
X = NSO_2Me, Y = NMe				

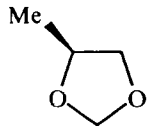
[a] Conformer to which the respective bands are assigned.

it was expected to have its absorption maximum at the same wavelength as the A form. Instead, a third, possibly planar conformer with negative $n \rightarrow \pi^*$ band was proposed. However, the appearance of a negative residue could also be explained by a difference in band-width (and/or wavelength of absorption maximum) between the $n \rightarrow \pi^*$ bands of the A and E forms.

The spectrum of **12a** shows a strong positive band at 205 nm, which was explained as the low-energy component resulting from interaction between the amide and sulphonamide $\pi \rightarrow \pi^*$ transitions. The negative band at longer wavelength was ascribed to the $n \rightarrow \pi^*$ transition of the dominant A form. The increased repulsion between R and R^1 in **12b** should lead to a predominance of the E form ($\Delta\varepsilon > 0$), while increase of the size of only R in **12c** should change the equilibrium back to a dominance of the A form.

In a more recent work, Gedanken and Polonski[47] have studied the vacuum UV isotropic and CD spectra of **9a** and **9b** and some analogues in the gas phase. Molecular mechanics calculations predicted two energy minima, the E and A forms discussed above, but not the planar B form previously[42,43] suggested for **9** and **10**. The CD spectrum of **9a** showed a positive $n \rightarrow \pi^*$ band at 227 nm ($\Delta\varepsilon = +1.2$), assigned to the A form, and a negative band ($\Delta\varepsilon = -0.7$) at 204 nm for the E form. The analogues with larger R and/or R^1 were calculated to have a larger population of the E form and showed only one $n \rightarrow \pi^*$ band ($\lambda_{max} = 205$ nm, $\Delta\varepsilon = -0.4$ to -0.6).

In the range 160–200 nm, all compounds showed CD bands at 180–182 and 161–165 nm; **9a** also showed a band at 173 nm. These bands were assigned to Rydberg-type transitions from the diether moiety to 3s, 3p and 3d levels, since quite analogous bands were observed in the spectrum of 4-methyl-1,3-dioxolane (**13**). No UV or CD band, which can be ascribed to a $\pi \rightarrow \pi^*$ transition in the ester group, has been observed at $\lambda > 160$ nm.

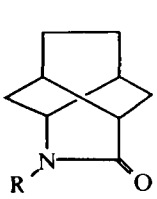


(13)

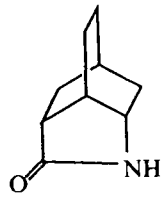
Meguro *et al.*[48,49] have used the Krönig–Kramer transform technique to extract information about CD bands in the vacuum UV region from ORD spectra recorded in the range 300–600 nm. In this way a band was found at 170 nm for chiral γ-lactones, which was split into contributions from the C=O group and the ring oxygen atom. The signs of these contributions were related to the absolute configurations at $C_{(2)}$ and $C_{(4)}$ and to the ring conformation.

C. Lactams with Non-planar Amide Groups

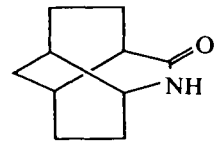
Much work has been directed to studies of systems with non-planar amide groups, inherently chiral chromophores, which may contribute in important ways to the CD spectra of crowded proteins and peptides. Blaha's group in Prague has synthesized and studied several rigid lactam systems containing more or less deformed amide groups[50–54]. The monoamides **14–17** have been prepared with known absolute configuration. X-ray crystallographic studies have been performed for **14a**, **15**[50] and **17**[51], whereas the structure of **16** was estimated from a Dreiding model[52]. The deformation was measured by the dihedral angles $\Delta\omega$, θ_N and θ_C (Figure 6, Table 2), where θ_N measures the pyramidality of the nitrogen atom. The signs of $\Delta\omega$ and θ_N are correlated, and often the simplified expression $\theta_N = -2\Delta\omega$ could be used[55]. The CD spectra of the



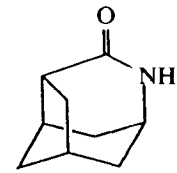
(**14a**) R = H
(**14b**) R = Me
(3*S*, 5*S*)



(**15**)
(3*S*)



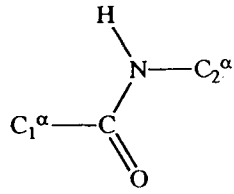
(**16**)
(1*R*)

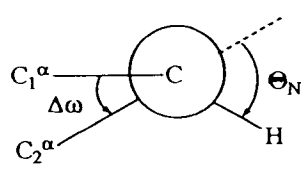


(**17**)
(3*R*)

five compounds display relatively strong n → π* bands in the range 228–230 nm (solvent cyclohexane) and π → π* bands with opposite signs in the range 192–205 nm (Table 3). Compounds **14** and **15** also showed a shoulder between these bands with the same sign as the n → π* band. This may correspond to a 'mystery band' observed earlier in CD spectra of simple amides[56] and following *ab initio* calculations assigned to a n → 3s Rydberg-type transition[57]. Although the n → π* transition of **15** with nearly planar amide group is stronger than in 'normal' chiral amides, it is considerably weaker than for the structurally similar compounds **14**. The rotational strength of the n → π* transition of **15** may be attributed mainly to the one-electron effect[41]. The sign obeys the Schellman quadrant rule for amides[58]. For the other compounds, the non-planarity of the amide group dominates the rotational strength of the n → π* and π → π* transitions. The comparison between **14a** and **16** is particularly instructive. Their carbon skeletons have the same senses of twist, but the $\Delta\omega$ values have opposite signs, and so have the corresponding CD bands. Evidently the twist sense determines the signs of the CD bands.

Several semiempirical quantum-chemical calculations of rotational strengths of non-planar amides have been reported. The Prague group used a CNDO/S-CI method based on the procedure of Gould and Hoffmann[59] for calculations on **14a** and **14b** and found agreement in sign and reasonable agreement in magnitude for the rotational strengths





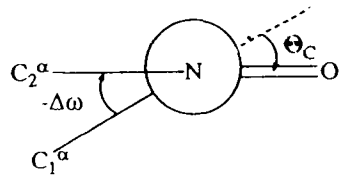


FIGURE 6. Specification of angles $\Delta\varepsilon$, θ_N and θ_C, defining amide group non-planarity

TABLE 2. Deformation angles (deg) for the non-planar lactams **14-17**

Compound	$\Delta\omega$	θ_N	θ_C	Reference
14a	−14.5	+14.1	+5.0	50
15	+1.2	+10	+2	50
15	+1,2	+10	+2	50
16	+14.5	−15		52
17	+14.7 − +18.2	−10.7	+4.8	51

of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions[60]. According to model calculations on several non-planar conformations of formamide, torsion alone about the C(=O)—N bond gives the same sign to the rotational strengths of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, whereas simultaneous torsion about the C—N bond and pyramidalization of the nitrogen atom gives opposite signs, positive $n \rightarrow \pi^*$ and negative $\pi \rightarrow \pi^*$ transitions for positive $\Delta\omega$, in agreement with experiments[61]. Similar calculations on the *E* and *Z* forms of non-planar *N*-methylacetamide, including solvent effects, led to qualitatively equivalent results[62].

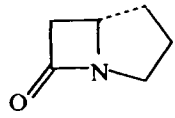
Boyd and coworkers[63] have studied the CD spectrum of 1-carbapenam (**18**) as a simple model for penicillins, and could reproduce its $n \rightarrow \pi^*$ transition, using EHT or CNDO/S wave functions. In this work the 'mystery band' mentioned above is also discussed. Although a Rydberg type of transition is dismissed for solution spectra, no alternative is proposed.

Woody[64] has developed a general perturbation method for the treatment of non-planar amides. Taking wave functions for a planar amide as the zero-order wave functions and modifying the matrix elements for deviation from planarity in terms of

TABLE 3. CD spectral data for the non-planar lactams **14–17**

		λ_{extr} nm ($\Delta\varepsilon$)[a]		
Compound	Solvent	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$	Other[b]
14a[53]	C_6H_{12}	232 (−9.2)	197 (+9.5)	215 (−2.3)
	MeCN	228 (−11.2)	196 (+10.1)	216 (−1.2)
	MeOH	219 (−11.7)	196.5 (+7.7)	
14b[54]	C_6H_{12}	230 (−11.5)	205 (+17.1)	218 (−3.0)
	MeCN	226.5 (−15.2)	205.5 (+20.3)	
	MeOH	219.5 (−10.0)	203 (+13.8)	
15[50]	C_6H_{12}	228 (−4.27)	192 (+18.8)	204 (−0.7)
	MeCN	226 (−5.6)	193 (+20.6)	
	MeOH	216 (−7.5)	195 (+20.3)	
16[52]	C_6H_{12}	230.5 (+5.1)	200 (−15.8)	
	MeCN	226 (+6.4)	200 (−15.3)	
	MeOH	218 (+8.6)	200 (−13.8)	
17[51]	C_6H_{12}	230 (+6.9)	198 (−0.1)	
	MeCN	226 (+10.3)	197 (−4.7)	
	MeOH	218 (+13.0)	<190	

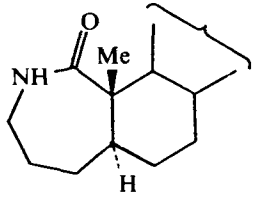
[a] After curve resolution.
[b] 'Mystery band.'



(18)

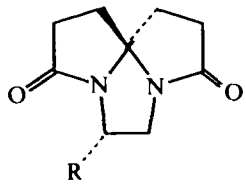
$\Delta\omega$ and θ_N, he could derive explicit expressions for the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ rotational strengths as functions of the deviation angles. It was found important to use a wave function for the carbonyl lone pair delocalized over the carbonyl group. The method is useful to analyse the effects of non-planarity of amide groups on the CD spectra of proteins and peptides.

Monocyclic seven-membered lactams are known to assume *quasi*-chair conformations with nearly planar amide groups ($\Delta\omega = \pm 4.2°$ in ε-caprolactam)[65]. Klyne's group[66] has studied a large number of seven-membered lactams *cis*- and *trans*-fused with cyclohexane rings in 3,4-, 4,5-, 5,6- and 6,7-positions. Several of the compounds showed signs for the $n \rightarrow \pi^*$ transition in agreement with Ogura's rule (see Reference 17, p. 81), while others showed opposite signs and, in some cases, much higher intensities than expected and absorption at longer wavelength. Such deviations were found for compounds fused in 3,4- and 6,7-positions and were ascribed to deviations from planarity of the amide group. For 2-aza-A-homo-5α-cholestan-1-one (**19**) $\Delta\omega = -20°$ was found by X-ray crystallography[67]. Instead of the expected $\Delta\varepsilon$ value near +3, a value of −11.1 was observed, in agreement with the sign of the twist angle.

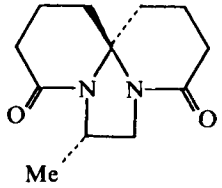


(19)

The Prague group has studied several chiral di- and polycyclic dilactams. Some of these are formally dipeptides and will be discussed in Section IV.B, but compounds **20**[68,69] and **21**[70] will be treated here. The CD spectra of compounds (+)-**20** and (+)-**21** showed two positive bands at $\lambda > 200$ nm and negative absorption at shorter wavelengths. Both groups of compounds have non-planar amide groups, compound (+)-**20**



(**20a**) R = H
(**20b**) R = Me
(**20c**) R = *i*-Bu



(**21**)

with $\Delta\omega = +11°$[71], $\theta_N = -32°$ and (+)-**21** with about half of this deformation. The interpretation of the CD spectra is the same for the two groups of compounds. The signs of the $n \rightarrow \pi^*$ transitions are determined by the sense of non-planarity of the individual amide groups, while the $\pi \rightarrow \pi^*$ transitions are dominated by the exciton mechanism and give positive couplets for the (+)-compounds. A CNDO/S calculation for (−)-**20a** gave correct signs for the three first transitions[68].

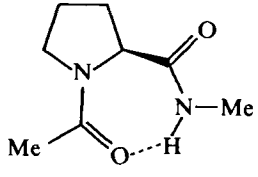
A different kind of non-planarity is encountered in chiral *N*-acylaziridines, for which the pyramidal nitrogen atom leads to a sign for the $n \rightarrow \pi^*$ transition, which is opposed to that predicted by the sector rule[72].

IV. AMINO ACIDS AND DIPEPTIDES

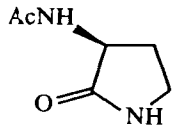
A. *N*-Acylamino Acid Derivatives

CD studies of small peptide building blocks have continued with increasingly sophisticated methods. As simple model compounds containing the essential structural units of dipeptides, *N*-acetylamino acid *N*-methylamides have been the subject of continuing interest with respect to conformational properties in solvents of different polarity and hydrogen bonding capacity.

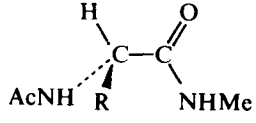
Madison and Kopple[73] have made a study combining CD and NMR measurements with force-field calculations including solvation effects in water and calculations of rotational strengths arising through interaction between the two $n \rightarrow \pi^*$ and two $\pi \rightarrow \pi^*$ transitions with the Schellman matrix method[74] as a function of $N^{\alpha}—C^{\alpha}$ and $C'—C^{\alpha}$ dihedral angles ϕ and ψ[75]. Their aim was to rationalize the drastic changes in the CD spectra, which occur when the solvent is changed from chloroform and dioxane over more polar solvents to water. Three model compounds were used: *N*-acetyl-*S*-proline *N*-methylamide (Ac-Pro-NMe) (**22**), 3-(*S*)-acetamidopyrrolidin-2-one (**23**) and *N*-acetyl-*S*-alanine *N*-methylamide (Ac-Ala-NHMe) (**24a**). In **22**, ϕ is restricted to near −60°, and in **23**, ψ is restricted to *ca* −140°, whereas **24a** has considerably greater conformational freedom. The main conformations discussed and their ϕ and ψ values are shown in Table 4.



(**22**)



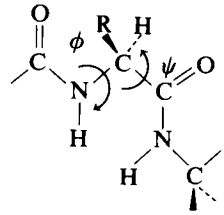
(**23**)



(**24a**) R = Me
(**24b**) R = *i*-Bu
(**24c**) R = *i*-Pr
(**24d**) R = *t*-Bu
(**24e**) R = CH_2OH

The CD spectra of **22** and **24a** showed strong negative $n \rightarrow \pi^*$ bands in non-polar solvents (the region near 200 nm is not shown for these solvents), much stronger for **22** than for **24a** ($\Delta\varepsilon = -15$ versus -6). On the basis of calculations of rotational strengths as functions of ϕ and ψ, the C_7 conformation was considered to be strongly dominant for **22** and somewhat less so for **24a**. This conformer, which is stabilized by an intramolecular hydrogen bond in a seven-membered ring, is not available to **23**, which showed nearly zero intensity in the $n \rightarrow \pi^*$ region in non-polar solvents. In polar and especially in hydrogen-bonding solvents the $n \rightarrow \pi^*$ bands in the spectra of **22** and **24** decreased and a negative band appeared, at 205 nm for **22** and at 195 nm for **24a** ($\Delta\varepsilon$

TABLE 4. Conformers of *N*-acetylamino acid amides



Conformer	ϕ	ψ	Occurs in
C_5	−150°	+150°	β-Sheet
P_{II}	−80°	+150°	Polyproline II
C_7	−80°	+80°	γ-Turn
α_R	−80°	−50°	Right-handed helix
3_{10}	−50°	−10°	3_{10}-Helix

ca −6). This is in all likelihood the low-energy component of a negative $\pi \rightarrow \pi^*$ couplet. Under the same conditions, the spectrum of **23** changed via moderately strong negative $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands in acetonitrile to one strong negative $n \rightarrow \pi^*$ band ($\Delta\varepsilon = -7.3$) at 210 nm and no visible $\pi \rightarrow \pi^*$ band in water. The spectral changes are consistent with about equal populations of the C_7, α_R and P_{II} conformations for **22** and **24a** in acetonitrile, while **23** is assumed to have two conformations with $\phi = 60°$ and 180° in less polar solvents, and one with $\phi = 100°$ in water. The results for **23** are in agreement with those proposed by Nielsen and Schellman in 1971[76].

Dungan and Hooker[77] have also studied **24a** together with its serine analogue **24e**. They analysed the experimental spectra, which give more details than those in Reference 73, with the aid of conformational energy and rotational strength maps. The latter were calculated with the aid of a modification[78] of the Schellman method[76] The best agreement for experimental spectra in solvents of low polarity was found with spectra calculated for the $C_{7,eq}$ conformation (equatorial side chain). The spectra recorded in polar solvents could not reasonably be explained by a simple equilibrium between two forms but required at least three, among which C_5-type conformers were suggested to be important. The spectra of **24e** showed somewhat less solvent sensitivity than those of **24a**, and **24e** may be less conformationally mobile.

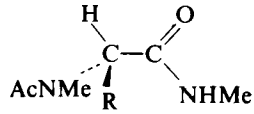
The Prague group has studied the series **24a–d**, with increasing bulk of the side chain, and included **22** as a rigid model[79]. The solvents for most of the compounds were acetonitrile, ethanol, water, trifluoroethanol (TFE) and hexafluoroisopropanol (HFP). The CD spectra above 185 nm displayed the long-wavelength component of a $\pi \rightarrow \pi^*$ couplet and a $n \rightarrow \pi^*$ band. The signs and intensities of these bands varied strongly with structure, temperature and solvent polarity, but the solvent and temperature sensitivity decreased with increasing bulk of the side chain. Three spectral types could be discerned: A, with negative $n \rightarrow \pi^*$ and positive $\pi \rightarrow \pi^*$ band; B, with both bands negative; and C, with positive $n \rightarrow \pi^*$ and negative $\pi \rightarrow \pi^*$ band. The spectra were analysed by the modified factor method mentioned in Section I[21]. The first subspectrum represented the common structural characteristics of the conformers of all molecules, and the second represented the A or C contributions (with opposite signs) assigned to two conformers with nearly enantiomorphous CD spectra. A third conformer was necessary to explain the appearance of the CD spectra, and its contribution could be included in the second

subspectrum. The third and fourth subspectra represented effects of side chain and solvent.

The spectrum of compound **24d** is predominantly of A-type, most strongly so in HFP, while some contribution of B-type is observed in acetonitrile and water. The spectra of the more flexible compounds **24a**, **24b** and **24c** are mainly of B-type in acetonitrile and water, with a clear contribution of C-type for **24a** and **24b** in water. However, the A contribution dominates for all these compounds in HFP. Spectra for **22** are only reported in TFE and HFP and are of B-type with a change towards C with lowered temperature. The A-type spectrum was assigned to a right-handed α-helical conformation (α_R), the C-type to another helical type (3_{10}) and the third conformer was with less certainty assumed to be an extended form (C_5). The authors do not agree with Madison and Kopple[73] about the importance of the P_{II} conformation.

Delaney and Madison[80] have studied the conformational effects of methyl substitution in positions 2 and 3 (*syn* and *anti*) of the proline ring in **22**, using NMR, IR and CD spectroscopy. The results indicate that the 2-methyl group stabilizes the C_7 form by shortening the hydrogen bond. This form is thought to have a substantial concentration even in water solution. The hydrogen bond in the C_7 form of the *syn*-3-methyl isomer is longer than in **22** with concomitant shift of the equilibrium towards the α_R and P_{II} forms, while the *anti*-3-methyl isomer seems to have nearly the same conformational behaviour as **22**.

The Prague group[81] has also reported a CD study of a series of N^{α}-methyl-N^{α}-acetylamino acid *N*-methyl amides (**25**). These compounds showed quite strong negative $n \rightarrow \pi^*$ bands ($\Delta\varepsilon \leq 26.6$) at 223–227 nm and positive $\pi \rightarrow \pi^*$ bands at 187–190 nm (solvent acetonitrile). The moderate solvent and temperature dependence of the spectra indicate that the conformational mobility of **25** is much smaller than that of **24**, and the



(25)

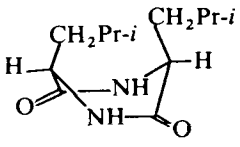
appearance of the CD spectra was explained by a strong contribution from a non-planar N^{α}-$COCH_3$ chromophore caused by the methyl substitution. The importance of a sterically enforced non-planarity is shown by the increasingly negative $n \rightarrow \pi^*$ bands with increasing bulk of the side chain and increasing solvent polarity (stronger solvation of the amide groups). However, in acetonitrile solution indications for a superimposed negative $\pi \rightarrow \pi^*$ couplet can be observed.

B. Diketopiperazines and Other Cyclic Dipeptides

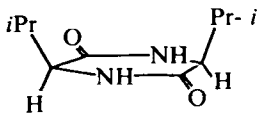
The CD spectra of typical diketopiperazines in the near-UV region have been carefully studied[82–84], and the relations between signs and intensities of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions and the ring conformations were elucidated by calculations. Bowman and coworkers[85] have studied UV and CD spectra in the vacuum-UV region to 135 nm of cyclo(L-alanyl-glycine) = c(L-Ala-Gly), of c(L-Ala-L-Ala) and of c(L-Pro-L-Pro) in water, acetonitrile and HFP solution. The first two compounds showed negative $\pi \rightarrow \pi^*$ couplets, strongest for c(L-Ala-L-Ala), centred near the strong UV band in the range 184–187 nm. Strong positive bands also appeared at 143 nm, with a positive shoulder at 152 nm for c(L-Ala-Gly). No bands ascribable to $n \rightarrow \pi^*$ transitions are seen. The CD spectrum of c(L-Pro-L-Pro) was quite different, with a negative $n \rightarrow \pi^*$ band at 219 nm

(in HFP), an unsymmetrical positive couplet at 203 and 174 nm ($\pi \rightarrow \pi^*$) and a more symmetrical, strong positive couplet at 159 and 140 nm. Based on a theoretical treatment utilizing interaction between the various expected transitions (a modification of the independent systems approach by Tinoco)[86] the authors came to the conclusion that the bands at short wavelengths ($\lambda < 160$ nm) are due to $\sigma \rightarrow \sigma^*$ transitions. However, this result depends on the choice of basis functions, and an alternative rationalization is discussed in Section V.E, as is the importance of the geometry of the compounds for the appearance of the CD spectra.

Tanihara *et al.*[87] have studied the CD spectra of c-(L-Leu-L-Leu) (**26**) and c(L-Val-L-Val) (**27**). Compound **26** shows a negative $\pi \rightarrow \pi^*$ couplet, and in dioxane solution also a negative $n \rightarrow \pi^*$ band at 227 nm, while **27** shows a positive $n \rightarrow \pi^*$ band and a single negative $\pi \rightarrow \pi^*$ band at 200 nm. These results were rationalized by different conformations, a boat-shaped diketopiperazine ring with negative fold (angle between the amide planes)[83] for **26** with flag-pole oriented (axial) side-chains due to an attractive steric effect, but a planar ring for **27**, in which no exciton coupling can take place.



(**26**)

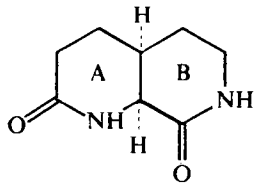


(**27**)

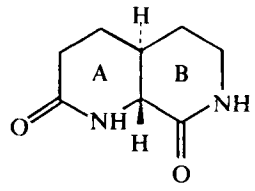
Goodman and coworkers[88] have compared solution conformations of the *N*-methylated diketopiperazines c-(*S*-NMeAla)$_2$, c-(*S*-NMeVal)$_2$ and c-(*S*-NMePhe)$_2$ with previously determined crystal structures[89], which all showed boat forms with negative fold and axial side-chains. The Ala compound showed a positive $\pi \rightarrow \pi^*$ couplet with negative $n \rightarrow \pi^*$ band, indicating positive fold. The other two diketopiperazines showed CD spectra (negative $n \rightarrow \pi^*$ band and positive $\pi \rightarrow \pi^*$ couplet) indicating solution conformations in agreement with the crystal structures.

The modified factor technique of Pancoska and collaborators[21] has been tested on a series of diketopiperazines, c(L-Pro-L-Aa) and c(L-Pro-D-Aa), where Aa represents Gly, Ala, Val, Leu and Tle.

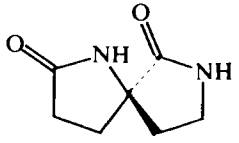
The Prague group has prepared three bicyclic dipeptide analogues, all with known absolute configuration, the diazadecalinediones **28** and **29**[90] and the spirodilactam **30**[91].



(**28**)



(**29**)



(**30**)

The CD spectrum of the *cis* form **28** (solvent acetonitrile) consists of a positive $n \rightarrow \pi^*$ band at 224 nm ($\Delta\varepsilon = +4.2$) and the long-wavelength component of a negative $\pi \rightarrow \pi^*$ couplet at 203 nm ($\Delta\varepsilon = -7.8$), and that of the *trans* isomer **29** of a very weak (+0.27) band at 250 nm, a stronger negative $n \rightarrow \pi^*$ band (−2.52) at 224 nm and a component

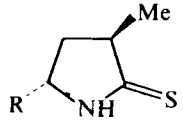
of a positive $\pi \rightarrow \pi^*$ couplet (+11.6) at 196 nm. The spectra showed only moderate sensitivity to changes in solvent (water, TFE) and temperature. Based on molecular structures from an X-ray crystallographic study, the signs of the $\pi \rightarrow \pi^*$ couplets were rationalized by the coupled oscillator mechanism. The sign of the $n \rightarrow \pi^*$ transition in **28** is in agreement with the amide quadrant rule, assuming that the one-electron mechanism gives a small negative contribution in the A ring and a large positive contribution in the B ring. For **29**, the quadrant rule predicts similar but oppositely signed contributions for the two rings, but the amide group in the B ring is twisted ($\Delta\omega = -17°$, $\theta_N = +19°$) and this effect probably dominates. The weak positive band at 250 nm is interpreted as a residue from a broad, weak $n \rightarrow \pi^*$ band originating in the A ring.

The CD spectrum of (*R*)-**30** in acetonitrile [228.5 (+6.53), 215 sh (+2.99), 197.5 (−4.0), positive end absorption at 181 nm] has not yet been interpreted, but it seems as if it displays two positive $n \rightarrow \pi^*$ bands and a negative $\pi \rightarrow \pi^*$ couplet. Some similar, very interesting compounds and their CD spectra have also been reported without interpretation[92].

V. SULPHUR AND SELENIUM ANALOGUES

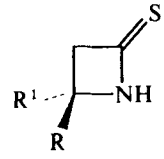
A. Thiolactams

Kajtar and coworkers[20] have studied the solvent and concentration dependence of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in 3-methylpyrrolidine-2-thione and its 5-methyl analogue (**31a** and **b**). In very dilute cyclohexane or carbon tetrachloride solutions the two bands were of opposite signs and similar intensity, indicating that the rotational strengths have their main origin in the one-electron mechanism. With increasing concentration, the $\pi \rightarrow \pi^*$ absorption gradually showed couplet character, while at the same time the $n \rightarrow \pi^*$ band was shifted to shorter wavelengths. The spectra showed nearly isosbestic behaviour, which indicates that only two main species are involved, the monomer and a cyclic hydrogen-bonded dimer. The $\pi \rightarrow \pi^*$ couplet has its origin in coupling between the transitions in the two chirally oriented thioamide groups in the dimer.



(**31a**) R = H
(**31b**) R = Me

Polonski and Milewska[93] have studied some optically active β-thiolactams (**32**) with phenyl or ester groups on C-4 and with known absolute configurations. The $n \rightarrow \pi^*$ bands had the same signs as in the parent lactams and substantial intensities ($|\Delta\varepsilon| = 0.65$–$3.3$), contrary to the prediction by the octant rule[94], since C-4 is close to a nodal surface. Better predictions were made by Weigang's sector rule for lactams[46].

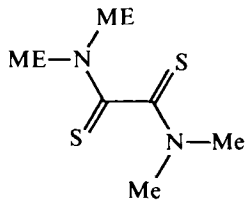


(**32**)

Contrary to the $n \rightarrow \pi^*$ bands, the $\pi \rightarrow \pi^*$ bands were quite weak and difficult to measure.

B. Dithiooxamides

Dithiooxamide is the simplest chromophoric system containing two thioamide groups. Tetrasubstituted dithiooxamides are known to be twisted by about 90° around the C—C bond and to have barriers to passage through the planar state >25 kcal mol[95], and consequently their chirality is stable at ambient temperature. Mannschreck and co-workers[96] have performed a partial resolution of *N,N,N',N'*-tetramethyldithiooxamide (**33**) by liquid chromatography on triacetylcellulose. The CD spectrum of this simple axially chiral molecule displayed seven bands at $\lambda > 200$ nm (I to VII from long to short wavelength, Table 5). The four weak bands at long wavelengths (I–IV) were principally assigned to $n \rightarrow \pi^*$ type transitions. Due to interactions between the two thioamide groups through bonds and through space, the sulphur lone pair orbitals (n) and the



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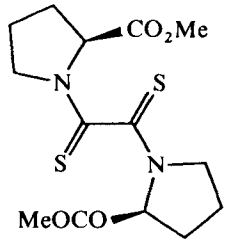


(**34**)

highest occupied and lowest empty π orbitals (π^0 and π^-, respectively) each split into two, designated by suffixes − and +, giving rise to four $n \rightarrow \pi^*$ transitions. A careful analysis of symmetries and interactions allowed the authors to conclude that $(+)_{365}$-**33** has the (*R*) configuration. The strongest evidence was presented by bands V and VI, which were interpreted as a couplet arising through interaction between the $\pi \rightarrow \pi^*$ transitions in the two thioamide groups. Analysis of the $n \rightarrow \pi^*$ transitions gave correct signs for three of them while leaving the fourth undecided. Band VII was not assigned, but an earlier proposal[97] that it should be due to a $n \rightarrow \sigma^*$ transition was rejected. The assignment of the absolute configuration of **33** was confirmed by Sandström and

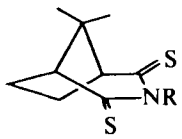
TABLE 5. CD spectra of dithiooxamides and dithioimides

Compound	Solvent	λ_{extr} nm ($\Delta\varepsilon$)
33[96]	EtOH	411 (+0.06, I), 381 (−0.23, II), 343 (+2.7, III), 308 (+1.7, IV), 276 (−15.5, V), 248 (+17.9, VI), 211 (+19, VII)
34[98]	EtOH	412 (+0.06, I), 390 (−0.14, II), 362 (+4.5, III), 313 (+5.9, IV), 280 (−19.2, V), 250 (+3.03, VI)
35a[99]	C_6H_{12}	491 (−0.14), 473 (+0.94), 423 (−0.27)
35b[99]	C_6H_{12}	502 (+1.24), 433 (−0.66)
36[99]	C_6H_{12}	489 (+1.07), 416 (−0.11)

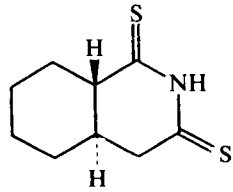
coworkers[98] in an X-ray crystallographic study of (*S,S*)-dimethyl *N,N'*-dithiooxalylbisprolinate (**34**), which showed (*R*)-configuration for the dithiooxamide moiety and gave a CD spectrum quite similar to that of $(+)_{365}$-**33** (Table 5). A CNDO/S calculation reproduced the signs and gave assignments in agreement with those given by Mannschreck and collaborators[96] for the first six transitions.

C. Dithioimides

In this group of compounds also, interaction between the sulphur lone pairs is possible. Polonski[99] has reported the CD spectra of three dithioimides (**35**, **36**), which display n_-–π^* bands in the range 473–502 nm and n_+–π^* bands at 416–433 nm (Table 5). The weak band at longer wavelength in the spectrum of **35a** is probably a residue of the broad n_+–π^* band. Stronger bands at shorter wavelengths are mentioned but no signs are given. With one exception, the signs agree with those for the $n \rightarrow \pi^*$ transitions of the parent imides.



(**35a**) R = H
(**35b**) R = Me



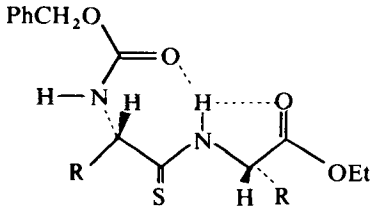
(**36**)

D. Endothiodipeptides

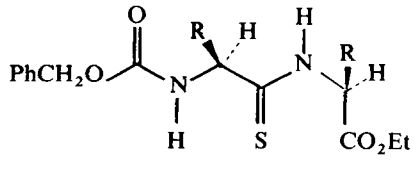
Several authors[100–104] have described the preparation of protected endothiodipeptides (**37**), most of them by reaction of the oxygen analogues with Lawesson's reagent or analogues[105,106], but, except for the study by Kajtar's group[107], only very few chiroptical data have been reported. Kajtar and coworkers have studied a series of benzyloxycarbonyl protected endothiodipeptide esters (**38**), composed of Gly, Ala, Val, Phe and Pro. The compounds showed typical thioamide CD spectra with $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands and a third band, possibly due to a $\sigma_n \rightarrow \pi^*$ transition[20] (Table 6). The spectra showed a remarkable solvent effect, in that the $n \rightarrow \pi^*$ bands had opposite signs

$$YNH—CHR^1—CS—NH—CHR^2COX$$

in DMSO and in CCl_4 and other less polar solvents. In mixtures of dimethyl sulphoxide and carbon tetrachloride the spectra passed through isosbestic points, indicating that the spectra changes are caused by changes in an equilibrium between only two conformers. Addition of small amounts of DMSO (<1%) to a carbon tetrachloride solution was sufficient to cause large changes in the spectrum. The two conformers were identified as **38A** and **38B** with the aid of NMR chemical shifts, NOE effects and IR spectra. The hydrogen bonded species **38A** seemed to be preferred in solvents of low polarity. Analysis of the signs of the $n \rightarrow \pi^*$ transitions in the two conformers led to an octant rule (Figure 7), while the signs and intensities of the thioamide $\pi \rightarrow \pi^*$ bands were rationalized by a combination of coupling of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition by the one-electron mechanism and non-degenerate exciton coupling between the $\pi \rightarrow \pi^*$ transitions in the thioamide, ester and carbamate chromophores. The first mechanism



(38A)



(38B)

seems to be more important in form **38A**, where the thioamide and ester groups are coplanar and no coupling results. Consequently, the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands were often more similar in intensity in DMSO than in CCl_4 solution, and of opposite signs in the former solvent.

Insertion of thiopeptide bonds in polypeptide chains has been shown to induce folded backbone conformations[108], and Hollosi *et al.*[109] have rationalized this in a study of the influence of hydrogen bonding on the conformations of a large variety of models including *N*-(thio)acetylamino acid *N*-methyl amides and analogous endothiodipeptides. Analysis of the thioamide $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands in different solvents revealed the

TABLE 6. CD spectra of protected endothiodipeptides[107]

Compound	Solvent	λ_{extr} nm ($\Delta\varepsilon$)
Z[a]-Alat-Ala-OEt	C_6H_{12}	357 (−1.3), 268 (+0.92), 214 (+5.7)
	Me_2SO	347 (+2.4), 269 (−10.2)
Z-Prot-Pro-OEt	$CHCl_3$	358 (+3.0), 279 (−14.4), 233.5 (+6.2)
	Me_2SO	354 (+3.5), 279 (−13.0)

[a] Z = $PhCH_2OCO$, Ala = (*S*)-$MeCH(NH_n)CO-$,
Alat = (*S*)-$MeCH(NH_n)CS-$(n = 1 or 2)
Pro and Prot are the corresponding (*S*)-proline residues.

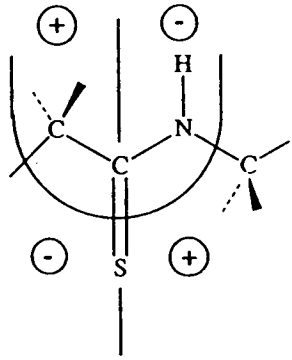


FIGURE 7. The octant-type sector rule for thioamide $n \rightarrow \pi^*$ transitions (upper octants)[107]

various intra- and intermolecular hydrogen bonds and the types of chain turns that gave rise to backbone folding. The results were in agreement with those from studies by NMR and IR spectroscopy[110,111].

E. Thio Analogues of Diketopiperazines

CD spectra of compounds from this group have been studied by Kajtar's group[112]. As reasonably rigid structures, cyclic (*S*)-prolyl-(*S*)-proline, c(Pro-Pro) and its mono- and dithio analogues c(Prot-Pro) and c(Prot-Prot) were first selected. The geometry of c(Prot-Prot)[113] is strikingly similar to that of c(Pro-Pro)[114], with a boat-shaped piperazine ring with the C_α atoms in the bow-stem positions and a 'fold angle' between the thioamide planes of $+30°$.

The CD spectrum of c(Prot-Pro) (Figure 8) showed a weak positive $n \rightarrow \pi^*$ band at

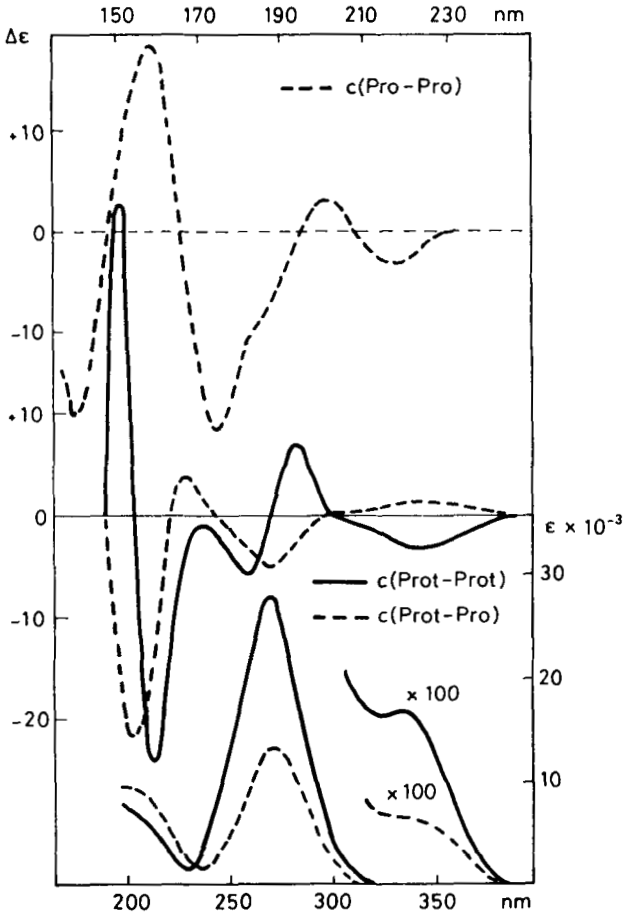


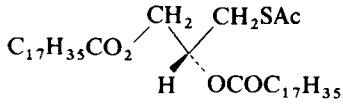
FIGURE 8. CD spectrum of c(Pro-Pro) in HFP (upper part) and CD and UV spectra of c(Prot-Pro) and c(Prot-Prot) in ethanol (lower part)[112]

350 nm, a negative thioamide $\pi \rightarrow \pi^*$ band at 275 nm, a weak positive band at 233 nm ascribed to the amide $n \rightarrow \pi^*$ transition, and a strong negative band at 208 nm, then tentatively ascribed to a thioamide $n \rightarrow \sigma^*$ but now[20] to a $n_\sigma \rightarrow \pi^*$ transition. In the spectrum of c(Prot-Prot) the thioamide $n \rightarrow \pi^*$ band was stronger and negative, and the 275- and 208-nm bands were replaced by a positive and a negative couplet, while the 233-nm band was missing. This spectrum shows a remarkable similarity to that of c(Pro-Pro)[85] (Figure 8, after appropriate wavelength shift), which indicates that the same mechanisms are responsible for creation of rotational strength. According to calculations by Hooker *et al.*[83] the negative rotational strength of the $n \rightarrow \pi^*$ transition in c(Pro-Pro) arises from coupling of the $n \rightarrow \pi^*$ transition quadrupole with the $\pi \rightarrow \pi^*$ electronic transition moment in the opposite amide group (the μ-m mechanism)[41], while the positive couplet centred at *ca* 190 nm was explained by coupling between the amide $\pi \rightarrow \pi^*$ transitions. Bowman *et al.*[85] (Section IV.B) assigned the couplet centred at *ca* 150 nm in the spectrum of c(Pro-Pro) to coupling between $\sigma \rightarrow \sigma^*$ transitions. This couplet seems to correspond to the one at 208 nm for c(Prot-Prot), for which an origin in $\sigma \rightarrow \sigma^*$ transitions seems unlikely. An $n \rightarrow \sigma^*$ or an $n_\sigma \rightarrow \pi^*$ transition is a more attractive rationalization, but more detailed calculations on c(Prot-Pro) and c(Prot-Prot) are highly desirable.

The CD spectra of monocyclic dithiodiketopiperazines like c(Alat-Alat) are essentially similar to those of the oxygen analogues. Two couplets are seen in the same regions as for the dithioproline analogue, but with opposite signs. This is in agreement with the known steric relation between c(Pro-Pro) on one side and c(Ala-Ala) and analogues on the other. The side chains in the second group tend to be axial, which leads to diketopiperazine rings with negative folding angles, i.e. nearly enantiomeric to that in the proline derivatives, although considerably more flexible[115].

F. Thiol Esters

$n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in thiol esters appear at longer wavelengths than in the oxygen analogues, as has been observed in ORD and CD spectra[116]. Gronowitz and coworkers[117] observed a positive $n \rightarrow \pi^*$ band at 270 nm ($\Delta\varepsilon = +0.33$) and a negative $\pi \rightarrow \pi^*$ band at 228 nm ($\Delta\varepsilon = -1.0$, solvent hexane) for (*R*)-2,3-distearoyloxypropyl thiolacetate (**39**) and similar bands for analogous triesters of 1-thioglycerol.



(39)

Gawronski and Radocki[118] have proposed octant rules for both thiol ester transitions, the $n \rightarrow \pi^*$ system with a plane of intersection along the C=O bond and the $\pi \rightarrow \pi^*$ system with an intersection along the R—C bond (Figure 9).

Thiol esters with α-heteroatoms show still larger bathochromic shifts compared to simple thiol esters. The UV spectra of ethyl α-alkylthiothiolpropionates (**40**) show $n \rightarrow \pi^*$ bands at *ca* 285 nm, $\pi \rightarrow \pi^*$ bands at 236 nm and a third band at 195 nm (Table 7). IR spectra show the presence of two rotamers of **40**, one with *gauche* and one with *syn* orientation of the C_α—S and C=O bonds[120]. The former dominates for **40a** and the latter for **40b**. The CD spectra of both compounds (Table 7, Figure 10)[119] show five

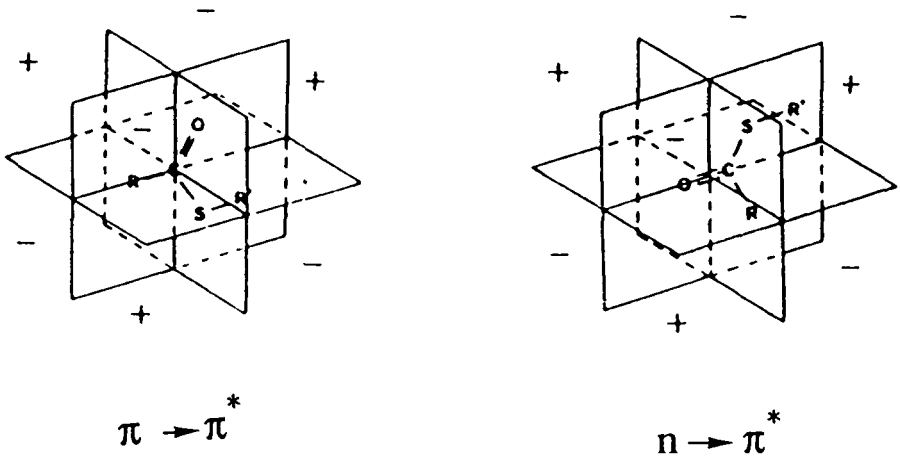
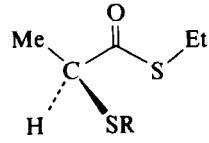


FIGURE 9. The octant-type sector rule for the n → π* and π → π* transitions in thiol esters[118]

bands with $\lambda > 190$ nm, but at somewhat different wavelengths. They may be ascribed to three bands from each rotamer. The lower intensity of the bands of **40b** may be ascribed to the near coplanarity of the C_α—S bond and the thiol ester group.



(40a) R = Et
(40b) R = *t*-Bu

G. Selenolactams

Polonski[121] has prepared two isomeric chiral selenolactams (**41** and **42**). Substitution of selenium for sulphur leads to bathochromic shifts of the n → π* transition from 305

TABLE 7. UV and CD spectra of **40a** and **40b**, solvent EtOH

Compound	λ_{extr} nm (ε or Δε)
40a (UV)	282 (580), 235.5 (3860), 195 (5500)
(*R*)-**40a** (CD)	287.5 (+7.0), 249.5 (−1.75), 229 (−2.40), 216 (+4.7), 200 (−13.0)
40b (UV)	277s (490), 236 (3330), 195 (5560)
(*R*)-**40b** (CD)	281.5 (+2.50), 233.5 (−0.84), 215 (+3.1), 207 (+2.9), 191.5 (−2.4)

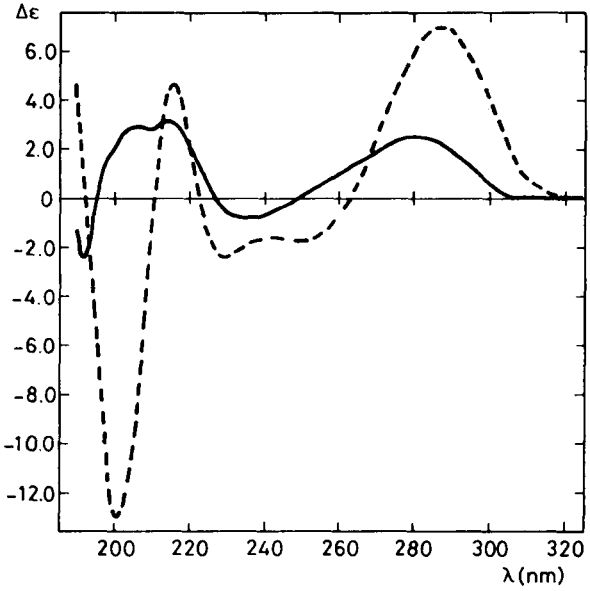
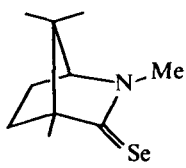


FIGURE 10. CD spectra of **40a** (- - - - -) and **40b** (———) in ethanol[119]

to 400 nm and of the $\pi \rightarrow \pi^*$ transition from 270 to 300 nm. The signs of the $n \rightarrow \pi^*$ transitions are the same as for the sulphur and oxygen analogues.



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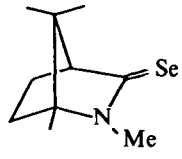
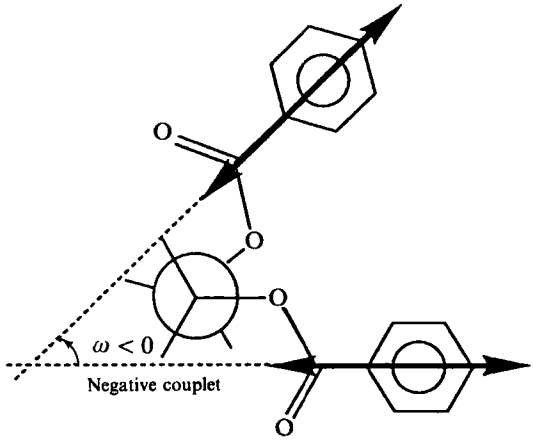


(42)

An additional band at 435 nm is ascribed to an $n \rightarrow \pi^*$ singlet–triplet transition. Additional bands of moderate intensity are observed in the range 200–250 nm.

VI. DEVELOPMENT OF 'THE DIBENZOATE CHIRALITY METHOD'

This method, which is based on the coupled oscillator mechanism[15], was originally devised to determine the relative orientation of OH groups in cyclic 1,2-diols, which in general also amounts to determination of the absolute configuration[122]. The diols were transformed to dibenzoates or *p*-substituted dibenzoates. The benzoyloxy chromophore has a strong transition, which involves both the benzene ring and the carboxylate group, and which is alternatively described as a ^1L_a transition modified by interaction with the



(43)

carboxylate group or as a charge transfer transition. In any case the transition moment is oriented along the long axis of the benzoate group and is therefore also nearly parallel with the alkoxy C- -O bond (**43**). Interaction between the two benzoate transitions gives rise to a couplet in the CD spectrum, the sign and intensity of which depend on the sign and magnitude of the dihedral angle between the transition moments (equation 1,

$$R_{12} = \pm \frac{\pi}{2\lambda_1} [\vec{R}_{21} \cdot \vec{\mu}_2 \times \vec{\mu}_1] \tag{1}$$

degenerate case[41], where $\vec{\mu}_1$ and $\vec{\mu}_2$ are the transition moments, $\vec{R}_{21}$ the distance vector between their centres and λ_1 the wavelength of the transition). A positive dihedral angle corresponds to a positive couplet.

The coupled oscillator mechanism was also utilized to study the relative orientation of other chromophores with strong transitions of uniquely defined polarizations[15,122]. In the case that the chromophores have different transition energies (non-degenerate case), a different expression (equation 2)[41] describes the rotational strengths; ν_1 and ν_2 are the transition energies and V_{12} the energy of interaction. It follows that the rotational

$$R_{12} = \pm \left(\frac{-V_{12}\nu_1\nu_2[\vec{R}_{21} \cdot \vec{\mu}_2 \times \vec{\mu}_1]}{hc(\nu_2^2 - \nu_1^2)} \right) \tag{2}$$

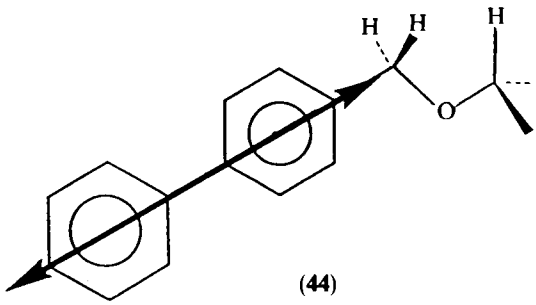
strength of the couplet with given geometry decreases with increasing difference in transition energy.

The dibenzoate chirality method is now a standard tool in organic stereochemistry. It has been developed in several directions, notably by the group of Nakanishi.

One important aspect concerns the additivity of CD effects in tri- and polybenzoates and analogues. The CD spectra of the various isomeric di-*p*-bromobenzoates of selected methylpyranosides gave CD spectra with couplets centred at 244 nm, reflecting the dihedral angles and distances between the chromophores. Each dibenzoate was characterized by its amplitude A (difference between extrema) in units of $\Delta\varepsilon$, positive or negative in agreement with the sign of the couplet. The A values measured for tri- and tetra-*p*-bromobenzoates of the same pyranosides agreed well with the values obtained by summation of the A values for the corresponding individual di-*p*-bromobenzo-

ates[123,124]. This pairwise additivity technique has been shown to be valid also for steroidal triols including an enone group[125] and for the T-2 trichothecene toxins.[126]

Because of the lability of ester groups in degradation of acylated oligosaccharides, *a*-phenylbenzyloxy groups were tried as alternative chromophores[127]. These groups display a strong long-axis polarized 'A' band at 253 nm ($\varepsilon = 20{,}000$)[128], and according to molecular mechanics calculations the orientation is analogous to that of the benzoates (**44**). This chromophore also obeyed the pairwise additivity rule.



(**44**)

Introduction of stronger chromophores, such as the *p*-methoxycinnamoyloxy group (C), gave stronger couplets centred at 311 nm and increased the sensitivity of the method. Systems containing one *p*-bromobenzoyloxy (B) and one C group gave split Cotton effects with one band near 244 and one near 311 nm. Weaker bands appeared near 280 and 315 nm, ascribed to interactions involving the ^1L_b transitions. In a systematic study[129,130] of the pairwise additivity rule, a 'basis set' of methyl α-D-glucosides was synthesized with all 24 combinations of either two B groups, two C groups, or one B and one C group and with acetoxy groups in the remaining positions to stabilize the stereochemistry. The CD spectra of 20 tri- or tetrachromophoric methyl α-D-glucosides were compared with the summation spectra obtained from the members of the basis set representing all the degenerate and non-degenerate pairwise interactions. In most cases the agreement between an experimental spectrum and the corresponding summation spectrum was excellent (Figure 11), and the deviations could be ascribed to steric mismatching, generally involving the orientation of the $C_{(6)}H_2OCOR$ group. Differences in $C_{(5)}$—$C_{(6)}$ dihedral angles between members of the basis set and deviating tri- or tetrachromophoric compounds could also be inferred from the corresponding $^3J_{H-H}$ values. Figure 12[131] shows the observed CD spectra of the homo and hetero B/C pairs of methyl α-D-galactoside (b–g) together with the observed spectrum of the 2,3-C-4,6-B derivative and that calculated by summation of the individual pair spectra (a).

The use of two different chromophores ('the bichromophoric exciton chirality method') gave tri- and tetrasubstituted glycosides with complex and highly characteristic CD spectra, which facilitate their identification. A microscale method for derivatization and cleavage of oligosaccharides and identification of the fragments has recently been described[132].

The extension of this technique to acyclic polyols seems like a formidable task because of the larger conformational mobility. In reality, the analysis of vicinal polyols (up to pentols)[133–135] and aminopolyols[136–138] has advanced to the same level as that of cyclic polyols. The clue to this progress was the selective acylation of the primary OH/NH_2 group with 9-anthroyl chloride or 9-anthroyltetrazole, followed by acylation of the secondary OH/NH_2 groups with *p*-methoxycinnamoyl chloride. The 9-anthroyl group (A) has a characteristic absorption with a strong, sharp band at 253 nm (^1B_b, long-axis

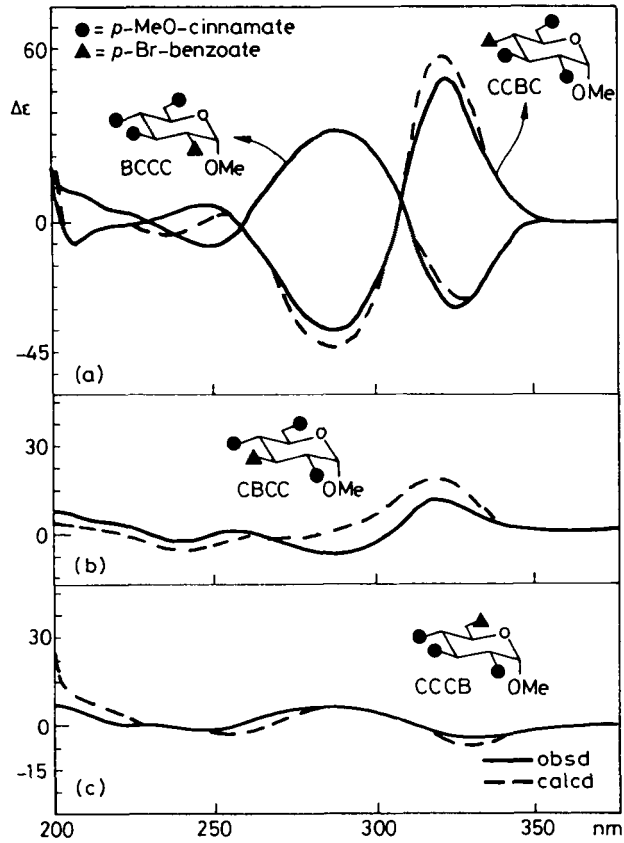


FIGURE 11. Comparison of calculated and experimental CD spectra for four monobenzoate tricinnamates of methyl α-D-glucopyranoside. Reprinted with permission from *J. Am. Chem. Soc.*, **109**, 5586 (1987). Copyright (1987) American Chemical Society

polarized, $\varepsilon = 185{,}000$), and a weaker band with vibrational fine structure around 350 nm (^1L_a, short-axis polarized). The individual interactions between the 1-A and 2- and 3-C groups, and between the 1,2- and 1,3-related C groups give rise to split Cotton effects, which sum up to CD spectra, which are quite characteristic for the stereochemistry of the polyol chain. In 'normal' cases, when the carbon chain assumes a planar zig-zag conformation, the orientation of the acyl groups can be inferred from simple models, but 1,3 C–C interactions may lead to population of *gauche* conformers. The conformer distribution has been analysed with the aid of $^3J_{H-H}$ values and by study of models, and the method has been developed to a micro-scale technique[138].

Harada and coworkers[139] have studied the CD spectra of a large number of di-*p*-bromobenzoates of 1-substituted 1,3-butanediols with (*S,S*) and (*R,S*) absolute configuration. The chain conformations were elucidated with molecular mechanics calculations and X-ray crystallography. Calculations on (2*S*,4*S*)-2,4-pentanediyl dibenzoate (**45a**) led to the prediction that a conformer with nearly planar zig-zag C_5 chain is the most stable one. In this conformation, which was also found in the crystal

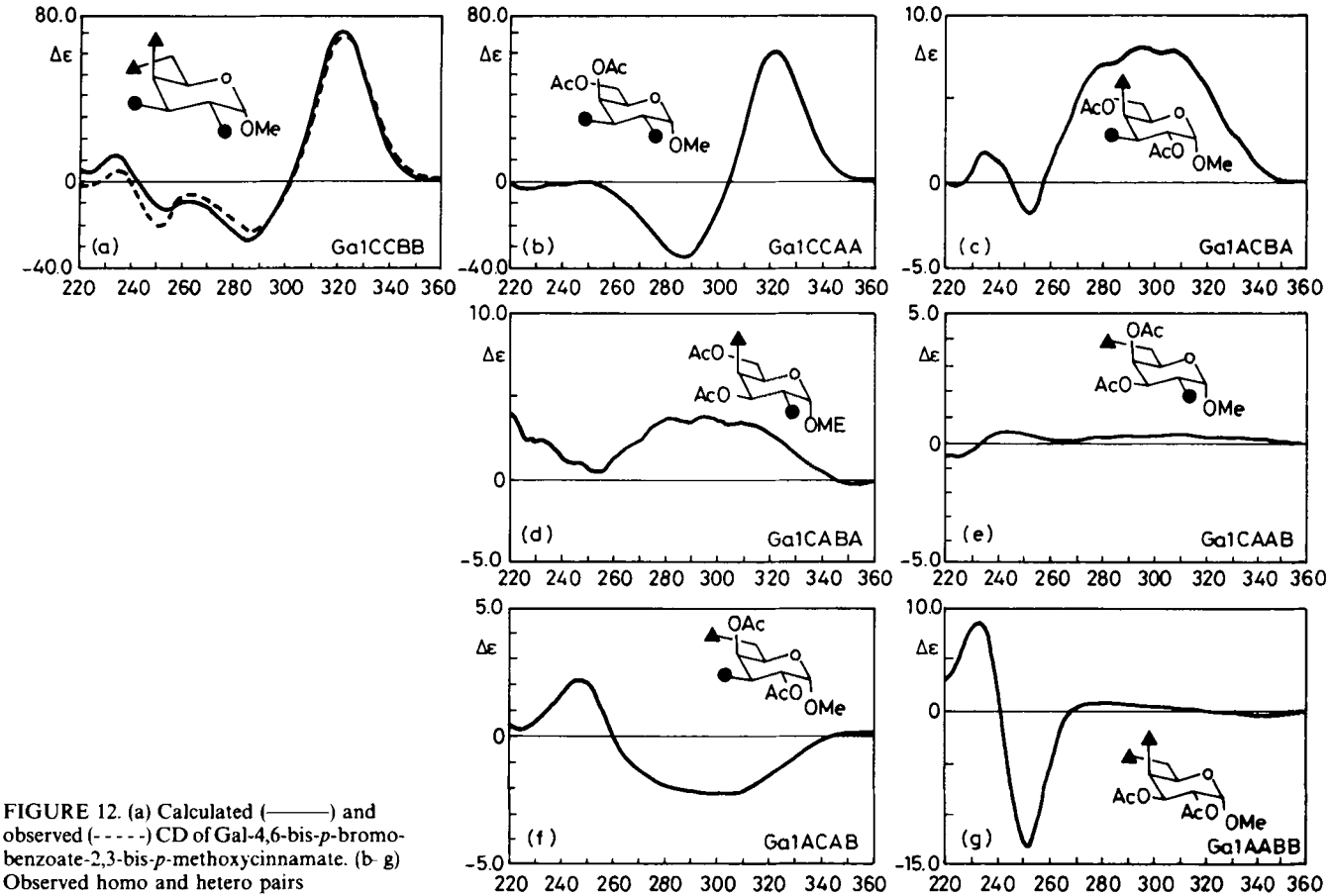
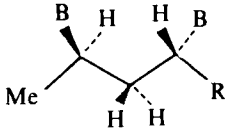
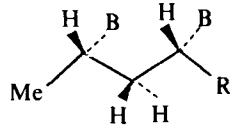


FIGURE 12. (a) Calculated (———) and observed (- - - - -) CD of Gal-4,6-bis-*p*-bromobenzoate-2,3-bis-*p*-methoxycinnamate. (b-g) Observed homo and hetero pairs

of the phenyl analogue, the *p*-bromobenzoate groups are *anti* with respect to the plane through the carbon chain, and the dihedral angle between the alcoholic C--O bonds is *ca* +120° (calculated +115° for **45a**, found +154° for **45b** in the crystal). The CD spectra of a wide variety of analogues with *anti* conformation displayed positive couplets centred at 243 nm with *A* values in the range +32 to +40. The presence of minor conformer(s) with low or negative *A* values could be inferred from the increase in the *A* value for **45c** from +34.4 at ambient temperature to +45.1 at −73 °C in ethanol solution.



(**45a**) R = Me
(**45b**) R = CH_2Ph
(**45c**) R = Pr



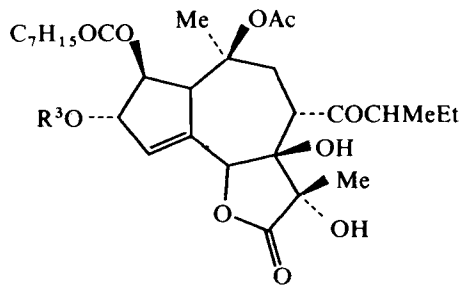
(**46a**) R = Me
(**46b**) R = Et

Similar calculations on (2*R*,4*S*)-2,4-pentanediyl dibenzoate (**46a**) also predicted a nearly planar C_5 chain even more dominant than for **45a**. In this conformer, the benzoate groups are *syn* with respect to the plane through the carbon chain, and the dihedral angle between the C—O bonds is nearly zero. Compound **46a** is a *meso* diastereomer, and the CD spectra of a large number of chiral analogues, like **46b**, showed no *p*-bromobenzoate couplet and, in general, very weak CD spectra.

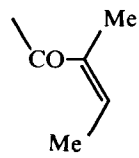
Analogues with only one centre of chirality (**45** or **46**, R = H) also showed couplets with *A* values half of those for the *anti* di-*p*-bromobenzoates.

Of the numerous other published applications of the theory of coupled oscillators in organic stereochemistry, only a few of special interest and pertaining to carboxylic acid derivatives will be mentioned.

Harada and coworkers[140] have shown how the absolute configuration of cyclic allylic



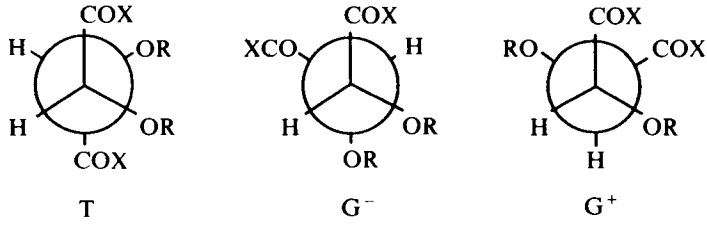
(**47a**) R^3 =



(**47b**) R^3 = COCHMeEt

alcohols can be determined from the sign of the Cotton effect of the benzoate at 229 nm. A similar technique was used by Lauridsen *et al.*[141] to determine the absolute configuration at $C_{(3)}$ of archangelolide (**47a**) and some analogues. The split Cotton effect due to coupling between the *Z*-2-methyl-2-butenoyloxy group and the cyclopentene double bond falls in the same wavelength range as the ester and lactone $n \rightarrow \pi^*$ bands, but the difference spectrum between **47a** and **47b** leaves only a negative band ($\Delta\varepsilon = ca - 6$) at 212 nm, from which the absolute configuration at $C_{(3)}$ could be deduced.

The conformations of tartaric acid and its derivatives have been the subject of study for a long time. The free acid, its salts and esters are generally considered to prefer the *trans* conformation (**48**, T). However, Gawronski and coworkers[142] have shown that, while diethyl *O,O*-dianisoyltartrate (**48**, X = OEt, R = anisoyl) gave a negative couplet centred at 260 nm, in agreement with the *trans* form, the *O,O*-dianisoyl-bis(*N,N*-dimethyl)amide (**48**, X = NMe_2, R = anisoyl) gave a strong positive couplet, indicating a preponderance of the *gauche* form G^-. The G^+ form should not give a couplet at all.



(48)

The G^- form was also found to make up the solid state by an X-ray crystallographic study of both tetramethyl tartramide (**48**, X = NMe_2, R = H) and its *O,O*-dibenzoyl derivative. The conformational difference between tartaric acid and esters on the one hand and amides on the other was ascribed to attractive *gauche* effects between the RO groups and between the $CONMe_2$ groups, of which the latter should not exist in the acid and the esters.

VII. ACKNOWLEDGEMENTS

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CHAPTER 4

Mass spectrometry of carboxylic acid derivatives

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I. INTRODUCTION

During the past decade the nature of mass spectrometric studies has changed significantly. In contrast to previous studies focussing on structural assignments, mass spectrometry has changed in a direction more centralised on a general understanding of individual types of reactions of ions in the gas phase. This is partly due to the

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introduction of new specialized techniques, such as tandem mass spectrometry, including neutralization–reionization mass spectrometry, and elaborate bimolecular ionization methods.

An introductory section on tandem mass spectrometric techniques is given with special emphasis on carboxylic acid derivatives. The following discussion is subdivided according to the possible reaction pathways, i.e. fragmentations and rearrangements, which appear typical for carboxylic acid derivatives.

The report covers primarily the literature in the period 1978–1990, a continuation of the report by Tam[1].

II. MASS SPECTROMETRY

The development of tandem mass spectrometry techniques has contributed significantly to an understanding of the fundamental aspects as well as to the analytical applications of ions in the gas phase. This is in particular true for carboxylic acid derivatives.

Unimolecular reactions of ions are studied extensively since the fragmentations of isolated ions provide fundamental information concerning such reactive systems[2]. Mass spectrometry has clearly been a useful technique, since reactions take place under collision-free conditions and the ionic species can be selected and identified with a high degree of specificity[3,4].

A. Metastable Ions

The ions observed as metastable ions in the mass spectrometer correspond to processes in the μs time frame[2]. Due to the duality of the reaction rate and the available internal energy, only processes with rather low-energy requirements are consequently observed[2]. Hence, the metastable ion spectra may not directly reflect the initial stable ion structures[4]. This is nicely reflected by the metastable ion spectrum of the molecular ion of ethyl acetate (Figure 1). Recent literature reviews[5–7] give excellent discussions on the role of metastable ion dissociations. It appears nevertheless reasonable to summarize the more important aspects.

It is generally assumed that similar product ion abundances indicate that the metastable parent ions exhibit identical structures. It should, however, be remembered that the abundance ratios can be highly sensitive to variations in internal energies. Hence, based on a different ratio only, it cannot unambiguously be concluded that the parent ion structures are different[4].

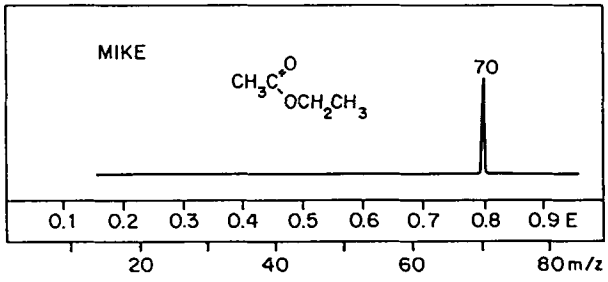


FIGURE 1. Metastable ion spectra of the molecular ion of ethyl acetate (H. Egsgaard and L. Carlsen, unpublished)

Closely related to the metastable ion structure is the determination of kinetic energy release, which appears as a sensitive probe to reaction dynamics[2,4,5]. A comprehensive analysis of the kinetic energy release is in general rather complicated and requires additionally detailed information regarding the mass spectrometric system[2].

However, even used as a qualitative probe the kinetic energy release appears rather useful. Thus, two isomeric metastable ions showing the same fragments as well as peak shapes, i.e. identical kinetic energy releases, probably arise from identical precursors[4]. On the other hand, if a significant difference is observed, it must be concluded that the observed fragmentations take place via different structures/transition states. Finally, it should be noted that the kinetic energy release reflects the strain of the transition state of the fragmenting species directly, i.e. tight systems show the highest release[8,9].

B. Collision Activation

The above-mentioned sensitivity of metastable ion spectra to variation in internal energy can be surmounted by excitation of the ion of interest by collision with a target gas at low pressure (*ca* 10^{-6} mm Hg)[3,4,10,11]. Collision activation has been used extensively in ion structure analyses[3]. Differences observed in collision activation mass spectra of isomeric ions can be directly related to structural differences. This conclusion seems to be generally valid. However, the ions which give rise to the metastable ion spectra can make up quite a large fraction of the decomposing ions following collision activation[4]. The effect may become particularly important using such instruments operating with moderate translational energies[4]. However, by focussing on the endothermic processes, i.e. the processes observed in the collision activation mass spectra only, the effect of initial internal energy may be reduced. In Figure 2 the collision activation mass spectrum of ethyl acetate is shown. The differences compared to the metastable ion spectrum shown in Figure 1 are striking.

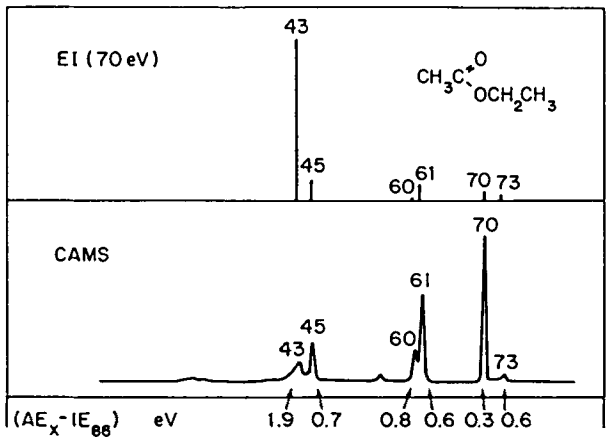


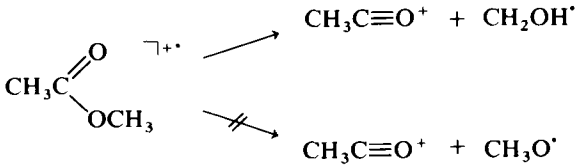
FIGURE 2. Collision activation mass spectrum (CAMS, 3 kV translation energy) of the molecular ion of ethyl acetate. The 70 eV electron impact (EI) mass spectrum of ethyl acetate is included for comparison. Energy requirements for the individual processes are indicated (H. Egsgaard and L. Carlsen, unpublished)

C. Neutralization/Reionization

The technique of neutralization/reionization mass spectrometry (NRMS), introduced by McLafferty, invokes the formation of fast neutrals from a preselected ion beam and the deflection of any residual ions, followed by a collision-induced reionization of the neutrals and a subsequent mass spectrometric analysis[12–16].

The NRMS technique has been used successfully to distinguish between ion structures, which by other means are not distinguishable, i.e. in situations where fast isomerizations take place after collision activation, however, prior to dissociation[4].

The fast neutral species may well originate from ordinary fragmentations, i.e. metastable ions. Thus, the NRMS experiments have made accessible studies on 'the other half of the mass spectrum'[12]. Indeed, a number of interesting aspects have already been disclosed. In the case of methyl acetate the general fragmentation leads to an acetyl ion and a 'CH_3O' species. It would *a priori* be expected that the latter exhibits methoxy structure. However, by NRMS it is possible unequivocally to distinguish between $CH_3O^{\cdot}$ and $CH_2OH^{\cdot}$ (Figure 3). Hence, methyl acetate apparently gives rise predominantly to the formation of the latter[17].



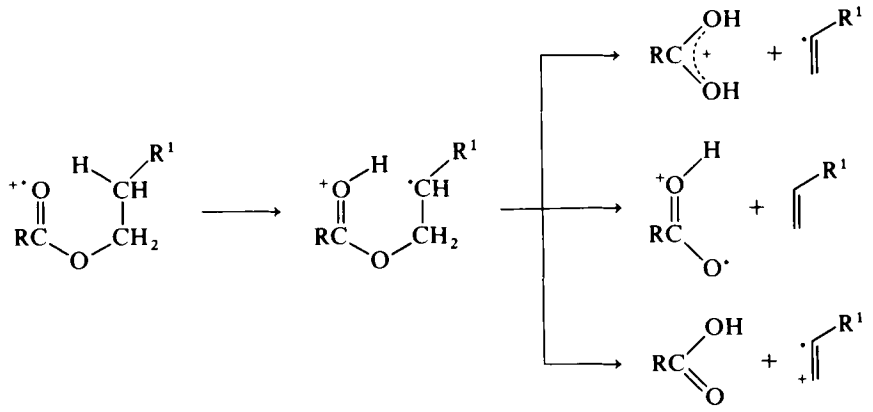
III. FRAGMENTATION PROCESSES

In addition to general fragmentation pathways, a series of more specialized techniques has been introduced, leading to the possible structural characterization of long-chain, functionalized acid derivatives.

A. General Fragmentations

Three reaction mechanisms appear as particularly important in the fragmentation of carboxylic acid derivatives:

(a) Radical-site initiation, which arises from the tendency to electron pairing[18]. Thus, the odd electron will be engaged in forming a new bond to an adjacent atom.



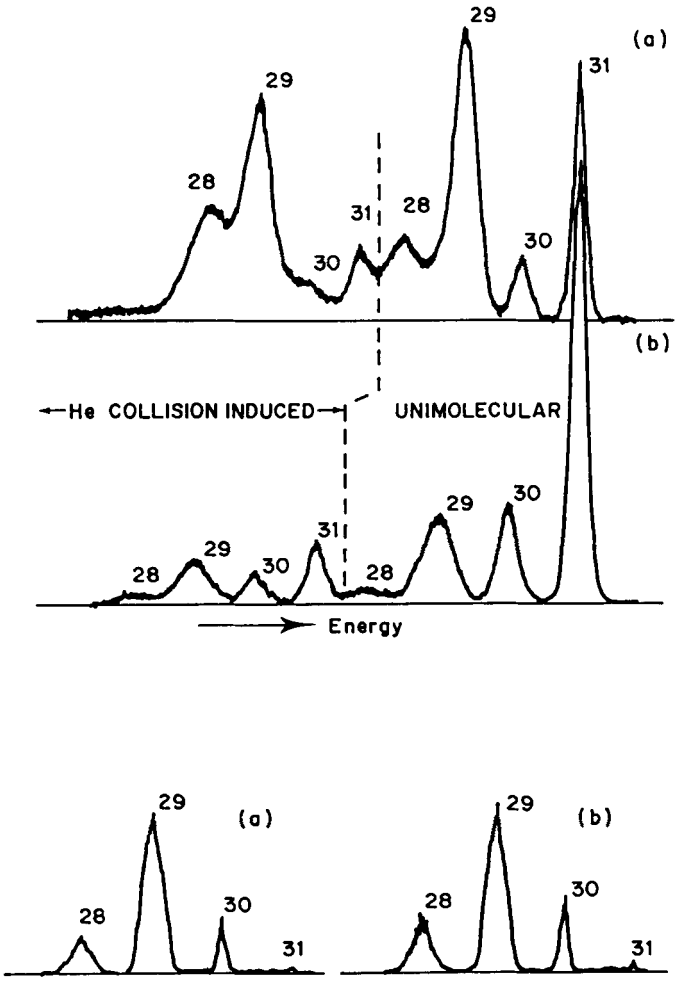
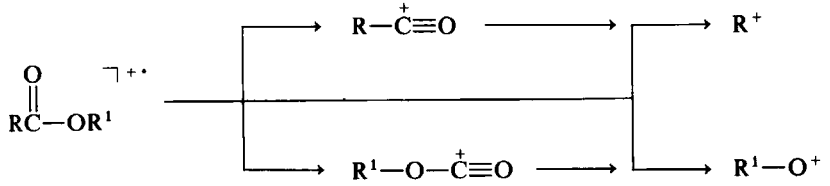


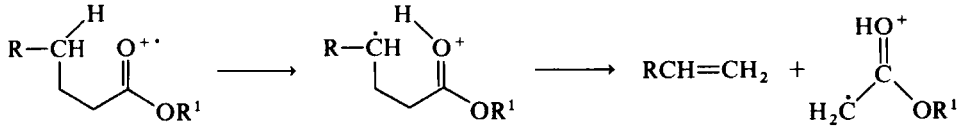
FIGURE 3. (top) He–CIDI (a) and O_2 (b) mass spectra of H_3, C, O˙ radicals from unimolecular (high-energy region of spectra) and He-collision-induced (low-energy region) fragmentation of $[CH_3COOCH_3]^{+\cdot}$. (bottom) O_2–CIDI mass spectra of CH_3O˙ radicals from (a) unimolecular and (b) He-collision-induced electron loss from mass-selected CH_3O^- ions [J. L. Holmes and J. K. Terlouw, *Org. Mass Spectrom.*, **21**, 776 (1986)]

Consequently, this is accompanied by a cleavage of a second bond to that atom leading to an α-cleavage.

(b) The charge-site initiation which, on the other hand, involves attraction of an electron pair[18]. For the carbonyl functionality, electron-pair attraction to the charge site yields a resonance-stabilized structure followed by inductive cleavage to give the alkyl ion. It should be noted that the reaction products are complementary to those of the α-cleavage.



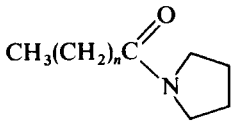
(c) Far the most important radical-site rearrangement is the McLafferty rearrangement[18]. In the case of carboxylic acid derivatives, the transfer of a γ-hydrogen to the carbonyl oxygen is highly favoured by the 6-centred transition state. The reactions in general take place with characteristic low-energy requirements. The reaction may be formulated as being a result of a concerted mechanism. However, a discussion in terms of a step-wise process appears more fruitful[18], i.e. an initial cleavage causing the change of the radical site followed by an α-cleavage.



Turning to the amides, strong parallels between the fragmentations of the primary amides and those of the corresponding acids in general can be drawn[18]. However, a significant increase in the abundance of the molecular ion is frequently observed.

In the case of secondary and tertiary amides, the fragmentation becomes heavily influenced by the strong directing force of the nitrogen. Hence α-cleavages, giving rise to abundant closed-shell ions, are predominant. As a general feature the cleavage of the C—N bond is more pronounced than the corresponding reactions in esters and the free acids[18].

An interesting analytical application of the charge-stabilizing effects of nitrogen is the structural determination of fatty acids by studying the corresponding pyrrolidinyl derivatives[19–21].



This property of the mass spectra of pyrrolidines is a result of a particularly favourable fragmentation pathway. The fragmentation is apparently initiated by the abstraction of a hydrogen from the aliphatic side-chain, induced by the pyrrolidine group. The resulting radical site, somewhere along the side-chain, causes the rupture of the latter giving rise to even-electron fragments of every possible length. Thus, the charge will be localized in the amide structure and consequently a rather clear-cut picture develops.

The successful analyses of long-chain alcohols as nicotinates are due to a comparable effect extended by the pyridine nucleus[22].

B. Remote Fragmentations

The determination of the structures of modified fatty acids, based on collision activation mass spectrometry of molecules with metal cations or the carboxyl ion ($RCOO^-$), is one of the most significant achievements in this area[23].

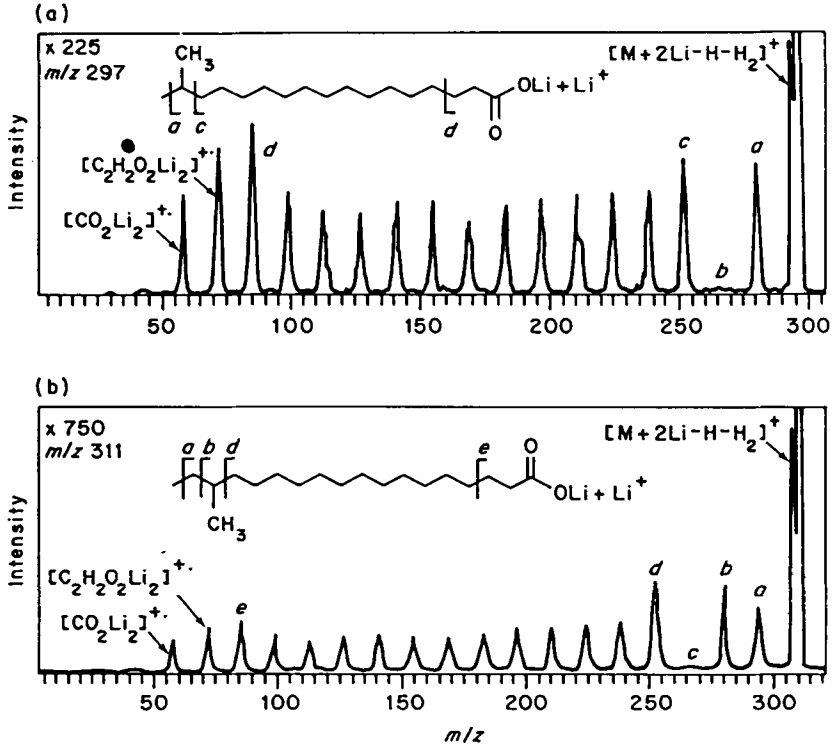
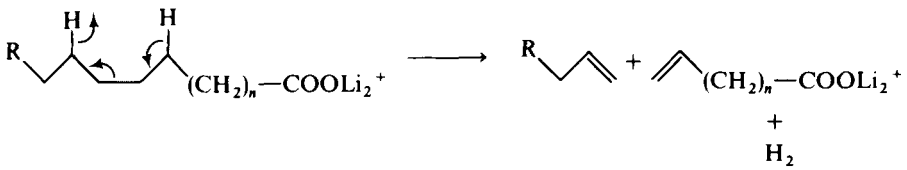


FIGURE 4. Collision activation mass spectra of $[M + 2Li—H]^+$ ions of iso- and anteiso-methyl-substituted fatty acids. (a) 16-methylheptadecanoic acid (iso-), (b) 16-methyloctadecanoic acid (anteiso-). Ions represented by *b* in (a) and *c* in (b) are formed by decompositions that involve the methyl branch[23]

Fast atomic bombardment (FAB) studies have shown that the cationization apparently is affected in a FAB matrix saturated with either alkali iodide or hydroxide[24]. The eventual choice of the appropriate reagent obviously plays a crucial role as the relative abundances of the cationized molecules as well as the collision-induced fragmentations are significantly influenced[23,24].

Cationized molecules remain almost undetected using the higher alkali ions, i.e. Rb^+ and Cs^+, whereas abundant signals have been obtained using Li^+[23]. The application of LiI leads to abundant $[M + Li]^+$ and $[M + 2Li—H]^+$ ions[23]. The subsequent collision-activated analysis obviously is highly facilitated by the application of Li^+, since the other alkali cations exhibit significantly lower bond energies and are therefore preferably lost during the collision activation process. This unambiguously gives rise to diminished signals for the structural informative charge-remote fragment ions[24].

The application of LiOH appears as highly advantageous as reagent, since rather abundant $[M + 2Li—H]^+$ ions as well as highly diagnostic collision-induced mass spectra are developed[23] (cf Figure 4). The collision-induced fragmentations are consistent with a mechanism involving a 1,4-hydrogen elimination to produce an alkene and a terminally unsaturated lithiated carboxylate[24].



In the case of unsaturated as well as branched acids a distinct perturbation of the charge-remote fragmentation, caused by the presence of double bonds (Figure 5) or the substituents, develops[25]. Thus, fragmentations involving the branched carbons as well as possible double bonds are virtually absent.

A similar approach using negative chemical ionization has been reported[26]. By application of HO^- ions as reagent gas, $RCOO^-$ ions were produced using either the free acids or their methyl esters[27,28].

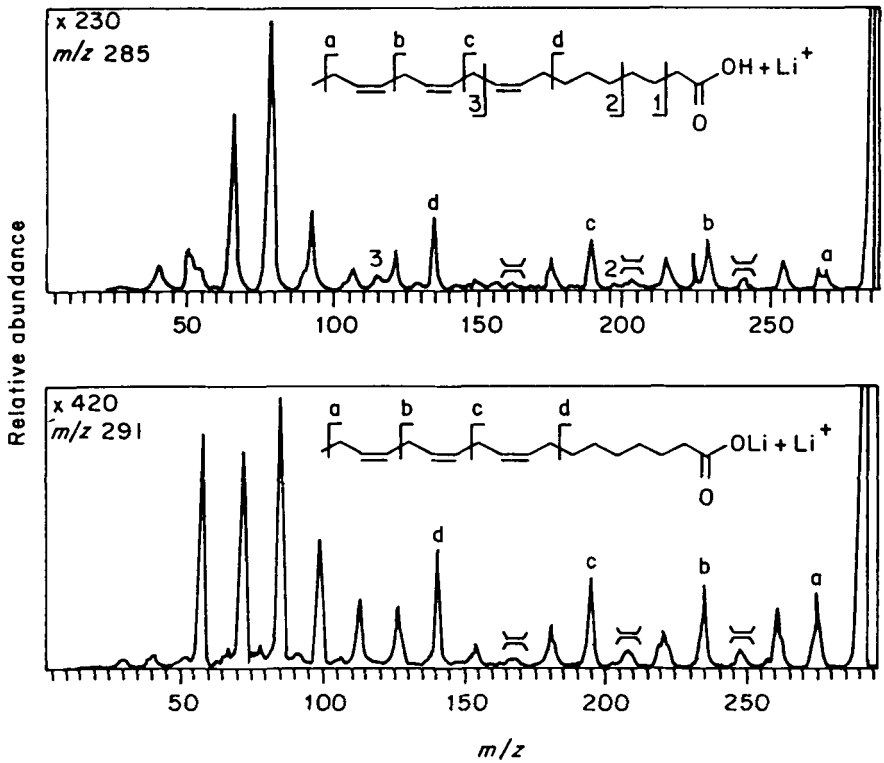
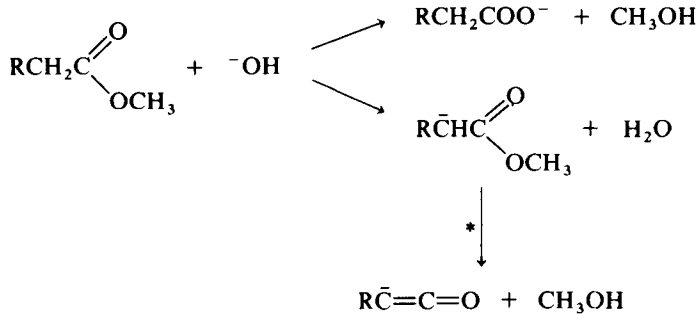


FIGURE 5. Collision activation mass spectra of linolenic acid $[M + Li]^+$ ions (top) and $[M + 2Li—H]^+$ ions (below). Ions a–d represent fragments with the Li^+ ion attached to the carbonyl group; ions 1–3 represent fragments with the Li^+ ion attached to the double bond. Symbols for double bonds are shown at locations where the daughter ions formed by cleavages at double bonds would be seen[24]



Collision activation (CA) of the $RCOO^-$ ions showed that charge-remote fragmentations occur, and hence decisive information concerning the original structure can easily be obtained. It is important to note that this method can be applied advantageously in GC-MS/MS studies on fatty acid methyl esters[27]. However, the CA approach involving $RCOO^-$ anions for, e.g., highly unsaturated acids will lead to incomplete structural information[23]. On the other hand, in the case of special functionalized acids, such as epoxy acids, the '$RCOO^-$ strategy' may appear as the method of choice[23]. In addition to negative-ion mass spectra obtained by chemical ionization, the FAB technique has been successfully applied[29–31].

Finally, it should be noted that the internal energy needed to promote remote-site fragmentations is rather high, approximately 50 kcal mol^{-1} [32].

In summary, it can be concluded that collision activation analyses of cationized carboxylic acids, in particular the $[M + 2Li—H]^+$ cations and the $RCOO^-$ anions, can be recognized as important and complementary techniques for analysing this important class of compounds.

C. Chemical Ionization

A significant development in organic mass spectrometry has been its application to stereochemical problems. Hence, simple geometric isomers frequently exhibit distinctly different electron-impact-induced fragmentation patterns. However, as a result of an increasing complexity of the molecules under investigation, the observed differences may vanish. The possible application of chemical ionization may strongly reinforce the picture.

The study of maleic and fumaric acid as well as the corresponding phenyl esters constitutes an illustrative example to elucidate the advantages of the use of chemical ionization[33]. In the case of the free acids, the two isomers are readily differentiated by means of electron impact mass spectrometry[34]. However, the corresponding phenyl esters exhibit only very minor quantitative differences when scrutinizing the electron impact mass spectra. Turning to the chemical ionization mass spectra, on the other hand, rather clear-cut pictures with significant differences can be seen (Figure 6). Thus, the $[MH—PhOH]^+$ and MH^+ ions are of equal intensity in the case of phenyl fumarate, whereas the MH^+ ion in the case of maleate amounts to approximately 20% relative to the $[MH—PhOH]^+$ ion[33] (cf Figure 6).

The behaviour of methyl esters of saturated carboxylic acids under chemical ionization conditions appears to be fairly well understood[35]. Obviously the interaction between the reagent ion and the carboxyl group initially leads to the formation of a protonated ester[36]. However, the relative importance of the possible interaction between the reagent ion and the alkyl chain apparently increases rapidly with increasing alkyl chain length[15].

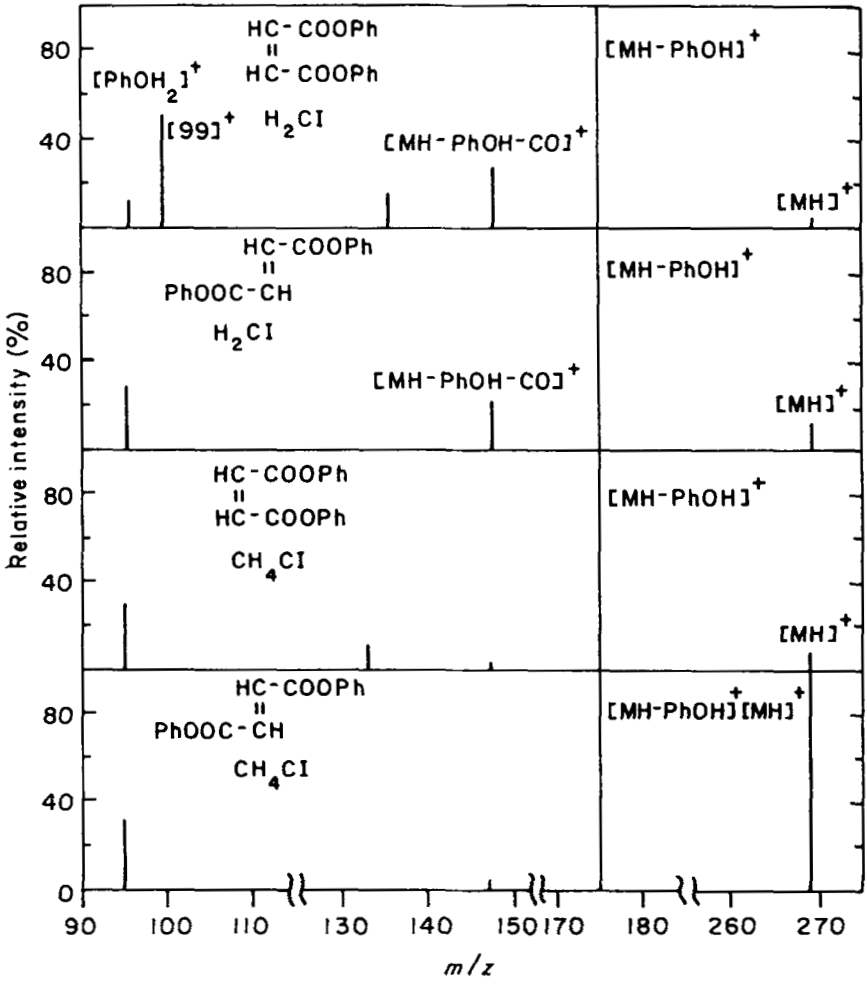
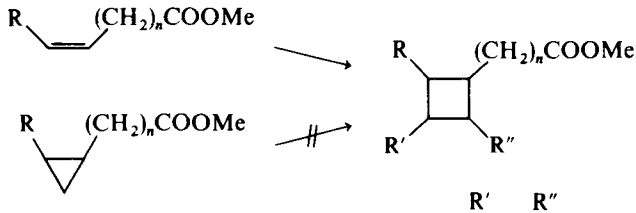


FIGURE 6. Chemical ionization mass spectra of phenyl maleate and phenyl fumarate[33]

In the case of unsaturated acid methyl esters a somewhat different behaviour is recognized. Thus, the possible presence of double bonds in the alkyl chain gives rise to an elimination of *CO* and/or CH_2CO, which is indicative for protonation of the double bond[36].

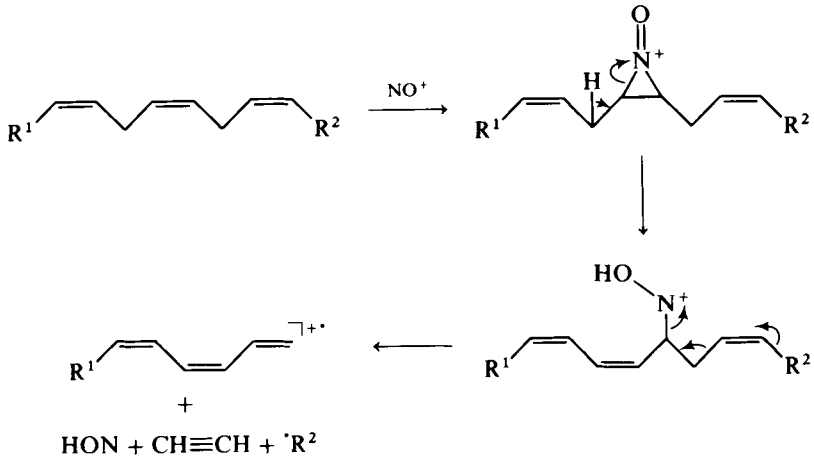
The possible generation of specific adduct ions by chemical ionization is an additional benefit obtained through the operation of the bimolecular ionization process. Thus, the use of an isobutane/vinyl methyl ether mixed reagent gas allows an immediate distinction between cyclopropanoid and mono-unsaturated fatty acid esters[37].



R'	R''
H	OMe
MeO	H

The spectra of the mono-enoic acid methyl esters display the characteristic adduct ions $[M + 59]^+$.

A related strategy applies to polyunsaturated acids, e.g. to the homoconjugated acid ('linolenic acid unsaturation') and the tetraenic acid ('arachidonic acid unsaturation'), which is based on chemical ionization with NO[34,38]. The diagnostic ions arise from the addition of the NO^+ ion to the double bond followed by hydrogen transfer, elimination of HON and formation of an ionized conjugated triene[34].



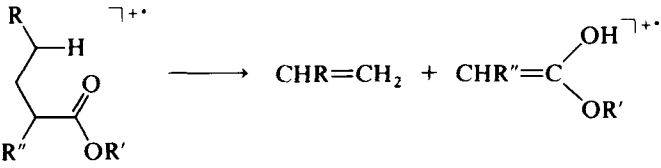
The analytical impact of the above procedures furnishes two important improvements, i.e. the gas chromatographic/mass spectrometric combination and in-source derivatization.

IV. REARRANGEMENTS OF MOLECULAR IONS

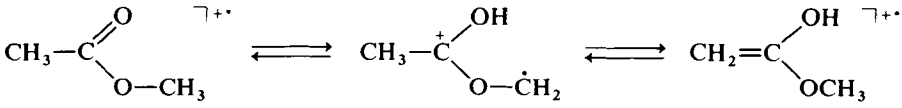
The steps by which molecular ions of carboxylic acid derivatives rearrange fall into three major categories, i.e. tautomerism, formation of distonic ions and formation of ion-neutral complexes. It is noteworthy that all three categories play major roles in the above-discussed fragmentation of carboxylic acid derivatives.

A. Keto–Enol Tautomerism

The ionized keto–enol systems are characterized by the reversal of the relative stabilities of the single species compared to their neutral counterparts. Thus the ionized enols are the thermodynamically favoured tautomers by approximately 15–20 kcal mol^{-1}, the two tautomers being separated by a barrier of *ca* 50 kcal mol^{-1} [39–41]. In general, the ionized enols are easily available by the loss of an alkene from a suitable precursor of the carboxylic acid derivative[42].



Compelling evidence as to the operation of consecutive 1,4-hydrogen shifts has been presented[43].



In the case of the carboxylic acids the corresponding tautomerism apparently has to proceed via a less favourable 1,3-hydrogen shift.

Kinetic energy release studies for the $HO^{\cdot}$ loss has led to the conclusion that the rate of interconversion between the keto and enol forms is apparently slow compared to the rate of fragmentation[42]. In order to explain the metastable fragmentations, non-ergodic behaviour has been brought into play[44].

In the case of amides a similar picture is shown. Thus, the enol of acetamide can conveniently be obtained via a McLafferty rearrangement of, e.g., hexanoic acid amide[45].

Significant differences in the unimolecular fragmentation patterns of the keto and enol tautomers of acetamide were disclosed (cf Table 1). The role of the enol radical cation as a central intermediate in processes of ionized carboxylic acid derivatives is compelling.

TABLE 1. Unimolecular fragmentation patterns (relative abundances) of keto and enol forms of acetamide[45]

	Keto	Enol
$CH_3^{\cdot} + CH_2NO^+$	13	54
$NH_2^{\cdot} + C_2H_3O^+$	2	25
$NH_3 + C_2H_2O^{+\cdot}$	1	2
$CO + C_2H_5N^{+\cdot}$	74	14
$C_2HO^{\cdot} + NH_4^+$	10	5

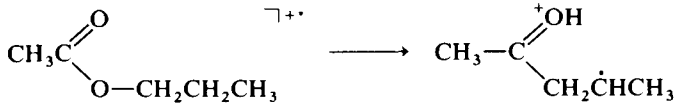
B. Distonic Ions

The term 'distonic ions' describes radical cations, which are formally generated by ionization of a zwitterion or a biradical[46]. Hence distonic ions exhibit, as a consequence, a separation of the charge and the radical function. It should be emphasized that the distonic ions in general appear as rather stable species, residing in significant potential wells, even in cases where the neutral counterpart is highly labile. Distonic ions have recently been reviewed comprehensively by Hammerum[47].

$^{\cdot}CH_2ClH^+$ $^{\cdot}CH_2CH_2OH_2^+$ $^{\cdot}CH_2CH_2CH_2NH_3^+$

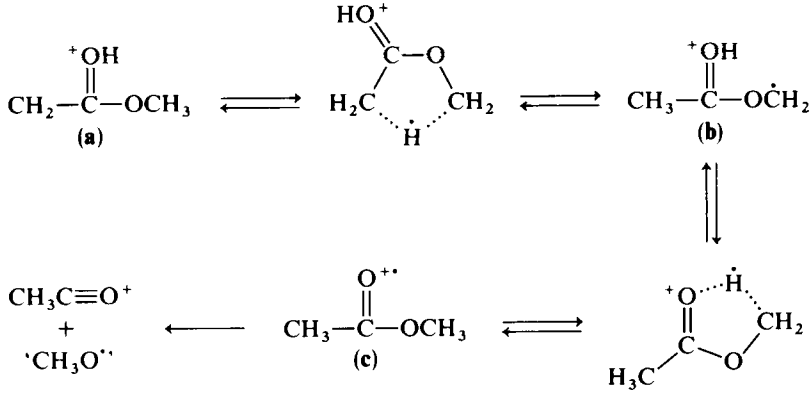
α-distonic β-distonic γ-distonic

It appears that early studies on aliphatic carboxylic acid esters provided the first evidence for the existence of distonic ions in the gas phase[48].

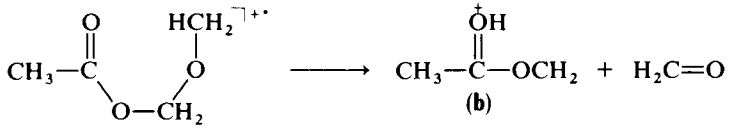


It can be noted that only few radical cations of aliphatic esters are stable as such[47].

Methyl acetate has been studied in great detail by numerous groups, giving rise to a new and more complete picture of the rather rich chemistry of this molecule. It appears that in addition to the keto/enol isomerization (cf Section IV.A) the distonic ion structures apparently play an important role.



The intermediacy of structure **b** was unambiguously demonstrated by McLafferty and coworkers[49] in a study of ionized methyl acetate and its hydrogen-rearranged isomers. The ion structure of **b** was generated by a specific δ-hydrogen rearrangement of ionized methoxymethyl acetate[49].



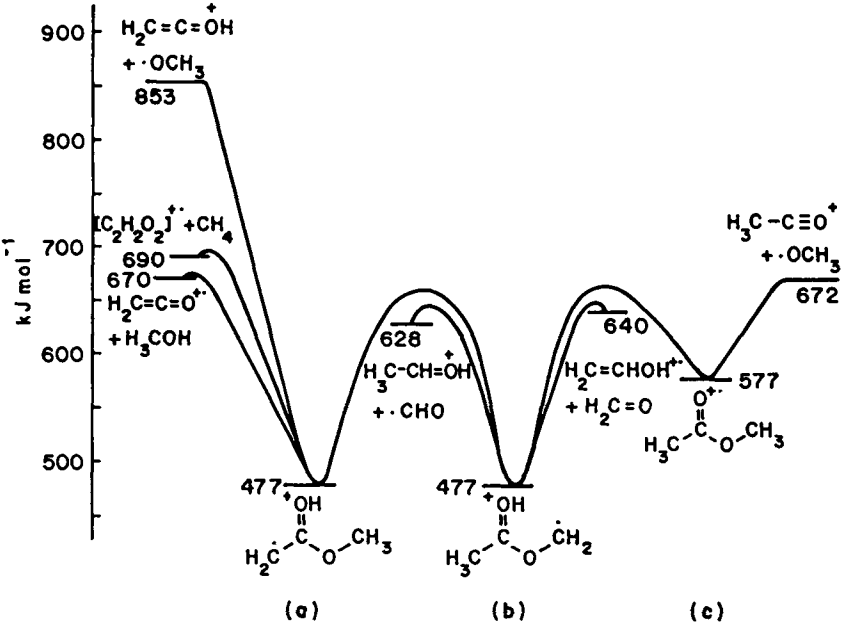
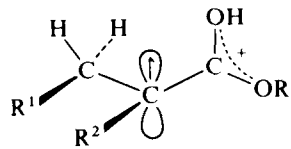


FIGURE 7. Potential energy diagram for the unimolecular fragmentation of methyl acetate[49]

The two isomers **a** and **b** are apparently separated by a barrier, the two activation energies being close to identical (Figure 7). The slightly lower barrier for the **a**–**b** isomerization than for the **b**-**c** isomerization was supported by H/D experiments. Thus the enol structure, **a**, specifically labelled in the hydroxyl group, reveals a slightly lower degree of H/D isomerization than that of **a** labelled in the methoxy group[49]. Further evidence may be found in the metastable spectra of CH_3COOCD_3 and CD_3COOCH_3, the latter showing the highest degree of H/D isomerization, pointing to a **b**–**c** equilibrium as the rate-determining step in the isomerization.

Turning to the higher aliphatic carboxyl acid esters, an even more complex pattern develops, since the side-chains are rearranged as a result of a series of 1,2-hydrogen shifts. In addition, experimental evidence for 1,2-shifts of the C(OH)OR moiety has been presented. However, in all cases it appears that a common crucial intermediate, from which the eventual dissociation takes place, is the enol cation of general structure[50]



Distonic ions appear as being of importance in the case of other carboxylic acid derivatives as well. Thus, especially low aliphatic carboxylic acids have been studied extensively. The observed radical elimination in all cases takes place from the 1,1-diol

structures (cf the above structure[51,52]. In addition detailed insight in the homolytic 1,*n* (*n* = 1–5) rearrangements was obtained[51]. Finally, it should be noted that even within homologous series strikingly different dissociation reactions can be encountered. Thus, methyl acetate rearranges as discussed above to the distonic ion $CH_3C(OH^+)OCH_2^{\bullet}$ (*vide supra*), which decomposes in a metastable manner predominantly to $^{\bullet}CH_2OH$ and CH_3CO^+. In contrast, methyl proprionate isomerizes into a different distonic ion, $^{\bullet}CH_2CH_2C(OH^+)OCH_3$ which gives rise to $CH_3O^{\bullet}$ and $CH_3CH_2CO^+$[53].

From recent studies it becomes clear that detailed investigations of complex reaction mechanisms, as outlined above, rely on an interplay between extensive theoretical studies and experimental work based on mass spectra[54].

C. Ion–Neutral Complexes

An ion–neutral complex is a non-covalently bonded aggregate between an ion and one or more neutral molecules, in which at least one of the involved species can rotate freely[55].

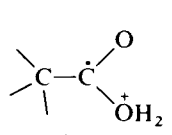
There has been an increasing number of examples demonstrating unambiguously that this type of complex plays crucial roles in unimolecular gas-phase chemistry[56]. Hence, gas-phase ions of the latter structure type in which the neutral part, e.g. H_2O, is depicted as strongly bounded to a π-electron system have been found as characteristic fragment ions in the mass spectrum. An illustrative example is the ketene radical cation complexed with water, an ion–neutral complex which clearly relates to the carboxylic acid functionality[57].

Experimentally, an ion structure corresponding to this complex was generated by CH_2O loss from ionized 1,3-dihydroxyacetone[57].

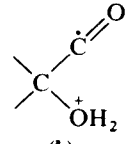
$$HOCH_2\overset{\overset{O}{\|}}{C}CH_2OH^{\urcorner+\bullet} \longrightarrow H_2O\cdots CH_2{=}C{=}O^{\urcorner+\bullet} + CH_2{=}O$$

Even though the detailed MS/MS investigation unambiguously supports the proposed structure, a definite assignment is not possible[57].

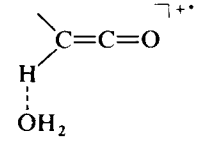
In general, the commonly applied techniques will *a priori* not be able to distinguish between possible isomers, such as **a**, **b** or **c**. The distonic ion structure **a** was predicted



(a)



(b)



(c)

to be thermodynamically more favourable. However, completely free motion of the water molecule around the ketene radical cation was calculated to take place at internal energies of *ca* 2.4 kcal mol^{-1} above the heat of formation of **a**. Thus, an identification of the actual reaction coordinate was not possible. An extremely low kinetic energy release (*ca* 0.2 meV) for the dissociation reaction, however, supports the structural assignment[57].

$$C_2H_2O, H_2O^{\urcorner+\bullet} \longrightarrow CH_2{=}C{=}O^{\urcorner+\bullet} + H_2O$$

A related situation arises in the $C_2H_5NO^{+\bullet}$ system, where both the decarbonylation of CH_3CONH_2 and ion/molecule reactions of ionized ketene with NH_3 generate

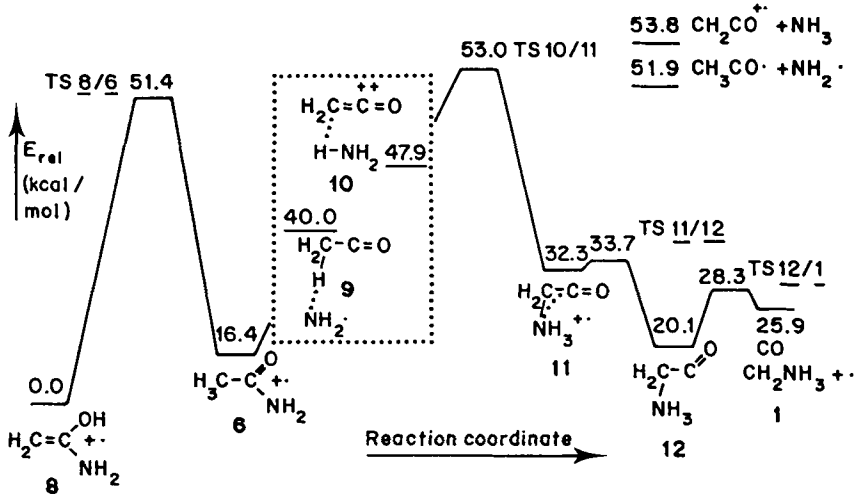
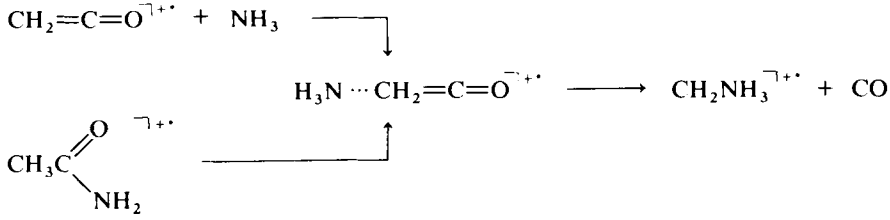


FIGURE 8. Reaction pathways of the potential energy surface of some $C_2H_5NO^{+\cdot}$ species[45], calculated at MP3/6-31G(d)//3-21G + ZPE (energies are given in kcal mol^{-1} relative to $CH_2{=}C(OH)NH_2^{+\cdot}$)

$CH_2NH_3^{+\cdot}$. The two fundamentally different processes are linked by common intermediates, which are suggested to be hydrogen-bridged complexes[45].



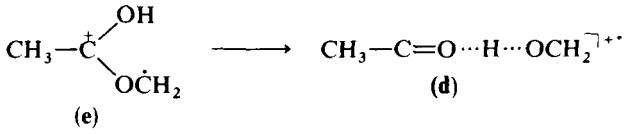
In Figure 8 the potential energy diagram for the $C_2H_5NO^{+\cdot}$ surface is shown. According to the potential energy surface of the $C_2H_5NO^{+\cdot}$ system, CO expulsion from the $NH_3\cdots CH_2CO^{+\cdot}$ can take place without hydrogen scrambling[45].

It is noteworthy that hydrogen-bridged ion structures, as introduced above, are odd-electron species and hence distinctly different from the even-electron counterparts, i.e. the proton-bonded species.

The potential of hydrogen-bridged molecule/radical ion pairs as key intermediates in, e.g., the fragmentation of aliphatic esters was not considered seriously before the appearance of the theoretical studies by Heinrich and coworkers[58].

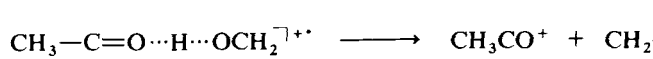
In the case of methyl acetate, a minimal-energy-requirement path was located, the

hydrogen-bridged radical ion/dipole complex (**d**) apparently being generated via a rearrangement of the distonic ion (**e**)[58].



(**e**) (**d**)

The complex, in its $^2(A'')$ state, is the direct precursor to the observed fragments[58].

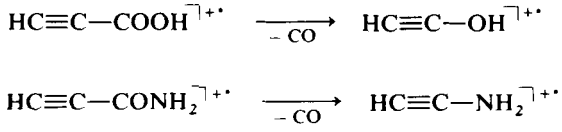


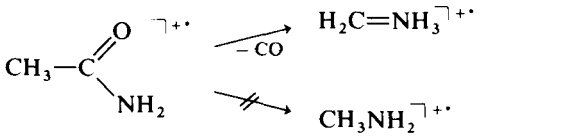
In conclusion, it appears that mechanisms invoking ion-neutral complexes apparently explain a number of otherwise 'mysterious' reactions. As in the case of distonic ions such investigations rely heavily on high-level molecular orbital calculations, which limit the size of the systems that can be studied.

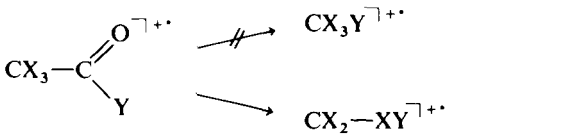
V. SKELETAL REARRANGEMENTS

Electron impact ionization in general leads to consecutive fragmentations of the primarily generated molecular ion. Fragmentations formally corresponding to the extrusion of a small neutral species, such as CO_2 and CO etc., are often observed. This type of fragmentation is explained in terms of skeletal rearrangements[59].

The tendency of carboxylic acid derivatives to undergo this type of skeletal rearrangements is not as pronounced as, e.g., in aromatic ketones etc.[59]. Small aliphatic acids and their derivatives have, however, been used advantageously as precursors to desired ion structures, which have been accessible only with difficulty, if at all, by other routes[60–64].







It is interesting to note that the loss of CO from acetylenic acid derivatives apparently takes place by a simple extrusion reaction[61–63]. The skeletal rearrangements of acet-

amide, which leads to an ylidic ion structure, on the other hand, most probably takes place via hydrogen-bridged intermediates[45].

The structure of $CX_3Y^{+\bullet}$ ions generated from appropriate halogenated acyl halides likewise possess well-defined ylidic ion structures[60,64].

It can be concluded that, apparently, the 'simple' skeletal rearrangements are frequently not really simple. Hence, only in a few cases do the ions correspond to formal losses of small neutral species have actually the structures which *a priori* could have been expected.

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CHAPTER 5

Nuclear magnetic resonance of acids and acid derivatives

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I. INTRODUCTION

Nuclear magnetic resonance (NMR) is becoming more sophisticated not only in terms of both higher fields and more elegant pulse sequences, but also by making more nuclei readily accessible and therefore also becoming more useful. The nuclei, ^{1}H, ^{13}C, ^{15}N, ^{17}O), central atoms of acid derivatives, can all be observed more or less routinely. Furthermore, the NMR technique has been extended from being a typical solution technique to also becoming a solid state technique. In the study of the functional groups and their nearest nuclei, it is optimal to include all available nuclei and appropriate isotopes to yield a matrix of information including chemical shifts, isotope effects on chemical shifts and coupling constants. These are illustrated in Table 1.

The chemical shift has always been a very useful parameter in structure elucidation. By the increasing availability not only of isotropic shifts, but also of shift principal tensor elements, this parameter may become even more useful.

Some essential properties of acids and acid derivatives can be represented by a number of motifs as shown in Figure 1. The motifs represent (A) the charge distribution and reactivity of acid derivatives, (B) the importance of relative orientations, planarity and rotational barriers, (C) conjugation and substituent effects, (D) hydrogen-bonding and inter-molecular effects and (E) titration effects and p*K*a determinations. This review briefly outlines how NMR in its broadest sense, as shown in Table 1, can be used to characterize these important features.

In addition to the experimental progress, also the theoretical understanding of chemical shift, chemical shift tensors and isotope effects on nuclear shielding has increased to a point where useful hints may be obtained from such calculations.

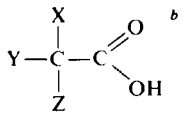
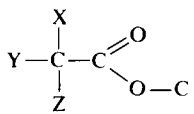
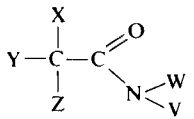
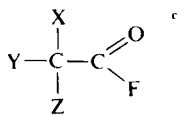
This review deals primarily with acid and acid derivatives. Thio compounds are not inferred unless specifically mentioned.

II. NOMENCLATURE AND ABBREVIATIONS

A. Nomenclature

The present review deals with NMR in both the liquid state and the solid state. For the liquid state the symbol δ is used to describe the chemical shift; σ in solid state work

TABLE I. NMR parameters

	Chemical shift	Isotope effect	Coupling constants
 [b]	H, $^{2}H^{d}$, ^{13}C, ^{17}O	$^{1}\Delta C(^{18}O)$, $^{2}\Delta C{=}O(D)$, $^{1}\Delta^{13}C(^{13}C)$, $^{2}\Delta^{13}C(^{13}C)$	$^{1}J(CO,C)$, $^{2}J(CO,C)$, $^{3}J(CO,C)$, $^{2}J(CO,H)$, $^{3}J(CO,H)$, $^{1}J(\underline{C}{=}O,^{17}O)$
	^{1}H, ^{13}C, ^{17}O	[a]	[a] + $^{2}J(CO,O,C)$, $^{3}J(CO,O,C,C)$, $^{3}J(CO,O,H)$
	^{1}H, ^{13}C, ^{17}O, ^{15}N	[a] + $^{1}\Delta N(D)$, $^{2}\Delta C{=}O(ND)$, $^{3}\Delta C_{z}(ND)$, $^{1}\Delta C{=}O(^{15}N)$, $^{1}\Delta^{13}C(^{15}N)$, $^{1}\Delta^{15}N(^{13}C)$	[a] + $^{1}J(N,H)$, $^{1}J(CO,N)$, $^{2}J(CO,N,C)$, $^{2}J(CO,N,H)$, $^{3}J(CO,N,H)$, $^{2}J(C,C{=}O,N)$, $^{3}J(C,C,C{=}O,N)$,
 [c]	^{1}H, ^{13}C, ^{17}O, F	[a] + $^{3}\Delta F(D)$, $^{2}\Delta^{19}F(^{18}O)$	[a] + $^{1}J(C{=}O,F)$, $^{2}J(C,C{=}O,F)$, $^{3}J(H,F)$, $^{2}J(^{17}O,F)$

[a] As for acids. [b] For thio derivatives the ^{35}S resonance in itself is in most cases too broad to be useful. In the case of coupling constants substitute O by S. However, derivatives have been investigated to a much lesser extent. [c] For acid chlorides the chlorine resonance cannot be observed in NMR. [d] Also referred to as D.

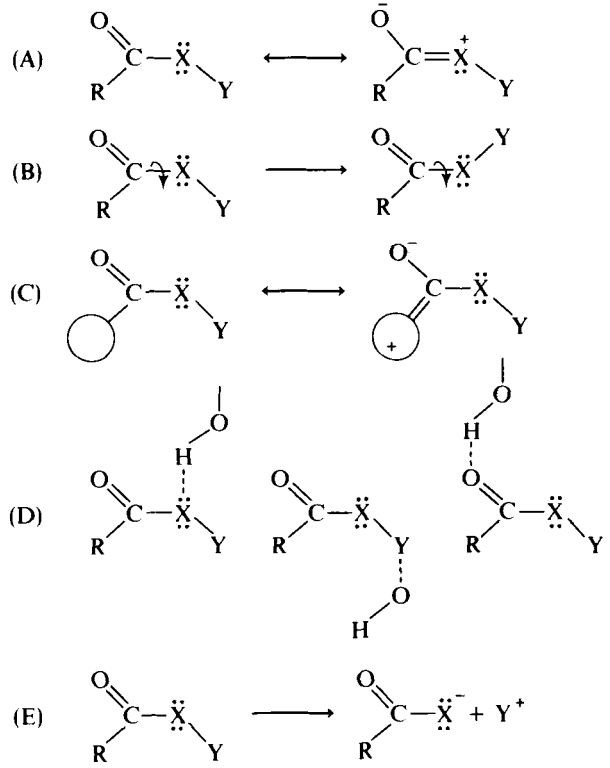


FIGURE 1. Motifs illustrating basic properties of acid derivatives. For X=N one lone-pair is replaced by H, R or φ

is used to describe the shielding. The distinction between the nuclear shielding, σ_i, and the chemical shift, δ_i, will be maintained according to suggestions by Jameson[1]; δ is used whenever the given number is relative to a reference. This means that some data have been renamed compared to the original papers. Primary isotope effects are defined as ${}^{p}\Delta = \delta H - \delta D$, whereas secondary isotope effects are given according to Hansen[2] as ${}^{n}\Delta = \delta X(H) - \delta X(D)$.

B. Abbreviations

2D	two-dimensional
ASIS	aromatic solvent induced shift
BPTI	bovine pancreatic trypsin inhibitor
DEPT	distortionless enhancement of polarization transfer
DSP	dual substituent parameter
GIAO	gauge invariant atomic orbitals
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HSMQC	heteronuclear single-multiple-quantum coherence

IGLO	individual gauge for localized orbitals
INDO-S	intermediate neglect of differential overlap—Spectroscopy
INEPT	insensitive nuclei enhanced by polarization transfer
LIS	lanthanide induced shift
LORG	localized orbital/local origin
MAS	magic angle spinning
MM	molecular mechanics
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
RAHB	resonance assisted hydrogen bonding
SCFPT	self-consistent field perturbation theory
UFLEFS	uniform linear electric field effect

III. CHEMICAL SHIFTS

The chemical shift is an invaluable tool in the assignment of chemical structures and is also a valuable way of assessing a number of molecular properties.

The terms chemical shift and chemical shielding are used throughout the paper. For a distinction between shielding and shift see Section II. It is important to remember that both parameters are tensors and that the chemical shift observed in solution is an averaged parameter. It is therefore also important to determine the principal tensor elements, σ_{11}, σ_{22} and σ_{33} (see Table 2). Other interesting descriptors are the anisotropy given as

$$\Delta\sigma = \sigma_{11} - (\sigma_{22} + \sigma_{33})/2 \qquad (\sigma_{11} > \sigma_{22} > \sigma_{33})$$

and the average nuclear shielding

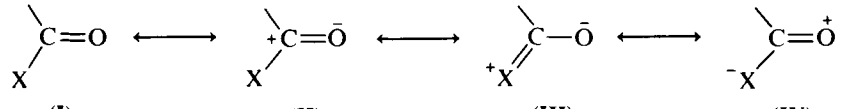
$$\bar{\sigma} = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3$$

Recently, a very elegant way of representing nuclear shielding has been described, in a fashion similar to organic chemistry (Jorgenson–Salem points)[3,4].

A. ^{13}C Chemical Shifts

The chemical shift range is ~160 to 183 ppm as illustrated in Scheme 1. Chemical shifts of acids, esters and other acid derivatives are tabulated extensively in References 5–9. The key feature of the carbonyl group in organic chemistry is the partial positive charge at the carbonyl carbon. This feature is less outspoken in acids, esters and other acid derivatives as compared to ketones and aldehydes. This is in line with the chemical shift range for acid derivatives (see above) compared to that of ketones and aldehydes, 180–220 ppm.

If the positive charge is delocalized via the unsaturated parts of the molecule (Figure 1C) the chemical shift moves upfield.



(I) (II) (III) (IV)

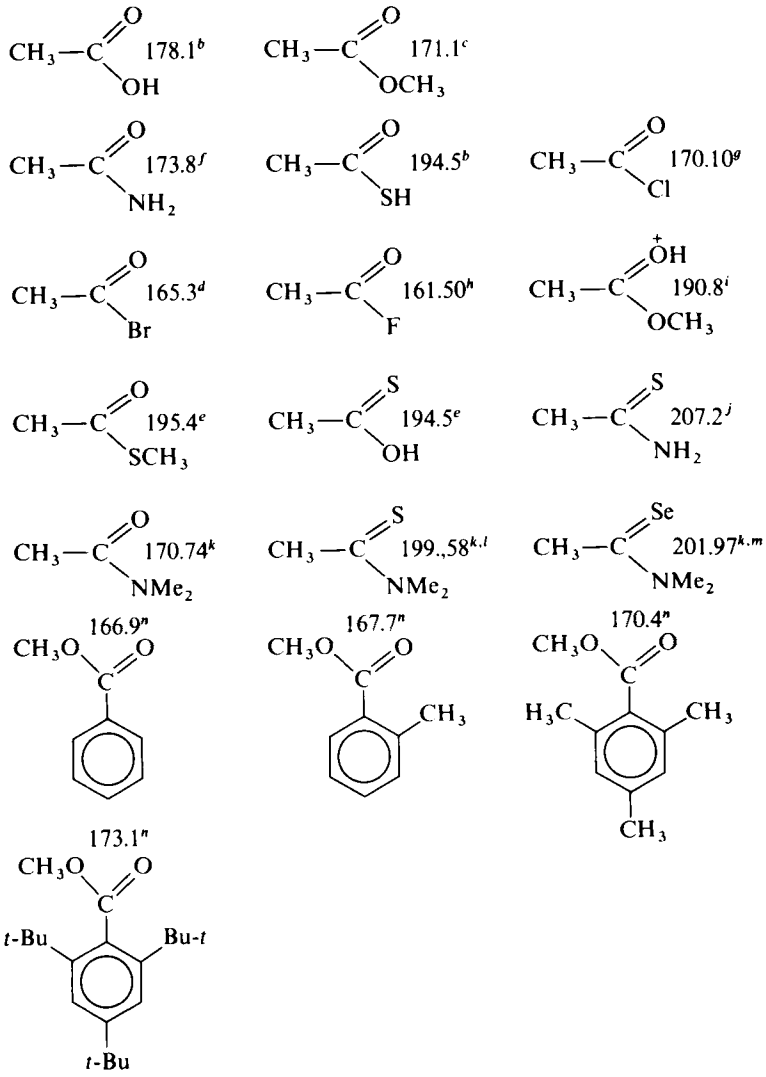
(1)

Wehrli and Wirthlin[5] extend this argument to cover the X substituent, which places a positive charge at the carbonyl carbon (1). Judging from acids, esters and amides this

TABLE 2. ^{13}C shielding tensor elements of carbonyl carbons[a]

	δ_{11}	δ_{22}	δ_{33}	$\bar{\delta}$[b]	$\Delta\delta$[c]	Reference
Methyl acetate	265.8	158.8	118.8	181.1	−93.5	43
Acetic anhydride	279.8	140.8	114.8	178.5	−95.5	43
Acetic acid[d]	263.8	179.8	103.8	182.5	−118	44
Acetic acid[s]	302	155	105	184		41
Acetic acid[t]	292	146	96	178		41
Benzoic acid-d_6[e]	231	188	103	174	−107	14
Benzoic acid[f]	238	180	103	174	−106	18
Pyromellitic acid[g]	262.3	167.8	104.3	178.1	−110.8	40
Pyromellitic acid[h]	246.3	161.7	105.9	171.3	−98.1	
Malonic acid[i]	243.3	178.3	107.3	176.3	−103.5	40
	247.3	173.8	110.3	177.1	−100.3	
Ammonium malonate	240.6	173.6	102.2	172.1	−104.9	46
Glycine	243.8	179.8	105.9	176.5	−105.9	47
l-Alanine	242.8	182.8	106.8	177.5	−160.8	48
l-Serine	238.2	180.2	106.2	174.9	−103	49
l-Threonine	240.2	164.7	105.0	170	−97.45	21
l-Asparagine[j]	239.5	179.0	108.6	175.7	−100.65	50
l-Asparagine[k]	245.5	195.9	87.8	176.4	−132.9	
Glycylglycine(GlyGly*[l])[m]	243.4	176.4	87.2	169.0	−122.7	51
AlaAla	243.1	176.5	88.4	169.3	−121.4	22
l-[^{13}C]AlaAla[n]	243.3	170.1	94.3	169.2	−112.4	52
Ac-[^{13}C]GlyAlaNH$_2$	241.4	184.2	89.3	171.6	−124	52
Ac-[^{13}C]GlyTyrNH$_2$	241.8	164.8	94.6	167.0	−109	52
Ac-[^{13}C]GlyGlyNH$_2$	242.3	183.5	94.1	173.3	−122	52
(Gly*)$_n$I[n](β)[o]	243	174	88	168.3	−121	38
(Gly*)$_n$II(3_1)	243[p]	179	94	172.0	−117	38
(Gly*)$_5$[q]	242	179	93	171.3	−118	38
(Ala, Gly*)$_n$(α)	244	178	94	171.3	−118	38
(Leu, Gly*)$_n$(α)	242	179	94	171.7	−117	38
(Asp(OBzl), Gly*)$_n$(α)	243	178	95[r]	172	−116	38
(Asp(OBzl), Gly*)$_n$(ω)	243	178	95[r]	172	−117	38
(Val, Gly*)$_n$(β)	242	171	93	168.7	−114	38
(Val, Gly*)$_n$(β)	242	171	93	168.7	−114	38
Acrylamide	257.8	173.8	78.8	173.5	−142	58
Acetyl fluoride	—	—		161		45
Acetyl fluoride[s]	300	114	79	164	−128	41
Acetyl fluoride[t]	288	120	76	162		41

[a] Original chemical shift data are often given relative to liquid benzene. These have been converted to TMS by subtracting 127.8 ppm. Values are rounded off. More shielding tensors are given in References 3 and 12.
[b] Defined as $(\delta_{11} + \delta_{22} + \delta_{33})/3$.
[c] Defined as $\delta_{33} - (\delta_{11} + \delta_{22})/2$.
[d] Temperature 83 K.
[e] Room temperature.
[f] Temperature 55 K.
[g] Twist angle between the aromatic ring and the carboxyl group is 74°.
[h] Angle 18°.
[i] The two carboxylic acid groups are different in the crystal.
[j] COO^- carbon.
[k] $CONH_2$ carbon.
[l] The asterisk * indicates C=O carbon.
[m] Standard abbreviations are used.
[n] [^{13}] indicates that the peptide is enriched.
[o] Letters in parentheses show conformation.
[p] Given in paper as 343, but this is clearly a misprint.
[q] Random.
[r] Tentative.
[s] IGLO.
[t] LORG.



SCHEME 1. Typical $^{13}C{=}O$ chemical shifts of acid derivatives[a]

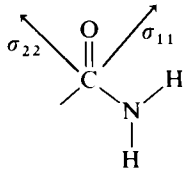
[a] Solvent $CDCl_3$ unless otherwise stated. [b] Taken from Reference 10b. [c] Taken from Reference 10b. [d] Taken from Reference 10c. [e] Taken from Reference 6. [f] Taken from Reference 10f. [g] Taken from Reference 10e. [h] Taken from Reference 305. [i] Taken from Reference 10g. [j] Taken from Reference 9. [k] Taken from Reference 68. [l] The corresponding thiobenzamide gave a $\delta CS = 199.74$ ppm. [m] The corresponding selenobenzamide gave a $\delta CSe = 204.58$ ppm. [n] Taken from Reference 78.

could be correct. However, an extension to acyl fluorides shows that the resonance structure (**I IV**) must be included. The participation of this resonance structure is supported by the high stretching frequencies ν_{CO} for acetyl fluoride[11].

When discussing the range of chemical shift it must be realised that a good part of this spread is caused by substituents. For aliphatic carboxylic acids and esters the α-effect is ~10 ppm, whereas the β-effect is ~2 ppm and the γ-effect is almost negligible[8]

1. Carbonyl chemical shift tensors

The double-bond structure of the carbonyl group is reflected in the chemical shift anisotropy of the C=O group. The chemical shift of the carbonyl carbon is a tensor property as shown in **2**. For an amide σ_{22} is approximately along the C=O bond, whereas σ_{33} is perpendicular to the C=O,N plane. Shielding tensors are given in Table 2 together with the averaged chemical shifts, δ, and the anisotropy, $\Delta\delta$. These values reveal that the π-electron structure plays an important role in the nuclear shielding. The anisotropy determines the width of the powder spectrum, and also the relaxation in those cases in which chemical shift anisotropy is an important factor[12].



(2)[a]

[a] σ_{33} is perpendicular to the O,C,N plane and with the origin at C=O.

An inspection of Table 2 shows that acids have large α_{33} values and amides somewhat smaller ones. Both groups show larger values than ketones[13]. The trend is therefore similar to that found for many other chemical and spectroscopic properties.

The value of σ_{22} is roughly constant for the acid derivatives, acids and amides; σ_{22} values for ketones and aldehydes are much larger[13]. Both methyl acetate and acetic anhydride show quite significantly lower values.

Kempf and colleagues[14] conclude, based on molecular orbital calculations, that the variation in σ_{22} is due primarily to variation in the excitation energy of the n-π* electronic transition. Lattice effects may be responsible for some of the variations in σ_{22}[15].

One such lattice effect is hydrogen bonding[16]. Pines and coworkers[17] suggest that σ_{22} gradually rotates away from the carbonyl bond as the molecule changes from a ketone to an ester, to an asymmetrical carboxylic acid group and finally to a symmetrical carboxylic acid group (both C—O bonds are of approximately the same length). A study of benzoic acid at various temperatures shows that two different molecules exist in the unit cell[18]. An extrapolation to zero K shows that one of the molecules has a shielding tensor along the C=O bond. At room temperature, an average of the two structures yields an apparent angle of about 24°. The results at room temperature are similar to those reported by Kempf and colleagues[14]. The rotation of σ_{22} at room temperature is in that case clearly an effect of external conditions. The tensor elements of oxalic acid dihydrate have been redetermined and δ_{33} differs from the original study[19]. Different crystal forms are suggested as a reason for this discrepancy[20].

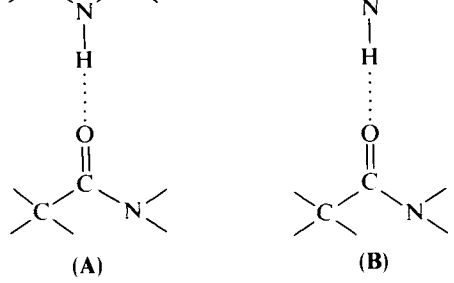
Hydrogen bonding is also observed in crystals of amino acids[21]. The individual variations in σ_{22} observed in the dipeptides are linked to hydrogen bonding in

the crystal[22]. On the basis of these findings Oas and coworkers[22] question the use of chemical shift tensors of model compounds in orientational studies as proposed by Harbison and colleagues[23].

By measuring the chemical shift anisotropy and knowing the shielding tensor elements, Cornell and group determined the orientation of the C=O bond in gramicidin A in a lipid bilayer membrane[24–27].

Saitô and colleagues[28] investigated chemical shifts in a large number of proteins. Factors influencing the chemical shift of the amide backbone carbonyl carbon chemical shift are hydrogen bonding and the structure of the protein (α_R and α_L helices, β-plated sheets). Hydrogen bonding is strongly connected to the structure. They[28] found that the carbonyl carbon resonance of the α-helix is displaced downfield compared to β-plated sheets. A similar conclusion is reached by Kainosho and coworkers[29,30]. The change in the chemical shift is considered a consequence of the change in the mean excitation energy, ΔE. Tonelli[31,32] considers the change as caused by steric effects and hence of γ-type. γ-effects were originally suggested to arise because of polarization of C—O bonds. It is found that COOH groups in amino acids cause an effect at the γ-carbons, although the effects are difficult to quantify[33].

However, as noted above, hydrogen bonding could also be a contributing factor. Ando and coworkers[34] investigated two different types of hydrogen-bond patterns, **3 A** and **3 B**, in the solid state, thereby also being able to estimate distances[35].



(A) (B)

(3)

For type **A** they observed a linear, low field shift with decreasing $R_{O\cdots N}$ distance, whereas for type **B** a linear high field shift is observed with decreasing $R_{O\cdots N}$ distance. The C=O···N angle is 153°. This is slightly larger than average[35]. The authors suggest that the 'length effect' is more important than the 'direction effect'[34].

Kempf and collaborators[14] have pointed out that the σ_{11} is dominated by the singlet–singlet σ-π^* excitation and σ_{22} by the $n \rightarrow \pi^*$ transition.

Theoretical calculation showed that for case **3 B**, σ_{11} varied strongly, while σ_{22} varied to some extent in both cases[34]. It is worth mentioning that case **3 B** to a large extent resembles the effect of a titration (see Section III.A.5.a and b). Hydrogen-bonding clearly plays a role, but the presence of an intramolecular oxygen (i.e. the intra-residue C=O oxygen) could also be important, as demonstrated in Figure 2.

A correlation between the NH O=C distance or NH O=C distance and the carbonyl chemical shift (CS) difference (the difference is given as the δCO of the residue in BPTI—the δCO of the random coil value) has been suggested[36].

Plots of δCO vs φ and ψ angles of proteins have also been suggested[37]. Glycine-

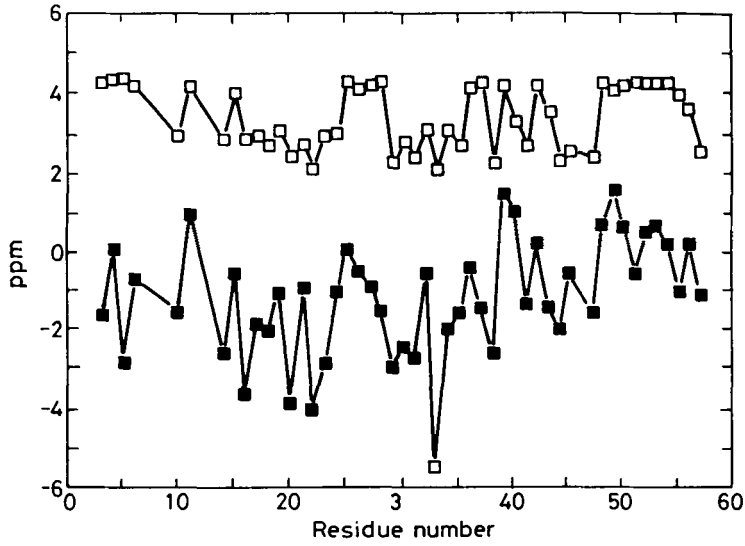


FIGURE 2. Plot of $\Delta\delta$C=O—■—■— vs. the intermolecular distance

R(C—O...H—N)—□—□—

of BPTI[36]

containing polymers show a significant difference between β-sheets and α-helical structures. CO resonances of α_R helices are generally displaced downfield with respect to those in the β-sheet[39]. σ_{22} and σ_{33} values vary whereas σ_{11} is fairly constant. However, the variations in σ_{22} and σ_{33} are not parallel. The observation of $\bar{\sigma}$ is thus less descriptive[38].

A picture of how individual shielding tensors behave is now emerging. The chemical shifts of pyromellitic acid[40] show a low-field shift for the most twisted carboxylic acid group, in good agreement with findings in solution (see Section III.A.6). The anisotropy increases when the conjugation is removed and approaches the value for acetic acid. The growing empirical knowledge of individual shielding tensor elements combined with a deeper theoretical understanding of the factors influencing these will also make studies of isotropic carbonyl chemical shifts more useful.

2. *Theoretical calculations*

Theoretical calculation of chemical shifts has now reached a high level of accuracy, and also a level making such calculation useful for the practising chemist. A comparison of the different methods is conducted using acetic acid, acetaldehyde and acetyl fluoride. The individual gauge for localized orbitals (IGLO) and the localized orbital/local origin (LORG) methods are compared. The results are similar. Agreement between calculated and theoretical results is best for the isotropic values of C=O carbons whereas σ_{11} is calculated to be too large and σ_{33} too small as seen from Table 2[41]. The value of σ_{22} lies approximately along the amide C=O bond and σ_{11} is in the amide plane perpendicular to the C=O bond, as seen from **2**. Theoretical calculations tend to align σ_{11} and the C=O bond to a larger extent than the experimental results[34,42].

3. Isotropic carbonyl chemical shifts

Carbonyl chemical shifts depend (as discussed) on the nature of the X substituent, on mesomeric effects, steric effects, electric field effects and hydrogen bonding. All these factors will be discussed in the following.

a. Correlations. Conjugation in aromatic or olefinic acid derivatives has been investigated either through analysis of C=O chemical shifts or through analysis of aromatic ring carbon chemical shifts. For amides ^{15}N chemical shifts can be used (see Section III.D.4) and ^{17}O also acts as a reporter nucleus (Section III.E.2). The dual substituent parameter approach[53–55] (DSP) has been used in a number of cases. Bromilov and coworkers[56] investigated *p*-substituted acid derivatives[56,57]:

for para-substituted benzoyl fluorides

$$\Delta CO = -2.58\sigma_I - 1.04\sigma_R^{\circ\,56} \quad (1)$$

$$\Delta CO = -2.5\sigma_I - 1.3\sigma_R^{BA\,57} \quad (2)$$

for ethyl benzoates

$$\Delta CO = -2.6\sigma_I - 1.1\sigma_R^{\circ\,57} \quad (3)$$

for benzoic acids

$$\Delta CO = -2.3\sigma_I - 0.5\sigma_R^{BA\,57} \quad (4)$$

$$\text{or } \Delta CO = -2.58\sigma_I - 1.04\sigma_R^{\circ\,56} \quad (5)$$

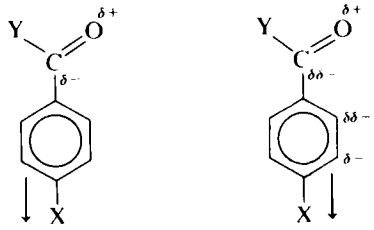
for thiobenzamides

$$\Delta CO = -2.8\sigma_I + 1.1\sigma_R^{+\,57} \quad (6)$$

for benzamides

$$\Delta CO = -2.4\sigma_I - 0.4\sigma_R^{BA\,57} \quad (7)$$

The work of Bromilov and coworkers[56] showed that the inductive (field) contribution to the chemical shift for the first atom of a conjugating side-chain was dominated by π-polarization. They[57] also found that the chemical shift goes upfield for most substituents, also for NO_2 and CN, which are mesomerically electron-withdrawing. This is termed a reverse effect and is explained by considering that polarization of the aromatic system plays a vital role. Two different types of polarization are considered, local and extended polarization. The net polarization is a 'sum' of these two effects. The effect of localized polarization is illustrated in **4A** and that of extended polarization in **4B**.



(4)

The dipoles of the substituents induce a transfer of π-electron density in the carbonyl group from the oxygen to the carbonyl carbon, where the increased electron density leads to a high-field shift.

For *N*,*N*-dimethylamides the Swain–Lupton approach[58] gave

$$\delta_{CO} = -1.91F - 1.50R + 171.5^{58} \quad (8)$$

$$\delta_{C-1} = 3.20F + 16.7R + 135.68^{58} \quad (9)$$

For benzoic acid

$$\delta_{CO} = -1.34F - 0.76R + 167.09^{58} \quad (10)$$

Kosugi and Furuya[59] investigated a series of linear free energy (l.f.e.) relationships and found for benzoic acid the best agreement with the Swain–Lupton[55] equation. The same holds true for the anions. For 4′-nitrophenyl benzoates substituted in the 4-position O'Connor and coworkers[60] obtained

$$\delta_{CO} = -1.0F - 0.05R - 0.03 \quad (11)$$

using an updated Swain–Lupton equation[61].

Jones and Wilkins[58] conclude that transmission is heavily dominated by field effects. Electron-withdrawing substituents at the *para*-position lower the π-electron density at C-1. For the C=O group they increase the shielding through a field-induced change in the polarization of the amide group π-electron system. The C=O group seems to contain a poorer reporter nuclei than the neighbouring nuclei C-1, ^{15}N (Section III.D.4) and ^{17}O (Section III.E.2). For substituted thiophene-2-carboxylic acids[62] a DSP analysis gave:

for substituted 2-acids

$$\delta_{CO} = -2.86\sigma_I + 0.42\sigma_R^{BA} \quad (12)$$

for substituted 2-carboxylates

$$\delta_{CO} = -4.23\sigma_I - 1.16\sigma_R^{BA} \quad (13)$$

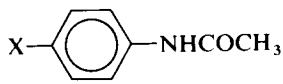
for substituted 3-acids

$$\delta_{CO} = -2.81\sigma_I - 0.74\sigma_R^{BA} \quad (14)$$

for substituted 3-carboxylates

$$\delta_{CO} = -4.11\sigma_I - 1.10\sigma_R^{BA} \quad (15)$$

These results support the polarization scheme found for benzene derivatives. DSP analysis has also been performed on pharmaceutically interesting acetanilides[62,63].



(5)

A comparison with 4′-nitrobenzoates shows that the $NHCOCH_3$ group (**5**) is less strongly cross-interacting than the ester groups. The effect of X is transmitted well beyond the benzene ring[60].

For α-monosubstituted *N*,*N*-diethylacetamides it is found that δ_{CO} correlates with σ_L (a localized electrical parameter)[64,65].

The ^{13}C chemical shifts of carboxyl carbons of substituted benzoic acids show a linear relationship with pK_a values for *m*-substituted and electron-withdrawing *p*-substituents[65,66]:

$$\delta_{CO} = 0.81pK_a - 8.87 \tag{16}$$

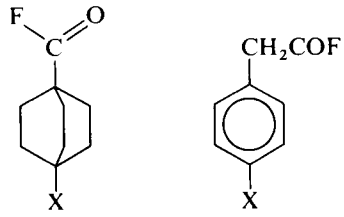
Obviously, many different correlations can be established. One exists linking C=O and C=S chemical shifts[65] of amides and thioamides[67]:

$$\delta_{CS} = 1.45\delta_{CO} - 46.5 \text{ ppm} \tag{17}$$

However, the range of compounds for which such a relationship is useful is limited[68].

The resonance forms of acid fluorides (see **1**) make it impossible to divide the polar field effects into independent mechanisms originating from the π-electron system and from polarization effects of the π-system[69]. For *p*-substituted benzoyl fluorides the fluorine atom chemical shift may be used to monitor effects of the *para*-substituent. It was concluded that the COF group is best regarded as a single entity[70,71].

For molecules like **6A** the COF group is detached from the aromatic system and for both **6A** and **6B** the C=O and C—F bonds are polarized by a direct field effect[72].

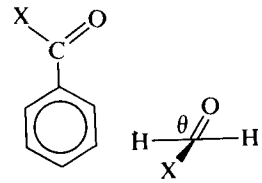


(A) (B)

(6)

The essential result of the correlation investigations is clearly to pin-point the nuclei best suited as reporter nuclei.

b. Conjugation Aromatic carbonyl compounds have been investigated in great detail[13]. The isotropic chemical shift of aromatic carbonyl compounds is related to the twist angle θ[73,175] (see **7**). If the carbonyl group is twisted out of the plane of the aromatic



(7)

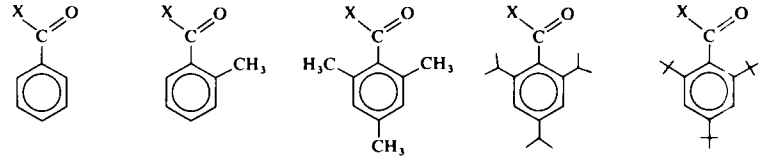
ring, the C=O chemical shift moves to low field (high frequency)[74–77]. This was clearly demonstrated for the shift tensors of pyromelitic acid (Table 2). An equation has been proposed[75].

$$\cos^2\theta = \delta(C{=}O)^{\theta} - \delta(C{=}O)^{90}/[\delta(C{=}O)^{0} - \delta(C{=}O)^{90}] \tag{18}$$

where $\delta(C{=}O)^{\theta}$ is the measured carbonyl shift, $\delta(CO)^{90}$ is the chemical shift of a model compound in which the carbonyl group is twisted 90°, and $\delta(C{=}O)^{0}$ is the chemical

TABLE 3. Carbonyl chemical shifts (ppm) of sterically hindered acid derivatives[a]

X	δ	θ	δ	θ	δ	θ	δ	θ	δ	θ
OCH_3	166.9	0°	167.7	21°	170.4	49°	171.3	44°	173.1	90°[d]
Cl	168.2	0°	—[b]	—[b]	170.4	39°	170.9	57°	173.8	90°[d]
$N(CH_3)_2$	171.1	0°	—[b]	—[c]	171.2	—	173.3	—	173.5	90°[d]



[a] Reference 78.
[b] Not given.
[c] The difference in chemical shifts between $\theta = 0°$ and $\theta = 90°$ is too small to make a determination.
[d] Assumed to be 90°.

shift of the planar reference compound. The difficulty of this method lies in the difficulty of obtaining reference values, both δ(C=O)[90] and also δ(CO)[0] in the case of a non-planar compound.

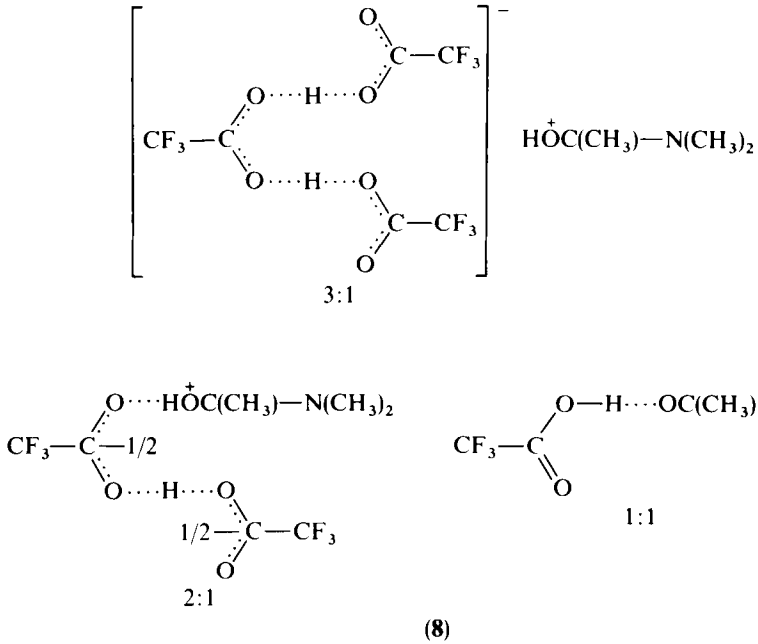
This equation gave Leibfritz[78] the twist angles of esters, *N*,*N*-dimethylamides and acid chlorides as shown in Table 3. The angle for the 2-methyl derivatives is clearly much larger than observed in X-ray studies (see also Section III.E.3). A plausible reason could be that the direct effect of the methyl group on the CO chemical shift has not been taken into account. A second source of uncertainty is the assumption that the 2,6-di-*t*-butyl derivatives are twisted 90° out of the plane[78].

4. Hydrogen bonding and protonation

a. Hydrogen bonding. Hydrogen bonding has been discussed in the solid state. It was found that for the non-charged case (Section III.A.1) hydrogen bonding to the C=O groups leads to a low-field shift[34].

For amides in solution, the effects are more difficult to follow. The low-field shift caused by hydrogen bonding to the carbonyl groups is counteracted by hydrogen bonding to the N—H bond[79].

b. Solvent effects The changes of chemical shifts upon addition of trifluoroacetic acid were investigated. No protonation is assumed. Addition of trifluoroacetic acid to a solution of an ester leads also to a low-field shift of the carboxyl carbons. Begtrup concludes that hydrogen bonding rather than protonation takes place[80]. Branched alkyl acetates show slightly increased effects in primary, secondary and tertiary series at the carboxyl and the α carbon. However, the ratio $\Delta\delta$C—O/$\Delta\delta$C=O varies. This is tentatively explained by assuming a change in hydrogen bonding at the C=O carbon vs the C—O. These studies may also be used to estimate basicity parameters[81]. Samoilenko and coworkers[82] investigated the system trifluoroacetic acid/*N*,*N*-dimethylacetamide and found a 1:1 complex, and also that protonation takes place as shown



(8)

in **8**. Fast exchange occurs in all stages and the amount of each complex depends on the mol% of trifluoroacetic acid.

The dependence of ^{13}C chemical shifts on the dielectric constant of the medium has been calculated using INDO/S (Incomplete neglect of differential overlap) together with the solvation model. A change in the C=O chemical shift of acetic acid of 8.8 ppm to low field is found in going from a dielectric constant of 1 to a value of 80 (water)[83].

5. *Titration shifts*

a. Theory. The chemical shift of a carbonyl carbon is influenced by a change due to a charge at the group itself or due to a charge at a neighbouring group. The charges reside typically at COO^-, or NH_3^+ groups. Titration of carboxylic acid groups leads to a significant shift of the carboxylic acid carbon itself as observed both in carboxylic acids[84] and in amino acids, but there are also changes in the chemical shift of carbonyl carbons quite far away. Examples are aspartic acid and glutamic acid. Titration of the α-carboxylic acid leads to changes in the chemical shift of side-chain carboxylic acid carbon of aspartic or glutamic acid or at the amide carbon, as in asparagine and glutamine[85].

Observation of carbonyl titration shifts are used to determine individual pK_a values for all titrating parts of a molecule even if the pK_a values are very similar. This is demonstrated very nicely in proteins.

The theory for titration shifts was outlined by Batchelor[86]. The changes in the chemical shifts due to a uniform electric field are, as formulated by Buckingham[87],

$$\delta_{el} = E_i A_{ij} r_j + E_i E_j B_{ijk} r_k + \cdots \tag{19}$$

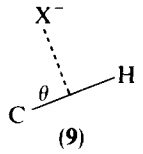
where E_i are components of the field vector, r_j is a unit vector of a coordinate system fixed in the molecular framework, while A_{ij} and B_{ijk} are second- and third-order tensor elements.

The second-order term of equation 19 has not been evaluated. As the field from a point change decreases with distance, the linear term, the first term of equation 19 has to be written as

$$\delta_{\text{linear}} = E_i A_{ij} r_j + a_{ij} \partial E_i / \partial r_j \tag{20}$$

The first term of equation 20 is referred to as the uniform term and the second as the gradient term. The uniform term decreases with the square of the distance to the field source, whereas the gradient term falls off with the third power of the distance[88]. The uniform term will hence dominate for bonds far away from the field source. The uniform field linear electric field effect (UFLEFS) term also depends in general on the cosine of the angle (see **9**) between the field and the polarized bond:

$$\partial_{\text{UFLEFS}} = A_z(C) E \cos\theta \tag{21}$$



(9)

The angle is easily determined for C—H, C—C and C—C bonds, whereas for other groups like acid groups or amides it is less obvious. In addition, the $A_Z(C)$ has to be determined. For carboxylate anions this is estimated to be about 3×10^{-11} esu, which is of the same order of magnitude as for C=C bonds[88].

b. Results. Titration shifts for amino acids and proteins[88–101] have been studied intensively. It has been noted that the first C(=O)NH carbonyl carbon after the C terminal shifts to high field when the terminal carbon is deprotonated. This has been explained by Christl and Roberts[90] by assuming an intramolecular hydrogen bond.

The titration shifts of most peptides in which the C-terminal carboxylic acid group titrates are usually confined to the first peptide bond. One exception is clearly the pentapeptide Aib-Ala-Aib-Ala-Aib, which is supposed to be 'helical'[91]. For a larger peptide, bovine pancreatic trypsin inhibitor (BPTI), titration shifts due to the titration of the terminal carboxylic acid as well as the two aspartic and glutamic acid carboxylic acid groups of the side-chain can be observed[98–100]. In addition, effects due to the OH group of tyrosine or the NH_3^+ titration were observed[99]. pK_a values were determined[98,99]. Also, the titration shifts can be related to the distance and angle between the field direction and the C=O bond[100].

Long-range effects of electric field effects were observed in unsaturated fatty acids. Distance can be estimated knowing the appropriate parameters of equations 19–21[102]. Intercharge distances are also estimated in flexible systems. COO^- carbon chemical shifts in trimethylamminoalkanoates (structure **10**) are found to vary strongly with the

$$(CH_3)_3\overset{+}{N}(CH_2)_nCOO^-$$

(10)

number of intervening methylene groups. Effects up to $n = 7$ are seen. The results are discussed in terms of electric field effects, in terms of distance and in terms of effective electric fields. The authors find evidence for folding induced by electrostatic attraction and hydrophobic coiling[103].

Salt bridge formation can also influence C=O chemical shifts[104].

pK_a values in non-aqueous solution have been determined using the so-called

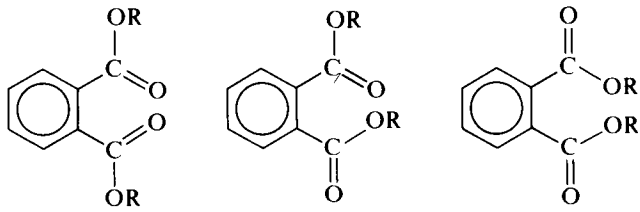
'co-titration', adding an acid of a well-known pK_a. The method relies on an estimation of the effect of a dielectric constant different from water[105]. The problem is similar to that encountered in proteins in which the dielectric constant of the interior may well be different from that of the surrounding water.

c. Theoretical calculations. C=O chemical shifts depend on nearby charges as seen in the previous section and on salt bridge formation. Furthermore, the chemical shift is a tensor property. Better correlations are usually found between properties and the principal tensor elements than with average chemical shifts (Section III.A.2). It would thus be interesting to see how an external charge influences ^{13}C chemical shifts. Theoretical calculations (LORG)[106] of acetamide show that the average C=O chemical shift depends on orientation. A negative charge along the C—C bond gives rise to a distinct low-field shift, whereas a negative charge opposite the C—C bond gives rise to a high-field shift[107]. It should be noted that this direction almost coincides with σ_{11} (Section III.A.1). Furthermore, the ^{17}O as well as the ^{15}N, and to a lesser extent the ^{13}C, chemical shifts of the methyl groups also depend on the position of the charge[107].

6. Conformation of carbonyl compounds

The orientation of the carbonyl group plays an essential role in determining the chemical properties.

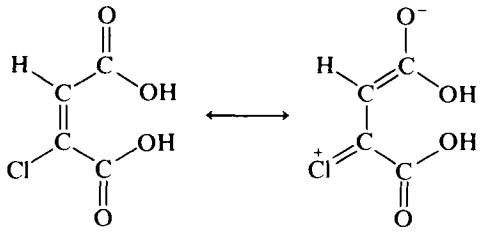
A discussion of this subject can be divided into two parts: the determination of the twist angle and the determination of the preferred orientation. The first question has been addressed by means of chemical shifts of the carbonyl groups (Section III.A.3.b).



(11)

The complexity of the problem of determining both the twist angle and the orientation can be illustrated in the case of phthalic esters (**11A–C**). This problem has been treated both by means of ^{13}C and ^{1}H chemical shifts[108] as well as by $^{n}J(CO,C)$ coupling constants[109]. Three planar conformations **A**, **B** and **C** together with the non-planar ones can be suggested. Bruck and Rabinowitz[108] advocate **A** on the grounds that the system thus constitutes a non-cyclic aromatic system with 10π electrons. Carbon–carbon coupling constants in the dimethyl ester and in phthalic anhydride are fairly similar[109], but all coupling constants are slightly smaller in the ester. This has been connected to a slight twist of the ester groups[109]. The orientations of α,β-unsaturated dicarboxylic acids (**12,13**) are discussed by Williamson and coworkers[110]. They find a decreased substituent influence in dicarboxylic acids compared to the anhydride, which indicates a twist of the carboxylic acid groups.

The preferred conformation in this case corresponds to **11C**. An argument in favour of this structure is better conjugation between the carbonyl group and the double bond (**12**).



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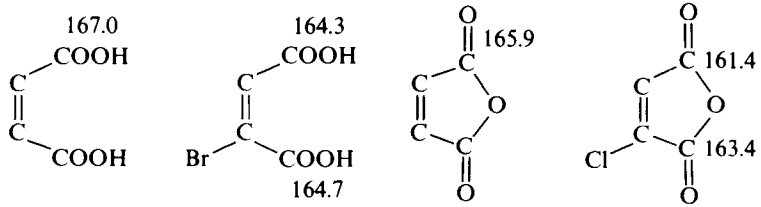
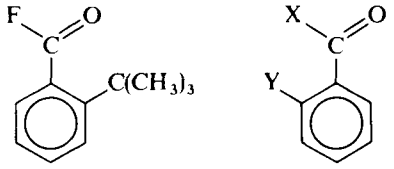


(13)

Substituents at the double bond cause a high-field shift of the carbonyl carbon chemical shift[110].

Bruck and Rabinovitz conclude that monoesters are planar[108]. A recent study of 2-ethyl and 2-*t*-butylbenzoic acid shows that these can also be considered planar. The same holds true for benzoyl fluoride derivatives.[111] (**14**. It is hence concluded that it is the interaction of the X substituent with the Y substituent (in most cases H) that causes the twist of the substituents in acids and esters (**15**). If both *o*-positions are substituted, the carboxylic acid group is twisted out of the ring plane[78,113]. Further discussion of this point can be found in Section III.E.3.



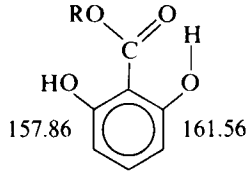
(14) (15)

Lanthanide induced shifts (LIS) are also used to estimate the direction of the carbonyl group in esters[114,115] and amides[116]. However, Ceder and Beijer[114] warn that the conformation of the organic molecule may change as a consequence of complexation.

7. Effects on aromatic carbons

The directional dependence of the chemical shifts of carbons in the vicinity of a COX group may be determined either (i) from solid state spectra, or (ii) from ^{13}C spectra of a cooled solution in which the rotamers are frozen out, or (iii) from chemical shift comparisons or (iv) from isotopic perturbation of equilibrium studies. The solid state spectra are either determined on single crystals (from such studies shielding tensors can be obtained, see Section III.A.1) or by means of MAS (magic angle spinning)[117] spectra of powders. The latter technique is becoming very widespread. The effects of carboxylic

acid groups are observed in pyromellitic acid[40], exemplifying the effects of a conjugated and non-conjugated group. It is clearly seen that the *o*-carbon ^{13}C chemical shifts become different, whereas the carbons further away are not influenced to any degree. Cooling down leads to different chemical shifts as described for benzaldehydes and acetophenones[118,119]. Esters are normally more difficult to freeze out. An example is **16**, which shows that the two *ortho* carbons clearly have different chemical shifts[120]. A study of deuterium equilibrium isotope effects on methyl 2,6-dihydroxy-4-methylbenzoate gives likewise an estimate of the difference in chemical shifts between C-2 and C-6, about 3.7 ppm[121,122].



(16)

Twisting the carbonyl group also leads to a high-field shift of the *o*-carbons as seen for 2,6-dimethylbenzoic acid derivatives[77,123, 229].

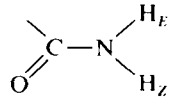
B. ^{1}H Chemical Shifts

^{1}H NMR of acid derivatives has been investigated for almost 40 years. it is not our intent to cover this enormous span of work, which has been reviewed extensively[124,125], but to highlight a few topics that are becoming very useful although they have been known for a long time.

1. Assignments

For primary and secondary amides it can be stated tentatively that: 'The low field proton can be ascribed to the proton *trans* to the C=O group'[126]. For tertiary amides the assignment of the two resonances of the CH_3 groups is somewhat complicated. This has been reviewed by Lewin and Frucht[126]. They conclude that three methods may be used safely: (i) NOE (Nuclear Overhauser Effects), (ii) ASIS (aromatic solvent induced shifts) and (iii) lanthanide induced shifts (LIS). No general rules can be given.

For primary amides of proteins the above rule also holds and it was noted that $^1J(NH_E) \sim 90$ Hz, whereas $^1J(NH_Z) \sim 87$ Hz[127] (see also section V.B.3).



(17)

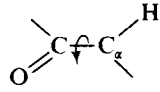
2. NH chemical shifts

NH chemical shifts of proteins are now becoming very abundant. The chemical shift shows normally a rather large spread, 6–11 ppm. This spread is ascribed to hydrogen bonding and to the presence of electrostatic effects. Wagner and coworkers[128] have correlated δNH to the $1/r^3$ distance to the nearest oxygens for BPTI (bovine pancreatic

trypsin inhibitor). NH resonances may incidentally be very close to a benzene ring and very severe high-field shifts are the result. One such example is the NH_Z of the asparagin side-chain of residue Asn-44 and Gly-37 NH of BPTI. Both are very close to the surface of the aromatic ring of Tyr-35 and shifted upfield 4.3 and 3.5 ppm, respectively[129]. NH chemical shifts of proteins and peptides depend clearly also on hydrogen bonding.

3. H-α chemical shifts

These depend on the solvent, but are mainly determined by inductive effects from the COO groups[130]. Electric field effects are probably also operative. ^1J(C, H) couplings have been determined (see Section V.A.10) and depend on the orientation of both the C=O and the N—H moieties of proteins. It thus seems promising to investigate further the δH-α structural dependence.



(18)

Amino acid residues in helices have δCH chemical shifts upfield by 0.4 ppm, those of the β-sheet 0.4 ppm downfield from random coil values[131].

4. δNH temperature sensitivity

Chemical exchange as such is treated in Section VII. A consequence of exchange, e.g. with solvent, is the finding that the position of the NH resonances is temperature dependent[132–134]. The change of temperature may simultaneously cause a conformational change. This clearly complicates matters, but it does also create a possibility of following this conformational change via the NH exchange rates and the temperature coefficients.

The temperature coefficient generally reflects the accessibility of water and hydrogen bonding. Concerning the different exchange mechanisms (see Section VII.1), for non-hydrogen-bonded amides a $\delta NH/dT$ of 10 ppb per deg is found[132] while for hydrogen-bonded N protons the temperature coefficients are close to zero. The change in chemical shift is generally towards high field upon an increase in temperature. Yamazaki and Abe found for model peptides like N-methylated and acetylated amino acids that the temperature coefficients are of the order of 6–11.4 ppb per deg depending on the solvent. They were largest at high concentrations in $CDCl_3$[135].

The dependence of $\delta NH/T$ vs solvent dielectric constants was investigated by Llinas and Klein[136] for a buried ornithine NH. The slope changes from negative for pyridine to positive for DMF, DMSO and H_2O. The authors suggest that the thermally activated process probably changes from H-bond formation to H-bond breakage upon decrease of solvent polarity, again clearly linking NH temperature coefficients and exchange.

5. COOH proton chemical shifts

The chemical shift of the acid proton is particularly interesting. In organic solvents this resonance is often broad due to exchange. It may, however, be studied in the solid state using modern multiple pulse techniques[137].

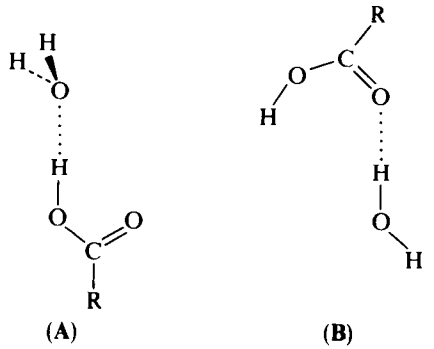
a. The ^1H chemical shift tensor. The principal values of the ^1H NMR chemical shift tensor and the related parameters, $\sigma_\perp$ and $\sigma_\parallel$, as well as the shielding anisotropy,

TABLE 4. ^{1}H principal tensor elements of acids

	δ_{11}[a]	δ_{22}	δ_{33}	$\bar{\delta}$	$\delta_\perp$	Reference
α-$(COOH)_2$	−19.3	−17.1	−1.5	−12.6	−18.2	138
α-$(COOH)_2$	−20.5	−20.5	−2.7	−14.6	−20.5	139
β-$(COOH)_2$	−21.6	−21.6	4.2	−13.0	−21.6	140
$KH(COO)_2$	−26.0	−26.0	3.3	−16.2	−26.0	140

[a] Note the change in nomenclature, compared to the references.

$\Delta\sigma$, have been investigated as descriptors of the hydrogen bonds of acids and other hydrogen bonds involving OH groups (Table 4).



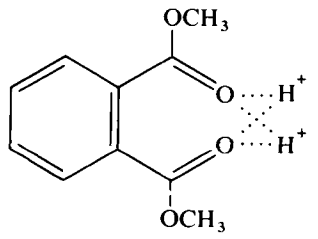
(19)

Rohlfing, Allen and Ditchfield[141] calculated ^{1}H chemical shifts of two dimers involving acids and water and representing the different typical geometries as shown in **19** in order to take into account geometry and charge distribution. SCFPT theory (self-consistent-field perturbation theory) with GIAO (gauge invariant atomic orbitals) for *ab initio* calculation of shift tersors were used. An analysis of calculated[141] and experimental results[142] vs $R_{O\cdots O}$ showed good correlation for $\delta O\underline{H}$ and for $\delta_\perp$, whereas $\delta_\parallel$ did not correlate well with $R_{O\cdots O}$. However, the change in $\delta_\parallel$ is much smaller. $\delta O\underline{H}$ is typically deshielded 2–3 ppm upon dimer formation. Analysing the shift components it was found that $\delta_\perp$ decreases whereas $\delta_\parallel$ increases. Since the anisotropy, $\Delta\delta$, is equal to $\delta_\parallel - \delta_\perp$, a large charge is observed in this parameter. It is also found that it is the nature of the proton acceptor that dominates the influence on the proton shielding tensor changes due to hydrogen bonding.

The correlation between $\delta O\underline{H}$ and $R_{O\cdots O}$ seems rather promising. An extension to weak hydrogen bonds may also exist[140]. However, a straightforward transfer to the liquid state does not seem possible[140]. Nevertheless, such solid state studies have made the ^{1}H chemical shift of hydrogen-bonded acids much more useful.

6. Protonation and deprotonation

The COOH chemical shift in solution generally changes depending on concentration and reaches a maximal change of 2 ppm. If an amide and an acid are mixed, protonation



(20)

may take place. This is true for a mixture of amides and CF_3SO_3H or CH_3SO_3H. This leads to a change to low field of 5.3–5.7 ppm, whereas the OH proton of acetic acid only shifts 0.8 ppm and that of dichloroacetic acid 3.4 ppm. A shift of 5 ppm is taken as evidence for protonation[143].

Protonation of phthalic acid[144] and phthalic esters[145] are reported and an interesting structure of type **20** was suggested based on ^1H chemical shifts. ^1H chemical shifts of a large number of aliphatic acids and their anions have been analysed[146] and data for olefinic acids are also available[147]. The changes in ^1H chemical shifts are generally small, but can in suitable cases be used to measure pK_a values etc., although ^{13}C chemical shifts seem more suitable (see Section III.B.6).

C. ^2H Chemical Shifts

^2H NMR, also known as D NMR, can, despite a spin equal to 1, rather easily be studied because of the low quadrupolar moment.

D NMR is mostly used in connection with solid state studies of the acid proton (deuterium) resonance and in studies of primary isotope effects.

1. Chemical shifts

Deuterium chemical shifts contain in general the same information as ^1H chemical shifts except for cases with large primary isotope effects. The interest in deuterium NMR lies mostly in determination of the quadrupole coupling constants $e^2q\ Q/h$ (see also Section III.E.1). Linear correlations between the latter and $R_{O\cdots O}$ distances for acids have been found[142].

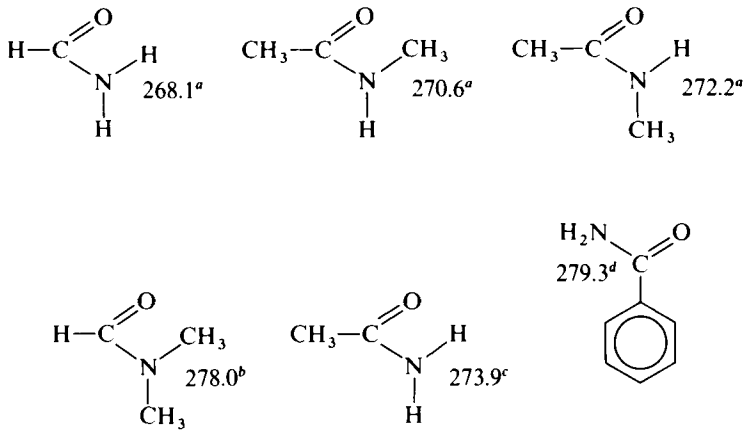
2. Primary isotope effects

Primary isotope effects, $^P\Delta$, are defined as $^P\Delta = \delta H - \delta D$. They are shown to be in hydrogen-bonded systems and have been used to distinguish between a single and a double potential well[148]. However, the results obtained for acids in organic solvents, are different from those in water[149] (see Section VI).

Primary isotope effects are parallel to secondary isotope effects on carbon[13,148].

D. ^{15}N Chemical Shifts

In the discussion of ^{15}N NMR it should be remembered that the sensitivity of ^{15}N is low because of a low gyromagnetic ratio and because of its low natural abundance, 0.37%. At a natural abundance level the sensitivity is 3.8×10^{-6} times that of protons. This problem can be overcome by enrichment or by use of indirect detection schemes. The former is becoming rather easy for, e.g., proteins by means of genetic engineering.



SCHEME 2. Typical ^{15}N chemical shifts of amides

[a] Reference 211a. Solvent DMSO. Depends on solvent. [b] Reference 211b. Solvent DMSO. Depends on solvent. [c] Reference 211c. Neat liquid. Depends on solvent. [d] Reference 211d. Solvent DMF.

The indirect detection schemes rely on ^{n}J(H,N) couplings. The larger the coupling the better the results. One-bond couplings of amides are of the order of 90 Hz (see Section V.B.3) and are therefore very appropriate. Long-range couplings can be used for amide nitrogens with no directly attached protons. One further factor to take into account is the negative gyromagnetic ratio. This may lead to nulling of signals under some circumstances.

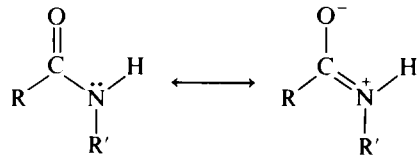
The ^{15}N chemical shift range is large, ~900 ppm. However, this is not so important in the present content. For amides a rather narrow range is observed, and for proteins (see Section III.D.1.c) the range is only 30 ppm. ^{15}N NMR has been reviewed in several contexts[150–155]. For typical ^{15}N chemical shifts see Scheme 2. A fact that may cause some confusion is the different choice of reference in different papers and the fact that an external reference is often used. For an account of the problems involved, see Reference 152. The most frequently used reference is external nitromethane.

Indirect detection. Several 1D techniques and modifications exist. INEPT (Insensitive Nuclei Enhanced by Polarization Transfer) is a typical polarization experiment[156]. Another sequence is DEPT (Distortionless Enhancement by Polarization Transfer)[157]. For an overview, see Reference 158. 2D techniques include the multiple quantum coherence experiment (HMQC)[159], heteronuclear single-multiple-quantum coherence (HSMQC)[160] and multiple-bond correlation spectra (HMBC)[161–163]. 3D versions are also available, such as NOESY-HMQC[164,165]. Very recent pulse schemes rely strongly on heteronuclear coupling constants[166].

1. ^{15}N chemical shifts of amides

a. General trends. ^{15}N chemical shifts are sensitive to back-donation effects of lone-pair electrons at the nitrogen atom as described by **21**. ^{15}N chemical shifts seem very useful in a characterization of the nature of the amide group.

Solvent polarity clearly could influence the proportion of **A** to **B**. Form **B** is stabilized by hydrogen bonding at the oxygen atom as well as at the N—H bond. A change in



(A) (B)

(21)

the **A** : **B** ratio likewise is expected to change the rotational barrier, a well-known amide property. Varying the charge distribution is also likely to influence, e.g. N–H exchange rates. The ^{15}N chemical shift of amides may thus be used to gauge a number of fundamental properties of the amide group. However, in order to do so the contributions from simple substituent effects have to be estimated.

α-Effects can be of both signs, whereas the β-effect is roughly -5 to -15 ppm per alkyl substituent. The γ-effect is normally small, not exceeding 1 ppm and increasing the shielding. δ-effects are in most cases negligible[152].

The planarity of the amide groups is also likely to influence the **A**:**B** ratio.

A complete movement of one NH proton leading to a new tautomer or a tautomeric equilibrium can clearly also be investigated by ^{15}N chemical shifts (see Section III.D.5).

b. ^{15}N chemical shift tensors. ^{15}N chemical shift tensors for amide groups have not been investigated as much as the carbonyl carbon shift tensor[167,171]. It is shown for small peptides that the shift tensor elements differ somewhat from one peptide to another (see Table 5) whereas their molecular orientations do not (see Figure 3). Some of this variation can, however, be ascribed to lattice effects[168].

Utilization of solid state ^{15}N information is important in two types of systems, both in the insoluble protein cases and in solid-like cases like membranes or other large biological assemblies[170–174]. The information gathered from such systems may eventually be useful in material science studies. Furthermore, the use of solid materials has the advantage that structure information is available from X-ray studies[39] (see next section).

c. ^{15}N chemical shifts of proteins. The easy access to ^{15}N enriched proteins and the occurrence of one type of residue in many different environments in a protein has made ^{15}N of proteins a very valuable source of information concerning factors influencing ^{15}N chemical shifts of amides. ^{15}N chemical shifts of proteins have now been investigated in a rather large number of proteins[175–198].

^{15}N chemical shifts of amide backbone nitrogen depend most likely on the following factors: (a) the type of side-chain, glycine or other; (b) the flanking residues; (c) hydrogen

TABLE 5. ^{15}N chemical shift principal tensors of peptides[a]

Molecule	σ_{11}	σ_{22}	σ_{33}	Angle
AlaAla	65.3	78.1	215.5	106
$AcGlyAlaNH_2$	85.1	85.1	229.4	100
$AcGlyTyrNH_2$	52.1	77.1	209.3	98
GlyGly · HCl	57.3	59.8	210.0	99
$AcGlyGlyNH_2$	40.7	64.2	210.6	100

[a] From Reference 169.

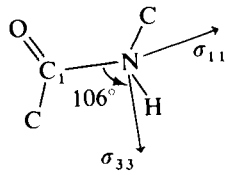


FIGURE 3. Orientation of the ^{15}N chemical shift tensor in the plane of the peptide bond

bonding; (d) non-bonded interactions. In order to get a measure of these effects, values for random coil proteins are needed[177–179]. These have been obtained from small peptides and *N*-acetylamino acids[180]. However, correction had to be made for the flanking residues on both the amide and carboxy ends according to Kricheldorf[181]. A final set of reference chemical shifts for random coil proteins is given in Reference 179.

This led to the following interesting conclusions: 'All amino acids cause a downfield shift compared to glycine and the effects of neighbouring groups become large with increasing bulkiness of the side chain'[179]. These findings support the findings by Kricheldorf[181].

The fact that even the random coil values are average values[178] clearly weakens the approach and only large differences in ^{15}N chemical shifts of proteins can at present be evaluated.

The ^{15}N chemical shifts of proteins vary typically from 103 to 134 ppm. Within the same residue, leucine, a spread of 15 ppm is observed in a protein[187].

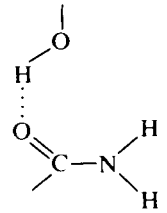
Glushka and collaborators[177–179] did not observe any clear correlation between downfield shift and intramolecular hydrogen bonding. This was ascribed to the presence of solvent. However, in view of the results of theoretical calculations (Section III.D.2) the ^{15}N chemical shift could depend both on hydrogen bonding at the NH and CO sites, and also on the direction of the hydrogen bond towards the C=O oxygen.

A correlation between the torsional angle ψ and ^{15}N chemical shift was observed for β-sheet residues of BPTI[178].

^{15}N chemical shifts of homopolypeptides gave, for α_R-helices, chemical shifts between 97.0 and 99.2 ppm and, for β-sheets, between 99.5 and 107.0 ppm. A comparison of homopolymers with the same residue showed that ^{15}N in the α-helix always resonates at higher field than the β-sheet. On this basis Shoji and coworkers[39] concluded that a significant conformational dependence is present.

2. *Hydrogen bonding*

The effects on hydrogen bonding have been investigated. From straightforward arguments, hydrogen bonding to the N—H bond (see **22**) should lead to increased double-bond character and a larger negative charge at the oxygen and at the nitrogen.

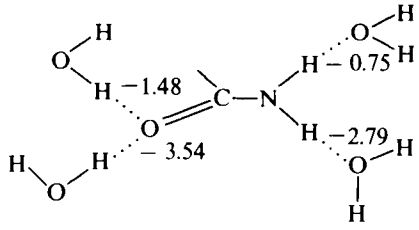


(22)

Similarly, hydrogen bonding at the C=O group will lead to a more positive charge at nitrogen.

These predictions fit the original studies on simple amides and alumichrome[199] where hydrogen bonding leads to deshielding[181,182,200,201].

Theoretical calculations of ^{15}N chemical shifts suggest stereospecific solvation chemical shift changes[201] as indicated in **23**. This suggestion has not yet been verified experimentally, but opens a possible use of ^{15}N chemical shifts in the study of the importance of orientation of the hydrogen-bond donor or acceptor bonds.



(23)

The description of effects of hydrogen bonding has focused on relocalization of the lone-pair electrons. However, it should not be overlooked that the water oxygen may in itself cause an electric field effect, as recently found for ammonium ions[202]. Deshielding effects are observed in protonating media in line with effects observed by hydrogen bonding. They can be explained by increasing delocalization of the lone pair. For a general discussion of solvent effects see Reference 152, p. 81. Hydrogen-bonding effects on ^{15}N have been used to elucidate the hydrogen-bond structure of gramicidin S, a symmetrical decapeptide[203]. ^{15}N chemical shifts can also be used to monitor hydrogen bonds in base-pairing of nucleotides[204].

3. Rotational barriers

Since nitrogen shieldings are sensitive to back-donation effects of lone-pair electrons at the nitrogen atom concerned, and since the delocalization of the pair increases the C—N bond order, one may expect to observe some relationship between nitrogen shielding and barriers to internal rotation in amides. Correlations with limited fit were found[205]. Ureas and thioureas show a reasonable correlation if effects of alkyl substituents are accounted for[206]. Increased delocalization of the lone-pair electrons leads to a general low-field shift of the nitrogen. For a full discussion of rotational barriers see Section VIII.

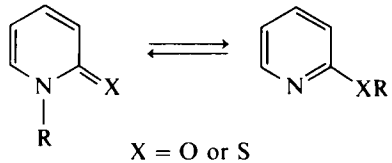
4. Correlations

Correlations have been related to rotational barriers (see the previous section). A ^{15}N NMR study of *meta*- and *para*-substituted benzamides and thiobenzamides showed that ^{15}N chemical shifts are very sensitive to substituent effects. A dual substituent parameter analysis showed excellent correlations of ^{15}N chemical shifts against field and resonance effects. Thioamides were also investigated and showed higher sensitivity to substituents. However, π-electron densities at nitrogen showed the same sensitivity for both amides and thioamides[207]. For homopeptides, a correlation between $^{13}C{=}O$ chemical shifts and ^{15}N chemical shifts is found[39]. Similarly one could expect a correlation between $\delta\underline{N}$ and $\delta\underline{H}$, but no such correlation was found[195]. N$\underline{H}$ chemical

shifts are temperature dependent (see Section III.B.4). Llinas and collaborators[182] found for alumichrome that ^{15}N chemical shifts vary with temperature in a fashion similar to $\delta N\underline{H}$.

5. Tautomerism

^{15}N chemical shifts are very suitable to study tautomerism involving nitrogen, because of large chemical shift differences between singly and doubly bonded nitrogens.



X = O or S

(24)

For R = alkyl (see **24**) no equilibrium exists and an estimate of the 'frozen' ^{15}N chemical shifts is obtained. This difference is typically 100 ppm. The large difference in chemical shifts makes ^{15}N chemical shifts a useful tool for the estimation, or at least for the determination, of the preferred tautomer[208]. Other examples are 2-hydroxy[209], 2-thioxypyrazines[209] and pyridinethiols[210].

E. ^{17}O NMR Chemical Shifts

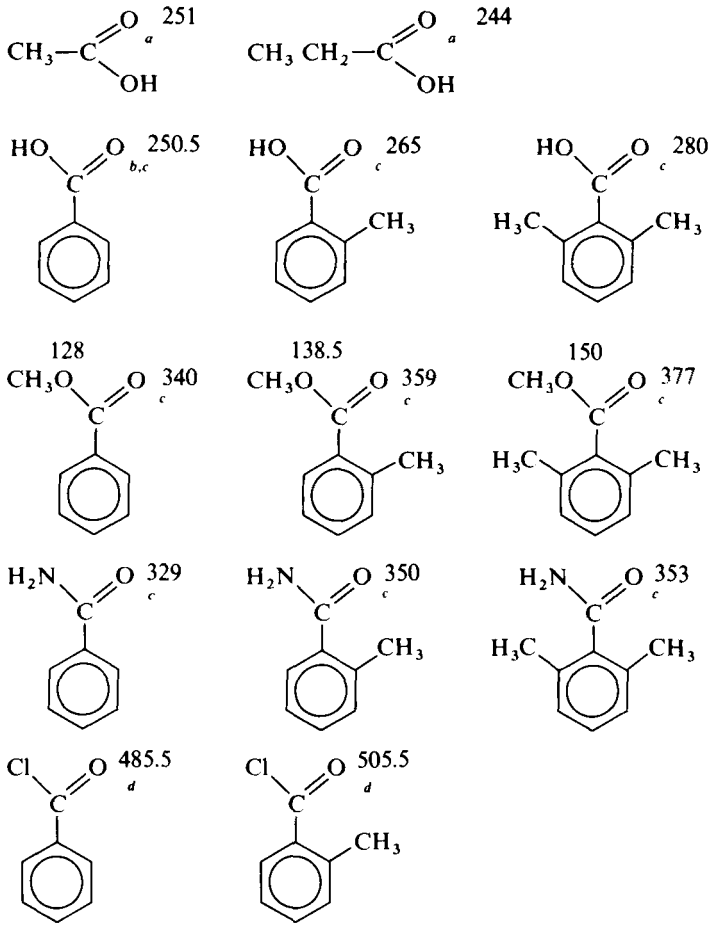
^{17}O is not an easy nucleus to observe for the reasons described below. Nevertheless, ^{17}O chemical shifts have in recent years proven to be a very versatile tool in the study of aromatic carbonyl compounds and amino acids. ^{17}O has very recently been reviewed and ^{17}O NMR data have been extensively tabulated[212–215]. ^{17}O NMR has shown great promise in the study of hydrogen bonding, in detection of out-of-plane twist in aromatic compounds and detection of steric hindrance in general. These are the areas that will be covered primarily in this section.

1. Characteristic features

The natural abundance is 0.037% and the gyromagnetic ratio, γ, is $-3.626.4$ rad s^{-1} gauss^{-1}. The unusual feature, compared to ^{1}H, ^{13}C and ^{13}N, is the spin, I, which is 5/2 and the associated quadrupole moment, which is -2.6×10^{-26} cm^2. The chemical shift range (Scheme 4) is approximately 1000 ppm including inorganic compounds, but closer to 400 ppm for organic compounds[212]. The ^{17}O chemical shift is normally referred to the oxygen resonance of H_2O. The drawback of ^{17}O NMR are the broad resonances. This is due to short T_2 relaxation. The T_1 and T_2 relaxation times are dominated by quadrupole relaxation, because of the quadrupole moment:

$$\frac{1}{T_2} \sim \frac{1}{T_1} = \frac{3}{40}\frac{2I+3}{I^2(2I-1)}\left(1+\frac{\eta^3}{3}\right)\left(\frac{e^2q^2Q}{\hbar}\right)^2 T_c \qquad (22)$$

η being the asymmetry factor, T_c the rotational correlation time, I the nuclear spin and $e^2q^2Q/\hbar$ the quadrupole coupling constant.



SCHEME 3. Typical ^{17}O chemical shifts of acids, esters and amides

[a] Taken from Reference 234. [b] Chemical shifts are average values. See text. [c] Taken from Reference 226. [d] Taken from Reference 231.

By increasing the temperature and thereby reducing the viscosity, excessive line widths may be reduced. In consequence of these features it can be said that enrichment is necessary; resonances are difficult to observe in large molecules with large correlation times and spectra are best recorded in low-viscosity solvents at high temperatures.

The oxygen is often a terminal nucleus (this is always so for double-bonded oxygens). This makes oxygen a very good reporter atom and more clear-cut correlations can often be established than for, e.g., the nearby carbons. As will be seen below, ^{17}O chemical shifts are very sensitive, a fact that often more than counteracts the inconveniences of broad resonances. For esters and lactones, both the doubly- and singly-bonded oxygen may be observed.

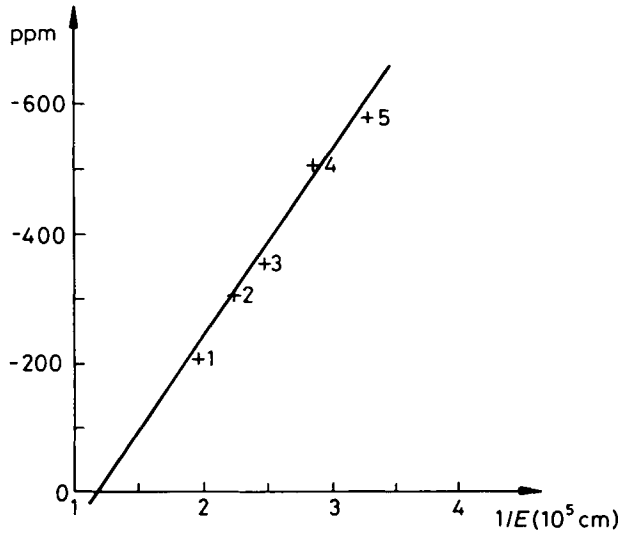


FIGURE 4. ^{17}O chemical shifts vs $1/E$ where E is the energy of the lowest-energy transition, 1 refers to $(NH_2)_2CO$, 2 to $HCONH_2$, 3 to $CH_3COOC_2H_5$, 4 to CH_3COCl and 5 to CH_3CHO[218]

2. *Correlations*

A linear relationship between ^{17}O chemical shifts and the lowest-energy transition (n–π^*) as obtained from UV or visible spectra was realized as early as 1961[216]. de Jeu[217] later extended this treatment. For second-row elements the paramagnetic term is dominating. The paramagnetic contribution can be written as

$$\sigma_p^A = \frac{-2e^2h^2\langle r^{-3}\rangle_{2p}\sum Q_{AB}}{3m^2c^2\Delta E} \tag{23}$$

where Q_{AB} consists of charge density and bond-order matrix elements for the unperturbed wave functions $\langle r^{-3}\rangle_{2p}$ is the average radius of the $2p$ orbital, e, m and c are constants and the most important feature for this discussion is the average energy, ΔE. The largest contribution to this is the n–π^* transition. Figgis and coworkers[218] observed in accordance with equation 23 that the ^{17}O chemical shifts are proportional to $1/E$ (see Figure 4). The relation holds for a range of 600 ppm. It is likewise tempting to correlate ^{13}C of carbonyl compounds with $\lambda^{n-\pi^*}$. This was first attempted by Savitsky and coworkers[219] for ^{13}C chemical shifts. They observed for cyclic and acyclic ketones that the ^{13}C resonance shifts to lower field with increasing $\lambda_{max}^{n-\pi^*}$. de Jeu[217] showed that a relationship between $\delta\underline{C}{=}O$ and $\delta^{17}O$ could be established for ketones and aldehydes but not for a broader group of carbonyl containing compounds.

An important recent study by Risley[220] has shown that $\delta^{17}O$ and $^1\Delta^{13}(C^{18}O)$, one-bond isotope effects, correlate very well. One of the few exceptions is the ether-type oxygen of benzoic acid anhydride. It should also be noted that no single bonded ester oxygens are included. This relationship makes both $\delta^{17}O$ and $^1\Delta^{13}(C^{18}O)$ more versatile.

3. Conjugation and steric effects

Since $\delta^{17}O$ of aromatic ketones, esters, etc. correlate with $\lambda_{\pi-\pi^*}$ one would also expect $\delta^{17}O$ to correlate with substituent effects, and consequently with the twist of the cox group, out of the aromatic ring plane. ^{17}O chemical shifts of *p*-substituted benzoic acids correlate with Hammet σ and σ^+ constants[221,222]. By increasing the size of the *o*-substituent a low-field shift of the C=O resonance is observed (see Scheme 4). This has been shown extensively for acetophenones[223,224]. Non-planar situations have been observed in both aromatic and olefinic esters[225,226]. An excellent correlation between $\delta C=^{17}O$ and torsion angles, as determined from molecular mechanics (MM) calculations, is obtained for esters, acids and amides[226] (data are shown in Scheme 4). A comparison of results obtained by different methods is given in Table 6. Some discrepancy concerning *o*-substituted derivatives is obtained for angles determined by different methods. One interesting point is that the single bonded $\delta C-^{17}O$ data also correlate well with the MM values[226]. A danger is, of course, that the ^{17}O data also correlate with angles multiplied by a scaling factor. More data, especially X-ray data of sterically hindered esters, ketones and amides, are urgently needed in order to clarify this problem.

TABLE 6. Twist angles in 2-methylbenzoic acid as determined by different methods

	Angle	Reference
^{13}C chemical shift	25	227
MM^2 calculations	29	226
X-ray	10	228
UV	41	230
$^2J(CO, C)$	~0	229

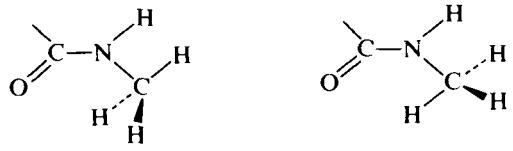
The ^{17}O chemical shifts of *p*-substituted acid chlorides[231] gave good correlations with Brown's[232] σ^+ constants and with DSP parameters:

$$\delta^{17}O = 21.3\sigma_I + 22.1\sigma_R^+ \quad (24)$$

The σ_I and σ_R dependence is similar to that observed for acetophenones[233]. This is also in agreement with the finding that ^{17}O chemical shifts of ketones and acid chlorides are similar.

^{17}O chemical shifts of unsaturated ketones and amides correlate with nuclear quadrupole coupling constants. One exception is the group of acyl chlorides. A correlation is also found with the π-electron density at the β-carbons[234].

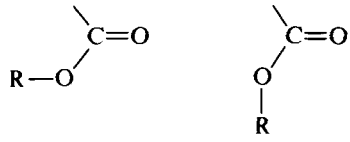
Torsion angles and electronic effects are also studied in *N*-arylacetamides and aryl acetates. Torsion angles are again obtained from MM calculations. ^{17}O shift correlates with Hammet's σ[235].A DSP study of 5-substituted uracils showed a good correlation with ^{17}O chemical shifts at position 2, but not at position 4. This was related to therapeutic ability[236]. Steric strain as, e.g., realized in small rings gives rise to low-field shifts. The effects are correlated to in-plane bond angle distortions[237–239]. Similar effects are seen upon cyclization. For six-membered rings the cyclization effect is ca 5 ppm[240]. Van der Waals interactions lead to low-field chemical shifts[237]. Theoretical calculations[203] show that ^{17}O chemical shifts of *N*-methylformamides depend on the conformation of the methyl group as shown in **25**. For **25A** an upfield shift compared to formamides was predicted whereas for **25B** a downfield shift was predicted. These



(A) (B)

(25)

findings raise two questions: how important are van der Waals effects, e.g., in *o*-substituted benzoyl compounds, and does the ^{17}O chemical shift of C=O groups depend on the orientations of nearby lone pairs as illustrated in **26**.



(A) (B)

(26)

4. Hydrogen bonding

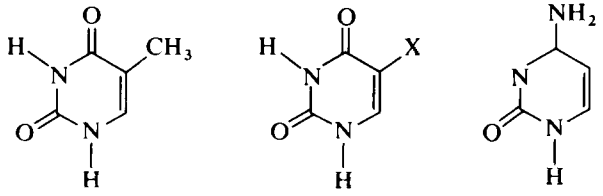
Solvent effects and especially hydrogen bonding are realized as being important. For acetone a significant solvent effect was observed in early studies[216]. Hydrogen bonding affects $\lambda_{max}^{\pi-\pi^*}$ for acetone. A plot of $\delta^{17}O$ vs this parameter for acetone in water is linear, whereas a similar plot for the ^{13}C chemical shift is curved. The C=O resonance is shifted upfield by dilution. A similar finding can be expected for esters whereas the situation is more complex[241–246] for amides (see Figure 1). Hydrogen bonding to the C=O group again leads to an upfield shift[245,246], whereas hydrogen-bonding to the N—H group also leads to an upfield shift, but less clearly[242,244].

Hydrogen bonding is also important for ^{17}O chemical shifts of amino acids, proteins[247,248] and nucleic acids[249,250]. Amino acids, proteins and peptides[247,248,251–254] have been investigated in detail. Hydrogen bonding and titrations are in some cases related. Long-range titration effects may be observed in, e.g. *N*-acetylproline. This shows *cis/trans* isomerism (**52**). Hydrogen bonding is a possibility in the *trans* form. Titration effects are observed at the acetyl carbonyl oxygen, which are slightly different for the two forms. Titration experiments in general show that ^{17}O chemical shifts of the carboxylic acid oxygen are shifted to low field (high frequency) by about 13–18 ppm[251,252] upon deprotonation. The side-chain carboxyl group shows a low-field shift of *ca* 24 ppm[251]. Deprotonation of the primary α-amino group leads to a low-field shift of the α-carboxylic oxygen of −2.3 to −3.9 ppm (serine and threonine, *ca* 1.5 ppm). The titration shifts are explained by an inductive shift to low field, counterbalanced by an electric-field-effect shift to high field[252].

Hydrogen bonding is also a very important property of the nucleic acid bases. This property has been studied by ^{17}O NMR[236,249,250], using [2,4-$^{17}O_2$]-thymidine (**27A**), [2,4-$^{17}O_2$]-uracil (**27B**, X = H) and [2-^{17}O]-cytosine (**27C**).

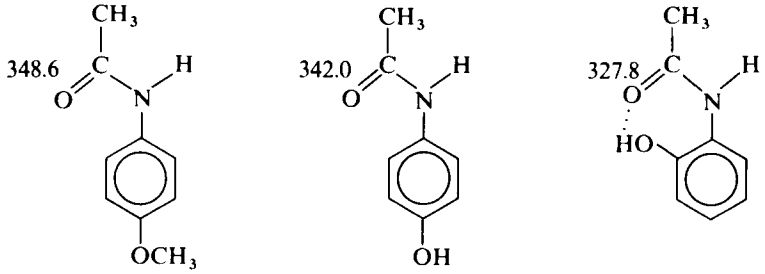
Fiat and coworkers[248] showed that ^{17}O chemical shifts are a quite sensitive probe as indicator of the sites and degree of hydrogen bonding.

It is seen that ^{17}O gives complementary information to the $^{2}\Delta C{=}O(ND)$ isotope effects (see Section IV.A.2). Interactions between water and nucleosides are also studied[255,256].



(A) (B) (C)

(27)



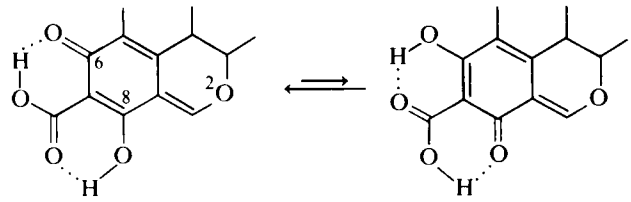
(A) (B) (C)

(28)

Inter- and intramolecular hydrogen bonding is inferred to explain the high-field shifts observed in **28B** and **28C**[235]. However, these may just be ordinary substituent effects.

5. Biosynthetic labelling

^{17}O has not so far been used as extensively as ^{18}O (see Section IV.C) in biosynthetic labelling studies, although some examples exist. Using multiple-labelled [^{13}C, ^{17}O] acetate Sankawa and coworkers[257] produced citrinin giving rise to three oxygen resonances. One is believed to be O-2, the others are the oxygens at C-6 and C-8. A similar study using [^{13}C, ^{18}O] acetate leads to $^{1}\Delta^{13}C^{18}O$ isotope effects (see Section IV.C). According to Risley[220] these two parameters give parallel information.



(29)

The unusual ^{17}O chemical shifts point towards a tautomeric equilibrium as seen in citrinin (**29**). Another interesting point is that this equilibrium involves an acid group and that the C=O oxygens in question are hydrogen-bonded. This clearly affects the ^{17}O chemical shifts, but also the $^{1}\Delta C(^{18}O)$ in a manner analogous to the discussion for esters in Section IV.C.

6. Linewidth studies

As ^{17}O has a quadrupole moment, the linewidth depends, as shown in equation 22, on the correlation time. Conversely, linewidth studies may therefore be used in studies in which the correlation time is expected to change, such as in dimerisation or polymerization. A related phenomenon is often a change in the hydrogen-bond patterns[243,248]. Different hydrodynamic models were also tested[258].

IV. ISOTOPE EFFECTS ON NUCLEAR SHIELDING

Isotope effects, especially deuterium isotope effects, on nuclear shielding are now well documented[259–268] and also one-bond oxygen-18 isotope effects are well represented[259,264].

Isotope effects on nuclear shielding are usually easy to measure and the differential nature of the effects means that a number of difficulties found with chemical shifts, such as solvent effects, are removed. Isotopes are normally considered electronically non-perturbative. However, they represent in some cases a small perturbation, but large enough to lift the degeneracy of some symmetrical systems thereby providing otherwise non-measurable information[265].

Isotope effects on nuclear shielding are in essence vibrational effects and are hence expected to be large in those cases in which isotope substitutions cause a large change in the vibrational frequencies. One such case is clearly hydrogen bonding.

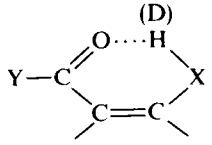
Furthermore, Jameson[260] has recently formulated a theory for long-range isotope effects on nuclear shielding. This enables a resolution of the effects into an electronic and a vibrational term. The former is supposed to be dominant and long-range isotope effects can thus be expected to lead to information about electronic properties.

A. Deuterium Isotope Effects

1. $^{n}\Delta C(OD)$

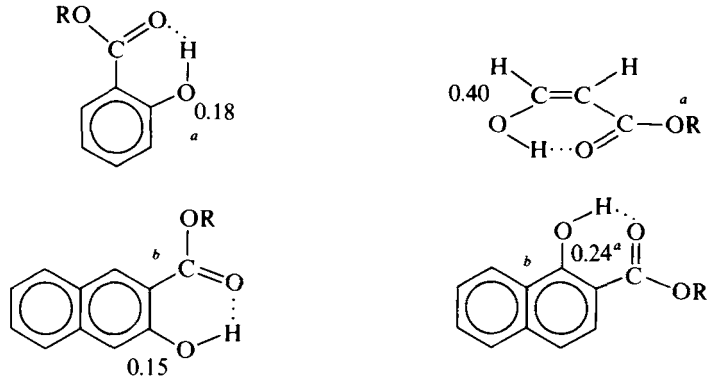
Isotope effects on the carbonyl carbon can be of different types. These are $^{2}\Delta C{=}O$ (Hα), by substitution of the H-α protons, or $^{2}\Delta C{=}O(ND)$, by substitution of the amide proton. Furthermore, long-range effects at $\underline{C}{=}O$ are also observable in hydrogen-bonded cases. $^{2}\Delta C(OD)$ is also a very important parameter in hydrogen-bonded cases as shown below.

Intramolecular hydrogen bonding can be monitored by means of $^{2}\Delta$ C-1(XD) isotope effects (**30**), which are large in hydrogen-bonded systems, or through the effects at the carbonyl carbon involved in the hydrogen bond, $^{n}\Delta CO(XD)$.



(30)

The $^{2}\Delta$C-1(XD) effects have been investigated in a number of aldehydes, ketones and esters[266–268]. Good correlations have been obtained between $^{2}\Delta$C-1(XD) and $\delta X\underline{H}$[266]. $^{2}\Delta$C-1(XD) is seen to depend on bond order as illustrated in Scheme 4. On the other hand, $^{2}\Delta$C-1(OD) effects of esters are smaller than for aldehydes and ketones[266–269]. This can be related to the lesser ability of the ester to act as electron attractor. The



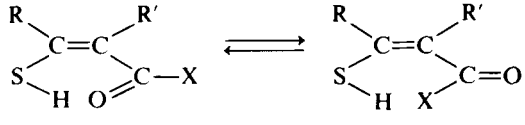
SCHEME 4. $^2\Delta C(OD)$ of intramolecularly hydrogen-bonded compounds

[a] From Reference 267. [b] From Reference 269.

$^2\Delta C$-1(XD) isotope effects reflect the ability of the system to take part in resonance-assisted hydrogen bonding (RAHB)[268] For a full discussion of this principle see References 270 and 271.

The effect of the donor can be estimated from a comparison of similar β-oxoesters and enamine esters[266–268]. The OH group of the former forms the stronger hydrogen bonds.

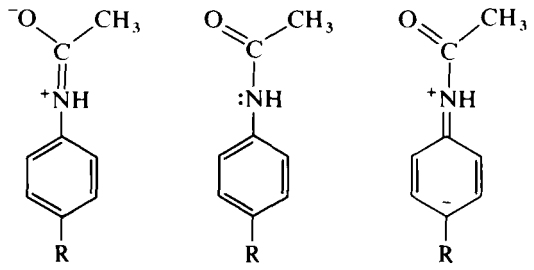
Thioxoesters have been studied by IR spectroscopy and two conformations of the ester groups are inferred[272] (**31**). The conformational equilibrium is determined by the R and R′ substituents. The NMR study enabled a determination of the percentage of rotamer **B** by using the value $^2\Delta CS(D) = 0.22$ ppm (R = *t*-Bu) as the value for pure **31A**. This value has since been confirmed using cyclic esters with the esters group structurally confined to structure **A**[274]. Studies of thioxothioesters showed very similar behaviour[274]. Combing data from References 272 and 273 it can be shown that δSH and $^2\Delta C(SD)$ correlate well. Furthermore, $^2\Delta C(SD)$ and $^n\Delta C{=}O(D)$ also correlate.



(31)

2. $^2\Delta CO(ND)$

Two-bond isotope effects, $^2\Delta CO(ND)$ of simple amides, were investigated by Feeney and coworkers[275] by simply dissolving the amides in a mixture of H_2O and D_2O. Anilides show slightly larger isotope effects than aliphatic amides[276]. Morales-Riós and Joseph-Nathan[277] have recently studied a series of acetanilides and found that $^2\Delta C$-1(ND) and $^2\Delta CO(ND)$ show change in opposite directions upon electron delocalization from the *p* substituents. Electron donor substituents induce larger shifts in $^2\Delta CO(ND)$

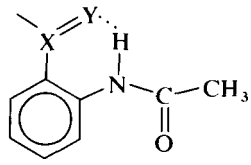


(A) (B) (C)

(32)

than acceptors. These results are discussed in terms of the canonical forms **32A** and **32C**. An increase in **32A** is supposed to increase $^2\Delta$CO(ND).

Two-bond isotope effects, $^2\Delta$CO(ND), have also been investigated in hydrogen-bonded amides[278] of type **33**. The idea was to correlate the $^2\Delta$C-1(ND), being a measure of the hydrogen-bond strength, with $^2\Delta$CO(ND)[278,279]. A reasonable correlation is obtained but, as indicated in Reference 277, substituents at the aromatic ring may also play a role. The reason for the interest in amides is their widespread occurrence in biological compounds. For model compounds good correlations between δN<u>H</u> and $^2\Delta$CO(ND) have been established[278,279], but this is not the case for proteins[280].

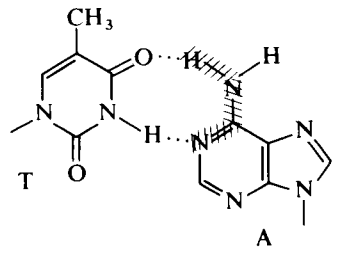


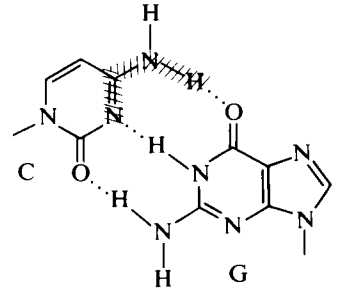
(33)

Nucleosides have been studied by Reuben[281] using parameters taken from aromatic amides. A different conclusion[282] was reached by a low-temperature approach. In the light of the RAHB theory[270,271], and since amides and aromatic carbons show dramatically different isotope effects[278], it is probably appropriate to divide the various parts of the nucleosides into different categories (see **34**). The hatched parts of **34** are likely to show larger (and aromatic-like) isotope effects due to resonance than, e.g., the amide parts of thymidines. For guanosine the picture is less simple due to the possibility of extensive delocalization. $^2\Delta$CO(ND) effects have also been investigated in **35**[283], but no isotope effect was observed at the CONH carbon.

In bilirubin an isotope effect, $^2\Delta$CO(ND) = 0.106 ppm, was observed[283]; $^2\Delta$CO(ND) of small peptides is close to 0.08 ppm[13,284]. $^2\Delta$CO(ND) isotope effects have been used for assignment purposes in ^{13}C spectra of proteins[285–287]. The use of isotope splitting may also be used to monitor exchange for amide protons not measurable by other NMR techniques (see Section VII.B).

The secondary two-bond isotope effects $^2\Delta$CO(ND) compare well with primary isotope effects, which again are proportional to δO<u>H</u>[148].





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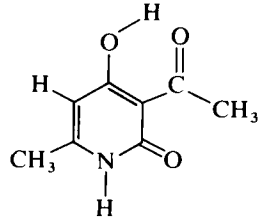


(35)

3. $^2\Delta CO(D)$

Deuterium substitutions in methyl groups of a series of carbonyl compounds including acid derivatives have been investigated[288,289]. $^2\Delta CO(D)$ isotope effects were early found to be negative for acetone[290] and for other ketones[291,292]. They are only slightly negative for acids[288,289], amides and acid fluorides[288].

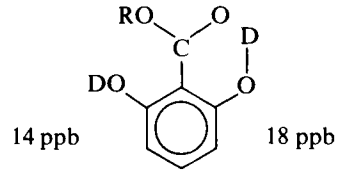
Arrowsmith and Kresge[289] plotted $^2\Delta C(D)$ vs δC for a number of trigonal carbons (including acid derivatives, ketones and aldehydes) and found a linear relationship. The larger the chemical shift the more negative the isotope effect which was taken as evidence for a hyperconjugative interaction between the $CH_{3-x}D_x$ group and the C=O group[287]. This type of hyperconjugative interaction in relation to isotope effects was originally suggested by the groups of Ernst[293] and of Forsyth[294] and has recently been reviewed[291].

Isotope effects of mixed origin may be observed in amino acids dissolved in trifluoroacetic acid[295]. A regressional analysis gave $^2\Delta CO(OD) = 0.23$ ppm.

4. Isotopic perturbation of equilibrium

Isotopic perturbation of equilibrium has been used to demonstrate that for the intramolecular hydrogen bond of the RAHB type 1 the OH bond is stronger than the OD bond[121,122]. Isotopic perturbation of equilibrium can also be used to gauge the anisotropy of the ester groups in such compounds keeping in mind the effects of electron relocalization due to hydrogen bonding.

Low-temperature studies enable one to distinguish between isotope effects due to hydrogen-bonded and non-hydrogen-bonded protons as shown in **36**. Such studies also give δOH of the free and the hydrogen-bonded proton[267].



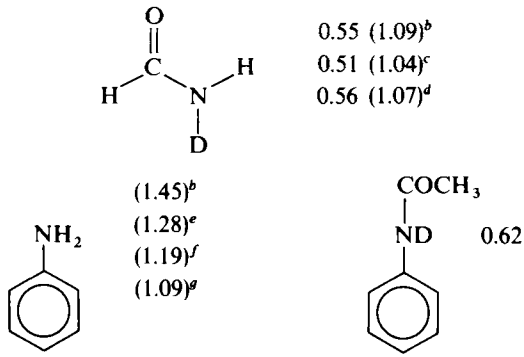
(36)

B. $^n\Delta$N(D)

1. $^1\Delta N(D)$

Isotope effects with ^{15}N have been studied to some extent. $^1\Delta$N(D) values of simple amides are similar to values obtained for amines (*ca* 0.6 ppm)[296], and due to their large magnitude they are rather easy to observe. One complication exists, namely that due to the quadrupole moment of deuterium, a triplet with a ^1J(ND) coupling of *ca* 90/6.5 may be observed. However, depending on the symmetry of the surroundings of the deuterium this can collapse partially or fully, leading to a broad resonance[268].

The one-bond isotope effects are seen to vary slightly with the solvent (Scheme 5). One-bond isotope effects of enamines are found to increase with hydrogen bonding. A similar trend is expected for amides. A plot of $^2\Delta$C(ND) vs $^1\Delta$N(D) is given in Figure



SCHEME 5. $^1\Delta$N(D) of amides and amines[a]

[a] Taken from Reference 296 Values in parentheses are for the dideuteriated species. [b] neat liquid (H:D, 1:1). [c] 1:2(w/v) in H_2O:D_2O (1:1). [d] 1:1 (w/v) in DMSO. [e] 50% (w/v) in $CDCl_3$. [f] 15% (w/v) in $CDCl_3$. [g] 5% (w/v) in $CDCl_3$.

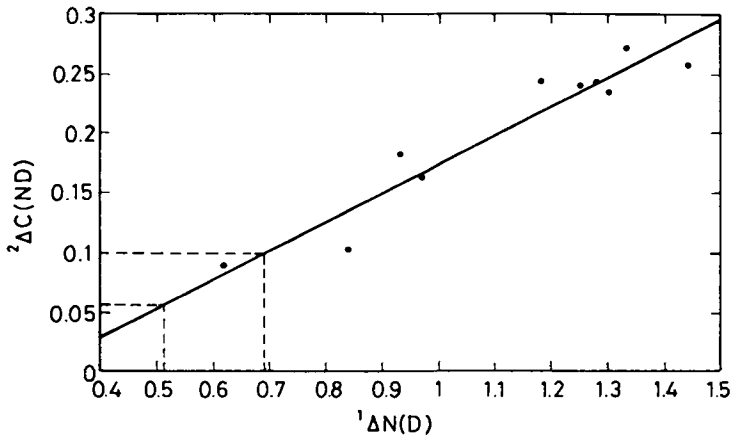
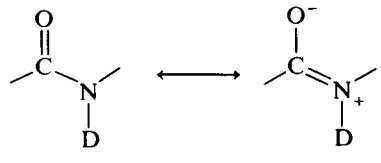


FIGURE 5. $^1\Delta N(D)$ vs $^2\Delta C(ND)$ for amides and enamines. Data taken from References 278 and 296

5. The very similar values for amides and amines and the fact that they fall on the same line justify the use of the graph of Figure 5 to estimate $^1\Delta N(D)$ of, e.g., proteins (broken lines). A range of 0.51–0.69 ppm can be estimated. A very recent study of calmodulin showed that $^1\Delta N(D)$ of the back-bone amide nitrogen varied from 0.58 to 0.85 ppm[297]. The linear correlation between $^2\Delta C(ND)$ and $^1\Delta N(D)$ indicates that the two parameters depend on similar factors. $^2\Delta C(ND)$ increases upon hydrogen bonding and so does $^1\Delta N(D)$. Furthermore, $^2\Delta C(ND)$ depends on the C—N bond order, suggesting that this is also the case for $^1\Delta N(D)$.

It is seen from **37** that hydrogen bonding at both the C=O and the N—H ends will lead to an increase in **37B**, possibly leading to larger isotope effects. Hydrogen bonding will also have an effect on the ^{15}N chemical shifts (see Section III.D.2).



(A) (B)

(37)

2. $^3\Delta N(D)$

This type of isotope effect also showed a small negative three-bond isotope effect[296].

C. $^1\Delta^{13}C(^{18}O)$

^{18}O isotope effects on ^{13}C chemical shifts were studied intensely in carbonyl compounds. ^{18}O isotope effects are in most cases only observed over one bond. ^{17}O isotope

effects have not been reported because of line broadening of the neighbouring carbon resonances. $^1\Delta C(^{18}O)$ isotope effects have recently been reviewed[2,259,264]. These effects are normally only observable in enriched compounds. The use of super-high resolution made possible observations in acetone[300].

Jameson and Osten[298] summarized the factors that influence isotope effects as follows: $(\partial\sigma^a/\partial\Delta_{AX})_e$ depends on the bond properties, and is the greater the stronger the bond. It is therefore expected to correlate with bond order and the spin–spin coupling, J_{AX}. It also depends on the absolute shielding of the nucleus[299] and largely on the paramagnetic term. The smaller shielding gives the largest derivatives. This has been demonstrated for a number of compounds[301] leading to equation 25:

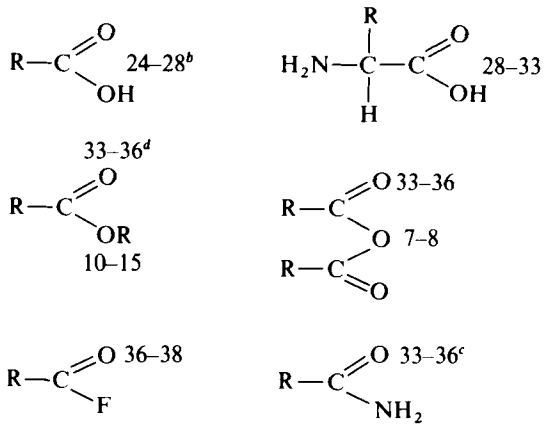
$$^1\Delta^{13}C(^{18}O) = 4.16 \times 10^{-2} - 4.38 \times 10^{-4}\delta^{13}C \qquad (25)$$

The shielding is, as discussed in Sections III.A.1, III.B.5.a and III.D.1.b, a tensor property. Stretching of the bond is expected to have the largest effect on the tensor elements perpendicular to the bond[298].

One-bond ^{18}O isotope effects are very suitable for the investigations of compounds containing C=O and C—O groups. $^1\Delta^{13}C(^{18}O)$ isotope effects follow the bond order as seen in Scheme 6 for single and double bonds. This fact enables a distinction between the two oxygen atoms of esters, whereas in acids and carboxylates the two oxygens are equivalent and the isotope effects are an average between double-bond and single-bond values.

The values of amino acids are slightly larger than those of acids[264]. The order for acids, esters, amides, etc. is demonstrated in Scheme 6.

The magnitude of isotope effects for carboxylic acids depends on pH. They show a maximal value at pH = pK_a[302,303]. The increase in $^1\Delta C(^{18}O)$ appears to arise from differences in pK_a values between the ^{16}O and ^{18}O labelled acids. The isotope effects may therefore be used in the determination of pK_a values of carboxylic acids (see also Section VI).



SCHEME 6. Characteristic $^1\Delta C(^{18}O)$ isotope effects of acid derivatives[a]

[a] In ppb. Taken from Reference 264. [b] Values depend on pH (see text). At pH ~ pK_a, $\Delta C(^{18}O)$ is 38 44 ppb. [c] For lactams $^1\Delta C(^{18}O)$ ~ 28 ppb. [d] For lactones $^1\Delta C(^{18}O)$ ~ 37 ppb.

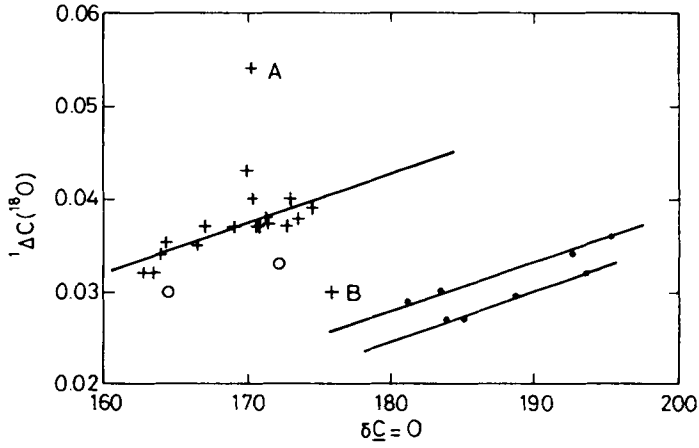
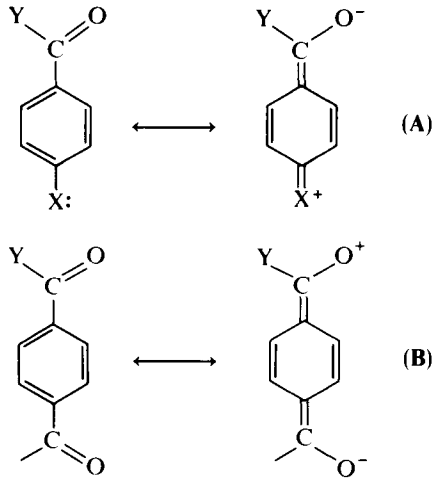


FIGURE 6. $^{1}\Delta C(^{18}O)$ plotted vs $\delta C{=}O$ for esters and ketones[a,b]

[a] Data taken from References 305–330. [b] + Ketones and esters without hydrogen bonds; ● denote ketones with intra-molecular hydrogen bonds, ○ denotes esters with intra-molecular hydrogen bonds.

Risley and Van Etten have established that $^{1}\Delta C(^{18}O)$ do not depend to any significant degree on solvent or temperature. Furthermore, the isotope effects are additive[264].

Substituent may, of course, influence the magnitude of the effects. A carbonyl group conjugated with an electron-donating substituent group (**38A**) has a smaller isotope effect than one conjugated with an electron-withdrawing substituent (**38B**)[304].

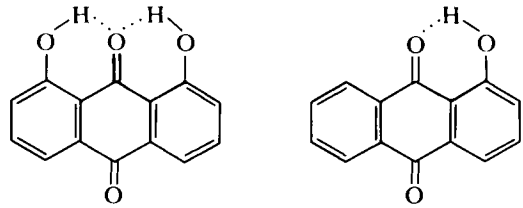


(38)

Everett established, as mentioned, a linear relationship between $^{1}\Delta C(^{18}O)$ and $\delta^{13}C{=}O$ including all types of carbonyl compounds[301].

$^{1}\Delta C(^{18}O)$ of a large number of ketones and esters are plotted vs C=O chemical shifts

in Figure 6. The range of compounds is narrower than that originally used by Everett[301]. No distinction is made between ketones and esters as they should both fit. However, as indicated in Reference 13 hydrogen-bonded compounds seemed to fall outside the line defined by Everett [please note that the sign of the $^1\Delta C(^{18}O)$ axis should be positive in Reference 13 with the sign convention used in that review, whereas it is negative in the original paper]. The finding that $^1\Delta C(^{18}O)$ is small in hydrogen-bonded compounds is supported by 'internal' comparisons. For ravenillin $^1\Delta$ is 27 ppb (with an intramolecular hydrogen bond), whereas it is 37 ppb in the corresponding triacetate (without a hydrogen bond)[312]. For kinamycin one CO is hydrogen-bonded ($^1\Delta CO$ = 30 ppb) while the other is not ($^1\Delta CO$ = 40 ppb)[310]. A similar picture is seen for averufin[311]. From Figure 6 it is clearly seen that ketones with a hydrogen bond (marked ●) fall off the normal line. It can even be suggested that compounds with two hydrogen bonds to an oxygen (**39A**) fall further off the line than compounds with only one hydrogen bond. This means that both OH groups form hydrogen bonds simultaneously.



(A) (B)

(39)

Having established a relationship between $^1\Delta C(^{18}O)$ and δC=O for esters and ketones (Figure 6), it can also be noted that the two esters with hydrogen bonds (marked with ○ in Figure 6) also fall off the line. Similarly, $^1\Delta C(^{18}O)$ is smaller in ethyl 3,5-methylorsellinate (intramolecular hydrogen bond) than in the corresponding diacetate[314].

Hydrogen bonding does have a decreasing effect at $^1\Delta C(^{18}O)$ of esters, but to a lesser extent than for ketones, in line with the weaker hydrogen bond formed. Point A of Figure 6 is from a cyclization reaction study of Kocovsky and Turecek[329]. They claim that the oxygen is only incorporated at the C=O positions of the isolated lactone. The observed $^1\Delta C(^{18}O)$ = 54 ppb is clearly very much larger than in any other singly labelled ester or lactone. Considering the large body of data available, it is probably timely to re-investigate these reactions.

Point B of Figure 6 is for narasin methyl ester[324]. The position seems more appropriate for an acid than for an ester.

The finding that $^1\Delta C(^{18}O)$ is lower in hydrogen-bonded compounds is in accord with a very recent finding that $^1\Delta C(^{18}O)$ and $\delta^{17}O$ are proportional[220]. This is a very interesting finding, as it suggests that $^1\Delta C(^{18}O)$ may be used to detect steric stain or twisting of sterically crowded carbonyl groups out of the aromatic plane etc. (see Section III.E.3).

Two points for acetyl and benzoyl fluoride[305] (160.5 ppm, 38 ppb; 156.9, 36 ppb) also fall outside the original correlation.

Citrinin[257] (**29**) shows the very interesting feature of a carboxyl group hydrogen-bonded to both a carbonyl and a phenolic group (see also Section III.E.5).

A hydrogen-bonded C=O is shown in Figure 6 (marked with ●) to have a $^1\Delta C(^{18}O) < 35$ ppb. The hydrogen-bonded phenol carbon from a number of compounds, namely ravenillin[312], tajixanthon[30], averufin[311], oxytetracyclin[308], and kinamy-

TABLE 7. ^{17}O, ^{13}C chemical shifts and $^{1}\Delta C(^{18}O)$ of citrinin[a]

Position	$\delta^{17}O$[b]	Bond type	$\delta^{13}C$[b]	$^{1}\Delta C(^{18}O)$[c]
6	279	C=O	183.7	39(34)[d]
8	179	C—O	177.2	39(42)[d]

[a] From Reference 257.
[b] In ppm.
[c] In ppb.
[d] Numbers in brackets are from a second incorporation experiment.

cin[310], can be seen to have a one-bond isotope effect at carbon from a singly bonded oxygen, $^{1}\Delta C—O$, close to 10 ppb. It is therefore difficult to envisage how a tautomeric mixture as shown in **29** can lead to $^{1}\Delta C(^{18}O)$ values of 39 ppb, unless the hydrogen bonds are very weak indeed. However, as discussed in Section III.E.1, $\delta^{17}O$ and $^{1}\Delta C(^{18}O)$ correlate. The ^{17}O chemical shifts of citrinin would, according to the graph of Risley[220], give rise to $^{1}\Delta C(^{18}O)$ values of 26 and 31 ppb. Both values are again much smaller than the other reported ones for citrinin[257].

^{18}O is very well suited to reaction mechanism studies according to a review by Risley and Van Etten[264]. Reactions cover oxygen exchange between solvent and acids, enzyme catalyzed hydrolysis, oxidation reactions leading to lactones or acid anhydrides and decarboxylation reactions.

D. $^{n}\Delta^{17}O(D)$

Three-bond deuterium isotope effects $^{3}\Delta^{17}O(D)$ on ^{17}O chemical shifts have been determined in deuterated acetic acid[331]. The magnitude can be explained[331] by assuming a directional dependence as found for the fluorine atom of deuterated acetyl fluorides[288] (see next section).

E. $^{3}\Delta F(D)$

Three-bond deuterium isotope effects on fluorine chemical shifts, $^{3}\Delta F(D)$, have been observed in deuterated acetyl fluorides and α-deuterated propionyl fluorides. The findings of a $^{3}\Delta F(D)_{gauche} = -55$ ppb and $^{3}\Delta F(D)_{trans} = 61.8$ ppb show that orientation is very important. The study also showed that the rotamer populations of acetyl fluoride (I in Figure 7) (1 : 1 : 1) are changed slightly in acetyl fluoride-d_1 and d_2[288] (Figure 7). It is the rotamers with a deuterium *trans* to fluorine that are increased.

F. $^{1}\Delta^{13}C(^{15}N)$

This kind of isotope effect is observed in enriched proteins and is small, 0.2 ppm[332].

G. $^{1}\Delta^{13}C(^{13}C)$

These isotope effects are generally very small[2,262].

V. COUPLING CONSTANTS

Due to, e.g., the Karplus[333] relationship for three-bond couplings, coupling constants constitute a strong tool in structural studies. Many different types of coupling constants

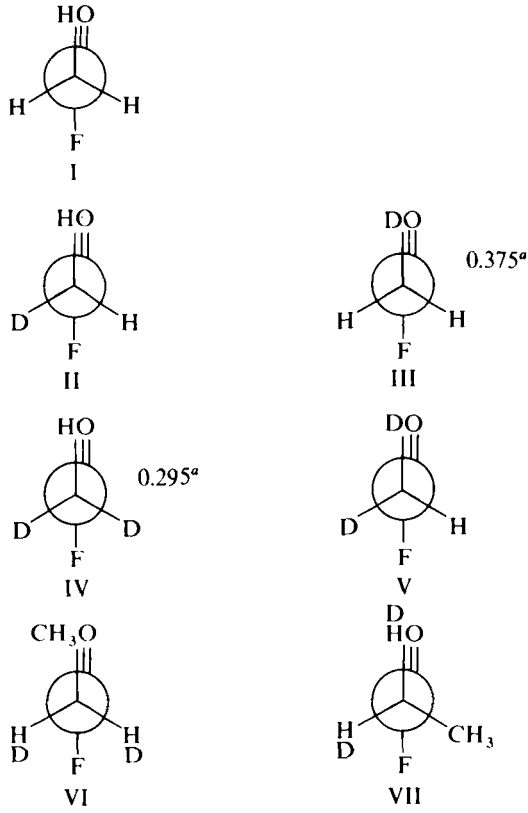


FIGURE 7. Rotamers of deuteriated acetyl and propionyl fluorides. [a] refers to rotamer populations

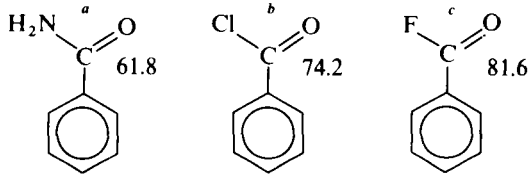
can be measured as demonstrated in Table 1, and with the increasing amount of data available not only three-bond couplings are shown to be useful in structural studies, but also one- and two-bond coupling constants.

A. ^{n}J(C=O, C)

1. ^{1}J(C=O, C)

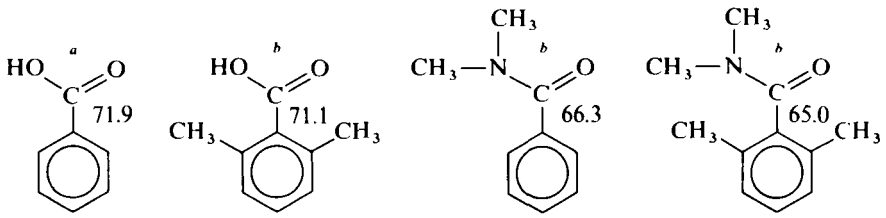
One-bond carbon–carbon coupling constants have been tabulated in recent reviews[334 341]. An early investigation of $CH_3C(=O)X$ derivatives found no definitive trends between ^{1}J(C=O,C) with simple hybridization or with effective nuclear charge densities[342].

^{1}J(C=O,C) is well established in aromatic ketones, aldehydes and acid derivatives[342-344]. ^{1}J(C=O,C) is different in the different types of acid derivatives, as seen in Scheme 7. The difference in magnitude is related to the difference in the inductive effects of the X substituent. Olah and coworkers[345] investigated substituent effects in aromatic acid derivatives. Twist of the carboxyl group out of the ring plane has a relatively minor effect, as seen in Scheme 8, although a trend to smaller values is noticed[77].



SCHEME 7. One-bond carbon–carbon coupling constants of aromatic carbonyl compounds.

[a] Taken from Reference 77. [b] Taken from Reference 345. [c] Taken from Reference 112.

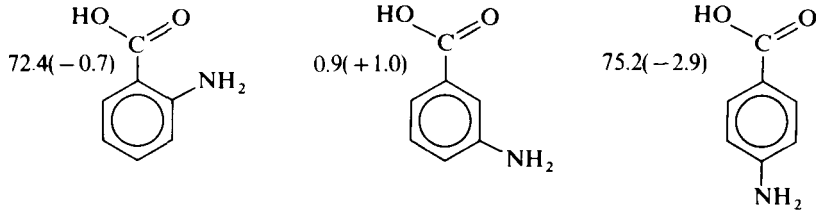


SCHEME 8. Comparison of one-bond carbon–carbon coupling constants of sterically hindered acids and amides

[a] Taken from Reference 229. [b] Taken from Reference 77.

^1J(C=O,C) coupling constants were reported in cycloalkane carboxylic acids and decrease with increasing ring size[346–348].

One-bond carbon–carbon coupling constants have been investigated in a number of amino acids. ^1J(C=O,C) does not vary very much with pH[348–357]. ^1J(C=O,C) coupling constants are influenced by electric field effects. This was suggested in the study of ^1J(C=O,C-γ) of aspartic acid[85]. A study of *o*-, *m*-, and *p*-aminobenzoic acids, together with the corresponding cations and anions, revealed that chemical shifts and ^1J(C=O,C) coupling constants could not in any way be correlated with change on the carboxylic



^1J(CO,C) of aminobenzoic acids[a,b]

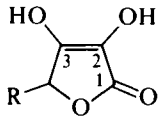
[a] Values relative to benzoic acid. [b] Taken from Reference 85.

carbons as calculated from INDO wave functions. Qualitatively, the shift from the neutral to the cationic case is shown in **40** in parentheses.

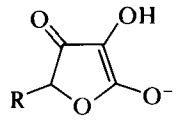
The value for 4-aminobenzoic acid is much larger than for benzoic acid. The NH_2 group acts similarly to OH and OCH_3. To what extent electric field effects play a role is difficult to judge in these compounds[358].

Temperature and solvent can also influence ^1J(C=O,C). The one-bond coupling constants in methyl acetate change +0.0018 Hz per degree whereas for sodium acetate the variation is −0.0003 Hz per degree. ^1J(C=O,C) of *p*-bromophenyl acetate varies from 60.08 to 59.78 Hz with a change in solvent from benzene to chloroform[359].

One-bond carbon–carbon couplings of ascorbic acid and its anion (**41A,B**) have been discussed in terms of bond lengths[13,360].



(A)



(B)

(41)

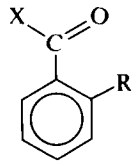
2. ^2J(CO,C)

Two-bond couplings are rather different in aromatic and aliphatic systems due to the inherent property of sign. ^2J(CO,C) is normally negative in aliphatic compounds and normally positive in aromatic systems. The sign clearly has to be taken into account and so has the possibility of very small couplings. Other factors influencing coupling constants are substituents and relative substituent positions.

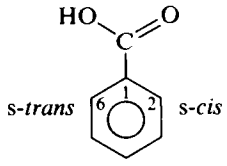
For a series of couplings between side-chain carbons it was apparent that electron-withdrawing substituents decrease geminal and vicinal couplings provided the substituent is attached to one of the carbons on the pathway[341].

The magnitude of two- and three-bond J(CO,C-arom) couplings have been investigated in a number of aromatic ketones, aldehydes and acid derivatives[77,109,112]. These couplings show a dependence on the orientations of the C=O bond as illustrated for the esters and acids of Scheme 9.

It has been established firmly (see **42**) that if R = CH_3 then the C=O groups will point towards the methyl groups. The two-bond coupling to C-2 is termed ^2J(CO,C) s-*cis* and the one to C-6, ^2J(CO,C) s-*trans* (**43**).

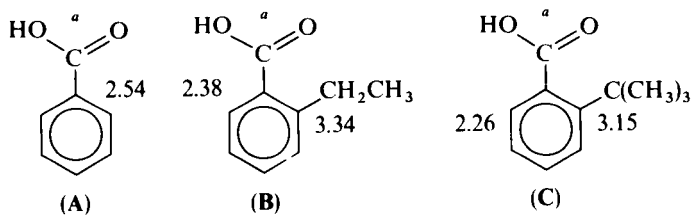


(42)

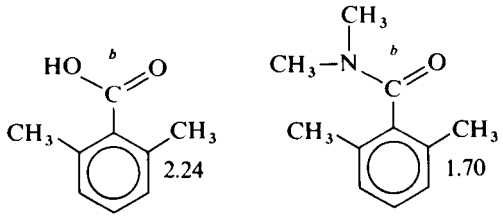


(43)

The signs of coupling constants are important[361] especially for two-bond coupling. ^2J(CO,C) couplings are positive in methyl benzoate[362], *N,N*-dimethyl-1-naphthamides[177] and phthalates[109]. In methylbenzoic acid and methyl benzoate average couplings are obtained. A comparison of couplings in **A**, **B** and **C** of Scheme 9 shows that both



(A) (B) (C)



(D) (E)

SCHEME 9. ^2J(CO,C)

[a] Taken from Reference 112. [b] Taken from Reference 77.

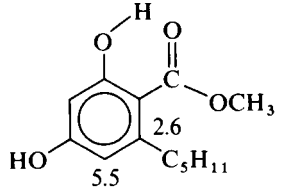
two-bond coupling constants are positive[112]. A standard set of parameters has been estimated for acids[77]:

$$^2J(\mathrm{CO, C})_{s\text{-}cis} = 3.59 \text{ Hz}; \; ^2J(\mathrm{CO, C})_{s\text{-}trans} = 1.82 \text{ Hz}$$

$$^2J(\mathrm{CO, O})_{twist} = 1.95 \text{ Hz}$$

For aromatic acids and their derivatives it is found that $^2J(\mathrm{CO,C})_{s\text{-}cis} > {}^2J(\mathrm{CO,C})_{s\text{-}trans}$.

This is opposite to findings with aldehydes and ketones[77,229]. The corresponding values for freely rotating acid derivatives normally fall within the range of values for $^2J(\mathrm{Co,C})_{s\text{-}cis}$ and $^2J(\mathrm{CO,C})_{s\text{-}trans}$.



(44)

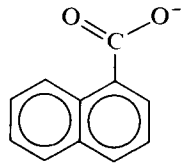
A more recent example is methyl olivetolate and similar compounds (**44**)[363] in which the ester group is presumably held in one particular conformation by an intramolecular hydrogen bond. As only one ^2J(CO,C) coupling is measured, it still remains to be seen how this system conforms with the above-mentioned findings, but the $^2J(\mathrm{CO,C})_{s,trans}$ seems to be on the high side.

A number of factors influence two-bond carbon–carbon couplings. It is essential to consider substituents of the alkyl group in order to estimate the direct substituent effects. It was shown that these effects were small, but should definitely be taken into account.

Theoretical calculations (*vide infra*) show that the rotamer distribution of, e.g., the methyl group plays a minor role[112], ^2J(CO,C-arom) couplings depend also on the bond order of the aromatic bond and ^2J(CO,C-arom) couplings of cyclic compounds depend also on bond angles. ^2J(CO,C-arom) will decrease in magnitude if the C=O bond is twisted out of the ring-plane, as seen for derivates with either 2,6-dimethyl substitution (**B** in Scheme 9) or with an *o-t*-butyl group (**C** in Scheme 9).

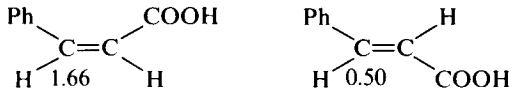
The orientational dependence is therefore similar to that observed for ^2J(C,H) couplings of carbohydrates[341] or ^2J(C,C-arom) of compounds with a sp^3 hybridized carbon with an electronegative substituent[364].

^2J(C=O,C) has been used to predict the conformation or the degree of twist of a series of similar compounds, such as nicotinamide[229], 8-nitro-1-naphthoic acid[77], 2-acetylcyclophane[365], 2-biphenylcarboxylic acid[366] and 9-anthracenecarboxylic acid[367]. The case of diethyl phthalates has been discussed in Section III.A.6. The carboxyl anion in 1-naphthoate takes up a preferred orientation as shown in **45**[77].



(45)

Two-bond ^2J(CO,C) couplings across double bonds show features similar to those of the aromatic compounds, but less clearcut[77,368,369].



(A) **(B)**

(46)[77]

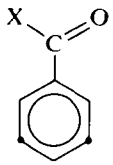
A rather interesting observation is pointed out by Krivdin and Della[341], who suggest that the smaller coupling in **46B** is a feature that can be used for assignment purposes of olefins substituted with acid or ester groups. ^2J(C=O,C) across aliphatic bonds are expected to behave similarly to ^2J in aromatic compounds[77] and are generally of the order of 0 to -1.9 Hz[369]. A standard value of -1 Hz[370] is evaluated for a series of compounds, a magnitude of 1.6 to 2.0 Hz is arrived at and a negative sign is assumed[371].

An interesting case is[372] **47**, again pointing towards the possible structural dependence of ^2J(CO,C). Two-bond couplings in general are discussed in References 373 and 374. Barfield and Walter[374] found a vague correlation between ^2J(CO,C) and ^2J(CO,H).

(47)

3. ^3J(CO,C)

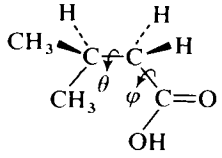
Two different types of three-bond couplings have been described in detail. One is from a side-chain carbonyl carbon to an aromatic carbon (see **48**) and the other is from a carbonyl carbon through aliphatic bonds.



(48)

a. ^3J(CO,C-arom). This type of coupling shows dependence on the orientation of the C=O group and on the bond order of intervening bonds[77,112,229], but to a lesser extent than ^2J(CO,C-arom).

b. ^3J(CO,C). Calculations by Barfield[375] have shown that ^3J(C,C) values depend upon the orientation of the terminal substituents in carboxylic acids (angles denoted by φ in **49**. The FPT INDO calculations on 3-methylbutanoic acid showed that only for $\theta = 0$ is the φ angle of great importance. The influence is minimal for $\varphi = 0$, and at a



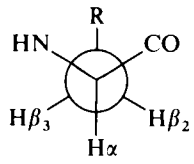
(49)

maximum for $\varphi = 35°$ and $\varphi = 225°$. If this trend is fully operative, it may to some extent make it difficult to use ^3J(CO,C) in conformational analysis. However, ^3J(CO,C) couplings have shown some promise. For a full discussion of the use of ^3J see Section V.A.9.

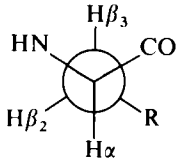
^3J(CO,C-γ) is especially useful in the conformational study of amino acids with two γ-carbons like valine and leucine, since these only have one H_β proton (**50B**). ^3J(CO,C-γ) coupling shows a pronounced pH dependence[85,355,356,376] caused by a change in rotamer populations.

^3J(CO,C-γ) couplings can be used to determine pK_a values[376]. Aspartic is a very characteristic example[85]. The increase in the ^3J(CO,CO) coupling with pH is an effect of an increase in the population of rotamer III of **50A**.

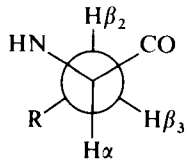
A very elegant study is the use of ^{18}O labelling to make the two carboxylic acid groups of succinic acid non-equivalent (**51**). The analysis gave ^3J(CO,CO) = 2.2 Hz for the diacid and ^3J(CO,CO) = 4.2 Hz for the dianion. This increase in ^3J(CO,CO) with pH can be explained if the acid is predominantly *gauche*, whereas the dianion is *ca* 100% *trans* (antiperiplanar)[303].



I

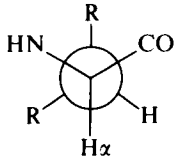


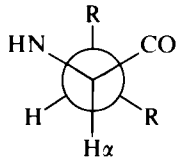
II

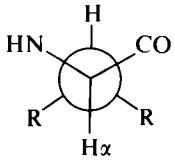


III

(A)

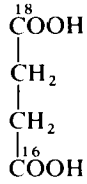






(B)

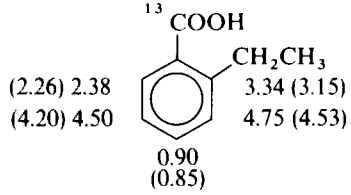
(50)

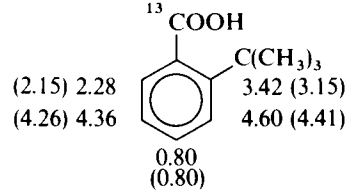


(51)

4. Medium effects

A change of medium may induce a conformation change as a result of a specific solvation process. An example is the ^{n}J(CO,C) carbon–carbon couplings of *o*-alkyl substituted benzoic acids. Both show generally smaller coupling constants in DMSO-d_6 than in $CDCl_3$ (values in parentheses in **52**). This was attributed to specific solvation of the freely rotating carboxyl groups in the polar medium[112].





(52)

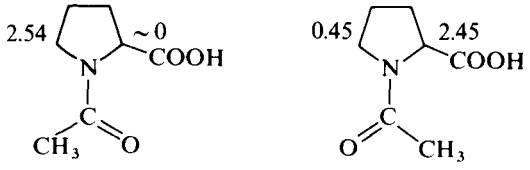
5. ^{n}J(CO,C)

Long-range carbon–carbon couplings are generally small, 0.1–0.7 Hz[377].

6. ^{2}J(C=O,X,C) and ^{2}J(C=O,X,H)

Two-bond coupling constants across a hetero atom are observed in esters, lactones or amides.

a. $^2J(C{=}O,N,C)$ *and* $^2J(C{=}O,N,H)$. $^2J(C{=}O,N,C)_{s\text{-}trans}$ is shown to be positive and larger than $^2J(C{=}O,N,C)_{s\text{-}cis}$[337]. A study of a series of compounds confirms that $^2J(C{=}O,N,C)_{s\text{-}trans} > {}^2J(C{=}O,N,C)_{s\text{-}cis}$[378,379]. The former fall in the range 2–3 Hz, whereas the latter are smaller, 0.5–0.9 Hz. It is therefore correct to assume that all $^2J(C{=}O,N,C)_{s\text{-}trans}$ couplings are positive. This has been used to explain the larger couplings observed in five-membered nitrogen heterocycles[337,380]. Studies of $^2J(C{=}O,N,C)$ may be used to determine the *cis/trans* ratio. The method can in principle be used in peptides and proteins[378] (see **53**), but has also been applied to amides in general[337].



trans *cis*

(53)[378]

$^2J(C{=}O,H,N)$ couplings were investigated by Dorman and Bovey[381]. A detailed investigation paired with sign determination shows features similar to those described for $^2J(C{=}O,N,C)$[382].

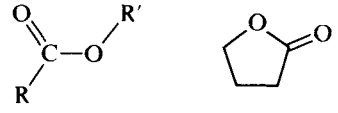
The stereospecificity of geminal couplings across nitrogen is considerably less pronounced in thioamides than in amides (**54**)[336].

(54)

Combined $^2J(CO,N,C)$ and $^3J(C,C)$ couplings are observed in five-membered lactones[334].

b. $^2J(C{=}O,O,C)$. A standard value for this coupling is −1.5 Hz (for four-membered rings −4 Hz must be added)[383]. The sign is negative in esters[369].

The geometry in esters is probably as depicted in **55A**[384]. The *s-cis* geometry is in line with a negative coupling constant. A positive coupling constant is to be expected in cyclic compounds in analogy with the result for amides. The large $^{2,3}J(C{=}O,O,C{=}O)$ coupling observed in phthalic anhydride is taken as evidence for a positive coupling[380]. $^2J(C{=}O,O,C)$ couplings clearly have to be explored in detail, since valuable structural information about esters can be deduced from them.



(A) **(B)**

(55)

A number of interesting $^2J(CO,O,C)$ couplings are observed in lactones (**55B**). These are of course a combination of a two-bond path through oxygen and a three-bond

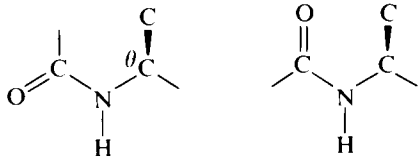
C=O,C,C coupling path. The couplings range from 0.7–2.8 Hz in aldono-1,4-lactones and are assumed to be positive[385,386].

7. ^3J(C=O,N,C,C) and ^3J(C=O,N,C,H)

^3J(C=O,N,C,C) depends on the dihedral angle[371]:

$$^3J(\text{C=O,N,C,C}) = 1.84\cos^2\theta - 0.23\cos\theta + 0.51 \tag{26}$$

For $\theta = 180°$, $^3J = 2.6$ Hz, which is a rather small value for a three bond coupling (see **56**). As the experimental data are obtained from cyclic compounds, only the *cis* orientation is represented. Theoretical calculations show similar magnitudes for the *cis* and *trans* arrangements[382] of the carbonyl group as shown in **56A** and **56B**. The pH



(A) (B)

(56)

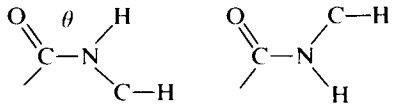
dependence of ^3J(CO,C,N,C-δ) of [*S*]-proline demonstrates how this parameter may be used to gauge the conformational change with pH. ^3J(CO,C,N,C-δ) = 1.4 Hz at pH 1.3, 2.4 Hz at pH 6.1 and 4.75 Hz at pH 8.3. This increase reflects the decrease in the CO,C,N,C angle with increasing pH[355]. An equation for ^3J(C=O,N,C,H) was first formulated by Gavrilov and collaborators[388]:

$$^3J(\text{C=O,N,C,H}) = 9\cos^2\theta - 4.4\cos\theta - 0.8 \tag{27}$$

This has since been tested further in cyclic compounds[371] leading to

$$^3J(\text{C=O,N,C,H}) = 3.96\cos^2\theta - 1.83\cos\theta + 0.81 \tag{28}$$

where θ is the dihedral angle as shown in **57A**. As ^3J(C=O,N,C,H) is derived from cyclic compounds, primarily fragments shown in **57A** are represented. Data for the **57B** fragment seem to fall outside the equation[371]. Various data are given in Reference 382. ^3J(C=O,N,C-α,H) have recently been determined in a polypeptide[387].



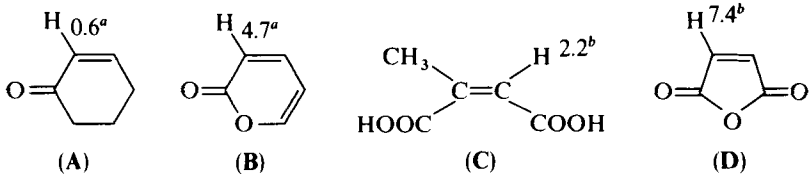
(A) (B)

(57)

8. ^2J(CO,H)

These couplings show some promise as a conformational probe[391]. A comparison of **A** and **B** in Scheme 10 clearly shows the importance of the direction of the extra oxygen. The position *trans* to the substituent leads to a positive contribution.

For **C** in Scheme 10 the conformation is unknown, but the small ^2J(CO,H) do not support the conformation shown with the CO and the H *trans* to each other. The extra



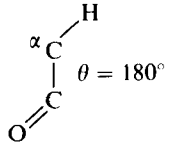
(A) (B) (C) (D)

SCHEME 10. Orientational dependence of ^2J(CO, H)

[a] Taken from Reference 389. [b] Taken fromReference 390.

increase found for **D** is ascribed to the extra steric strain[390]. The similarity to ^2J(CO,C -arom) is obvious (Section V.A.3.a).

^2J(CO,H) couplings have been determined in amino acids[392–396] and peptides[351,397–400] and fall in the range -4.8 to -7.2 Hz for the former. The rather wide range is partly due to differences in pH. No clear difference has so far been seen between amino acids and peptides. This type of coupling may be observed in proteins. Preliminary results show that ^2J(C,H) values are small for a dihedral angle close to 180° (see **58**)[400]. This prediction is not supported by theoretical studies[402,403].



(58)

9. ^3J(CO,H-β)

Three-bond carbon–hydrogen couplings were used to determine the rotamer populations in a large number of amino acids and peptides, and they were also used to determine dihedral angles. In both cases a Karplus-type behaviour is relied upon. The determination of rotamer populations rely on $^3J(\text{CO,H-}\beta)_{gauche}$ and $^3J(\text{CO,H-}\beta)_{trans}$. These have been determined and are shown to depend on substituents at the β-carbon. The analysis based on $^3J_{gauche}$ and $^3J_{trans}$ relies on the assumption that the different types of *gauche* couplings are identical.

As seen from Figure 8 *one* coupling constant does not unambiguously define the problem, as four different angles correspond to one coupling constant value. Furthermore, a very difficult problem is the distinction between one fixed conformation and a rotational averaging one. Again, an ensemble of couplings may be helpful. The use of ^3J(CO,H) coupling should therefore be combined with other three-bond couplings like ^3J(H,H), ^3J(CO,C) (Section V.A.3.b) and ^3J(N,H) (Section V.B.4).

^3J(CO,H-β) couplings may also be used to achieve stereospecific assignments of proteins to assure more accurate structures using distance geometry procedures[402].

^3J(CO,C) can usually be observed in small molecules without enrichment. For larger and more complex molecules new pulse techniques are useful[403–405]. Moving to larger molecules usually leads to line broadening[404–406]. This is very nicely demonstrated in the case of *N*-decyl-aspartic acid[406].

For proteins, techniques like HMBC[161] will not yield accurate coupling constants,

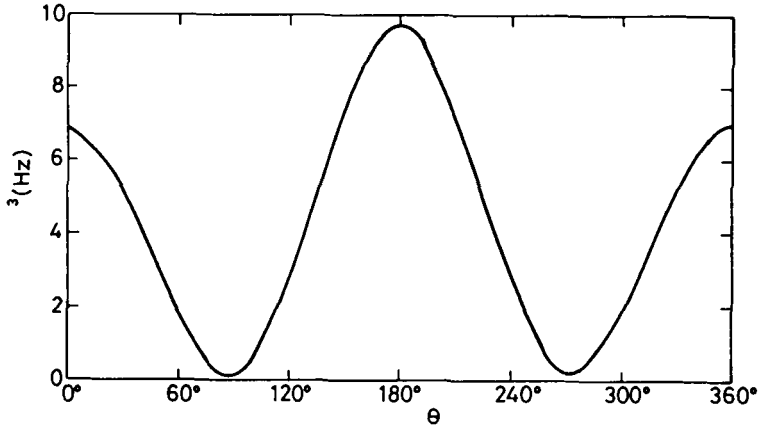


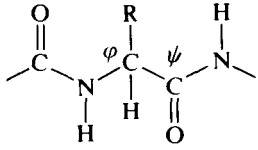
FIGURE 8. Schematic Karplus curve

but the magnitudes may be estimated from intensities[400]. The configuration of the more complex β-phenyl aspartic acid, with two asymmetric carbons, has been assigned[407].

^3J(CO,H) can also be used to determine rotamer populations of acids in general as demonstrated by Rennekamp and Kingsbury[408].

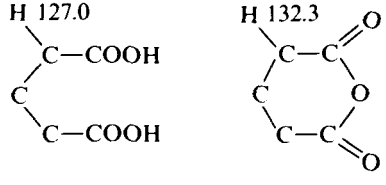
10. ^1J(C-α, H-α)

The one-bond C-α,H-α carbon–hydrogen coupling (**59**) has been investigated in cyclic peptides in order to elucidate the influence of substituent orientation on this parameter[408].



(**59**)

A dependence on the lone-pair orientation of the NHCO fragment is expected[391] since lone-pair generally influences the one-bond coupling. Von Philipsborn and coworkers[409] found that the orientation of the NHCO fragment had an influence on



(**A**) (**B**)

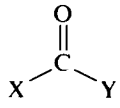
(**60**)

^1J(C-α,H-α). The access to this type of coupling constant in peptides and proteins has become more easy with the invention of the HMQC technique[159]. Further refinement of this kind of data could lead to a useful way of determination of φ and ψ angles of proteins. ^1J(C-α,H-α) have also been determined in dicarboxylic acids and anhydrides (**60**).

The increase in ^1J(C-α,H-α) is ascribed by the authors[410] to the larger electronegativity of the anhydride. The present author believes that the effect could well be of orientational origin. For olefins a similar, but more outspoken, difference is seen[410].

11. ^2J(X,C=O,Y)

The two-bond coupling across a carbonyl group ^2J(X,C=O,Y) (see **61**) has been noted because of its large positive magnitude. A positive coupling was also observed for the similar ^2J(H,C=O,H). This is caused by overlap between the P_y orbital (the orbital in the HCO plane) and the two C—H bonds[411]. ^2J(C,C=O,C) is close to 12 Hz[337]. Even larger couplings of the type ^2J(C,C=O,F) are observed in acid fluorides (**61**; X = CH_3, Y = F). ^2J(C,C=O,F) couplings are of the order of 61 Hz[412]. Theoretical calculations (Scheme 11) predict this kind of coupling poorly[112].

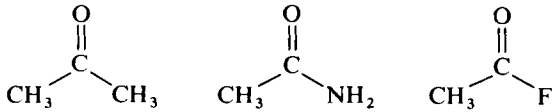


(61)

Yet another coupling is ^2J(C,C=O,^{15}N). These are observed in amides (**61**; X = CH_3, Y = NH_2). They are probably negative, because of the negative gyromagnetic ratio of ^{15}N. The coupling constants are large, about 9–10 Hz[413,414]. A logical extension would be to measure ^2J(C,C=O,^{17}O). This has so far not been reported.

12. ^1J(C=O,F)

In aromatic acid fluorides, ^1J(C=O,F) is predicted to depend on the degree of twist of the FC=O group leading to numerically larger values of the coupling in the case of no conjugation[112]. This is observed experimentally, since the coupling of acetyl fluoride[305,416] is larger than that of benzoyl fluoride[305].



15[a] 9.5[b] 61[c]

SCHEME 11. Comparison of two-bond couplings, ^2J(X,C=O,Y)

[a] Taken from Reference 415. [b] Taken from Reference 413. [c] Taken from Reference 305.

B. ^{n}J(N,C)

1. ^{1}J(N,C)

The one-bond coupling involving carbon and nitrogen is mostly small[150–155]. One-bond couplings are normally positive, but due to the negative gyromagnetic ratio ^{1}J(N,C) is mostly negative.

One-bond couplings are often determined by the *s*-character of the orbitals at the involved nuclei.

The relationship

$$^{1}J(\mathrm{C,N}) = -125 \times s(^{13}\mathrm{C})s(^{15}\mathrm{N}) \tag{29}$$

has been suggested[416]. Furthermore, theoretical calculations have shown that only the Fermi-contact term is important for the amides[417,418]. The inability of equation 29 to fully describe the one-bond ^{1}J(C=O,N) coupling is ascribed to the lone-pair on nitrogen[6]. Protonation or delocalization[152] of the lone-pair is therefore likely to lead to an increase (numerically).

An increase was indeed found in proton-donating solvents[419]. For cyclic peptides a similar trend is found using trifluoroethanol or trifluoroacetic acid[420]. Berger noticed that protonation effects are larger in *trans*-amides[421]. On the other hand, no significant differences were observed between *cis*- and *trans*-amides[421].

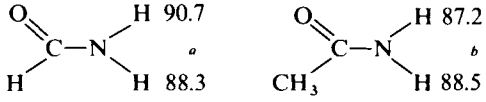
^{1}J(N,C) couplings are observed in proteins[199,285,333]. A value in an unfolded protein is 15.6 Hz[333]. A smaller value was found in subtilisin inhibitor. As hydrogen bonding is assumed to lead to larger couplings and as the value becomes normal in the unfolded protein, this is taken as evidence for a non-planar amide moiety[333].

2. ^{2}J(N,C)

These couplings were not observed in simple amides[414]. Studies on diketopiperazines confirm that they are small and therefore not useful in stereochemical studies[422].

3. ^{1}J(N,H) of amides

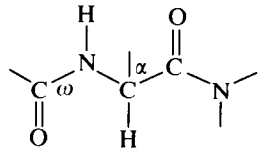
This type of coupling is large and negative, *ca* −90 Hz. $^{1}J(\mathrm{NH}_{trans})$ is slightly larger than $^{1}J(\mathrm{NH}_{cis})$[423] (see **62**). This trend has been confirmed for side-chain amide groups of peptides[424]. ^{1}J(N,H) couplings do not vary much and hence ^{1}J(N,H) depends very little on the solvent[425–427], although it increases slightly in protonating solvents[428,429], e.g. from 90 Hz in H_2O to 92.5 Hz in TFA[428].



(62)

[a] Taken from Reference 425. [b] Taken from Reference 424.

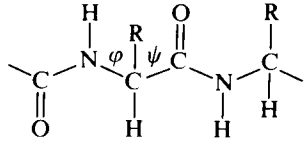
^{1}J(N,H) of proteins fall in the range 90–98 Hz for T4 lysosyme[193] (previously[195] given as 87 ± 3 Hz). Thioredoxin gave a range of 90.5–101.5 ± 2 Hz[184]. LeMaster and Richards[184] noted that ^{1}J(N,H) of proteins depend to a certain degree on the type of amino acid. Llinas and coworkers[182] found that ^{1}J(N,H) of glycines vary with the deviation in the ω angle from 180° (see **63**).



(63)

4. ^3J(N,H)

Two different types of three-bond nitrogen–proton couplings (see **64**) are interesting as demonstrated in peptide fragments, ^3J(N,C-α,C-β,H-β) and ^3J(N,C=O,C-α,H-β).



(64)

a. ^3J(N,C-α,C-β,H-β). This coupling is in principle similar to ^3J(H-α, H-β), ^3J(CO, H-β) and ^3J(CO,H-γ) already discussed. However, ^3J(N,H) is rather small. Sogn and coworkers[424] estimated $^3J(\mathrm{N,H})_{trans} \sim -4.8$ Hz and $^3J(\mathrm{N,H})_{gauche} = -1.8$ Hz. McIntosh and collaborators[193] found that very few resonances involving $^3J(^{15}\mathrm{N,H}\text{-}\beta)$ could be observed in an HMBC spectrum. This is partly due to the small magnitude of ^3J(N,H-β), but could also be due to passive couplings[200].

^3J(N,H-β) clearly could lead to stereospecific assignments, similarly to ^3J(CO,H-β) (Section V.A.9). It still remains to be seen how practical this approach is, considering the small couplings.

b. ^3J(N,C=O,C-α,H-α). This coupling has been treated experimentally leading to the equation

$$^3J(\mathrm{N,C{=}O,C\text{-}\alpha,H\text{-}\alpha}) = -4.6\cos^2\theta + 3.0\cos\theta + 0.8 \qquad (30)$$

It has been measured in a number of peptides[424,432–435], as it may lead to information about the ψ angle (see **64**). Theoretical calculations on *N*-methylacetamide predict opposite signs for $^3J(\mathrm{N,H\text{-}\alpha})_{gauche}$ and $^3J(\mathrm{N,H\text{-}\alpha})_{trans}$, a severe complication if true in practice[436].

c. ^3J(H-α, NH)

The H-α proton of amides may serve as a probe of the orientation of the amide groups relative to the side-chain either by use of ^3J(H-α,NH) to determine the φ angle (see **64**) or by analysis of δH-α chemical shifts (Section III.B.3). This has been demonstrated for peptides and proteins.

This three-bond coupling has been shown to follow a Karplus relationship:

$$^3J(\mathrm{H\text{-}\alpha,\ N\underline{H}}) = A\cos^2\theta - B\cos\theta + C\sin^2\theta \qquad (31)$$

Slightly different values for *A*, *B* and *C* are given by different authors: Bystrov and coworkers[437] give 9.8, 1.1 and 0.4; Cung and collaborators[438] give 9.4, 3.2

and 0 and Ramachandran's group[439] gives 8.6, 1.7 and 1.5. More recently these values have been determined in proteins, leading to values (5.4, 1.3, 2.2)[440] or (6.4, 1.4, 1.9)[441]. ^3J(H-α,NH) can also be used for localizing a helical structure[441].

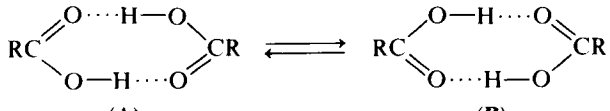
For small peptides, values of the order of 7.8 Hz are obtained. This value depends slightly on the nature of the side-chain. Branching at the β-carbon tends to increase the coupling. A change to more polar solvents also increases the coupling, as seen in dioxane (8.5) compared to DMSO-d_6 (8.9)[442].

Recently, improved methods for measuring ^3J(H-α,NH) couplings in proteins have been proposed[443,444].

VI. HYDROGEN BONDING

Hydrogen bonding has been a major theme throughout this chapter. A few special subjects are discussed in the following.

Proton motion in carboxylic acid dimers (with two identical R groups) converts the dimer into an energetically degenerate state (see **65**). The proton motion has been shown to be a simultaneous classical proton jump and a quantum mechanical tunneling along the hydrogen bond[445–450]. However, in the solid state the degeneracy is often lifted due to distortions leading to a slightly asymmetric double minimum potential (Fig. 9).



(A) (B)

(65)

The dynamics of the hydrogen bond has been investigated in benzoic, glutaric and *p*-formylbenzoic acid by means of ^{1}H T_1 measurements, which show an increase in the activation energy of approximately 8 kJ mol^{-1} for the deuterated species.

The change in activation parameters is seen as a consequence of the difference in the O—O distance ($R_{O\cdots O}$), which upon deuteration changes from 2.44 to 2.63 Å[452]. The increase in distance upon deuteration has been explained by tunnelling[453]. The two hydrogen-bonding oxygens are drawn together by the tunneling motion of the proton[453]. Since deuterium tunnels less easily, the effects become smaller.

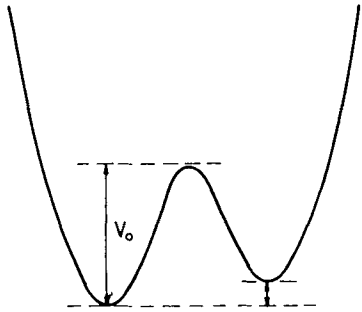
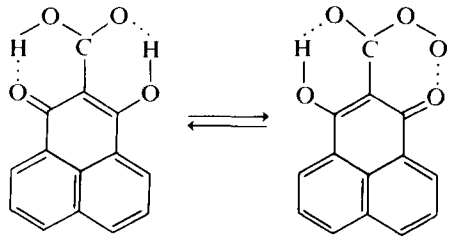


FIGURE 9. Potential curve for proton (deuteron) transfer in hydrogen-bonded carboxylic acids

Other acids have been preliminarily investigated and the authors[451] suggest proton transfer to be a general phenomenon in dicarboxylic acids.

Hydrogen bonding in the solid state can also be studied ^{13}C and ^{2}H chemical shifts. A series of monoprotonated dicarboxylic acids, potassium hydrogen malonate (KHM), succinate (KHS) and phthalate (KHPh), ammonium hydrogen glutarate (AHG), the *cis–trans* isomers of ammonium hydrogen maleate (AHM) and fumarate (AHF) andma-maleic and fumaric acid were investigated[454]. KHM and AHM were found to have symmetrical hydrogen bonds. For AHG the deuterated compound showed two resonances for the carbonyl carbon (and also less clearly for other carbons) with a splitting of 6.5 ppm and positioned symmetrically around the resonance from the protio compound. This splitting was taken as evidence for a lowering of the symmetry.

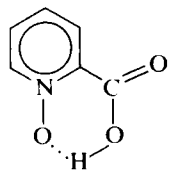
The δ OH proton is used to estimate the R_{O-O} distance[454]. The compounds described above, hydrogen succinate, hydrogen maleate and hydrogen phthalate, are shown to have a double-minimum potential in aqueous solution. This finding is based on the finding that ^{18}O substitution decreases acidity and that the ^{13}C NMR resonance is different for the carboxylic acid and the anion[149]. The finding of a double-minimum potential is different from that of Altman and coworkers[148] in non-polar solvents. Hydrogen bonding and hydrogen transfer is found in the system (**66**).



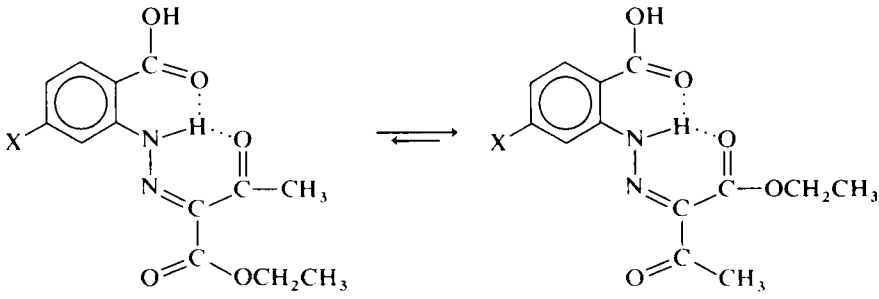
(**66**)

The OH resonance was observed at 15.6 ppm accounting for both OH protons. The ^{13}C spectrum showed a total of 9 resonances, again underlining the fast averaging. The tautomerism involves a double proton transfer. The system is very similar to that found in citrinin (**29**)[455].

Hydrogen bonding in N-oxides (**67**) has been investigated[456,457]. Furthermore, the preferred conformation of **68** is shown to be the one forming a hydrogen bond with a CH_3COOR group (ester) rather than with a $CH_3C{=}O$ group (ketone)[458]. This is rather unusual. Hydrogen bonding has also been discussed in 2-nitroanilides[459].



(**67**)



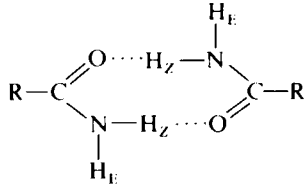
(68)

VII. NH EXCHANGE

The exchange of amide protons is constantly under investigation as the mechanism is understood only incompletely and because NH exchange is a very useful parameter in the discussion of protein dynamics and protein folding. It is outside the scope of this review to cover the vast area of amide exchange in proteins[460-463], but we will highlight some recent and very interesting findings. Hydrogen bonding has been discussed extensively in connection with NH exchange.

A. Hydrogen Bonding and Mechanism

The hydrogen-bonded H_Z atom of **69** undergoes OH^- catalysed exchange only 1/70 as fast as H_E. In simple primary amides H_E undergoes base-catalysed exchange 2–3 times faster than H_Z. The latter difference has been attributed to the greater stability of the *Z*-imidate (**70**) which is formed upon proton abstraction. Taking this into account,



(69)

(70)

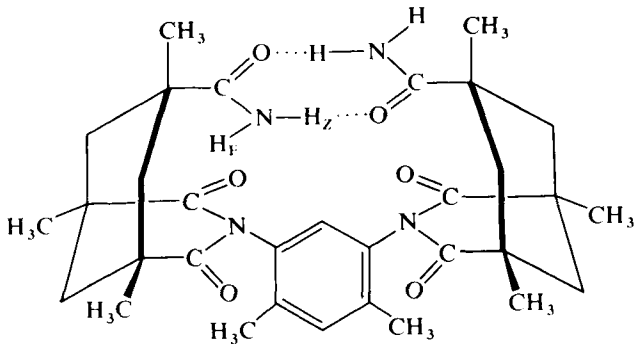
a direct effect of hydrogen bonding is that H_Z (which is hydrogen bonded) is exchanged 30 times slower than H_E in a base-catalysed reaction[464]. Furthermore, the base-catalysed exchange occurs by direct abstraction of H_Z in the hydrogen-bonded situation. No rotation occurs in the imidate ion on the time scale of exchange, which means that no interchange of H_E and H_Z occurs.

Acid catalysis can either occur via O- (equation 32) or N-protonation (equation 33):

$$XCH_2CONH_2 + H^+ \rightleftharpoons XCH_2O(OH)=NH_2^+ \rightleftharpoons XCH_2C(OH)=NH + H^+ \quad (32)$$

$$XCH_2CONH_2 + H^+ \rightleftharpoons XCH_2CONH_3^+ \quad (33)$$

Perrin[463,464] has shown that both mechanisms are possible. If X is electron withdrawing, the exchange via O-protonation (equation 32) is favoured, whereas if X is electron donating the N-protonation becomes dominant. For N-protonation intramolecular hydrogen bonding is of little importance, as was elegantly demonstrated by the use of **71**. This is ascribed to fast rotation in the $XCH_2CONH_3^+$ species around the C—N bond. The fast rotation is described to be similar to that found for ammonium ions[465]. The O-protonation (equation 32) mechanism becomes more predominant in less polar solvents.



(71)

Backbone amide exchange is used to elucidate protein structure and protein dynamics. The electron-withdrawing CONH— substituent[463] at the C-α carbon of proteins makes the N-protonation mechanism less likely. It is furthermore shown that steric hindrance could prevent the rotation around the C—N bond, making this mechanism even less likely for buried protons[464].

Backbone NH exchange rate of BPTI corrected for electrostatic effects showed that NH exchange of surface NH protons occurred from a conformation similar to the crystal structure[466]. Comparisons with static accessibilities suggested strongly that *O*-protonation is dominant[467,468]. A mechanism involving a chain transfer of charge through intermolecular hydrogen-bonded amides was suggested as a means of diffusionless catalysis[467]. Exchange of buried side-chain amide NH groups of Asn-43 and Asn-44 of BPTI showed that H_E and H_Z exchange at indistinguishable rates[469].

B. Monitoring of exchange

The NH exchange rates cover a very wide range, when both simple amides and proteins are considered. For slow exchanges simple recording of spectra at different times is sufficient[466].

The use of deuterium labelling enables observation of two resonances as discussed in Section IV.A.2. The splittings in the ^{13}C spectrum are generally small, 30–100 ppb. These splittings enable determination of the exchange rate, *ca* 40 times per second[470], on a 300 MHz NMR instrument. Faster exchange rates may be observed using saturation

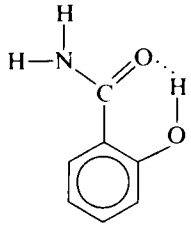
transfer techniques[464]. Recently, an elegant pulse labelling technique to observe events in the millisecond range has been described[471].

VIII. HINDERED ROTATION

A. Rotational Barriers

Rotational barriers have been discussed in Section III.D.3. Hindered rotation of amides is a very important feature leading to resolvable *cis* and *trans* isomers of monosubstituted amides and to non-equivalent protons of primary amides or methyl (alkyl) groups of tertiary amides. The assignment problems involved are discussed in sections III.B.1.

The equivalence is in itself direct evidence of a low rotational barrier. This is the case for, e.g., benzamide, whereas for *o*-substituted amides with bulky substituents non-equivalence may be observed due to steric hindrance to planarity and therefore poorer

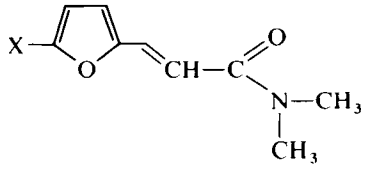


(72)

conjugation (see Figure 1). For *o*-substituents like OH or NH_2 the barrier is still low, due to intramolecular hydrogen bonding and the supposedly more planar structure (72).[472]

NMR methods are well suited to study rotational barriers, since the range of investigations may be varied by the use of either ^1H, ^{13}C or ^{15}N NMR, as well as by the use of different magnetic field strengths and different temperatures.

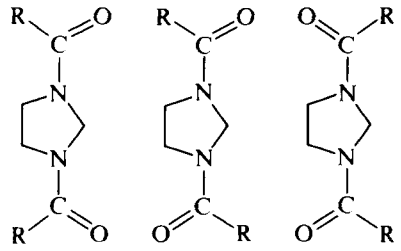
^{13}C NMR combining line-shape analysis and saturation transfer techniques was used to investigate the activation energy of the *cis–trans* barrier to rotations of the anti-hypertensive drug, captopril[473]. Friedl and collaborators[474] compared rotational barriers of **73** with the similar 4-substituted benzene derivatives and found larger barriers



(73)

to rotation in the former class. A DSP (dual substituent parameter) analysis of $\Delta G^{\#}$ gave $\rho_I = 6.07$ and $\rho_R = 3.11$ for the furans and $\rho_I = 3.43$ and $\rho_R = 2.02$ for benzene using the R^+ scale. The authors found that polar effects are the dominant factor. Had it been resonance effects one would have expected to find decreased barriers in case of electron-withdrawing substituents. *N*-cycloalkylformamides show both *E* and *Z* forms for *N*-cyclopropyl, *N*-cyclobutyl and *N*-cyclopentyl derivatives, whereas the *N*-cyclohexyl and *N*-cycloheptyl compounds do not[475]. Barriers to rotation are $\Delta G^{\#} \sim 73.2$, 78.2 and 79.0 kJ mol^{-1} for the first three compounds[475]. The *cis–trans* problem of

N-substituted amides becomes more complex with two secondary amide groups[476]. Examples are **74A–C**. The relative percentages at low temperature are 3.5:80:16.5[476].

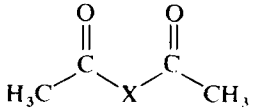


(A) (B) (C)

(74)

For *N,N*-diacetyl-*N,N*-dimethyl hydrazine it was found that interconversion occurs by successive 180° rotations[477].

Raban and coworkers[478] studied diacetamide (**75**) and compared the NMR results with those of the enolate anion of 2,4-pentanedionate (**76**). Again both *Z,Z* and *E,Z* forms are possible.



X = NH (**75**)

X = CH^- (**76**)

B. Non-equivalence

The chemical shift difference of the two methyl groups of *N,N*-dimethylamides has been discussed in terms of electric field effects (Section III.A.5.a). No clearcut connection was found[479].

Non-equivalence of terminal CH_3 groups was found for *N,N*-dialkylamides with long alkyl groups[480].

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CHAPTER 6

ESR studies of organic free radicals from carboxylic acids and their derivatives

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I. INTRODUCTION

The technique of electron spin resonance (ESR) spectroscopy[1] provides a remarkably sensitive method for obtaining detailed information about the formation and reactions of free radicals. For example, through the application of this approach it is often possible to obtain not only the identification of a potentially short-lived free radical or radical-ion but also to determine details of hybridization, delocalization and conformation. The technique thus also offers a unique means to establish the nature of free-radical species formed in a reaction pathway—be this photolytic or radiolytic in type or free-radical induced; kinetic studies of formation and decay will often provide additional mechanistic evidence.

This review commences with a brief consideration of some of the most important facets of ESR spectroscopy—for example, the relationship of spectra to radical structure, and the use of ancillary techniques for radical generation and study—with emphasis on the chemical and physical properties of carboxylic acid-derived radicals. In the subsequent sections emphasis is placed upon the factors which govern the reactions of radicals of different type with aliphatic and aromatic carboxylic acids—and the chemical properties of carboxylate-derived radicals. Finally special attention is paid to the contribution of ESR spectroscopic studies to the understanding of the factors which underlie the particularly complex free-radical chemistry of amino acids and related compounds.

II. ESR SPECTRA OF RADICALS AND RADICAL-IONS FROM CARBOXYLIC ACIDS AND THEIR DERIVATIVES

A. Introduction to Methods of Study

A variety of methods in which radicals are believed to be generated can be employed in conjunction with ESR spectroscopy[2]. These include radiation techniques, the thermolysis or photolysis of covalent bonds, electron-transfer reactions (including electrochemical oxidation or reduction or transition metals such as Ce^{IV} or Fe^{II}) and reaction with a first-formed radical (e.g. ·OH from radiolysis of water or from metal–peroxide reactions: see reactions 1 and 2). Examples of these approaches will be described below.

$$H_2O \xrightarrow{\gamma\text{-radiolysis}} HO\cdot, e^-, H\cdot \qquad (1)$$

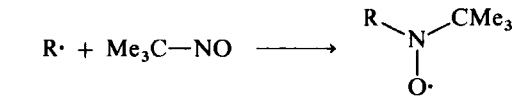
$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO\cdot + OH^- \qquad (2)$$

The technique itself is very sensitive (under favourable conditions a sample containing only *ca* 10^{-8} mol dm^{-3} of a radical can be successfully studied) but it must be remembered that most free-radicals are very short-lived indeed—because they decay by diffusion-controlled self-termination reactions ($2k_t \simeq 10^9$ dm^3 mol^{-1} s^{-1} for small radicals in fluid solution at room temperature). For that reason, many successful studies have been carried out using *in situ* approaches— that is with *continuous* generation of free radicals in fluids by direct photolysis, radiolysis or flow-system techniques. The spectrum is normally recorded as a scan of applied magnetic field (B) in a continuous-wave experiment (with fixed microwave frequency) providing not only detailed information through analysis of the splittings but also a measure of the steady-state *concentration* of radicals. Once a spectrum is obtained, it is sometimes possible to carry out *kinetic* (time-resolved) studies on radical decay via use of flash photolysis, pulse radiolysis or stop-flow techniques (see e.g. Reference 3).

Some radicals or radical-ions are much longer-lived—either as a result of a considerably decreased $2k_t$ (which is typical of very hindered free radicals or of radicals and

radical-ions with extensive delocalization) or because they have been generated in a relatively rigid, solid matrix which prevents self-reaction. In the latter circumstances the spectra tend to be broadened through the occurrence of electron–nuclear dipole–dipole interactions (averaged out in fluid media), though characterization and detailed structural information can often be obtained from the anisotropic spectra, especially if single-crystal studies can be made [1].

In cases where radical concentrations are too low to be detected even by more conventional ESR approaches—or where a radical's spectrum is broadened beyond detection—the *spin-trapping* technique often offers a valuable alternative[4]. The reaction under investigation is then carried out in the presence of a low concentration of a spin trap such as 2-methyl-2-nitrosopropane (MNP) or 5,5-dimethylpyrroline-*N*-oxide (DMPO). These compounds are very effective scavengers for most types of reactive free radical (see reactions 3 and 4, respectively), giving much longer-lived (and hindered) nitroxides whose ESR parameters (especially the β-proton splittings) provide evidence for the nature of the addend radical.



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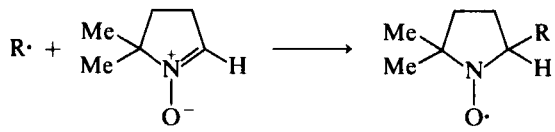


(4)

B. Structural Information from ESR Splittings

ESR spectra of free radicals normally show hyperfine splittings from nuclei which possess a magnetic moment and which are close to the radical centre. Though splittings may be seen from, for example, ^{14}N, ^{19}F, ^{31}P etc., and even ^{13}C (as 'satellite' lines) spectra are normally dominated by splittings from *protons* in the radical concerned. The *patterns* are governed by the number of equivalent protons: $^{\cdot}CH_3$ gives a 1:3:3:1 (quartet) pattern from the 3 α-protons, the *t*-butyl radical $^{\cdot}CMe_3$ gives a decet from the β-protons and $^{\cdot}CH_2CH_3$ gives a triplet of quartets. The precise *values* (magnitudes) of the splittings depend upon the hybridization, delocalization and conformation of the radical and, in particular, whether the radical has the unpaired electron in a *p*- or π-type orbital (such as $^{\cdot}CH_3$ or the delocalized benzene radical-anion $C_6H_6^{\cdot-}$) or a σ-type (or *s*-containing orbital) such as the phenyl radical $(C_6H_5^{\cdot})$[1,2]. This concept will be illustrated with parameters from a variety of carboxyl-derived radicals[5].

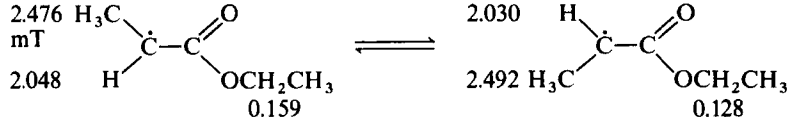
1. *p- and π-type radicals*

Examples of planar π-type radicals are provided by the carboxyl-conjugated species $\cdot CH_2CO_2H$, $\cdot CHMeCO_2H$, $\cdot CHMeCO_2Me$ and many related examples, most of which have been obtained via reactions of $\cdot OH$ and $^tBuO\cdot$. For these radicals the α-proton splitting is approximately 2.0 mT[5–7], (1 mT $\equiv$ 10 G) this being somewhat reduced compared to the methyl radical (2.3 mT) because of spin-withdrawal by the carboxyl group (see structures **1** and **2**); it is generally believed[2] that for most planar π-radicals the value of the α-proton splitting [$a(\alpha\text{-H})$] is proportional to the unpaired spin density (ρ_α) on the adjacent carbon atom, the value of the proportionality constant $Q(\alpha\text{-H})$ being

(−) 2.3 mT. This delocalization, which places spin density on oxygen, also causes small but discernible increases in the g-value of the carboxyl-conjugated radicals (compare 2.0033 for $\cdot CH_2CO_2H$ with 2.0026 for $\cdot CH_3$)[8]. This diagnostically useful parameter, which is a measure of the field needed for resonance for a given fixed microwave frequency (and which thus resembles the chemical shift in NMR spectroscopy), is a reflection of the coupling of spin and orbital angular momentum. The orbital angular momentum is largely quenched for most organic radicals in solution (e.g. $\cdot CH_3$), but spin–orbit interactions cause increases from the spin-only value of 2.0023 when the unpaired electron is delocalized onto atoms with unshared pairs of electrons[8].

(1) (2)

Spittings from β-protons are believed[2,6,7] to reflect both the spin density at the radical centre (ρ_α) and the dihedral angle (θ) between the β C—H bond and the orbital of the unpaired electron [$a(\beta\text{-H}) = B\rho_\alpha \cos^2\theta$). For freely-rotating methyl groups, the rotationally-averaged value of $\cos^2\theta$, i.e. $\langle\cos^2\theta\rangle$, is $\frac{1}{2}$, and differences in $a(\beta\text{-H})$ for radicals of this type reflect changes in the spin density ρ_α: the comparison of $a(\beta\text{-H})$ for $\cdot CHMeCO_2H$ (2.5 mT)[7] with that for $\cdot CH_2Me$ (2.69 mT) confirms that the carboxylate group does indeed withdraw electron density from C_α, and a value of *ca* 7% may be calculated for the extent of delocalization. Further evidence for the extent of spin-withdrawal, and hence degree of double-bond character in the $^{\cdot}C—CO$ bonds in radicals of this type, derives from the observation[9] of non-equivalent proton splittings in $\cdot CH_2CO_2Me$ (α-protons) and $\cdot CMe_2CO_2Me$ (β-protons), and some related radicals, as well as the detection of *two* conformers **3** and **4**, with separate ESR signals, from $\cdot CHMeCO_2Et$ at low temperature (two isomers of $\cdot CHMeCO_2D$ have also been detected in γ-irradiated succinic acid at low temperature[10]). From the collapse of the individual signals from $\cdot CHMeCO_2Et$ as the temperature is raised, the barrier to rotation for interconversion **3** and **4** is calculated as 47 kJ mol^{-1}, which indicates a delocalization energy of about 40 kJ mol^{-1} (similar to that obtained for corresponding carbonyl-conjugated radicals[11]). It should be noted, however, that CO_2H and CO_2R substituents are considerably less effective at spin delocalization than CN (spin-withdrawal *ca* 15%)[2], —C(O)R (*ca* 16%) and —SR (*ca* 20%: see Reference 12); unlike OH or OR groups the carboxyl group does not cause distortion from planarity at the radical centre (see References 5 and 13, and references cited therein).

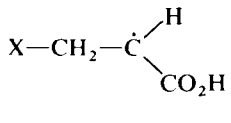


(3) (4)

Unlike α-proton and β-methyl proton splittings in radicals like $\cdot CHMeCO_2R$, splittings from *β-methylene* (CH_2) and *methine* (CH) protons vary widely in a way which reflects the *conformational* preferences of the groups attached to the radical centre. This is believed to underlie, for example, the differences observed in the β-CH_2 splitting for some acrylic acid adducts (**5**): values of 2.76, 2.38, 2.50 and 2.48 mT are observed for adducts of[14] $\cdot OH$, $\cdot CH_3$, NH_3^{+} and[15] SO_4^{-}, respectively (see also Reference 16). In

each case there is still rapid rotation about the $C_\alpha—C_\beta$ bond but conformational preferences and weightings differ: the differences in splittings, though small, are very helpful for correct radical diagnosis, and have proved invaluable in distinguishing monomer, dimer and polymer radicals involved in the initial stages of liquid-phase acrylate polymerization[17].

Non-equivalences of the β-proton splittings in radicals of the type **5**, $X = CR^1R^2R^3$ are attributable in part to the *chirality* of the neighbouring carbon atom (see Reference 18), and in cases where line-broadening is detected this extra observation provides evidence for *restricted rotation* about $C_\alpha—C_\beta$. The non-equivalence detected in some polymeric radicals of related type is attributed to the adoption of a fixed or highly restricted geometry[7,19] and a convincing rationale has been provided[19b], on the basis of solution studies, for the well-known '5 + 4' spectrum of sharp and broader lines observed for radical **6** in irradiated polymethylmethacrylate (details of the conformational preferences have been obtained using the $\cos^2\theta$ relationship). A detailed conformational analysis has also been presented[20] of some radicals of the type $RCH_2\dot{C}HCO_2^-$ formed by electron bombardment of amino acids and dipeptides in a solid matrix at low temperature and evidence has been obtained for restricted rotation about the $C—CH_3$ bond (with E_a 2–4 kJ mol^{-1}) in radicals of the type $—\dot{C}MeCO_2^-$ at 20 K[21].



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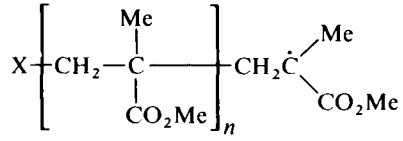
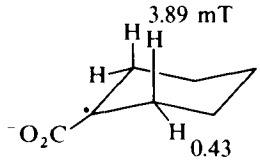


(6)

A conformational analysis has been carried out[22] for the cyclic radicals **7** and **8**, trapped in solids. The low-temperature spectrum for **7** shows non-equivalent β-proton splittings, typical of a chair-type conformation with a very large axial splitting (typical of θ_{ax} 19°): study of the alternating line-width effect, which characterizes the occurrence of ring-flipping and 'intermediate' exchange rates for the interconversion of axial and equatorial splittings, gives a value of *ca* 16 kJ mol^{-1} as the barrier for interconversion. In the corresponding radicals from cyclopentane-carboxylic acid and -carboxylate (e.g. **8**) non-equivalent β-proton splittings are also observed at very low temperatures, which characterize a puckered ring (probably half-chair in type); the barrier to interconversion of these conformers is estimated as 4–6 kJ mol^{-1}. For the radicals **9** and **10** attention has been focussed on the hybridization at the radical centre[23]: for the former, a (^{13}C) is 3.8 mT, typical of a planar radical centre (cf also **7** and **8**), whereas the value for the latter (4.9 mT) indicates some distortion from planarity, though much less so than in the cyclopropyl radical itself.



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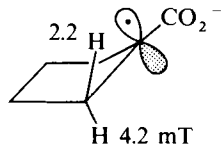

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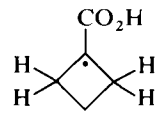

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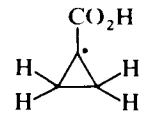


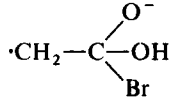
(10)

Halogenated carboxyl-conjugated radicals detected by ESR include $^-O_2CCF_2\dot{C}FCO_2^-$ (trapped in a single crystal of irradiated sodium perfluorosucci-

nate[24] and some analogous α-Cl and -Br (e.g. $\cdot CHBrCO_2H$)[25] and α-iodo (e.g. $\cdot CHICO_2NH_2$)[26] radicals in rigid matrices: splittings from halogen nuclei (including ^{129}I) have been analysed in terms of planar radicals with appreciable π-overlap between the orbital of the unpaired electron and *p*-orbitals on the halogens (I > Br > Cl). Detailed analysis has been presented of the geometry and delocalization in $\cdot CBrFCO_2H$ and $\cdot CClFCO_2H$, also formed in irradiated solids[27]. There are crucial differences between the spectra of two families of radicals originally attributed the structure $\cdot CR_2Br$[28]. In one type, derived from simple alkyl bromides, α-bromo acids, esters and amides, the bromine hyperfine tensor has a maximum value of *ca* 10 mT and a small isotropic (average) value, typical of the bromoalkyl structure **11**: the other type, formed only from α-bromocarboxylate derivatives, has a much larger bromine splitting (isotropic value *ca* 15 mT) and smaller proton interaction. It was originally suggested[27] that electron-attachment and bromine migration give the radical-anion **12**, but a related spectrum, with similar bromine parameters, derived from $BrCF_2CONH_2$ is attributed[29] to a σ* radical-anion structure, with the unpaired electron residing in the antibonding C—Br orbital (with delocalization onto F and CO p-orbitals, **13**): this is the precursor of $\cdot CF_2CONH_2$. Detailed spectral analyses have been provided for the analogous σ* radical-anions formed by X-irradiation of *N*-chloro- and *N*-bromo-succinimide[30]. The solid-state data for $^{\cdot 13}CF_2CO_2^-$ suggest that this radical is non-planar at the radical centre (cf $\cdot CF_3$)[31].

$\cdot CHBrCO_2H$
a(Br) 0.53 mT
a(α-H) 2.0 mT

(11)



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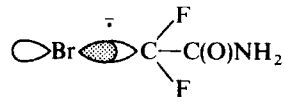
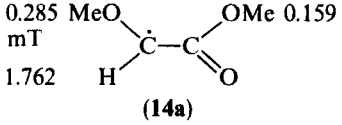


(13)

A variety of other delocalized radicals with extra α-substituents (both of +M and −M type) has also been studied by ESR. For example, glycine reacts with ·OH to give $\cdot CH(NH_2)CO_2H$ in acid solution[32] [this form, with conjugation to both +M and −M groups, possesses considerably more stabilization than the zwitterionic isomer $\cdot CH(NH_3^+)CO_2^-$] and the spectrum of the corresponding anion $\cdot CH(NH_2)CO_2^-$ has been reported in basic solutions[32–34]. The radical $\cdot CH(NH_3^+)CO_2H$ has pK_a values of < 1.0 and 6.6, compared with values of 2.35 and 9.78 for the parent glycine molecule[34]. Results of structural interest include the observation of line-width effects in the spectrum of $\cdot CH(NH_2)CO_2H$ (which reflect the occurrence of proton exchange) and non-equivalent amine-proton splittings in the anionic form; the low α-proton splittings of 1.18 and 1.38 mT, respectively (cf 2.3 mT for $\cdot CH_3$), reflect the extent of delocalization[34]. This is also a feature of related sulphur-conjugated radicals, including $\cdot CH(S^-)CO_2H$ [*a*(α-H) 1.34 mT], formed from ·OH and mercaptoacetate[35], and a series of radicals including $\cdot CH(CO_2H)SC(CO_2H)=CH(CO_2H)$, with *a*(α-H) 1.44 mT, formed via 1,4-shift of hydrogen in a precursor vinyl radical (see later)[36]: in the latter case the ease of reaction is evidently associated with delocalization of the unpaired electron onto both S and CO_2H. It is also clear that substitution of a carboxylate group together with an oxygen substituent at the radical centre overcomes the tendency to bending which is typical of aliphatic $\cdot CR_2OH$ and $\cdot CR_2O^-$ radicals: for $\cdot CMe(O^-)CO_2^-$ *a*(α-^{13}C) is 1.409 mT, consistent with a planar structure[37].

Radicals with these types of substituents may provide examples of species stabilized by the so-called 'capto-dative' effect in radicals which possess both +M and −M α-substituents[38]. It is argued that there is then an enhanced (thermodynamic) stabilization and delocalization (over and above that of the sum of the effect of individual components) which is revealed by studies of, for example, the ease of radical formation

by C—C fission in substituted ethanes, *cis–trans* isomerization of substituted ethenes and cyclopropanes, and thermolysis of azo compounds—as well as in the extent of unpaired-electron delocalization as revealed by ESR spectroscopy. Many examples of α-CN, α-MeO-disubstituted benzyl and allyl radicals have been analysed (in terms of splittings and barriers to rotation: see e.g. Reference 38). It is clear that for related carboxyl-conjugated radicals [see e.g. the radical $\cdot CH(OMe)CO_2Me$, for which isomers **14a** and **14b** are detected[39,40], as well as the analogues $\cdot CH(SMe)CO_2Me$[41] and $\cdot CHClCO_2Me$[42]] the effects of OR and CO_2R are additive (as is indeed the case for related radicals discussed above with α-OH, O^-, S^- and SR substituents) and also that the C(O)R group is more effective as a potential 'capto' substituent than CO_2R[40]. However, it is believed that caution should still be exercised in drawing more detailed conclusions simply from the magnitudes of a(α-H) and/or a(α-Me)—because of potential change in geometric and conformational properties as well as their influence on the appropriate Q-values. It should be noted that no inherent *kinetic* 'stabilization' (i.e. persistence) results for the combination of OMe and CO_2Me in a small aliphatic radical (radical **14** has a diffusion-controlled self-reaction rate constant in fluid solution in the range 5×10^8–2.5×10^9 $dm^3\ mol^{-1}\ s^{-1}$). In contrast, the radical **15**, produced by thermolysis of the corresponding dimer ($\Delta H^{\ominus}$ 173 kJ mol^{-1}), is much longer-lived, a persistence which must reflect a *steric* effect of the bulky β-Bu^t substituent[42]: the low a(β-H) value clearly indicates that this radical occupies a locked conformation with the β C—Bu^t bond eclipsing the orbital of the unpaired electron. Splittings from Sn and Cl nuclei have been observed in the spectrum of analogous radical complexes with $SnCl_4$. The longevity of certain pyridinyl radicals, e.g. 1-alkyl-4-carboalkoxylpyridinyl, is also notable[38].



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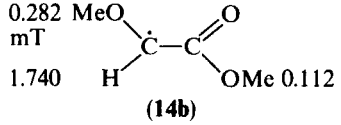

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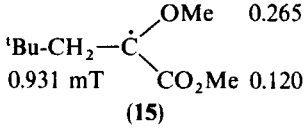
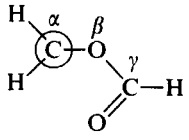


(15)

Radicals of the type $\cdot CHROCHO$ and $\cdot CHRCH_2OCHO$ show long-range splittings (γ and δ, respectively) from the formyl proton[43], and INDO calculations provide the basis for conformational analysis. For $\cdot CH_2OCHO$ and $\cdot CH_2CH_2OCHO$, with long-range splittings of 0.21 and 0.218 mT, respectively, the *s-trans* conformations **16** and **17** are believed to be predominant. A related approach to some β-acetoxy-substituted radicals [with emphasis on a(β-H) and a(ε-H)] indicates that conformation **18** is increasingly favoured as α- or β-alkyl groups are incorporated[44]. Juxtaposition of a +M



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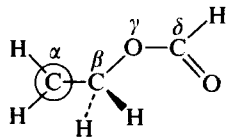

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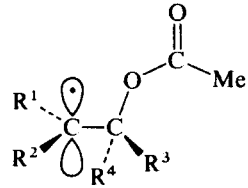


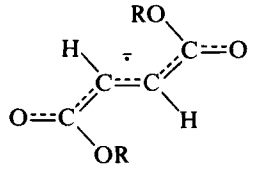
(18)

group (α) and a $-I$ group (β) (e.g. OMe and OAc, respectively) causes the appropriate radicals to be effectively *locked* in this conformation[16].

2. *Radical-ions from carboxylic acids and their derivatives*

Irradiation of acids and their derivatives in solid matrices at low temperature can lead to the detection of the appropriate *radical-anion* formed via electron attachment, $[R\dot{C}(O^-)OH]$[21,45]. These, like the corresponding α-dihydroxy-substituted and α-difluoro and di-alkoxy analogues[46], are believed to be considerably distorted from planarity at the radical centre. This is believed to underlie the observation of line-width alternation in the quartet splittings from the radicals $\cdot CMe(O^-)OH$, $\cdot CMe(O^-)_2$ and $\cdot CMe(O^-)NH_2$ generated in solid matrices at *ca* 77 K, and which is interpreted in terms of restricted rotation about $\cdot C—CH_3$[21]. The barrier is estimated as *ca* 21 kJ mol^{-1} for the dianion and *ca* 13 kJ mol^{-1} for the other radicals. The use of INDO calculations and the observation of a high α-^{13}C splitting indicate that the angle of bending at the radical centre in $\cdot CMe(O^-)OH$ is *ca* 35°, with an inversion barrier of *ca* 20 kJ mol^{-1}[47]. The ^{13}C-splitting of the radical-anion of $(MeO)_2C=O$ clearly indicates its pyramidal nature[48].

When the carboxylic grouping is attached to a conjugated π-system, however, electron attachment often yields the corresponding *delocalized* π-type radical-anion. For example, γ-irradiation of maleates in 2-MeTHF yields the radical-ions **19**, which isomerize after photolysis to the *trans* isomers (also obtained from fumarates and assigned the appropriate geometry)[49]: analysis of the spectra indicates that there is *ca* 40% of the unpaired spin density on each alkene carbon atom (Ċ—C̄) which explains the considerable extent of single-bond character and ease of isomerization. Electron-transfer to maleic acid in aqueous solution has been achieved with the effective one-electron donors $\cdot CO_2H$, CO_2^- and $\cdot CMe_2NH_2$[50]. Particularly interesting phenomena analysed include rapid intramolecular proton transfer in **20** [and, at high pH, its di-anionic analogue], and the identification of $\cdot C(OH)_2CH=CHCO_2^-$ (pH 4–5). Use of electron-bombardment of liquid solutions of α, β-unsaturated acids[51] and reduction of acids and esters (and related compounds) with solvated electrons in liquid ammonia[52] has also been employed as a source of these and related radical-anions, including e.g. $CH_2=CHCO_2^{2-\cdot}$. More details of pK_a values, conformational analyses and sophisticated MO calculations have been provided[52].



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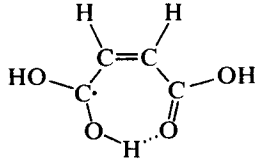
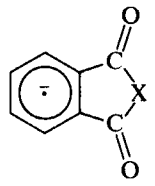


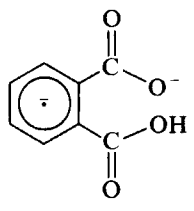
(20)

Flash-photolysis, with excimer laser radiation (λ 308 nm) of substituted benzenes in the presence of aliphatic amines in a variety of solvents, has also been used to generate radical-anions via electron-transfer[53]. The signals from the radicals detected (including carboxylic examples **21** and **22**) show chemically-induced dynamic electron polarization (CIDEP) effects which originate in the reaction of their *triplet-state* precursors. Rapid electron-transfer reactions, and the existence of several different forms (related by proton-loss or internal hydrogen bonding: see e.g. **22** and **23**) can be distinguished.

Under appropriate conditions ESR spectroscopy can be used to demonstrate the



(21) X = O, NH



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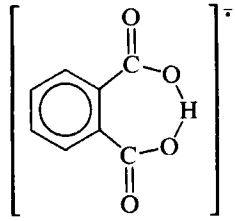
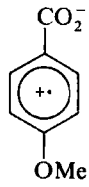


(23)

formation, structure and reactions of *radical-cations* formed by electron-loss from acids, esters and their derivatives. For example, an *in situ* pulse radiolysis/ESR investigation[54] has allowed the characterization of some aromatic radical-zwitterions (e.g. **24**) derived by oxidation of methoxylated benzoic acids with Tl^{2+}, Ag^{2+} and $SO_4^{\bullet-}$. The splittings are very similar to those of the radical-cations from structurally related methoxybenzenes (e.g. anisole), indicating that the carboxyl group has little influence on spin distribution. These π-type radicals do not undergo decarboxylation (resonance structures of the type **25** do not contribute significantly to the resonance hybrid: see later) and it has been shown[55] using flow techniques that $^{\ddagger}ArCO_2^-$ and $ArCO_2^{\bullet}$ have distinct existences and characteristically different reactions (e.g. rapid decarboxylation of the latter).

γ-Irradiation of rigid matrices of aliphatic esters (e.g. in $CFCl_3$) at very low temperature allows the parent radical-cations to be directly observed in certain circumstances. The σ-type radical-cations of methyl and ethyl formate [with the unpaired electron largely confined to the in-plane $2p$ orbital on oxygen (**26**)] can apparently be stabilized at 4.2 K[56], and the neopentyl esters of formic, acetic and propionic acid give detectable parent radical-cations (with the spin density localized mainly in the neopentyl group, largely in the C—CMe_3 bond; see **27**) up to 77 K[57]. Reactions of these species are described later.



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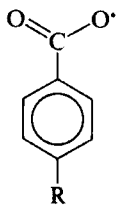

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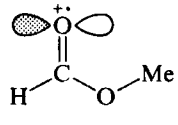

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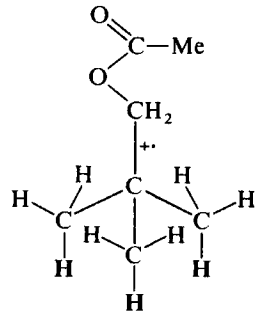
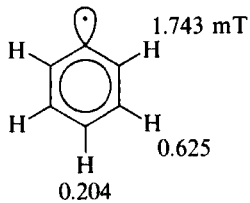


a(3H) = 3.15 mT

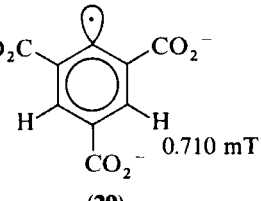
(27)

3. *Carbon- and oxygen-centred radicals of σ-type*

The term σ-radical is customarily employed to denote species in which the unpaired electron resides predominantly in an orbital (usually with significant *s*-character) *in* the plane of the σ-bond skeleton: examples are provided by the phenyl, vinyl and formyl radicals (with the spin largely in sp^2-type orbitals). Such radicals (see e.g. the reviews in Reference 2) are characterized by very large ^{13}C splitting from the α-carbon (the magnitude of the isotropic central-atom splitting reflects extent of *s*-character, and hence direct electron–nuclear interaction, in the unpaired electron's orbital); for the vinyl radical, two very different β-proton splittings are detected[58] at low temperature (when radical-centre inversion is slow). Examples of aryl radicals in fluid solution detected by ESR include phenyl itself (**28**) and some carboxylate derivatives, including **29**[59]: the ^{13}C splittings of the latter species, notably the value for the radical centre of 13.7 mT, are characteristic of its σ-character (and reveal the operation of through-bond transmission of spin-density: cf. proton splittings for **28**). This structure is in marked contrast to the π-delocalized structure of cyclohexadienyl adducts, formed, for example, from attack of ·OH on aromatic carboxylates[60].

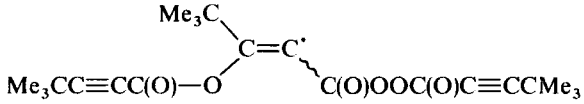


(**28**)



(**29**)

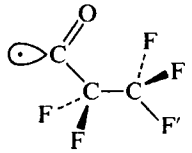
Vinyl radicals have been obtained both in solid matrices by the irradiation of alkynic acids (e.g. $CH{\equiv}CCO_2H$ and $CH{\equiv}CCO_2Me$) and hydrogen-atom bombardment of propiolic acid (to give $CH_2{=}\dot{C}CO_2H$)[61] and in solution by addition reactions of first-formed alkyl radicals in a flow system[62] and by photodecomposition of bis(alkynoyl)peroxides[63]. It has been suggested[61] that the radical $CH_2{=}\dot{C}CO_2H$ [with a(β-H) 5.3 mT, for two equivalent protons] is linear, with the unpaired electron in a *p*-orbital, although rapid inversion cannot be ruled out; in vinyl radicals $^{-}O_2CCR{=}\dot{C}CO_2^-$ formed by addition of R· to butynedioic acid some small long-range coupling to protons in R is observed[62]. More convincing structural evidence derives from the observation[63] of an α-^{13}C splitting of 8.3 mT in the radical **30**, formed in the photolysis of $[Me_3CC{\equiv}CC(O)O]_2$, which is clearly a bent vinylic σ-radical.



(**30**)

A variety of acyl (RCO·) σ-radicals have also been successfully characterized. These include MeCO· and C_6H_5CO· (generated by reaction of sodium atoms with the acid chlorides RCOCl at 72 K using a rotating cryostat)[64]: for these (and both HCO· and HO_2CCH_2CO·) it is shown that the unpaired electron lies in a σ-type orbital, with ρ_c *ca* 0.55 and ρ_O *ca* 0.20. It is known from fluid solution studies[65] that PhCO· shows a dominant interaction between the unpaired electron and the *meta*-proton *trans* to the unpaired electron. The radical $PhCH_2CO$· has a(α-^{13}C) and a(β-^{13}C) 12.83 and 5.06 mT,

respectively, in agreement with a σ-radical structure: comparison between the $a(\beta\text{-H})$ value of 0.4 mT in $CH_3CO\cdot$ and the much lower coupling for $PhCH_2CO\cdot$ (< 0.04 mT) is evidence for an unusual angular dependence of the proton hyperfine splittings[66], a conclusion supported by the results of other related studies. For example, the perfluoropropionyl radical ($CF_3CF_2CO\cdot$) has the typical low g-value of an acyl radical (2.00075) together with a (1F) 1.61, a (2F) 0.444 mT[67]: the single fluorine splitting is assigned to one of the γ-fluorines (F′), probably 'locked' into a conformation suitable for 'W-plan' interaction (**31** and **32**), and the small triplet splitting originates from the two β-fluorines. At −100 °C the cyclopropylacyl radicals **33** and **34** can be distinguished[68], and a kinetic and thermodynamic analysis of the interconversion of the two conformers at higher temperature has been presented: the very large β-proton splitting in the (eclipsed) conformer **33** with the β-H antiperiplanar to the SOMO, is notable. For a series of saturated acyclic analogues the values of $a(\beta\text{-H})$ correlate well with the NMR coupling constants ($^3J_{CHCHO}$) in the corresponding aldehydes, and it is concluded[68] that the radicals and parents have similar structures. INDO calculations suggest that hyperfine splitting is greatest when the angle (θ) between the β-H and the C=O group is zero—i.e. when the unpaired electron is antiperiplanar to β-H[69] [$(Bu^t)_2CHCO\cdot$, with $a(\beta\text{-H})$ *ca* 1.1 mT probably adopts this conformation[69,70]].



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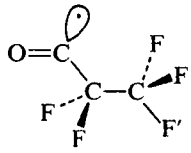

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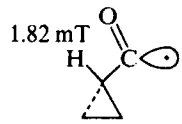

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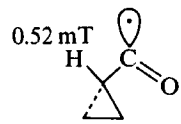
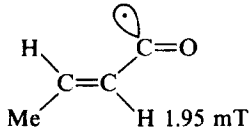


(34)

Alkenylacyl radicals have been prepared both via radical reactions of unsaturated aldehydes[71] (cf **35**: the *s-trans* structure is suggested on the basis of INDO calculations) and by direct photolysis (with C—O fission) of some bis(alkenacyl) peroxides (e.g. **36** and **37**) from bis [(*E*)-4,4-dimethylpent-2-enoyl] peroxide[63]. Related alkoxycarbonyl radicals, e.g. $CH_2{=}CHOCO\cdot$ (from vinyl formate)[63] and[72] $Bu^tOCO\cdot$ (from *t*-butyl formate), have been reported: the low g-value and high ^{13}C splitting (18.3 mT) described for the latter are entirely as expected for a σ-radical.



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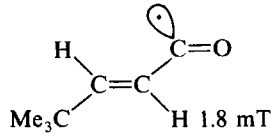

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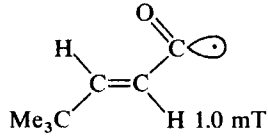
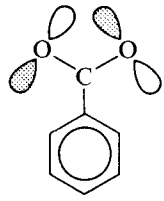


(37)

ESR spectroscopy has provided crucial evidence concerning the structure of carbonyloxyl (acyloxyl) radicals ($RCO_2\cdot$) and it is clear that these are σ-type radicals rather than π-species. For example, unambiguous evidence for a $^2B_2$ ground state for benzoyloxyl, with the unpaired electron delocalized between the *in-plane* 2p-orbitals on oxygen (**38**), rather than the carbonyl π-orbitals (**39**), is provided by the results of solid-state studies of the ^{17}O-splitting in $C_6H_5CO_2\cdot$ obtained from both carbonyl- and peroxy-labelled benzoyl acetyl peroxide[73]. INDO, MINDO and SCF calculations on $HCO_2\cdot$ support this view[74].

The direct detection of carbonyloxyl radicals in solution, as opposed to rigid matrices, has provided a real challenge, largely as a result of their rapid decarboxylation. However,



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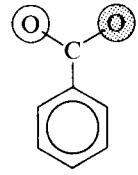
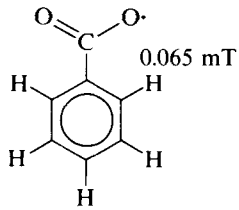


(39)

Yamauchi and his colleagues[75] showed that spectra from $ArCO_2\cdot$ generated by laser flash photolysis (303 nm) of diaroyl peroxides could be detected by fast-response time-resolved ESR. Subsequently, Ingold and his coworkers have successfully employed direct UV photolysis of diacyl peroxides in cyclopropane or Freon 11 at low temperature to yield well-resolved spectra of carbonyloxyl radicals ($RCO_2\cdot$) of various types (R = aryl[76], and[63,77] alkenyl, alkynyl and alkoxyl), all of which might be expected to have relatively strong $R—CO_2\cdot$ bonds (and hence longer-lived than saturated aliphatic counterparts).

The g-values of $ArCO_2\cdot$ are typically 2.012, characteristic of this type of species, which show very small hyperfine splitting(s) from the *ortho*-proton(s) in the aromatic ring (see **40**: splitting from ortho-fluorine and chlorine substituents is also noted)[76]. The ^{13}C splitting from the carboxyl carbon is only 1.33 mT. INDO calculations also suggest that these radicals may have an equilibrium structure with unequal C—O bond lengths. The alkyne-substituted analogue $Me_3CC{\equiv}CCO_2\cdot$ has g 2.0125 in $CFCl_3$ at 160 K, and ^{13}C-splittings of 1.33 and 4.92 have been measured for the α- and β-carbon atoms[77]: as with $ArCO_2\cdot$, the former value confirms that there is little spin density on the carboxyl carbon. Direct photolysis of (*trans*-$Me_3CCH{=}CHCO_2)_2$ leads[63,77] to the detection of the alkenoyl analogue **41** with proton-splittings of 0.213 and 0.046 mT. Solid state studies have also allowed the characterization of $HO_2CCH{=}CHCO_2\cdot$ and $HO_2CC{\equiv}CCO_2\cdot$ (see Reference 78).



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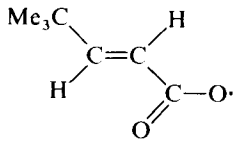


(41)

C. Derivation of Kinetic Information from ESR Studies

In principle it is possible to obtain kinetic information from ESR experiments on short-lived free radicals by both *steady-state* analysis and *time-resolved* studies; brief reference will be made to examples of these approaches.

When a short-lived organic radical (R·) is obtained by the rapid reaction of a first-formed radical (e.g. ·OH) generated from a metal–peroxide redox couple in a flow system, it can be shown[79] that conditions can be established such that a pseudo-steady-state analysis is appropriate (the radicals detected are those formed *in* the cavity). In general terms the rate of radical formation is equal to the rate of radical destruction;

for a simple system involving M^{n+} and H_2O_2 (to give ·OH) and an excess of RH (to scavenge ·OH) it follows that equation 5 applies (where k_{in} is the rate constant for radical generation, $2k_t$ is the termination rate for R· and t is the time between mixing and observation). This equation can be used, via measurement of [R·], to estimate values for k_{in} (where $2k_t$ is known) or for $2k_t$ if k_{in} can be separately determined—e.g. via spectrophotometry. More detailed analysis has been described, involving steady-state experiments in which either $[H_2O_2]$ or t is varied, and computer simulation techniques have also been applied to obtain k_{in} and $2k_t$[80].

$$k_{in}[M^{n+}][H_2O_2] = 2k_t[R\cdot]^2 \tag{5}$$

In typical flow experiments with peroxides—and in which values of k_{in} are typically between 10^2 and 10^5 $dm^3\ mol^{-1}\ s^{-1}$—the steady-state concentrations of radicals R· detected are typically *ca* 10^{-6} mol dm^{-3} (for species with $2k_t$ *ca* 2×10^9 $dm^3\ mol^{-1}\ s^{-1}$). Many examples have been given in which kinetic information can be obtained about subsequent rapid reactions of (R·), rate constants for which have been obtained by steady-state analysis or simulation on the assumption of known rates of termination of the radicals (mostly diffusion-controlled, $2k_t$ *ca* 10^9 $dm^3\ mol^{-1}\ s^{-1}$). These include, for example, the removal of [R·] by reaction with, e.g., M^{n+} or H_2O_2[81], acid-catalysed conversion of R^1· into R^2· [e.g. ·$CH(OH)CH_2OH$ into ·CH_2CHO][82], reaction of R^1· with R^2H to give R^2· (cf Me· with $EtCO_2H$ to give ·$CHMeCO_2H$, with k *ca* 3×10^3 $dm^3\ mol^{-1}\ s^{-1}$)[83], and unimolecular decomposition or rearrangement (e.g.[84] the 1,2-shift of OAc in ·CH_2CMe_2OAc). As a simple rule of thumb, it can be shown that in these cases the *secondary* (B·) rather than *primary* radical (A·) will be detected if the pseudo-first-order rate constant for conversion of A· into B· is $>ca\ 10^3\ s^{-1}$[84]. When both radicals are detected, approximate rate constants can be derived.

Similarly, under steady-state *photolysis* conditions, information can be obtained about the rate constants for radical transformation reactions, and the types of approach (with examples) have been reviewed by Griller and Ingold[85,86]. For instance, simple steady-state analysis can be applied to the competitive generation of secondary radicals (e.g. the reaction of 'BuO· to give R^1· and R^2· from R^1H and R^2H). The rate constant for unimolecular radical reactions (e.g. the conversion of R· into S· by fragmentation or rearrangement) can be determined if both R· and S· can be simultaneously detected (and their concentrations measured) and if $2k_t$ for S· can be measured (see Scheme 1)[85]. Unimolecular radical reactions which proceed via well-established rates can then be used as reliable 'clocks' for determining by ESR the rates of their competing radical–molecule reactions[86].

Photolysis (e.g. via 'BuO·)	⟶	R·	
R· + R·	⟶	non-radical products	(6)
R·	⟶	S·	(7)
R· + S·	⟶	non-radical products	(8)
S· + S·	⟶	non-radical products	(9)

SCHEME 1

Steady-state analysis on [S·] gives

$$k_7[R\cdot] = 2k_9[S\cdot]^2 + 2k_8[R\cdot][S\cdot] \tag{10}$$

Rearranging this gives

$$\frac{1}{[S\cdot]} = \frac{2k_9[S\cdot]}{k_7[R\cdot]} + \frac{2k_8}{k_7} \tag{11}$$

A plot of $1/[S\cdot]$ vs $[S\cdot]/[R\cdot]$ (varied by changing the light intensity) gives a straight line of slope $2k_9/k_7$.

Radical termination rates—from which other rate constants for competing reactions can thereby be obtained—are best derived directly from time-resolved photolytic experiments with a shutter or sector (and computer collection and averaging of decays)[86]. This technique has largely been developed by Fischer and his coworkers[3] and used for the determination of accurate data (as a function of solvent and temperature) for the self-termination of a variety of alkyl radicals (e.g. *t*-butyl[87] and benzyl[88]). In more complex systems [in which, for example, first-formed radicals add to alkenes ($\cdot CH_2CO_2CMe_3$ to $CH_2{=}CHX$ or $CH_2{=}CX_2$) or fragment ($\cdot CO_2CMe_3$ to CO_2 and $\cdot CMe_3$)[3]] the rate equations for radical decay (mixed first and second order) can be solved via numerical integration to give the required rate constants. The technique is appropriate for radical–molecule reactions for which the rate constant is in the range $10–10^6$ dm^3 mol^{-1} s^{-1} and for first-order reactions for which it is in the range $10–10^5$ s^{-1}. Examples of the use of these techniques will be presented in the next section.

III. RADICAL REACTIONS OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

A. Introduction

The short-lived nature of most free radicals in liquid solution necessitates the use of methods for continuous radical generation for study by ESR spectroscopy, as noted above, and several such methods have been employed for the study of acids and acid-derived radicals, radical-cations and radical-anions.

For example, the hydroxyl radical can be generated in a number of ways including reaction of hydrogen peroxide with a low-valent metal ion (e.g. Ti^{III} and Fe^{II}) in a continuous-flow system (reaction 2)[83], direct photolysis of hydrogen peroxide (reaction 12)[90] and pulse radiolysis of aqueous solutions (reaction 13)[91]: these methods have all been employed to study reactions of the hydroxyl radical with carboxylic acids and their derivatives in aqueous solution (see below). These approaches can be extended by employing different peroxides: for example, the sulphate radical-anion ($SO_4^{\cdot-}$) is readily formed from the reaction of titanium(III) with peroxomonosulphate (reaction 14)[92] or peroxodisulphate[93], or by photolysis of peroxodisulphate solutions[94].

$$H_2O_2 \xrightarrow{h\nu} HO\cdot + \cdot OH \tag{12}$$

$$H_2O \xrightarrow{e^-} HO\cdot, H\cdot, e_{aq}^- \tag{13}$$

$$Ti^{III} + HOOSO_3^- \longrightarrow Ti^{IV} + HO^- + SO_4^{\cdot-} \tag{14}$$

Addition of appropriate reactants to such solutions allows production of other reactive species whose reactions may then be studied. For example, the reaction of $SO_4^{\cdot-}$ with chloride ion gives Cl· (reaction 15) or, at high chloride concentrations, $Cl_2^{\cdot-}$ (reaction 16)[95] and methyl radicals can be readily generated by reaction of HO· with DMSO (reaction 17)[83].

$$SO_4^{\cdot-} + Cl^- \longrightarrow SO_4^{2-} + Cl\cdot \tag{15}$$

$$Cl^{\cdot} + Cl^{-} \rightleftharpoons Cl_2^{\cdot -} \quad (16)$$

$$HO^{\cdot} + Me{-}\overset{\overset{O}{\|}}{S}{-}Me \longrightarrow \left[Me{-}\overset{\overset{O^{\cdot}}{|}}{\underset{\underset{OH}{|}}{S}}{-}Me \right] \longrightarrow Me^{\cdot} + MeSO_2H \quad (17)$$

The reaction of peracids with metal-ions (reaction 18)[96] and photolysis of acyl peroxides (e.g. reaction 19)[63,97] has been employed to generate carbonyloxyl radicals. Direct photolysis of carboxylic acids and their anions in the presence of metal-ion catalysts can also generate concentrations of radicals high enough for detection by ESR spectroscopy, though the radicals formed depend upon the precise conditions used. Thus irradiation in the presence of cerium(IV)[98] and titanium dioxide[99] leads to decarboxylation of the acid or anion (reactions 20 and 21, respectively), whereas photolysis in the presence of the uranyl ion[100] gives α-carboxyalkyl radicals (reaction 22).

$$Ti^{III} + CH_3C(O)OOH \longrightarrow Ti^{IV} + HO^{-} + CH_3CO_2^{\cdot} \quad (18)$$

$$PhC(O)OOC(O)Ph \xrightarrow{h\nu} 2PhCO_2^{\cdot} \quad (19)$$

$$RCO_2H \xrightarrow[Ce^{IV}]{h\nu} R^{\cdot} + CO_2 + H^{+} \quad (20)$$

$$RCO_2^{-} \xrightarrow[TiO_2]{h\nu} R^{\cdot} + CO_2 \quad (21)$$

$$R'CH_2CO_2H \xrightarrow[UO_2^{2+}]{h\nu} R'\dot{C}HCO_2H \quad (22)$$

Radical-anions have been generated using a number of techniques. These include reduction of the parent compound by alkali metals, reduction by high-energy electrons (generated by pulsed radiolysis) and by X- and γ-ray radiolysis of frozen solutions in, e.g., 2-methyltetrahydrofuran[101,102]. Radical-cation generation can be brought about either in the liquid phase by oxidation with $SO_4^{\cdot -}$ (via electron-transfer)[54] or $HO^{\cdot}$ (via addition/elimination, see later)[103] or, especially in the solid state, via radiolysis or photolysis[102,104].

B. Aliphatic Acids and their Derivatives

1. *Saturated acids*

The rate and selectivity of radical attack on saturated aliphatic carboxylic acids and their derivatives has been shown to be highly dependent upon the nature of the attacking radical. The electron-withdrawing effect of the carbonyl group present in these compounds means that electrophilic radicals, such as $HO^{\cdot}$ and $Cl_2^{\cdot -}$, react relatively slowly with acids and their derivatives, and reaction is found to occur mainly at sites removed from the functional group; in contrast, nucleophilic radicals such as methyl and phenyl react rapidly, primarily at the α-position, to give the more stable α-carboxyalkyl species. For instance, compare the reactions of $HO^{\cdot}$ and $Me^{\cdot}$ with propanoic acid[83]. The former reacts to give approximately equal concentrations of the two radicals **42** and **43** formed by hydrogen-abstraction (reactions 23 and 24, respectively)[83]. The overall rate of reaction

is relatively slow ($k = 2 \times 10^8$ dm^3 mol^{-1} s^{-1})[105] compared, for example, to that for reaction of ·OH with methanol [(reaction 25), $k = 1.0 \times 10^9$ dm^3 mol^{-1} s^{-1}][106]. On the other hand, the methyl radical reacts with propanoic acid by H-abstraction almost exclusively from the α-position (reaction 26)[83]; this reaction is relatively fast (with $k = 3 \times 10^3$ dm^3 mol^{-1} s^{-1})[83] compared to other reactions of Me· under similar conditions (for example, the rate constant for hydrogen abstraction by methyl from methanol is 2.2×10^2 dm^3 mol^{-1} s^{-1})[107].

$$HO\cdot + CH_3CH_2CO_2H \longrightarrow H_2O + CH_3\dot{C}HCO_2H \quad (23)$$
(42)

$$HO\cdot + CH_3CH_2CO_2H \longrightarrow H_2O + \cdot CH_2CH_2CO_2H \quad (24)$$
(43)

$$HO\cdot + CH_3OH \longrightarrow H_2O + \cdot CH_2OH \quad (25)$$

$$Me\cdot + CH_3CH_2CO_2H \longrightarrow MeH + CH_3\dot{C}HCO_2H \quad (26)$$
(42)

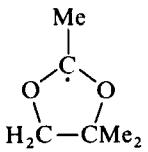
The deactivating nature of the carbonyl group towards electrophilic attack also explains the observation that the hydroxyl radical reacts with esters at the *alkyl* rather than the *acyl* side chain (see, for example, the reaction of HO· with ethyl ethanoate, which undergoes attacks at the ethyl group[83,108]; reactions 27 and 28).

$$HO\cdot + CH_3C(O)OCH_2CH_3 \longrightarrow H_2O + CH_3C(O)OCH_2CH_2\cdot \quad (27)$$

$$HO\cdot + CH_3C(O)OCH_2CH_3 \longrightarrow H_2O + CH_3C(O)O\dot{C}HCH_3 \quad (28)$$

As might be expected, the reaction of a number of *t*-butyl esters with HO· or RO· gives signals from the corresponding β-acyl substituted radicals (e.g. reaction 29)[84]. For example, the reaction of ·OH with ^{t}BuOAc (studied using a flow system) gives an ESR spectrum from $\cdot CH_2CMe_2OAc$[84]. However, these signals are accompanied by those of the radical $\cdot CMe_2CH_2OAc$, formed via a 1,2-acetoxy shift[84]: steady-state calculations allow a rate constant of *ca* 10^3 s^{-1} to be estimated for this rearrangement at room temperature in aqueous solution. It has been demonstrated[84,109] by ESR spectroscopy that this reaction does not proceed via the cyclic dioxolan-2-yl free radical (**44**), since such species (detectable in reactions of 1,3-dioxolan) do not undergo ring-opening under these conditions. This rearrangement—at least for simple acyclic analogues—is believed to be concerned and to proceed via a five-membered cyclic transition state (see e.g. **45**) to give products in which the carbonyl and ether oxygens of the starting material are interchanged.

$$CH_3C(O)OCMe_3 + RO\cdot \longrightarrow CH_3C(O)OCMe_2CH_2\cdot + ROH \quad (29)$$



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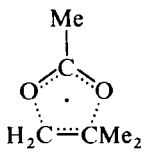

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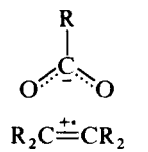


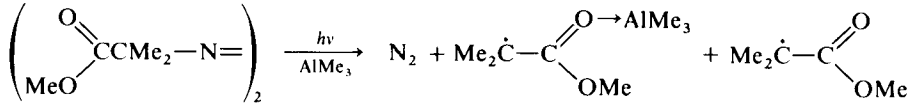
(46)

However, recent kinetic and ^{18}O-labelling studies have established that a different mechanism may also be followed under certain circumstances[110]: thus, retention of the ^{18}O-carbonyl label in this function in the 1,2-rearrangement of a related steroidal

example is interpreted in terms of a more rapid rearrangement, either through a three-membered transition state or a tight anion/radical-cation ion pair (**46**). Further, the rearrangement of $\cdot CH_2CMe_2OC(O)CF_3$ into $CF_3C(O)OCH_2CMe_2\cdot$ is considerably faster than the rearrangement of $\cdot CH_2CMe_2OAc$ under comparable conditions ($k_{75\,°C}$ = $7 \times 10^4\ s^{-1}$ in hydrocarbon solvents)[111]. This, and the acceleration of the rearrangement brought about by the incorporation of a cyano group in the acetate function [for $\cdot CH_2CMe_2OC(O)CH_2CN$], provides further evidence for a charge-separated transition state in this example.

Spin-trapping studies of some ω-carboxyalkyl radicals have also revealed the occurrence of intramolecular hydrogen-abstraction reactions which give α-carboxyalkyl radicals (reaction 30; cf the reaction of alkyl radicals discussed earlier). Relative rates of rearrangement are estimated as 0.03, 0.1 and 0.25 for 47, n = 1, 2, 3 and 4, respectively[112]. α-Carboxyalkyl radicals have also been observed to form complexes with $AlMe_3$ with bonding via the carboxyl function (reaction 31)[113].

$$\underset{\textbf{(47)}}{\cdot CH_2(CH_2)_nCH_2CO_2Et}\ , \longrightarrow\ CH_3(CH_2)_n\dot{C}HCO_2Et \qquad (30)$$



(31)

ESR flow system and photolysis studies of the reactions of $SO_4^{\cdot-}$ with carboxylic acids and their anions reveal quite a different pattern of behaviour to that shown by $\cdot OH$ and alkyl radicals. For example, ethanoic acid reacts with $SO_4^{\cdot-}$ to give primarily the methyl radical, accompanied by signals from the carboxymethyl radical (**48**) at higher substrate concentrations[114]. The methyl radical evidently arises from hydrogen abstraction by $SO_4^{\cdot-}$ from the acid group (reaction 32) followed by rapid decarboxylation (reaction 33). The carboxymethyl radical (**48**) is believed to be formed by reaction of Me· with the parent acid (reaction 34). Propanoic and longer-chain acids react similarly[114] to give alkyl radicals obtained by decarboxylation and also show hydrogen abstraction by $SO_4^{\cdot-}$ from the β and more remote positions of the alkyl chain (e.g. reaction 35).

$$SO_4^{\cdot-} + CH_3CO_2H \longrightarrow HSO_4^- + CH_3CO_2\cdot \qquad (32)$$

$$CH_3CO_2\cdot \longrightarrow Me\cdot + CO_2 \qquad (33)$$

$$Me\cdot + CH_3CO_2H \longrightarrow MeH + \underset{\textbf{(48)}}{\cdot CH_2CO_2H} \qquad (34)$$

$$SO_4^{\cdot-} + CH_3CH_2CO_2H \longrightarrow HSO_4^- + \cdot CH_2CH_2CO_2H \qquad (35)$$

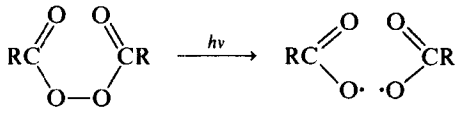
Carboxylate anions are more reactive (and selective) in their reaction with $SO_4^{\cdot-}$[114]; compare, for example, the rate of attack on ethanoate anion ($k = 1.2 \times 10^7\ dm^3\ mol^{-1}\ s^{-1}$) with that for ethanoic acid ($k = 2 \times 10^4\ dm^3\ mol^{-1}\ s^{-1}$)[114]. The anions undergo electron-transfer from the carboxylate group (reaction 36) to give the appropriate alkylcarbonyloxyl radical (**49**), which gives an alkyl radical via decarboxylation. Some of the longer-chain carboxylate anions also show evidence of hydrogen-abstraction by $SO_4^{\cdot-}$ (but to a lesser extent than that of the parent acids). Attack on the carboxylates

by the alkyl radicals also leads to the relatively rapid formation of carboxyl-conjugated radicals (reaction 37)[114].

$$SO_4^{\cdot-} + RCO_2^- \longrightarrow SO_4^{2-} + RCO_2^{\cdot} \quad (49) \qquad (36)$$

$$Et^{\cdot} + CH_3CH_2CO_2^- \longrightarrow EtH + CH_3\dot{C}HCO_2^- \qquad (37)$$

Simple aliphatic carbonyloxyl radicals (**49**) such as those formed by reaction of carboxylates with $SO_4^{\cdot-}$ have not been directly observed by ESR, since decarboxylation is extremely rapid; for instance, the rate of decarboxylation of the methylcarbonyloxyl radical (**49**, R = Me) is estimated to be *ca* $10^9\ s^{-1}$ at 25 °C in aqueous solution[115]. However, related examples of this type of radical have been observed when generated at low temperature, by photolysis of acyl peroxides (reaction 38), when the C_α-$CO_2^{\cdot}$ bond strength is enhanced (e.g. for radicals **50** and **51**)[63,77]. Corresponding aromatic analogues are described below.



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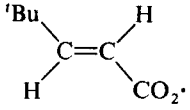
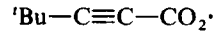


(**50**)



(**51**)

The reactions of *substituted* carboxylic acids tend to be dominated by the effects of the substituent, as illustrated here by some reactions of halogenated carboxylic acids and amides[116]. For example, HO· reacts mainly by hydrogen-abstraction (e.g. reaction 39), the rate of attack being much greater than that of the unsubstituted acid: compare also, for example, the rate of attack upon ethanoic acid ($k = 2 \times 10^7\ dm^3\ mol^{-1}\ s^{-1}$)[117] with that on chloroethanoic acid ($k = 8 \times 10^7\ dm^3\ mol^{-1}\ s^{-1}$)[118]. In contrast, Ph· and $CO_2^{\cdot-}$ react primarily by processes which lead to loss of the halogen atom[116]: the phenyl radical itself reacts by halogen-abstraction (reaction 40) whereas $CO_2^{\cdot-}$ probably produces a radical-anion which undergoes subsequent loss of halide ion (reaction 41).

$$HO^{\cdot} + BrCH_2CO_2H \longrightarrow H_2O + Br\dot{C}HCO_2H \qquad (39)$$

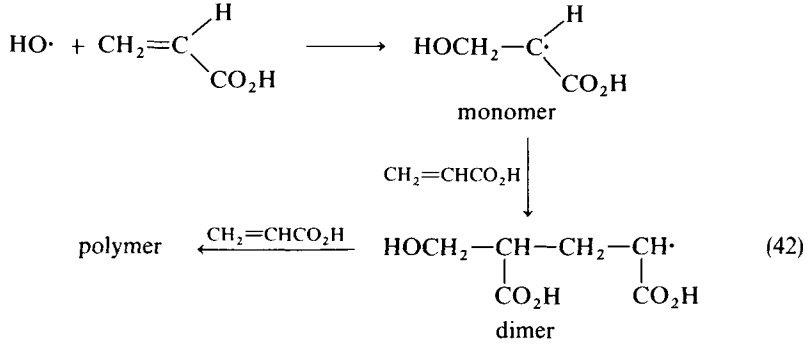
$$Ph^{\cdot} + BrCH_2CO_2H \longrightarrow PhBr + {\cdot}CH_2CO_2H \qquad (40)$$

$$CO_2^{\cdot-} + BrCH_2CO_2H \longrightarrow CO_2 + [BrCH_2CO_2H]^{\cdot-} \longrightarrow Br^- + {\cdot}CH_2CO_2H \qquad (41)$$

2. *Unsaturated acids*

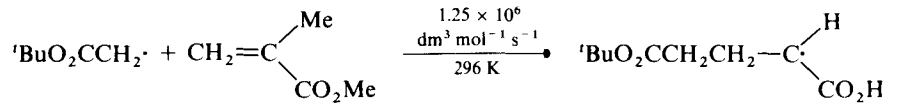
The reactions of unsaturated aliphatic acids with initiating radicals are dominated by reactions involving the alkenic π-bond(s): for example, most of the radicals observed with alkenic carboxylic acids and derivatives are simply those formed by addition to the alkenic double bond (e.g. reaction 42)[119]. Important further reactions of the radical-adducts studied by ESR include addition to the parent compound, which leads ultimately to the formation of oligomers and polymers, a process which is in widespread

use, for example, in the production of polyacrylates. In a series of pioneering studies, Fischer[14,17] has determined the structure of the initial radical-adducts of a number of acrylic acids and esters (e.g. with ·OH or alkyl radicals). Using a continuous-flow system, he was able to study the early stages of polymerization (with observation of monomeric, dimeric and polymeric radicals) as a function of alkene concentration (see e.g. reaction 42)[17].



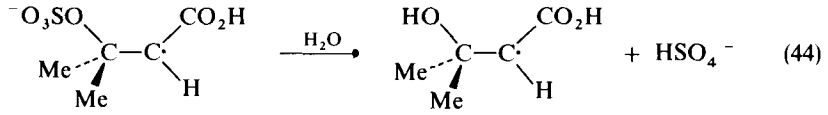
(42)

Later work[89,119,120] on the rate of radical addition to alkenes, using time-resolved intermittent photolysis and ESR spectroscopy to follow radical decay, has revealed the importance of polar electronic effects upon both the site and rate of radical-addition reactions. Of particular interest is the finding that for the 'ambiphilic' radical $\cdot CH_2CO_2{}^tBu$ (^tBu· radical[119] and electrophilic oxygen-centred radicals) the rate of reaction with a series of alkenes is substantially enhanced when the alkene contains either −M groups (see e.g. reaction 43) or +M groups (e.g. with $CH_2{=}CHOEt$)[89]. This is interpreted in terms of an increase in the favourable interaction of the SOMO of $\cdot CH_2CO_2{}^tBu$ either with the LUMO of the former (lowered by −M groups) or the HOMO of the latter (raised by +M groups).



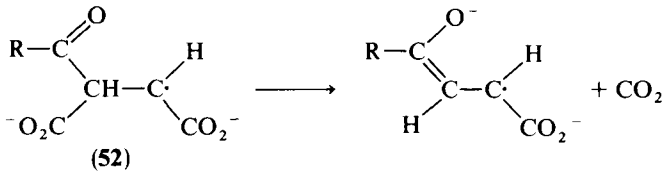
(43)

Reaction of $SO_4^{\cdot-}$ or Cl· with alkenic acids in aqueous solution usually leads to the observation of signals from the corresponding adducts in the ESR spectrum[15]: with certain alkyl-substituted acids, however, the corresponding *hydroxyl*-adduct is observed. Though it has been suggested that direct electron-transfer (to give a radical-cation) and hydration may be occurring, it seems more likely that this represents nucleophilic attack on the initial adduct-radical (via either an S_N1 or S_N2 mechanism), with displacement of a good leaving-group (e.g. reaction 44)[15].



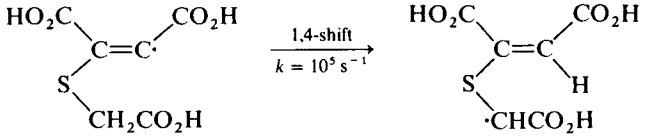
(44)

Acyl-radical addition to maleate or fumarate anions gives α,β-dicarboxylate radicals (**52**) whose ready decarboxylation has been studied (reaction 45)[121].



(52) (45)

Alkynoic acids also react primarily by addition of the attacking radicals, though the vinyl (σ) radicals formed in these reactions are extremely reactive and are very rarely observed directly by ESR. More usually, spectroscopic experiments involving continuous radical generation (e.g. via flow-system studies) lead to the detection of *secondary* radicals which characterize the occurrence of novel rapid reactions of the initial species. Intramolecular hydrogen shifts, identified for vinyl radicals formed from butynedioic acid, include the 1,4-, 1,5- and 1,6- examples[36,122] shown in reactions 46–48, respectively; for reaction 47 and 48, the overall mechanism is deduced by the observation of radicals formed via fragmentation and cyclization, respectively (approximate rate constants deduced by steady-state analysis of ESR experiments are indicated)[122]. This approach also allows intermolecular examples to be characterized (see, for example, reactions 49 and 50)[123].



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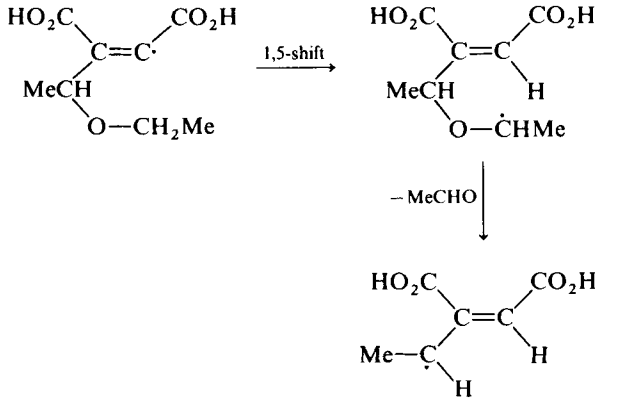
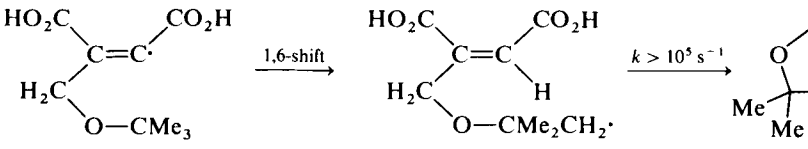
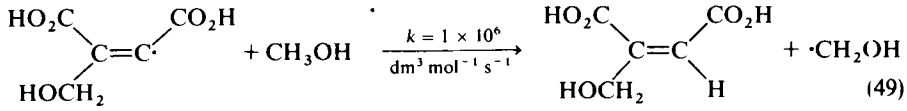


(47)



(48)



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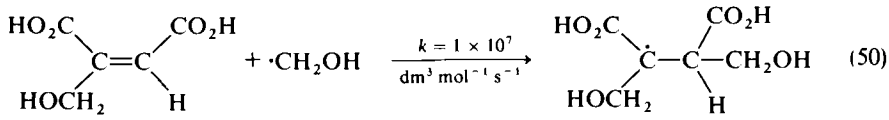


(50)

Studies of the addition of the hydroxyl radical (generated from the Ti^{III}/H_2O_2 continuous-flow system) to butynedioic acid and its anions also reveal some particularly unusual reactions (see Scheme 2)[124]. At low pH and high concentrations of the acid, the ESR spectrum is dominated by signals from two pentadienyl species formed by addition of the initial hydroxyl adduct to the parent alkyne followed by rapid 1,5-hydrogen shift[124]. At low alkyne concentrations, these signals are replaced by those of the carboxymethyl radical (**53**), apparently formed by intramolecular 1,4-hydrogen abstraction and rearrangement followed by decarboxylation and decarbonylation.

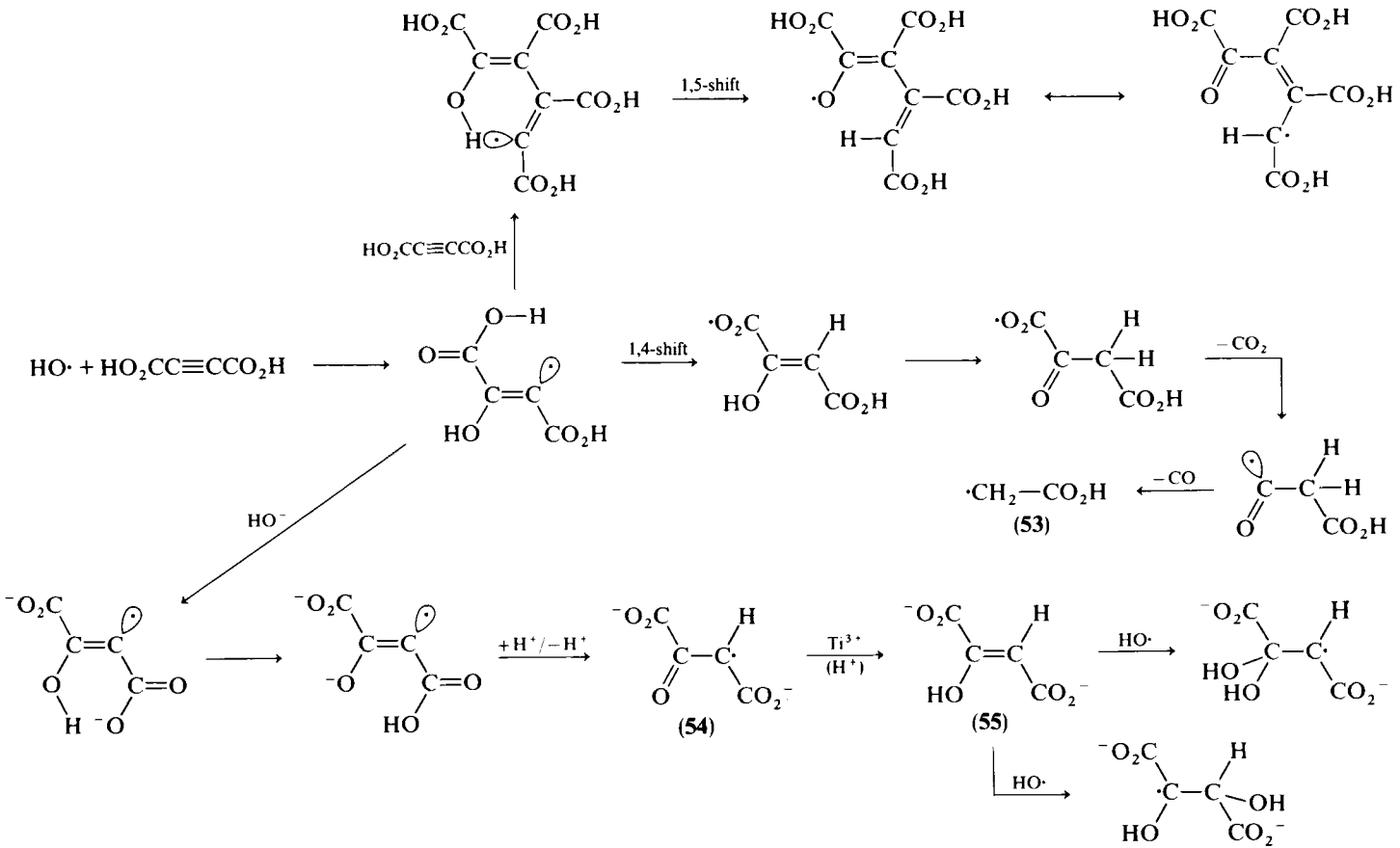
At higher pH values, when the carboxylate groups are ionized, the carbonyl-conjugated species (**54**) is detected; this is believed to be formed by rearrangement of the initial adduct (see Scheme 2)[124]. The mechanism is believed to involve proton-transfer from the hydroxyl group onto the α-carboxylate followed by protonation at carbon. Also observed are radicals formed as a result of reduction of the carbonyl-conjugated radical (**54**) by titanium(III) followed by addition of HO· to the enol (**55**; see Scheme 2). Under certain conditions, the signals from radical **54** are observed in emission, a novel example of CIDEP (Chemically Induced Dynamic Electron Polarization). This observation has been shown to depend upon both the pH and the ligand used to complex the titanium(III)[124].

3. *Aliphatic radical-anions*

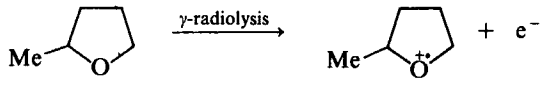
Information on the structure, formation and behaviour of the radical-anions of carboxyl-containing compounds largely derives from studies of electron capture in both rigid matrices (via γ- and X-ray irradiation)[101,102] and aqueous solution (pulse radiolysis)[125]. In the former type of study, it is customary to use 2-methyltetrahydrofuran as both the solvent and electron donor; radiation-induced electron-transfer is brought about at low temperatures (see reactions 51 and 52)[29,102], conditions under which the radical-anion is normally long-lived.

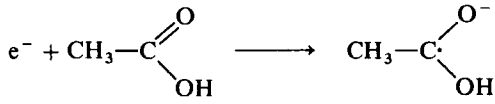
The approach has been applied to a variety of acids and their derivatives, including those with halogen substituents, for which unusual properties are observed. Changes which occur when the matrices are annealed often allow subsequent reactions of these species to be monitored, including halide ion loss from σ- and π-type radical-anions (e.g. reactions 53 and 54)[21,126]. Subsequent photolysis of the the trifluoroethanamide radical-anion brings about a different mode of fragmentation (reaction 55)[127]. Halogen loss observed in the reaction of $CO_2^{\cdot-}$ with haloacids in aqueous solution (at room temperature) may also involve formation of an undetected radical-anion (reaction 41; see earlier)[116].

The reduction of unsaturated carboxylates has been investigated by pulse radiolysis of aqueous solutions. Alkenic dicarboxylates tend to form stable radical-anions (reaction 56) whereas those of monocarboxylates and alkynic carboxylates are rapidly protonated to give the hydrogen-atom adduct (e.g. reaction 57)[125].


HO· + HO2CC≡CCO2H
HO2CC≡CCO2H
1,4-shift
1,5-shift
HO⁻
−CO2
−CO
·CH2—CO2H
(53)
+H⁺/−H⁺
Ti3+
(H⁺)
HO·
(54)
(55)
HO·

SCHEME 2


(51)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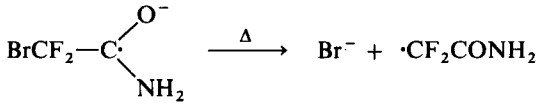
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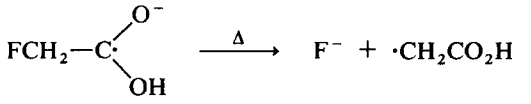
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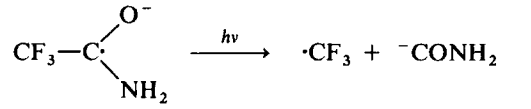
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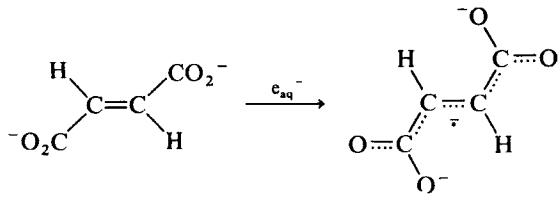
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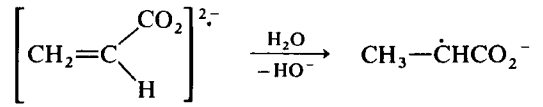
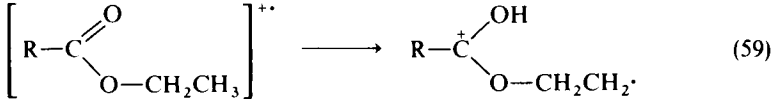

(57)

Whereas formation and fragmentation of organic radical-cations in the gas phase has been well studied by mass spectrometry (electron impact) techniques, detailed characterization of their behaviour in solid and liquid phases is much less well advanced; however, considerable recent progress has been made in the combination of ESR techniques with γ-ray irradiation of solid freon solutions[102,104]. This is an efficient method for radical-cation generation since the electron-transfer from solute to freon solvent is readily achieved and electron return prevented by loss of chloride ion from the trichlorofluoromethane radical-anion (reaction 58).

$$M + CFCl_3 \xrightarrow{\gamma\text{-radiolysis}} M^{+\cdot} + CFCl_3^{\cdot -} \longrightarrow \cdot CFCl_2 + Cl^- \qquad (58)$$

One-electron oxidation of most acids and their derivatives generates unstable radical-cations which undergo rapid fragmentation[104]. In contrast, those of esters show a variety of different rearrangements which depend upon the structure of the alkyl group. Thus a 1,5-intramolecular hydrogen shift has been observed for ethyl ester radical-cations

(reaction 59); isotopic labelling has revealed that rearrangment via an alkene radical-cation is also possible (cf reaction 60)[128]. An alkene radical-cation is detected in the oxidation of *i*-butyl and *t*-butyl ethanoate esters, evidently formed via a McLafferty-type rearrangement (reaction 61)[129]: in this case, formation of the alkene radical-cation is favoured by the extra stabilization provided by the alkyl substituents. Neopentyl esters also display an intramolecular hydrogen-transfer, and subsequent rearrangement gives a 'distonic' tertiary radical-cation (i.e., where the radical centre and the positive charge are separated) (reaction 62)[130].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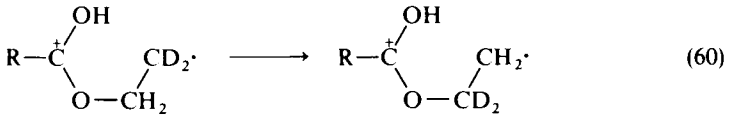
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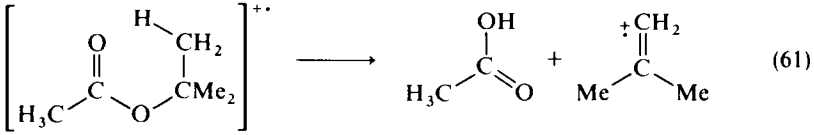
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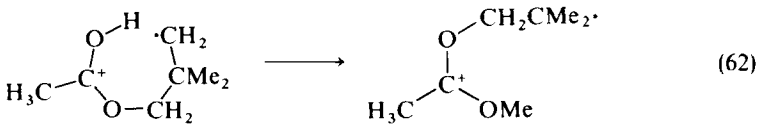
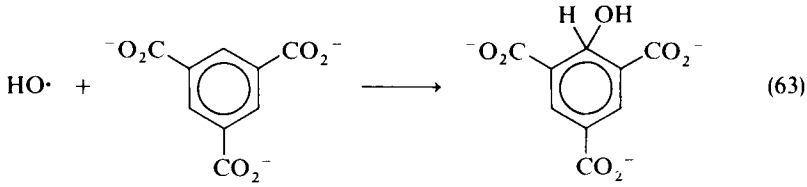

(62)

C. Reactions of Aromatic Carboxylic Acids and their Derivatives

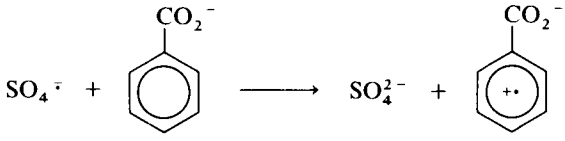
The reaction of most initiating radicals with aromatic acids and their derivatives occurs primarily by addition to the aromatic ring to form cyclohexadienyl radicals (e.g. reaction 63)[2]. These species typically show large hyperfine splittings from groups in the *ortho* and *para* positions where the unpaired electron-density is greatest[2]. They also show large β-H splittings if addition occurs at an unsubstituted position.


(63)

In contrast, $SO_4^{\cdot-}$ reacts to give the appropriate aromatic radical-cation via abstraction of an electron from the ring (reaction 64)[54]. An alternative route to the radical-cation is often available via the acid-catalysed dehydration of the initial hydroxyl adduct

(reaction 65)[103]. For most benzoate anions and related polycarboxylate anions, the radical-cations (zwitterions) rearrange to give the appropriate arylcarbonyloxyl radicals, which then undergo decarboxylation (reaction 66)[55]. Evidence for the (usually undetectable) intermediate radical-cation is provided by the finding that the reaction of $SO_4^{\cdot-}$ with some methoxy-substituted analogues gives long-lived, detectable radical-zwitterions (e.g. **56**; see also earlier)[54].

The phenyl radicals thus formed have been detected directly and by spin-trapping; their formation is often characterized by the observation of signals from the aryl-radical adducts of the parent compound (e.g. reaction 67)[59].



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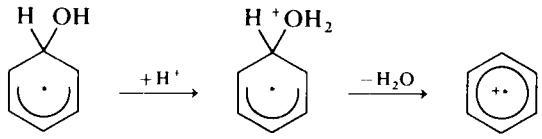

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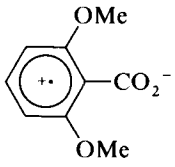

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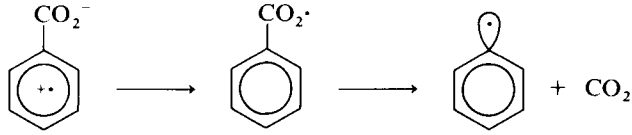
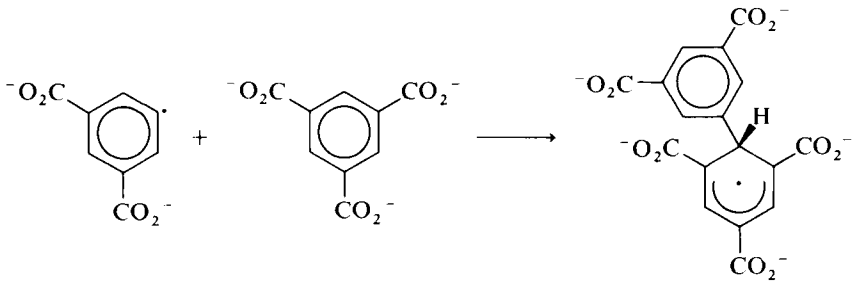


(66)

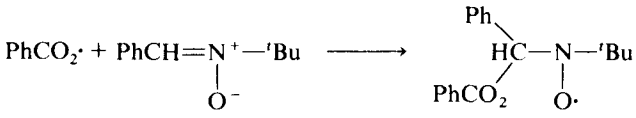


(67)

Decarboxylation of arylcarbonyloxyl radicals is much slower than that of their aliphatic counterparts; for example, the rate of decarboxylation of the benzoyloxyl radical ($PhCO_2\cdot$) has been measured as $2 \times 10^6\ s^{-1}$ in CCl_4 at 297 K[131]. As noted

earlier, this greater kinetic stability has allowed direct detection of these species by ESR at low temperature[76]. Other reactions of these radicals are also important and may compete with the fragmentation process; for example, hydrogen abstraction from a suitable substrate may occur (e.g. reaction 68)[131] and spin-trapping of the appropriate carbonyloxyl radical has also been achieved by addition to nitrones (reaction 69)[132] or to the nitromethane anion[55]. A rapid 1,5-hydrogen-shift has been reported for the 2-methylbenzoyloxyl radical (reaction 70)[55].

$$PhCO_2^{\cdot} + Et_3SiH \longrightarrow PhCO_2H + Et_3Si^{\cdot} \tag{68}$$



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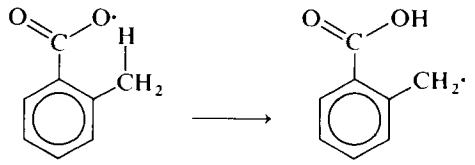
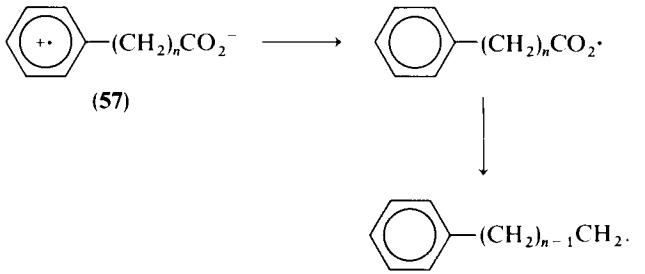


(70)

The radical-cations of aryl-substituted aliphatic acids and their anions exhibit a number of interesting reactions, revealed by ESR. For example, above pH 3 the radical-cations of phenylethanoate, phenylpropanoate and phenylbutanoate anions (**57**, $n = 1$, 2 and 3, respectively) and some branched analogues undergo rapid decarboxylation[103], presumably preceded by electron-transfer (reaction 71). This may be via through-space electron-transfer or involve a cyclic intermediate (e.g. reaction 72)[103]. As the pH is lowered, signals from the decarboxylated radicals (**58**) are replaced by those of the benzylic radicals (**59**)[103]; it is believed that protonation of the carboxyl group makes electron-transfer less favourable so that loss of an α-proton becomes the major reaction pathway (reaction 73) (a typical reaction of alkylbenzene radical-cations)[103].



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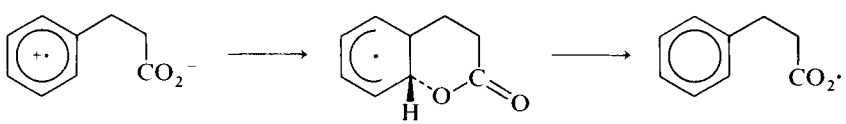

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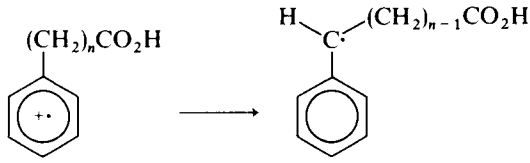


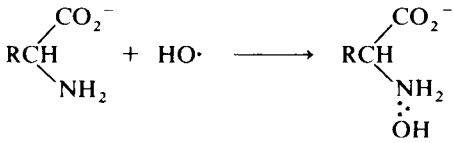
(59) (73)

D. Radical Reactions of Amino Acids and Peptides

Much of the detailed knowledge that has been obtained on the mechanisms and products of the reactions of amino acids and peptides has arisen as a result of the continuing interest in understanding the precise chemical basis of radiation damage in biological systems. Much of the work carried out in the area has concentrated on the reactivity and selectivity of a relatively few attacking species (chiefly HO·, H· and e_{aq}^-) and the differentiation between damage instigated by these species ('indirect' damage) versus the 'direct' action of ionizing radiation on DNA and proteins (and their constituent parts).

1. Main-chain chemistry

Elucidation of the chemical effects of the reactive species generated by ionizing radiation and suitable biomimetic systems on the peptide back-bone has arisen chiefly through the study by ESR, pulse radiolysis and product analysis of reactions of the simplest amino acid glycine. As noted earlier, reaction of HO· with this amino acid in aqueous solution in the absence of O_2 is pH dependent, reaction at low pH resulting in hydrogen abstraction at an α C—H bond to give a species believed to be $\cdot CH(NH_2)CO_2H$ and at higher pH $\cdot CH(NH_2)CO_2^-$ [32–34]. Recent studies have, however, thrown some doubt as to the extent of reaction at the α-carbon at high pH with both glycine and most of the other amino acids with aliphatic side-chains[133]. On the basis of the yield of CO_2 produced during γ-irradiation of the free amino acids in aqueous solution it has been suggested that when there is a free electron pair at the nitrogen (i.e. the amino acid is ionized at both the amine and carboxyl functions) hydroxyl attack occurs at this position, possibly by way of an initial adduct (**60**) (which contains a 2-centre–3-electron bond, $2\sigma/1\sigma^*$, symbolized as ∴) to give an α-aminoalkyl radical and CO_2 (reactions 74 and 75). The reason why this process has only relatively recently been suggested may arise from the fact that the α-aminoalkyl radicals produced by this reaction are strongly reducing species[133] and would therefore be destroyed rapidly by, for example, reaction with H_2O_2 (and hence would not be observed in ESR experiments which employed H_2O_2 as a source of HO·)[134].



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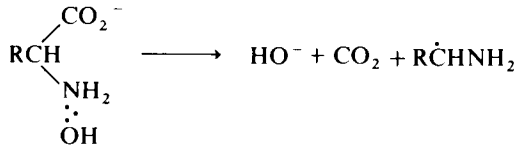
At pH 7, however, this reaction occurs to only a very minor extent (on account of the protonation of the amino group) and reaction of HO· with alanine $[H_3N^+CH(CH_3)CO_2^-]$, for example, has been shown by ESR to occur mainly at the α



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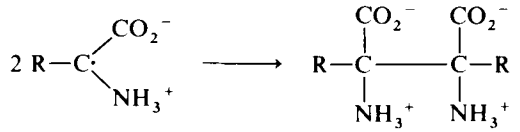
C—H position and to a lesser extent on the side chain (see later)[135–139]. Product studies have demonstrated that these back-bone radicals undergo a number of subsequent reactions which result in the ultimate formation of ammonia and a keto acid[140–145]. Detailed examination of these systems have demonstrated that the initially generated radicals can undergo either dimerisation (reaction 76) or, more commonly, disproportionation (reaction 77)[146–148]. The imino acid generated by the latter process undergoes spontaneous hydrolysis (reaction 78) to yield the keto acid and ammonia[146,147].



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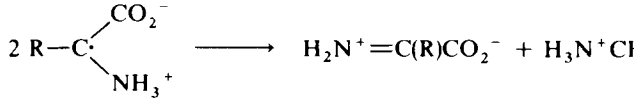

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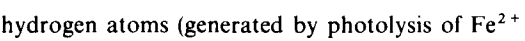

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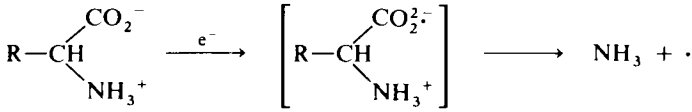
Reaction with hydrogen atoms (generated by photolysis of Fe^{2+} ion in 6M-H_2SO_4 glasses at 77 K) proceeds in a similar manner, with hydrogen abstraction again observed at the α C—H position with both glycine and alanine, though in this case the radicals detected are those of the protonated derivatives due to the nature of the glass (e.g. $H_3N^+\dot{C}HCO_2H$ from glycine)[149].

In contrast, reaction of the hydrated electron or photogenerated electrons with these two amino acids occurs to give deaminated products (reaction 79)[147–151]. This process has been suggested on the basis of ESR studies carried out at 77 K on 12M-LiCl/D_2O glasses to occur without the intermediate production of the dianion radical (**61**) as a stable entity[151], though this species can be observed under different circumstances[152]. Studies carried out on the analogue β-alanine ($H_3N^+CH_2CH_2CO_2^-$) have not provided evidence for reductive deamination, which suggests that this process will only occur when there is a single carbon unit between the initial electron acceptor (the C=O bond) and the group eliminated[153].

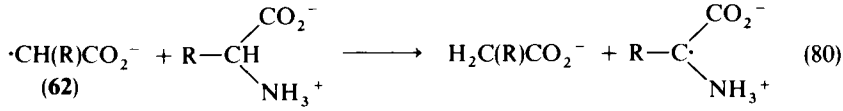


(79)

(**61**)

(**62**)

Subsequent warming and recooling (annealing) of these samples results in spectral changes which have been interpreted in terms of hydrogen-atom abstraction from the parent compound by **62** (reaction 80)[151]. The α-carbon radical generated by such a process has also been demonstrated to cross-terminate with **62** to yield the imino acid



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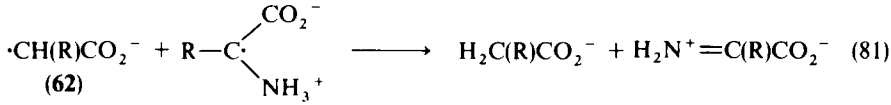
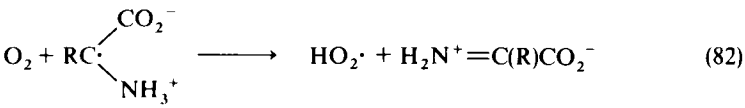


(81)

(reaction 81) which hydrolyses as illustrated above (reaction 78). Similar reactions have been postulated to occur in aqueous solution[148,150].

Direct irradiation (γ- or X-rays) of these amino acids in the solid state yields similar species together with additional radicals[154]. Thus glycine gives ESR signals not only from $H_3N^+CH_2CO_2^{2-}$ by electron attachment (and hence $H_2\dot{C}CO_2^-$ and $H_3N^+\dot{C}HCO_2^-$ on annealing, see above) but also features assigned to $H_2\dot{N}^+CH_2CO_2^-$ (alternatively formulated as $H_2NCH_2CO_2^{\bullet}$) and $H_3N^+\dot{C}H_2$, both of which are believed[154–156] to arise from the positive hole engendered by the radiolysis. Subsequent annealing results in the loss of the features from these species, and the appearance of $H_3N^+\dot{C}HCO_2^-$; the fate of $H_3N^+\dot{C}H_2$ is not known.

The presence of oxygen produces dramatic changes in the observed behaviour; high concentrations result in a decrease in the extent of reductive deamination produced by e^- as the electron is preferentially scavenged by oxygen to yield the superoxide radical $O_2^{\bullet-}$. The reaction of HO· with these amino acids is not affected directly by oxygen, though the α-carbon radical generated by H-atom abstraction has been shown to react with oxygen to yield eventually HO_2· (reaction 82)[157]; the imino acid thus formed hydrolyses immediately (reaction 78)[147].



(82)

Inclusion of glycine and alanine into simple peptides (e.g. gly-gly) or model peptides (including *N*-acetyl amino acids) results in essentially similar behaviour. Thus reaction of HO· in the absence of oxygen has been shown by ESR[158–162] and other techniques[163–165] to result in preferential attack at the α-carbon sites, and in particular at those away from the strongly deactivating protonated amino group at the N-terminus, with these sites accounting for approximately 90% of the hydroxyl radicals consumed[166]. A similar selectivity is observed with H· attack[159]. Direct UV photolysis of aliphatic peptides in concentrated solutions at low temperature (77 K) produces a complex mixture of radicals which can be detected by ESR and identified after annealing[167]. With most dipeptides containing only hydrocarbon side-chains, the methyl radical, ·CHO and $\cdot N{=}CH_2$ are observed; raising the temperature to 120 K results in an increase in the concentration of $\cdot N{=}CH_2$ and at even higher temperatures back-bone α-carbon radicals predominate. The imino radicals are believed to arise via direct peptide bond cleavage (to give RĊO and $\cdot NHCH_2CO_2H$) and subsequent breakdown of the latter. The methyl radicals observed are thought to arise from C—C bond cleavage in isopropyl groups or related structures.

ESR spin-trapping studies using 2-methyl-2-nitrosopropane have demonstrated that direct photolysis at 210–230 nm[168], or photolysis in the presence of dyes[169] or quinone photosensitizers[170,171], can result in oxidative decarboxylation of the free carboxyl

group in a number of small peptides. The subsequent fates of these decarboxylated and directly ionized species have not been studied in any great detail, though extensive studies have been carried out on the reactions of the α-carbon radicals produced either by H-atom abstraction or as a result of annealing processes (see above). In the absence of oxygen these species primarily undergo dimerization[148]; in the presence of oxygen the situation is much more complex and reactions 83–91 have been postulated to occur (Scheme 3).

$$-C(O)NHCH(R)CO_2^- + HO\cdot \longrightarrow -C(O)NH\dot{C}(R)CO_2^- + H_2O \quad (83)$$

$$-C(O)NH\dot{C}(R)CO_2^- + O_2 \longrightarrow -C(O)NHC(OO\cdot)(R)CO_2^- \quad (84)$$

$$-C(O)NHC(OO\cdot)(R)CO_2^- \longrightarrow -C(O)N{=}C(R)CO_2^- + HO_2\cdot \quad (85)$$

$$-C(O)NHC(OO\cdot)(R)CO_2^- + HO_2\cdot \longrightarrow -C(O)NHC(OOH)(R)CO_2^- + O_2 \quad (86)$$

$$-C(O)NHC(OOH)(R)CO_2^- + H_2O \longrightarrow -C(O)NHC(OH)(R)CO_2^- + H_2O_2 \quad (87)$$

$$-C(O)NHC(OH)(R)CO_2^- \rightleftharpoons -C(O)N{=}C(R)CO_2^- + H_2O \quad (88)$$

$$-C(O)NHC(OH)(R)CO_2^- + H_2O \longrightarrow -CO_2H + NH_3 + RC(O)CO_2^- \quad (89)$$

$$2{-}C(O)NHC(OO\cdot)(R)CO_2^- \longrightarrow -C(O)NHC(O\cdot)(R)CO_2^- + O_2 \quad (90)$$

$$-C(O)NHC(O\cdot)(R)CO_2^- + O_2 \longrightarrow -C(O)NHC(O)(R) + CO_2 + O_2^{\cdot-} \quad (91)$$

SCHEME 3

The diacetamide produced in reaction 91 is hydrolytically labile and is easily converted to the free amide and carboxylic acid. In cases where the α-carbon site is not situated at the carboxyl terminus, as illustrated above, the final reaction 91 is replaced by reactions 92 and 93.

$$-C(O)NHC(O\cdot)(R)C(O)NHR' + O_2 \longrightarrow -C(O)NHC(O)R + O{=}C{=}N{-}R' + HO_2\cdot \quad (92)$$

$$O{=}C{=}N{-}R' + H_2O \longrightarrow CO_2 + H_2NR' \quad (93)$$

It should also be noted that in oligo-peptides the occurrence of an intramolecular H-atom abstraction (reaction 94) has been postulated to account for the increased yield of ammonia[148].

$$-CH(R)\sim\sim C(O\cdot)(R)- \longrightarrow -\dot{C}(R)\sim\sim C(OH)(R)- \quad (94)$$

In oxygen-free systems electron-attachment occurs at the carbonyl group of the peptide bond, as observed with the free amino acids, and the radical-anion thus formed rapidly protonates in aqueous solution (reaction 95)[172,173]. The subsequent fate of this type of radical has been the subject of some controversy. Product analysis studies have suggested that the major fate of this species is reaction with an α-carbon-backbone

$$RC(O)NHR \xrightarrow{e^-} R\dot{C}(O^-)NHR \xrightarrow{H_2O} R\dot{C}(OH)NHR \quad (95)$$

$$R\dot{C}(OH)NHR + RC(O)NH\dot{C}(R)- \longrightarrow 2\ RC(O)NHCH(R)- \quad (96)$$

$$R\dot{C}(OH)NHR \longrightarrow RCONH_2 + R\cdot \quad (97)$$

radical generated by HO· attack with the consequent regeneration of the parent molecule (reaction 96)[173], rather than dissociative deamidation (reaction 97).

In contrast to the room-temperature pulse-radiolysis studies in aqueous solution, which suggest that reaction 97 is only of very minor importance[173–175], direct ESR studies carried out on irradiated *N*-acetyl amino acids in aqueous glasses at low temperature do show evidence for this process as the electron-adducts generated via the first part of reaction 95 are annealed[151,152,176]. Furthermore, the carbon-centred radicals R· generated by this deamidation reaction have also been detected[177] at room temperature in aqueous solution after γ-irradiation of various peptides by use of the spin trap 2-methyl-2-nitrosopropane (reaction 98) and subsequent separation of the adducts by column chromatography.

$$^tBu—N{=}O + R\cdot \longrightarrow {}^tBu—N(O\cdot)—R \quad (98)$$

It has been suggested[148] that these differences may be due to the way in which the experiments are performed. In systems where the irradiation dose is large and over a short period of time (i.e. high dose rate) a high concentration of transient species will be generated which would favour the occurrence of reaction 96, whereas if the dose rate is low and/or the transients are rigidly held (as would occur in glass matrices) the unimolecular dissociation (reaction 97) will predominate.

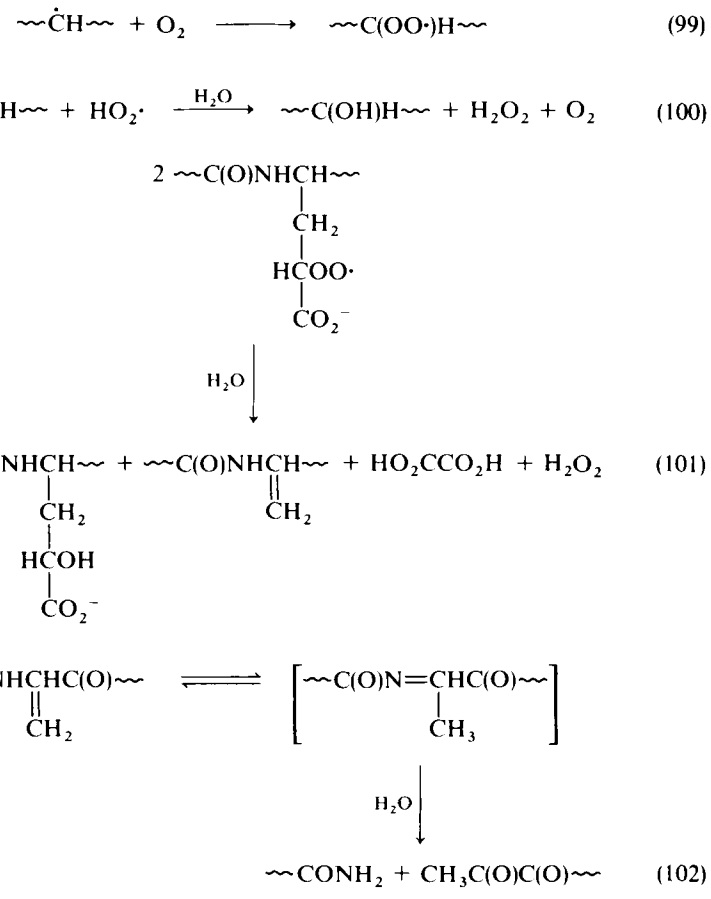
It should be noted that with di- and higher peptides of glycine and alanine there is a preference for electron attachment at the carbonyl group nearest the N-terminus with the subsequent loss of the protonated amino group as ammonia[153,178]; this selectivity decreases dramatically with increasing numbers of alternative carbonyl groups in larger peptides[176,177].

2. *Side-chain chemistry*

a. Aliphatic residues. It has been demonstrated, particularly with the aliphatic side-chains, that increasing the number of side-chain C—H bonds produces a concomitant decrease in attack on the backbone[147]. With the unsubstituted hydrocarbon side-chains HO· attack is essentially random, though with a slight degree of selectivity towards sites which yield the most stable carbon-centred radicals. As might be expected, the less reactive and hence more selective hydrogen atom has a greater preference for such sites; thus, for example, only attack at the tertiary position is observed[149] with valine $[H_3N^+CH(CO_2^-)CH(CH_3)_2]$ whereas HO· attack occurs at both this site and at the terminal methyl groups of the valine side-chain in glycyl-valine[160]. Introduction of other substituents onto the hydrocarbon side-chain results, in the majority of cases, in

increased selectivity of attack. Thus it has been demonstrated, by both product analysis[180] and ESR (direct studies[137,181-183] and spin trapping[162,184]), that reaction of HO· with glutamic acid $[H_3N^+CH(CO_2^-)CH_2CH_2CO_2^-]$ occurs primarily at the position α to the carboxyl side-chain (presumably due to stabilization of the resulting radical by spin delocalization onto the ionized carboxyl group), reaction with serine and threonine occurs α to the hydroxyl group[134-137] and with arginine α to the $-NH(C=NH)NH_2$ group[162]. In a few cases attack occurs preferentially at positions away from the substituent; this, for example, occurs with lysine where attack occurs away from the strongly-deactivating protonated side-chain amine group[162]. Similar behaviour is observed with hydrogen atoms[149].

In the absence of oxygen the major fate of most of these species is dimerization[185] (see below for exceptions) whereas in its presence a complicated series of reactions can occur which have some analogies to that described earlier. The peroxyl radical formed by initial addition of oxygen (reaction 99) can either react with HO_2· (reaction 100) or itself (via a Russell-type mechanism to give an alcohol and an aldehyde or ketone); the latter type of reaction (e.g. reaction 101) can have important consequences, as the unsaturated product formed is readily hydrolysed to give an amide and a keto acid (reaction 102). Thus side-chain attack can lead to cleavage of the peptide back-bone[148].



The behaviour of the α-hydroxyalkyl radicals generated by attack of HO· on the side-chains of serine and threonine, in the absence of oxygen, is somewhat different to that outlined above. It has been demonstrated[134] that with both of these species elimination of ammonia can occur (though by slightly different mechanisms). For serine the initial α-hydroxyalkyl radical readily deprotonates at the hydroxyl group at physiological pH (pK_a estimated as 7.0); the ketyl radical so produced (reaction 103) rapidly eliminates ammonia with a rate constant of $2.4 \times 10^6\ s^{-1}$ at 190 K (reaction 104). With threonine, evidence has been presented to suggest that the elimination occurs from the unionized α-hydroxyalkyl radical (reaction 105).

$$H_3N^+CH(CO_2^-)\dot{C}HOH \rightleftharpoons H_3N^+CH(CO_2^-)CHO + H^+ \quad (103)$$

$$H_3N^+CH(CO_2^-)\dot{C}HO^- \longrightarrow NH_3 + \cdot CH(CO_2^-)CH{=}O \quad (104)$$

$$H_3N^+CH(CO_2^-)\dot{C}(OH)Me \longrightarrow NH_4^+ + \cdot CH(CO_2^-)CMe{=}O \quad (105)$$

Reaction of e^- with these amino acids and peptides is very similar to those previously described for glycine, in that trapping of the electron occurs predominantly at the carbonyl bond(s) of the back-bone with little reaction at the side-chain even when this is a carboxylic acid, amide, amine or hydroxy group[165,175-179].

b. Sulphur-containing side-chains. ESR experiments[186] in conjunction with pulse radiolysis studies[187,188] have demonstrated that reaction of HO· with the sulphur-containing amino acids cysteine, cystine and methionine is dominated by initial attack at the sulphur centre rather than attack on the back-bone; there are, however, important differences between these substrates. With cysteine, H-atom abstraction from the —SH group predominates, with $k \simeq 10^{10}\ dm^3\ mol^{-1}\ s^{-1}$ [189]. In the absence of oxygen and at physiological pH the major fate of this thiyl radical (—CH_2S·) is reaction with the anion of another cysteine residue to generate (reversibly) the disulphide radical-anion (reaction 106)[190]. In the presence of O_2 both of these species undergo further reactions, the former to give the thiylperoxyl radical in a relatively slow, reversible, reaction[191] (reaction 107), (which ultimately results in the formation of RSO_2H and RSO_3H species)[192], and the latter to form the disulphide and the superoxide radical. In the absence of O_2 the thiyl radicals ultimately self-terminate (reaction 108) or abstract hydrogen from other components (reaction 109)[187,190].

$$H_3N^+CH(CO_2^-)CH_2S\cdot + {}^-SCH_2{\sim\!\sim} \rightleftharpoons {\sim\!\sim}CH_2S\overset{\cdot}{-}SCH_2{\sim\!\sim} \quad (106)$$

$$H_3N^+CH(CO_2^-)CH_2S\cdot + O_2 \rightleftharpoons H_3N^+CH(CO_2^-)CH_2SOO\cdot \quad (107)$$

$${\sim\!\sim}CH_2S\cdot + \cdot SCH_2{\sim\!\sim} \longrightarrow {\sim\!\sim}CH_2S{-}SCH_2{\sim\!\sim} \quad (108)$$

$${\sim\!\sim}CH_2S\cdot + RH \longrightarrow {\sim\!\sim}CH_2SH + R\cdot \quad (109)$$

ESR studies have also been of major importance in demonstrating that reaction of HO· with cystine occurs via two main pathways: dissociative addition (to yield RSOH and RS·) and oxidation (giving $RSSR^{\ddagger}$ and HO^-)[186].

Reaction of e^- with cysteine occurs almost quantitatively at the —SH group to give a radical identical to that obtained by H-atom abstraction from the side-chain of alanine, and HS^- [193]. The former radical in the presence of oxygen forms a peroxyl radical; in the absence of oxygen it is believed to abstract hydrogen from excess cysteine (the reverse of reaction (109)[194]. This particular process may, however, be more complicated than it initially appears, as ESR studies on irradiated penicillamine in various solvents have

demonstrated that at 4.2 K electron capture occurs at the free carboxyl group and at higher temperatures dissociative electron capture occurs to give NH_3[195]. With methanol as the solvent, however, reaction occurs in a process analogous to that observed with cysteine, yielding HS^- and $\cdot CMe_2CH(NH_3^+)CO_2^-$[196]. Attachment of e^- to cystine gives the disulphide anion, which reacts further as outlined above[187].

In contrast to the above, reaction of e^- with methionine $[H_3N^+CH(CO_2^-)CH_2CH_2SCH_3]$ occurs mainly at the back-bone carbonyl bond, though ESR spin-trapping studies have also demonstrated[197] the occurrence of C—S bond cleavage (reactions 110 and 111) presumably via the mediation of a short-lived radical-anion.

$$RCH_2SMe \xrightarrow{e^-} RCH_2\cdot + {}^-SMe \qquad (110)$$

$$RCH_2SMe \xrightarrow{e^-} RCH_2S^- + \cdot Me \qquad (111)$$

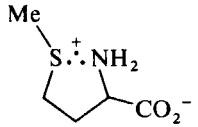
The reaction of $HO\cdot$ with methionine[188] and methionine-containing peptides[198] has been the subject of considerable interest. Initial reaction has been shown to occur primarily at the sulphur atom to give an adduct (**63**; reaction 112) though direct ESR studies[199] have also demonstrated the formation of low concentrations of sulphur-conjugated radicals produced by H-atom abstraction at the C—H bonds α to the sulphur atom (reaction 113).

$$RCH_2SMe + \cdot OH \longrightarrow \underset{\textbf{(63)}}{RCH_2\dot{S}(OH)Me} \qquad (112)$$

$$RCH_2SMe + \cdot OH \longrightarrow R\dot{C}HSMe + RCH_2SCH_2\cdot + H_2O \qquad (113)$$

The former of these species has been demonstrated[188] to undergo further reaction which results, with the free amino acid, in decarboxylation and the generation of an α-aminoalkyl radical (reaction 114). The exact mechanism of this process has been the subject of considerable discussion. ESR studies[186] have played a crucial role in demonstrating that the initial addition product (**63**) can undergo conversion into either the molecular radical cation $R_2S^{\ddagger}$ or a complex dimeric species $[R_2S\therefore SR_2]^+$ with a 2-centre–3-electron ($2\sigma/1\sigma^*$) bond between the two heteroatoms[200]. The first of these can also be stabilized by interaction with the electron pair on a suitably placed heteroatom (either nitrogen, oxygen or halogen) to given an analogous 2-centre–3-electron bonded species. A transient intermediate of this form (**64**) is believed[188] to be the crucial intermediate in the transfer of damage from the sulphur to the carboxyl end of the molecule, which ultimately results in the loss of CO_2. Similar types of species,

$$H_3N^+CH(CO_2^-)CH_2CH_2\dot{S}(OH)Me \longrightarrow H_2NCHCH_2CH_2SMe + CO_2 + H_2O \qquad (114)$$



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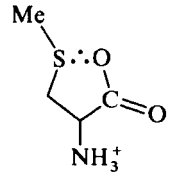
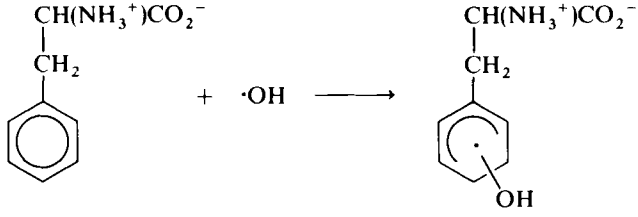


(65)

containing sulphur–carboxylate bonds, have been observed in sterically constrained derivatives of methionine[201], and it has been suggested on the basis of ESR spin-trapping studies[199] that a five-membered ring such as **65** is an intermediate in the decarboxylation of *S*-methylcysteine.

Though such an intermediate has been shown not to be formed with *N*-acetyl methionine, recent studies have demonstrated[198] that long-range electron-transfer reactions can occur in a number of methionine-containing peptides which result in decarboxylation of free carboxyl groups (situated either on side-chains or at the carboxyl terminus). These reactions, which have considerable electronic and steric constraints, are believed to occur via an 'outer sphere' electron transfer from the carboxylate function to the sulphur radical-cation which is the major, initial site of attack.

c. Aromatic and related side-chains. As might be expected with these substrates reaction with HO· occurs primarily by addition at the aromatic ring, with little direct hydrogen-atom abstraction from either the α-carbon position or the intervening methylene groups(s). Thus with phenylalanine, for example, reaction occurs to give a mixture of hydroxycyclohexadienyl radicals (reaction 115) by addition at any of the aromatic ring positions; the ESR spectra of these species are readily detected in aqueous solution, though exact analysis of the mixture of radicals involved remains a problem[202]. At neutral pH, in the absence of oxygen, the major fate of these species has been suggested to be either disproportionation (reaction 116) to give a molecule of the parent and a tyrosine, or dimerization[203]. In the presence of oxygen the hydroxycyclohexadienyl radicals form peroxyl radicals in a reversible reaction; these radicals are believed to be the precursors of the various isomeric tyrosines detected as products[204].



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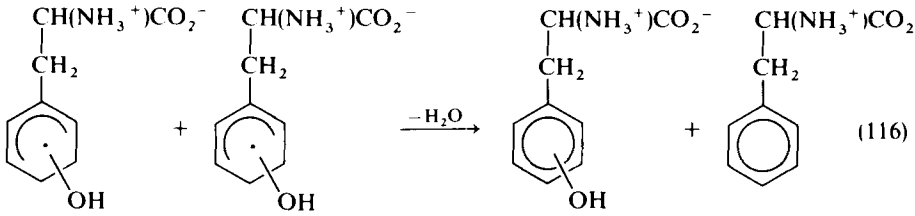
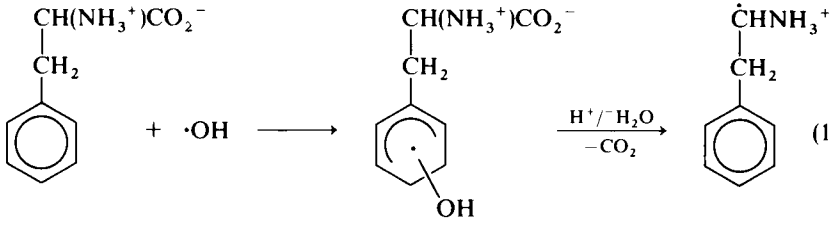


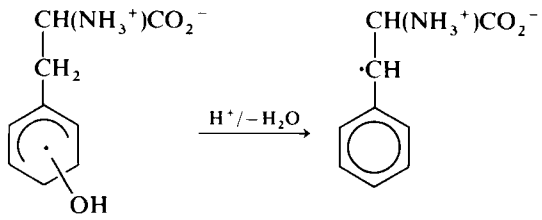
(116)

At low pH values (and in the absence of oxygen) these initial adducts have been shown to undergo further reactions[103,205]. With the free amino acid this results in either decarboxylation and formation of the α-aminoalkyl radical (reaction 117), or loss of a methylene hydrogen to give a benzylic radical (reaction 118). Both of these species are believed to arise via the formation of the aromatic radical-cation by acid-catalysed loss of water (reaction 119) and, for the former species, formation of a cyclic intermediate in a process analogous to those outlined earlier for phenylpropionic acid (reaction 72) and *S*-methylcysteine (structure **65**). The benzylic radical is believed to be formed only at very low pH by loss of a proton from the methylene group of the radical cation. Similar

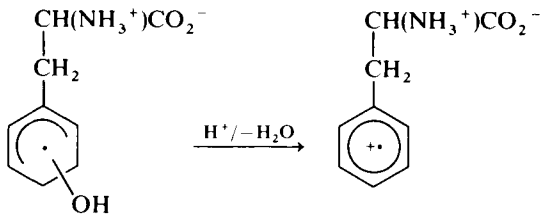
processes are observed with other powerful one-electron oxidants (e.g. $SO_4^{\cdot-}$) which can give rise to the radical-cation directly[103]. Whether similar processes occur with phenylalanine peptides has yet to be determined, though it is interesting to note that formation of the phenylalanine radical-cation has been observed by ESR in alkaline (8 M NaOD) glasses at 77 K after direct UV photolysis of a variety of peptides[206].



(117)



(118)



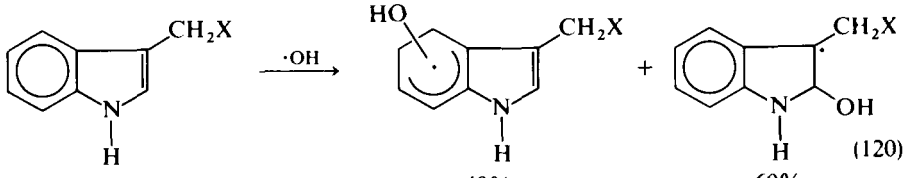
(119)

In oxygen-free solution both the peptide carbonyl group and the aromatic ring can act as acceptors for e^-; with pulse radiolysis, studies on *N*-acetylphenylalanine indicate that *ca* 50% reacts at each site[207]. The radical-anion, formed by electron capture by the ring, rapidly protonates in aqueous systems and the subsequent chemistry of the resulting cyclohexadienyl radical appears to be analogous to that of the hydroxyl analogues (i.e. dimerization in the absence of oxygen and formation of peroxyl radicals and subsequently tyrosine isomers in its presence[203]).

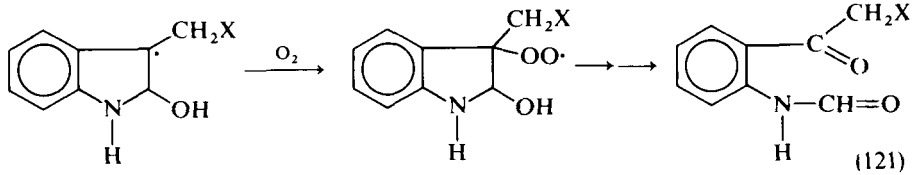
The chemistry of the tyrosine side-chain is dominated by the phenolic OH group. Reaction of either free tyrosine or a variety of tyrosine-containing peptides with HO· in solution results in the detection by both ESR and optical spectroscopy of the tyrosinyl phenoxyl radical either as a result of direct H-atom abstraction or via initial HO· addition and the rapid elimination of H_2O[148]. Similar behaviour is observed with other oxidants (e.g. Ce^{4+}, $KMnO_4$, $SO_4^{\cdot-}$) and direct UV photolysis, though the reaction in these cases is believed to occur via initial formation of the radical-cation and subsequent rapid deprotonation[206,208]. The major fate of these species in both deoxygenated and oxygenated solutions appears to be dimerization through carbon–carbon or carbon–oxygen–carbon cross-links[209,210]. Recent studies have demonstrated cross-links with other materials, including the DNA base thymine, a process which may be of consider-

able importance in radiation damage[209,210]. The detection[211] of low concentrations of the important biological molecule DOPA (3,4-dihydroxyphenylalanine) in the presence of O_2 suggests that some of the phenoxyl radicals must react with oxygen to form peroxyl radicals, though this reaction has been suggested to be both slow and reversible.

Reactions of both e^- and HO· with tryptophan occur almost exclusively by addition at the indole group; pulse radiolysis and ESR studies have suggested that approximately 40% of the HO· radicals add to the aromatic ring with the remainder at the C_2-position (reaction 120)[212–214]. Attack at the latter position results, in the presence of oxygen, in the generation of the corresponding peroxyl radical and ultimately the generation of formylkinurenine (reaction 121)[213].



(120)

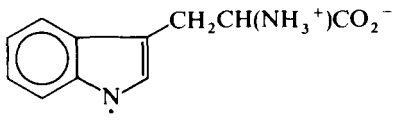


(121)

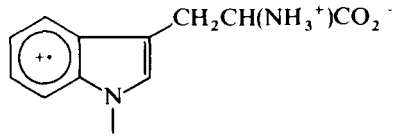
X = $CH(NH_3^+)CO_2^-$

Reaction with e^- results in electron capture and subsequent protonation to give the H-atom adduct[212,213,215]. In the absence of oxygen this species has been suggested to cross-terminate with the hydroxyl-adduct to regenerate the parent molecule, in order to account for the extremely low yield of tryptophan destruction in γ-irradiation experiments[148].

Radiolysis with ESR detection has resulted in the detection of three major species in single-crystal studies[216]. These are the deaminated product (presumably formed by electron capture at the carboxyl group; cf reaction 79), the hydrogen-atom adduct to the aromatic ring, and the indolyl radical **66**. The latter may arise from the radical-cation **67** via deprotonation. The radical-cation itself has been detected in other low-temperature studies and in direct UV photolysis experiments of both tryptophan and various peptides; this species is also believed to be the precursor of **66** observed on oxidation of tryptophan with other powerful oxidants.



(66)

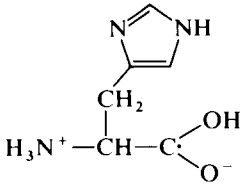


(67)

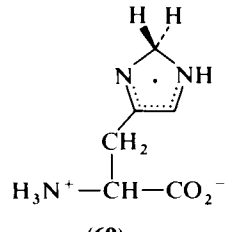
Product analysis[217], ESR[218] and pulse radiolysis studies[207,219] have demonstrated that the major radicals arising from reaction of HO· with histidine residues in solution

arise from addition to the ring. In the presence of oxygen, peroxyl-radical formation results in the detection[217] of a complex series of products which include asparagine and aspartic acid (as a result of ring opening) and imidazolylacetic acid; the presence of the latter material suggests that some attack on the back-bone α-carbon also occurs. Addition of e^- also occurs at both the ring and peptide back-bone; the relative proportion of these two pathways is pH dependent, with the protonated ring being more reactive than the unprotonated (formed at pH > *ca* 7.8)[175,219]. Reaction at the back-bone results in deamination as discussed earlier.

The radical species formed on irradiation of histidine at low temperatures appear to be dependent on the precursor employed. With the hydrochloride monohydrate[220] the protonated radical anion **68** is the major species; this is tranformed into the deaminated radical at higher temperatures. ENDOR studies[221] have identified three major radicals at 4.2 K, namely **68**, a C-2 radical resulting from decarboxylation and the radical-cation formed by ionization. Photobleaching and annealing results in the generation of an H-atom adduct (**69**); this species, which is also observed as a result of H· attack[149], is the only species observed at room temperature. With the free base, **68** is the major radical at both low and room temperature[222]; these differences are possibly due to the absence of water of crystallization in the latter case[222].



(68)



(69)

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CHAPTER 7

Vibrational analysis of acid derivatives

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I. INTRODUCTION

Infrared and Raman spectroscopy are two ways of studying vibrational transitions. Since the number of bands and the intensities in the two spectra are controlled by different phenomena, such as changes in dipole moment, polarizability and molecular geometry, we can consider these techniques as complementary. Hitherto Raman spectroscopy has had little impact on analysis, the main reasons being the lack of tables of characteristic bands in Raman and the relatively high costs of Raman instruments.

Conventional laser Raman spectroscopy has significant limitations. One of the main problems is fluorescence which, even if weak, is enough to obscure the other Raman signals, which are extremely weak. Another problem is excessive heating and dissociation with absorbing samples. Calibration and the low resolution are other problems in conventional laser Raman spectroscopy. All these problems can now be addressed by Fourier Transform (FT) Raman Spectroscopy using near-infrared excitation (Nd–YAg laser). The introduction of FT infrared and Raman must result in a renaissance of vibrational spectroscopy. We want to emphasize that vibrational spectroscopy is much more than a method for identification and a thorough study of the combined spectra allows important structural and chemical data to be obtained.

The vibrational bands are molecular properties, rather than single bond properties, so every compound has its own unique spectrum. The spectrum serves as a fingerprint of the compound. The major application of vibrational spectroscopy for organic chemists arises from the correlation bands in specific parts of the spectrum with certain functional groups.

In this work we will discuss the most typical bands in the infrared and Raman spectra for several functional groups. To give an idea of the character of the bands, the average potential energy distribution for these typical bands is also mentioned. When a molecule possesses symmetry it is possible to determine many features of its spectrum without any additional information. The interpretation is possible by use of the group theory; several authors have covered the application of group theory in spectroscopy and discussion of this theory is outside the scope of this work.

Raman spectroscopy has several distinct advantages over infrared: thus, the vibrational spectra from 4000 to 10 cm^{-1} can be recorded with one instrument and with absolutely no changes in the optical components.

Under ideal experimental conditions, the ratio of the intensities of a given band observed in solution, using two different polarizations, is about 0.75 unless the vibration involved retains the full symmetry of the molecule, when the ratio can be between 0 and 0.75. These polarization measurements are very useful to characterize the different fundamentals. For example, with simple molecules such as formamides, acetamides, thioamides, esters and carboxylates only C_s symmetry can be considered, and all vibrations in the plane of the molecule are totally symmetric and can be polarized. So we can easily distinguish between, for example, the δNCX (in-plane deformation—polarized) and πNCX modes (out-of-plane deformation—not polarized).

Water is a very weak Raman scatterer and is an ideal solvent for Raman studies.

Overtones and combination bands are mostly less intense in Raman, so we can better distinguish between bands due to fundamentals and other bands in Raman spectra.

A. Fundamental Vibrations

Consider a molecule with N atoms; this molecule exhibits $3N - 6$ internal vibrations ($3N - 5$ for linear molecules). Since an N-atomic molecule has $N - 1$ bonds (acyclic molecule), $N - 1$ vibrations can be regarded as stretching vibrations, the other $2N - 5$ ($2N - 4$ for linear molecules) being deformation modes.

All these vibrations are called *normal vibrations*. In general, a normal vibration is defined as a molecular motion in which all the atoms of the molecule move in phase with the same frequency.

In a vibrational spectrum we always observe more bands than the number of normal vibrations. The supplementary bands are caused by *overtones* at frequencies $2\nu_i, 3\nu_i, \ldots$ where each ν_i is a fundamental vibration. Selection rules, derived from group theory, also permit *combination bands* and *difference bands* $\nu_i + \nu_j, 2\nu_i + \nu_j, \nu_i - \nu, 2\nu_i - \nu_j, \ldots$, where ν_i and ν_j are fundamentals. The intensities of overtones and combination bands are generally very weak, especially in the Raman spectra, but may sometimes be considerably enhanced by Fermi resonance.

The fundamental vibrations can be classified into three types:

(i) A fundamental can be described by one internal coordinate (or one set of internal coordinates), which will generate a dominant coefficient in the potential energy distribution, and is generally described as a pure vibration and classified as a *localized group frequency* (νXH modes can all be described by the XH bond length as internal coordinate and all have about 95% νXH character in the potential energy distribution). The carboxyl frequency is one of the most characteristic band frequencies of organic molecules and is described as a typical localized group frequency.

(ii) When a fundamental arises in a distinct region, but the motion of the atoms, during this vibration, are very complex and cannot be described by a simple set of symmetry coordinates, then we classify this vibration as a *zone frequency* or *localized group frequency*. This fundamental is also very useful for analytical purposes. A typical example is the Amide II band in secondary amides at 1550 cm^{-1} which exhibits about 50% νCN and 50% δNH character.

(iii) A third category of normal modes in which the potential energy is spread over many internal coordinates, even in other functional groups, is observed with different profiles at different frequencies and is designated as a *delocalized group frequency*, especially occurring in the lower frequency region. Since coupling effects generally become more important with decreasing frequency and since the skeletal modes of organic molecules are very complex, these delocalized group frequencies cannot be used for identification purposes.

Hence, special attention for characterization is mainly focused on the higher frequency bands.

B. Interactions on Fundamental Vibrations

Some of the important interactions that affect the pattern of the vibrational spectra are mass effects, vibrational coupling, electronegativity effects, Fermi resonance, conjugation and hydrogen bonding. Various types of correlations have been reported in the literature. It is very important to remember, when attempting to make structural deductions from vibrational spectra, that all these factors can lead to significant shifts of frequencies and altered intensities. Therefore we will describe some of these important

interactions, and more detailed examples will be given in the description of the typical functional groups.

1. The electronegativity effect

Any change in the electronic distribution of a band affects its force constant and consequently the frequency. A change in the electronegativity of a substituent also changes the contribution of the polar resonance form and the frequency will be altered.

The variation of the band position and intensity for a particular vibration with electron-donating or electron-withdrawing character of substituents is very well known. For example, the νCO in X—$CONH_2$ molecules increases with increasing electronegativity of the X-group. The νCO increases from monohalogenated to trihalogenated derivatives, despite the mass effect, and is found at higher frequencies for fluoro compounds than for bromo compounds, where both mass effect and electronegativity effect work in the same direction. One primordial requirement for this effect is the coplanarity of the different bonds. In vinyl compounds such as $H_2C{=}CYX$ a linear relationship is found between the CH_2 deformations and the group electronegativity of the CXY group. This effect is much more reduced in non-planar systems such as in phosphates or sulphates and explains the relatively stable position of the group frequencies of the phosphates and sulphates[1]. The X—C≡N compounds all exhibit intense νCN bands in the Raman spectra, as the intensity depends on the change of polarizability in the CN group. The infrared intensity, however, depends on the change of dipole moment and, by changing the group electronegativity of X, one can easily understand that $\partial\mu/\partial Q$ can be minimal for a given electronegativity of X. Although this νCN is allowed in both infrared and Raman, a very intense Raman band and no infrared band will be observed for these compounds where $\partial\mu/\partial Q \approx 0$.

2. Vibrational coupling

In *trans* secondary amides, the unperturbed δNH and νCN modes should appear in the same region. Vibrational (*energy*) coupling between these modes results in two quite distinct bands at about 1550 cm^{-1} and 1250 cm^{-1}. Both bands entail high νCN and δNH character. On deuteration, this energy coupling is removed and the practically pure νCN and δND modes are observed at about 1480 cm^{-1} and 950 cm^{-1}.

In *cis* secondary amides, no such coupling occurs and νCN for these compounds is situated in the 1480–1500 cm^{-1} region, while the δNH appears at about 1350–1400 cm^{-1}. On deuteration νCN is only slightly lowered by about 10–15 cm^{-1}; the pure δND is observed in the 1000 cm^{-1} region.

Vibrational (*mass*) coupling is observed when two vibrational modes exhibit about the same masses and force constants. In oxamidates, exhibiting both amide and carboxylate functions, a strong coupling between the δNCO and δCO_2^- modes has been observed and calculated. When there is a large mass difference (for example, vibrations involving hydrogen atoms) the remainder of the molecule exerts only little influence on the bond vibrations. This is the reason why the C—H vibrations were identified as localized group frequencies and often can be treated as a separable group. The νCN frequencies in HCN (2096 cm^{-1}), DCN (1928 cm^{-1}) and TCN (1724 cm^{-1}) clearly show the increasing vibrational coupling with increasing mass.

Since coupling effects appear more frequently with decreasing frequency and since the skeletal modes of most organic molecules are consequently very complex, the special attention for identification is focused mainly on the higher frequency fundamentals.

3. Mass effect

The stretching vibration in a simple diatomic molecule can be regarded as an oscillation of the two masses connected by a spring and Hooke's law can be applied as a first approximation. The vibrational frequency is then given by

$$\bar{\nu}\,(\mathrm{cm}^{-1}) = \frac{1}{2\pi}\sqrt{\frac{f}{\mu}}$$

where f is the force constant and μ the reduced mass.

For stretching vibrations of individual bonds in more complex molecules, we can also apply this approximation. Mass effects may be employed as confirmatory evidence for assignments by use of isotopes. Deuterium, nitrogen-15, oxygen-18 and stable metal isotopes such as Ni-58 and Ni-64 have been employed for identification of some bands.

The fundamental vibrations, useful for diagnostic purposes, are molecular properties, rather than single bond properties. Changes in the mass of a portion of the molecule can alter the frequency of a fundamental not directly involved in this mass change. For example, in $M(CH_3)_4$ compounds the CH_3 rocking modes are observed at 1280 (M = C), 869 (M = Si), 830 (M = Ge), 776 (M = Sn) and 767 cm^{-1} (M = Pb)[2].

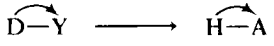
4. Fermi resonance

Fermi resonance can occur between vibrations of the same symmetry, if the unperturbed frequencies are nearly alike. When resonance occurs, the two bands are changed in intensity and frequency, so they appear very well separated. If the resonance is close, the intensities of the two bands approximate the average of the unperturbed intensities. Fermi resonance is manifested by a considerable increase in the intensity of the expected weaker band (generally an overtone or combination band). Probably the best known example of Fermi resonance is given by the spectrum of CO_2.

5. Hydrogen bonding

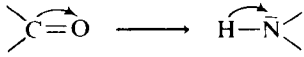
Hydrogen-bond interactions of the type X—H···Y may be regarded as an intermediate stage in the transfer of the proton from the donor species (X—H) to the acceptor (Y). When the donor is not a strong enough acid and the acceptor is not a strong enough base to realize complete proton transfer, a partial bond is formed between the proton and the base (Y) which weakens the X—H bond and alters its characteristics.

Hydrogen bonding can also be interpreted in terms of the donor–acceptor theory[3].



Y is generally more electronegative than D and A is more electronegative than hydrogen. The hydrogen bond is caused by electron transfer from atom Y to the hydrogen atom. This electron transfer generates the *pile-up effect* where electron density is transferred from the rest of the molecule to atom Y, resulting in an elongation of the D—Y bond. The effect on the other molecule (or other part of the molecule for an intramolecular hydrogen bond) is called the *spill-over effect* and electron density is spread from the hydrogen over the rest of the molecule. This effect results in an elongation of the H··A bond.

Let us consider the following situation:

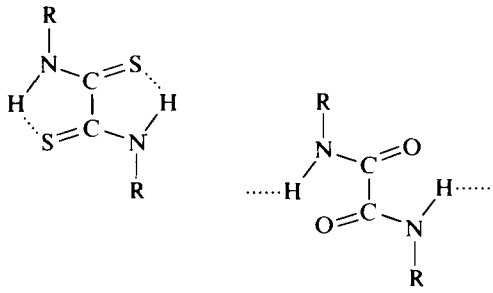


The hydrogen bonding becomes stronger when the oxygen and nitrogen atoms are closer and when O, H and N are more linear. The stronger the hydrogen bond, the longer will be the C=O and N—H bonds, resulting in lower force constants and lower frequencies for the νCO and νNH modes.

In earlier spectroscopic work on hydrogen bonding, attention was mainly focused on the shifts of these two stretching modes. Now it is clear that this interest must be extended to the half-band width and to the increased intensity, which also considerably increases with increasing bond strength. The deformation modes and especially the πN—H modes are also strongly affected by hydrogen bonding and shift to higher frequency by increasing hydrogen-bond strength.

Infrared spectroscopy is certainly the best technique used in qualitative and quantitative experimental studies of hydrogen bonding. A typical example is the study of oxamides and dithiooxamides[4]. Secondary oxamides in the solid state all exhibit broad νNH bands at about 3300 cm^{-1} and νCO at 1675 cm^{-1}, indicating some hydrogen bonding. In dilute solutions we observe the rather sharp νNH at 3450 cm^{-1} and νCO at 1685 cm^{-1}, indicating an *intermolecular* hydrogen bond in the solid state and concentrated solutions.

Secondary dithiooxamides show their νNH in the solid state at 3200 cm^{-1} and the νCS at about 850 cm^{-1}. Even in very dilute solutions no change is observed and both the νNH and νCS modes remain with the same profile, intensity and frequency. So in secondary dithiooxamides we must consider *intramolecular* hydrogen bonds (Scheme 1).



SCHEME 1

Recently a method has been developed to distinguish between inter- and intramolecular hydrogen bonding for products which are not soluble in the usual solvents[5].

When a sample is cooled, the thermal agitation of the molecules is diminished, resulting in a shortening of the intermolecular distances, while the intramolecular distances remain almost unaffected.

NN'DHEDTO (Figure 1) exhibits both types of hydrogen bonding: intramolecular N—H···S and intermolecular O—H···O hydrogen bridges. Another interesting feature is the fact that in the unit cell two different oxygen-oxygen distances are observed, resulting in two different O—H···O systems[6]. The solid state spectrum of NN'DHPEDTO exhibits two different νOH bands and one νNH at 3170 cm^{-1} (Figure 2a).

In 1,4-dioxane one broad νOH forming hydrogen bonds with the solvent and the intramolecular νNH at 3170 cm^{-1} are observed (Figure 2b). In very dilute solution of CS_2 the free νOH is observed at about 3640 cm^{-1} and the intramolecular νNH is still at 3170 cm^{-1}.

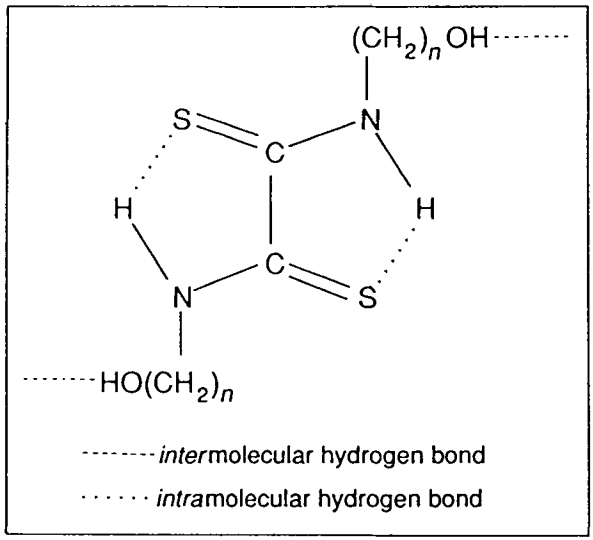


FIGURE 1. The model molecule: $n = 2$, *N,N'*-dihydroxyethyldithiooxamide (NN'DHEDTO); $n = 3$, *N,N'*-dihydroxypropyldithiooxamide (NN'DHPrDTO); $n = 5$, *N,N'*-dihydroxypentyldithiooxamide (NN'DHPeDTO)

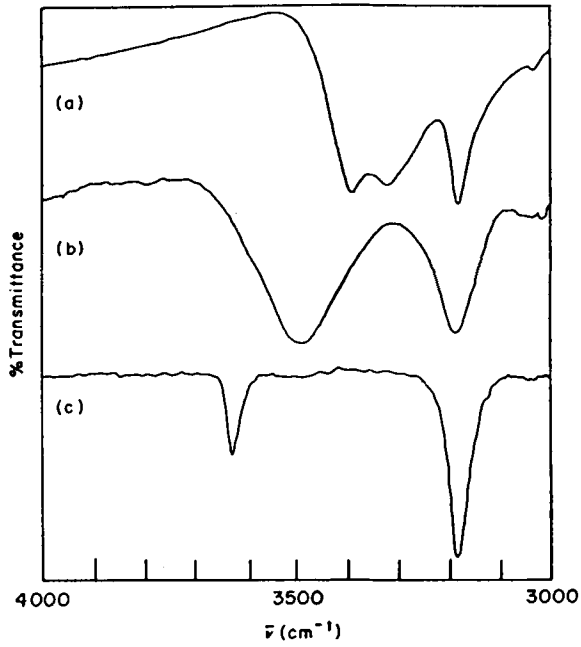


FIGURE 2. NN'DHPeDTO in solution: (a) solid state—KBr: intermolecular H bonds between different NN'DHPeDTO molecules; (b) solution—1,4-dioxane: intermolecular H bonds between NN'DHPeDTO and 1,4-dioxane; (c) solution—CS_2: no intermolecular H bonds, free νOH vibration

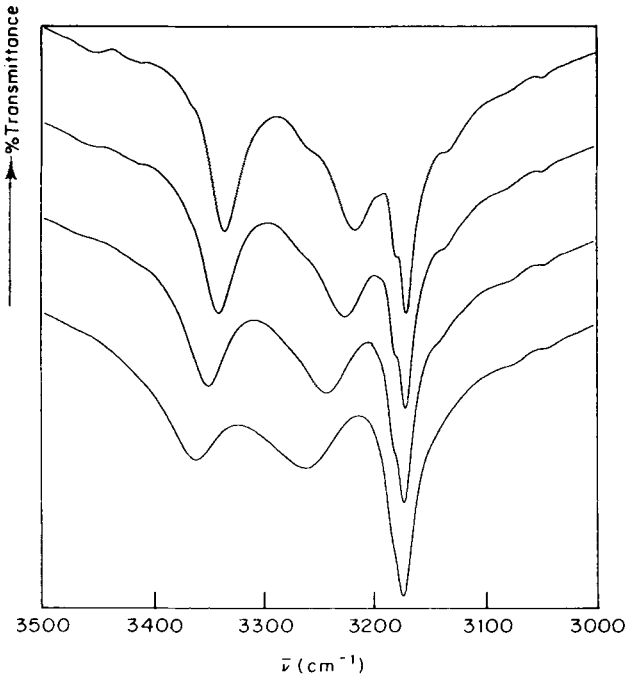


FIGURE 3. NN'DHEDTO: νOH, νNH region at 77 K (top), 143 K, 203 K and 293 K (bottom)

Figure 3 shows the solid state spectrum of NN'HEDTO at different temperatures. The highest νOH, exhibiting the weakest hydrogen bond (O···O distance 2.785 Å), shifts from 3360 cm^{-1} to 3334 cm^{-1} ($\Delta\nu$ = 26 cm^{-1}) on cooling whilst the strongest one (O···O distance 2.721 Å) shifts from 3260 cm^{-1} to 3217 cm^{-1} ($\Delta\nu$ = 43 cm^{-1}). The intramolecular νNH practically remains unaffected from 3172 cm^{-1} to 3170 cm^{-1} ($\Delta\nu$ = 2 cm^{-1}).

C. Solid State Spectra

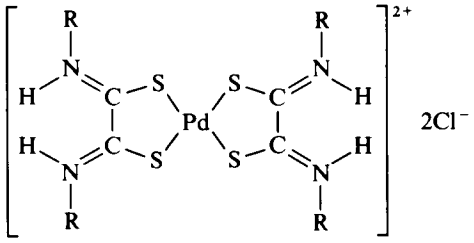
In view of the easy and popular use of the pellet technique for spectra of solids we must note that this technique, because of several possible factors (Christiansen effect, refractive index, polymorphism, distortion of crystalline structure, etc.) giving rise to anomalies, is not ideal for quantitative analysis. Moreover, the number of bands depends on the geometry of the molecules in the crystal, and in the solid state the spectra correspond to the unit cell rather than to the free molecule. Because of intermolecular interactions in the unit cell, bands in the solid state often show splitting, which disappears in the solution spectra.

A freshly prepared pellet is practically always of better quality, the deciding factor for the ageing process of the pellet is the relative humidity of the surrounding atmosphere. During this process water from the surrounding atmosphere enters into the disk and diffuses through the whole pellet. The alkali halide recrystallizes into larger crystalline particles and the baseline is consequently no more perfect. Penetrating water sometimes forms hydrates or even dissolves the compound temporarily; this compound is then

transported through the whole disk, resulting in a more homogeneous distribution: on drying, the water evaporates while the compound crystallizes into smaller particles and is better 'dissolved' in the disk, resulting in a stronger absorption[7,8].

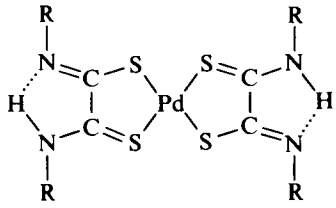
Polymorphism can considerably change the spectra[9]. Identical spectra always indicate identical products, but the opposite is not always true.

Sometimes reactions can occur during the pressing of the pellet, especially with compounds where the ions of the disk replace the anions of the compounds under investigation. This substitution sometimes leads to real reactions. *N,N'*-disubstituted dithiooxamides react in acid media with $PdCl_2$ to give the complex shown in Scheme 2[10].



SCHEME 2

This compound is stabilized by strong N—H···Cl hydrogen bonds. By pressing the pellet in a NaF matrix, we substitute the chloride ion by fluoride and the N—H···F system is formed. In this system, however, HF is formed, resulting in deprotonation of the complex, giving a compound (Scheme 3) which exhibits strong intramolecular hydrogen bonds. The formation of HF is clearly proved by the presence of $NaHF_2$ in the NaF pellet. Evans[11] calculated that a sharply defined energy level, involved in only a weak transition from the ground state (an overtone or combination band), interacts with the levels of a strong and broad absorption band, so that a transmission window (called an Evans window) may be observed in the broad absorption band. So one can state that an Evans hole is present when the spectral minimum (the window) corresponds to the frequency of the overtone or combination band.



SCHEME 3

A typical example of these Evans windows is given in Figure 4, where the γOH region of RHNCSCSNHR (R = CH_2CH_2OH) is given at different temperatures. The γOH appears at about 730 cm^{-1} at room temperature and shifts to about 800 cm^{-1} at very low temperature. The broad profile of the γOH at low temperature clearly shows an Evans window at about 808 cm^{-1}.

Infrared and Raman spectra of solid hydrates often contain minima in the OH stretching region. These minima are the best known Evans windows, caused by Fermi resonance between the broad and intense νOH band (ν_1) of water and a relatively narrow

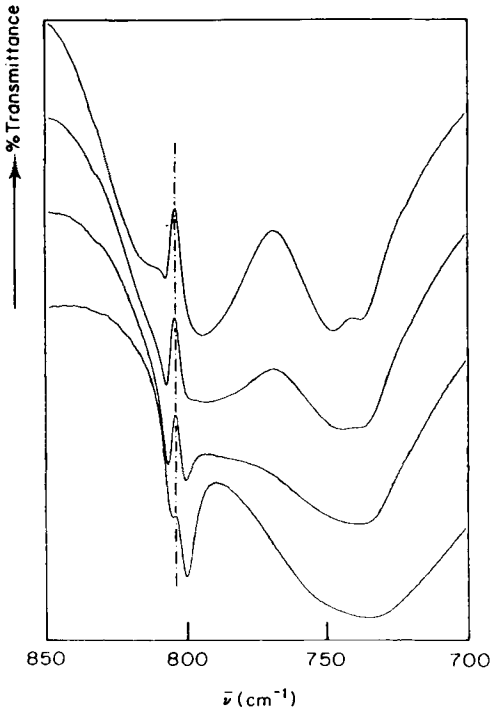


FIGURE 4. NN'DHPrDTO: Evans window (808 cm^{-1}) in the γOH band at 77 K (top), 143 K, 203 K and 293 K (bottom)

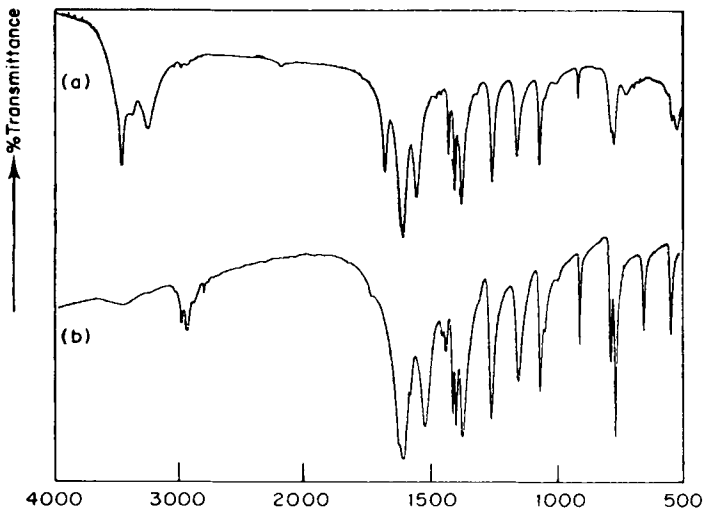


FIGURE 5. (a) $CSN(CH_3)_2COOK \cdot H_2O$; (b) $CSN(CH_3)_2COOK$

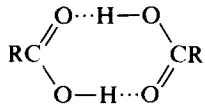
band due to the overtone of the δH_2O (ν_2) of water. This phenomenon can lead to multiple bands in the solid state, all belonging to the same broad νOH but split in different bands by the Evans windows.

The water bands due to 'humidity' are very well known, but crystal water or coordinated water can give very well defined bands in infrared and Raman. $(CH_3)_2NCSCOOK \cdot 1\ H_2O$ gives a very nice example of this phenomenon (Figure 5).

II. THE FUNCTIONAL GROUPS

A. The Carboxylic Acid Function

Carboxylic acids exist normally in the dimeric form, exhibiting very strong hydrogen bonding.



Even in the vapour phase and in dilute solution in some polar solvents, this association is still observed to some extent. The hydrogen bonding affects considerably the carbonyl and hydroxyl group vibrations. As one can practically always consider the dimeric form, the carbonyl frequencies are remarkably constant and are only slightly influenced by the phase or the solvent. The data obtained from different solution spectra should be very similar to those obtained from the solid state in KBr pellets, indicating this dimeric form. However, long-chain polymers or complex cyclic structures can occur when the hydrogen bonding is weaker and the spectra in solution and in the solid state are different.

Ng and Shurvell[12] studied the Raman spectra of acetic acid–water mixtures. Factor analysis indicated the presence of five bands in the carbonyl region. Four of these were assigned to the νC=O of monomers, cyclic dimers and free and hydrogen bonded carbonyl frequencies of linear polymeric species, while the fifth component in this region is due to the bending mode of water. Chang and coworkers[13] investigated the infrared and Raman spectra of isotopically substituted formic acids, in which interesting features are the frequency shifts between the dimers and the monomers. The ν_{as}OH (dimer) is about 450 cm^{-1} less than the νOH (monomer), another large difference of about 275 cm^{-1} is obtained between the πOH (monomer) and the infrared active out-of-phase combination of πOH (dimer). The vibrational frequency of this out-of-plane mode in the dimer is higher, because the hydrogen bonding in the dimer has the effect of causing a much more rigidly planar structure. Also, the δOH mode is for the same reason observed at higher frequency for the dimer. The C=O double bond is longer in the dimer and the infrared active ν_{as} C=O double bond is situated at about 100 cm^{-1} higher than the Raman active ν_sC=O. The C—O single bond shows the opposite trend and an upward shift of the same magnitude is observed in the dimer.

The νOH of the monomer is observed at about 3550 cm^{-1} for some compounds in the gas phase and in very dilute solutions. In the liquid and the solid state, the dimeric form is generally predominant resulting in broad bands with different sub-maxima between 3000 cm^{-1} and 2250 cm^{-1}. The νOH of the dimeric form generally appears as a mean peak near 3000 cm^{-1} and a number of satellite bands in the 2800–2300 cm^{-1} region. Since only very few compounds give absorptions in this 2800–2300 cm^{-1} region and the fact that the νOH develops an irregular structure with distinct sub-maxima,

makes this region very valuable for identification in the infrared spectra, despite the fact that these bands are often broad and weak. The νOH should, according to the theory, be observed as an intense Raman band; the non-identification of this band is discussed by Bertie and Michaelian[14].

In very dilute solutions in non-polar solvents, two carbonyl frequencies are often observed: the highest frequency corresponds to the monomer, and about 20 cm^{-1} at lower frequency we observe the carbonyl stretching mode of the dimer. Practically all data on these carbonyl frequencies have been obtained from dimeric forms in the liquid or solid state, so these values are consequently used for diagnostic purposes. The dimeric form exhibits a centre of symmetry and the $\nu_{as}C{=}O$ is infrared active and is always about at 30 cm^{-1} higher frequency than the Raman active $\nu_s C{=}O$. This difference in the infrared and Raman carbonyl stretching mode is the most unambiguous proof of a dimeric structure. These bands appear as very intense in infrared and of medium intensity in the Raman spectra. Saturated aliphatic acids give very intense infrared $\nu_{as}CO$ bands between 1725 and 1700 cm^{-1}. A strong electronegative group will increase the carbonyl frequency (for CCl_3COOH ν_{as} 1742 cm^{-1}, ν_s 1687 cm^{-1}). For CF_3COOH the monomer in the gas phase gives a band at about 1820 cm^{-1}. Most α-halogenated acids also show some conformers, resulting in a splitting of the carbonyl bands[15].

In unsaturated acids some conjugation is expected, leading to lower carbonyl frequencies. For acids exhibiting strong intramolecular hydrogen bonds these carbonyl frequencies are lowered to about 1650 cm^{-1}.

Carboxylic acids always give two typical bands in the 1500–1100 cm^{-1} region, due to strong coupling of the νC—O and δOH modes. A band of medium to weak intensity is observed near 1400 cm^{-1}. This band can sometimes not be detected due to the very weak intensity and the overlapping by CH deformations also occurring in this region. The 1210 cm^{-1} band appears as rather intense in infrared and less intense in Raman. High carbonyl values are mostly accompanied by low values of this typical band in the 1250 cm^{-1} region. This effect is very obvious in halogenated acids where the high νC=O double-bond stretching mode is accompanied by a band below 1235 cm^{-1}. These two typical bands appearing in the 1400 cm^{-1} and 1250 cm^{-1} region are the coupled vibrations of νC—O single bond and δOH. The lowest band exhibits the highest νC—O character. As we have strong coupled vibrations, the potential energy distribution (P.E.D.) is often dependent on the method of calculating the force field and for some halogenated acetic acids in the highest contribution of δOH calculated for the lowest band[16]. Deuteration uncouples these two vibrations; the νC—O is then observed at about 1350 cm^{-1} and the δOD in the 1000 cm^{-1} region.

The πOH in the dimeric structures is generally observed as a typical broad band of medium intensity in infrared and weak in Raman in the 960–875 cm^{-1} region. The πOD is situated at about 750 cm^{-1}. This typical πOH band and the two different carbonyl stretching modes in the infrared and Raman spectra are the best proof of the dimeric structure of the acids.

Further confirmation for the identification of carboxylic acids can easily be obtained in aqueous solution from the Raman spectra on passing from the acid to the salt.

$$RCOOH \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} H^+ + RCOO^-$$

The νC=O of the acid appears at about 1720 cm^{-1}, while the $\nu_{as}CO_2^-$ of the salt is situated in the 1600 cm^{-1} region. The typical fundamentals and their P.E.D. values for the carboxylic acid are shown in Table 1.

TABLE 1. Typical fundamentals for the carboxylic acid function

Dimer

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νOH	3000–2200	s.br.	—	98 νOH
νCO=O	1740–1700	v.s.	s	60 νC=O, 20 νC—O
νC—O	1300–1200	s	m	50 νC—O, 40 δOH
δOH	≈1400	m.-w.br.	v.w.	60 δOH, 30 νC—O
δCO_2	750–600	m	var.	40 δCO_2, 20 δOH
πOH	950–900	m.s.br.	v.w.	90 πOH
ν(O—H···O)	200–180	s	—	

Monomer

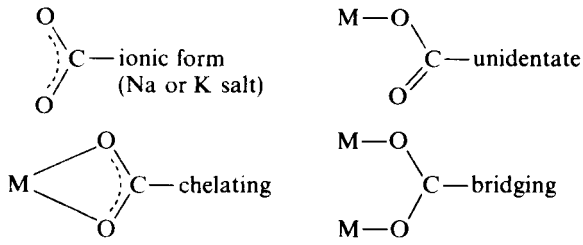
Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νOH	3180–3550	s	—	98 νOH
νCO=O	1780	v.s.	s	70 νC=O, 20 νC—O
νC—O	≈1230	s	m	45 νC—O, 25 δOH, 20 δCO_2
δOH	≈1200	m.br.	—	60 δOH, 35 νC—O
δCO_2	700–650	m	m	60 δCO_2, 20 δOH
πOH	650	m.s.	—	90 πOH

Deuterated compounds (region cm^{-1})

	Monomer	Dimer
νOD	2640	2050
νC=O	1750	1700
νC—D	1150	1250
δOD	900	1000
δCO_2	600	700–600
πOD	500	700

B. The Carboxylate Function

A carboxylate ion can coordinate to metals in a number of ways[17], and the carboxylate modes are situated at different frequencies relative to values for the free carboxylate, usually taken as those of the sodium or potassium salts (Scheme 4). The free carboxylate



SCHEME 4

TABLE 2. Typical fundamentals for the carboxylate group

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu_{as}CO_2^-$	1650–1600	v.s	w	80 $\nu_{as}CO_2^-$, 20 $\rho_sCO_2^-$
$\nu_sCO_2^-$	1400–1350	m	s	65 $\nu_sCO_2^-$, 20 νCC
$\delta_sCO_2^-$	850–600	var.	var.	40 $\delta_sCO_2^{\cdot-}$

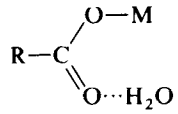
ion exhibits two equal CO bonds and the fundamentals can be described as $\nu_{as}CO_2^-$ exhibiting the highest frequency in the 1650–1600 cm^{-1} region and $\nu_sCO_2^-$ situated in the 1400–1350 cm^{-1} region (Table 2).

The first band appears as a very strong and generally broad band in infrared and as a medium strong band in the Raman spectra. The second band is the most intense band in the Raman spectra and appears less intense in infrared.

Some indication about the conformation in the molecule can be obtained from the depolarization ratio of these bands in the Raman spectra[18] and splitting of these bands can be due to crystal effects and rotational isomers. The δCO_2^- mode is strongly coupled with other deformations in the molecule. It has been shown that the OCO bond angle is very sensitive to the kind of bonding, so an increase of the angle implies a force constant reduction, also leading to a frequency decrease in the δCO_2^- mode. The coupling and the influence of coordination make this mode not characteristic. The δCO_2^- appears in a wide range 800–600 cm^{-1} with variable intensity[18,19].

Unidentate coordination removes the equivalence of the two oxygen atoms and a pseudo-ester configuration is obtained. The carboxylate group is then no longer described by the $\nu_{as}CO_2^-$ and $\nu_sCO_2^-$ modes but by a νC=O (the carbonyl group is not coordinated) usually at higher frequency than the $\nu_{as}CO_2^-$ and a νC—O (the carbonyl group is coordinated) generally situated at slightly lower frequency than the $\nu_sCO_2^-$. So a larger difference between the two carboxylate frequencies compared with the free carboxylate is an indication of unidentate coordination.

However, strong hydrogen bonding between the free carbonyl group and water molecules elongates the non-coordinate carbonyl bond and lowers the frequency.



Hence it would be unwise, if there is no large difference between the two carboxyl fundamentals, to conclude that there is no unidentate coordination. Chelation and bridging should not alter the bond orders and it has been suggested that bidentate coordination should give separations slightly less than the ionic values, but not all chelating or bridging bidentate carboxylate groups have low separation values[20] and some have suggested that the separation for chelating compounds should be less than for bridging compounds[21].

C. The Amine Function

1. *Primary amines*

The vibrational spectra of primary aliphatic amines often exhibit interesting features. Fermi resonance from coupling of the fundamental NH_2 stretching modes with the first overtone of δNH_2 and strong hydrogen bonding with electronegative atoms cause a

shift broadening and splitting of the νNH_2 bands. This shift to lower frequency can overlap with the CH stretching region. This makes the measurements and assignments in the 3000 cm^{-1} region very complicated[22]. The ν_{as} and $\nu_s NH_2$ modes appear as rather intense bands in infrared and Raman, the $\nu_{as}NH_2$ at 3380 cm^{-1} is more intense in infrared while the $\nu_s NH_2$ at 3320 cm^{-1} is more intense in Raman. Bellamy and Williams[23] developed an empirical relation between the two NH_2 stretching modes:

$$\nu_s NH_2 = 3455 + 0.876\,\nu_{as}NH_2\ (cm^{-1})$$

This relationship only holds when the two NH bonds are equivalent and when the frequency shift due to Fermi resonance is negligible. Most primary amines generally show a third band near 3200 cm^{-1}; this first overtone of the δNH_2 mode can be intensified by Fermi resonance with the NH_2 stretching modes. The δNH_2 mode appears in the 1600 cm^{-1} region as a very intense infrared band and extremely weak in Raman. The out-of-plane NH_2 deformation is observed as a broad and intense infrared band in the 830–720 cm^{-1} region; its position is more sensitive to changes in hydrogen bonding than in the cases of stretching modes.

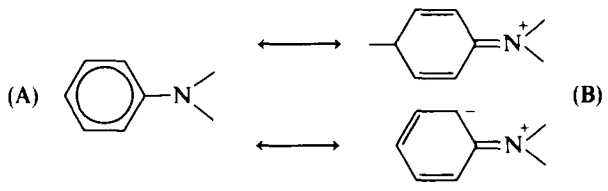
2. *Secondary amines*

The most characteristic band for the secondary amine group is the νNH appearing in the 3320 cm^{-1} region as a strong infrared and medium strong Raman band. This band is lowered by hydrogen bonding and also by branching at the α-carbon atom. Other typical bands are the ν_{as}CNC at about 1150 cm^{-1} and the ν_sCNC in the 900 cm^{-1} region. The ν_{as}CNC appears more intense in infrared and the 900 cm^{-1} band is generally very intense in Raman. The δNH and πNH modes appear rather intense and broad in infrared and very weak in Raman at respectively about 1500 cm^{-1} and 720 cm^{-1}.

3. *Tertiary amines*

Tertiary amines do not exhibit NH bands; the fundamentals occur in the fingerprint region and are often obscured by other bands. To identify a tertiary amine group, one can add some acid, such as HCl, and the tertiary amine hydrochloride $R_3N^+Cl^-$ can then be identified by multiple absorptions between 2700 and 2400 cm^{-1}. These absorptions move to higher frequency in the order Cl < Br < I due to the different hydrogen bond strength in the $NH^+\cdots X^-$ system. The ν_{as}CNC arising at about 1060 cm^{-1} is strong in infrared and less intense in Raman. The ν_sCNC appears as an intense Raman band in the 800 cm^{-1} region and is weak and often obscured by other bands in infrared.

The νCN for aromatic amines is situated at higher frequency, due to the increased contribution of resonance forms B (Scheme 5). The typical fundamentals for the amines are listed in Table 3.



SCHEME 5

TABLE 3. Typical fundamentals for the Amine function

Primary amines				
Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu_{as}NH_2$	3380	v.s.	s	98 $\nu_{as}NH_2$
$\nu_{s}NH_2$	3320	s	v.s.	98 $\nu_{s}NH_2$
δNH_2	1600	v.s.	v.w.	80 δNH_2
νCN	1050	m.w.	m.	40 νCN, 40 νCC
Secondary amines				
Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νNH	3320	s	m.s.	98 νNH
ν_{as}CNC	1150	m.s.	m.w.	50 ν_{as}CNC
ν_{s}CNC	900	m.w.	s	40 ν_{s}CNC, 30 νCC
δNH	1500–1450	s	v.w.	80 δNH
πNH	750–700	s.br.	v.w.	80 πNH
Tertiary amines				
Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
ν_{as}CNC	1070–1050	m.s.	s	—
ν_{s}CNC	840	m.w.	s	—

D. The Alcohol Function

The vibrational spectra of some simple alcohols were studied by Tanaka[24] and Perchard and Josien[25] studied the infrared and Raman spectra of twelve isotopes of ethanol. The study of alcohols is very complex due to the highly polar nature of the OH group, which leads to strong hydrogen bonding and consequently alters the profile, intensity and frequency of the fundamentals involving the OH group.

The free OH can only be observed in the gas phase and in very dilute non-polar solvents. Hydrogen bonding especially decreases the νOH and increases the deformation modes. For example, in the most simple alcohol, methanol, in the gas phase the νOH is observed at 3681 cm^{-1} and δOH at 1345 cm^{-1}; in the liquid state, when strong hydrogen bonding influences these vibrations, the νOH is a rather broad band situated at about 3330 cm^{-1} while the δOH increases to 1420 cm^{-1}. The δOH appears in the CH deformation region (1450–1400 cm^{-1}) and is practically always coupled with these deformations; the strength of the hydrogen bonding also alters the profile and the position of this band. The πOH mode is situated in the liquid state in the 700–600 cm^{-1} region.

The OH deformations all appear as rather broad bands of medium intensity in infrared and are all rather weak in the Raman spectra. All alcohols give rise to strong infrared bands in the 1000–1050 cm^{-1} region; this band is of medium intensity in the Raman spectrum. The band is only slightly influenced when the hydrogen bonding is changed by dilution. This band has mainly νCO and some νCC character and must be regarded as the most typical fundamental vibration in alcohols.

The second more or less characteristic band in the fingerprint region appears in a rather broad region 950–750 cm^{-1} as medium intense infrared band and the most intense

TABLE 4. Typical fundamentals for the alcohol group

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νCO	1050	v.s.	m.s.	60 νCO, 30 νCC
ν_sCCO	950–750	m	v.s.	50 νCC, 20 νCO, 20 δCCO

Associated			*Free*		
Fundamental	Region (cm^{-1})	IR	Fundamental	Region (cm^{-1})	IR
νOH	3400–1900	very broad sub. maxima	νOH	3700–3500	Sharp s.
δOH	1480–1400	m.br.	δOH	1300–1200	m.
πOH	900–550	m.br.	πOH	650	m.
ν(OH···X)	$\approx$200	m.br.			

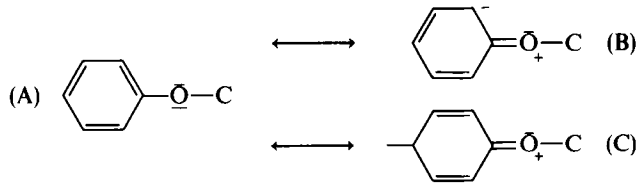
Raman band. This band can be regarded as a ν_sCCO. The intense infrared band, ascribed to the νCO, generally increases in frequency by branching on the α-carbon; the opposite is found for the νCCO (primary alcohol 950 cm^{-1}, secondary alcohol 820 cm^{-1}, tertiary alcohol 750 cm^{-1}).

The characteristic bands for the alcohol group are given in Table 4.

E. The Ether Function

Perchard[26] and Snyder and Zerbi[27] reported on the vibrational assignments of simple ethers. In the ether group we generally distinguish three different characteristic group frequencies.

The ν_{as}COC appears in the 1140–1100 cm^{-1} region as a very intense infrared and less intense Raman band. This band is observed at about 1125 cm^{-1} for aliphatic ethers; branching on the α-carbon atom slightly increases this frequency. This fundamental is always observed at higher frequencies for aromatic ethers (diphenyl ether, ν_{as}COC 1240 cm^{-1}) due to the higher contribution of resonance forms B and C (Scheme 6).



SCHEME 6

This higher contribution increases the CO bond order and concentrates the negative charges on the *ortho* and *para* positions. When electron-repelling groups such as methyl are positioned on the aromatic ring in *ortho* or *para* positions, then the contributions of resonance forms B and C are reduced and the ν_{as}COC is observed at higher frequencies for *meta* than for *ortho* or *para* substituents. The opposite is observed for electron-attracting groups such as halogens. Vinyl ethers also give rise to an increased ν_{as}COC mode (1200 cm^{-1}) due to the high contribution of resonance form B:

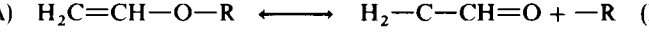


TABLE 5. Typical fundamentals for the ether function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu_{as}COC$	1100–1140	v.s.	m.w	60 $\nu_{as}COC$, 30 νCC
$\nu_{s}COC$	900–800	m	v.s.	40 $\nu_{s}COC$, 30 νCC
δCOC	500–430	m.s.	var.	40 δCOC, 30 δCCO

This higher contribution of B results in an increased $\nu_{as}COC$ and a decreased $\nu C{=}C$ mode. Vinyl ethers often exhibit conformers, due to rotation of the vinyl-carbon–oxygen bond, which results in a splitting of the $\nu C{=}C$ frequency.

The $\nu_{s}COC$ appears as the most intense Raman band and less intense infrared band in the 900–800 cm^{-1} region. Branching on the α-carbon atom generally decreases this frequency. This band is observed for dimethyl ether at 924 cm^{-1}, for diethyl ether at 845 cm^{-1}, for di-isopropyl ether at 798 cm^{-1} and for di-butyl ether at 700 cm^{-1}. This shift to lower frequency on branching at the α-carbon atom is also observed for the $\nu C{-}O$ mode in alcohols.

The δCOC mode is strongly coupled with other deformations of ether, such as δCCO and δCCC modes, and is not very diagnostic for the ether group. This band is of medium intensity in infrared and of variable intensity in Raman.

The typical fundamentals and their average P.E.D. values for the ether groups are given in Table 5.

F. The Nitrile Function

Nitriles are easily characterized by the $\nu C{\equiv}N$ appearing in the 2180–2280 cm^{-1} region. This band is easily recognizable since generally no other fundamentals appear in this region. However the frequency, the half-band width and the intensity are highly influenced by the substituents, especially on the α-carbon atom, and the intensity shows much larger variations than the band position.

Van Haverbeke and Herman[28] studied some simple nitriles and concluded that the influence on the nitrile band intensity could be represented by considering the effective induction constant [σ^{x}_{eff} [29]] and that the infrared intensity passes through zero for $\sigma^{x}_{eff} \approx 0.45$. Van Haverbeke also calculated that this value corresponds to a minimum in the dipole moment. So it is very well possible that for some nitriles, the $\nu C{\equiv}N$ is too weak to be observed; these bands, however, all appear as very intense Raman bands, due to the high polarizability of the nitrile group. This is a clear illustration of the limitation of using only infrared for identification of particular functional groups.

Conjugation lowers the $\nu C{\equiv}N$ considerably. Electron-attracting groups such as the nitro group decrease the intensity and increase the frequency; electron-donating groups such as amino exhibit the opposite effect.

The $\nu C{-}C(N)$ generally appears as a typical sharp infrared band of medium intensity in infrared and more intense in the Raman spectra, in the 1250–1150 cm^{-1} region.

The $\delta C{-}C{\equiv}N$ mode is also highly characteristic for aliphatic nitriles and arises as an intense band in infrared and less intense in Raman at about 650 cm^{-1}. The typical fundamentals for the nitrile group are shown in Table 6.

G. The Ester Function

Esters generally appear in the *cis* configuration and conformers of esters have been extensively studied[30]. The vibrational analysis of simple esters has been fully de-

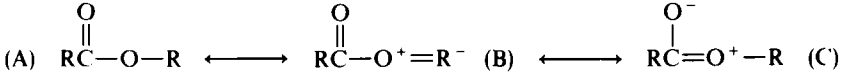
TABLE 6. Typical fundamentals for the nitrile function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu C{\equiv}N$				
Aliphatic	2270–2240	var.	v.s.	90 νCN
Aromatic	2240–2220	var.	v.s.	85 νCN, 10 CC(N)
Conjugated	2225–2205	var.	v.s.	80 νCN, 20 $\nu CC(N)$
$\nu C{-}C(N)$	1250–1150	m.s.	s	60 $\nu C{-}C(N)$, 20 νCC
$\delta C{-}C{\equiv}N$	≈ 650	s.	m.	40 δCCN

scribed[31–34] and a number of characteristic bands in infrared and Raman are very well known.

The most intense infrared band appears in the 1760–1730 cm^{-1} region and is of medium intensity in Raman. This characteristic band exhibits 65% $\nu C{=}O$ double-bond character and contributions of other vibrations in the ester group.

A second band appears in the 1300–1200 cm^{-1} region, is strong in infrared and rather weak in Raman. This second characteristic band has mainly $\nu C{-}O$ single-bond character. When an electron-withdrawing group such as vinyl or phenyl is placed on the singly bonded oxygen, the carbonyl frequency will rise, since the contribution of the resonance form B will be more important than that of C.



Vinyl esters exhibit the carbonyl frequency at 1700 cm^{-1}. Here, the higher contribution of resonance form B will result in an increased $\nu C{=}O$ double-bond and a lower $\nu C{-}O$ single-bond character.

A third stretching mode, generally called νOR, is situated in the 1000–900 cm^{-1} region, appears of medium intensity in infrared and variable intensity in Raman. This band is often difficult to assign due the overlap with CH-rocking and νCC modes. This band exhibits about 60% νOR character and sometimes strong coupling with νCC.

Two deformations with respectively high δCO_2 and ρCO_2 character appear with variable intensity in the 800–400 cm^{-1} region. Both bands can be polarized and are strongly coupled vibrations, especially with deformations in other functional groups, exhibiting approximately the same masses and force constants[34]. Another in-plane deformation appears in the 350 cm^{-1} region, and is also of variable intensity due to strong coupling, and has mainly δCOR character.

The typical fundamentals and their average P.E.D. values are given in Table 7 for the ester group.

TABLE 7. Typical fundamentals for the ester function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu C{=}O$	1760–1730	v.v.s	m.	65 νCO, 15 $\nu C{-}O$, 10 δCO_2
$\nu C{-}O$	1300–1200	v.s.	w.	50 $\nu C{-}O$, 10 OR, 15 γCO_2
$\nu O{-}R$	1000–900	m.	w.	60 $\nu O{-}R$, 15 δCO_2 (+25 νCC)
δCO_2	800–600	var.	var.	50 δCO_2 + other def.
ρCO_2	650–400	var.	var.	60 ρCO_2, 15 δCOR
δCOR	350	m.w.	m.w.	40 δCOR, 30 ρCO_2

H. The Amide Function

1. Primary amide

The vibrational spectra of primary amides have been extensively studied[35-41] and this functional group has received attention involving the planarity. Most authors agree that the amide hydrogens are situated in the NCO group plane, although the loss of this situation is relatively easy, as some experimental evidence shows[42].

Infrared spectra of primary amides exhibit a complicated pattern in the NH_2 stretching region (3450–3100 cm^{-1}). Hydrogen bonding affects the position of these bands, and especially the first overtone of the νCO and Fermi resonance between the first overtone of the δNH_2 and the $\nu_s NH_2$ have been studied[43].

The $\nu_{as}NH_2$ is observed as an intense band in the 3400 cm^{-1} region in infrared; the $\nu_s NH_2$ is more difficult to assign in infrared due to Fermi resonance and the low intensity. These bands are rather weak in Raman, where the $\nu_s NH_2$ appears as more intense than the $\nu_{as}NH_2$. The $\nu_{as}ND_2$ and $\nu_s ND_2$ modes appear respectively in the 2500 and 2350 cm^{-1} region. The $\nu_{as}ND_2$ can easily be assigned since there are no overtones or Fermi resonance in this region.

The δNH_2 vibration appears as a medium weak infrared and weak Raman band in the 1600 cm^{-1} region, while the ρNH_2 is situated at about 1150 cm^{-1}; this band is of medium intensity in infrared and an intense rather broad band in Raman. The δND_2 and ρND_2 modes are observed respectively in the 1150 cm^{-1} and 950 cm^{-1} region.

The two out-of-plane NH_2 deformations appear in the 800–600 cm^{-1} region as rather broad bands. The ωNH_2 at the highest frequency is generally weak in infrared while the lower τNH_2 is rather intense. These bands can hardly be detected in the Raman spectra. The ωND_2 and τND_2 modes are situated in the 600–500 cm^{-1} region. The only intense Raman band due to the NH_2 group is the ρNH_2 mode appearing in the 1150 cm^{-1} region. This band is always easy to assign in the Raman spectra.

The νCO appears as the most intense infrared band in the 1680 cm^{-1} region, and is of medium intensity in Raman and shifts only slightly ($\approx$20 cm^{-1}) on deuteration, due to the coupling with δNH_2, which is removed on deuteration. The frequency of this νCO increases with increasing electronegativity on the α-carbon atom. This frequency increases from monohalogenated to trihalogenated derivatives and is higher in fluoro than in chloro compounds with the same number of halogen atoms (CF_3CONH_2 νCO = 1719 cm^{-1}).

All primary amides exhibit an infrared band of medium intensity in the 1400–1300 cm^{-1} region. This band appears as the most intense band in the Raman spectrum and is highly characteristic for the primary amide function. It has high νCN character, coupled with δNH_2 and ρNH_2 modes and, for the deuterated products, is observed in the 1450 cm^{-1} region. The fact that this fundamental appears in the alkyl deformation region makes this vibration sometimes hard to detect in infrared, but the intensity factor makes it very easy to observe in Raman.

The high νCN and relatively low νCO modes in amides are easily explained by assuming a considerable contribution of the polar form B in the real structure.

$$\text{(A)}\quad \overset{O}{\overset{\|}{R}}C-NH_2 \longleftrightarrow \overset{O^-}{\overset{|}{R}}C=\overset{+}{N}H \quad \text{(B)}$$

The in-plane δNCO and ρNCO modes are located in the 760–600 cm^{-1} and 550–450 cm^{-1} region, as bands of variable intensity in infrared and generally of medium intensity in Raman. These in-plane deformations appear as polarized bands in the solution Raman spectra and can be distinguished from the non-polarized out-of-plane

TABLE 8. Typical fundamentals for the Primary amide function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu_{as}NH_2$	≈3400	v.s.	w	99 $\nu_{as}NH_2$
ν_sNH_2	3250–3200	m.s.	m.w.	99 ν_sNH_2
νCO	1680	v.v.s.	m.s.	70 νCO, 20 νCN, 10 δNH_2
νCN	1400–1350	m.s.	v.v.s.	45 νCN, 15 δNH_2, 15 ρNH_2
δNH_2	1600	m.w.	w	60 δNH_2, 20 νCO, 10 νCN
ρNH_2	1200–1100	m.	s.	70 ρNH_2, 10 νCO, 10 νCN
δNCO	780–600	m.s.	m.w.	50 δNCO, 20 ρNCO, 10 νCC
ρNCO	600–450	m.s.	w	50 ρNCO, 20 δNCO
ωNH_2	850–600	m.w.br.	v.w.	80 ωNH_2
τNH_2	800–600	s.br.	v.w.	80 τNH_2
πNCO	500	m.	m.w.	40 πNCO

πCO mode, generally situated at slightly lower frequency. The NCO deformations shift to slightly lower frequency on deuteration ($\Delta \approx 15\ cm^{-1}$).

Strong coupling between these deformations and deformations in other functional groups of the molecule can occur, especially when comparable masses and force constants are observed. Strong coupling has indeed been calculated for primary amides also exhibiting carboxylate or ester functions. As these deformations can be associated with vicinal modes of neighbouring functional groups, they can only be described as 'zone frequencies' and are consequently not useful for characterization.

The typical fundamentals for the primary amide group are shown in Table 8.

2. *Secondary amide*

The secondary amide group is probably the most studied and best characterized functional group, and its importance in relation to the structure and behaviour of proteins and other natural products is obvious. Secondary amides generally appear in the *trans* form[44–47] and seven bands, generally called the amide I to VII, are assigned and characterized.

The νNH appears as an intense band in infrared and weak in the Raman spectra at about $3330\ cm^{-1}$ for methyl derivatives and at slightly lower frequency for non-branched compounds. The effect of steric hindrance on the frequency and intensity of this νNH mode has been demonstrated[46]. A decrease in frequency and intensity has been observed for bulky groups such as tertiary butyl and isopropyl.

In addition to the main $3300\ cm^{-1}$ band, all secondary amides exhibit weak bands appearing as shoulders on the low-frequency side of the intense νNH. These bands are absent in the Raman spectra and studies of the deuterated compounds clearly indicate that these bands can be described as overtones (2 × Amide I, 2 × Amide II) and combination bands (Amide I × Amide II).

The most intense infrared band appears at about $1660\ cm^{-1}$, is of medium intensity in Raman and has mainly νCO character. Electrophilic substituents on the nitrogen atom slightly increase the frequency of this amide I band.

Coupling between the δNH and νCN modes give rise to the amide II and amide III bands in *trans*-secondary amides[46,48]. The amide II appears in the $1550\ cm^{-1}$ region as an intense and broad band in infrared and medium strong in Raman. This most characteristic band shifts to lower frequency and intensity for branched alkyl substituents, and it should be noted that the intensity change is more apparent than the frequency change. The amide III band appears medium strong in infrared and more

intense in Raman. The amide II band has mainly δNH character while the amide III band exhibits higher νCN character in these typical coupled vibrations.

The amide V band has pure πNH character and appears as a strong and broad infrared band, and very weak Raman band in the 700 cm^{-1} region. Strong hydrogen bonds are characterized by low νNH and high πNH values. The πNH frequencies are more sensitive to changes in hydrogen bonding.

Other fundamental in-plane deformations are the amide IV (mainly δNCO) and amide VI bands (mainly ρNCO), which appear respectively in the 850–650 cm^{-1} and 500–350 cm^{-1} region. Both deformations are described as localized frequencies and appear in a broad region with rather variable intensity. These bands are, considering the region and variable profile, not very useful for diagnostic purposes.

The amide VII band, described as an out-of-plane deformation of the NCO group, is located in the 500–400 cm^{-1} region and is also not a characteristic band.

The νNR, δNR and πNR modes are strongly dependent on the mass and electronegativity of the substituent and can consequently not be classified as typical *trans*-secondary amide bands.

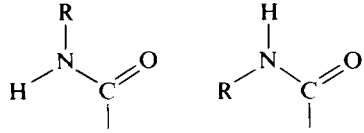
The νND appears at about 2450 cm^{-1} for the deuterated products; the amide I′ is situated at lower frequency ($\Delta \approx 20$ cm^{-1}) compared with the amide I band. As there is no coupling between δND and νCN in the deuterated compounds, we observe the more pure vibrations in the deuterated compound.

The amide II′, exhibiting high νCN character, is located in the 1450 cm^{-1} region as less intense in infrared and more intense in Raman, compared with the intensity of the amide II band. The nature of this band is very complex and can best be described as a typical zone frequency.

The amide III′ band is observed at 950 cm^{-1} as a typical broad and rather strong infrared band, while it appears less intense in Raman.

The πND (amide V′) is situated in the 550 cm^{-1} region as a typical broad band of medium to strong intensity in infrared and sometimes undetectable in Raman.

Cyclic amides such as diketopiperazines and δ-valerolactame exhibit the *cis*-secondary amide group.



trans *cis*

The main vibrational difference between these two isomers is the fact that the νCN and δNH modes appear as more pure vibrations, respectively in the 1460 cm^{-1} and 1360 cm^{-1} region. The force field and the character of these *cis*-secondary amide bands has been fully investigated.

The νNH and νCO for the *cis* structures are generally situated at lower frequency, while the opposite is observed for the πNH mode. This is explained by the great interaction force constants obtained between the CO and NH modes in the *cis*-configuration[49].

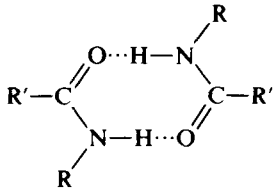
Jones and Smith[50] studied the geometrical isomerism of the secondary non-cyclic amide group in very dilute solutions and observed predominantly *trans* configurations. A very small percentage of the *cis* isomers has also been observed. The νNH *trans* appears in the range 3490–3450 cm^{-1} and weak bands or shoulders due to the νNH *cis* are found about 40 cm^{-1} lower in frequency.

The abundance of *cis* and *trans* isomers of the amide group depends mainly on the size of the neighbouring alkyl substituents. Steric interaction between the *N*-alkyl

substituent and the carbonyl oxygen atom appears to be the reason that some of the molecules have some *cis* character. However when the *N*-alkyl substituent becomes sufficiently large (*t*-butyl) an additional steric interaction takes place between the *N*-alkyl group and the alkyl group on the α-position of the secondary amide, and the molecule then reverts to the *trans* form.

At higher concentrations, in addition to a band of an intermolecular *trans*-amide there is also a distinct band corresponding to the dimer of a *cis*-amide[51] (Scheme 7). In cyclic amides such as lactams $(CH_2)_nCONH$ with $n < 7$, the CONH group is constrained to adopt the *cis* configuration. For $n = 7$, the two isomers coexist in comparable proportions and for $n > 7$ the *trans* configuration is predominant. Thio analogues exhibit similar conformational equilibria[52] but they consistently absorb at lower frequencies.

The typical fundamentals for the secondary amide group are shown in Table 9.



SCHEME 7

3. *Tertiary amide*

Vibrational force fields have been calculated for simple tertiary amides such as dimethylformamide[53,54], dimethylacetamide[55,56] and dimethylcyanoformamide[57] and only a few bands are really characteristic for this functional group.

The νCO appears as a strong band in infrared and of medium intensity in Raman. Here the low frequency is due to the mass effect, as the νCO can best be described as

TABLE 9. Typical fundamentals for the secondary amide function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νNH	3300	v.s.	w.	99 νNH
νCO (I)	1600	v.v.s.	m.	65 νCO, 25 νCN, 10 δNCO
δNH (II)	1550	v.s.br.	v.s.	50 δNH, 30 νCN
νCN (III)	1250	v.s.	v.v.s.	40 νCN, 30 δNH
δNCO (II)	850–600	m.s.	m.w.	50 δNCO, 30 νRN
πNH (V)				90 πNH, 10 πNCO
ρNCO (VI)	500–350	m.s.	m.w.	70 ρNCO, 10 δNCO
νR—N	1150	m.	w.	50 νRN, 20 νCN, 20 δNCO
νND	2450	v.s.	m.	94 νND, 4 νCN
νCO (I')	1645	v.v.s.	m.	64 νCO, 20 νCN, 15 δNCO
νCN (II')	1450–1480	v.s.	v.s.	40 νCN, 15 νCO, 15 νNR
δND (III')	950	s.	v.s.	85 δND, 10 νNR
δNCO (IV')	730–600	m.s.	m.w.	50 δNCO, 20 νRN, 10 ρNCO
πND (V')	550	m.br.	w.br	90 πND, 10 πNCO
ρNCO (VI')	530–450	m.s.	m.w.	70 ρNCO, ωδNCO
νR—N	1150	m.	w.	50 νRN, ωνCN, 20 δNCO

TABLE 10. Typical fundamentals for the tertiary amide function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νCO	1660	v.s.	m.	60 νCO, 30 νCN
νCN	1500	m.	m.s.	40 νCN, 20 νCO, 30 δ CH
	1400			
ν_{as}RNR	1250	s.	w.	80 ν_{as}RNR, 10 δNCO
ν_{s}RNR	800–750	s.	v.s.	50 ν_{s}RNR, 20 δNCO, 20 νCC
δNCO	650	m.s.	m.	50 δNCO, 40 δRNR
ρNCO	350	m.s.	m.w.	50 ρNCO, 20 δRNR, 20 δNCO
πCO	500–400	m.	m.w.	40 πCO

the ν_{as}NCO. The substitution of hydrogen by alkyl groups increases the masses on the nitrogen, so the νCO is observed at the highest frequency for the primary amide group (1680 cm^{-1}) and at a clearly lower frequency (1660 cm^{-1}) for the tertiary amide group.

The spectral region in the 1480–1380 cm^{-1} region is largely dominated by the CH deformations. The νCN (amide) strongly mixes with these deformations and can hardly be detected in the infrared spectrum. In the Raman spectrum, however, one can clearly assign the most intense polarized band appearing in this region to the νCN amide mode.

The intense infrared band situated at about 1250 cm^{-1} has mainly ν_{as}RNR character and the intense Raman band appearing in the 800–750 cm^{-1} region has mainly ν_{s}RNR character. These bands are only slightly influenced by the mass effects of the alkyl group. These bands decrease by about 20 cm^{-1} when methyl is substituted by ethyl, while further decrease in frequency by increasing the mass of the alkyl group is very small.

The deformation modes appearing in the 650–350 cm^{-1} region are all strongly coupled vibrations; the δNCO and ρNCO modes can be polarized, while the πNCO (better described as πCO) is not polarized.

The typical fundamentals for this tertiary amide group are given in Table 10.

1. The Thioamide Function

1. Primary thioamide

The characterization of the thioamide bands and their use for diagnostic purposes have been the subject of numerous papers, and the result of the various authors are frequently in disagreement, even for the simplest thioamides. For example, the wide variation in the assignment of the νCS mode undoubtedly arises from vibrational coupling. Various studies of some thioamides did not lead to any useful characterization and correlation[58–60]. A complete vibrational analysis and comparison of several simple thioamides has been worked out and a model for characterization of thioamides has been proposed[61].

In the infrared spectra three bands are generally observed in the NH_2 stretching region, situated at slightly lower frequency compared with the primary amides. The band exhibiting the highest frequency is assigned to the $\nu_{as}NH_2$, while the two lower bands are due to Fermi resonance of the $\nu_{s}NH_2$ and the first overtone of δNH_2[62]. It has also been observed[61] that the infrared intensity ratio $\nu_{as}NH_2/\nu_{s}NH_2$ is a good measure for the conjugation in the molecule. Thus, for example, in dithiooxamide[63] and in cyanothioformamide[64] both bands appear with the same intensity. This conjugation is observed especially for molecules where the functional group linked to the thioamide group and the thioamide groups are coplanar, or almost coplanar. This coplanarity is strongly reflected in the high νCC value observed in these conjugated molecules[63]. Highly

conjugated molecules containing a thioamide function are often coloured, and resonance Raman effects can strongly influence the intensity of the Raman bands.

The δNH_2 modes at 1600 cm^{-1} always appears as an intense and rather broad band in the infrared spectrum and can be regarded as a very good diagnostic band for the identification of the primary thioamide group. For the primary amides, the δNH_2 appears rather weak and can sometimes not be detected due to overlapping with other bands.

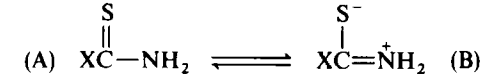
The other NH_2 modes appear with variable intensity. They are not typical and can be compared with the bands of the primary amides. The ρNH_2 is situated in the 1230–1130 cm^{-1} region while the ωNH_2 and the more intense τNH_2 are situated in the 750–600 cm^{-1} region.

In the context of the possible non-planarity around the nitrogen atoms, the following remark should be made regarding the out-of-plane assignments of the NH_2 group. Non-planarity around the nitrogen atom results in a double minimum potential for the wagging mode[65], so obviously in this case the vibrational levels are split. Consequently, the wagging mode should appear as a doublet with different intensities. In most infrared spectra one intense and one weak band are observed in this 750–650 cm^{-1}, which are generally described as the wagging and twisting modes. However, it may be possible that both are wagging modes split by a strong anharmonic double minimum potential. In such cases we must accept that the twisting mode is overlapped or appears too weak to be detected in infrared. These out-of-plane modes are generally too weak to be observed in the Raman spectra.

Frequencies ranging from 1570 cm^{-1} to 850 cm^{-1} have been attributed to the stretching frequencies of the NCS group in thioamides. The extreme variations in the spectra, and consequently in the assignments, are undoubtedly due to different vibrational coupling in the functional group and fundamentals of the rest of the molecule. A band appearing in the 1400 cm^{-1} region, shifting to higher frequency on deuteration, shows a variable profile and intensity in infrared and Raman. Force-field calculations indicate that the highest contribution in this complex vibration is due to νCN, but strong coupling must be considered with δNH_2 and νCS, other fundamentals of the primary thioamide group.

In most of the systems, the νCS is not localized and important contributions of νCS have been calculated for bands appearing in the region 1200 cm^{-1} to 600 cm^{-1}. The most important coupling is with the δNCS and νCC modes. Especially the last coupling is different for molecules exhibiting some conjugation and consequently a higher νCC. This partially explains the broad region of bands with high νCS character. In the 900–700 cm^{-1} region no infrared bands are really diagnostic, but the Raman spectra often exhibit intense bands due to the coupling of the νCC and νCS modes; these bands are polarized and can easily be used for identification.

The δNCS mode always appears in the 700–600 cm^{-1} region as an intense Raman band. The narrow profile of the band allows one to distinguish between this mode and the broad NH_2 out-of-plane motions. The relatively high νCN and low νCS values obtained in thioamides, compared with the region of the $\nu C{=}S$ double bond ($\approx$ 1200 cm^{-1}) and the νCN single bond ($\approx$ 1100), is explained by assuming considerable ionic contribution (B) in the real structure.



This high contribution of the polar resonance form B is also reflected in the higher dipole moment for thioamides compared with amides[66]. Amine salts exhibiting the NH^+

TABLE 11. Typical fundamentals for the primary thioamide function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
$\nu_{as}NH_2$	3300	v.s.	w.	99 $\nu_{as}NH_2$
ν_sNH_2	3150	variable	m.	98 ν_sNH_2
δNH_2	1600	v.v.s.	m.	70 δNH_2, 30 νCN
ρNH_2	1130–1230	m.s.br.	v.w.	60 ρNH_2, 15 νCS
νCN	$\approx$1400	variable	variable	40 νCN, 20 δNH_2, 20 νCS
νCS	950–800	m.s.	s.	50 νCS, 30 νCC, 15 δNCS
δNCS	700–600	m.	v.s.	70 δNCS, 20 νCS
ρNCS	550–400	m.	s.	60 ρNCS, 20 δNCS
ωNH_2	750–640	w.br.	—	70 ωNH_2
τNH_2	750–650	s.br.	—	70 τNH_2

group all give rise to very low $\nu(NH^+)$ stretching modes in the 3000 cm^{-1} region. The high contribution of the polar resonance form B in thioamides also explains the lower values ($\Delta \approx 100\ cm^{-1}$) of the NH_2 stretching modes compared with the primary amides. These shifts are not dependent on hydrogen bonding.

For the deuterated compounds, the νCN appears at higher frequency and exhibits more νCN character. The spectrum is consequently different from the normal spectrum in the 1200–800 cm^{-1} region, due to different coupling especially with δND_2 and ρND_2 modes. For example, the δND_2 appears as an intense Raman band at 1230 cm^{-1} in the spectrum of dithiooxamide, where the intensity is due to the high coupling especially with the νCC in this conjugated molecule. The ρND_2 appears in the same region as the νCC and νCS modes and strong coupling is also observed. So we can conclude that deuteration of primary thioamides, in order to characterize the functional group, is of very limited use.

The typical fundamentals for the primary thioamide group are given in Table 11.

2. *Secondary thioamide*

The nature of the secondary thioamide function has been fully investigated in several papers[61,67–69] and the typical bands can be designated as Thioamide I, II, ... bands in analogy with the amide bands[70].

The νNH generally appears at lower frequency (3200 cm^{-1}) compared with the amide: this is explained by assuming a greater contribution of the polar resonance form in the thioamide group[71].

The most intense infrared band in the 1550 cm^{-1} region is of medium intensity in Raman and shifts only slightly to lower frequency on alkyl and ND substitution. This band decreases in frequency in organic solvents and increases in frequency on complexation with soft acids, which are strongly coordinated to sulphur. This typical band, called the Thioamide I band, has high νCN character.

The δNH mode (Thioamide II band) is for all CH_3 derivatives assigned to an intense and broad band in infrared and of medium intensity in Raman. For the CD_3 derivative and other alkyl substituents, this band is observed at about 1400 cm^{-1}. The frequency difference of about 50 cm^{-1} observed for all CH_3 derivatives in the normal products is due to coupling with the δCH_3 modes (the CH_3 group on the nitrogen of the thioamide). The fact that for the deuterated CH_3 compounds the same band profile in the 1380–1470 cm^{-1} region as for the amides is observed (this profile is completely different for the normal CH_3 products) allows us to conclude that for all CH_3 derivatives a considerable coupling with the δCH_3 must be considered[72]. The δND appears as a relatively broad band of variable intensity in the 1000–850 cm^{-1} region. Both the

TABLE 12. Thioamide I and νNR values for KOOCCSNHR

KOOCCSNHR	Thioamide I (cm^{-1})	νNR (cm^{-1})
NH CH_3	1530	1170
ND CH_3	1510	1150
NH CD_3	1517	1141
ND CD_3	1504	1130
NH C_2H_5	1523	1154

variable intensity and the wide region indicate strong coupling with the νCS and νCC modes also appearing in this region. The δNH/δND ratio also indicates that these vibrations are not very pure, which is unexpected considering the low mass of the hydrogen atom.

Secondary thioamides all exhibit two very intense Raman bands in the 650–1100 cm^{-1} region, indicating strong coupling between the νCC and νCS modes. For molecules, exhibiting some conjugation, the band with the highest νCC character is located at the highest frequency, while the lowest band situated in the 850 cm^{-1} region has a high νCS character, increases in frequency in solution and decreases on complex formation with soft acids such as Ag^+, Pt^{2+} and Pd^{2+}. This characteristic Thioamide III band has high νCS character.

The Thioamide IV (δNCS) and Thioamide VI (ρNCS) bands are for all secondary thioamides identified as rather intense polarized bands in the Raman spectra in the 700–400 cm^{-1} region.

The typical πNH (Thioamide V) appears as an intense and broad infrared band in the 700 cm^{-1} region, and is practically undetectable in the Raman spectra. The πND is situated at about 530 cm^{-1}, indicating very pure vibrations considering the πNH/πND ratio.

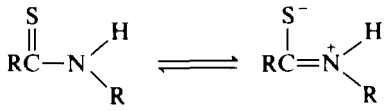
The bands assigned to the νNR modes always appear in the 1170–1120 cm^{-1} region. The influence of H/D substitution and alkyl substitution on the Thioamide I and νNR mode in KOOC–CSNHR is given in Table 12.

The changes in frequency in the solid state and in solution, for disubstituted dithiooxamides with general formulae RHNCSCSNHR, cannot be due to changes in hydrogen bonding, as all secondary dithiooxamides exhibit strong intramolecular hydrogen bonds[68,73] (Table 13). These changes from the solid state to solution of the

TABLE 13. Thioamide bands of RHNCSCSNHR in different aggregation states

	R	Solid (cm^{-1})	CCl_4	$CHCl_3$	Dioxane
Thioamide I	CH_3	1540	1535	1535	1533
	C_2H_5	1533	1529	1528	1525
	Liq. C_3H_7	1520	1520	1518	1516
Thioamide II	CH_3	1355	1360	1361	1351
	C_2H_5	1392	1390	1389	1385
	Liq. C_3H_7	1400	1400	1400	1395
Thioamide III	CH_3	870	880	878	—
	C_2H_5	832	841	842	841
	Liq. C_3H_7	895	900	829	900
Thioamide IV	CH_3	693	680	687	700
	C_2H_5	712	688	688	700
	Liq. C_3H_7	711	699	699	703

different thioamide bands are due to the high contribution of the polar resonance form B in the solid state.



The small difference in the δNH and πNH modes clearly proves the intramolecular hydrogen bonds in these compounds.

The typical fundamentals for the secondary thioamide group are given in Table 14.

3. *Tertiary thioamide*

The nature of the fundamental vibrations of the tertiary thioamide group is very complex and only a few bands can be described as characteristic for this group.

The most intense bands in infrared appear at 1550 cm^{-1}, are weak in Raman and exhibit high νCN character since these bands shift to higher frequency on coordination with soft acids. Another intense infrared band in the 1250 cm^{-1} region practically does not change in intensity and frequency in solution and when coordinated to soft acids. This band is of medium intensity in Raman and has high ν_{as}RNR character.

Very strong coupling effects have been calculated for the νCC, νCS and ν_sRNR modes in the 1000–700 cm^{-1} region[74]. None of these bands is really characteristic for the tertiary thioamide group, since they appear with different profiles at different frequencies. The band with the highest νCS character shifts to considerably lower frequency on coordination with soft acids. This band also shifts ($\Delta \approx 10\ cm^{-1}$) to higher frequency in solution and is polarized in the Raman spectra.

Two intense Raman bands, mainly with δNCS and ρNCS character, arise respectively in the 550–500 cm^{-1} and 500–350 cm^{-1} region and can also be described as characteristic for the tertiary thioamide group.

The typical fundamentals for the tertiary thioamide group are given in Table 15.

J. Other Thio Compounds

1. *Thiols*

The νSH mode appears in the 2550 cm^{-1} as a weak band in infrared and rather intense in Raman. Since the νSH is practically the only fundamental appearing in this region, this band is easy to identify and consequently very characteristic.

TABLE 14. Typical fundamentals for the secondary thioamide group

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νNH	3200	s.	m.	98 νNH
δNH (II)	1350–1400	s.br.	w.	60 δNH, 20 νCN, 15 δCH
νCN (I)	1550	v.vs.	m.	60 νCN, 10 δNH
νCS (III)	950–800	m.s.	v.s.	50 νCS, 25 νCC, 20 δNCS
δNCS (IV)	700–550	m.w.	v.s.	50 δNCS, 15 νCS, 15 νCC
πNH (V)		v.s.	v.w.	80 πNH
ρNCS (VI)	550–400	m.w.	s.	70 ρNCS, 15 δNCS

TABLE 15. Typical fundamentals for the tertiary thioamide group

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νCN	1550	v.s.	m.	75 νCN, 15 ν_sRNR
ν_{as}RNR	1250	s.	w.	80 ν_{as}RNR, 10 νCN
ν_sRNR	900–800	var.	m.-s.	40 ν_sRNR, 30 ν_sRNR, 20 νCC
δNCS	550-550	m.s.	v.s.	60 δNCS, 15 ρNCS, 20 δRNR
ρNCS	350-500	m.	s.	50 ρNCS, 20 δNCS, 20 ρRNR

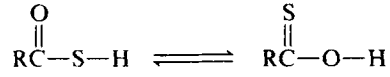
The fundamental with high νCS character is situated in the 700 cm^{-1} region and appears as a medium intense infrared and rather strong Raman band. The band with high δSH character is identified as a medium intense band in infrared and Raman and is situated in the 1000–900 cm^{-1} region.

The characteristic bands and average P.E.D. values for this group are given in Table 16.

2. Thio acids

Vibrational spectra of thio and dithio acids have not attracted much attention in the past. Fausto and coworkers[75] studied the conformers of thioformic and dithioformic acid and a high degree of vibrational coupling has been calculated, especially for the fundamentals occurring in the lower frequency region.

These thio compounds show some resonance Raman effect, and the intensity of the bands in the Raman spectra can vary according to the wavelength of the laser line. Generally CS fundamentals appear rather intense in Raman due to the higher polarizability of sulphur compared with oxygen. Monothiocarboxylic acids exist as a tautomeric mixture of thiol and thione forms.



In general, the thio structures predominate over the thione forms[76]. In acids one can consider several resonance forms:

The contribution of resonance form B is higher when X is sulphur compared with oxygen, so the νCO in thiols is situated at slightly lower frequency than the carbonyl band in carboxylic acids.

TABLE 16. Typical fundamentals for the thiol function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
νSH	2590–2550	w.	v.s.	98 νSH
νCS	700–600	var.	s.	40 νCS, 30 νCC, 20 δSH
δSH	1000–900	m.	m.	50 δSH, 30 νCS

TABLE 17. Typical fundamentals for thioacid and dithioacid functions

RCOSH			RCSSH		
Fundamental	Region (cm^{-1})	P.E.D.	Fundamental	Region (cm^{-1})	P.E.D.
νSH	2550	98 νSH	νSH	2500	98 νSH
νCO	1660	80 νCO	νC=S	120–1000	50 νC=S, 30 νC—S
δSH	1000–900	60 δNH, 20 νCS	δSH	1050–950	40 δSH, 20 C=S, 20 C—S
νCS	700	50 νCS, 20 δSH, 20 δOCS	νC—S	700	50 νC—S, 30 δSCS
δOCS	400–500	60 δOCS, 20 νCS	δSCS	400–300	40 δSCS, 30 νC—S

The νSH appears as a typical band in the 2540 cm^{-1} region. Another band which is not very characteristic for the thioacid group arises in the 1000 cm^{-1} region. This band disappears on deuteration and has high δSH character. Two other bands at about 700 cm^{-1} and 450 cm^{-1} have high νCS and δOCS character and are also not very characteristic.

The fundamentals in dithio acids are all strongly coupled. The νSH appears at lower frequency for the dithio acids compared with the thio acids, in the region 2500 cm^{-1}. This band is the only diagnostic band in the high-frequency region. The rather intense infrared band arising in the 1000–1100 cm^{-1} region entails high νC=S character. A broader band at slightly lower frequency at about 950 cm^{-1} disappears on deuteration and has high δSH character. The νC—S single bond and the δSCS mode are situated respectively in the 700 cm^{-1} and 350 cm^{-1} region. These bands are strongly coupled vibrations, also with other functional groups. The typical thioacid fundamentals are shown in Table 17.

3. Thiol esters

Thiol esters all exhibit the carbonyl modes at lower frequency ($\approx$1675 cm^{-1}) compared with the normal esters[77]. This is due to the higher contribution of resonance form B in the thiol esters.

$$\text{(A)}\quad RC(=O)-X-R' \rightleftharpoons RC(-O^{-})=X^{+}-R' \quad \text{(B)}$$

The other stretching modes all have a very complex character and are not useful for diagnostic purposes.

K. Aldehyde and Ketone Functions

The νCO appears very intense in infrared and less intense in Raman in the 1720 cm^{-1} region and the introduction of halogens into the α-position results in an increase in this mode (CF_3CHO νCO 1770 cm^{-1})[78], Fermi resonance exists between the aldehyde νCH and 2 δCH[79] and these bands appear respectively in the 2820 cm^{-1} and 2720 cm^{-1} region. The lower band appears more strong in the Raman spectra, while the highest band is often obscured by other CH stretching modes. Since aldehydes with a large variety of side groups give rise to the same doublet caused by Fermi resonance, we can consider these two bands as typical aldehyde bands.

TABLE 18. Typical fundamentals for the aldehyde and ketone function

Fundamental	Region (cm^{-1})	IR	Raman	P.E.D.
Ketone function				
νCO	1720	v.s.	s	70 νCO
ν_{as}CO(O)C	1160–1120	m.s.	w	40 ν_{as}CC(O)C
ν_{s}CO(O)C	800–700	m	s	40 ν_{s}CC(O)C + 40 νCC
Aldehyde function				
νCO	1730	v.s.	v.w.	70 νCO
νCH	2820	—	v.w.	—
Fermi reson.	2720	w	m	—

Other aldehyde vibrations such as δCO and πCO modes are very sensitive in frequency and intensity to branching on the alkyl group and to electronegativity effects and cannot be regarded as typical for the CHO group.

The πCH appears very weak in the 900–700 cm^{-1} and is hence useless for correlation purposes.

The νCO appears at slightly lower frequency for ketones and is practically the only characteristic band. Other less useful bands appear in the 1150 cm^{-1} (ν_{as}COC) and 800 cm^{-1} region (ν_sCOC).

The typical bands for ketones and aldehydes are given in Table 18.

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CHAPTER 8

Acid–base properties of carboxylic acids, esters and amides

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I. GENERAL INTRODUCTION

One of the most important features of physical organic chemistry is to relate energy differences between molecules with changes in molecular structure and properties. Acid–base equilibria constitute a substantial part of data suitable for such correlations, and high precision measurements were carried out for large series of organic compounds.

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The simple relation between the logarithm of the ionization constants and the free energy of the reaction provides data sets convenient for the creation of substituent effect theories.

A most fruitful and seminal theory in physical organic chemistry, which links together acid–base equilibria and substituent effects, was elaborated by Hammett[1] and is known as the Hammett equation or Linear Free Energy Relationship (LFER). Very soon LFER exploded into a variety of simple and multicomponent correlation equations, which relate equilibrium constants to discrete sets of substituent constants responsible for inductive, mesomeric, steric, field and other effects. Beyond thermodynamic correlations, various extrathermodynamic correlations emerged supported by important work by Leffler and Grunwald[2].

New studies give additional and more detailed information, and thus exploration of new domains became possible. Thus, the influence of solvent composition, temperature, intramolecular hydrogen bonding and conformational equilibria on simple dissociations has been explored. In many cases, a second ionization process is possible in a more acidic or a more basic environment. Moreover, very important information could be gained from gas-phase acid–base equilibria, in which all phenomena concerning solute–solvent interactions are absent. Extrathermodynamic relationships utilizing IR, NMR and other data, and relative acidity or basicity parameters studied by indirect methods also add a huge amount of information on acid–base equilibrium phenomena.

The acidity of the carboxyl group was reviewed in this series a long time ago[3]. Hydrogen bonding of the carboxyl group[3,4] and of derivatives of carboxylic acids was described[4]. Acid–base properties of amides[5] and acid chlorides[6] were also summarized twenty years ago.

The purpose of this chapter is to focus attention on more recent studies about acidity–basicity equilibria and complex formation of carboxylic acids, esters, and amides.

II. EQUILIBRIUM CONSTANTS

Most organic compounds are weak acids and/or weak bases. Among the many chemical equilibria, proton transfer continues to attract a great deal of attention. The main reasons for this are: the unique role of proton in chemistry, the wide occurrence of proton transfer processes, the possibility of studying hydrogen isotope effects, the relationships existing between kinetic and/or equilibrium data for families of similar compounds, the relationships between reactivity and structure, the effect of solvents on proton-transfer reaction and recent studies on gas-phase proton-transfer reactions.

The rates of proton-transfer reaction in a somewhat arbitrary classification are fast, slow or very slow. Our attention will be devoted to slow reactions, for which appropriate equilibrium constants can be defined and measured by experiment.

The definition of weak bases or weak acids used in this chapter is that of Bronstedt[7]: A weak organic acid is a compound which liberates a proton and produces a negative ion (equation 1). Any compound that contains a carbon–hydrogen bond or an oxygen–hydrogen bond is a potential acid. For aqueous media one can compare relative acid strengths by examining equilibrium constants (equation 2). If reaction 1 proceeds almost to completion, we can say that the acid AH is much stronger than water (solvent). The larger the numerical pK_a value ($= -\log K_a$), the weaker the acid (Figure 1). A

$$AH + H_2O \rightleftharpoons A^- - H_3O^+ \tag{1}$$

$$K_a = \frac{[A^-][H_3O^+]}{[AH][H_2O]} \tag{2}$$

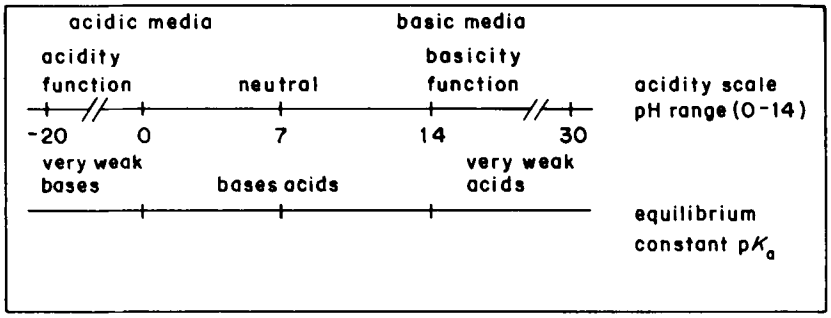


FIGURE 1. Medium acidity and acid and base strength

number of acidic compounds ionize in dilute alkaline media so effectively that the concentration of anions $[A^-]$ can be measured, and appropriate pK_a values can be evaluated. The state of equilibrium, however, lies far to the left for many varieties of organic compounds, and their weak acidic properties cannot be observed and detected in water. In such cases more concentrated alkaline solutions, or even very basic solutions, are necessary to remove the proton from the organic molecule:

$$AH + OH^- \longrightarrow A^- + HOH \tag{3}$$

to obtain measurable concentration of $[A^-]$. The term *weak acids* or *pseudoacids* are then usually applied[8].

On the other hand, a weak organic base is a compound having a lone electron pair(s) to which a solvated proton can be attached and a positive species or ion thus formed (equation 4),

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O \tag{4}$$

$$K_b = \frac{[BH^+][H_2O]}{[B][H_3O^+]} \tag{5}$$

In aqueous media we can compare the base strengths by examination of the equilibrium (equation 5) for reaction 4. If the reaction proceeds almost to completion, the base is much stronger than water or solvent. For many organic compounds, however, the equilibrium lies far to the left, and their basic properties cannot be observed and detected in water. A number of compounds react with solvated protons in acidic media of various concentrations so effectively that the concentration of the positive species can be measured, and $pK_b (= -\log K_b)$ can be calculated. Such compounds are known as *weak bases*. The atoms having lone electron pairs are most frequently nitrogen and oxygen. Oxygen bases are weaker than nitrogen bases of similar structure due to the higher electronegativity of oxygen. The structure of the resulting organic cations is very varied and, as the final structure, a carbonium ion is formed.

The strengths and structures of weak bases have been investigated and reviewed to a greater extent than that of weak acids. Investigations of weak bases have been mainly conducted in solutions of strong acids (sulphuric, perchloric) and even in so-called superacids in which further chemical reactions of the cationic species are arrested. On the other hand, weak acids have been studied mainly in solutions of strong bases and even with addition of DMSO to increase the strength of the basic medium.

The measure of acidity which results from autodissociation of water molecules

$$HOH = H^+ + OH^- \tag{6}$$

is useless in solutions of strong acids (HCl, H_2SO_4, $HClO_4$) or in solutions of strong bases (NaOH, KOH). Even so, numerous organic acids and bases can be studied by a variety of experimental methods.

In general, two approaches have been developed to describe medium effects in strong acids or bases. One of them was introduced by Hammett[9] and established the acidity function H_0 as an extension of the pH scale. It was believed that acidity functions as in equation 7, where c_{H^+} is the acid concentration and the quantities f are the activity coefficients, provide a quantitative measure of the tendency of the medium to protonate the organic base. It was found later that the acidity of the medium depends also on the chemical nature of the base, due to solvation[10],

$$H_0 = -\log c_{H^+} - \log(f_B f_{H^+}/f_{BH^+}) \tag{7}$$

For various classes of organic bases, different acidity functions have been introduced and reviewed[11]. While originally an impression of great complexity of the acidity function concept was created[12], new results derived from characteristic vector analysis of acidity functions for various strong acids indicate linearity among them[13]. In other studies, the medium effect on pK_{BH^+} is separated from the changes in $[H^+]$ to define an excess acidity function[14]. The concept of acidity function stressed water as a standard state for equilibrium measurements and the extrapolation of aqueous pK_{BH^+} data from ionization measurements in highly non-aqueous acidic media.

The second approach was developed by Bunnett and Olsen[15] on the basis of linear free energy relationships, and leads to the fundamental equation

$$\log K/K_0 = (1 - \phi)(H_0 + \log c_{H^+}) \tag{8}$$

Bagno and Scorrano[16] have reviewed previous studies and tend to explain acidity dependences in terms of LFER medium effects. In strongly acidic solutions the basicity depends on two factors, reflecting stabilization of the cation by internal charge delocalization and solvation (or, more frequently, hydration). There is competition between the organic cation BH^+ and H_3O^+ to find the number of water molecules necessary for hydration. The hydrogen ion is extremely solvent-dependent for the stabilization of its positive charge. Increasing the concentration of the acid decreases the number of water molecules available to solvate H_3O^+. Concentration profiles of various species present in sulphuric acid were investigated and help us to understand the role of water[17,18]. Despite the important role of water as the agent solvating both H_3O^+ and BH^+, its concentration is omitted in the thermodynamic pK_{BH^+} equation.

In contrast to numerous and varied studies carried out in concentrated solutions of strong mineral acids, relatively few investigations have been reported in highly basic media[19], such as solutions having concentrations of sodium hydroxide up to 12 M in water or in non-aqueous solutions[11,20] and by addition of dipolar aprotic solvents[11]. Hydroxide ion is the strongest base that can exist in water. The number of water molecules usually hydrating each OH^- is between 3 and 6[21]. Dipolar aprotic solvents, such as DMSO, added to aqueous alkaline media will increase the basicity by desolvating OH^- ions[22]. Other solvents of this type are sulpholane and HMPA.

Producing highly basic media in this way, basicity can be varied continuously over a wide range, ion association is reduced or absent and the concentration of the base remains constant.

The acidity function concept has been adapted to describe the basicity of media. The acidity function H_- for an electrically neutral weak acid in reaction

$$AH + OH^- \rightleftharpoons A^- + H_2O \tag{9}$$

is defined as follows:

$$H_- = -\log a_{H^+} \frac{f_{A^-}}{f_{AH}} = -\log \frac{K_w a_{H_2O}}{a_{OH^-}} \frac{f_{A^-}}{f_{AH}} \tag{10}$$

In this equation f_{A^-} and f_{AH} are the activity coefficients of the anion and acid, respectively, and K_w is the dissociation constant of water.

III. pK_a CALCULATION FROM EXPERIMENTAL DATA SETS

A. Single-step Protolysis in the pH Region

Equations 1, 3 and 4 describe various single-step protolysis reactions commonly met in organic chemistry. Such reactions are most conveniently followed by spectrophotometric or potentiometric titration[23]. At every stage of titration, proton-transfer equilibria are established very rapidly (e.g., equation 1), and relationships exist between the pH and the concentrations of various species. The equilibrium constant could be expressed by equation 2 or 11,

$$K_1 = a_{H^+} \frac{a_{A^-}}{a_{AH}} \tag{11}$$

where K_1 is the dissociation constant for a single-step reaction and the a values represent the activities of ions and molecules.

Solving for the concentration of organic species (assuming that the activity coefficient equals one in dilute solution), and assuming that only A^- and AH absorb electromagnetic radiation in agreement with absorption laws, one can express the equilibrium constant as

$$K_1 = a_{H^+} \frac{A - A_{AH}}{A_{A^-} - A} \tag{12}$$

or

$$pK = pH - \log \frac{A - A_{AH}}{A_{A^-} - A} = pH - \log I \tag{13}$$

where A is the absorbance of the mixture of ionized and unionized species. The equilibrium constant pK could be computed from the above equation or evaluated by a graphical procedure. When plotting $\log I$ vs pH one will obtain a straight line. pH for $\log I = 0$ is equal to pK (see Figure 2).

Equation 13 could be applied for numerical evaluation of pK, especially if A_H and/or A_{A^-} are not precisely known, or are not experimentally accessible. After the necessary mathematical rearrangement the following equation:

$$A = \frac{A_{AH} a_{H^+} + A_A k}{a_{H^+} + K} C \tag{14}$$

contains three unknowns, A_{AH}, A_{A^-} and K which could be computed[24,25]. Various other methods to find the pH value at the inflection point of a typical titration curve (Figure 3), have been proposed[23].

It is possible to determine dissociation constants using only optical data in the absence of pH measurements[26]. This method is restricted to single-step protolysis of very pure and stable compounds.

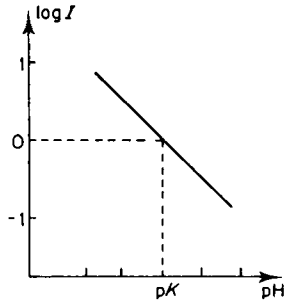


FIGURE 2. Plot of ionization ratio vs acidity

B. Two-step Protolysis in the pH Region

An unbranched two-step protolytic system consists of equilibria of the following forms:

$$AH_2 = AH^- + H^+ \quad \text{and} \quad AH^- = A^{2-} + H^+ \tag{15}$$

The full description of the system needs knowledge of the dissociation constants K_1 and K_2, the quotient K_1/K_2, the absorbances of AH_2, AH^- and A^{2-} and the concentration profiles of all species over the studied acidity range.

If the total concentration of the organic compound studied is a constant C, then

$$C = [AH_2] + [AH^-] + [A^{2-}] \tag{16}$$

and the concentration of individual species is a function of the acidity of the medium a_{H^+}:

$$[AH_2] = \frac{Ca_{H^+}^2}{H}, \quad [AH^-] = \frac{CK_1a_{H^+}}{H}, \quad [A^{2-}] = \frac{CK_1K_2}{H} \tag{17}$$

where $H = a_{H^+}^2 + K_1a_{H^+} + K_1K_2$.

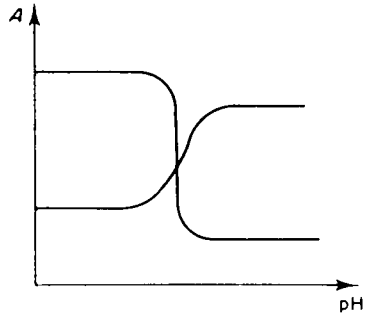


FIGURE 3. Typical titration curves

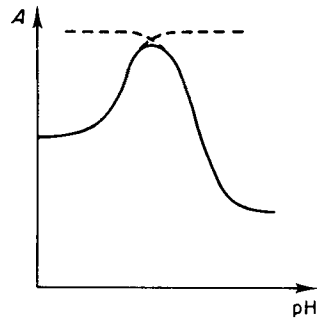


FIGURE 4. Comparison of two theoretical titration curves with the experimental one (solid line)

Finally, the following equation will express the absorbance vs the acidity of the medium:

$$A = C\frac{A_{AH_2}a_{H^+}^2 + A_{AH^-}a_{H^+} + A_{A^-}^2 - K_1K_2}{a_{H^+} + K_1a_{H^+} + K_1K_2} \tag{18}$$

Typical titration curves are presented in Figure 4.

The same equations are applicable for describing potentiometric titration curves. The various methods for pK evaluations have been reviewed[23].

Equation 18 is used in various computer programs to calculate pK_1 and pK_2 and other parameters[27]. In iterative methods of computation, a set of estimated absorbances and dissociation constants is introduced (A_{AH^2}, A_{AH^-}, $A_{A^{2-}}$, K_1 and K_2) and then continuously varied until the theoretical titration curve shows best agreement with the experimental data[27]. Often the 'SPSS' (Statistical package for social science) is used for this purpose[28].

The results allow one to draw dissociation curves, which show the relationship between the concentrations of various species and pH (see Figure 5). Two points of intersection permit the determination of acidity constants:

$$\begin{aligned}[AH_2] = [AH^-] \text{ and } pH = pK_1\\ [AH^-] = [A^{2-}] \text{ and } pH = pK_2\end{aligned} \tag{19}$$

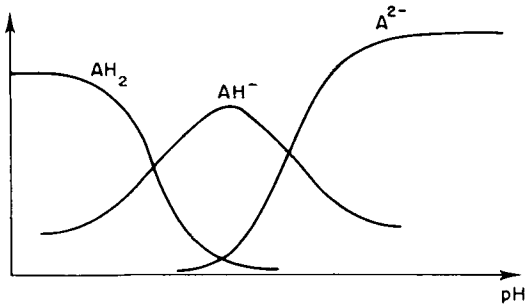


FIGURE 5. Concentrations of species AH_2, AH^- and A^{2-} as functions of pH

and the third one follows the condition

$$[AH_2] = [A^{2-}] \text{ and } pH = \frac{pK_1 + pK_2}{2} \tag{20}$$

The problems and advantages related to two-step and three-step acid–base equilibria were discussed and reviewed elsewhere[23].

C. Protolysis Beyond the pH Region

The above considerations were more or less restricted to the pH region, however various equilibria occur in highly acidic or basic media. The rationalization of the experimental data allows the application of either the acidity function strategy or the free energy strategy.

1. Acidity function strategy (AFS)

AFS applies the equation

$$pK_{BH^+} = H_0 - \log(C_B/C_{BH^+}) = H_0 - \log I \tag{21}$$

to calculate equilibrium constants for protonation reactions. $\text{Log}\,(C_B/C_{BH^+})$ can be calculated from experimental measurements in a set of solvents of various acidity, described by the appropriate acidity functions. The task can be solved by a graphical method or by computation. A plot of $\log(C_B/C_{BH^+})$ vs acidity function is a straight line, and at the equilibrium of $C_B = C_{BH^+}$, $\log I = 0$, and thus $pK_{BH^+} = H_0$. One must be aware that this is true only when the slope of the above plot is unity. If not, it gives only information on the value of H_0 at half-protonation. The acidity function concept was introduced by Hammett[13] for non-charged bases, but subsequently it was discovered that its general applicability is restricted to a given class of bases, and that each class of base follows its own acidity function[14,15,17].

The best acidity function with which to follow the protonation of various —COX groups is the amide acidity function H_A[29], introduced by Yates and Stevens[30]. The slope of the $\log I$ vs H_A plot is very close to unity.

Values of pK_{BH^+} calculated from equation 21 are constant within an experimental error limit only if the appropriate acidity function is applied, otherwise the computed pK_{BH^+} values vary systematically with the acidity. Finding the appropriate acidity function is not very easy, because many different sets are available. Papers by Zalewski[13] and Cox and Yates[11] give a complete set of references to more than 400 different acidity functions for various acids and solvents.

2. Free energy strategy (FES)

FES was developed by Bunnett and Olsen[15] and has been applied widely by Bagno and Scorrano[16]. The fundamental equation 22 fails to stress its LFER character:

$$\log K = (1 - \phi)(H_0 + \log C_{H^+}) + \log K_0 \tag{22}$$

On substituting the value of K, we get

$$\log \frac{C_{H^+} C_B}{C_{BH^+}} = (1 - \phi)(H_0 + \log C_{H^+}) + \log K_0 \tag{23}$$

$$-\log C_{H^+} + \log \frac{C_{BH^+}}{C_B} = (1 - \phi)(H_0 + \log C_{H^+}) + pK_0 \tag{24}$$

and, after rearranging,

$$H_0 + \log \frac{C_{BH^+}}{C_B} = \phi(H_0 + \log C_{H^+}) + pK_0 \tag{25}$$

the value of pK_0 (or pK_{BH^+}) can be found as the intercept of the plot of $[H_0 + \log(C_{BH^+}/C_B)]$ vs $(H_0 + \log C_{H^+})$, and ϕ as the slope. This strategy is particularly important with many acid systems for which only H_0 has been determined.

Recent improvement of the Bunnett–Olsen model supported by the excess acidity function[14] leads to the equation

$$-\log C_{H^+} + \log \frac{C_{BH^+}}{C_B} = m^*X + pK_{BH^+} \tag{26}$$

where pK_{BH^+} is the intercept of the plot of $[\log(C_{BH^+}/C_B) - \log C_{H^+})$ vs excess acidity function X, m^* being the slope[16].

The Bunnett–Olsen treatment of equilibria in mineral acids, as described by H_0, has been compared with the 'excess acidity function' procedure. Both methods give the same results and conclusions[31]. The importance and necessity of describing the protonation properties of weak bases with two parameters (pK_{BH^+}) and ϕ or m^*) is also emphasized[16]. Acidity function strategies provided by H_0 and X acidity functions have been compared[32]. In some cases nearly correct thermodynamic quantities are available from H_0. The excess acidity function method has been compared with the target testing procedure[33].

Both strategies apply to acidic and basic media, as a general rule. The AFS has been applied more frequently in basic media, however the Bunnett–Olsen method has also been accepted[34,35]. The excess acidity function procedure in basic media, e.g. DMSO/KOH[36], has also been used with good results.

D. Thermodynamic Aspects

The ionization constant K is related to the standard free energy of ionization ΔG° through the equation

$$\Delta G^\circ = RT \ln K = -2.3RT\, pK \tag{27}$$

Additional information can be obtained by accurate measurements of equilibrium constants K over a wide range of temperatures and use of the simple van't Hoff equation

$$R \ln K = A + B/T \tag{28}$$

where $A = \Delta S^\circ$ and $B = -\Delta H^\circ$ give mean values for the standard entropy and enthalpy changes for the temperature range examined. The straight line relationship between $\ln K$ and $1/T$ is valid usually in small ranges of temperatures, and in fact is only a part of a curve, which could be expressed by the general multiparameter equation[37,38]

$$R \ln K = A + B/T + C \ln T + DT + ET^2 + FT^3 \tag{29}$$

or a set of various similar equations with less parameters. The dependence of equilibrium constants on temperature (and pressure) has been reviewed recently by Blandamer and coworkers[39], who used computer-based analytical routines and stated that 'there is no universally correct method of analyzing equilibrium and kinetic data'. Each method applying linear or non-linear equations with less or more temperature variables[40,41] has its own constraints and limitations which can lead to different results of ΔH°, ΔS° and

ΔC_p° estimates. Special emphasis of the ΔH° vs ΔS° relationship for reaction series has been used to formulate the iso-kinetic and iso-equilibrium postulate

$$\Delta H^\circ = \beta \Delta S^\circ \tag{30}$$

and to characterize the blend of enthalpy and entropy contributions to the total substituent effect. Krug, Hunter and Grieger[42] indicated that the compensation pattern for ΔH° vs ΔS° data pairs is the usual statistical compensation between regression parameters in the van't Hoff equation. The reason is the usual range of variation of the independent parameter, that of $1/T$. Due to this statistical compensation, a linear relationship ΔH° vs ΔS° does not necessarily imply that a chemical phenomenon is responsible for it. In fact most of such works cited in the literature appear to be indistinguishable from the statistical compensation effect[42]. Distinction of the chemical effects from the statistical ones is possible when plotting ΔH° vs ΔG° evaluated for data pairs in a reaction series, when the harmonic mean could be found from the experimental data in question. This procedure relies on the following assumptions:

(i) Experimental temperatures are measured with much greater accuracy and precision than equilibrium constants.

(ii) The van't Hoff equation is adequate to represent equilibrium data over the temperature range studied.

(iii) The data were measured at the same temperature for the whole reaction series.

(iv) Errors of equilibrium data are normally distributed with zero mean.

These assumptions are commonly accepted and agree with common sense. The fundamental thermodynamic relationship

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{31}$$

at the iso-equilibrium temperature $T = \beta$ could be rewritten[43,44]

$$\Delta H^\circ = \beta \Delta S^\circ + \Delta G_\beta^\circ \tag{32}$$

Thus at temperature γ such that

$$\gamma = \frac{\beta}{\beta - T} = 1/(1 - T/\beta) \tag{33}$$

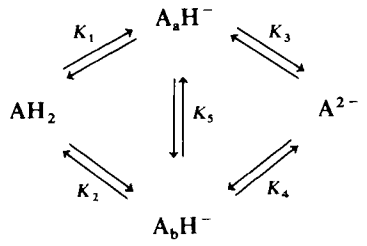
we have

$$\Delta H^\circ = \gamma \Delta G + (1 - \gamma)\Delta G\beta \tag{34}$$

A linear relationship between ΔH° and ΔG should be expected with slope γ. This relationship is superior to ΔH vs ΔS and to ΔS vs ΔG[42].

E. Branched Acid–Base Equilibria

Equilibria involving two or more dissociable groups in one molecule introduce a problem of simultaneous dissociation, or, in other words, branching. There is no simple way to describe the order in which the groups will dissociate. The number of various species existing in a branched dissociable system depends on the number of reacting groups s, and equals 2^s. Only if the dissociating groups are equal, as, for example, in phthalic acid, the problems due to branching disappear. Scheme 1 shows an example with two different dissociable groups where four species are present with four ionization constants K_1 through K_4 and one tautomeric equilibrium constant K_5. The constants K_1–K_4 are called *microscopic dissociation constants*, and they are the equilibrium constants for particular equilibria involving individual species present in solution. When more than one such species exists simultaneously in solution, the microscopic dissociation constant may or may not be determined distinctly. Experimentally determined



$$K_1 = \frac{[A_aH^-][H^+]}{[AH_2]} \qquad K_2 = \frac{[A_bH^-][H^+]}{[AH_2]}$$

$$K_3 = \frac{[A^{2-}][H^+]}{[A_aH^-]} \qquad K_4 = \frac{[A^{2-}][H^+]}{[A_bH^-]}$$

$$K_5 = \frac{K_1}{K_3} = \frac{K_4}{K_3}$$

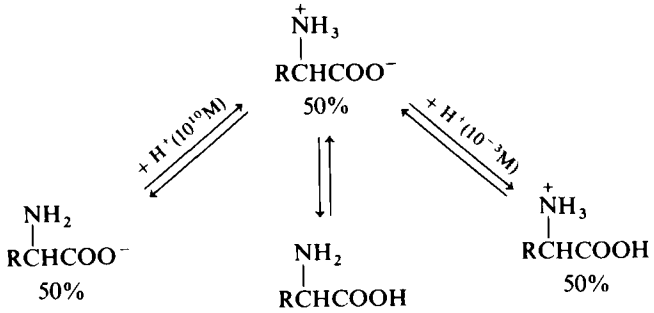
SCHEME 1. Dissociation diagram of a compound with two dissociable groups

protonation constants are named *macroscopic dissociation constants* because the actual sites where the protons reside are not specified and may not be unique. If the two tautomers are treated together as AH^- species, all systems, simplify to an unbranched two-step system (see Section III.B) with two macroscopic dissociation constants. The relationship between the macroscopic and microscopic constants is given by equation 35,

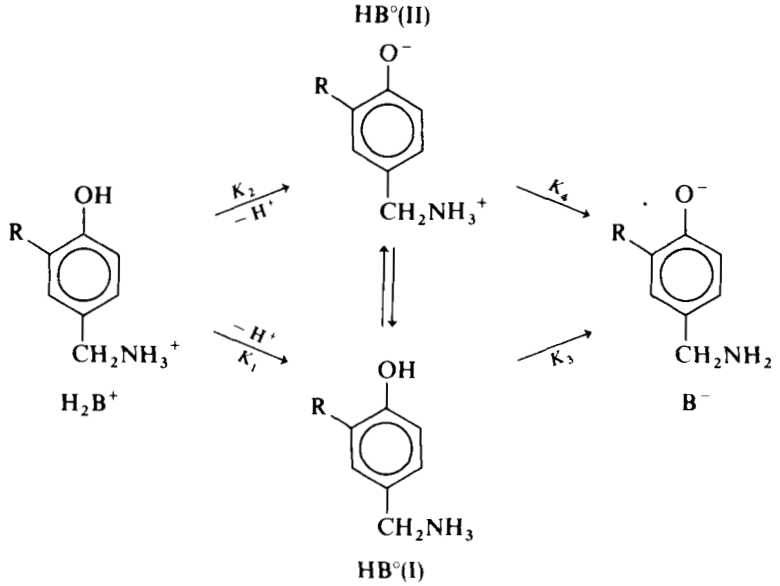
$$K_I = \frac{[AH^-][H^+]}{[AH_2]} = K_1 + K_2$$

$$K_{II} = \frac{[A^{2-}][H^+]}{[AH^-]} \qquad \frac{1}{K_{II}} = \frac{1}{K_3} = \frac{1}{K_4} \tag{35}$$

Studies of micro- and macroscopic dissociation constants are often performed for various amino acids. For example, the dissociation of an α-amino acid with equilibrium constants approximately 3 and 10 pK units is shown in Scheme 2. The tautomeric



SCHEME 2. Dissociation diagram at equilibrium states in acetic or alkaline media. Concentration of α-amino acid $RCHNH_2COOH$ is approximately $0.5\text{–}10^{-5}$% while other species are at equilibrium (50%)



SCHEME 3. Dissociation diagram of a compound with two dissociable groups of comparable strength

equilibrium is shifted towards the zwitterion, at both equilibrium states, at pH = 3 and pH = 10. These minor interferences in the macroscopic (thermodynamic) protonation constants usually may be neglected without serious error. The lower path on the scheme is negligible due to traces of free amino acid.

This situation breaks down when the two dissociable groups have comparable dissociation constants, as in *p*-(methylamino)phenol (Scheme 3). The microscopic pK_a of the phenol group is approximately 10, and microscopic pK_a of the methylammonium ion is 9.7. Owing to the similar basicity of the two dissociable groups in H_2B^+, both $HB^{\pm}$ species coexist at concentrations of comparable magnitude.

$$H_2B^+ = HB^{\pm} + H^+$$

$$K_D = \frac{HB^{\pm}(II)}{HB^{\pm}(I)} = 0.5$$

$$K_a = \frac{[HB^{\pm}][H^+]}{[H_2B^+]} + \frac{([HB^{\pm}(I)] + [HB^{\pm}(II)])[H^+]}{[H_2B^+]} \tag{36}$$

$$= \frac{[HB^{\pm}(I)][H^+]}{[H_2B^+]} + \frac{[HB^{\pm}(II)][H^+]}{[H_2B^+]} = K_1 + K_2$$

The macroscopic dissociation constant K_a is defined by equation 36 and equals the sum of the microscopic dissociation constants K_1 and K_2. The value of K_a could also be measured directly by UV spectrophotometry, in which absorbances of H_2B^- and $HB^{\pm}$ differ. However, the evaluation of K_1 and K_2 is possible only if the spectra of $HB^{\pm}(I)$ and $HB^{\pm}(II)$ are known. Again the second macroscopic dissociation constant

$$K_b = \frac{[B^-][H^+]}{[HB^{\pm}]} = \frac{[B^-][H^+]}{([HB^{\pm}(I)][HB^{\pm}(II)])} \tag{37}$$

$$\frac{1}{K_b} = \frac{[HB^{\circ}(I)][HB^{\circ}(II)]}{[B^-][H^+]} = \frac{1}{K_3} + \frac{1}{K_4}$$

may be evaluated experimentally, if the concentration of B^- and the sum of the concentrations of HB° could be measured.

The idea of microscopic dissociation constants is interesting and important as being directly related to the particular functional group. The advantage of this situation is that microscopic constants are closely related to the chemical structure; the disadvantage lies in the acceptance of that constant as a thermodynamic one, which represents the molecule as a whole.

When the number of dissociable groups in the molecule is larger, the number of macro- and microscopic dissociations increases very rapidly, and the solution of the titration curve becomes a difficult task. To solve it one can choose among various computer procedures[45] and experimental methods.

The pK assignment may be based on extrapolation from an unbranched system, assuming that chemical blocking of one dissociable group (e.g. by esterification) will leave the pK of the second group essentially unchanged, or on spectral features of particular groups in UV-VIS, IR, laser–Raman or NMR spectroscopy, and most often on a combination of them.

IV. ACID–BASE PROPERTIES OF CARBOXYLIC ACIDS

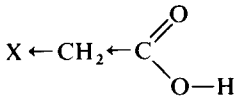
A. Acidity of Carboxylic Acids

Acidic properties of carboxylic acids have been studied for a very long time. The experimental data were reported in numerous research papers, tabulated and reviewed in this series of books[3] as well as in other sources[46–48].

1. Aliphatic and alicyclic carboxylic acids

Aliphatic carboxylic acids are weak electrolytes in water solution. Depending on the structure and type of substituents pK_a varies in the range of 0–7 pK_a units. Data for some selected carboxylic acids are listed in Table 1, which shows the influence of structural features and substituents on the pK_a value in water.

Formic acid is strongest among unsubstituted aliphatic carboxylic acids. Acetic acid due to the + I effect of the methyl group is weaker by 0.99 pK_a units. Acidities of further acids with longer chains are similar to each other, as the inductive effect diminishes after two bonds. Electronegative substituents diminish the strength of the O—H bond in the carboxyl group



and increase the acidic properties. Monohalogeno acetic acids are much stronger than acetic acid itself; di- or tri-halogeno acids are again much more acidic. An interposed CH_2 group between the carboxyl group and the place of substitution decreases the acidity approximately tenfold (2-Cl and 3-Cl propionic acids, 2-Br and 3-Br propionic acids).

The relationships between electronic properties of the substituents and pK_a were utilized by Taft for establishing the σ^* inductive scale of substituents[50]. This scale was also supported by measurements of pK_a for a series of 4-substituted-bicyclo[2.2.2]-octanecarboxylic acids[51] and 4-substituted cyclohexanecarboxylic acids[52] in which

TABLE 1. Acidity of selected aliphatic carboxylic acids

Acid	pK_a[a]	$-\Delta G°$[b]
Formic	3.767	—
Acetic	4.757	0.0
Propionic	4.877	−0.08
Butyric	4.817	−0.09
i-Butyric	4.857	—
Valeric	4.837	—
i-Valeric	4.777	—
Hexanoic	4.857	—
i-Hexanoic	4.847	—
Trimethylacetic	5.027	—
Fluoroacetic	2.587	2.96
Difluoroacetic	1.307	—
Trifluoroacetic	0.217	2.31
Chloroacetic	2.867	—
Dichloroacetic	1.237	—
Trichloroacetic	0.637	—
Bromoacetic	2.897	—
Cyanoacetic	2.467	3.12
Methoxyacetic	3.567	1.62
Hydroxyacetic	3.827	—
Aminoacetic	2.347	—
2-Chloropropionic	2.877	—
3-Chloropropionic	3.987	—
2-Bromopropionic	2.967	—
3-Bromopropionic	3.987	—

[a] Compiled from Reference 3.
[b] From Reference 49.

TABLE 2. pK_a values of substituted cyclic acids

Substituent X	4X-Bicyclo[2.2.2]octane-carboxylic acids in 50% EtOH	4X-Cyclohexanecarboxylic acids	
		in 50% EtOH	in water
H	6.74	6.40	4.90
OH	6.32	6.07	4.69
COOEt	6.31	6.03[a]	4.66[a]
Br	6.08	—	—
CN	5.90	5.74	4.48
Cl	—	5.89	4.58
COOH	—	—	4.37
OMe	—	6.02	4.66

[a] Data for COOMe.

TABLE 3. Comparison of pK_a values for saturated and unsaturated acids

Acid		pK_a
Propionic	CH_3CH_2COOH	4.877
Acrylic	$CH_2{=}CHCOOH$	4.255
Vinylacetic	$CH_2{=}CHCH_2COOH$	4.335
Allylacetic	$CH_2{=}CHCH_2CH_2COOH$	4.676
trans-3-Substituted acrylic acids		
3-Et		4.693
3-i-Pr		4.695
3-OMe		4.701
3-Cl		3.850
3-Br		3.790
3-J		3.710
3-CF_3		3.740
3-Ac		3.15
3-NO_2		2.58
Acetic	CH_3COOH	4.757
Benzoic	C_6H_5COOH	4.20
Phenylacetic	$C_6H_5CH_2COOH$	4.31
β-Phenylpropionic	$C_6H_5CH_2CH_2COOH$	4.66
γ-Phenylbutyric	$C_6H_5CH_2CH_2CH_2COOH$	4.75
trans-Crotonic	$CH_3CH{=}CHCOOH$	4.63
Tetralic	$CH_3C{\equiv}CCOOH$	2.65
trans-Cinnamic	$PhCH{=}CHCOOH$	4.44
Phenylpropiolic	$PhC{\equiv}CCOOH$	2.33

other electronic effects do not operate. The pK_a values for such acids are collected in Table 2.

The presence of unsaturated bonds in the alkyl chain also increases the acidity of carboxylic acids, and a similar effect is produced by an aromatic ring (Table 3). A triple bond conjugated with the carboxyl group increases the acidity approximately 100 times more than an olefinic bond.

2. *Aromatic carboxylic acids*

Aromatic carboxylic acids are weak acids with pK_a values in the range of 3–5 pK_a units in water. The dissociation of benzoic acids in water has been used by Hammett for the foundation of LFER (equation 38), since it answered the natural requirements imposed on a reference reaction, namely high accuracy and precision of measurements, availability of data for a wide range of chemical species, high sensibility to structural changes and precise knowledge of the reaction mechanism.

$$\log K/K_0 = \rho\sigma \tag{38}$$

The pK_a values for some benzoic acids in water are presented in Table 4. The difference between pK_a^H of benzoic acid and pK_a^x of a given x-substituted benzoic acid is, by definition, known as the substituent constant[1]:

$$pK_a^H - pK_a^x = \sigma \tag{39}$$

TABLE 4. pK^a values of substituted benzoic acids in water[48]

Substituent	*para*	*meta*
H	4.202	4.202
Me	4.370	4.252
Et	4.353	—
i-Pr	4.354	—
t-Bu	4.389	4.204
F	4.141	3.865
Cl	3.9863	3.834
Br	4.0020	3.809
I	3.995	3.856
NO_2	3.442	3.460
CN	3.551	3.596
Ac	3.700	3.825
OMe	4.494	4.093
$SiMe_3$	4.192	4.089
CHO	3.75	3.85
c-Pr	4.42	4.28
NH_2	4.83	4.41

TABLE 5. Reaction constants ρ for the dissociation of substituted benzoic acids in various solvents

Solvent	pK_a^H	ρ	Reference
H_2O 25 °C	4.202	1.000	1
EtOH 10%	4.37	1.10	53
EtOH 30%	4.84	1.14	53
EtOH 50%	5.48	1.52	53
EtOH 75%	6.29	1.67	53
EtOH 85%	6.77	1.52	53
EtOH 100%	10.02	1.60	54
n-PrOH	8.60	1.50	54
n-BuOH	8.81	1.44	54
t-BuOH 22%	4.78	1.33	53
t-BuOH 32%	5.28	1.55	53
t-BuOH 90%	8.59	1.89	53
Dioxan 43.5%	5.47	1.33	54
Dioxan 73.5%	7.03	1.44	54
Methyl acetate 10%	4.45	1.10	54
Methyl acetate 25%	4.996	1.08	54
Methylcellosolve 80%	6.58	1.10	54
Ethylene glycol	7.65	—	54
DMSO	11.0	2.6	54
i-Butyl methyl ketone	22.4	—	55

TABLE 6. Reaction constants ρ for the dissociation of various aromatic acids

Acid	Solvent	ρ^a	ρ^b
ArCOOH	H_2O	1.054 ± 0.043	1.00
$ArCH_2COOH$	H_2O	0.486 ± 0.011	0.562
$ArCH_2CH_2COOH$	H_2O	0.24	0.237
ArCH=CHCOOH (*trans*)	H_2O	0.418 ± 0.034	—
ArCH=CHCOOH (*cis*)	H_2O	0.400 ± 0.023	—
ArCOOH	50 % EtOH	1.576 ± 0.038	1.522
$ArCH_2COOH$	50 % EtOH	0.740 ± 0.028	—
$ArCH_2CH_2COOH$	50 % EtOH	0.385 ± 0.019	—
ArCH=CHCOOH (*trans*)	50 % EtOH	0.676 ± 0.010	0.68
ArCH=CHCOOH (*cis*)	50 % EtOH	0.634 ± 0.010	—
$Ar(CH_2=CH_2)_2COOH$	50% EtOH	—	0.449

[a] From Reference 56.
[b] From Reference 57.

Much work has been done on environmental effects on the pK_a of benzoic acids. Data in various solvents and solvent mixtures are available in the literature. In general, the solvent effect on pK_a is included in the reaction constant ρ (see Table 5).

The pK_a value of benzoic acid increases when water is replaced by alcohols, ketones, methylcellosolve and other solvents. The lower the solvation power of a solvent, the higher is the ρ value (see Table 5).

pK_a values of benzoic acids in binary solvents are claimed to be anomalous[53], most probably due to non-linearity between the polarity of a mixed solvent and its composition[58] or to sliding values of substituent constants. Hoefnagel and Wepster[53] suggested using a two-parameter Hammett equation with the hydrophobic parameter π:

$$\Delta pK = \rho\sigma + h\pi \tag{40}$$

to accommodate pK_a data in mixed solvents.

Intervening methylene groups between an aromatic ring and the carboxyl group decrease the ρ value. Also, the influence of *meta* and *para* substituents in a benzene ring is smaller than that of an *ortho* substituent. Dissociation constants for cinnamic acids are not dependent on configuration (*trans* or *cis*) and the effect of a benzene substituent is propagated through the chain approximately 2.5-fold worse than in benzoic acid. Data collected in Table 6 present regularities for water and 50% ethyl alcohol and are examples of general behaviour.

3. Thermodynamics of the dissociation of benzoic acids

The acidity of the carboxyl group in a variety of organic acids is still a key problem in physical organic chemistry. Benzoic acid and its derivatives are at the centre of interest, because of their applicability for the definition of the σ substituent constant in LFERs[59,60]. Benzoic acid solutions in water have been the subject of numerous investigations[61–71]. There are still essential uncertainties in the thermodynamic parameters ΔH°, ΔS° and ΔC_p as a function of the temperature for the ionization process. These parameters are necessary for understanding the nature of weak acids and to explain the role of water as a solvent. Careful studies of equilibrium constants derived

TABLE 7. pK_a values for aqueous benzoic acid as a function of temperature and estimated uncertainties[73]

Temperature	pK_a	esd	pK_a	Reference
5	4.2245	0.0018		
10	4.2148	0.0018		
15	4.2076	0.0016		
20	4.2034	0.0018		
25	4.1998	0.0030	4.1968	61
			4.1953	61
			4.2131	63
			4.204	67
			4.202	66
30	4.2013	0.0035		
35	4.2061	0.0033	4.205	65
			4.205	76
40	4.2115	0.0035		
45	4.2190	0.0037		
50	4.2287	0.0038	4.224	67
55	4.2400	0.0040		
60	4.2525	0.0043		
65	4.2665	0.0046		
70	4.2821	0.0048	4.269	67
75	4.2991	0.0052	4.251	65
80	4.3170	0.0057		

from conductance and electrometric methods suggest that an accuracy to the third decimal of pK_a values can be achieved[72]. Strong and colleagues[73] fitted their dissociation constants by various methods proposed[37,74,75]. The changes of pK_a with temperature are given in Table 7, and show a minimum at 25 and 30 °C.

The first two methods fit the experimental pK_a values within 0.02%, however at 25 and 30 °C deviations are substantial, possibly due to changes of ΔC_p over the temperature range. The three-term equation in Clarke and Glew's[37] analysis is superior to two-term equations.

$$pK_a = -75.5422 + 3136.34/T + 28.7965 \log T - 6.8140 \times 10^{-3} T \quad (41)$$

$$\Delta G = 14350.9 \times 131.7689 \log T - 345.6577 T - 3.1179 \times 10^{-2} T^2 \quad (42)$$

Only few ionization constants have been measured as a function of pressure[77,78]. The dissociation constants of benzoic acids to 250 °C and to 2000 bar provide a valuable contribution[79] to behaviour in hydrothermal conditions, and may have application for correlating the dissociation of substituted benzoic acids in terms of LFER[59]. Thermodynamic ionization constants of benzoic acid are presented in Table 8 at various temperatures (horizontal) and pressures (vertical). The numerical values are highest for 25 °C (at a given pressure) or for 2000 bar (at a given temperature). The effect of temperature at constant pressure on log K of benzoic acid could be described by the equation

$$\ln K = A + B/T + C \ln T + DT + ET^2 \quad (43)$$

Comparison of the data for benzoic acid and acetic acid shows large uniformity, suggesting the importance of the —COOH group, and the comparable roles of the hydrophobic end of both acids. This may be explained by the necessary breaking of the

TABLE 8. Thermodynamic ionization constants (10^5 K) of benzoic acid as a function of temperature and pressure (in bar)[a]

p	25	100	150.2	200.2	250.9
1	6.27	3.99	2.38	1.087	0.358
200	6.87	4.48	2.78	3.307	0.481
400	7.53	5.03	3.23	1.550	0.641
600	8.22	5.59	3.72	1.843	0.818
800	8.94	6.22	4.23	2.181	1.020
1000	9.67	6.88	4.76	2.524	1.237
1200	10.47	7.58	5.37	2.900	1.478
1400	11.29	8.30	6.04	3.328	1.741
1600	12.16	9.08	6.73	3.801	2.043
1800	13.12	9.91	7.52	4.298	2.422
2000	14.17	10.80	8.23	4.861	2.801
ΔH	−0.10	−10.6	−18.3	−33	−60.2
ΔS	−81.0	−112	−132	−164	−219

[a] Data compiled from Reference 79.

OH bond and the forming of a similar number of strong bonds between water molecules and each anion[79]. The large and negative entropy changes with the rise of temperature originate from the transfer of water molecules from a disordered structure to the hydration shell of the benzoate ion. The same is also true for the acetate ion. The large entropy changes predominate over ΔH changes.

Mono- and di-substituted benzoic acids have been the object of several studies in recent years to determine the substituent effect on the thermodynamics of the ionization. Conductivities of aqueous solutions of *ortho*-, *meta*- and *para*-toluic acids[80] and of various dimethylbenzoic acids[81] were measured over a wide range of temperatures (5–100 °C). pK_a values have been calculated using the paired ion model[82] and are presented in Table 9. The effect of temperature (in K) on pK_a is not linear but curved, and may be expressed by the equation

$$pK_a = A + B/T + C \log T + DT \tag{44}$$

which is simpler than for benzoic acid (equation 43).

The dissociation of fluorobenzoic acids[84,85] show a very similar pattern, and pK_a values at 25 °C are summarized in Table 10. Fluorine, with a van der Waals radius of 1.34 Å, is significantly smaller than a methyl group (r = 2 Å) and causes no steric effect on COOH; however, its electronegativity effect is stronger.

The carboxylate ion in fluoro acids is less attractive for H^+ ions and for water molecules. This explains the smaller changes in ΔS in fluorobenzoic as compared to methylbenzoic acids[85]. The plot of $R \ln K$ vs ΔS for mono- and poly-fluoro and methyl substituted benzoic acids[84] shows that acetic and benzoic acids occupy a position on the line of unit slope, such as $R \ln K = \Delta S$, and have zero value for the environmental entropy changes. From the evidence at hand it would appear that entropies of ionization of different carboxylic acids tend to have a common limiting value in hot water.

In explaining the thermodynamic data it is convenient to divide the acids into two classes, one with and one without *ortho* substituents. Acids without *ortho* substituents are weaker than benzoic acid and have pK_a values with minima around 25 °C. A consequence of such minima is that ΔH is zero at the minimum, which indicates that the energy added when the acid ionizes is matched by the energy of ion solvation, and $R \ln K_a$ is equal to the entropy of ionization. The *ortho* methyl acids are more acidic and

TABLE 9. Ionization constants for toluic acids[80] and various dimethylbenzoic acids[81] as a function of temperature

t	*ortho*	*meta*	*para*	2,6-	2,3-	2,5-	3,5-
5	3.8380	4.2837	4.3925	3.1003	3.6598	3.9338	4.3334
15	3.8644	4.2639	4.3740	3.1690	3.6962	3.9581	4.3185
25	3.8968	4.2576	4.3668	3.2425	3.7395	3.9871	4.3137
				3.246[a]	3.793[a]	3.975[a]	4.314[a]
35	3.9341	4.2626	4.3699	3.3177	3.7870	4.0232	4.3200
45	3.9759	4.2748	4.3808	3.3939	3.8387	4.0631	4.3340
55	4.0216	4.2942	4.3985	3.4717	3.8932	4.1064	4.3549
65	4.0700	4.3191	4.4227	3.5505	3.9509	4.1536	4.3817
75	4.1212	4.3496	4.4529	3.6304	4.0111	4.2034	4.4141
85	4.1737	4.3837	4.4880	3.7106	4.0737	4.2542	4.4515
95	4.2268	4.4192	4.5300	3.7914	4.1383	4.3197	4.4937

[a] Data for comparison from Reference 83.

show a decrease in entropy and enthalpy on dissociation. 2,6-dimethyl groups cause a twist of the carboxyl group, which in turn twists its oxygen out of plane. Thus the oxygen atoms are better exposed and more accessible to the solvent. However, in benzoic acid the carboxyl group is partly inaccessible to the water molecules. Both *m*- and *p*-toluic acids are weaker than benzoic acids, due to the small decrease in entropy which accompanies their ionization[80].

The effect of pure and mixed solvents on the pK_a value of benzoic acids has been studied for a long time, and its magnitude was attributed to the reaction constant ρ in the Hammett equation. Recent measurements of the molar conductance of diluted solutions of benzoic acids yield precise pK_a data in pure or aqueous alcohols[87-89] and allow one to interpret solute–solvent interactions. The experimental data for three isomeric nitrobenzoic acids and for benzoic acid in methanol, ethanol, n-propanol and their mixtures with water at 25 °C are presented in Table 11. The agreement between

TABLE 10. Acidity (pK_a) of fluorobenzoic acids at 25 °C

Substituent	pK_a		
o-F	3.4686[a]	3.262[b]	
m-F	3.8590[a]	3.886[b,c]	
p-F	4.1308[a]	4.147[b]	4.153[c]
2,4-diF	3.4380[a]		
2,6-diF	2.2356[a]		
2,3-diF	3.1014[d]		
2,5-diF	3.1078[d]		
3,5-diF	3.5242[d]		
penta-F	1.4821[d]		

[a] From Reference 84.
[b] From Reference 63.
[c] From Reference 86.
[d] From Reference 85.

TABLE 11. pK_a values of nitrobenzoic acids in alcohol–water mixtures

	Weight% of alcohol							
	0	10	20	30	40	50	60	70
				2-Nitrobenzoic acid				
MeOH	2.10	2.33		2.79		3.45		4.44
EtOH	2.195	2.499	2.853	3.277	3.554	3.814	3.960	4.137
PrOH	2.195	2.817	2.905	3.429	3.70	4.200	4.623	
				3-Nitrobenzoic acid				
MeOH	3.45	3.49		3.88		4.17		5.23
EtOH	3.495	3.587	3.984	4.217	4.440	4.711	5.061	5.50
PrOH	3.495	3.596	4.040	4.141	4.349	4.79		
				4-Nitrobenzoic acid				
MeOH	3.45	3.50		3.86		4.30		5.27
EtOH	3.450	3.788	3.938	4.227	4.365	4.486	4.739	5.27
PrOH	3.350	3.498	3.967	4.187	4.322	4.634		
				Benzoic acid				
MeOH	4.22	4.31		4.91		5.56		6.20
EtOH	4.195	4.321	4.683	5.217	5.494	5.712	5.96	6.28
PrOH	4.195	4.288	4.882	5.083	5.393	5.628		

new and older data, which were mainly derived by potentiometric methods[72,90,91], is very good.

The strength of acids studied in methanol–water mixtures decreases in the order 2-nitro- > 3-nitro = 4-nitro- > benzoic, and similar relations are found in other alcoholic mixtures. The differences in pK_a values of isomers could be explained on the basis of intramolecular hydrogen bonding and a blend of inductive/mesomeric electronic effects of substituents on the carboxyl group[72]. The solvent composition effect on the dissociation of these acids is very interesting. The plots of pK_a vs mole fraction of alcohol, or vs the inverse of the dielectric constant of the mixed solvent, is not linear[88,87]. This suggests a non-electrostatic contribution to the standard free energy of transfer from aqueous to alcoholic mixtures as playing a dominant role. In accord with the Born theory[92] specific solute–solvent interactions are thus of key importance. The molar Gibbs energy of transfer of carboxylate ions from water to alcohol shows a linear dependence on solvent composition only to 30%, rather than curves. This suggests that in more alcoholic solutions, specific solute–solvent interactions increase and start to play a very important role (Table 12).

TABLE 12. Molar free energy of transfer of acids from water to methanol–water solutions at 298 K[88]

Acid	10	30	50	70
Benzoic	0.51	2.97	7.65	11.30
2-Nitrobenzoic	1.31	3.94	7.70	13.35
3-Nitrobenzoic	0.23	2.45	4.11	10.16
4-Nitrobenzoic	0.29	2.34	4.85	10.39

4. *Dissociation of carboxylic acids in aqueous solutions of alkyl ammonium salts*

Investigation of protonation/deprotonation constants and of formation constants of O-ligands in solutions of various ionic strengths is important for the study of aqueous systems and biological fluids[93] as well as complex formation. Alkylammonium salts are often used for such purposes. The acidity of various carboxylic acids was investigated as a function of temperature (5–55 °C) and ionic strength in the range 0.04–1.00 provided by tetraethyl ammonium iodide. Some data are collected in Table 13. The relationship pK vs ionic strength, at a constant temperature, is a curved line with a minimum near

TABLE 13. Protonation constants of carboxylic acids in tetraethylammonium iodide of various ionic strengths and tetrabutylammonium bromide at 25 °C

Acid	Ionic strength I (mol dm^{-3})						7.75 molal Bu_4NBr
	0.04	0.16	0.36	0.64	1.00	calc. for $I = 0$	
Formic	3.596	3.547	3.549	3.580	3.625	3.735	
Acetic	4.614	4.573	4.591	4.645	4.718	4.750	
Cryanoacetic							3.95
Difluoroacetic							2.91
Trifluoroacetic							1.85
Phenylacetic							6.60
Propionic	4.735	4.702	4.733	4.804	4.900	4.868	7.26
2,2-Dimethylbenzoic	4.054	4.013	4.030	4.084	4.158	4.190	6.30
Salicylic	2.806	2.752	2.747	2.769	2.801	2.947	
Phenoxyacetic	2.990	2.97	3.01	3.09	3.20	3.13	
	Dicarboxylic acids						
Oxalic	4.039	3.949	3.970	4.056	4.174	4.314	
Malonic K_1	5.437	5.353	5.383	5.482	5.618	5.710	
K_2	2.71	2.67	2.70	2.76	2.85	—	
Succinic K_1	5.371	5.273	5.280	5.347	5.442	5.648	
K_2	4.075	4.041	4.069	4.138	4.230	—	
Tartaric K_1	4.090	3.988	3.987	4.044	4.125	4.369	
K_2	2.896	2.861	2.886	2.950	3.037	—	
Maleic K_1	6.052	5.987	6.050	6.194	6.389	6.318	
K_2	1.80	1.77	1.80	1.87	1.97	—	
Malic K_1	4.828	4.727	4.728	4.786	4.870	5.107	
K_2	3.329	3.290	3.310	3.367	3.444	—	
Phthalic K_1	5.144	5.079	5.141	5.285	5.479	5.410	
K_2	2.815	2.785	2.820	2.899	3.003	—	
	Tricarboxylic acids						
Citric K_1	5.995	5.848	5.858	5.958	6.099	6.411	
K_2	4.498	4.396	4.396	4.454	4.536	—	
K_3	2.992	2.953	2.973	3.029	3.106	—	
1,2,3-Benzene tricarboxylic K_1	5.85	5.69	5.69	5.77	5.89	6.27	
K_2	4.05	3.96	3.97	4.04	4.15	—	
K_3	2.72	2.70	2.75	2.84	2.97	—	
1,2,4-Benzene tricarboxylic K_1	5.12	4.97	4.99	5.09	5.23	5.537	
K_2	3.72	3.61	3.59	3.61	3.66	—	
K_3	2.35	2.32	2.36	2.44	2.55	—	

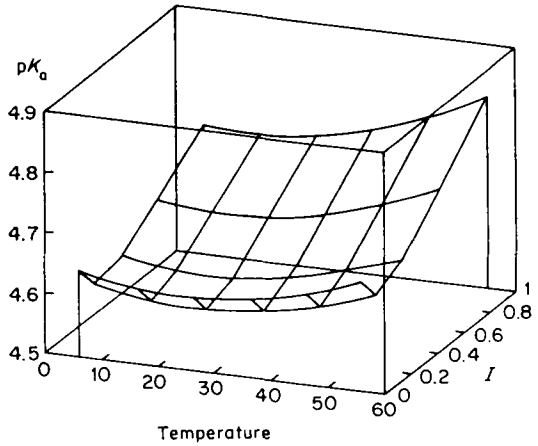


FIGURE 6. Variation of acetic acid acidity as a function of temperature and ionic strength

$I = 0.46$. The temperature also affects the pK: at a constant ionic strength the pK_a value reaches a minimum near 20 °C. All these changes are shown by Figure 6 for acetic acid.

The dissociation of substituted aliphatic acids in tetrabutylammonium bromide was investigated by Steigman and coworkers[94] and by Koppel's group[95]. The relationships between pK_a in tetrabutylammonium bromide and in water for a series of 37 aliphatic carboxyl acids and a variety of *o*-, *m*- and *p*-substituted benzoic acids is linear and the correlation coefficient and standard deviations are better than 0.960 and 0.22, respectively. Transfer of aliphatic carboxylic acids or *meta*- and *para*-substituted benzoic acids from water into salt solutions results in an increase of the influence of structural factors (such as substituent effects) due to the decrease of the electrophilicity of the medium.

5. Salt effect on pK_a

Primary salt effects on equilibria and kinetics were studied for many years[96,97] and were reviewed some time ago[98]. A point of key importance in the evaluation of equilibrium constants is the precise estimation of the activity coefficients of all species present. Various extensions of the Debye–Hückel theory were used[98] and recently the quasi-lattice theory was shown as being superior[99–101]. According to the 'structural theory of electrolyte solutions'[101], the partial excess free energy ΔG_{ex} of an electrolyte is given as

$$\Delta G_{ex} = \Delta G_{ii} + \Delta G_{is} \tag{45}$$

where ΔG_{ii} is the purely electrostatic interionic interaction contribution and ΔG_{is} is the independent excess free energy of the ion–solvent interaction. It has been shown[101] that

$$\Delta G_{ii} = a_t c = \frac{A_m(z_+ e)(z_- e)}{\varepsilon \bar{l}} N_A \tag{46}$$

Parameter a_t is a constant dependent on the electrolyte type and on the properties of the solvent, z_+ and z_- are the charges of the cation and of the anion, respectively; ε is the macroscopic dielectric constant; N_A is the Avogadro number; $\bar{l}$ is the average distance

between the nearest neighbour ions in the solution and A_m is a constant for the simplest lattice of the given electrolyte type. ΔG_{is} is given by the expression

$$\Delta G_{is} = b_i c = 2\nu RTV_s c \tag{47}$$

where ν is the number of ions in the electrolyte, V_s is a volume specific to every solute and b_i describes the salt influence on the non-ionic excess free energy of the acid–base equilibrium. Thus

$$\Delta G_{ex} = a_t c + b_i c \tag{48}$$

The dissociation constant of the reaction

$$AH \underset{}{\overset{K_c}{\rightleftharpoons}} A^- + H^+ \tag{49}$$

is expressed by the well-known formula

$$K_c = \frac{c_A \cdot c_{H^+}}{c_{AH}} \tag{50}$$

or

$$pK_c = -\log \frac{c_A \cdot c_{H^+}}{c_{AH}} \tag{51}$$

In the presence of 1:1 electrolytes the equation becomes

$$pK_c = pK_a + \Delta G_{ex} \tag{52}$$

Equation 48 enables this to be expressed in the form

$$pK_c = pK_a + 2a_t c + b_i c \tag{53}$$

or, after rearrangement,

$$pK_c - 2a_t c = pK_a + b_i c \tag{54}$$

Both equations (53 and 54) were applied[102] to experimental data sets pertaining to the salt effects on the acidity of various carboxylic acids taken from the literature. Figure 7 shows the relationships between pK_c and c of the salt added for benzoic

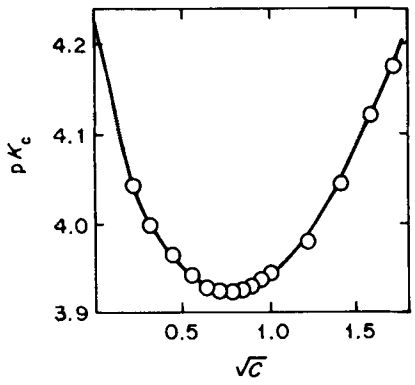


FIGURE 7. Relationship between acidity of benzoic acid and concentration of salt added

TABLE 14. The results of the linear regression treatment of the pK_c values of several carbocylic acids in aqueous solutions according to equation 54.

Acid	Salt added	pK_a	b_i	Correlation coefficient r	Standard deviation s	Reference
HCOOH	NaCl	3.768 ± 0.004	0.257 ± 0.002	0.9998	0.006	*a*
	KCl	3.776 ± 0.003	0.284 ± 0.002	0.9999	0.005	*a*
CH_3COOH	NaCl	4.773 ± 0.007	0.279 ± 0.002	0.9999	0.009	*b*
	NaCl	4.779 ± 0.006	0.279 ± 0.005	0.9989	0.015	*c*
	NaCl	4.797 ± 0.004	0.286 ± 0.002	0.9998	0.010	*d*
	KCl	4.792 ± 0.005	0.293 ± 0.002	0.9999	0.006	*c*
	KCl	4.800 ± 0.006	0.303 ± 0.005	0.9992	0.014	*d*
C_2H_5COOH	NaCl	4.906 ± 0.004	0.269 ± 0.002	0.9998	0.006	*a*
C_3H_7COOH	NaCl	4.845 ± 0.004	0.268 ± 0.002	0.9998	0.006	*a*
$(CH_3)_2CHCOOH$	NaCl	4.872 ± 0.003	0.260 ± 0.002	0.9999	0.005	*a*
C_4H_9COOH	NaCl	4.853 ± 0.003	0.266 ± 0.002	0.9999	0.004	*a*
$(CH_3)_3CCOOH$	NaCl	5.054 ± 0.006	0.244 ± 0.003	0.9995	0.009	*a*
$C_5H_{11}COOH$	NaCl	4.886 ± 0.004	0.266 ± 0.002	0.9998	0.006	*a*
$(CH_3)_2CH(CH_2)_2COOH$	NaCl	4.877 ± 0.004	0.268 ± 0.003	0.9997	0.007	*a*
$C_6H_{13}COOH$	NaCl	4.881 ± 0.003	0.267 ± 0.002	0.9999	0.005	*a*
$ClCH_2COOH$	NaCl	2.868 ± 0.003	0.247 ± 0.002	0.9998	0.005	*c*
$BrCH_2COOH$	NaCl	2.939 ± 0.006	0.245 ± 0.004	0.9993	0.011	*f*
ICH_2COOH	NaCl	3.193 ± 0.004	0.266 ± 0.003	0.9997	0.007	*f*
$HOCH_2COOH$	NaCl	3.857 ± 0.003	0.230 ± 0.002	0.9998	0.005	*e*
$Cl(CH_2)_2COOH$	NaCl	4.135 ± 0.003	0.261 ± 0.002	0.9999	0.004	*f*
$Br(CH_2)_2COOH$	NaCl	4.031 ± 0.004	0.260 ± 0.002	0.9996	0.009	*f*
$I(CH_2)_2COOH$	NaCl	4.114 ± 0.002	0.264 ± 0.001	0.9999	0.003	*f*
C_6H_5COOH	NaCl	4.251 ± 0.004	0.245 ± 0.004	0.9996	0.006	*g*
	KCl	4.242 ± 0.002	0.254 ± 0.001	0.9999	0.003	*g*
$C_6H_5CH_2COOH$	NaCl	4.337 ± 0.002	0.255 ± 0.001	0.9999	0.003	*g*
	KCl	4.342 ± 0.002	0.276 ± 0.001	0.9999	0.004	*g*
$C_6H_5(CH_2)_2COOH$	NaCl	4.699 ± 0.001	0.263 ± 0.001	0.9999	0.002	*g*
	KCl	4.700 ± 0.004	0.289 ± 0.003	0.9998	0.007	*g*
$2\text{-}HOC_6H_4COOH$	KCl	3.069 ± 0.004	0.241 ± 0.002	0.9997	0.007	*g*
$3\text{-}HOC_6H_4COOH$	NaCl	4.181 ± 0.004	0.241 ± 0.002	0.9997	0.007	*g*
	KCl	4.194 ± 0.003	0.247 ± 0.002	0.9998	0.005	*g*

[a] E. Larsson and B. Adell, *Z. Phys. Chem.*, **A156**, 381 (1931).
[b] A. von Kiss and A. Urmanczy, *Z. Phys. Chem.*, **A171**, 257 (1935).
[c] H. S. Harned and R. W. Ehlers, *J. Am. Chem. Soc.*, **55**, 652, 2379 (1933).
[d] S. Kilpi and A. Meretoja, *Z. Phys. Chem.*, **A179**, 371 (1937).
[e] E. Larsson and B. Adell, *Z. Phys. Chem.*, **A157**, 342 (1931).
[f] E. Larsson, *Z. Phys. Chem.*, **A165**, 53 (1933).
[g] T. G. Brockman and M. Kilpatrick, *J. Am. Chem. Soc.*, **50**, 1483 (1934).

acids[102]. The results of the linear regression treatment of the pK_c values, using equation 54, are presented in Table 14. The parameter $b_i c$ seems to be fairly independent of the acid structure and is slightly higher if KCl is added, as compared to NaCl. A similar procedure has been applied by Karelson[103] to a collection of pK_c data on dicarboxylic acids. The first step of the dicarboxylic acid dissociation

$$AH_2 \underset{}{\overset{K_{a1}}{\rightleftharpoons}} AH^- + H^+ \qquad (55)$$

TABLE 15. The results of the statistical data treatment of the pK_{1c} values of some dicarboxylic acids in aqueous solutions[a] according to equation 54

Acid	Electrolyte added	pK_a	Δb	Correlation coefficient r	Standard deviation s
$CH_2(COOH)_2$	NaCl	2.895 ± 0.006	0.229 ± 0.004	0.9993	0.010
	KCl	2.904 ± 0.005	0.246 ± 0.003	0.9995	0.009
$(CH_2)_2(COOH)_2$	NaCl	4.263 ± 0.005	0.240 ± 0.003	0.9996	0.008
	KCl	4.272 ± 0.004	0.258 ± 0.002	0.9998	0.006
$(CH_2)_3(COOH)_2$	NaCl	4.385 ± 0.005	0.267 ± 0.003	0.9997	0.008
	KCl	4.396 ± 0.003	0.286 ± 0.002	0.9999	0.005
$(CH_2)_4(COOH)_2$	NaCl	4.472 ± 0.005	0.269 ± 0.004	0.9995	0.009
	KCl	4.481 ± 0.006	0.289 ± 0.004	0.9995	0.010
$(CH_2)_5(COOH)_2$	NaCl	4.543 ± 0.006	0.277 ± 0.004	0.9995	0.010
	KCl	4.551 ± 0.004	0.297 ± 0.003	0.9998	0.007
$(CH_2)_6(COOH)_2$	NaCl	4.573 ± 0.005	0.275 ± 0.003	0.9996	0.009
	KCl	4.588 ± 0.005	0.299 ± 0.003	0.9997	0.008
$(CH_2)_7(COOH)_2$	NaCl	4.598 ± 0.005	0.276 ± 0.003	0.9997	0.008
	KCl	4.604 ± 0.003	0.296 ± 0.002	0.9999	0.006
cis-$(CH)_2(COOH)_2$	NaCl	1.984 ± 0.009	0.205 ± 0.005	0.9979	0.015
	KCl	1.988 ± 0.006	0.228 ± 0.004	0.9992	0.010
trans-$(CH_2)(COOH)_2$	NaCl	3.083	0.256	0.9999	0.004
	KCl	3.087 ± 0.005	0.256 ± 0.003	0.9997	0.005

[a] B. Adell, *Z. Phys. Chem.*, **A185**, 161 (1939).

TABLE 16. The results of the nonlinear regression analysis of the pK_{2c} data for dicarboxylic acids in aqueous solutions[a] according to equation 59

Acid	Electrolyte added	pK_{2a}	r_0	b_1	Standard deviation s
$CH_2(COOH)_2$	NaCl	5.852 ± 0.019	4.86 ± 0.48	0.217 ± 0.011	0.011
	KCl	5.902 ± 0.017	4.96 ± 0.44	0.250 ± 0.010	0.010
$(CH_2)_2(COOH)_2$	NaCl	5.832 ± 0.026	6.44 ± 0.81	0.256 ± 0.011	0.013
	KCl	5.801 ± 0.019	6.93 ± 0.63	0.282 ± 0.008	0.009
$(CH_2)_3(COOH)_2$	NaCl	5.590 ± 0.021	6.32 ± 0.65	0.278 ± 0.009	0.011
	KCl	5.572 ± 0.017	6.96 ± 0.59	0.280 ± 0.087	0.008
$(CH_2)_5(COOH)_2$	NaCl	5.594 ± 0.010	6.38 ± 0.30	0.283 ± 0.004	0.005
	KCl	5.604 ± 0.019	7.23 ± 0.64	0.290 ± 0.007	0.009
$(CH_2)_5(COOH)_2$	NaCl	5.593 ± 0.034	7.70 ± 1.23	0.269 ± 0.012	0.015
	KCl	5.618 ± 0.020	8.10 ± 0.76	0.282 ± 0.006	0.008
$(CH_2)_6(COOH)_2$	NaCl	5.604 ± 0.013	7.86 ± 0.50	0.275 ± 0.005	0.006
	KCl	5.601 ± 0.012	8.12 ± 0.47	0.294 ± 0.004	0.005
$(CH_2)_7(COOH)_2$	NaCl	5.601 ± 0.022	8.46 ± 0.88	0.268 ± 0.007	0.009
	KCl	5.642 ± 0.055	7.08 ± 1.87	0.309 ± 0.022	0.026
cis-$(CH)_2(COOH)_2$	NaCl	6.525 ± 0.017	3.44 ± 0.36	0.213 ± 0.014	0.011
	KCl	6.505 ± 0.006	3.46 ± 0.13	0.252 ± 0.005	0.004
trans-$(CH)_2(COOH)_2$	NaCl	4.649 ± 0.013	6.46 ± 0.39	0.243 ± 0.005	0.006
	KCl	4.657 ± 0.008	6.16 ± 0.24	0.273 ± 0.004	0.004

[a] B. Adell, *Z. Phys. Chem.*, **A185**, 161 (1939).

occurs in agreement with equation 54, and the results of regression analysis of the literature data are presented in Table 15.

The dissociation constant of the second step of the dicarboxylic acid dissociation

$$AH^- \rightleftharpoons A^{2-} + H^+ \tag{56}$$

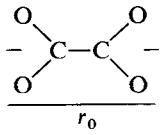
is given by the equation

$$K_{a2} = \frac{c_{A^{2-}} c_{H^+}}{c_{AH^-}} \tag{57}$$

and is affected by the activity coefficient of the diionic species, e.g.

$$^-OOC{-}(CH_2)_4{-}COO^-.$$

The final equation (59) describing the relation between pK_{2c} and the concentration of the ionic species includes the distance r_0 between the negative charges of the two carboxylate groups[103],



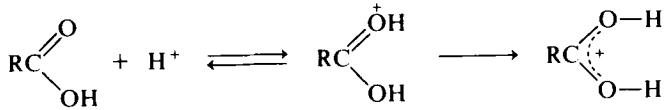
(58)

$$pK_{2c} + 0.572c = pK_{2a} + \frac{3.098}{a_0}(e^{-0.377a_0c} - 1) + b_i c \tag{59}$$

The parameters of this equation could be found by non-linear least-squares calculations and are given in Table 16. The agreement between experimental and calculated distances r_0 is satisfactory up to glutaric acid, and confirms the rigid *trans*-conformation of the aliphatic chain. With longer acids, the calculated distance is shorter, indicating twisting of the hydrocarbon chain. In the case of small interionic distances, the primary salt effect can be a powerful tool in the investigation of their separation.

B. Basicity of Carboxylic Acids

Carboxylic acids are suitable substrates for the study of basicity because their conjugate acids are intermediates in several important reactions including esterification. The carboxyl group is a weakly basic centre and substituents can only modify its basicity. This group is appreciably protonated in concentrated strong acids:



(60)

Olah and coworkers[104] concluded from the measurements of NMR spectra in the superacidic medium FSO_3H–SbF_5 at low temperatures, that various carboxylic acids are completely protonated and produced alkoxycarbonium ions under non-equilibrium conditions.

The structure of cations obtained by protonation of carboxylic acids has been of great interest[104–108]. It is assumed that protonation of the carbonyl group is the initial step, followed by delocalization of the positive charge over both oxygens or even over the rest of the molecule.

TABLE 17. Basicity of saturated carboxylic acids[a]

Acid	pK_{BH^+}
Acetic	−6.10
Propionic	−6.80
Phenylacetic	−7.71

[a] Data from: E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963).

Saturated carboxylic acids are very weak bases. Their basicity is still under dispute, because of experimental difficulties in measuring change of acid/ion concentrations caused by the acidity of the solvent. In this case UV/Vis spectrophotometry fails: the $\pi \rightarrow \pi^*$ band is located at 190–210 nm and shifts batochromically on protonation. Unfortunately, a weak $n \rightarrow \pi^*$ band shifts hipsochromically at the same time and overlaps with the $\pi \rightarrow \pi^*$ band, especially when protonation predominates and results are highly dependent on the wavelength at which the calculations are made[105]. Both hydrogen[109,110] and carbon[111] NMR were used to study protonation of aliphatic acids. Some numerical data on the basicity constants are collected in Table 17.

It is immediately obvious that saturated carboxylic acids are very weak bases: half-protonation occurs in sulphuric acid of concentration 80% or more. The length of the alkyl chain does not alter the basicity very much. Substituents of strong electronegative properties decrease the basicity, as expected.

The fact that the slope of the line B/BH^+ vs acidity function is much lower than unity means that the Hammett acidity function H_0 does not accommodate the protonation of the carboxyl group, and that the Hammett postulate is not obeyed[110]. Application of the assumptions of Bunnet–Olsen[15] or Marziano and coworkers[112] leads to pK_{BH^+} values in the range of −2 to −3.5 units, but these results are unlikely.

Unsaturated carboxylic acids were far more extensively investigated. The $\pi \rightarrow \pi^*$ absorption bands are located at longer wavelengths and their intensity is much higher as compared to saturated acids. Simultaneously, the $n \rightarrow \pi^*$ bands are relatively weaker, so that their contribution could be neglected. An earlier pK_{BH^+} investigation used the H_0 acidity function to express the acidity of the medium. Zalewski and Dunn, however, found[29] that the amide acidity function H_A developed by Yates and coworkers[113] describes also the protonation of the carboxyl group and other carbonyl-containing groups. Hence the older results based on the H_0 acidity function reflect only the acidity of the medium in terms of H_0 ($pK_{BH^+} \equiv H_0$) and are not true thermodynamic equilibrium constants.

In Tables 18 and 19 basicity data on various unsaturated and aromatic carboxylic acids are collected. Thermodynamic pK_{BH^+} values are reported and occasionally compared with H_0 values at half protonation. In many cases the locations of λ_B and λ_{BH^+} are also reported. Most data come from one laboratory, which is very important for further discussion. However, data from different sources are comparable.

1. Benzoic acids

Basicity constants of 12 *para*, 4 *meta* and 12 *ortho* monosubstituted and 4 multiply substituted benzoic acids are reported in Table 18 using H_A acidity function[114].

The relationships between basicity constants and the properties of the substituents in the *para* and *meta* positions is examined through a Hammett plot, shown in Figure 8.

TABLE 18. Basicity of benzoic acids

Carboxylic acids	pK_{BH^+}	λ_B	λ_{BH^+}	pK_{BH^+}	pK_{BH^+}
Benzoic acids					
H	-4.70 ± 0.05	233	261[a]	—	−7.26[c]
p-OH	-4.33 ± 0.04	258	280[a]	-7.30 ± 0.05[b]	−6.67[c]
p-OEt	-4.36 ± 0.06	260	299[a]	—	−6.68[c]
p-*t*-Bu	-4.48 ± 0.04	249	270[a]	—	—
p-Me	-4.52 ± 0.03	231	276[a]	7.52 ± 10[b]	−6.92[c]
p-*i*-Pr	-4.52 ± 0.03	250	278[a]	—	
p-Ph	-4.65 ± 0.04	275	300[a]	—	—
p-F	-4.92 ± 0.04	238	264[a]	-7.80 ± 0.05[b]	−7.30[c]
p-Cl	-4.97 ± 0.04	248	276[a]	-8.25 ± 06[b]	−7.48[c]
p-I	-4.95 ± 0.05	264	313[a]	-8.00 ± 0.10[b]	−7.80[c]
p-COOH	-5.02 ± 0.06	—	280[a]	—	—
p-CF_3	-5.34 ± 0.05	228	257[a]	-8.62 ± 0.10[b]	
p-NH_3^+	-5.43 ± 0.06	—	245[a]	-8.72 ± 0.12[b]	—
m-Me	-4.62 ± 0.06	239	266[a]	-7.70 ± 0.10[b]	−7.10[c]
m-NO_2	—	—	—	—	−7.97[c]
m-OH	-4.84 ± 0.04	240	258[a]	-8.08 ± 0.04[b]	−7.47[c]
m-OEt	—	—	—	—	−7.56[c]
m-Br	-5.14 ± 0.06	238	262[a]	-8.67 ± 0.12[b]	−7.65[c]
m-F	—	—	—	—	−7.62[c]
m-NH_3^+	-5.41 ± 0.03	231	248[a]	—	—
m-Cl	—	—	—	-8.61 ± 0.11[b]	−7.73[c]
m-I	—	—	—		−7.64[c]
o-Me	-4.75 ± 0.04	238	264[d]	−4.82[e]	−7.13[f]
o-Et	-4.89 ± 0.05	238	265[d]	−4.90[e]	−7.16[f]
o-F	-5.25 ± 0.04	231	258[d]	−5.23[e]	−7.60[f]
o-Cl	-5.40 ± 0.04	235	262[d]	−5.34[e]	−7.64[f]
o-Br	-5.46 ± 0.06	236	266[d]	−5.45[e]	−7.76[f]
o-I	-5.48 ± 0.05	—	268[d]	−5.45[e]	−7.78[f]
o-CF_3	-5.51 ± 0.06	277	250[d]	—	
o-OH	-4.40 ± 0.05	240	261[d]	—	6.78[f]
o-Ph	-4.57 ± 0.06	—	266[d]	—	
o-OMe	-4.01 ± 0.05	240	262[d]	—	−6.10[f]
o-NH_3^+	-3.96 ± 0.06	277	241[d]	—	
o-COOH	-3.71 ± 0.05	—	215[d]	—	−5.96[f]
2,4-Me_2	-4.49 ± 0.05	250	279[d]	—	
2,5-Me_2	-4.62 ± 0.05	246	270[d]	—	
2,6-Me_2	-5.05 ± 0.05	244[g]	281[d]	—	
2,4,6-Me_3	-4.86 ± 0.04	245[g]	282[d]	—	

[a] From Reference 114.
[b] From Reference 115.
[c] From Reference 116, H_0 at half-ionization.
[d] R. I. Zalewski, unpublished data.
[e] From Reference 117, recalculation of H_0 into H_A.
[f] From Reference 117, H_0 at half-ionization.
[g] Shoulder.

TABLE 19. Basicity of other aromatic and unsaturated acids

Carboxylic acids	pK_{BH^+}	λ_B	λ_{BH^+}
Salicylic acids (from Reference 114)			
H	-4.40 ± 0.05	245	260
4-Me	-4.11 ± 0.05	247	273
4-F	-4.53 ± 0.06	242	264
4-Cl	-4.67 ± 0.06	250	275
4-Br	-4.65 ± 0.04	252	284
4-OH	-3.93 ± 0.05	260	281
4-OMe	-3.96 ± 0.05	264	286
4-COOH	-4.75 ± 0.06	—	266
4-NO_2	-5.26 ± 0.06	—	268
4-NH_3^+	-5.35 ± 0.07	236	252
5-F	-4.76 ± 0.04	238	258
5-Cl	-4.88 ± 0.04	242	260
5-Br	-4.91 ± 0.06	238	262
5-OH	-5.51 ± 0.05	240	259
5-OMe	-4.65 ± 0.06	238	260
5-COOH	-4.92 ± 0.04	—	238
5-NO_2	-5.44 ± 0.07	—	246
5-NH_3^+	-5.50 ± 0.06	252	—
Acrylic acid	-4.41 ± 0.04	197	216[a]
Crotonic acid	-4.03 ± 0.03	209	235[a]
2,4-Hexadienoic acid	-3.30[b]		
Tiglic acid	-4.08 ± 0.10[c]		
Cyclopentencarboxylic acid	-4.05 ± 0.10[c]		
Cyclohexanecarboxylic acid	-3.88 ± 0.10[c]		
Cycloheptene carboxylic acid	-3.84 ± 0.10[c]		
Cinnamic acids (from Reference 118)			
H	-3.90 ± 0.07	278	321
p-NH_3^+	-4.32 ± 0.04	278	312
p-OMe	-3.62 ± 0.03	310	357
p-OH	-3.68 ± 0.04	306	357
p-Me	-3.81 ± 0.03	294	352
p-Cl	-3.95 ± 0.06	290	347
p-Br	-3.89 ± 0.10	294	351
p-NO_2	-4.46 ± 0.04	—	344
m-OMe	-4.00 ± 0.03	270	323
m-Me	-3.96 ± 0.03	279	337
m-OH	-4.00 ± 0.02	278	322
m-Cl	-4.22 ± 0.02	277	322
m-Br	-4.19 ± 0.03	277	322
m-NH_3^+	-4.35 ± 0.03	263	302
o-OMe	-3.80 ± 0.03	278	322
o-Me	-4.45 ± 0.03	270	328
o-OH	-3.86 ± 0.05	277	319
o-Cl	-4.27 ± 0.02	279	328
o-NO_2	-4.42 ± 0.15	250	303

[a] From Reference 28.
[b] From Reference 119.
[c] From Reference 120.

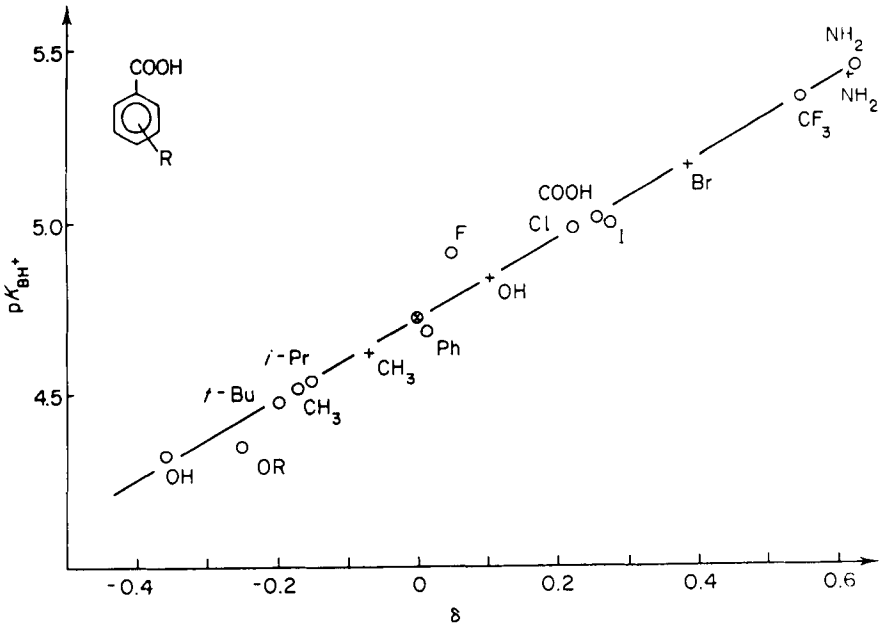


FIGURE 8. Hammett plot of *meta*(+) and *para*(○) substituted benzoic acids

TABLE 20. Correlation of pK_{BH^+} with substituent constants

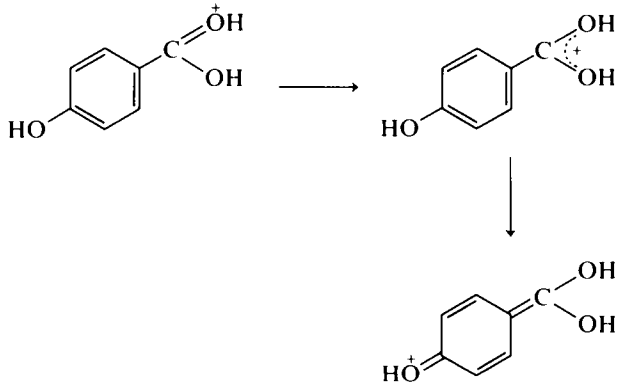
A. Hammett equation

	ρ	$pK^{\circ}_{BH^+}$	r^2	S	n
Benzoic acids	−0.94	−4.70	0.949	0.07	16
Salicylic acids	−1.18	−4.45	0.755	0.24	18
Cinnamic acid	−0.60	−3.89	0.894	0.80	14

B. Swain–Lupton equation

	$pK^{\circ}_{BH^+}$	ρf	ρr	r^2	S	n
Benzoic acids						
para	−4.65	−0.561	−0.331	0.972	0.05	11
Salicylic acids						
4-X (*para*)	−4.32	−0.565	−0.364	0.987	0.05	9
5-X (*meta*)	−4.79	−0.324	−0.003	0.045	0.32	7
Cinnamic acids						
4-X (*para*)	−3.89	−0.233	−0.222	0.950	0.08	7
5-X (*meta*)	−3.99	−0.307	−0.84	0.973	0.02	6

Only *p*-fluorine deviates significantly from the straight line. In all correlations the substituent constant for NH_3^+ was used instead of that for NH_2. Parameters of the Hammett equation are shown in Table 20. The negative slope with magnitude close to one means that electron donors increase the basicity through resonance stabilization of the positive charge to a degree comparable to the destabilization of the negative charge of carboxylates.



In addition, the correlation of experimental data has been performed with the Swain–Lupton multiparameter equation in order to determine the contribution of the inductive and mesomeric effects, ρf and ρr, respectively. The data are also presented in Table 20 and show good agreement between the Swain–Lupton model and the experimental results, however calculations were not performed for 4 *meta* acids.

Special interest is focused on *ortho*-substituted benzoic acids, and on multisubstituted acids with one *o*-Me group. It is not possible to apply correlation equations like that of Hammett or of Swain–Lupton for this case. Acids, bearing identical substituents in *para* and *ortho* positions, have basicities linked by two straight lines (see Figure 9), which are described by the following equations:

$$\begin{aligned} pK^{\circ}_{BH^+} &= 1.06\, pK^{p}_{BH^+} - 0.19 \quad \text{(a)} \\ pK^{\circ}_{BH^+} &= 1.42\, pK^{p}_{BH^+} - 2.05 \quad \text{(b)} \end{aligned} \tag{61}$$

This means that two different modes of transmission of electronic effects operate in *ortho*-substituted benzoic acids.

Ortho halo- and alkyl-substituted acids are slightly weaker bases than their *para* counterparts. The blend of inductive and resonance contributions is constant in *ortho*-substituted acids, and different but constant in *para*-substituted acids. Calculation with the Swain–Lupton equation indicates that in *ortho* derivatives the inductive effect is 1.5 times greater than in *para*, and the resonance effect is 0.5 times smaller than in the *para* position. The increased role of the inductive effect in the *ortho* position is due to the shorter distance than with *para* substitution; the decreased role of the resonance effect could be explained by similar and constant steric effects.

The remaining *ortho*-substituted acids behave in a less regular way (see Figure 9). *o*-Trifluoromethyl and *o*-phenyl substituents could cause distortion of the planarity between the carboxyl groups and the aromatic ring. Protonated salicylic methoxy-salicylic acids and *o*-phthalic acids are stabilized by a hydrogen bond, which increases the basicity as compared to *para* isomers. Mono-, di- and tri-methyl substituted acids

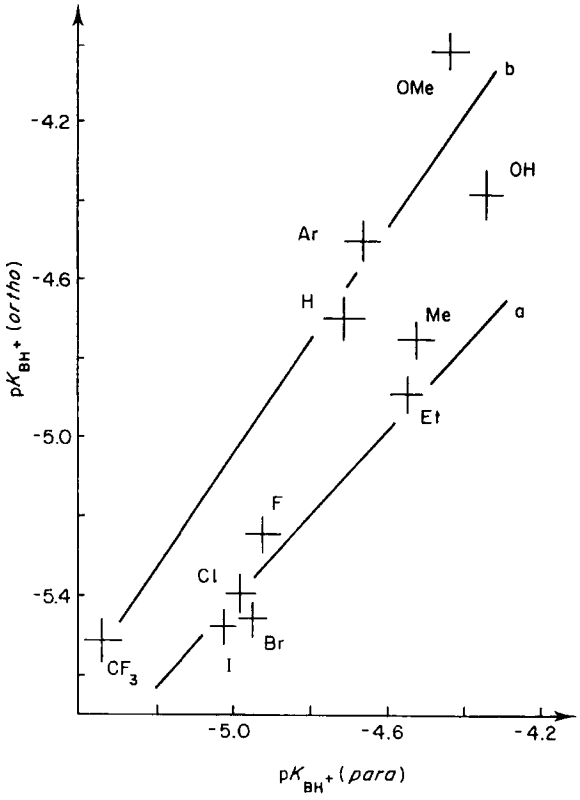
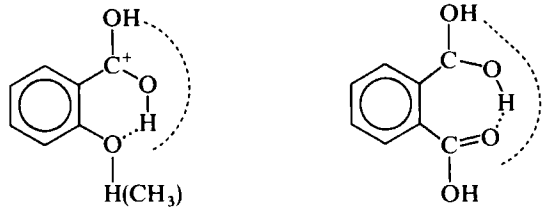


FIGURE 9. Basicity relationship between *para* and *ortho* isomers

constitute a special case. The methyl group is relatively large but does not produce a large steric effect, and its inductive and resonance effects are also rather small. 2-Methylbenzoic acid is only weaker than benzoic acid by 0.05 pK_{BH^+} units. The next methyl in



position 4 or 5 increases the basicity in a regular way as in *para* or *meta* monosubstituted acids; the effect of both substituents is additive (Figure 10). The basicity of 2,6-Me_2-benzoic acid is much less (0.30 pK_{BH^+} unit) than that of the 2-Me derivative. The effect of the second methyl group is much greater than that of the first, due to steric inhibition of resonance. 2,4,6-Me_3-benzoic acid is again stronger due to the presence of a *para* methyl group, which enhances the basicity. A strong steric effect is observed in the

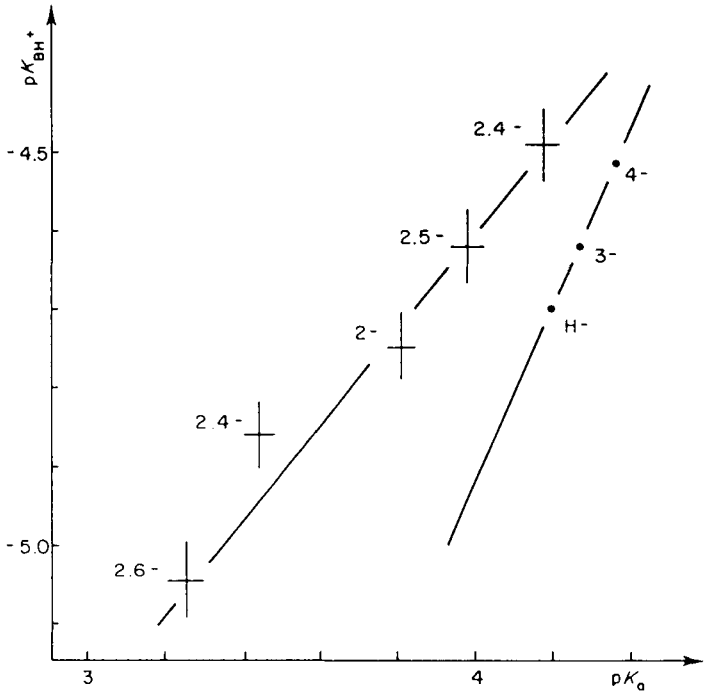


FIGURE 10. Relationships between acidity and basicity of Me-substituted benzoic acids

spectra of 2,4,6-Me_3-benzoic acid (Figure 11). In diluted acids the absorption band is weak and is present rather as a plateau in the range 230–250 nm. Protonation shifts the maximum towards a longer wavelength, and finally a very intensive maximum arises at 282 nm, characteristic of the protonated acid. Unprotonated 2,4,6-Me_3-benzoic acid is evidently non-polar. Coplanarity of the aromatic ring and the protonated carboxyl group is forced through resonance stabilization of the positive charge. Similar conclusions were drawn from studies of UV-spectra in 100% sulphuric acid[121,122] and from the decarboxylation of various aromatic acids in acidic media[122].

2. *Salicylic acids*

o-Hydroxybenzoic acid (salicylic acid) is a stronger base than benzoic acid due to the resonance and hydrogen bond stabilization of the protonated species. Salicylic acids substituted in position 4 and 5 are stronger or weaker bases (Table 19), in qualitative agreement with their electronic properties. The substituents can affect the basicity of the carboxyl group either according to the Hammett equation or through the influence on the acidity of the phenolic hydroxyl group, which in turn affects its interaction with the carboxyl group.

The additional effect is represented by the expression $\sigma_2\delta_p^-$ where δ_p^- denotes the substituent constants for substituents in phenols and amines. Both effects are additive

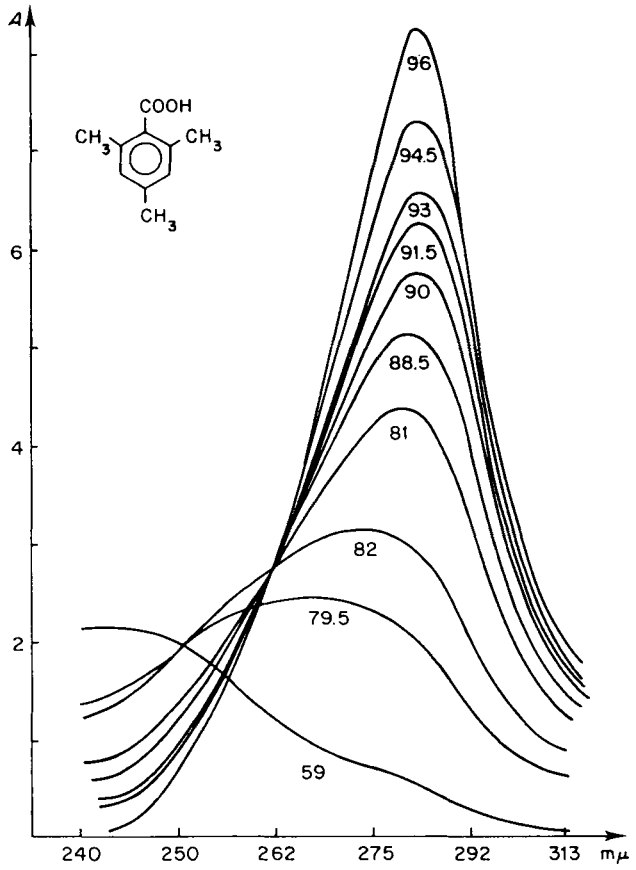


FIGURE 11. Absorption spectra of 2,4,6-Me benzoic acid in sulphuric acids. Numbers under spectra refer to conc. (%) of sulfuric acid

and, as a result, the Hammett equation becomes

$$\log(K/K_0) = \sigma_1\delta_{p,m} + \sigma_2\delta_p^- \tag{62}$$

The effect of the second substituent is constant for all compounds and is not significant as indicated by the magnitude of σ_2 derived by the least-squares method:

$$\Delta pK_{BH^+} = -1.78\sigma_{m,p} - 0.02\sigma_p^- \tag{63}$$

Hence the effect of substituents on the basicity of salicylic acids is in agreement with the Hammett equation. The relation between pK_{BH^+} and the substituent constants is shown in Figure 12.

The reaction constant $\rho = -1.18$ as compared with the ρ value for benzoic acids ($\rho = -0.94$) means that protonation of salicylic acids is more sensitive against electronic properties of 4- and 5-substituents.

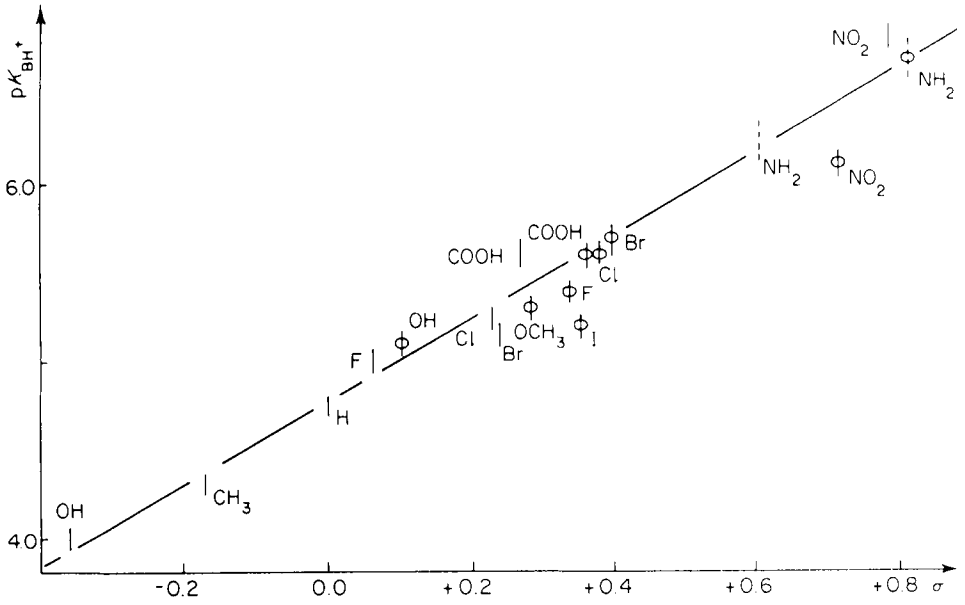


FIGURE 12. Hammett plot for 4- and 5-substituted salicylic acids (| and ϕ, respectively)

Examination of pK_{BH^+} data sets for salicylic acids with the Swain–Lupton dual parameter equation shows that the inductive effect from the *meta* position is higher than from *para*. The opposite is true for the resonance effect σ_r, as expected.

3. Cinnamic acids

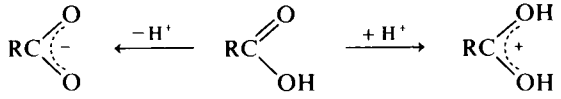
The basicity of cinnamic acid and 18 *ortho*-, *meta*- and *para*-substituted derivatives is presented in Table 19. An increase of basicity by electron donors and decrease by electron acceptor are in agreement with previous discussions. Quantitative considerations concerning the effect of substituents on the protonation in sulphuric acid are supported by the Hammett equation:

$$pK_{BH^+} = -(0.65 \pm 0.04)\sigma_{m,p} - 3.93 \pm 0.02 \qquad (64)$$
$$r = 0.978 \qquad n = 12$$

A negative and smaller than unity reaction constant ρ means that substituents affect the basicity less than in benzoic acid. *Ortho*-substituted cinnamic acids are in general weaker bases than the respective *para* isomers. The much weaker basicity of *o*-Me cinnamic acid could be explained by steric inhibition of resonance. The relatively high basicity of *o*-NO_2 cinnamic acid could result from additional stabilization of the positive charge by the *o*-nitro group. Cinnamic acid, as indicated by a value of pK_{BH^+} close to -3.90, is a much stronger base than benzoic acid ($pK_{BH^+} = -4.70$) and salicylic acid ($pK_{BH^+} = -4.40$). The only explanation is the basicity strengthening role of the conjugated olefinic bond, in addition to the presence of the aromatic ring.

4. Thermodynamics of benzoic acid protonation

Thermodynamic studies of the protonation reaction of carboxyl groups in highly acidic media are very rare[115]:



(65)

The thermodynamic parameters ΔG°, ΔG_{Thm}, ΔH° and ΔS° have been calculated using protonation constants pK_{BH^+} for a set of 12 *meta*- and *para*-substituted benzoic acids at 25 °C, 40 °C and 60 °C. The experimental data on basicity of benzoic acids are presented in Table 21. The basicity of benzoic acid has been expressed in terms of the Hammett acidity function H_0, since no data exist for H_A acidity functions at elevated temperatures. The effect of *meta*- and *para*-substituents on pK_{BH^+} is in good agreement with other literature sources[123,116,114]. Four acids, with R = H, *p*-J, *p*-NH_3^+ and *m*-Br, were omitted from further discussions due to the high uncertainty in their ΔG° and ΔH° values.

To avoid the misleading and uncertain relation between ΔH° and ΔS°, the procedure proposed by Krug and coworkers[124] was used; it applies a plot of ΔH° and $\Delta G^\circ_{\text{Thm}}$. The regression of enthalpy estimates on free energy estimates evaluated at the harmonic-mean of the experimental temperature range is satisfactory:

$$\delta\Delta H^\circ = 5.365 - 0.510\delta\Delta G_{\text{Thm}}, \quad n = 8, \quad r = 0.987 \tag{66}$$

The slope of the regression line −0.510 is equivalent to a function of isokinetic temperature $1/(1 - T/\beta)$ and leads to $\beta = -327$ K. The large difference in the harmonic mean of the experimental temperature and the isoequilibrium temperature suggests a strong chemical compensation effect, which was analysed based on the Krygowski and Guilleme approach[125] and Pitzer's assumption[126] for ionic reactions.

Protonation of benzoic acids follows the condition $(\beta/T) > 1$ and $\beta < 0$; thus the dominant contribution to $\delta\Delta G^\circ$ is $\delta\Delta H$, and in fact its $\delta\Delta H_{\text{int}}$ part. This means that the internal enthalpy contribution to the substituent effect in protonation of benzoic acids in strongly acidic media is much more important than in the dissociation of benzoic acids (with $\beta \sim 0$ K)[125,127].

Very similar conclusions could be drawn using the reported data on protonation of other weak bases[128]. The linear relationship between H° and ΔG° for nitroanilines and carbinols with a positive slope means that the isoequilibrium temperature is large and negative, exactly in line with benzoic acids.

C. Gas-phase Acidity and Basicity of Carboxylic Acids

1. General remarks

Gas-phase acidities and basicities are associated with energies of processes which can be written as

$$AH \longrightarrow H^+ + A^- \quad \text{anion proton affinity (gas-phase acidity)} \tag{67}$$

$$BH^+ \longrightarrow H^+ + B \quad \text{proton affinity (gas-phase basicity)} \tag{68}$$

TABLE 21. Basicity and thermodynamic parameters of benzoic acids

Substituent	$-pK_{BH^+}^{25}$	$-pK_{BH^+}^{40}$	$-pK_{BH^+}^{60}$	ΔG (kcal mol^{-1})	ΔG_{Thm} (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔS° (cal K^{-1} mol^{-1})	r^a	f^b
p-OH	7.30 ± 0.05	6.90 ± 0.07	6.40 ± 0.10	13.4 ± 0.2	13.5 ± 0.2	11.7 ± 0.2	−5.8 ± 0.5	0.999	0.019
p-Me	7.52 ± 0.07	7.12 ± 0.10	6.65 ± 0.06	12.3 ± 0.1	12.4 ± 0.1	11.3 ± 0.1	−3.5 ± 0.2	0.999	0.006
m-Me	7.70 ± 0.10	7.31 ± 0.08	6.96 ± 0.07	8.7 ± 0.8	8.6 ± 0.8	9.9 ± 0.8	3.1 ± 2.5	0.997	0.116
H	7.93 ± 0.07	7.25 ± 0.10	6.97 ± 0.08	13.9 ± 3.6	14.0 ± 3.6	12.3 ± 3.6	−5.3 ± 11.5	0.959	0.400
p-F	7.80 ± 0.05	7.50 ± 0.08	7.27 ± 0.07	3.0 ± 0.9	2.9 ± 0.9	6.8 ± 0.9	12.7 ± 2.8	0.992	0.179
m-OH	8.08 ± 0.04	7.75 ± 0.05	7.25 ± 0.10	10.6 ± 0.9	10.6 ± 0.9	10.8 ± 0.9	0.8 ± 2.4	0.998	0.095
p-Cl	8.25 ± 0.06	7.91 ± 0.06	7.58 ± 0.11	6.1 ± 0.5	6.0 ± 0.5	8.7 ± 0.5	8.6 ± 1.6	0.998	0.084
p-I	8.00 ± 0.10	7.86 ± 0.06	7.41 ± 0.08	4.6 ± 1.9	4.4 ± 1.9	7.8 ± 1.9	10.8 ± 6.2	0.970	0.341
m-Cl	8.61 ± 0.11	8.07 ± 0.10	7.50 ± 0.08	17.0 ± 0.5	16.8 ± 0.5	14.4 ± 0.5	−8.9 ± 1.6	0.999	0.050
m-Br	8.67 ± 0.12	8.00 ± 0.08	7.70 ± 0.13	13.1 ± 3.4	13.2 ± 3.4	12.4 ± 3.4	−2.4 ± 1.7	0.964	0.374
p-CF_3	8.62 ± 0.10	8.15 ± 0.07	7.75 ± 0.08	10.8 ± 1.1	10.7 ± 1.1	11.2 ± 1.1	1.6 ± 3.5	0.995	0.137
p-NH_3^+	8.72 ± 0.12	8.12 ± 0.06	7.91 ± 0.11	8.9 ± 3.4	8.9 ± 3.4	10.3 ± 3.4	4.8 ± 10.9	0.949	0.447

[a] Correlation coefficient in the van't Hoff equation
[b] Inclination of a special regression line.

The energies are the enthalpy of detachment of an ionic species from a neutral (equation 67) or a charged (equation 68) compound[129]. Each process could be also referred to the change of free energy quantity (properties quoted in brackets). The energies of the above reactions are not measured directly, but rather from a thermochemical cycle[130,131]

$$\left.\begin{array}{lll} AH \longrightarrow A^{\cdot} + H^{\cdot} & D(A{-}H) \\ A^{\cdot} + e^{-} \longrightarrow A^{-} & -EA(A^{\cdot}) \\ H^{\cdot} \longrightarrow H^{+} + e^{-} & IE(H^{\cdot}) \end{array}\right\} \quad (69)$$

and the equation

$$\Delta H^{\circ}\ \text{acid} = D(A{-}H){-}EA(A^{\circ}) + IE(H^{\cdot}) \quad (70)$$

where D, EA and IE are the bond dissociation energy, electron affinity and ionization energy, respectively. The difference between two processes, for example

$$A_1H + A_2^{-} \longrightarrow A_1^{-} + A_2H \quad (71)$$

is also frequently applied.

Using various mass spectrometry techniques, the relative abundances of the two ions can be determined under conditions where the reaction should be at equilibrium. MS techniques commonly used to solve the task are ion cyclotron resonance (ICR)[132,133], flowing afterglow[134] and pulsed chemical ionization mass spectrometry[135]. These methods will not be described further here. The conversion from relative free energies to relative enthalpies is done by determination of the temperature dependence of various equilibria, and application of the van't Hoff equation; or by determination of the entropies from statistical mechanics.

Once a relative scale of affinities or of free energy changes is constructed, it must be compared to some absolute value. Preferably, several absolute values for each of the species, covering the range of the scale, should be used to check the reliability and errors. The uncertainties of the relative affinities (equations 69 and 70) are commonly less than 0.2 kcal mol^{-1}, but they are more than 2 kcal mol^{-1} for the absolute values, due to the uncertainties of reference processes. The confirmation of the scale by a second technique (ICR vs chemical ionization mass spectrometry) is strongly recommended.

The most comprehensive compilation of such equilibrium affinity data, the 'Gas-phase ion and neutral thermochemistry'[136], is known under the acronym Giant (1988).

2. *Gas-phase acidities*

Gas-phase acidities for substituted aliphatic, alicyclic and aromatic carboxylic acids are presented in Table 22, which shows values of $-\Delta G^{\circ}$ and $-\delta\Delta G^{\circ}$[136–139] collected from the literature. Data are collected for particular families to demonstrate the effect of substitution.

Acidities of various families of carboxylic acids are well accommodated by the three-parameter equation

$$-\delta\Delta G^{\circ} = A_0 + \delta_{\alpha}\rho_{\alpha} + \delta_F\rho_F + \delta_R\rho_R \quad (72)$$

where δ and ρ are the reaction and substituent constants for α, F and R mode of transmission i.e., polarizability, the field and resonance, respectively.

It is immediately clear from the regression equation parameters in Table 23 that acidities of substituted acetic acids and bicyclo-[2,2,2]-octanecarboxylic acids does not contain a regression term associated with resonance. The blend of the field effect with a small contribution of the polarizability is controlling the acidity. The calculations for

TABLE 22. Comparison of various data sets on acidity of carboxylic acids in the gas phase

Acid	ΔG_{acid}[a]	$\delta\Delta G$[b]	$\delta\Delta G$
HCOOH	338.3 ± 2.0	—	—
MeCOOH	341.5 ± 2.0	0	0
CF_3COOH	317.4 ± 2.0	24.1	—
$NCCH_2COOH$	323.7 ± 2.0	17.8	16.0
MeCOCOOH	326.5 ± 2.8	15.0	—
CF_3CH_2COOH	326.9 ± 2.0	14.6	13.1
ICH_2COOH	327.7 ± 2.0	13.8	—
$HOCH_2COOH$	327.8 ± 2.0	13.7	—
$BrCH_2COOH$	328.2 ± 2.0	13.3	—
$ClCH_2COOH$	329.0 ± 2.0	12.5	12.0
$PhOCH_2COOH$	331.0 ± 2.0	10.5	—
FCH_2COOH	331.6 ± 2.0	9.9	9.6
$PhCH_2COOH$	334.5 ± 2.0	7.0	—
$MeNHCH_2COOH$	334.6 ± 62.0	6.9	—
H_2NCH_2COOH	334.7 ± 2.0	6.8	—
$EtOCH_2COOH$	335.0 ± 2.0	6.5	—
$MeOCH_2COOH$	335.3 ± 2.0	6.2	6.0
$MeCHClCH_2COOH$	334.8 ± 2.0	6.7	—
$C_6H_{11}CH_2COOH$	338.3 ± 2.0	3.2	—
1-Adamantanyl CH_2COOH	336.7 ± 2.0	4.8	—
t-$BuCH_2COOH$	337.8	3.7	—
c-$PrCH_2COOH$	338.8	2.7	—
c-$PenCH_2COOH$	338.5	3.0	—
$Br_2CHCOOH$	321.3	20.2	—
$Cl_2CHCOOH$	321.9	1.6	—
$F_2CHCOOH$	323.8	17.7	—
MeCHBrCOOH	329.8	11.7	—
EtCHBrCOOH	329.8	11.7	—
MeCHClCOOH	330.4	11.1	—
EtCHClCOOH	330.5	11.0	—
MeCH(OH)COOH	330.6	10.9	—
$H_2NCH(Me)COOH$	333.7	7.8	—
PhCH(Me)COOH	334.6	6.9	—
EtCOOH	340.4 ± 2.0	1.1	1.0
$MeCOCH_2CH_2COOH$	333.7	7.8	—
$ClCH_2CH_2COOH$	333.8	7.7	—
n-PrCOOH	339.5	2.0	—
$ClCH_2CH_2COOH$	338.5	2.8	—
i-PrCOOH	339.0	2.5	—
c-PrCOOH	339.0	2.5	—
1-Mec-PrCOOH	337.1	4.4	—
2-Mec-PrCOOH	338.8	2.7	—
n-BuCOOH	339.2	2.3	—
t-BuCOOH	337.6	3.9	—
i-BuCOOH	338.5	3	—
c-BuCOOH	338.8	2.7	—
n-PenCOOH	339.1	2.4	—
c-PenCOOH	338.6	2.9	—
c-HexCOOH	338.1	3.4	—

(*continued*)

TABLE 22 (*continued*)

Acid	ΔG_{acid}[a]	$\delta\Delta G$[b]	$\delta\Delta G$	$\delta\Delta G$
CH_2=CHCOOH	337.2	0	—	
MeCH=CHCOOH	339.1	−1.9	—	
Me_2C=CHCOOH	338.9	−1.7	—	
EtCH=CHCOOH	338.2	−1.0	—	
CH_2=$CHCH_2CH_2COOH$	337.3	−0.1	—	
CH_2=$CH(Me)_2COOH$	335.0	2.2	—	
CH_2=C(Me)COOH	337.1	0.1	—	
X-bicyclo[2,2,2]-octanecarboxylic acids[c]				
= H	337.2	0	0	0
4X = NO_2	328.4	8.8	8.7	—
COO^-	—	—	—	8.5
CN	328.6	8.6	8.4	8.4
Br	330.3	6.9	6.7	6.4
CF_3	330.7	6.5	6.3	6.4
Cl	331.0	6.2	6.2	6.5
F	331.6	5.6	5.6	5.6
COOMe	—	—	3.2	—
OMe	334.6	2.6	2.7	2.6
Me	336.2	1	0.9	0.9
3X = CN	330.7	6.5	—	6.4
Cl	333.2	4.0	—	3.9
OMe	336.5	0.7	—	0.9
2X = CN	328.9	8.3	—	7.9
X-bicyclo[2,2,2]-octenecarboxylic acids				
= H	335.3	0	—	0
4X = CN	326.2	9.1	—	8.4
Cl	328.8	6.5	—	6.2
CF_3	328.8	6.5	—	6.3
COOEt	331.9	3.4	—	3.2
Me	334.4	0.9	—	—
Cubanecarboxylic acids				
H	334.1	0	—	—
4-Br	329.4	4.7	—	5.7
4-COOMe	330.7	3.4	—	4.3
1-Adamantanecarboxylic acids				
H	330.0	0	—	0
3-Cl	331.4	4.6	—	5.1
Benzoic acids				
H	333.1	0	0	—
o-OH	318.4	14.7	—	—
Cl	327.9	15.2	—	—
NH_2	329.0	4.1	—	—
F	329.4	3.7	—	—
OMe	331.2	1.9	—	—
Me	330.9	2.2	—	—
m-CN	322.1	11.0	10.2	—
NO_2	322.7	10.4	10.8	—
CF_3	325.2	7.9	7.3	—

(*continued*)

TABLE 22 (*continued*)

Acid	ΔG_{acid}[a]	$\delta\Delta G$[b]	$\delta\Delta G$	
Cl	327.0	6.1	4.7	—
F	327.9	5.2	3.8	—
OH	330.4	2.7	—	—
OMe	331.2	1.9	0.5	—
Me	332.4	0.7	−0.7	—
NH_2	333.3	−0.2	−1.5	—
p-NO_2	—	—	11.1	—
CN	321.4	11.7	10.8	—
CF_3	325.3	7.8	7.7	—
CHO	325.8	7.3	—	—
Cl	327.3	5.8	4.3	—
COMe	327.3	5.8	—	—
OH	327.7	5.4	—	—
F	328.8	4.3	2.9	—
Me	332.8	0.3	−1.1	—
NH_2	334.0	−0.9	−2.3	—

[a] From Reference 136.
[b] From Reference 137.
[c] From References 138 and 139.

other alicyclic systems were not performed because the number of substituents available was too low. In contrast, the resonance term is large and very important in *meta*- and *para*-substituted benzoic acids. Polarizability contribution is absent in aromatic acids.

The plots of the acidities of benzoic acids in water solution and versus those in the gas phase[137] are not perfectly linear as is shown by Figure 13, in contrast to 4-substituted-bicyclo-[2,2,2]-octane-1-carboxylic acids shown by Figure 14. This suggests a pronounced distortion in aromatic acids, particularly for electroattracting substituents, by a resonance effect due to substituent hydration phenomena.

In aqueous solution the acidity of aliphatic carboxylic acids decreases with the increase of alkyl group size[140] while in the gas phase the acidity increases with the size of the alkyl group[136,141]:

	CH_3	Et	n-Pr	*i*-Pr	n-Bu	*i*-Bu	*t*-Bu	n-Pen
$\delta\Delta G°$ (kcal m^{-1}) gas phase	0	1.1	2.0	2.5	2.3	3.0	3.9	2.4

TABLE 23. Parameters of regression equation 72 for some acids

Acid	A_0	ρ_R	ρ_F	ρ_π	r
XCH_2COOH	−0.30 ± 0.05	0	24.6 ± 1.1	−3.9 ± 1.0	0.994
4X-Bicyclo-[2,2,2]-octanecarboxylic acids	−0.00 ± 0.03	0	12.9 ± 0.6	−1.1 ± 0.6	0.994
p-Benzoic acids	−0.20 ± 0.20	14.6 ± 0.7	15.0 ± 0.6	0	0.997
m-Benzoic acids	−0.10 ± 0.20	11.5 ± 0.9	14.7 ± 0.5	0	0.998

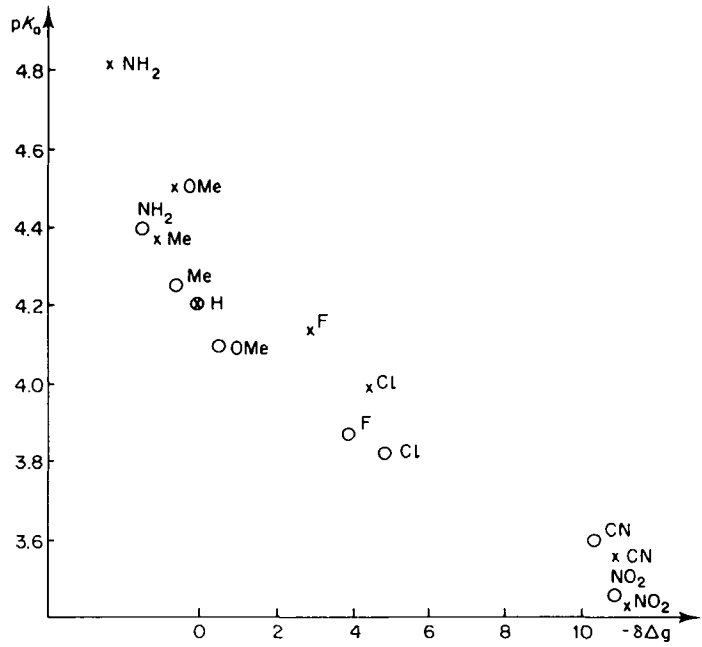


FIGURE 13. Plot of pK in water vs gas phase for benzoic acids

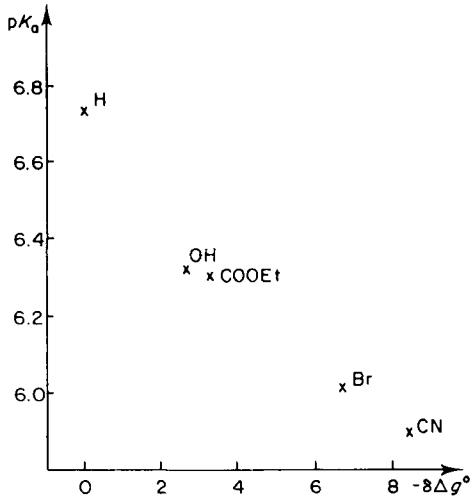
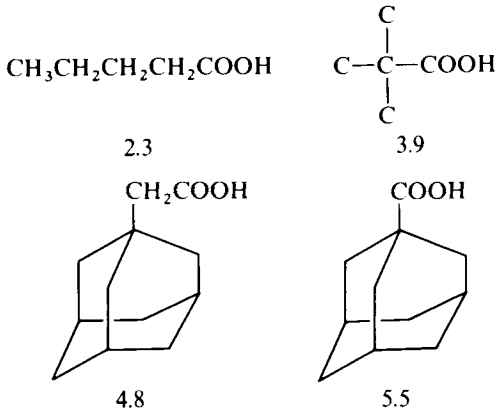


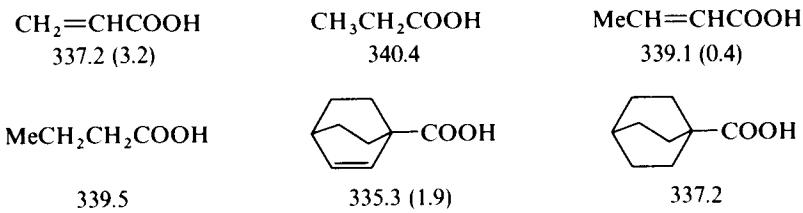
FIGURE 14. Plot of pK in water vs gas phase for bicyclo[2,2,2]-octane carboxylic acids

Acetic acid is weaker than formic acid by 3.4 kcal mol^{-1} as a result of the replacement of hydrogen on sp^2 carbon by a methyl group. Replacement of methyl by longer chains increases the acidity, however with diminishing strength. Branched groups have a stronger effect than straight chains of equal carbon number. This can be attributed to the stabilizing effect of the polarizability of the alkyl group on the negative ion. The strong effect of an α-tertiary carbon is observed for C_4 acids as well as for the adamantanecarboxylic acid and adamantyl acetic acid pair. In α-tertiary acids the distance between the tertiary carbon and the negative ion is closest and this maximizes the polarizability stabilization:

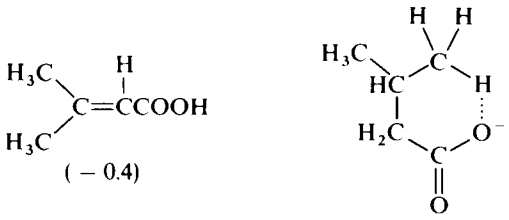


The strongest among these acids is 1-adamantanecarboxylic acid. This is a blend of the effects of a tertiary carbon and extensive carbon branching.

Conjugated double bonds increase the acidity of aliphatic carboxylic acids. Propenoic acid is stronger by 3.2 kcal mol^{-1} than propanoic acid. Similar findings hold also for other structures:



The origin of this effect is in the electron-withdrawing and field-inductive nature of the olefinic bond. The weak acidifying effect in β-methylcrotonic acid could be explained by the gain of acidity in the saturated analogue due to stabilization by hydrogen bonding.



The effect of a halide substituent is strongly acidifying, but decreases as the halide is more remote from the carboxyl group

$CH_3CH_2CH_2COOH$	$ClCH_2CH_2CH_2COOH$
2.0	2.8
$CH_3\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_2COOH$	$CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCOOH$
6.7	11 (kcal mol^{-1})

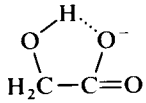
or when a strongly electronegative halide is replaced by a less electronegative one

FCH_2COOH	$ClCH_2COOH$	$BrCH_2COOH$	ICH_2COOH
9.9	12.5	13.3	13.8 (kcal $mol.^{-1}$)

or when the number of halide atoms is increasing:

FCH_2COOH	$F_2CHCOOH$	$BrCH_2COOH$	$Br_2CHCOOH$
9.9	17.7	13.3	20.2 (kcal mol^{-1})

The acidity changes by oxygen substituents occur in the order MeO < EtO < PhO < HO due to the field-inductive effect and to polarizability. Due to intramolecular hydrogen bonding, the anion of the hydroxy acid is well stabilized and its acidity



becomes larger. The gas-phase acidity of benzoic acids ($\delta\Delta G°$) has been measured and related to the $\Delta\varepsilon(A^-)$ value which describes the property of anion by HOMO, and the equation:

$$\delta\Delta G° = -\Delta D(A^-—H^+) = -\Delta D(A—H) + \Delta\varepsilon(A^-) \tag{73}$$

$\Delta\varepsilon(A^-)$ values were calculated directly[142] from the STO-3g approximation as eigenvalues of benzoate anions with the assumption that the substituent effect on the $\Delta D(A—H)$ (the homolytic bond dissociation energy) was negligible. Calculated $\Delta\varepsilon(A^-)$ and $\delta\Delta G°$ values for several *meta*- and *para*-substituted benzoic acids are collected in Table 24. The relationship between both variables is linear (*p*-OH excluded):

$$\delta\Delta G° = 0.881\Delta\varepsilon(A^-) + 5.227 \text{ kJ mol}^{-1},\ r = 0.987 \tag{74}$$

and shows that $\Delta\varepsilon$ is less sensitive towards substituent properties than $\delta\Delta G°$. The deviation of *p*-hydroxybenzoic acid from the straight line (see Figure 15) is due to the formation of a phenolate ion[143]. It is claimed[142] that $\Delta\varepsilon$ could be used as a substituent parameter similar to $\sigma_{m,p}$, however restricted to gas-phase equilibria and rates.

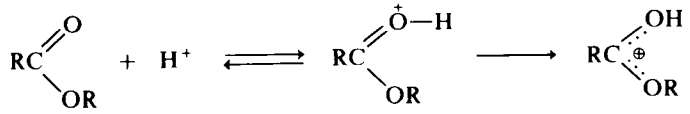
V. ACIDITY AND BASICITY OF ESTERS OF CARBOXYLIC ACIDS

The acid–base catalysed hydrolysis of esters is an important and widely studied organic reaction[144]. A complete investigation of the mechanism of this reaction requires an analysis of the dependence of the reaction rate on the acidity of the medium. This information is available only if the protonation–deprotonation parameters of the substrate can be measured exactly.

TABLE 24. Experimental gas-phase $\Delta(\Delta G^\circ)_x$ values at 600 K of substituted benzoic acids (kJ mol^{-1}), HOMO eigenvalues (ε) of the corresponding anions (a.u.) and $\Delta\varepsilon_x$ (kJ mol^{-1})

X	$\Delta(\Delta G^\circ)_x$	ε_x	$\Delta\varepsilon_x$	$\sigma_{m,p}$
p-NH_2	9.6	−0.1610	2.364	−0.660
m-NH_2	6.3	−0.1632	−3.415	−0.160
p-CH_3	4.6	−0.1611	2.101	−0.170
m-CH_3	2.9	−0.1619	0.000	−0.069
Unsubstituted	0.0	−0.1619	0.000	0.000
m-OH	−5.4	−0.1687	−17.862	0.121
p-F	−12.1	−0.1695	−19.963	0.062
m-F	−15.9	−0.1713	−24.691	0.337
p-OH	−17.2	−0.1641	−5.779	−0.370
m-CN	−42.7	−0.1820	−52.797	0.560
p-CN	−45.6	−0.1835	−56.737	0.660

Esters of aromatic and aliphatic carboxylic acids undergo protonation according to the equation



(75)

The reaction occurs in strong acidic media, and various aspects were studied in FSO_3H–SbF_5 solution at −60°C by ^1H NMR[104]. The protonated esters give well-resolved NMR spectra with slow exchange rates. The main resonance due to the proton on oxygen appears between −13.50 and −13.07 ppm in protonated formates, and between −12.72 and −12.25 ppm in other esters. This resonance is accompanied in

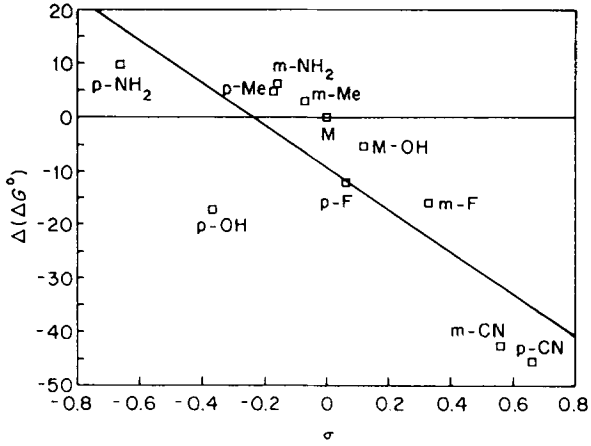
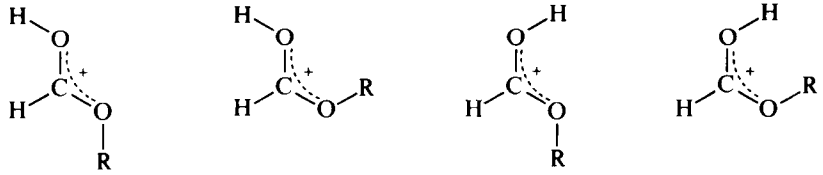


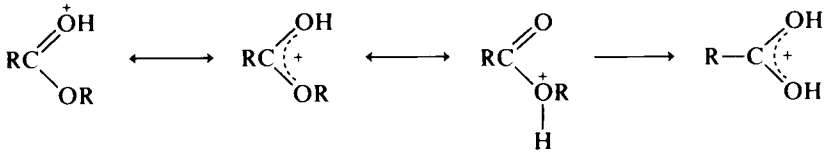
FIGURE 15. Plot of experimental gas-phase data vs $\sigma_{m,p}$

formates by small doublets and implies the presence of conformational isomers in protonated formates:

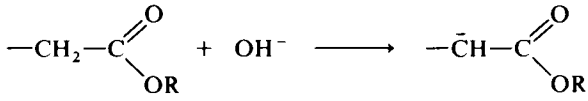


This phenomenon is not present in other esters.

An alcohol part of the ester is very important for its stability in the protonated state[104]. Thus protonated esters of primary alcohols are rather stable even at room temperature for long periods, however a large alkyl group in the acidic part is a destabilizing factor. Esters of secondary or tertiary alcohols were found to cleave between −40 and 20 °C to protonated carboxylic acids according to the mechanism



Deprotonation leads to a carbanion in strongly basic media. In weak acidic or basic solutions only traces of positive or negative ions are present.



A. Basicity of Aliphatic Esters

UV spectra of aliphatic esters are not convenient for absorbance measurements. The maximum of the $\pi \rightarrow \pi^*$ band is located near 200 nm and shifts batochromically on protonation, being simultaneously influenced by a strong medium effect and overlapping with a much weaker $n \rightarrow \pi^*$ band. For these reasons, reliable protonation parameters with this technique have only been obtained for aromatic esters. It has been demonstrated that this problem could be overcome by using H-NMR in various aliphatic compounds[145]. Unfortunately, estimation of protonation parameters by this technique is less precise than in the case of the UV indicator method. The NMR procedure stresses the assumption that chemical shifts of α hydrogens are more strongly affected by protonation than β hydrogens. NMR measurements at different acidities give the weighted-average chemical shift of the protonated and non-protonated species, and are independent of side reactions occurring by interaction of the base with the medium. Thus utilization of the position of the signal rather than its intensity is advantageous in the case of esters.

Protonation of several aliphatic esters was studied[16,146] and the results are shown in Table 25. Hammett acidity functions at half protonation are generally less than −7.0 units, showing that aliphatic esters are very weak bases. The slope of the ionization ratio vs H_0 is much less than one (its average is approximately 0.5), indicating that the Hammett acidity function does not properly describe the protonation. The Bunnett–

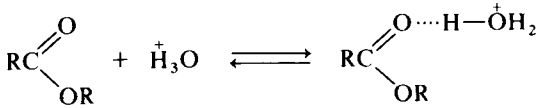
TABLE 25. Protonation of aliphatic esters[146]

	H_0[a]	Slope[b]	pK_{BH^+}[c]	pK_{BH^+}[d]	pK_{BH^+}[e]
MeCOOMe				−3.48[f] (0.34)	
MeCOOEt	−7.1 ± 0.1	0.51	−3.6 ± 0.3	−3.45 ± 0.17	−3.5 ± 0.2
MeCOOPr	−7.2 ± 1	0.68	−4.8 ± 0.3	−4.6 ± 0.4	−4.3 ± 0.3
MeCOOPr^i	−6.3 ± 1	0.51	−3.2 ± 0.3	−3.6 ± 0.1	−3.5 ± 0.2
MeCOOBu	−7.1 ± 0.1	0.54	−3.8 ± 0.3	−4.1 ± 0.2	−3.5 ± 0.2
MeCOOBu^i	−7.1 ± 0.1	0.54	−3.8 ± 0.2	−4.0 ± 0.2	−3.5 ± 0.3
$ClCH_2COOEt$	−9.5 ± 0.2	0.62	−5.9 ± 0.8	—	−4.2 ± 0.5
$CNCH_2COOEt$	−9.2 ± 0.3	0.38	−3.4 ± 1.4	—	−3.2 ± 0.2
$AcCH_2COOEt$	−8.4 ± 0.1	0.52	−4.3 ± 0.3	−3.7 ± 3	−3.2 ± 0.2
$PhCH_2COOEt$	−8.1 ± 0.1	0.83	−6.7 ± 0.7	—	−5.0 ± 0.5
EtCOOMe	−7.0 ± 0.1	0.51	−3.9	−3.3	−3.7
				−3.86[f] (0.42)	
$ClCH_2CH_2COOEt$	−8.2 ± 0.1	0.61	−5.0	—	−4.0 ± 5
PrCOOEt	−7.0	0.59	−4.1	−4.0	−3.7
i-PrCOOMe	—	—	—	−4.59[f] (0.51)	
i-BuCOOEt	−7.4	0.53	−3.9	−4.0	−2.9
t-BuCOOMe	—	—	—	−5.08[f] (0.55)	—
AcCHClCOOMe	−7.1	0.27	−1.9 ± 0.8	−2.3	−1.7
PhCH=CHCOOEt	—	—	—	−5.06[f]	—

[a] H_0 at half-protonation.
[b] Slope of line log I vs H_0
[c] Product of pK_{BH^+} product of H_E × slope.
[d] pK_{BH^+} by the Bunnett–Olsen method.
[e] pK_{BH^+} product of H_E × slope.
[f] From Reference 16 (the slope is given in parentheses).

Olsen procedure results in values between −2.3 and −5.1 for the thermodynamic pK_{BH^+} values, which are in general agreement with pK_{BH^+} values derived from the H_E acidity function[146].

The titration curves studied by Bagno and Scorrano[16] lead to the conclusion that the protonation is disturbed by a pre-protonation hydrogen-bonded structure:



Hydrogen-bonding and solvation phenomena are visualized by the value of the slope in Table 25. Increase of the slope from Me, through Et, Pr^i to Bu^t, is in line with the expected trend[16] for onium ions with decreasing solvation requirements. Solvation requirements and pK_{BH^+} values show opposite trends.

The effect of substituents in the acidic part of the ester on the half protonation is in the order CH_3 < Ph < Ac < CN < Cl, which could be explained by the inductive effect of these groups.

B. Basicity of Aromatic Esters

The basicity of aromatic esters has been investigated sporadically in the last years. For example, Edward and Wong[119] measured pK_{BH^+} of ethyl benzate and of ethyl

TABLE 26. Basicity of alkyl benzoates[147]

	pK_{BH^+}	λ_B	λ_{BH^+}
Methyl benzoate	−7.41	232.0	261.5
Methyl *p*-methylbenzoate	−5.35	242.6	278.0
Methyl *o*-methylbenzoate	−6.40	232.6	265.5
Methyl 2,6-Me_2-benzoate	−5.51	234.7	269.0

cinnamate by the indicator method in UV. To avoid problems caused by solvent–solute interactions, they used one of the multivariate statistical procedures (CVA) to clarify the spectral pattern. In addition, various ways of basicity calculations were used including H_0 or H_A acidity functions and the Bunnett–Olsen equation[15] to yield pK_{BH^+} values in the range −5.85 to −6.16 for ethyl benzoate and −4.83 to −5.56 for ethyl cinnamate. Cox and colleagues[147] investigated the basicity of four methyl esters: methyl benzoate, methyl *p*-toluate, methyl-*o*-toluate and methyl-2,6-dimethyltoluate by standard UV procedures at 10 °C. The results in Table 26 clearly describe those compounds as weak organic bases. The effect of the methyl substituent in the *para* position is base-strengthening much more than in the *ortho* position, where the electronic effect competes with the steric effect, which decreases the basicity by distortion of the coplanarity.

The same procedure has been used to determine the basicity of methyl cinnamates[148] in perchloric acid solution. Sulphuric acid has been used only to obtain the UV spectra of fully protonated cinnamates.

Methyl cinnamate with $pK_{BH^+} = -4.41$ is a weaker base than cinnamic acid ($pK_{BH^+} = -3.90$)[118] and a stronger one than methyl[149] and ethyl[147] benzoates, even after recalculation of pK_{BH^+} using the H_A acidity function (Table 27).

The effect of ring substituents on pK_{BH^+} in methyl cinnamates is clearly shown by Table 27. Electron-withdrawing substituents decrease the basicity, while electron-donating substituents increase it. This effect can be rationalized by application of the LFER:

$$pK_{BH^+} = -4.374 - 0.483\sigma_{m,p} \qquad r = 0.984,\ s = 0.023 \tag{76}$$

TABLE 27. Basicity data of methyl cinnamates[148]

Substituent	pK_{BH^+}	Slope[a]	λ_B	λ_{BH^+}
H	−4.407 ± 0.064	0.991	280	335
p-CH_3	−4.273 ± 0.071	0.994	287	342
p-OH	−4.164 ± 0.087	0.999	308	352
m-OH	−4.356 ± 0.082	0.974	277	317
m-Cl	−4.547 ± 0.036	0.968	281	322
p-Cl	−4.456 ± 0.062	0.970	286	341
m-Br	−4.517 ± 0.053	1.012	277	323
m-NO_2	−4.725 + 0.062	1.007	270	305
p-NO_2	−4.700 ± 0.53	0.910	—	322

[a] Versus H_A acidity function.

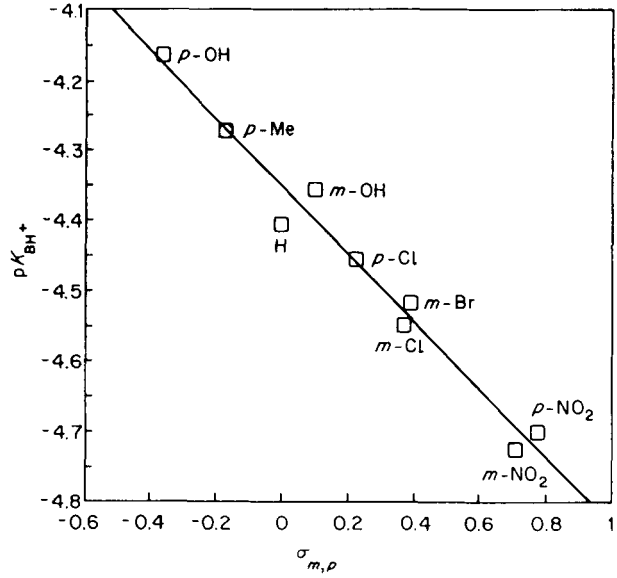


FIGURE 16. Hammett plot for the basicity of cinnamates

and visualized by Figure 16. The value of the reaction constant $\rho = -0.483$ is smaller than that for the protonation of cinnamic acids[118] ($\rho \approx -0.65$). This means that esters are less sensitive toward protonation than carboxylic acids.

C. Thermodynamics of the Protonation of Esters

The determination of the thermodynamic parameters of the protonation equilibrium (ΔG°, ΔH° and ΔS°) allows for a better description of the protonation process of esters. Thus, obtaining accurate pK_{BH^+} values in solution at different temperatures is of great importance. Bagno and coworkers[150] reported pK_{BH^+} data at three temperatures (25, 40 and 60 °C) for seven esters, mostly aliphatic (Table 28). Raising the temperature increases the basicity, as a general trend. Some irregularities are observed for methyl acetate, methyl isobutyrate and methyl cyclohexanecarboxylate, perhaps due to hydrolysis or to problems in the determination of the m^* value in the equation

$$\log B_{BH^+} - \log C_{H^+} - \log A_w = m^*X + pK_{BH^+} \tag{77}$$

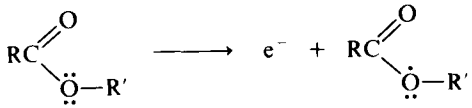
which was used to calculate the protonation constant. Values of m^* increase with alkyl substitution at the carbonyl group and are consistent with the interpretation of m^* as a solvation parameter. Values of ΔG° and ΔH° are calculated with rather satisfactory accuracy, however ΔS° values are doubtful. The relationship between ΔG° and ΔH° is linear, if methyl benzoate is excluded. ΔH° values for esters are more negative than for similar ketones[150] (-1.5 to -13 kcal mol^{-1}) while ΔS° values are positive but uncertain. The entropy term ($T\Delta S$) is in the range ≈ 5 kcal mol^{-1}, e.g. similar to that of other carbonyl bases[115] which are poorly solvated. The entropic and enthalpic factors compensate each other to some extent, and reflect an increase of solvation for the process $BH^+ \rightarrow B^- + H^+$ and better distribution of the positive charge when branching of the alkyl group increases.

TABLE 28. Thermodynamics of ester protonation[151]

t (°C)	m*	pK_{BH^+}	$\Delta G°$	$\Delta H°$	$\Delta S°$
Methyl acetate					
25	0.46	−3.90 ± 0.03	−5.32	−4.5	1.8
40	0.39	−3.35 ± 0.02	±0.04	±0.06	±2.1
60	0.47	−3.66 ± 0.04			
Methyl propionate					
25	0.57	−4.37 ± 0.04	−5.96	−3.3	9.0
40	0.53	−4.27 ± 0.03	±0.06	±0.06	±2.0
60	0.55	−4.12 ± 0.03			
Methyl isobutyrate					
25	0.57	−4.91 ± 0.07	−6.70	−1.4	16.2
40	0.54	−4.45 ± 0.03	±0.10	±0.8	±2.8
60	0.57	−4.54 ± 0.03			
Methyl cyclopropanecarboxylate					
25	0.58	−4.76 ± 0.09	−6.50	−4.9	4.6
40	0.55	−4.34 ± 0.04	−1.12	±0.8	±2.5
60	0.56	−4.21 ± 0.02			
Methyl cyclohexanecarboxylate					
25	0.59	−4.92 ± 0.07	−6.71	−5.0	6.5
40	0.62	−4.97 ± 0.03	±0.10	±1.2	±3.7
60	0.60	−4.60 ± 0.6			
Methyl 2,2-dimethylpropionate					
25	0.77	−6.56 ± 0.15	−8.95	−7.0	6.3
40	0.77	−6.21 ± 0.08	±0.21	±2.4	±7.7
60	0.78	−5.99 ± 0.12			
Methyl benzoate					
25	0.82	−7.05 ± 0.16	−9.62	−13.4	−12.8
40	0.81	−6.68 ± 0.12	±0.22	±3.3	±10.6
60	0.75	−6.00 ± 0.20			

D. Acid–Base Properties of Esters in the Gas Phase

The esters of carboxylic acids upon vapour phase ionization lose an electron from the non-bonding lone pair of the alkoxy oxygen[151]:



(78)

The change of alkyl substituent on the alkoxy oxygen (R') has a larger effect than a corresponding change of the alkyl group of the acidic part (R) on the (photo)-ionization potential measuring basicity. Hence the general relationship IP vs σ_I (inductive effect) must be replaced by two separate plots. The experimental data for several aliphatic esters are collected in Table 29. The slope for alkyl acetates is 16.0 and for methyl alkanoates it is 12.8[152]. The basicity of esters in the gas phase is reflected also by proton affinities, which increase in the sequence of the alcoholic radical: H < Me < Et <

TABLE 29. Basicity of aliphatic esters in the gas phase

Esters	IP[a]	IP[b]	IP[c]
Formates			
HCOOMe	10.82	10.85	10.85
Et	10.61	10.61	10.62
n-Pr	10.54	10.50	
n-Bu	10.50	10.52	
i-Bu	10.46		
Acetates			
MeCOOMe	10.27	10.25	10.27
Et	10.11	9.90	10.24
n-Pr	10.04	9.92	
i-Pr	9.99		
n-Bu	10.01		
i-Bu	9.97		
s-Bu	9.91		
CF_3COOEt	—	—	11.07
CCl_3COOEt	—	—	10.44
$ClCH_2COOMe$	—	—	10.35
Methylalkanoates			
HCOOMe	10.82		
MeCOOMe	10.27		
EtCOOMe	10.15	—	10.15
n-PrCOOMe	10.07	—	10.07
i-PrCOOMe	9.98	—	9.98
EtCOOEt	—	10.6	
$F_2CHCOOEt$	—	10.75	

[a] From Reference 151.
[b] From Reference 152.
[c] From Reference 153.

TABLE 30. Gas-phase basicities (relative to ammonia)[154]

Acid	ΔG
CH_3COOEt	4.2
CH_3COOMe	8.4
HCOOMe	14.6
CF_3COOBu	17.9
CF_3COOPr	18.1
CF_3COOEt	19.1
CF_3COOMe	22.0
NCCOOEt	21.4

n-Pr < n-Bu, although with diminishing effect, due to the inductive field effect (see Table 30)[154]. Wolf and Gruetzmacher in a very recent paper[155] measured proton affinity (basicity) of various esters, amides and carboxylic acids in order to determine the role of unsaturation in the acidic part as well as the position of protonation. Unsaturated

TABLE 31. Basicity in gas phase of saturated and unsaturated acids and esters

	PA (kJ mol^{-1})		PA (kJ mol^{-1})
CH_2=CHCOOH	820	CH_3CH_2COOH	802
CH_2=CHCOOCH$_3$	833	CH_3CH_2COOMe	838
CH_2=CMeCOOH	825	$CH_3CHMeCOOH$	820
CH_2=CMeCOOMe	843	$CH_3CHMeCOOMe$	843
CH_3CH=CHCOOH	833	$CH_3CH_2CH_2COOH$	812
CH_3CH=CHCOOMe	851	$CH_3CH_2CH_2COOMe$	837

acids and unsaturated esters are more basic than their saturated counterparts due to the expected stabilization by delocalization of the positive charge within the conjugated π-system. Esters are more basic than the corresponding acids (Table 31). Moreover, esters are protonated at the ether oxygen atom while acids are protonated at the carbonyl oxygen. Gas-phase acidities for three families of esters have been reported lately by Taft and Topsom[137] as $-\delta\Delta G^\circ$, and are shown in Table 32.

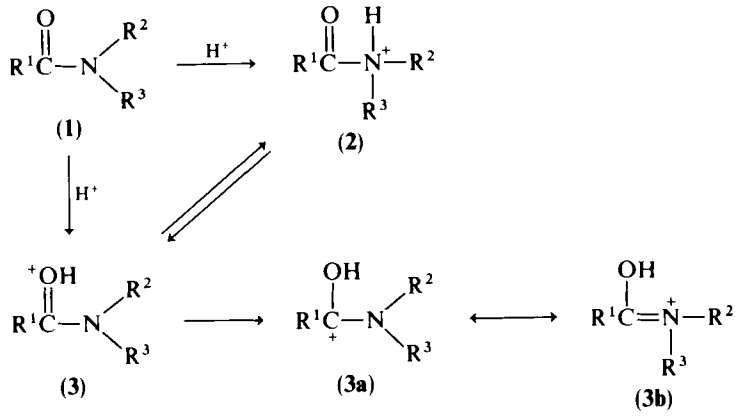
TABLE 32. Gas-phase acidities of esters ($-\delta\Delta G^\circ$)[137]

Substituent	Ethyl formates	Methyl benzoates	
		para	*meta*
NMe_2	−16.6	—	—
NH_2	—	−8.0	—
OMe	—	—	−1.5
F	9.0	2.2	4.1
Cl	—	2.0	3.6
t-Bu	—	−4.1	—
Et	−9.5	—	—
Me	−7.4	−2.3	−1.4
H	0	0	0
CCl_3	1.9	—	—
CF_3	8.8	5.7	5.5
CN	11.0	8.1	7.9
COOMe	—	1.7	—
NO_2	—	8.9	8.4

VI. ACID–BASE PROPERTIES OF AMIDES

A. Protonation of Amides

In a review on the chemistry of amides in this series[5,156] much attention was devoted to various aspects of amide basicity. The two potential sites of protonation in amides (N and O) may lead to two cationic species (Scheme 4).

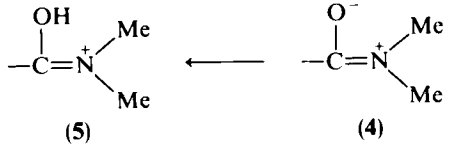


SCHEME 4

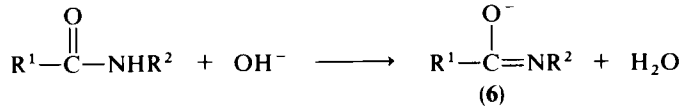
The more basic amino group, as compared to carbonyl group, suggests **2** as the most favoured structure for a protonated amide, although carbonyl oxygen protonation leading to structure **3** is also possible. The oxonium ion **3** is then stabilized by two resonance forms **3a** and **3b**, resulting in sharing of the positive charge between oxygen, carbon and nitrogen. The presently available evidence is in favour of form **3** and not of form **2**, as was postulated in the review by Katritzky and Jones[157].

Most of the supporting evidence comes from NMR studies in concentrated acids[158–161] such as sulphuric, deuterosulphuric and others. In the spectrum of *N*-methylacetamide a doublet of the methyl peak appears, due to spin–spin coupling with the proton bound to nitrogen. This doublet disappears on protonation and a single line appears as a result of rapid proton exchange in N—H. In strong concentrated acids a doublet, and not a triplet as expected for $-NH_2{}^+CH_3$ appears, suggesting O-protonation.

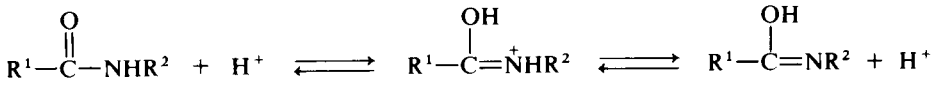
N,N-Dimethylamides show doublets for the methyl protons in neutral solvents due to the restricted rotation about the C—N bond. This doublet is observed in strong acidic solutions, suggesting O-protonation as in structure **5**:



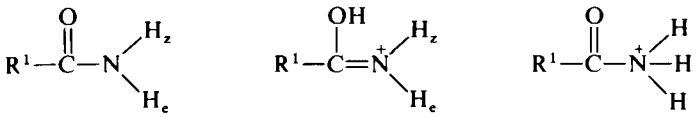
The dispute regarding the site of amide protonation is an important question for biochemists who study proton exchange in peptides and proteins[162,163], and the problem has been summarized recently[164]. The reaction is catalysed by bases and acids. Hydroxide removes the NH proton and gives the imidate anion **6**.



The structure of this ion was determined by NMR[165]. The reaction in acidic media has been accepted as involving N-protonation, as well as O-protonation:

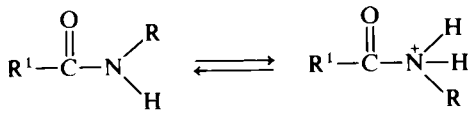


It is possible to distinguish between two mechanisms in acidic media by NMR. Protons in the amide and in the O-protonated amide are in different environments and they ought to exchange at different rates:



while in N-protonated amides the protons are equivalent, and should not show different exchange rates. Kinetic measurements were possible with ^{14}N quadrupole NMR with electronic decoupling[164].

The proton exchange in secondary amides can occur via N-protonation and not O-protonation. The same is applicable to dipeptides and proteins.



Protonation also depends on the size of R^1 and R^2[166]. While the basic site of *N,N*-disubstituted amides is the carbonyl oxygen, steric hindrance reduces the conjugation of CO with NR_2, and consequently the basicity of oxygen. Hence the basicity of the nitrogen atom becomes similar to that of HNR_2 in secondary amines.

B. Basicity of Amides

Aliphatic and aromatic amides are relatively strong bases. Their protonation occurs already in solutions of diluted strong mineral acids. Some of them are strong enough to be protonated in aqueous solutions in the pH range of acidity. For that reason sets of amides were used for establishing acidity functions H_0[9] and H_A[113,167]. An amide

TABLE 33. Amides used as indicators for developing the H_A acidity function

Amide	pK_{BH^+}
Pyrrole-2-carboxamide	−1.23
4-Methoxybenzamide	−1.44
3,4,5-Trimethoxybenzamide	−1.82
3-Nitrobenzamide	−2.42
4-Methyl-3,5-dinitrobenzamide	−2.69
2,3,6-Trichlorobenzamide	−3.30
2,4-Dichloro-3,5-dinitrobenzamide	−3.73
2,4,6-Trinitrobenzamide	−4.08

TABLE 34. Amide acidity function H_A for various strong acids

%	H_2SO_4	$HClO_4$	HCl
5	0.30	0.05	−0.47
10	−0.29	−0.35	−1.03
15	−0.70	−0.67	−1.50
20	−1.00	−0.95	−2.01
25	−1.25	−1.23	−2.55
30	−1.50	−1.50	−3.02
35	−1.74	−1.75	−3.56
40	−2.00	−2.05	−4.06
45	−2.24	−2.35	
50	−2.57	−2.70	
55	−2.77	−3.12	
60	−3.10	−3.55	
65	−3.38	−3.95	
70	−3.74	−4.45	
75	−4.15	−9.35	
80	−4.62		
85	−5.02		
90	−5.57		
95	−6.04		

acidity function has been developed specially to describe the protonation phenomena of that particular class of compounds[113], but was soon recognized as being more general and suitable also for other carbonyl compounds[25].

Amides used for developing the H_A acidity function and their pK_{BH^+} values are given in Table 33. These amides in combination with other similar compounds give a set of bases with strong overlapping of the function log B/BH^+ vs concentration of sulphuric[113,167–169], perchloric[170,171], hydrochloric[30,172] acids. The H_A acidity functions for these acids are given in Table 34.

1. *Basicity of aliphatic amides*

Aliphatic amides are stronger bases than aromatic ones. Despite the lack of systematic study, some regularities may be observed (see Table 35).

The basicities of acetamide and propionamide are comparable, with pK_{BH^+} in the range − 0.65 and − 0.57, respectively. Butyramide with pK_{BH^+} reported as − 0.73 or − 0.88 is slightly weaker, but still much stronger than benzamide.

The effect of the alkyl group in *N*e-alkylacetamides (Me, Et, *t*-Bu) is not very clear because pK_{BH^+} values are of similar magnitude: −0.42, −0.49 and − 0.41. According to Cox and coworkers[14], the *t*-butyl group is more base strengthening than the ethyl group. This trend is perhaps valid for methyl substituent if one accepts $pK_{BH^+} = -1.00$ reported by Edward and Wang[173]. A second alkyl group in *N*,*N*-dialkylamides increases the basicity by approximately 0.15 pK_{BH^+} units. The effect of alkyl groups on the pK_{BH^+} of amides is in line with their inductive effect. *N*-Benzyl acetamides reported in Table 35 are much weaker bases. Urea with $pK_{BH^+} = 0.05$ is the strongest base reported due to its two NH_2 groups. Me_4-urea is weaker by 0.2 units, perhaps due to steric distortion caused by the bulky methyl groups. Thiourea is weaker than urea by almost one pK_{BH^+} unit, due to lower electronegativity of the C=S group, as compared to C=O.

TABLE 35. pK_{bh^+} values of various aliphatic amides

Amide	pK_{BH^+}	Reference
DMF	-1.2 ± 0.5	174
	-1.13 ± 0.05	175
Acetamide	-0.62 ± 0.07	174
	-0.73 ± 0.02	14
	-0.35	173
N-Me acetamide	-1.00	173
	-0.42 ± 0.03	174
N-Et acetamide	-0.49 ± 0.01	14
N-*t*-Bu acetamide	-0.41 ± 0.01	14
N-benzyl acetamide	-1.08 ± 0.08	14
N-*p*-methoxybenzyl acetamide	-0.94 ± 0.04	14
N-*p*-chlorobenzyl acetamide	-1.23 ± 0.05	14
N,*N*-Me_2 acetamide	-0.28 ± 0.03	174
	-0.21	175
N,*N*-Et_2 acetamide	-0.33 ± 0.02	14
Propionamide	-0.57	173
Butyramide	-0.88	170
	-0.73	170
Urea	0.05	174
Me_4 Urea	-0.14	175
Thiourea	-0.9 ± 0.1	174
HMPA	-0.97	175

This discussion is only of qualitative value, since the aliphatic amides were investigated by different authors, who use various experimental techniques and models for pK_{BH^+} calculations.

2. *Basicity of aromatic amides*

Benzamide is a weaker organic base than alkyl amides, with pK_{BH^+} values reported by various authors close to -1.5 pK_{BH^+} units in terms of the H_A acidity function. The basicity of benzamides was studied by UV spectroscopy. The numerical data on pK_{BH^+} of *N*-alkyl-substituted benzamides are collected in Table 36. Most of these are weaker bases than benzamide. *N*-*t*-Butylbenzamide is the only exception found[14,176]. The basicity of these derivatives is governed by the inductive or polarizability effect and by steric interaction of bulky substituents.

The plot of pK_{BH^+} vs the σ_p polarizability substituent constant is shown in Figure 17 and it is linear. The scatter might result from steric interactions with the large *t*-butyl and *i*-butyl groups.

The second alkyl group in *N*,*N*-dialkylbenzamides strongly increases the basicity. The sequence of pK_{BH^+} values for benzamide, *N*-*i*-Pr and *N*,*N*-*i*-Pr_2 benzamides, namely -1.38, -1.50 and -0.71[176] units, demonstrates the importance of bulky substituents and the base-strengthening role of the steric factor. This is also true for ethyl groups in benzamide and for methyl groups in 1- and 2-naphthamide[177,178]. Data reported by Cox and colleagues[14] in Table 36 indicated that the effect of the first alkyl group in an amide is very weak but the effect of the second alkyl group is strong and increases in the order Me < Et < i-Pr.

The effect of *meta* and *para* substituents on the pK_{BH^+} value of benzamide is shown

TABLE 36. Basicity of *N*-alkyl substituted aromatic amides

Compound	$-\sigma_p$[a]	$-pK_{BH^+}$	mH_0[c]	Reference
Benzamide			1.54 ± 0.02	14
		1.54		179
		1.5	1.4	180
		1.54		181
		1.38		176
N-Me benzamide	0.33		1.46 ± 0.01	14
	0.33	1.50		179
	0.33	1.47	1.06	180
N-Et	0.48		−1.52 ± 0.08	14
	0.48	1.72		156
	0.48	1.50[b]		176
N-*i*-Pr	0.62		1.54 ± 0.06	14
	0.62	1.56[b]		176
N-*i*-Bu	0.61		1.50 ± 0.03	14
	0.61	1.66[b]		176
N-*s*-Bu	0.68		1.55 ± 0.03	14
	0.68	1.45[b]		176
N-*t*-Bu	0.76		1.34 ± 0.05	14
	0.76	1.34[b]		176
N-Benzyl		1.61[b]		176
N,*N*-Me_2			1.00 ± 0.02	14
		1.2		179
N,*N*-Et_2			1.14 ± 0.06	14
		1.08[b]		176
N,*N*-*i*-Pr_2			0.55 ± 0.03	14
		0.74[b]		176
Cinnamamide		1.15	1.16 ± 0.04	182
1-Naphthamide		192		178
		1.92	1.68	177
N-Me-		1.55	1.62	177
N,*N*-Me_2		1.37	1.21	177
2-Naphthamide		1.84		178
		1.88	1.54	177
N-Me		1.84	1.58	177
N,*N*-Me_2		1.3	0.98	177

[a] Substituent polarizability scales σ_p[183].
[b] Excess acidity method + target factor analysis.
[c] mH_0 denotes half-protonation.

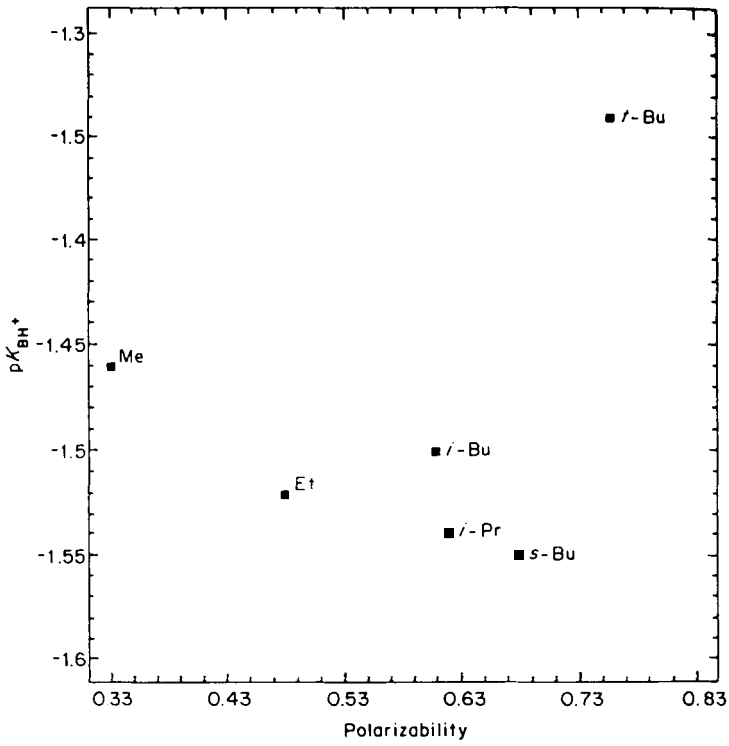


FIGURE 17. Plot of amide basicity vs *n*-alkyl polarizability

in Table 37. The data reported in this table originate from different laboratories and are somewhat divergent. Electron-donating substituents, such as *p*-OMe and *p*-CH_3, are base-strengthening. Electron-withdrawing substituents such as *m*-NO_2, *p*-NO_2 and *m*-Cl are base-weakening. The reaction constant is negative and larger than -1: this means that transmission of the substituent electrical effect is more effective and opposite to that of the dissociation of benzoic acids in water.

An *o*-Me group decreases the basicity of the amide by approximately 0.06 pK_{BH^+}.[181] and the next *o*-Me group decreases it by 0.22 pK_{BH^+}. This is due to steric inhibition of the resonance between the amide group and the phenyl ring. Substitution of a *p*-methyl group is again base-strengthening. It is difficult to analyse this effect quantitatively owing to lack of data for a larger series of compounds.

The *m*-nitro group is base-weakening in accordance with Hammett's σ constant[179]. A second *m*-NO_2 group decreases the basicity even more strongly[30].

The basicity of series of *meta*- and *para*-substituted N-Et and N-2,2,2-F_3 ethyl benzamides were studied by Farlow and Moodie[184] and are presented in Table 38.

The *N*-ethyl group weakens the basicity by its inductive effect and by attracting the lone pair on the nitrogen. The lone pairs on the carbonyl oxygen are more localized and less basic. This tendency is much stronger in the CF_3CH_2 derivative. The linear relationship between the two series is shown in Figure 18. Its slope is greater than one, which implies that the effect of the substituents in the *N*-CF_3CH_2 series is propagated more effectively.

TABLE 37. Basicity of *meta*- and *para*-substituted benzamides $-pK_{BH^+}$

Amide	$-pK_{BH^+}$			Reference
	H_A[a]	mH_0[b]	σ	
Benzamide	1.54			179
m-Br	1.93			179
	1.8	1.3	0	180
m-Cl	1.89		0.373	179
m-OMe	1.70		0.115	179
	1.80	1.84	0.115	180
m-Me	1.56		−0.07	179
	1.38	1.85		180
m-NO_2	2.10		0.71	179
p-Br	1.82		0.23	179
	1.54	1.33		180
p-Cl	1.77		0.227	179
	1.70	1.8		180
p-F	1.60		0.062	179
p-OMe	1.34			179
	1.18	1.19	−0.27	180
p-CH_3	1.47		−0.17	179
	1.42	1.27	−0.17	180
	1.47		−0.17	30
	1.34		−0.17	30
p-NO_2	2.22		0.78	179
	2.5	1.48	0.78	180
p-Ph	1.64		0.78	177
2-Me	1.8			30
2,6-Me_2	1.96			30
2,4,6-Me_3	1.70			30
3,5-$(NO_2)_2$	3.26			30
2,4,6-$(NO_2)_3$	4.08			30
3,5-$(NO_2)_2$-4Me	2.69			30
2,3,6-Cl_3	3.20			30
2,4-Cl_2-3,5$(NO_2)_2$	3.73			30
3,4,5-$(OMe)_3$	1.82			30

[a] Pertains to $H_{A(1:2)}$.
[b] Pertains to mH_0.

TABLE 38. Basicity of *N*-Et benzamides and *N*-CF_3CH_2 benzamides[184]

	$-pK_{BH^+}$(*N*-Et)	$-pK_{BH^+}$(N-CF_3CH_2)
N-Et benzamide	1.92	3.33
m-Br	2.40	3.64
m-Cl	2.18	3.62
m-Me	1.88	3.20
m-NO_2	2.54	3.83
p-Cl	2.21	3.71
p-OMe	1.60	2.70
p-Me	1.77	3.00

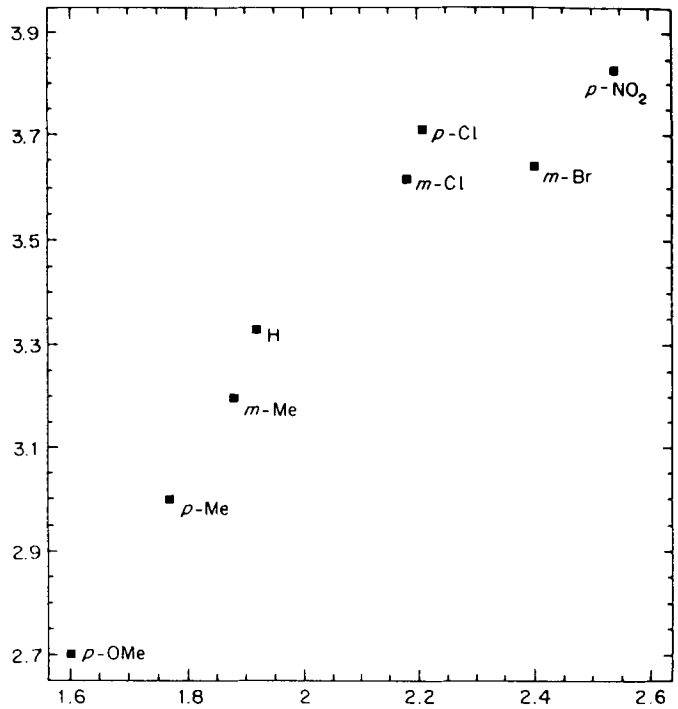


FIGURE 18. Plot of N—Et vs N—CF_3CH_2–benzamide basicity

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CHAPTER 9

Syntheses and uses of isotopically labelled acid derivatives

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ABBREVIATIONS

AADC	cerebral aromatic L-amino acid decarboxylase
ALA	δ aminolevulinic acid
Bn	$C_6H_5CH_2$ (benzyl)
BPMC	2-*sec*-butylphenyl *N*-methyl carbamate
Br-Me_2HBED	*N*-(2-hydroxy-3,5-methylbenzyl)-*N'*-(2-hydroxy-5-bromo-acetamidobenzyl)ethylenediamine-*N*,*N'*-diacetic acid
CAT	chloramine-T
CDA	carbonyl diimidazole
m-CPBA	*meta*-chloroperbenzoic acid
CSA	*dl*-camphor-10-sulphonic acid
DABCO	diazabicyclo[2,2,2]octane
DBTA	dibenzoyl tartrate monohydrate
DCC = DCCI	1,3-dicyclohexylcarbodiimide
DCT	dichloramine-T
DIBAH = DIBAL-H	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DBM	dibenzoylmethane
DMAP	4-dimethylaminopyridine
DOI	2,5-dimethoxy-4-iodophenylisopropylamine

DOPA	3-(3,4-dihydroxyphenyl)alanine
DTBP	2,6-di-*t*-butylpyridine
FASL	fatty acid spin labels
FAB	fast atom bombardment
FHA	16-fluorohexadecanoic acid
FBMHA	16-fluoro-3-methylhexadecanoic acid
GC–MS–SIM	gas chromatography–mass spectrometry–selected ion monitoring
GOT	glutamic/oxaloacetic acid transaminase
HAOS	hydroxylamine-*O*-sulphonic acid, H_2NOSO_3H
HLAD	horse liver alcohol dehydrogenase
HMPT	hexamethylphosphoric triamide
HOSU	*N*-hydroxysuccinimide
HPLC	high performance liquid chromatography
HVA	homovanillic acid
IBA	iodobenzoic acid
IPM	*N*-(*p*-iodophenyl)maleimide
JHO	juvenile hormone
$K(2.2.2)^+$	aminopolyether(2.2.2)–K_2CO_3 complex
LAH	lithium aluminium hydride
MA	maleic acid
MAG_3	mercaptoacetyltriglycine
MBS	*N*-hydroxysuccinimide ester
m-MeATE	*N*-succinimidyl-3-(trimethylstannyl)benzoate
MPPA	3-methyl-15-phenyl-pentadecanoid acid
MTP-cephalin	experimental compound of CIBA-GEIGY
MTBMH	methyl-16-trifluoromethane sulphonate-3-methylhexadecanoate
MVA	mevalonolactone
NCA	non-carrier added
NCS	*N*-chlorosuccinimide
NSP	*N*-succinimidylpropionate
PA	pyrrolizidine alkaloid
PBG	porphobilinogen
PDC	pyridinium dichromate or phthaloyl dichloride
PET	position emission tomography
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E_2
PGF_2	prostaglandin $F_{2\alpha}$
PMTE	Phorbol 20-methoxy trityl ether
QNB	quinuclidynyl benzylate
TBHP	*t*-butylhydroperoxide
TEA	triethylamine
TFA = TFAA	trifluoroacetic acid
THAM	2-amino-2(hydroxymethyl)-1,3-propane-diol
THP	tetrahydropyran
TIQ	1,2,3,4-tetrahydroisoquinoline
TMP	2,2,6,6-tetramethylpiperidine
TMSCl	trimethylchlorosilane
TMSDEA	*N*-trimethylsilyldiethylamine = *N*,*N*-diethyl-1,1,1-trimethyl-amine
TMSCN	trimethylsilylcyanide
TSA	*p*-toluenesulphonic acid
UL	uniformly labelled

I. GENERAL INTRODUCTION

Isotopically labelled carboxylic acids and their derivatives are the substrates or intermediates in the syntheses of numerous radiopharmaceuticals and of chemical compounds of practical importance. They are very often also used in biomedical, biochemical and physical studies. The procedures leading to labelled carboxylic acid derivatives have therefore been under continuous consideration and very much progress has been achieved in this field since the appearance of the first review chapter[1] in this series.

II. SYNTHESES AND APPLICATIONS OF ACID DERIVATIVES LABELLED WITH HEAVY ISOTOPES

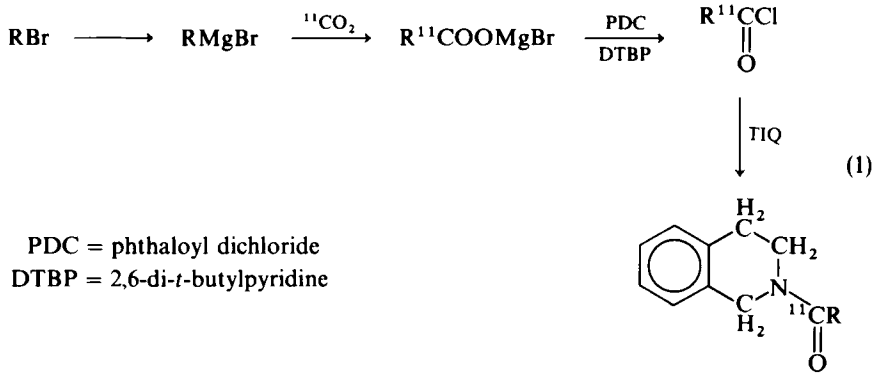
A. Syntheses of Carboxylic Acids Labelled with the Positron Emitting Nuclide ^{11}C

1. Synthesis of non-carrier added (NCA) [1-^{11}C] acid chlorides as labelling agents for amides

These acid chlorides

$$R^{11}C(=O)Cl,\ R = Me,\ Et,\ Pr \text{ and } t\text{-Bu}$$

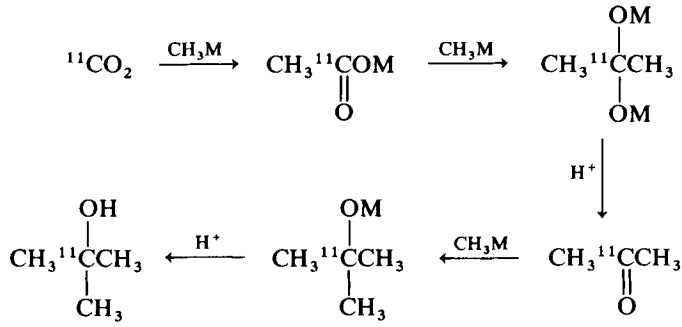
are useful agents for labelling amides. They have been prepared[2] with 40–60% yield and trapped by 1, 2, 3, 4-tetrahydroisoquinoline (TIQ) (equation 1):



(1)

PDC = phthaloyl dichloride
DTBP = 2,6-di-*t*-butylpyridine

Starting activities of cyclotron-produced [^{11}C]carbon dioxide were in the range 372–930 MBq, radiochemical yields 15–40% and specific activities 1, 1–2, 8 GBq μmol^{-1}. The isolated amides were found to be chemically and radiochemically pure. [1 – ^{11}C]-acetyl chloride has been applied to label the neurohormone melatonin[3]. The dependence of the $^{11}CO_2$-trapping efficiency and of the yield of [^{11}C]-acetate, -acetone and *t*-butanol, produced in the course of interaction of [^{11}C]-carbon dioxide with methylmagnesium halides or with methyllithium on the nature of the organometallic reagent, solvent, temperature and concentration has been investigated by Nagren and Langstrom[4] (equation 2):

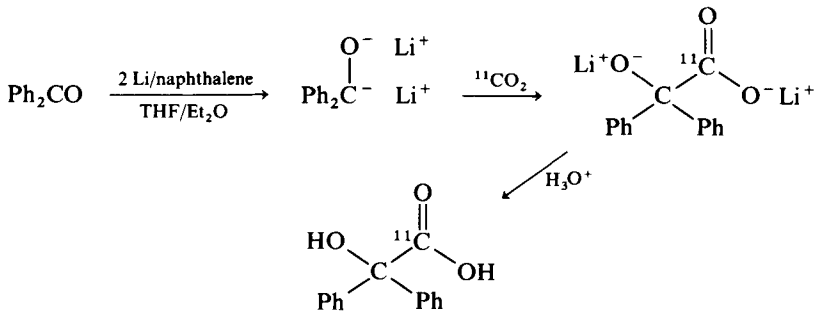


(2)

M = MgBr, MgCl, MgI, Li

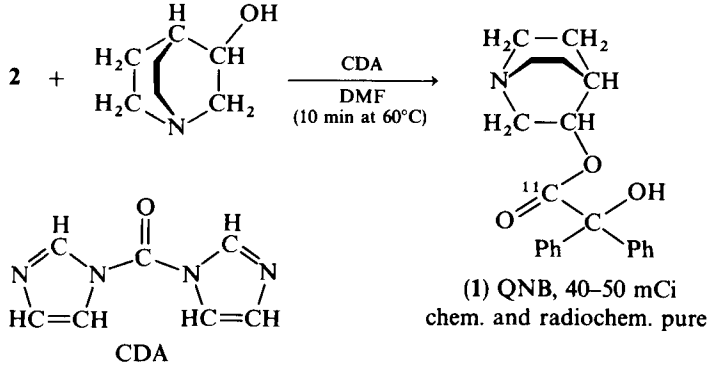
2. Synthesis of NCA [^{11}C]quinuclidinyl benzylate (QNB) **1**

This compound has been ^{11}C-labelled[5] in two main steps. In the first ^{11}C benzilic acid has been obtained[6,7] by carbonation of the benzophenone dianion with $^{11}CO_2$ (equation 3), while the second step was the esterification of [^{11}C]benzilic acid by quinuclidinol-3 in the presence of carbonyl diimidazole (CDA) (equation 4).



(3)

(**2**) 55–60% yield

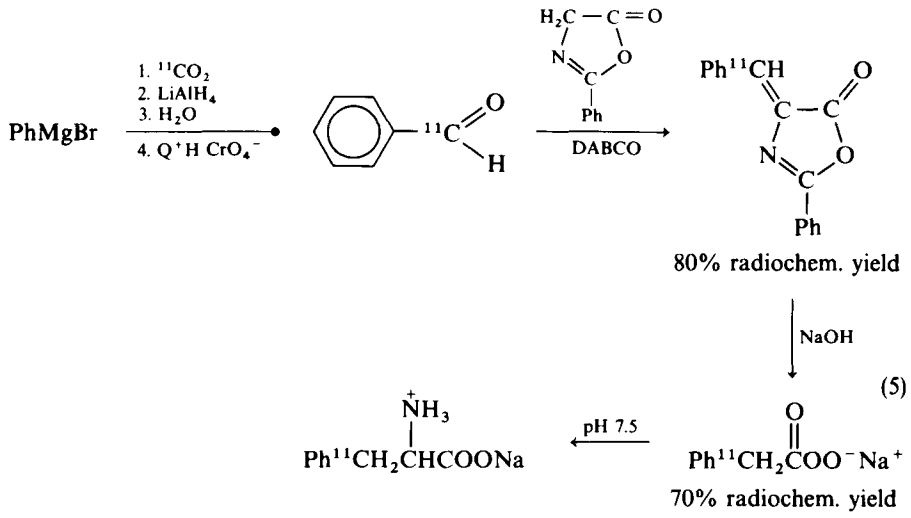


(4)

(**1**) QNB, 40–50 mCi
chem. and radiochem. pure

CDA

a. Synthesis of [3-^{11}C]phenylpyruvic acid. [3-^{11}C]Phenylpyruvic acid and [3-^{11}C]-phenylalanine were obtained[8] according to equation 5. This includes condensation of

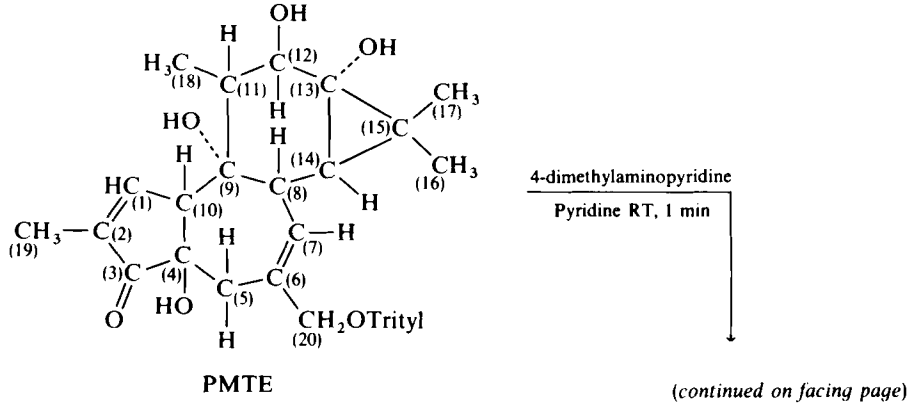


(5)

^{11}C-benzaldehyde[9] with 2-phenyl-5-oxazolone in the presence of diazabicyclo[2.2.2]octane (DABCO) resulting in [α-^{11}C]-4-benzylidene-2-phenyl-5-oxazolone, which is converted to [3-^{11}C]phenylpyruvic acid with sodium hydroxide, and enzymatic transamination of this α-keto acid catalysed by glutamic/oxaloacetic acid transaminase (GOT) (E.C.2.6.1.1). Phenylalanine has been obtained in 15–20% radiochemical yield. ^{11}C has been produced in a Van de Graaf accelerator in the ^{14}N(p, α)^{11}C nuclear reaction using nitrogen gas target.

3. Synthesis of NCA phorbol 13-[1-^{11}C]butyrate

Carbon-11 labelled phorbol ester (**2**) is a potentially useful positron emitting radioligand to bind protein kinase C, which is associated with neuronal functions in the brain[10–12]. (**2**) has been synthesized[13] by reaction of [1 – ^{11}C]propyl ketene (**3**) with the hydroxyl group at $C_{(13)}$ of phorbol 20-methoxy trityl ether, PMTE (equation 6).



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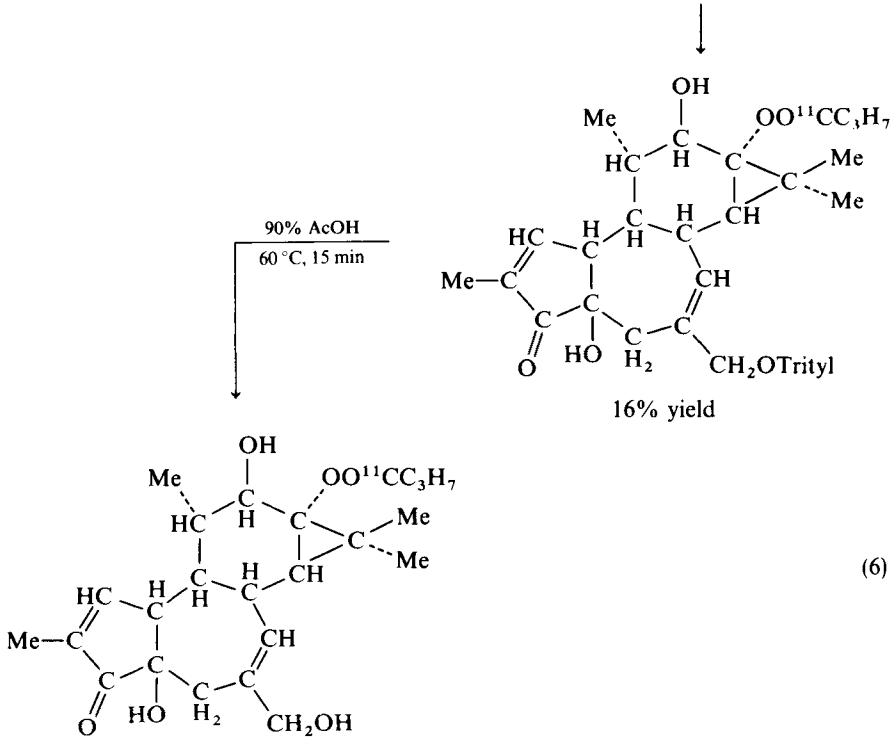


(6)

(**2**) [^{11}C]P13Bu, sp. act. 67 GBq μmol^{-1}
(1800 Ci μmol^{-1})
total radiochem. yield 3.2% based on $^{11}CO_2$

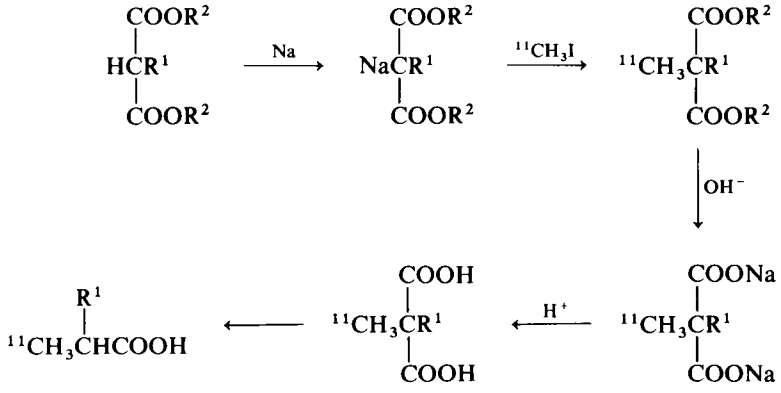
Use of [1 – ^{11}C]propyl ketene for the acylation of phorbol is a more effective procedure than the use of R^{11}COCl. The reactivity of the $C_{(13)}$-hydroxyl group is higher than that of the $C_{(12)}$-hydroxyl group. The $C_{(4)}$- and $C_{(9)}$-hydroxyl groups have such low reactivity that there is no need to protect them, but the highly reactive $C_{(20)}$-hydroxyl group had to be protected during a synthesis of $C_{(12)}$, $C_{(13)}$[1-^{11}C]dibutyrate.

4. Synthesis of α-(11C-methyl)-fatty acids

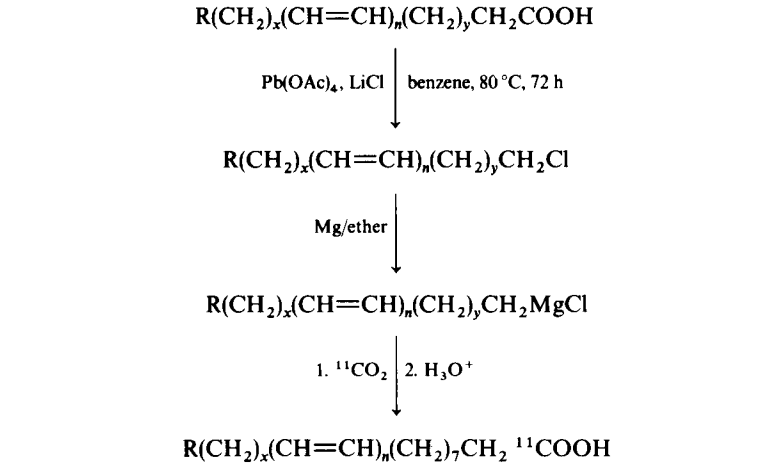
$^{11}CH_3CH_2COOH$, $Me_2CHCH(^{11}CH_3)COOH$ and $Me(CH_2)_{13}CH(^{11}CH_3)COOH$ have been prepared[14] by malonic ester synthesis (equation 7). 10 mCi of $^{11}CH_3CH_2COOH$ was obtained from 100 mCi of $^{11}CH_3I$ during 40 min. The behaviour of [3-^{11}C]- and [3-^{14}C]propionic acids in rabbit, mouse and rat was investigated by a variety of techniques. The distribution of the radioactivity in brain has been observed by radioautography.

5. Syntheses of 11C-unsaturated fatty acids

Unsaturated fatty acids labelled on the COOH group with ^{11}C have been obtained[15] according to equation 8, 9-octadecenoic acid-^{11}C, 9,12-octadecadienoic acid ^{11}C and



(7)

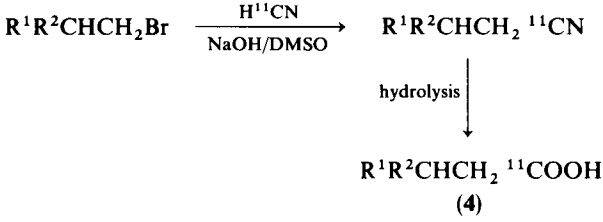


(8)

^{11}C-lineloic acid have been prepared in this manner. ^{11}C labelling of the arachidonic acid, an important precursor of prostanoids, is also under current study[15].

6. *Synthesis of ^{11}C-labelled fatty acids from H^{11}CN*

^{11}C-labelled palmitic acid, (1-^{11}C)heptadecanoic acid and other radiolabelled fatty acids have been used to study the myocardial metabolism *in vitro* and *in vivo* in animals and man. They have been synthesized by the Grignard reaction or by a more recent efficient synthesis[16] employing H^{11}CN (equation 9).



(9)

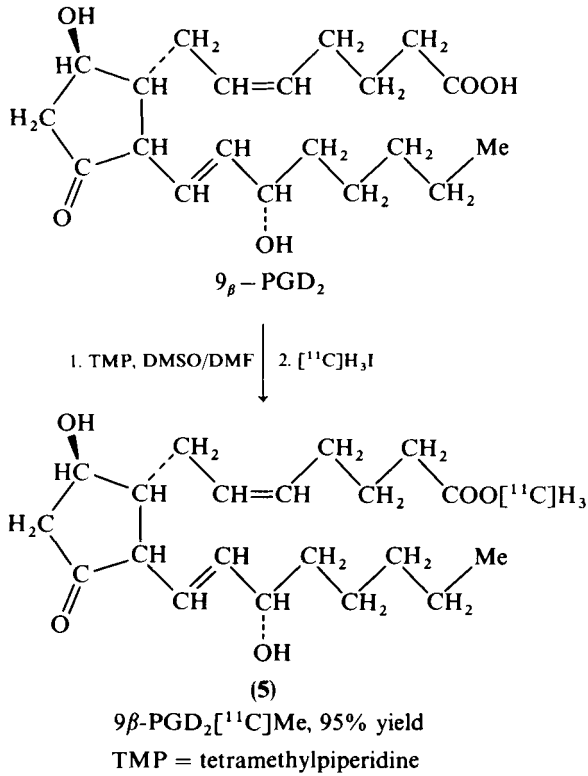
(4)

	R^1	R^2	Radiochem. yield (%)	HPLC radiochem. purity (%)	Synthesis time (min)
(4a)	$C_{12}H_{25}$	H	30	76	120
(4b)	$C_{13}H_{27}$	H	16	80	76
(4c)	$C_{14}H_{29}$	H	83	>96	73
(4d)	$C_{15}H_{31}$	H	70	93	59
(4e)	$C_{14}H_{29}$	Me	33–42	>94	60–86

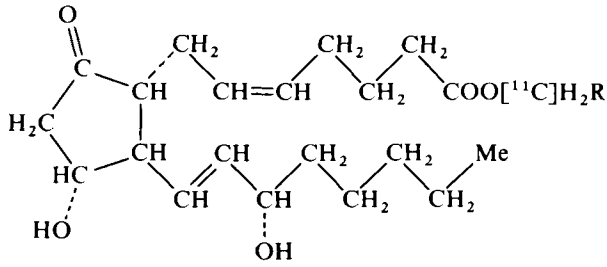
The products were (1-^{11}C)pentadecanoic, (1-^{11}C)hexadecanoic, (1-^{11}C)heptadecanoic, (1-^{11}C)octadecanoic and 3-methyl-(1-^{11}C)heptadecanoic acids. Higher radiochemical yields and purities were obtained in the alkaline hydrolysis of nitriles. The precursor of **4e** yielded a mixture of amide and carboxylic acid, and the amide was hydrolysed subsequently in conc. HCl/DMSO solution.

7. Syntheses of ^{11}C-labelled prostaglandin esters

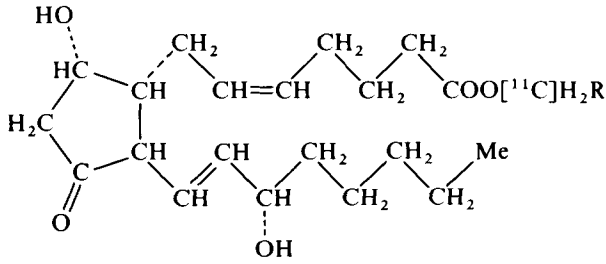
^{3}H-Autoradiography had shown that prostaglandins and prostaglandin analogues bind specifically to certain brain areas *in vitro*[17]. The alcoholic part of the prostaglandin esters has been ^{11}C-labelled[18] (equation 10) to permit positron emission tomography (PET) studies of their binding *in vivo*. Other prostaglandin esters (**6**–**9**) have also been synthesized. Competing side reactions could be overcome by optimization of the esterification procedure[18].



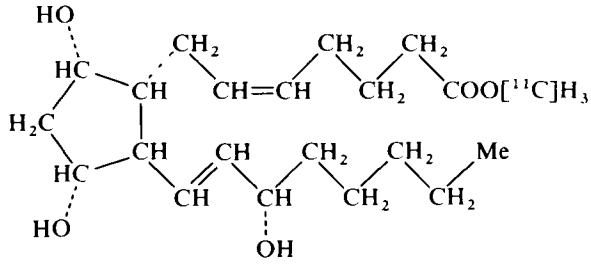
(10)



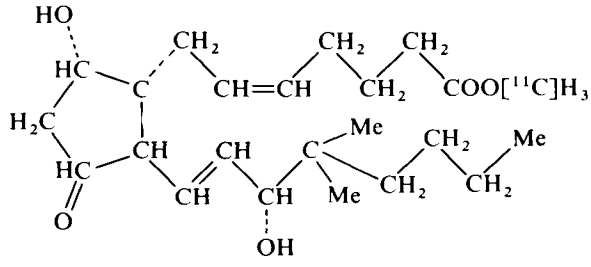
(6) $PGE_2[^{11}C]$ Ester, R = H, Me



(7) $PGD_2[^{11}C]$ Ester, R = H, Me



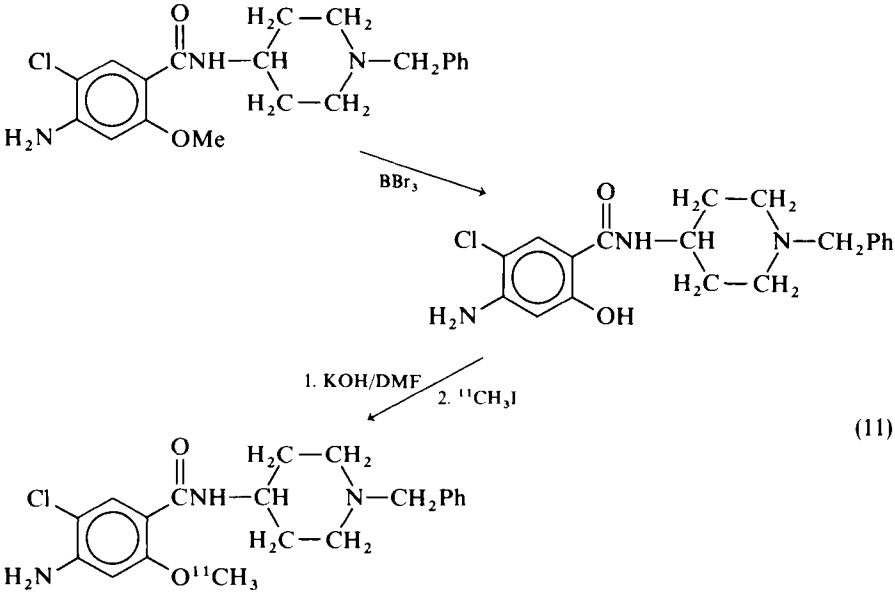
(8) $PGF_{2\alpha}[^{11}C]Me$



(9) $16,16'Me_2PGD_2[^{11}C]Me$

8. Synthesis of [^{11}C]clebopride

4-Amino-5-chloro-2-methoxy-*N*-(1-phenylmethyl-4-piperidinyl)benzamide (clebopride, **10**), a selective D_2 receptor antagonist[19], has been synthesized by O-demethylation of unlabelled clebopride with boron tribromide and subsequent methylation of norclebopride with [^{11}C]methyl iodide[19b] (equation 11).

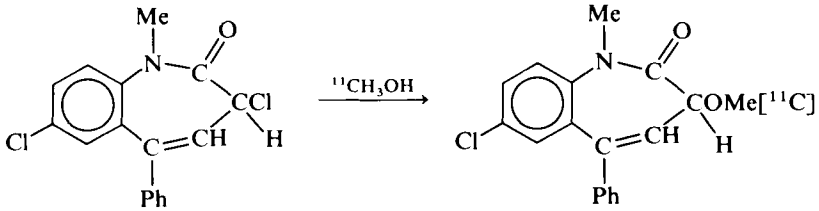


(11)

(**10**) 40% radiochem. yield; 98% radiochem. purity; sp. act 200 mCi mmol^{-1}

9. Syntheses of ^{11}C-labelled 3-methoxybenzodiazepines and benzodiazepine antagonist RO 15-3890

a. [^{11}C]Methanol has been used to label 3-methoxybenzodiazepines[20] with ^{11}C by direct nucleophilic substitution, avoiding the conventional conversion of [^{11}C]methanol to [^{11}C]iodomethane (equation 12).

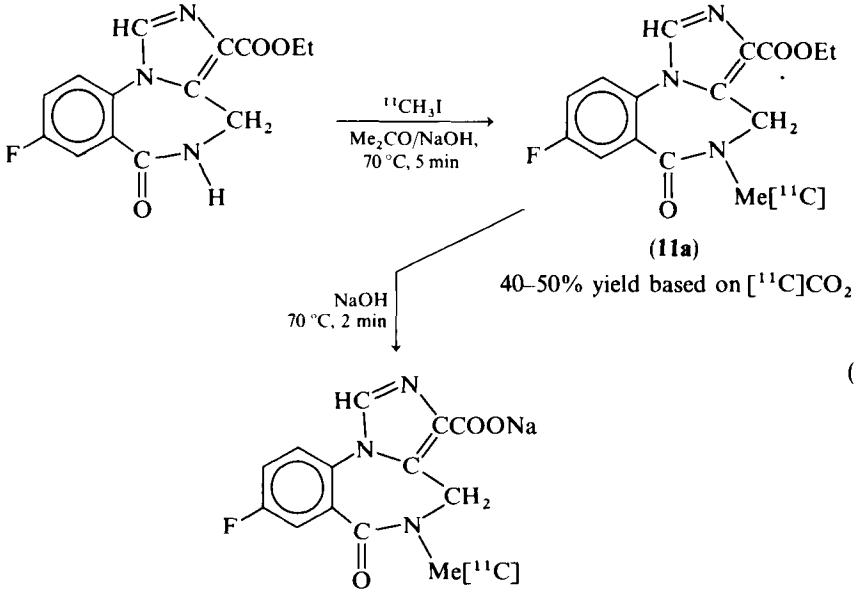


(12)

> 50% radiochem. yield
> 99% radiochem. purity

$$[^{11}C]CO_2 \xrightarrow[\text{MeCN, 80 °C, 15 min}]{LiAlH_4} {}^{11}CH_3OH$$

b. The benzodiazepine antagonist RO 15-3890, **11**, has been ^{11}C-labelled in two different positions[21] (equations 13 and 14). The specific activities of the products **11a** and **11b** was of the order 300–1300 Ci mmol^{-1}.



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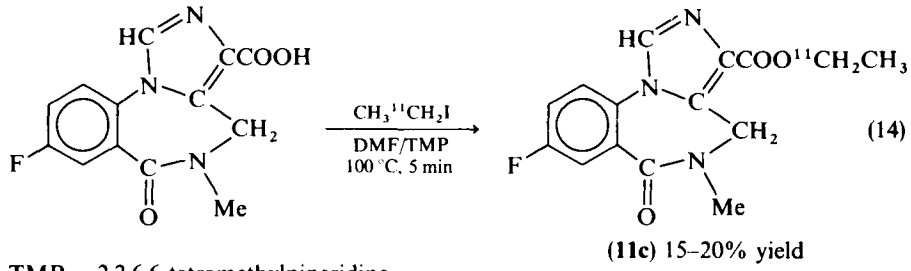


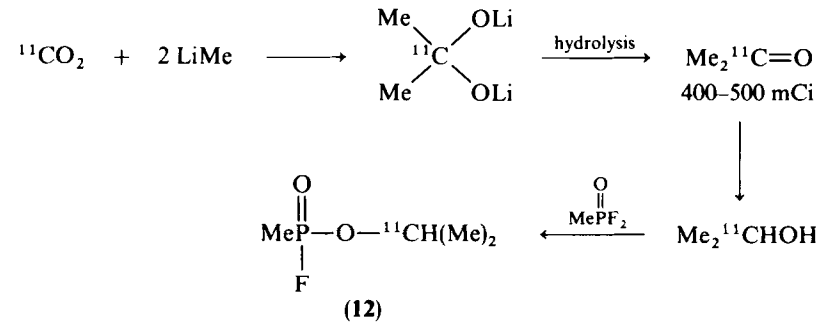
(14)

TMP = 2,2,6,6-tetramethylpiperidine

c. [^{11}C]Sarin, methylphosphonofluoridic acid [1-^{11}C]-1-methyl-ethyl ester (**12**), an extremely active cholinesterase inhibitor, has been prepared by reacting [^{11}C]isopropanol with the difluoride of methylphosphonic acid (equation 15)[22].

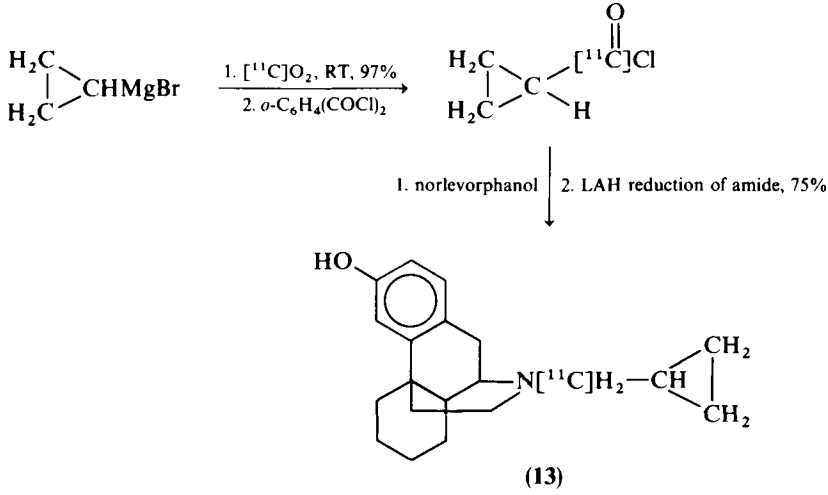
10. Synthesis of [^{11}C]cyclorphan

This compound, **13**, one of the opiate receptor antagonists[23], has been obtained[24a] by synthesizing first cyclopropane[^{11}C]carbonyl chloride and then using it to alkylate the norlevorphanol, followed by reduction of the intermediate [^{11}C]amide yielding [^{11}C]cyclorphan in 15% radiochemical yield (equation 16).



(15)

(12)



(16)

(13)

Biodistribution of **13** in different organs of mice has been studied but no specific binding and rapid clearance of **13** from the brain has been found. [^{11}C]cyclorphan is therefore not suitable as an opiate receptor binding ligand in positron-emission tomography (PET) experiments. Racemic [3-^{11}C]-labelled alanine, 2-aminobutyric acid, norvaline, leucine, DL-[3-^{11}C]valine and asymmetric L-[3-^{11}C]alanine, L-[3-^{11}C]norvaline and L-[3-^{11}C]valine as well as L-[3-^{11}C]phenylalanine have been synthesized by Antoni and Långström[24b–e] for biomedical research involving PET.

B. Syntheses of Carboxylic Acid Derivatives Labelled with the Positron Emitting Radionuclide-^{18}F

1. Synthesis of NCA [17-^{18}F]fluoroheptadecanoic acid

Nucleophilic ^{18}F-for-Br substitution in the methyl ester of 17-bromoheptadecanoic acid has been accomplished[25] with 94 ± 3% radiochemical yield under mild conditions in acetonitrile by using an equimolar complex of potassium carbonate and a macrocyclic aminopolyether to increase the nucleophilic character of ^{18}F-fluoride (equation 17). The strong nucleophilic activation of fluoride in this system is caused by the rather negligible interaction of this anion with the cationic complex $[2.2.2/K]^+$ which leads to the

appearance of 'naked' fluoride ions in acetonitrile. Carbonate counter ions provide the basic medium preventing HF formation.

$$\underset{\textbf{(15)}}{17\text{-}Br(CH_2)_{16}CO_2Me} + {}^{18}F^- \longrightarrow \underset{\textbf{(14)}}{17\text{-}{}^{18}F(CH_2)_{16}CO_2Me} + Br^- \quad (17)$$

$$\textbf{14} \longrightarrow 17\text{-}{}^{18}F(CH_2)_{16}COOH \quad (17a)$$

The reaction parameters applied in NCA [^{18}F]-fluoride introduction into alkanes and carboxylic acids have been reviewed by Block and coworkers[26].

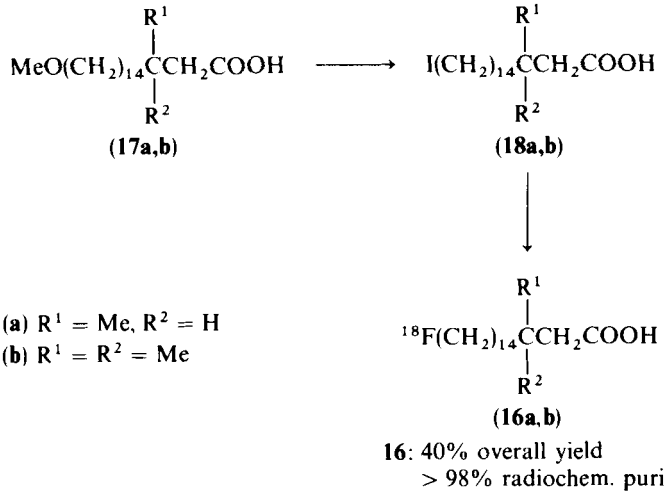
2. *Syntheses of [^{18}F]fluoro-3-methyl-branched fatty acids*

16-[^{18}F]Fluoro-3-methylhexadecanoic acid, '[^{18}F]FBMHA', and 16-[^{18}F]fluorohexadecanoic acid, '[^{18}F]FHA', have been prepared[27] from the corresponding triflates, (MTBMH) prepared in a twelve-step synthesis as shown by equation 18, with overall radiochemical yield 1%, radiochemical purity 97% and total time of the synthesis 2.5 h.

$$\begin{aligned}
&HOOC(CH_2)_{11}COOH \xrightarrow{\text{LAH/THF}} HO(CH_2)_{13}OH \xrightarrow{\text{dihydropyran/CHCl}_3} \\
&THPO(CH_2)_{13}OH \xrightarrow{p\text{-TsOH, pyridine}} THPO(CH_2)_{13}OTs\text{-}p \xrightarrow{\text{LiBr/acetone}} \\
&THPO(CH_2)_{13}Br \xrightarrow{\text{diethyl methylmalonate}} \\
&THPO(CH_2)_{13}C(Me)(COOEt)_2 \xrightarrow{\text{1. NaOH, 2. H}^+\text{, 3. }\Delta} \\
&THPO(CH_2)_{13}CH(Me)COOH \xrightarrow{\text{LAH/Ether}} \\
&THPO(CH_2)_{13}CH(Me)CH_2OH \xrightarrow{p\text{-TsOH, pyridine}} \\
&THPO(CH_2)_{13}CH(Me)CH_2OTs\text{-}p \xrightarrow{\text{NaCN/DMSO}} \\
&THPO(CH_2)_{13}CH(Me)CH_2CN \xrightarrow{\text{1. NaOH, 2. H}^+} \\
&THPO(CH_2)_{13}CH(Me)CH_2COOH \xrightarrow{\text{H}^+\text{, MeOH}} \\
&THPO(CH_2)_{13}CH(Me)CH_2COOMe \xrightarrow{\text{trifluoromethanesulphonic anhydride/CH}_2\text{Cl}_2} \\
&\underset{\text{MTBMH}}{TfO(CH_2)_{13}CH(CH_3)CH_2COOME} \longrightarrow [^{18}F]FBMHA
\end{aligned} \quad (18)$$

Fatty acids possessing β-methyl groups are potential candidates for studies of their metabolism in the myocardium[28], since they show high myocardial uptake, prolonged retention and high heart-to-blood ratio[29].

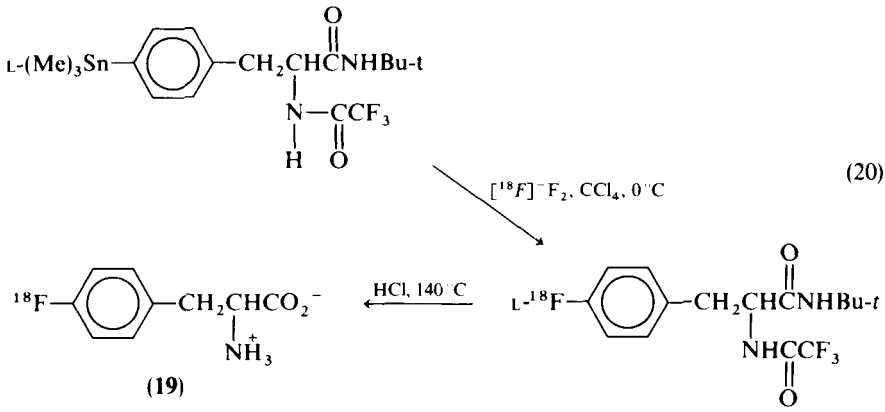
[^{18}F]-3-Methyl-branched ω-fluorofatty acids have also been radiochemically synthesized[30] by Goodman and Knapp. The [^{18}F]17-fluoro-3-(*R,S*)-methylheptadecanoic acid, **16a**, and [^{18}F]17-3,3-dimethylheptadecanoic acid, **16b**, were prepared by treatment of **17a,b** with Me_3SiCl, NaI and subsequent reaction of **18a,b** with CH_2N_2 followed by fluorination with K^{18}F(NCA) and Kryptofix 2.2.2 (equation 19).



(19)

3. *Synthesis of L-p-[^{18}F]-fluorophenylalanine* (**19**)

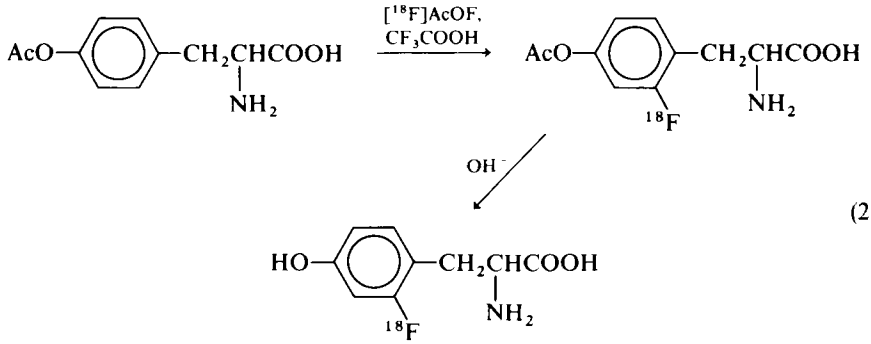
Electrophilic radiofluorinations of aromatic compounds with [^{18}F]-F_2 and [^{18}F]-CH_3CO_2F have been investigated by Stöcklin and coworkers[31]. Acetylhypofluorite, a mild electrophilic reagent[32] for aromatic fluorination, was found to be more selective than F_2, especially in CF_3COOH solvent. Regioselective radiofluorinations, very effective for both reagents, are usually achieved by electrophilic fluorodemetallation. **19** has been prepared[31] via fluorodestannylation (equation 20). **19** has been synthesized also by Guillaume and coworkers[33], using 600 mCi of ^{18}F obtained in the ^{18}O(p,n)^{18}F nuclear reaction.



(20)

4. *Synthesis of L-[2-^{18}F]fluorotyrosine* (**20**)

This has been prepared for studying protein synthesis *in vivo* by direct electrophilic fluorination of L-O-acetyltyrosine[34] with [^{18}F]AcOF (equation 21).

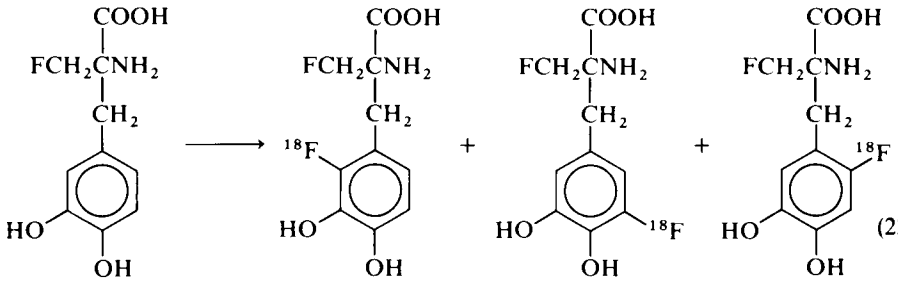


(21)

(20)

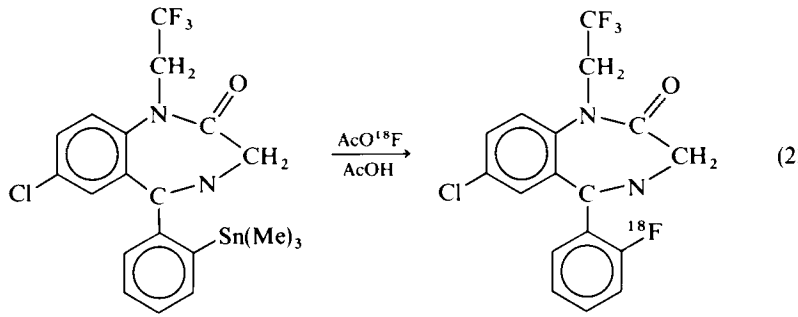
5. Synthesis of α-fluoromethyl-6-[^{18}F]fluoro-L-DOPA (**21**)

Compound **21**, a specific inhibitor of AADC (cerebral aromatic L-aminoacid decarboxylase), has been synthesized according to equation 22[35]. The distribution of **21** in rats has also been studied. ^{18}F-6-L-Fluorodopa has been synthesized in the reaction of AcOF with Hg-DOPA derivative by Adam and Jivan[36].



(22)

(22) (21)



(23)

(24)

(23)

20% incorporation of ^{18}F,
sp. act. about 1 Ci mmol^{-1}

6. *Synthesis of [^{18}F]-2-oxoquazepam* (**23**)

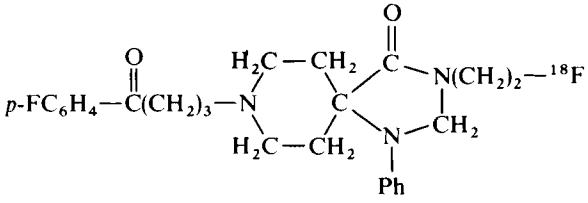
This benzodiazepine-1 antagonist has been radiolabelled by reacting trimethylstannyl-2-oxoquazepam **24** with MeCOO^{18}F/MeCOOH or [^{18}F]F_2/MeCN (equation 23) in an ultrasonic bath. The yields with [^{18}F]F_2 of **23** were less than 10%. Fluorination of **24** with MeCOO^{18}F yielded, besides **23**, de- and difluorinated compounds (by NMR and MS analysis)[37].

7. *Synthesis of N-[^{18}F]fluoroethylspiperone (FESP,* **25**)

This potent antagonist for D_2-receptors in rodents and primates has been prepared[38] by fluoroalkylation of spiperone with NCA [^{18}F]fluoroethyltosylate (equation 24). In the compounds $^{18}FCH_2CH_2X$, where X = MeSO—, Br— and TsO—, the last one is the most reactive. Fluoroethylation and fluoropropylation proceed in good yields, while fluoromethylated products are stable in special cases only. **25** has also been prepared by Satyamurthy and coworkers[39] to study the biochemistry of neuropsychiatric diseases in humans by positron emission tomography.

$$TsO(CH_2)OTs + NCA\ ^{18}F^- \xrightarrow[MeCN]{[K/2.2.2]^+} {}^{18}F(CH_2)_2OTs$$

Spiperone, MeCN, $[K/2.2.2]^+$, CO_3^{2-}

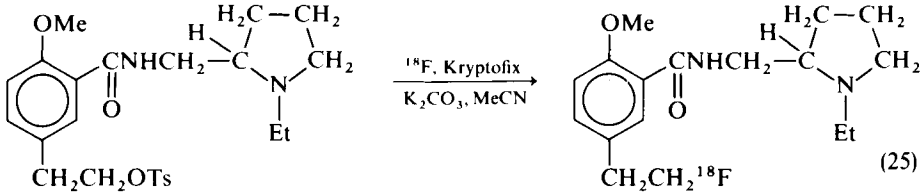


(24)

(**25**) FESP

8. *Synthesis of ^{18}F-labelled (S)-N-[(1-ethyl-2-pyrrolidinyl)-methyl]-5-(2[^{18}F]fluoroethyl)-2-methoxybenzamide* (**26**)

This compound, a PET radiotracer for dopamine D2 receptors in primates and humans[40-42], has been labelled[43] with the positron emitting ^{18}F fluoride by direct chemical reaction of a dried kryptofix-K ^{18}F complex with a solution of the tosylate **27** (equation 25). Fluorine-18 ($T_{1/2}$ = 109.7 min, E_{β^+} = 0.635 MeV) was found to be more convenient than the shorter half-life carbon-11 ($T_{1/2}$ = 20.3 min, E_{β^+} = 0.96 MeV) for



(25)

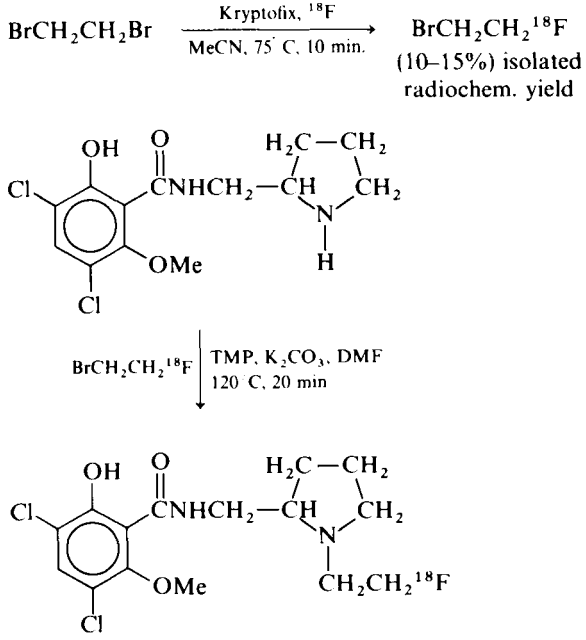
(**27**) (**26**)

Kryptofix 221: 4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8,8,5]tricosane

use both in the preparative and the medical part of the experiment. Specific activities of the benzamide neuroleptic **26**, obtained in 10–25% yields, varied in the range 600–800 Ci mmol^{-1} after purification of the product mixture by reverse-phase HPLC. The lipophilicity (octanol–water partition coefficients) of **26** has also been investigated[43,44].

9. *Synthesis of [ethyl-^{18}F]fluororaclopride* (**28**)

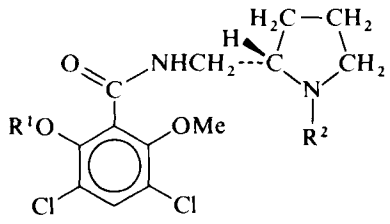
This has been radiolabelled as shown in equation 26 and used in the PET visualization of the dopamine D2 receptor-rich areas of the monkey brain[45a]. Carrier-free aqueous [^{18}F]fluoride has been obtained in the $^{18}O(p, n)^{18}F$ nuclear reaction using 20%.^{18}O-enriched water. 3,5-Dichloro-*N*-[1-{2-[^{18}F]-fluoroethyl}-2-pyrrolydinyl)methyl]-6-methoxysalicylamide **28b** and derivatives, medium affinity binding ligands, have also been synthesized by Satyamurthy and coworkers[45b] for accurate estimation of dopamine D-2 receptor densities[45c].



(**28**) 40% yield

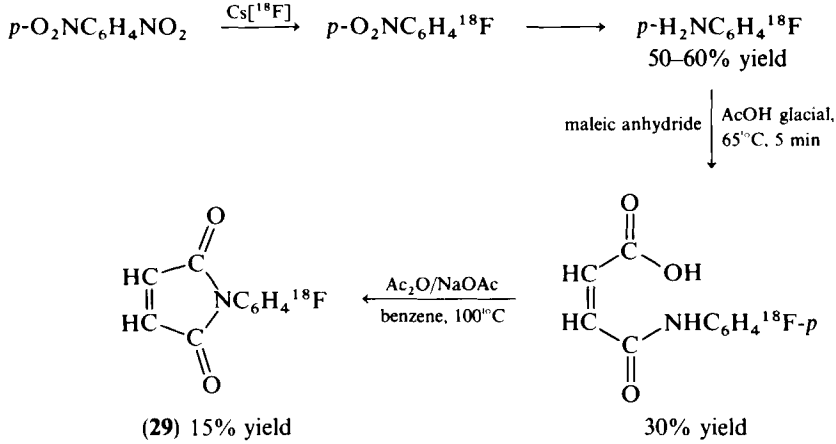
10. *Synthesis of ^{18}F-labelled N-(p-[^{18}F]fluorophenylmaleimide* (**29**)

29 and its derivatives have been obtained[46] (equation 27) for labelling monoclonal antibodies[47,48] with ^{18}F. *m*-Maleimido-*N*-(*p*-[^{18}F]fluorobenzyl)benzamide **30** has been prepared as shown in equation 28. **30** was the major product in aqueous medium, while in pure organic solvents (THF, CH_2Cl_2) it was a minor product. For biological experiments, compound **30** was bound to rabbit antibody fragment IgG[46–48].



(28a–e)

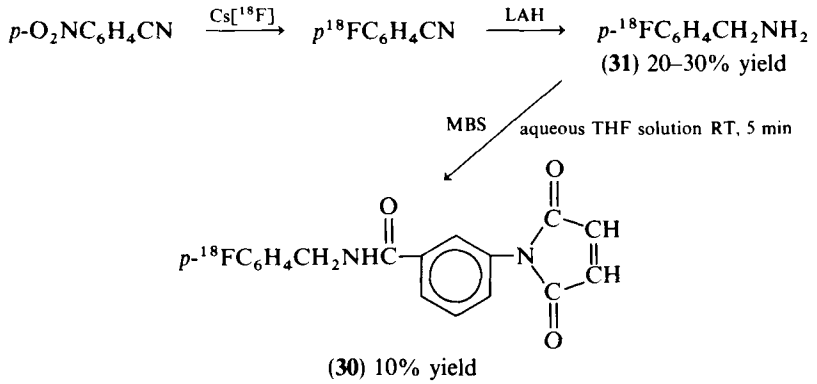
(a) $R^1 = H$, $R^2 = {}^{11}CH_2CH_3$
(b) $R^1 = Me$, $R^2 = CH_2CH_2{}^{18}F$
(c) $R^1 = H$, $R^2 = CH_2CH_2{}^{18}F$
(d) $R^1 = Me$, $R^2 = H$
(e) $R^1 = H$, $R^2 = H$



(29) 15% yield

30% yield

(27)

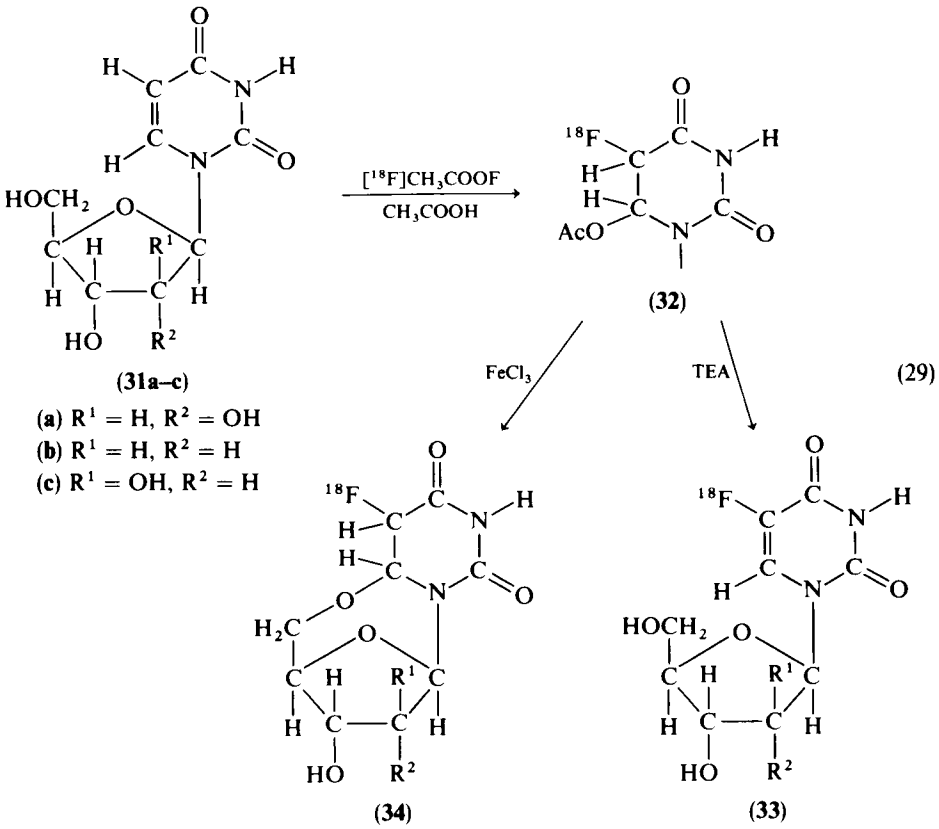


(30) 10% yield

(28)

11. Synthesis of (^{18}F)-5-fluoro-5,6-dihydrouracil nucleosides

These compounds have been prepared for tumour localization[49] by reaction of acetyl hypofluorite with uracil nucleosides, **31a–c**, giving a relatively stable 5-fluoro-6-acetoxy adduct **32**, which in the presence of triethylamine (TEA) yields the corresponding [^{18}F]-5-fluoro compound **33**, while use of Lewis acids resulted in formation of the cyclouracil nucleoside **34** (equation 29).



12. Synthesis and preparative applications of ^{18}F-labelled N-fluoropyridinium triflate (**36**)

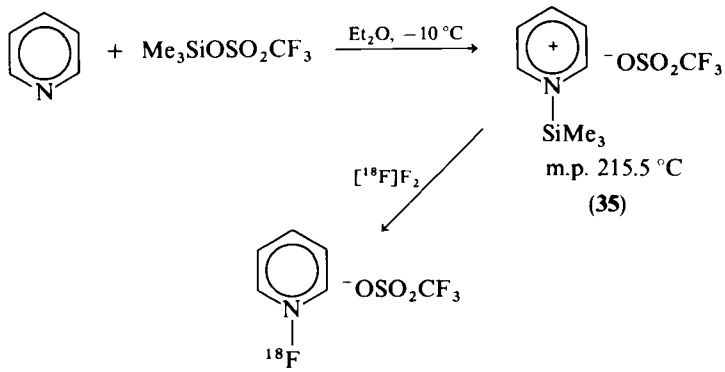
This new precursor in radiopharmaceutical preparations has been obtained[50,51] by cleavage of the N—$SiMe_3$ bond in trimethylsilylpyridinium triflate (equation 30) using gaseous $[^{18}F]F_2$, produced by the nuclear $^{20}Ne(d, \alpha)^{18}F$ reaction in neon[52], which contained 1% F_2. Compound **36**, in which fluorine is bound to a nitrogen atom of decreased electron density, attacks highly polarizable nucleophiles such as carbanions and is a useful electrophilic ^{18}F-labelling reagent for selective monofluorination of organic substrates (equations 31a–e).

The synthesis of 4-[^{18}F]fluoroproline is described elsewhere[53].

C. Syntheses of ^{13}C-labelled Carboxylic Acids and their Derivatives

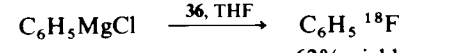
1. Synthesis of [1,2,3,4,5-$^{13}C_5$]palmitic acid (**45**)

This ^{13}C-acid (**45**) has been prepared[54–56] (equation 32) to study lipid metabolism by whole-body NMR[57,58]. Carbonylation of 1-undecane **39** with ^{13}CO under argon with a palladium-Stannous chloride catalyst gave [1-^{13}C]dodecanoic (lauric) acid (**40**). Reduction of **40** with diborane to the alcohol **41** and treatment with 48% HBr gave

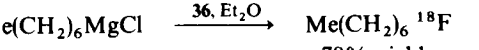


(30)

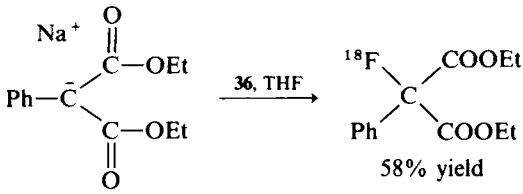
(**36**) 37 mCi, white crystals, m.p. 184 °C
sp. act. 1.67×10^{-4} Ci μmol^{-1}



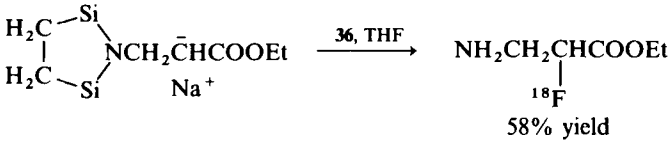
(31a)



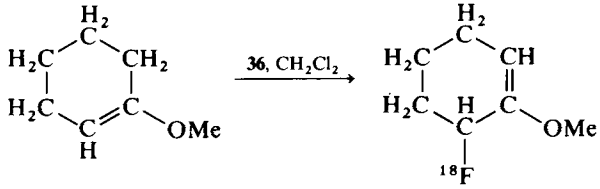
(31b)



(31c)



(31d)



(31e)

1-[1-^{13}C]bromododecane **42**, which in turn was used to alkylate selectively the 4-position of the Na^+, Li^+ mixed, bright-orange-coloured dianion of ethyl acetoacetate **38** to yield ethyl 3-oxo[1,2,3,4,5-$^{13}C_5$]hexadecanoate **43**. Reductive deoxygenation of the latter[59], followed by saponification of the ester **44**, produced [1,2,3,4,5-$^{13}C_5$]hexadecanoic acid (**45**) in 50% yield. The 3-oxo acid ester **43**, on hydrolysis and subsequent decarboxylation, yields 2-pentadecanone (**46**) which, in turn, after reductive deoxygenation, afforded n-pentadecane (**47**).

$$^{13}CO + H_2 \longrightarrow {}^{13}CH_3OH \xrightarrow{^{13}CO} {}^{13}CH_3{}^{13}CO_2Na \longrightarrow {}^{13}CH_3{}^{13}CO_2Et \longrightarrow {}^{13}CH_3{}^{13}CO{}^{13}CH_2{}^{13}CO_2Et \quad (32a)$$

(**37**) (**38**)

$$n\text{-}C_9H_{19}CH{=}CH_2 \xrightarrow{^{13}CO} n\text{-}C_{11}H_{23}{}^{13}CO_2H \longrightarrow n\text{-}C_{11}H_{23}{}^{13}CH_2OH \longrightarrow n\text{-}C_{11}H_{23}{}^{13}CH_2Br \quad (32b)$$

(**39**) (**40**) (**41**) (**42**)

$$n\text{-}C_{11}H_{23}({}^{13}CH_2)_4{}^{13}CO_2Et \longrightarrow n\text{-}C_{11}H_{23}({}^{13}CH_2)_4{}^{13}CO_2H \quad (32c)$$

(**44**) (**45**)

$$\mathbf{38} + \mathbf{42} \longrightarrow n\text{-}C_{11}H_{23}{}^{13}CH_2{}^{13}CH_2{}^{13}CO{}^{13}CH_2{}^{13}CO_2Et \quad (32d)$$

(**43**)

$$n\text{-}C_{11}H_{23}({}^{13}CH_2)_2{}^{13}CO{}^{13}CH_3,\ n\text{-}C_{11}H_{23}({}^{13}CH_2)_3{}^{13}CH_3$$

(**46**) (**47**)

Ethyl[1, 2, 3, 4-$^{13}C_4$]acetoacetate **38** has been prepared by self-condensation of ethyl[1,2-$^{13}C_2$]acetate (**37**) in cyclohexane catalysed by KH[60]. [1,2-$^{13}C_2$]acetate (**37**) has been prepared by treating sodium acetate with diethyl phosphite, $HOP(OC_2H_5)_2$.

2. Synthesis of methyl [2-^{13}C-2,2-D^2]- and [3-^{13}C-3,3-D^2]tetracosanoate

48 and **49** were prepared[61] according to equations 33 and 34. The ^{13}C was introduced

$$CH_3(CH_2)_{20}CH_2OH \xrightarrow[HMPA]{PBr_3} CH_3(CH_2)_{20}CH_2Br \xrightarrow{K^{13}CN}$$

(**50**) 85% yield

$$CH_3(CH_2)_{20}CH_2{}^{13}CN \xrightarrow[\text{refl.}]{H^+/MeOH}$$

90% yield

$$CH_3(CH_2)_{20}CH_2{}^{13}COOMe \xrightarrow[THF]{LiAlD_4} CH_3(CH_2)_{20}CH_2{}^{13}CD_2OD \xrightarrow[HMPA]{PBr_3}$$

87% yield 94% yield

$$CH_3(CH_2)_{20}CH_2{}^{13}CD_2Br \xrightarrow[100\ °C,\ 6\ days]{NaCN/Alumina,\ toluene}$$

(**53**) 97% yield

$$CH_3(CH_2)_{20}CH_2{}^{13}CD_2CN \xrightarrow{H^+/MeOH} CH_3(CH_2)_{20}CH_2{}^{13}CD_2COOMe \quad (33)$$

(**52**) 95% yield (**48**) 74% yield

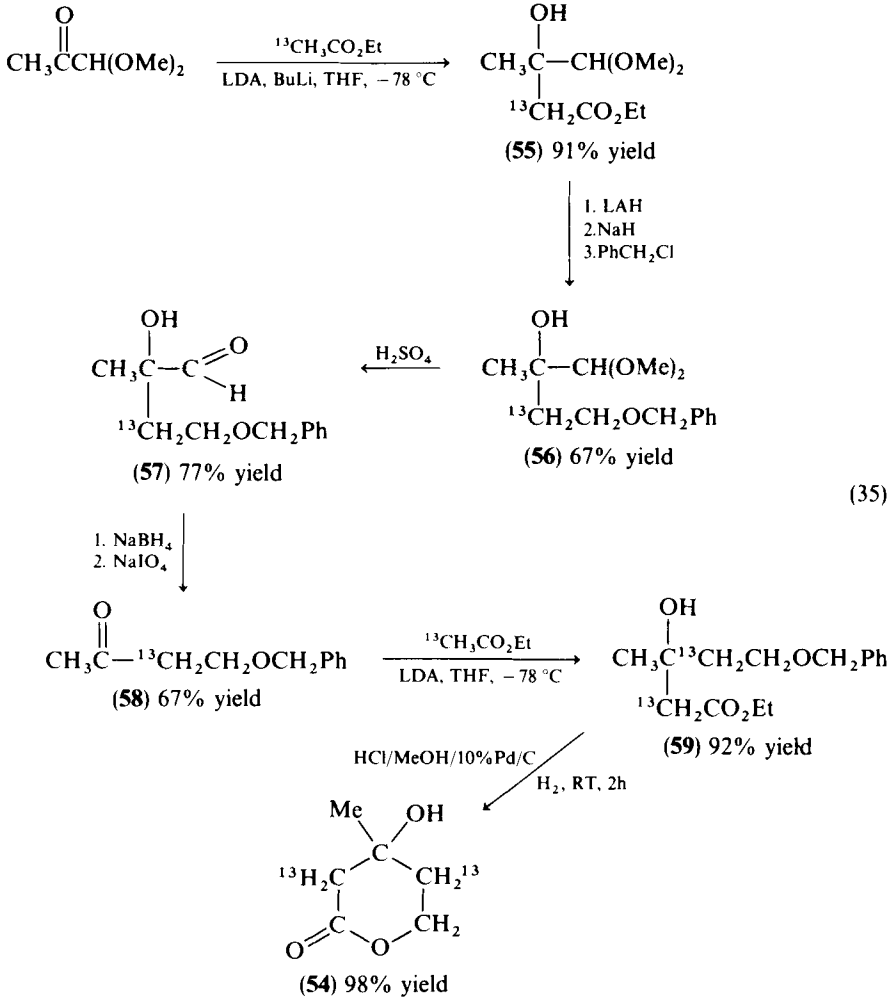
$$CH_3(CH_2)_{19}CH_2OH \xrightarrow[3.\ H^+\ 4.\ LiAlD_4]{1.\ PBr_3\ 2.\ K^{13}CN} CH_3(CH_2)_{20}{}^{13}CD_2OD$$

(**51**)

$$\xrightarrow{\text{carbon homologation}} CH_3(CH_2)_{20}{}^{13}CD_2CH_2COOMe \quad (34)$$

(**49**)

by cyanation using 18-crown-6-ether and potassium [^{13}C]cyanide in HMPA[62]. Triphasic catalysis has been used to introduce CN groups in successive homologations

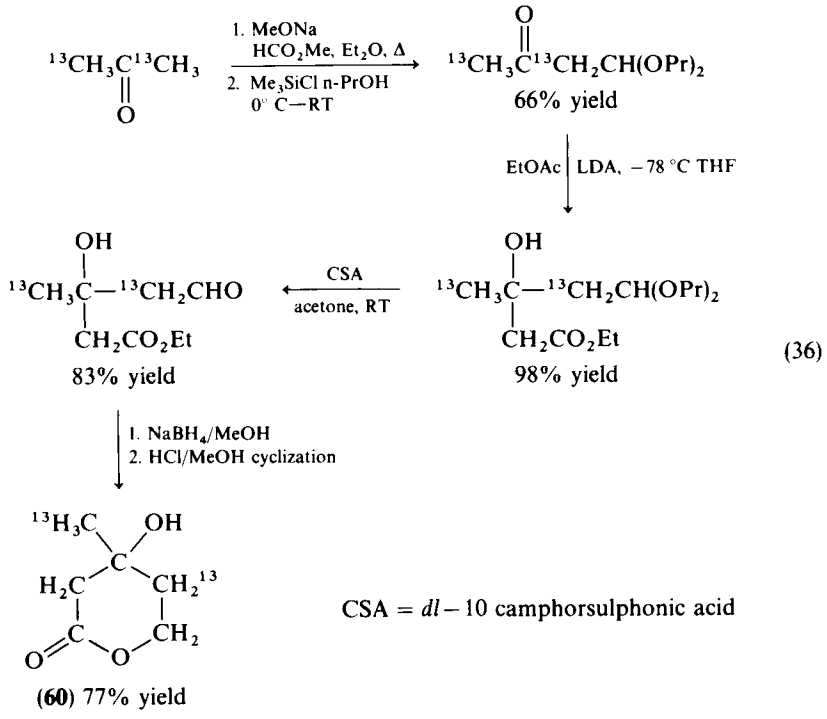


of the labelled compounds. Scrambling and deuterium exchange has been avoided in the last step of equation 33 by hydrolysing **52** in $CHCl_3$–MeOH/HCl without using a basic catalyst. Two isotopic isomers of tetracosanoic acid, doubly labelled with deuterium and carbon-13 at the $C_{(2)}$ and $C_{(3)}$ positions, were needed to determine the participation of α- and/or β-carbons and hydrogens in the biosynthetic mechanisms of production of alkanes, by decarboxylation or decarbonylation[62,63] of the corresponding fatty acids present in cuticular waxes of insects[64].

3. Synthesis of [2,4-$^{13}C_2$] and [4,6-$^{13}C_2$] doubly labelled mevalonolactones

a. (3RS)-[2,4-$^{13}C_2$]mevalonolactone (**54**), needed for elucidation of biosynthetic mechanisms[65], has been prepared[66] as shown in equation 35 which gave **54** in 28.4% overall yield starting from ethyl[2-^{13}C]acetate and pyruvic aldehyde dimethylacetal.

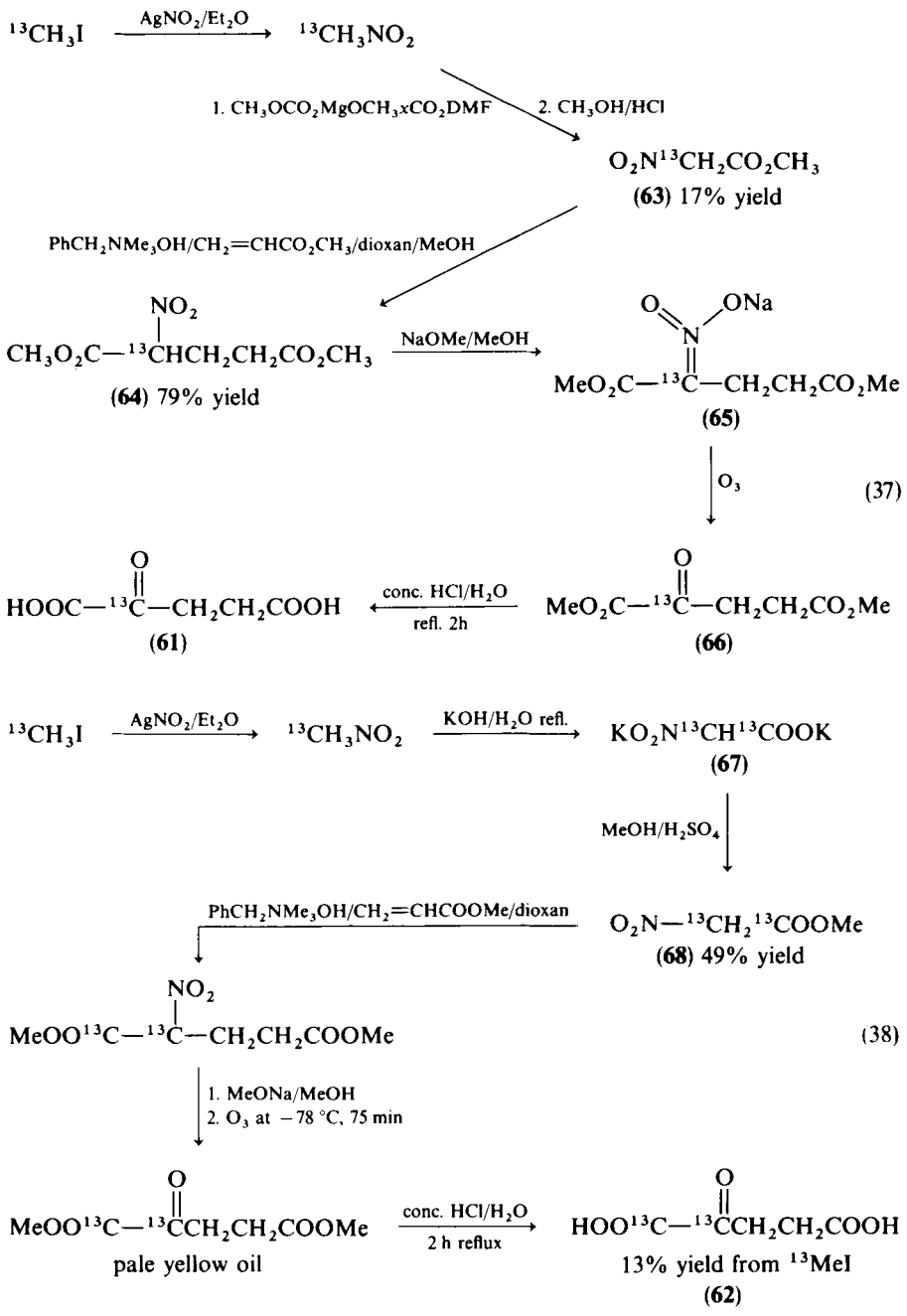
b. Synthesis of doubly labelled [4,6-$^{13}C_2$]mevalonolactone (**60**). This has been previously synthesized[67] from sodium [2-^{13}C]acetate in a rather low (5.4%) overall yield. The new synthetic route illustrated by equation 36 gave[68] **60** in 42% overall yield. **60** was needed to study the mechanism of biosynthesis of trichothecenes[69].



(36)

4. Synthesis of [2-^{13}C]- and [1,2-^{13}C]-labelled α-ketoglutaric acid

The compounds **61** and **62**, co-substrates in many biotransformations, catalysed by none haem iron-dependent oxygenases[70], have been synthesized[71] according to the schemes in equations 37 and 38. $^{13}CH_3NO_2$ reacting with an excess of magnesium methyl carbonate[72a] gave a magnesium chelate, which after treatment with acidified

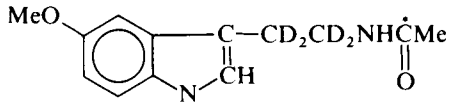


methanol yielded methyl nitroacetate-^{13}C (**63**). **63**) with methyl acrylate in 40% benzyltrimethylammonium hydroxide gave **64**, which in turn, with NaOMe, generated the

nitronate **65** that, after ozonolysis[72b], yielded α-keto[2-^{13}C]glutarate. Deprotection of **66** gave [2-^{13}C]α-ketoglutaric acid (5% yield starting from ^{13}MeI). α-Keto[1,2-^{13}C]glutaric acid (**62**) has been prepared similarly (equation 38).

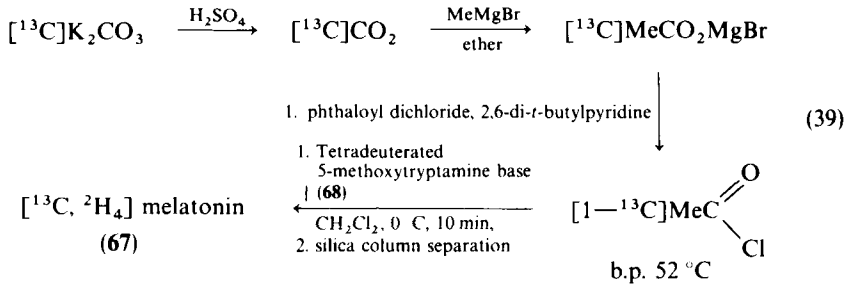
5. Synthesis of [^{13}C, $^{2}H_4$]melatonin

Acetyl chloride labelled with ^{11}C has been used to produce [^{11}C]-melatonin (**67**) and [^{11}C]-6-fluoromelatonin for positron emission tomography[73,74]. ^{13}C-labelled **67** has been obtained by using carbon-13 enriched carbon dioxide (equation 39). Tetradeuterio(carbonyl-^{13}C)melatonin **67** has been separated from the starting material **68** used in excess by elution from a silica column[75].



Ċ = ^{11}C or ^{13}C

(67)



(39)

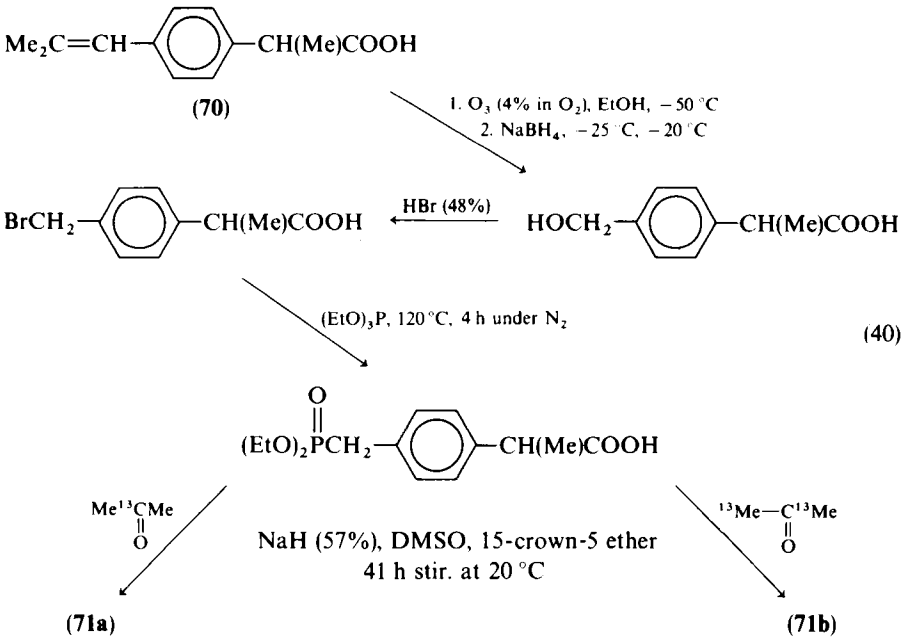
6. Synthesis of carbon-13 labelled ibuprofen

The drug 'Ibuprofen' (**69**) has been labelled[76] with ^{13}C either at the terminal methyl carbons, or at the methine carbon of the isobutyl side chain following the route in equation 40 which involves the removal of the isopropyl group in the isobutyl side chain of **69** via 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid **70**, followed by restoration of the isopropyl group by a Wittig reaction, using [1,3-^{13}C]acetone or [2-^{13}C]acetone.

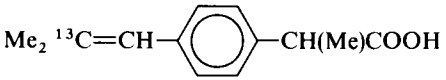
The low toxic ^{13}C-drug **69** can be administered at high doses and provides good detection sensitivity for non-invasive studies of biochemical changes of **69** in living cells of intact organisms by means of NMR spectroscopy[77].

7. Synthesis of δ-aminolevulinic acid (ALA) regioselectively labelled with ^{13}C

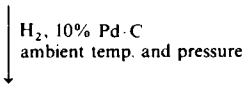
ALA has been labelled[78] with ^{13}C at positions 1, 2, 3, 4 or 5 for direct observation of enzymatic transformation from ALA to porphobilinogen (PBG) by high-field FT-NMR spectroscopy, which detects the ^{13}C-labelled position within the molecule without causing chemical degradation and permits one to study directly the biosynthetic process *in vivo*. The commercially available [5-^{13}C]ALA had been synthesized previously from [2-^{13}C]ethyl malonate[79] or from ethyl 4-oxobutyrate[80]. Recently[78] [5-^{13}C]ALA (**72**)



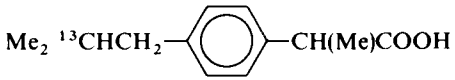
(40)



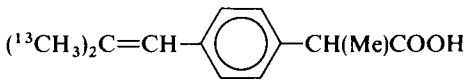
(71a) 34% yield



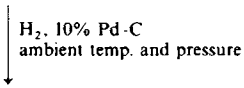
(40a)



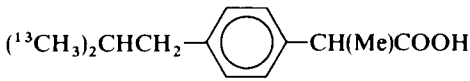
(69a) 91% yield



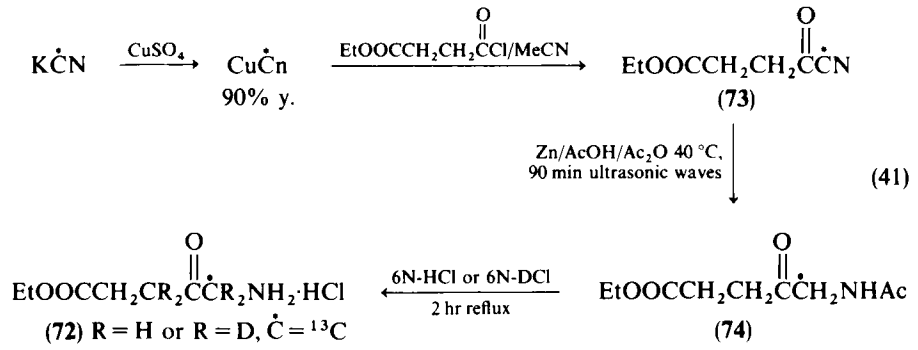
(71b) 31% yield



(40b)



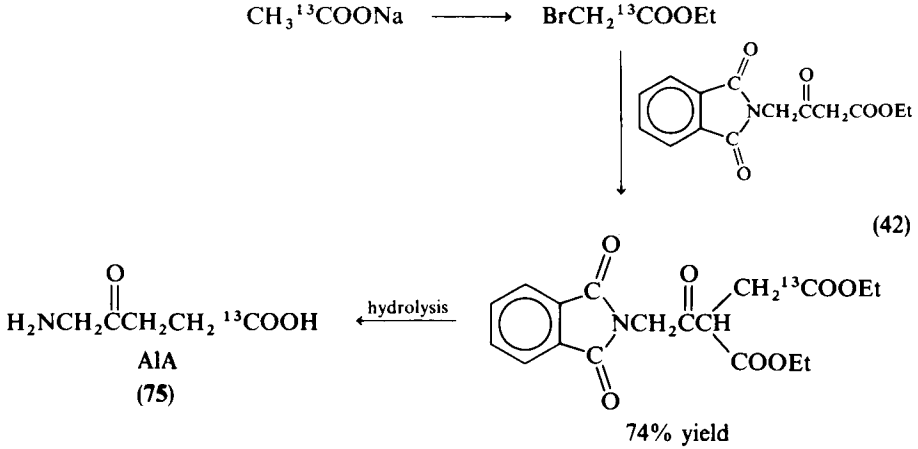
(69b) 94% yield



(41)

has been synthesized starting from [^{13}C]KCN according to equation 41 involving [^{13}C]copper cyanide, and the cyanoketone **73** which has been reduced[81] to give [5-^{13}C]*N*-acetyl-ALA ethyl ester (**74**) and, after hydrolysis, the product **72**. Using DCl in the last hydrolytic step ^{13}C- and deuterium-labelled ALA has been obtained.

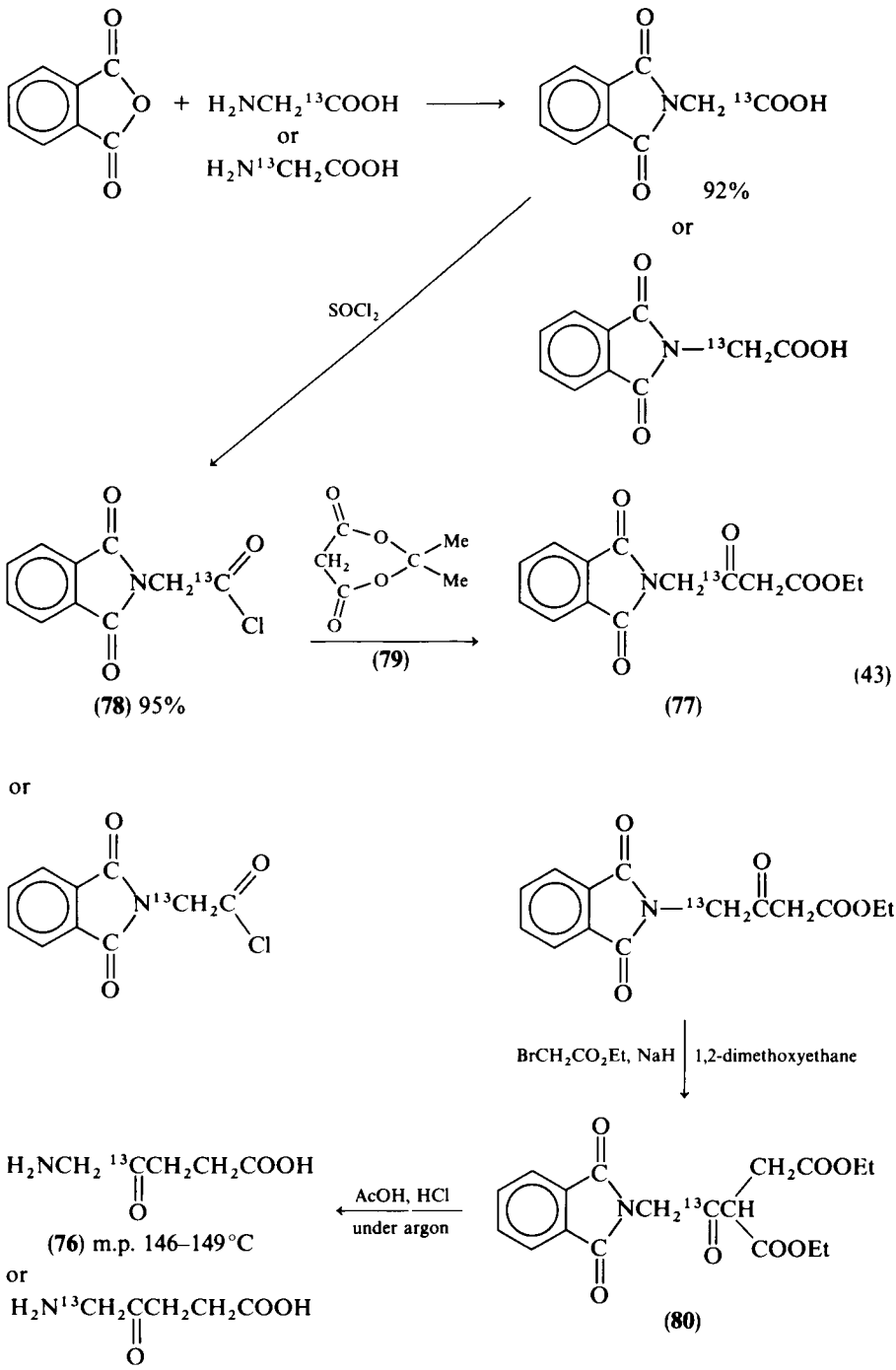
[1-^{13}C]ALA (**75**) has been synthesized, according to equation 42, from [1-^{13}C]ethyl bromoacetate and ethyl phthalimidoacetoacetate producing [1-^{13}C]-ethyl-3-ethoxycarbonyl-5-phthalimidolevulinate which, on hydrolysis gave [1-^{13}C]ALA (**75**) in high yield. [2-^{13}C]ALA has been obtained in the same manner using [2-^{13}C]sodium acetate as the starting isotopic compound.

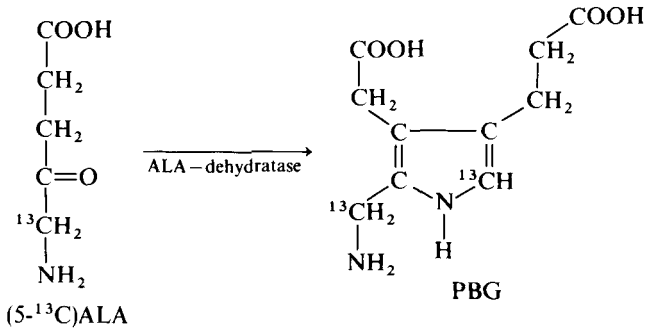


(42)

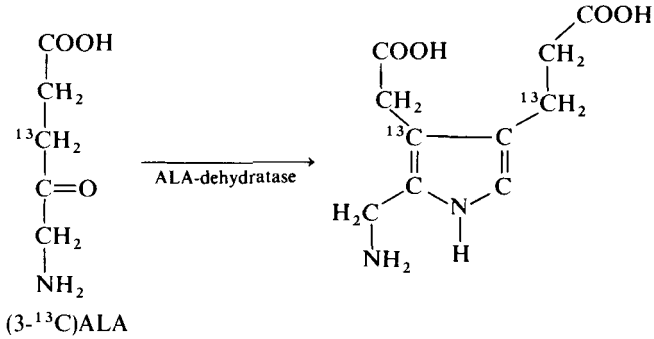
[4-^{13}C]ALA (**76**) or [5-^{13}C]ALA have been prepared following equation 43, through [1-^{13}C]N-phthaloyl glycine, [1-^{13}C]-phthalimido acetyl chloride (**78**), and obtaining from the latter the β-keto ester (**77**) by treating **78** with 2,2-dimethyl-4,6-dioxo-1,3-dioxane (**79**, Meldrum's acid) and finally reacting **77** with ethyl bromoacetate and sodium hydride to yield **80** and, after hydrolysis, the required product **76**. In a similar manner [5-^{13}C]ALA has been obtained. [3-^{13}C]ALA has been prepared using [2-^{13}C]-Meldrum's acid synthesized from [2-^{13}C]bromoacetate[82].

^{13}C-labelled ALA derivatives have been applied to study the enzymatic[83,84] conversion of ALA to ^{13}C-labelled porphobilinogen (equations 44a and 44b) by ^{13}C NMR, which shows directly the structure of ^{13}C-labelled PBG. Thus, the signal of [3-^{13}C]ALA at 36.8 ppm disappears and the new signals at 22.4 ppm and 118.4 ppm corresponding


+ $H_2NCH_2{}^{13}COOH$
or
$H_2N{}^{13}CH_2COOH$
$NCH_2{}^{13}COOH$
92%
or
$SOCl_2$
$N-{}^{13}CH_2COOH$
$NCH_2{}^{13}C$
Cl
Me
Me
(79)
$NCH_2{}^{13}CCH_2COOEt$
(78) 95%
(77)
(43)
or
$N{}^{13}CH_2C$
Cl
$N-{}^{13}CH_2CCH_2COOEt$
$BrCH_2CO_2Et$, NaH
1,2-dimethoxyethane
CH_2COOEt
$NCH_2{}^{13}CCH$
COOEt
(80)
AcOH, HCl
under argon
$H_2NCH_2{}^{13}CCH_2CH_2COOH$
(76) m.p. 146–149°C
or
$H_2N{}^{13}CH_2CCH_2CH_2COOH$



(44a)



(44b)

to [4-^{13}C, 8-^{13}C]-enriched PBG become larger. ALA is also the intermediate in the biosynthesis of heme, chlorophyl, vitamin B_{12}[78], and has also been reported as a herbicide.

8. Synthesis of ^{13}C-, ^{15}N- and ^{2}H-labelled metabolites of theophylline

N-(methyl-D_3)urea-^{13}C (**81**) has been prepared[85] according to equation 45. 1-(*Methyl-D_3*)*uric*-2,8-$^{13}C_2$ acid (**82**) has been obtained in a four-step synthesis[86,87] (equation 46). Subsequent methylation of **82** produced 1,3-di(methyl-D_3)uric-2,8-$^{13}C_2$ acid (**83**) (equation 47).

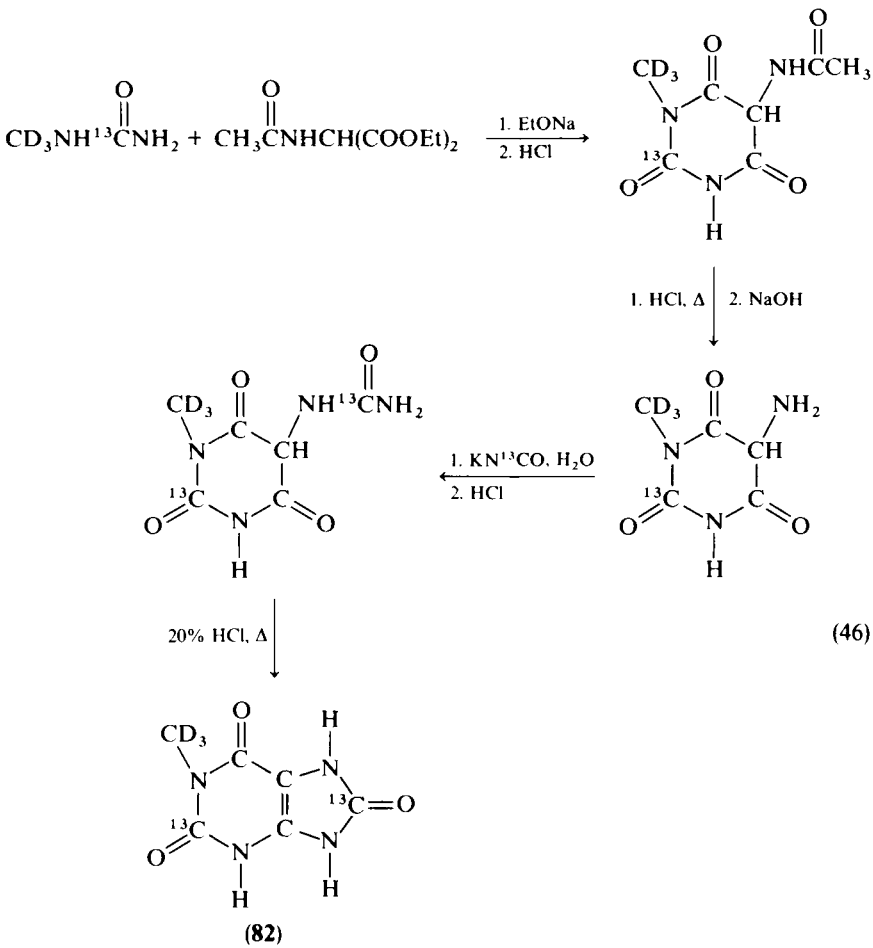
$$CD_3NH_3Cl + KN^{13}CO \longrightarrow \underset{\textbf{(81)}}{CD_3NH^{13}\overset{\overset{O}{\|}}{C}NH_2} + KCl \qquad (45)$$

3-(*Methyl-D_3*)*xanthine*-2-^{13}C,7-^{15}N (**84**) has been synthesized according to equation 48a.

1-(*Methyl-D_3*)*xanthine*-2-^{13}C (**85**) has been produced by reducing 1-(methyl-D_3)uric-2-^{13}C acid with formamide (equation 48b).

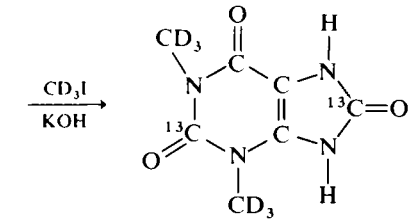
9. Synthesis of ^{13}C-labelled bile acids

Bile acids needed to study the catabolism of cholesterol in the liver have been ^{13}C labelled in the three terminal positions of their side chain by Byon and coworkers[88–90].


CD3NH13CNH2 + CH3CNHCH(COOEt)2
1. EtONa
2. HCl
1. HCl, Δ
2. NaOH
1. KN13CO, H2O
2. HCl
20% HCl, Δ

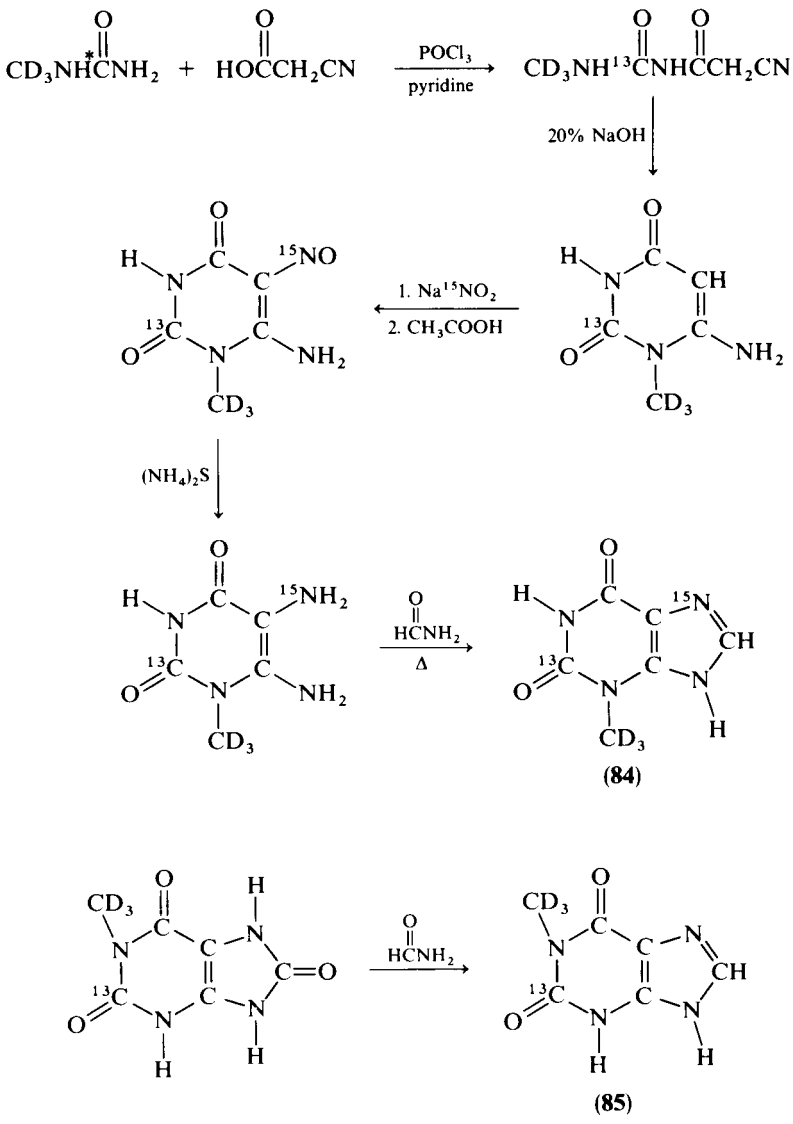
(46)

(82)


82
CD3I
KOH

(47)

(83)



(48a)

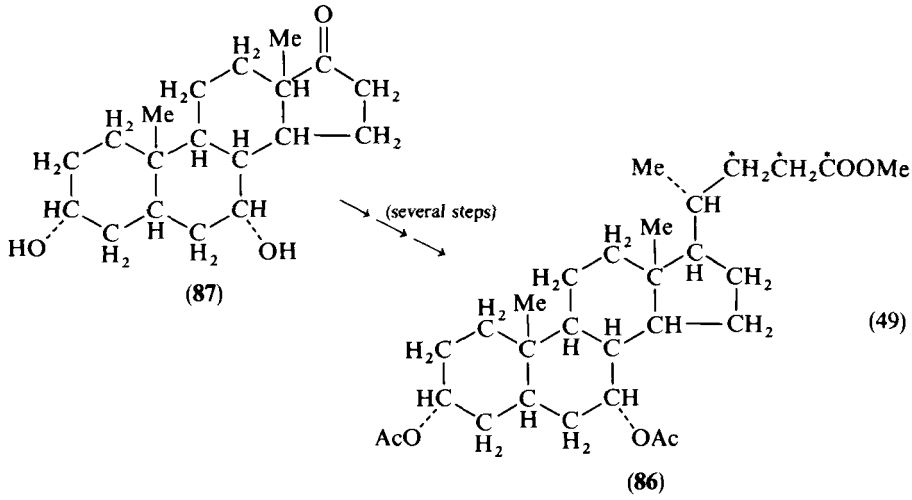
(84)

(48b)

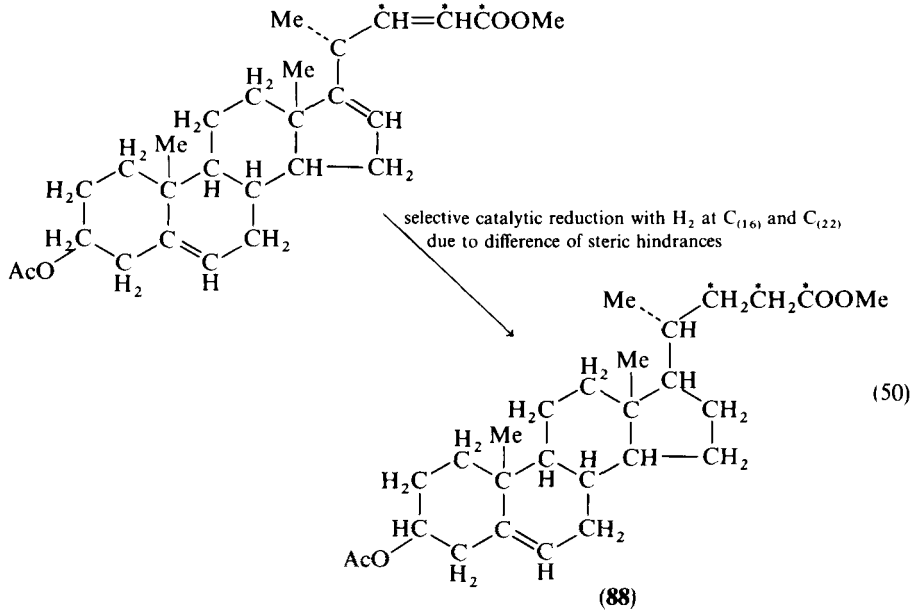
(85)

[22, 23, 24-$^{13}C_3$]-*Methyl* 3α, 7α-*diacetoxy*-5β-*cholan*-24-*oate* (**86**) has been prepared[90] from the diol **87**, 3α,7α-dihydroxy-5β-androstan-17-one[91] in a multi-step synthesis (equation 49).

Labelling of [22, 23, 24-$^{13}C_3$]*methyl* 3β-*acetoxychol*-5-*en*-24-*oate* (**88**) and [16, 17, 22, 23-$^{3}H_4$]-*methyl* 3β-acetoxychol-5-en-24-oate (**89**) has been carried out[92,93] (equations 50 and 51).



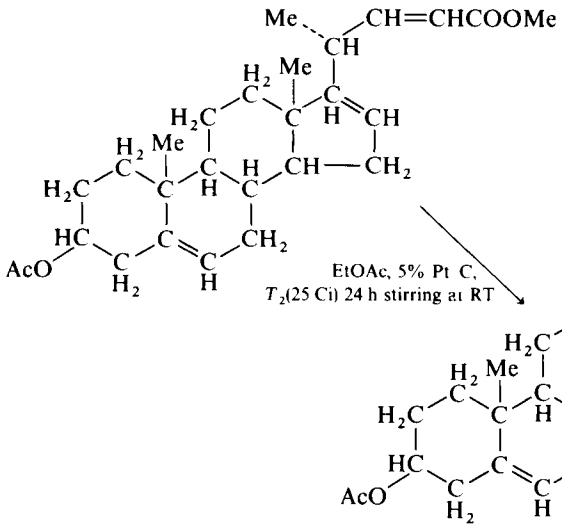
(87) (86) (49)



(88) (50)

10. Synthesis of ^{13}C- and ^{14}C-labelled CY 233-SR 90098

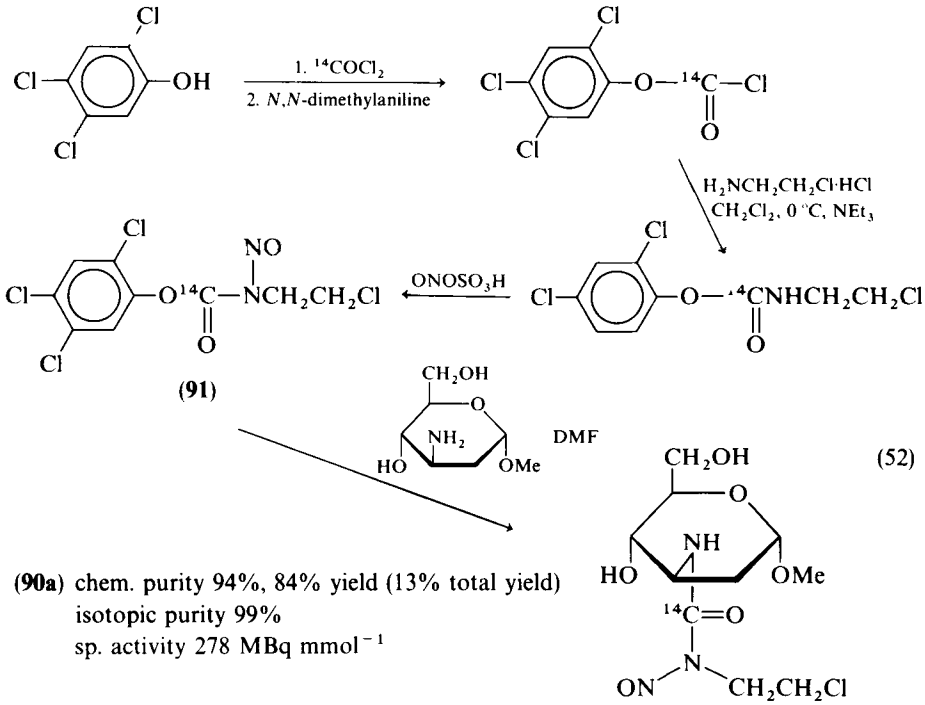
This new antitumor nitrosourea (**90**)[94] has been ^{14}C (or ^{13}C) labelled[95] either on the carbonyl group of **90a** (equation 52), or on the second carbon of the chloroethyl group **90b** (equation 53), or on the methyl group on the anomeric centre of the carbohydrate (equation 54). All the ^{13}C- or ^{14}C-labelled nitrosoureas are suitable for mechanistic studies of antitumor activity (molecular pharmacology and pharmacokinetics, Leukaemia L 1210, Lewis carcinoma, melanome B16, colon carcinoma C38).



(51)

(**89**) sp. act. 178 mCi mg^{-1}
17% yield (64.8 Ci $mmol^{-1}$ after purification)

a. Synthesis of methyl [(chloro-2-ethyl)-3 nitroso-3(^{14}C=O) ureido]-3 didesoxy-2,3 α-D -arabino-hexopyranoside (**90a**)



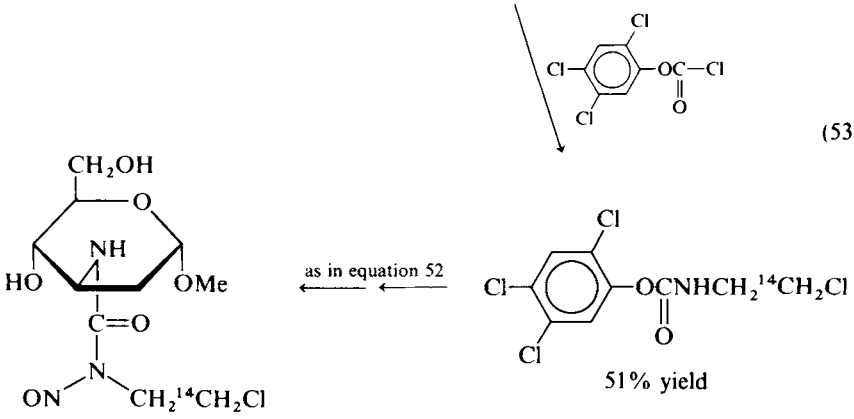
(**91**)

(52)

(**90a**) chem. purity 94%, 84% yield (13% total yield)
isotopic purity 99%
sp. activity 278 MBq $mmol^{-1}$

b. Synthesis of methyl[chloro-2-ethyl(^{14}*C-2))-3 nitroso-3 ureido]-3 didesoxy-2,3 α-D-arabino-hexopyranoside (***90b**)

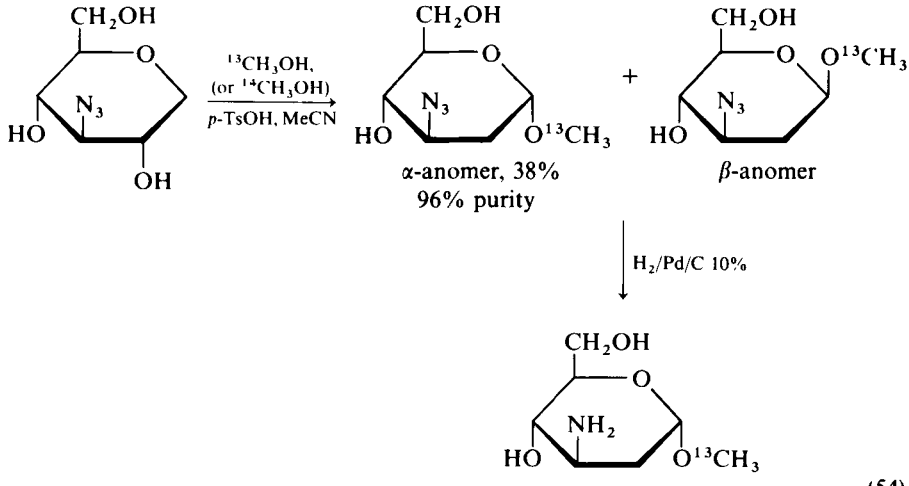
$$HO{-}{}^{14}CH_2CH_2NH_2{\cdot}HCl \xrightarrow[MeCN]{SOCl_2} Cl{-}{}^{14}CH_2CH_2NH_2{\cdot}HCl$$



(53)

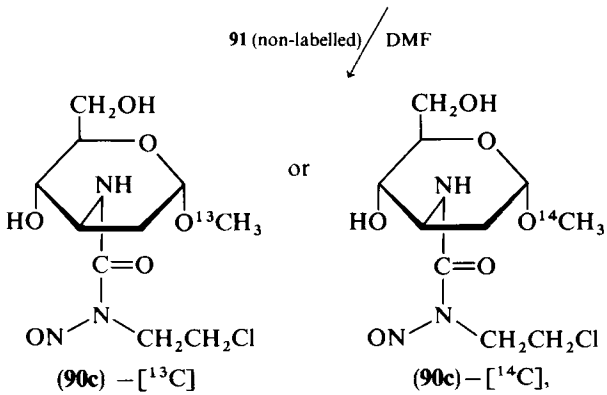
(90b) 44% yield (11% total yield)
chem. purity 99%
isotopic purity 99%
sp. act. 242 MBq mmol^{-1}

c. Synthesis of [methyl(^{13}*C)] or [methyl(*^{14}*C)][(chloro-2 ethyl-3 nitroso-3 ureido]-3 didesoxy-2,3 α-D-arabino-hexopyranoside,* **90c**-*[*^{13}*C] or* **90c**-*[*^{14}*C]*



(54)

(*continued overleaf*)



(90c) $-[^{13}C]$
66% yield (24% total yield)
96% chem. purity
96% isotopic enrichment

(90c) $-[^{14}C]$,
10% total yield
chem. purity 97%
isotopic purity 97%
sp. act. 437 MBq mmol^{-1}

D. Syntheses of ^{14}C-labelled Carboxylic Acids and their Derivatives

1. Microscale synthesis of volatile ^{14}C-labelled acid chlorides

The method of equation 55 was used[96] for obtaining volatile ^{14}C-labelled acid chlorides on a one-mmol microscale starting from carrier-free $Ba^{14}CO_3$. The excess of

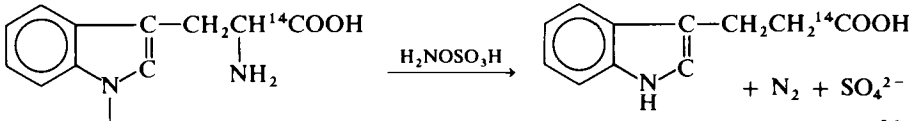
$$\begin{array}{l} RMgCl + {}^{14}CO_2 \longrightarrow R^{14}CO_2MgCl \\ \qquad\qquad\qquad\qquad\quad \Big\downarrow (COCl)_2 \\ \qquad\qquad\qquad\qquad\quad R^{14}COCl + CO + CO_2 + KCl + MgCl \end{array}$$

oxalyl chloride was destroyed with solid potassium stearate (equation 55). Oxalyl chloride has been chosen because it gives gases which allow one to monitor the progress of the reaction by observing the pressure. The volatile ^{14}C-acid chlorides have been isolated in the following yields: $Me^{14}COCl$, 82%, $Et^{14}COCl$, 88%; $Et^{14}COCl$, (obtained using EtMgBr), 85%; $Pr^{14}COCl$, 78%; *t*-$Bu^{14}COCl$, 57%. The above yields and radiochemical purities of the ^{14}C-acid chlorides have been determined by radio-TLC of their anilide derivatives.

$$(COCl)_2 + C_{17}H_{35}COOK \longrightarrow C_{17}H_{35}COCl + CO + CO_2 + KCl \quad (55)$$

2. Synthesis of ^{14}C-labelled carboxylic acids from ^{14}C-labelled amino acids

Various ^{14}C-labelled amino acids have been converted[97] to the corresponding carboxylic acids in high yield (70–90%) using excess hydroxylamine-*O*-sulphonic acid, H_2NOSO_3H, an efficient reagent for the small-scale synthesis of uniformly ^{14}C-labelled carboxylic acids-^{14}C(U) from α-amino acids-^{14}C(U)[98,99]. Equation 56 illustrates the method[100] for the case of 3-indolylpropionic acid, carboxyl-^{14}C (non-uniformly labelled).



10 μCi (92) 9 μCi, 90% yield (56)

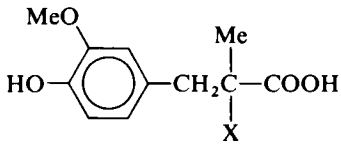
High yields (90–95%) have been obtained[100] with aqueous methanol or ethanol but, in water solvent, the yields of **92** and of 3-phenylpropionic acid-^{14}C(U) were 40 and 25% only.

The following ^{14}C-labelled carboxylic acids have been obtained in water–alcohol solvent medium from the corresponding ^{14}C-labelled amino acids: succinic acid-^{14}C(U) [90% from aspartic acid-^{14}C(U)], glutaric acid-^{14}C(U) [80% from glutamic acid-^{14}C(U)], β-hydroxybutyric acid-^{14}C(U) [90% from threonine-^{14}C(U)], isovaleric acid-^{14}C(U) [70% from valine-^{14}C(U)], 3-phenylpropionic acid-^{14}C(U) [94% from phenylalanine-^{14}C(U)], 3(4-hydroxyphenyl)propionic acid-^{14}C(U) [73% from tyrosine-^{14}C(U)], 3-indolylpropionic acid-carboxyl-^{14}C (90% from tryptophan-carboxyl-^{14}C), 3-(4-hydroxyphenyl)-propionic acid-carboxyl-^{14}C (73% from tyrosine carboxyl-^{14}C), 3-phenylpropionic acid-carboxyl-^{14}C (95% from phenylalanine-carboxyl-^{14}C).

Substitution of primary amino groups contained in natural products (e.g. in amino acids) by deuterium and tritium (equation 57) has been suggested originally[99] as an attractive field of application of this 'hydrodeamination' method.

$$RND_2 \xrightarrow{D_2NOSO_3D} RD + N_2 + SO_4^{2-} \qquad (57)$$

(*S*)-4-hydroxy-3-methoxy-α-methylphenylalanine (**93**) was 'deuterodeaminated' to give **94** in 31% yield. 6-Aminocaproic acid had also been deaminated by this method. A multistep mechanism has been proposed[99] for reaction 57, but was not corroborated with deuterium, ^{14}C or ^{15}N kinetic isotope effect studies.



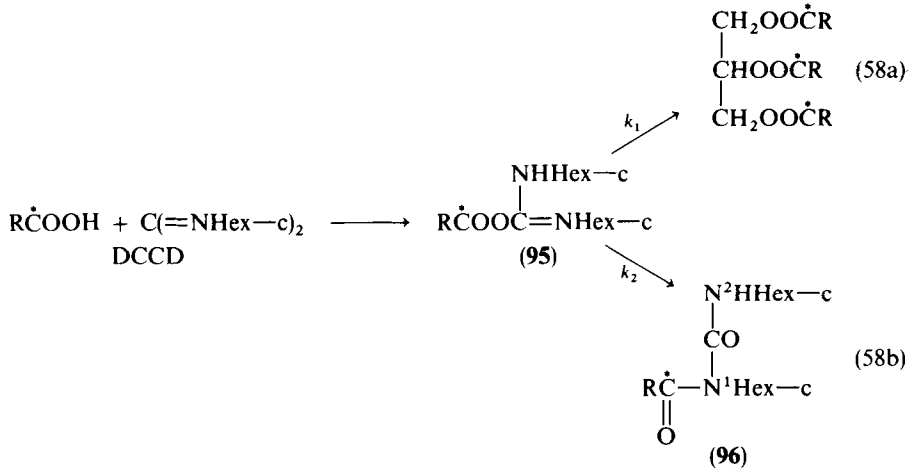
(**93**) X = NH_2
(**94**) X = D

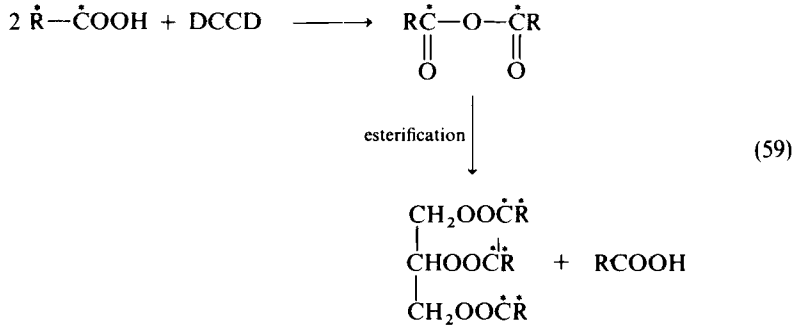
3. *Syntheses of ^{13}C- and ^{14}C-labelled esters*

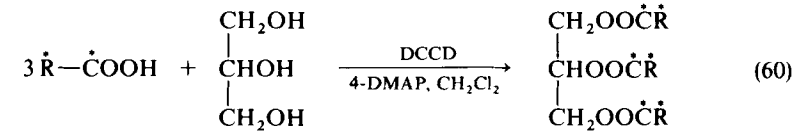
Use of the dicyclohexylcarbodiimide (DCCD), in the presence of 4-dialkylaminopyridine as condensing agent[101,102], in the esterification of organic acids with alcohols (equation 58a) is complicated[103,104] by the side reaction of equation 58b, in which the primarily formed *O*-acylisourea (**95**) is transformed[103,104] into N^1-acyl-N^1, N^2-dicyclohexylurea (**96**). Addition of 4-dimethylaminopyridine (DMAP) to the reaction mixture increased the k_1/k_2 ratio and improved the triglyceride yield by 20%. A further 20% increase in the yield of the glycerol-triester has been achieved[105] by gradual addition of DCCD to the reaction mixture. In such conditions the *O*-acyl isourea **95** reacts fast with the excess acid always present in the reaction medium to yield the fatty acid anhydride

(equation 59). The liberated free acid is converted again to the anhydride by the next portion of DCCD. Thus the undesirable side reaction 58b has been largely eliminated and [U-^{14}C]palmitic acid, [U-^{14}C]oleic acid as well as [9,10-^{3}H]stearic acid have been transformed (equation 60) into glycerol tri[U-^{14}C]palmitate (**97a**, 92% yield), glyceroltri[U-^{14}C]oleate (**97b**) in 87.5% yield and tri[9,10-^{3}H]stearate (**97c**) in 91% yield in radiochemical purities equal to 98.6%, 99.4% and 100%, respectively.

Triglicerides ^{14}C-labelled in the fatty acid portion find application in clinical biochemistry in the so-called 'breath tests'. It has been found that after the first β-oxidation step of glycerol-tri(1-^{14}C)-, (6-^{14}C)- and (11-^{14}C)-palmitates the intermediate formed undergoes fast oxidative destruction to low-molecular-weight fragments[106] and the rate







(**97a**) $\dot{R} = \dot{C}H_3(\dot{C}H_2)_{14}-$
(**97b**) $\dot{R} = cis-\dot{C}H_3(\dot{C}H_2)_7\dot{C}H=\dot{C}H(\dot{C}H_2)_7-$
(**97c**) glycerol tri[9,10—^{3}H]stearate

(**97a,b**) [U—^{14}C]
* = [U—^{14}C], uniformly ^{14}C labelled

of $[^{14}C]O_2$ evolution from the organism does not depend on the position of the ^{14}C-label. Hence, glycerol tri[U-^{14}C] palmitate can therefore be applied in 'breath tests'.

4. Synthesis of [1-^{14}C]-labelled perfluorooctanoic (PFOA), and perfluorodecanoic (PFDA **98***) acids*

These acids have surfactant properties[107] and are used for industrial purposes. They (**98**) have been ^{14}C-labelled in the $C_{(1)}$ position in 48% and 53% yields, respectively[108], by carbonation of perfluoroheptyllithium and perfluorononyllithium at -100 °C (equations 61 and 62).

$$\begin{array}{ccccc} CF_3(CF_2)_8COOH & \xrightarrow{Ag_2O} & CF_3(CF_2)_8COOAg & \xrightarrow{I_2} & CF_3(CF_2)_8I \\ & & 86\% & & 77\%,\ \text{m.p. } 43\text{–}44\ ^\circ C \end{array}$$

$$\downarrow \text{MeLi, ether, } -100\ ^\circ C$$

$$\begin{array}{ccccc} CF_3(CF_2)_8{}^{14}COOMe & \xleftarrow{CH_2N_2,\ \text{ether}} & CF_3(CF_2)_8{}^{14}COOH & \xleftarrow{{}^{14}CO_2} & CF_3(CF_2)_8Li \\ & & \textbf{(98)}\ 53\%, & & \\ & & \text{sp. act. } 4.53\ \text{mCi mmol}^{-1} & & \end{array} \quad (61)$$

$$CF_3(CF_2)_6COOH \xrightarrow{Ag_2O} \xrightarrow{I_2} \xrightarrow{CH_3Li} \xrightarrow{{}^{14}CO_2} CF_3(CF_2)_6{}^{14}COOH \quad (62)$$

48%, sp.act. 4.93 mCi mmol^{-1}.

5. Synthesis of cis-diamino-[1, 1-[1-^{14}]cyclobutanedicarbonyloxy (2)-O,O]platinum II

The antitumor agent carboplatin **99** is less toxic to normal liver and kidney cells than its parent compound *cis*-platin. **99** has been ^{14}C-labelled[109] in the multi-step sequence shown in equation 63. $(NH_3)_2PtI_2$ has been prepared[109] as shown in equation 63a.

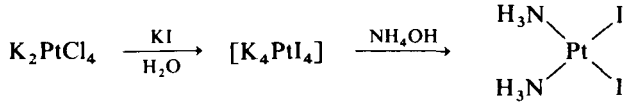
$$BrCH_2CH_2CH_2Br + {}^{14}CH_2(COOEt)_2 \xrightarrow[3,5\ \text{h reflux}]{\text{abs. EtOH, EtONa}} \textbf{(100)}\ 74\%\ \text{yield}$$

55 mCi

$$\downarrow \text{KOH, EtOH abs., } 60\ ^\circ C, 15\ \text{min}$$

$$\textbf{(101)} \xrightarrow[60\ ^\circ C,\ 3\ h]{(NH_3)_2PtI_2,\ AgNO_3,\ H_2O} \textbf{(99)}$$

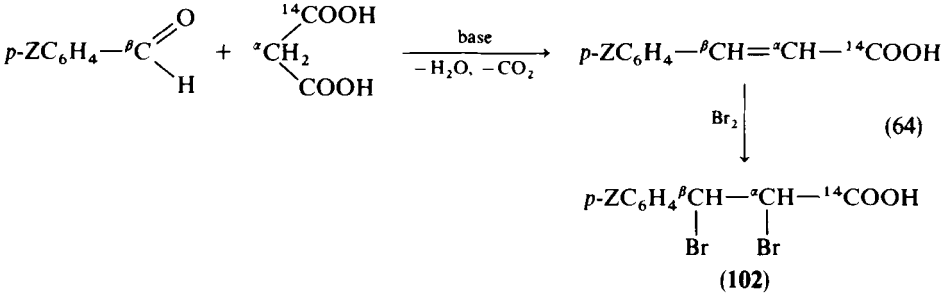
34% overall yield, sp. act.: 3.1 Ci mg^{-1}
99.2% radiochem. purity (63)



(63a)

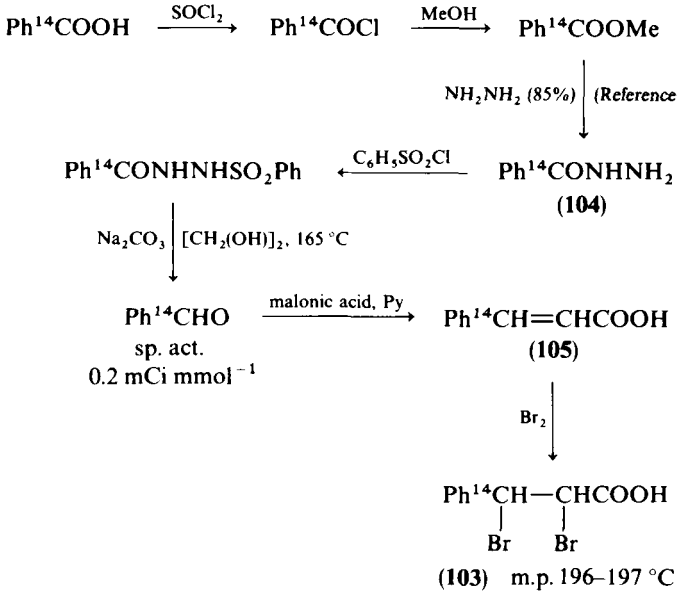
6. *Synthesis of ring-substituted α-, β- and carboxyl-^{14}C-labelled cinnamic acid dibromides*

These compounds, **102**, **103** with Z = MeO, Me, H, Cl and NO_2, labelled with carbon-14 at αC, βC and at the carboxyl group, have been synthesized[110] by the Perkin reaction (equation 64), using the appropriately ^{14}C-labelled synthons. Cinnamic acid dibromide-β-^{14}C (**103**) was obtained according to equation 65. ^{14}C-labelled cinnamic acid dibromides have been used in ^{14}C-kinetic isotope effect studies discussed in Section IV.



(64)

(102)

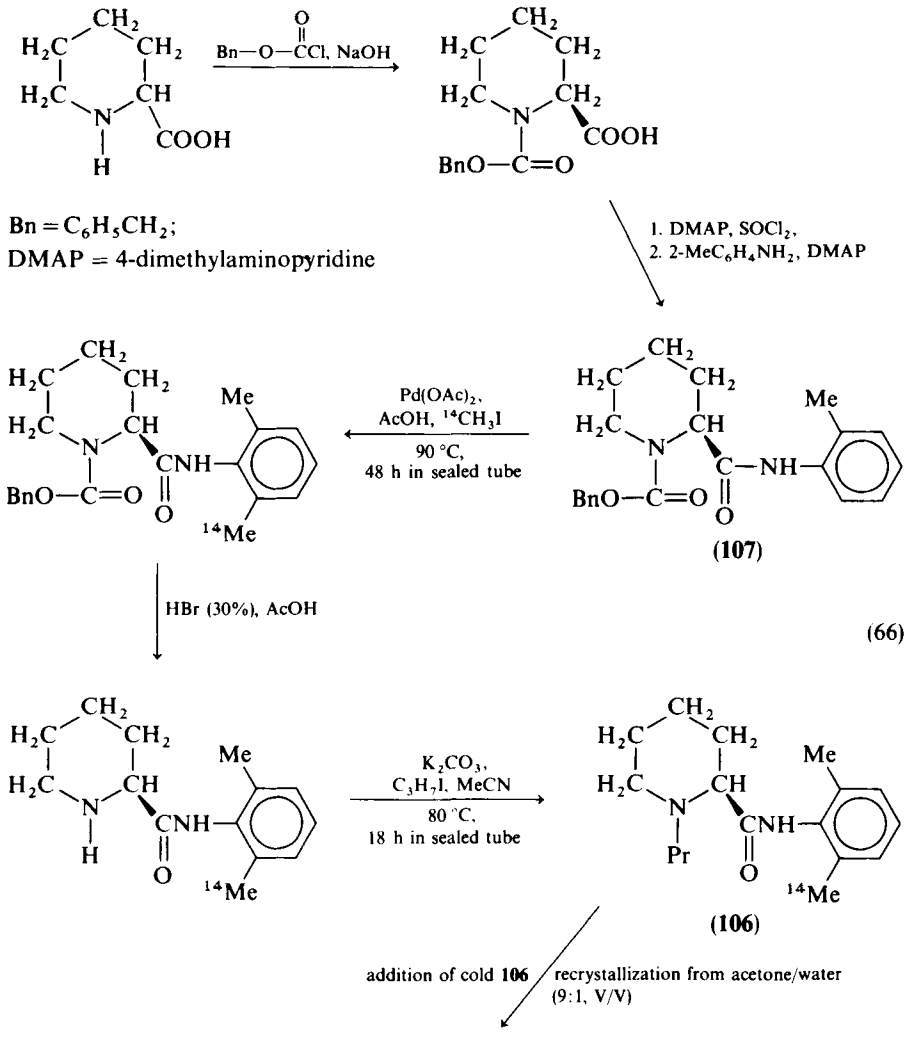


(65)

(103) m.p. 196–197 °C

7. *Synthesis of ^{14}C-labelled ropivacaine*

The ^{14}C-labelled local anaesthetic agent with low heart toxicity, (*S*)-*N*-(2, 6-[2-methyl-^{14}C]dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate (**106**) has been prepared[112] according to equation 66, starting with (*S*)-2-piperidine-carboxylic acid and using [^{14}C]methyl iodide in a Pd(II)-catalysed reaction with **107** to introduce the label into **106**.



(66)

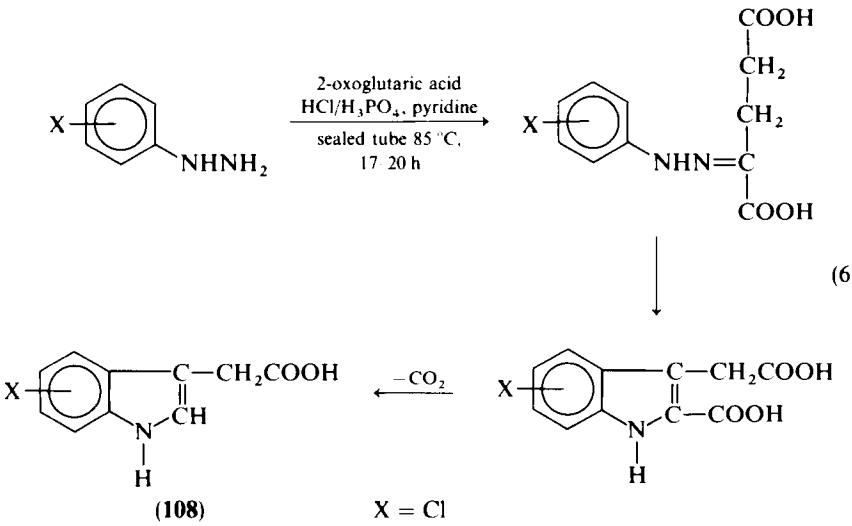
106—(*S*)

19% overall radiochem. yield 98.7% radiochem. purity,
100 ± 0.3% enantiomeric purity (by radio-HPLC)

8. Synthesis of ^{14}C-labelled halogen-substituted indole-3-acetic acid (IAA)

These biologically active acids **108**, showing plant growth promoting activity[113], have been prepared[114,115] according to equation 67 by reacting halogen-substituted phenylhydrazines with [^{14}C]-2-oxoglutarate. The yields varied with different substituted phenylhydrazines. The availability of different forms of radioactive 2-oxoglutarate permits one to obtain **108** labelled in four different positions (ring 2,3 and two side-chain carbons or as ^{14}C uniformly labelled compounds.

Using [^{14}C-U]-2-oxoglutaric acid the following ^{14}C-labelled halogen-substituted indole-3-acetic acids have been obtained: [^{14}C]-5,7-di-Cl-IAA, [^{14}C]-4-Cl-IAA, [^{14}C]-6-Cl-IAA and [^{14}C]-4,6 di-Cl-IAA.

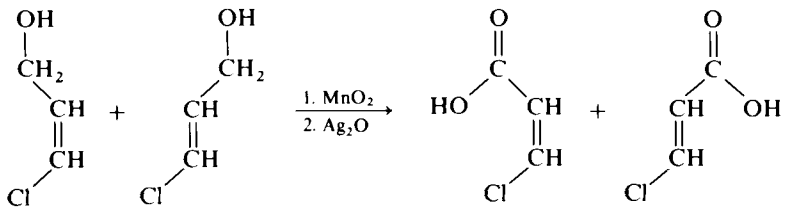


(67)

(108) X = Cl

9. Synthesis of cis/trans 3-chloroacrylic acid-[^{14}C-U]

This uniformly ^{14}C-labelled acid **109** has been synthesized[116,117] in a two-step oxidation reaction (equation 68) avoiding the distillation of the volatile radioactive aldehyde intermediate. Oxidation of the *cis/trans*-3-chloroallyl alcohol-[^{14}C-U] yielded the aldehyde which, on further oxidation by silver oxide, yielded **109** of 98% radiochemical purity. Using pure isomeric forms of 3-chloroallyl alcohol as starting ^{14}C-



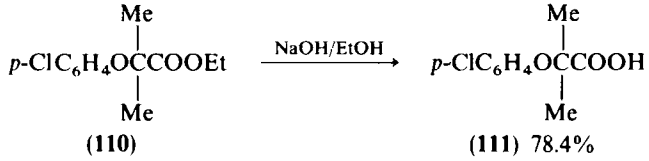
(68)

(109)-[^{14}C—U]
18% yield

labelled substrates, the isomerically pure carboxylic acids have also been obtained. Both ^{14}C-labelled *cis* and *trans* **109** were needed to identify the metabolites of 'TELONE' II soil fumigant degradation[116].

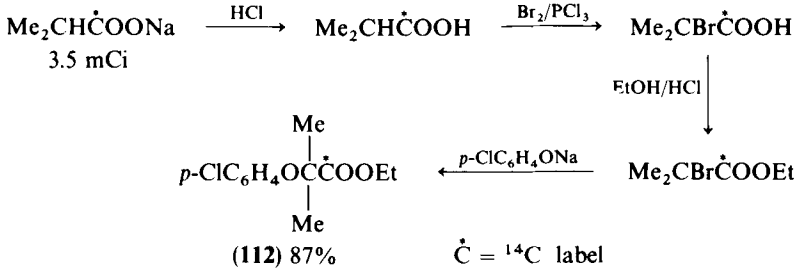
10. Synthesis of ^{14}C-labelled ethyl 2-(p-chlorophenoxy)-2-methyl propionates

Clofibrate (**110**), which rapidly hydrolyses by tissue and serum esterases to clofibric acid, 'CPIB' (**111**) (equation 69), is widely used as anti-hyperlipidemic agent[118] and has been labelled with ^{14}C in three different positions[119,120] and tested *in vivo*[121a,122a].



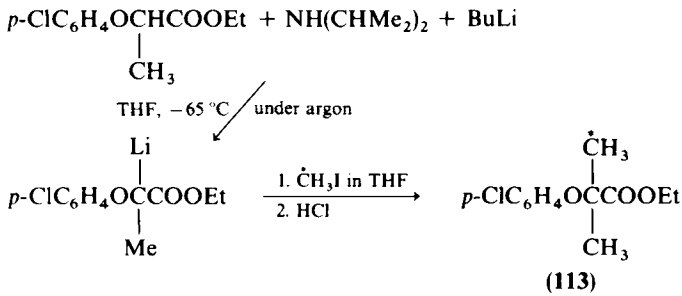
(110) (111) 78.4% (69)

a. Synthesis of ethyl-2-[p-chlorophenoxy]-2-methyl[1-^{14}C] propionate. This compound (**112**) has been prepared using commercially available [1-^{14}C]sodium isobutyrate as the starting labelled substrate (equation 70). The crude **112**, after purification, yielded [^{14}C]clofibrate (99.2% chemical purity, 99.5% radiochemical purity) of specific activity 1.1 μ-Ci mg^{-1}, (0.27 mCi mmol^{-1}) and 35% overall radiochemical yield for the synthesis.



(70)

b. Synthesis of ethyl 2-(p-chlorophenoxy)-[2-^{14}C]methyl propionate. This compound (**113**) has been synthesized according to equation 71. **113** was obtained after purification in 99.5% radiochemical purity, specific activity 7.3 Ci mg^{-1} (1.8 mCi mmol^{-1}) in 56.9% overall yield based on methyl iodide.



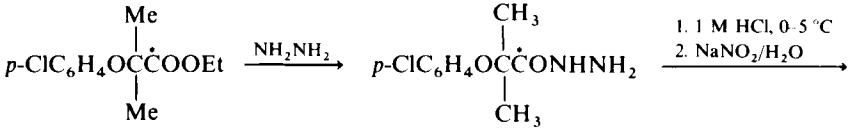
(113) (71)

c. Ethyl 2([U-^{14}C]-p-chlorophenoxy)-2-methyl propionate (**114**) has been prepared by condensing [U-^{14}C]-*p*-chlorophenol (5 mCi, 257.3 mg) with ethyl 2-bromo-2-methyl propionate in an overall yield of 61% based on *p*-chlorophenol. ^{14}C-Clofibric acid has

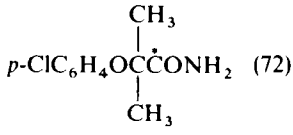
$$p\text{-}ClC_6H_4OC(Me_2)_2COOEt$$

(**114**) 99.7% radiochem. purity, sp. activity 12.2μCi mg^{-1} (2.96 mCi mmol^{-1})

been prepared from each of the three ^{14}C-labelled clofibrates by hydrolysis (equation 69). The labelled amides **115** have been synthesized as in equation 72. The white semi-crystalline solid **115** has been obtained in 62.7% overall chemical yield. Its radiochemical purity was 99.2%.



M.W. 242, 5

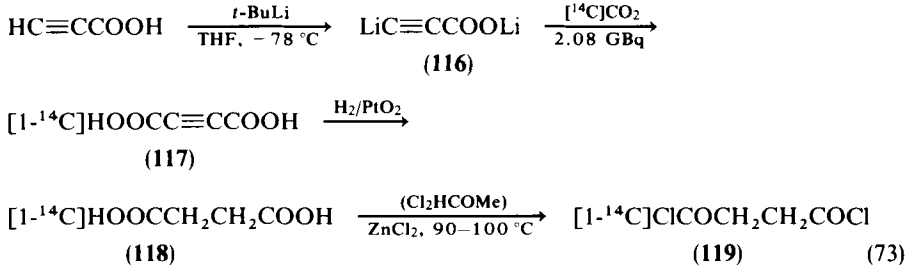


(72)

(**115**)

11. Synthesis of [1-^{14}C]labelled 2-butynedioic acid, succinic acid and succinyl chloride

These compounds have been prepared[121b] according to the method of equation 73.

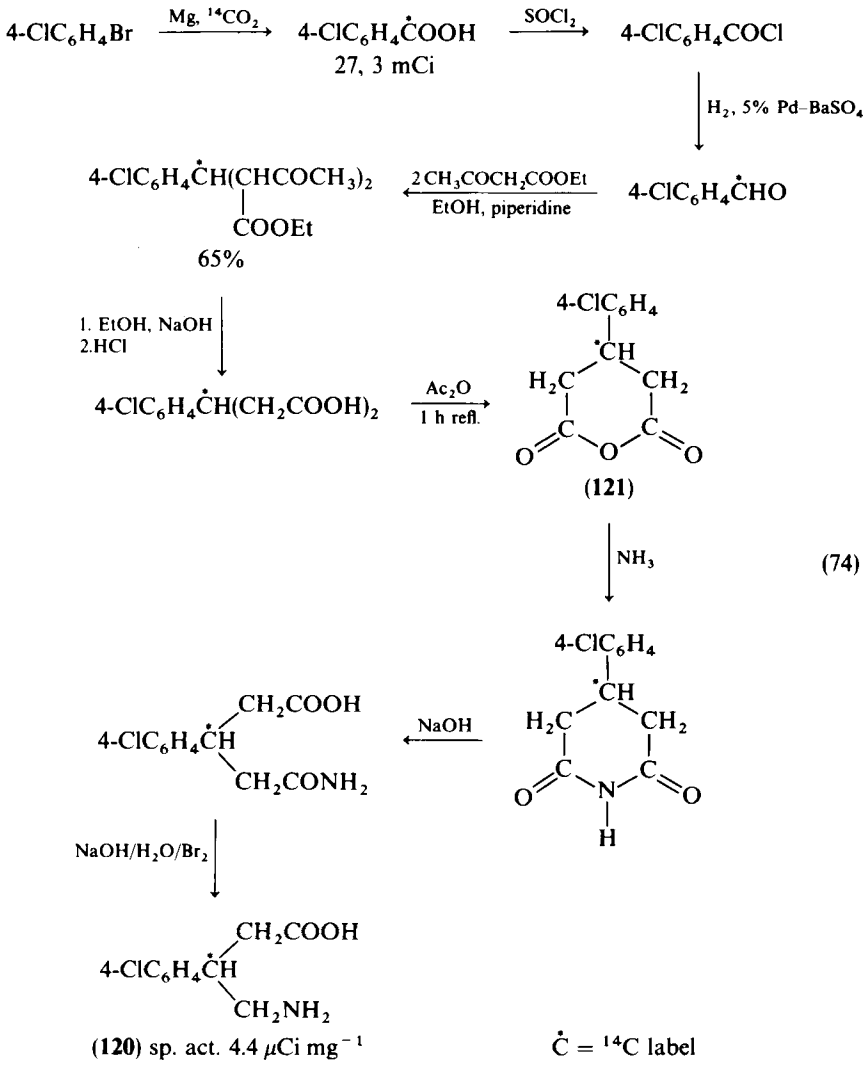


(73)

12. Synthesis of ^{14}C- and tritium-labelled 4-amino-3-(4-chlorophenyl)butyric acid ('Baclofen')

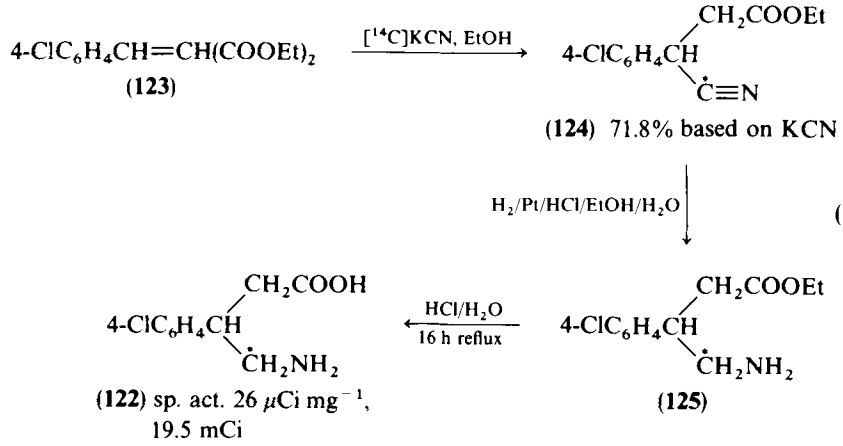
Baclofen is the active component in the muscle relaxant drug 'Lioresal^{R}', possessing the structural features of the γ-amino butyric acid (GABA) and a lipophilic substituent which facilitates its passage through the blood-brain-barrier[123].

a. Synthesis of 4-amino-3-(4-chlorophenyl)-[3-^{14}C]butyric acid. ^{14}C-Label has been introduced[124] in the metabolically stable 3-position of the butyric acid chain (**120**) in nine steps following the reactions shown in equation 74. The radiochemical yield of 4-amino-3-(4-chlorophenyl)-[3-^{14}C]butyric acid (**120**) based on 4-chlorobenzoic acid was 30% [or 48% based on 3-(4-chlorophenyl)-glutaric acid anhydride (**121**)].



b. Synthesis of 4-amino-3-(4-chlorophenyl)-[4-^{14}C]butyric acid (**122**). The ^{14}C atom has been incorporated into the 4-position of the acid chain as shown in equation 75. Condensation of chlorobenzaldehyde and malonic acid diethylester gave[125] 4-chlorobenzalmalonic acid diethyl ester (**123**). Addition of K^{14}CN to the double bond of **123** under heating in ethanol yielded cyano-propionic acid ethyl ester[126] (**124**). Conversion of **124** to aminobutyric acid ester (**125**) by catalytic hydrogenation with Pt and subsequent hydrolysis yielded **122**.

c. Synthesis of 4-amino-3-(4-chloro-[-3-^{3}H]phenyl)-butyric acid (**126**). This compound has been tritium labelled[124] in the benzene nucleus by catalytic bromine–tritium exchange as shown in equation 76. Any introduced labile tritium has been removed by



back-exchange with MeOH. The tritiated baclofen **126b** (specific activity 9.38 mCi $mmol^{-1}$ or 43.9 mCi mg^{-1} after dilution with non-radioactive material) has been stored in the solvent used for the chromatography consisting of *s*-ButOH–AcOH–H_2O(67:10:23) at liquid-N_2 temperature to minimize the rate of self-radiolysis. At room temperature a loss of radiochemical purity of 5% per month has been observed. Before use, the repurification of the product was carried out by column chromatography. The des-chloro compound **128** has been separated from **126** by column chromatography.

13. Synthesis of ^{14}C- and deuterium-labelled trimebutine

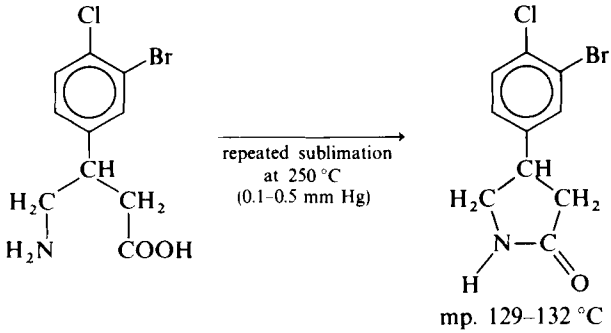
2-Amino-2-phenylbutyric acid-[1-^{14}C] (**129**), 2-amino-2-(pentadeuteriophenyl)butyric acid (**130**), 2-dimethylamino-2-(pentadeuteriophenyl)butyl 3,4,5-trimethoxybenzoate (**131**), 2-amino-2-phenyl-4,4,4-trideuteriobutyric acid (**132**), 2-dimethylamino-2-phenylbutyl[1-^{14}C]-3,4,5-trimethoxybenzoate (**134**) and 3,4,5-tri(trideuteriomethoxy)benzoic acid (**133**) have been obtained[127] as shown in equations 77–80 leading to production of 2-dimethylamino-2-phenylbutanol 3,4,5-trimethoxybenzoate (the drug trimebutine, having a modulator action on gastrointestinal tract motility[128]) labelled with carbon-14 and with deuterium atoms.

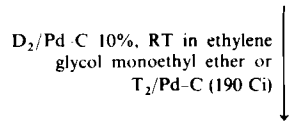
a. Carbon-14-trimebutine containing ^{14}C at the metabolically inert C-1 site in the 2-dimethylamino-2-phenylbutanol moiety has been synthesized as in equation 77.

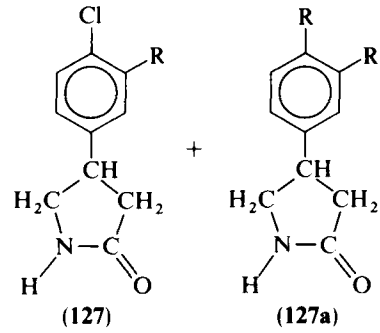
b. Pentadeuteriated trimebutine-$^2H_5$ (**131**) has been synthesized from commercially available hexadeuteriobenzene (equation 78).

c. The trideuteriated metabolite, 2-dimethylamino-2-phenyl-4,4,4-trideuteriobutanol (**135**) *was synthesized from CD_3I* in 13.1% yield (equation 79) and contained 92.8% D_3 species.

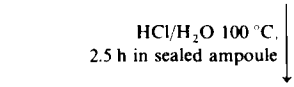
d. Nonadeuteriated 3,4,5-trimethoxybenzoic acid (**133**) has been prepared from gallic acid by methylation with hexadeuteriodimethyl sulphate[129] (equation 80).

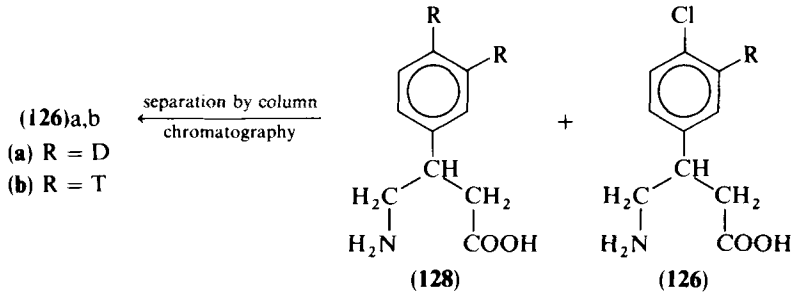

Cl
Br
CH
H_2C
CH_2
H_2N
COOH
repeated sublimation
at 250 °C
(0.1–0.5 mm Hg)
Cl
Br
CH
H_2C
CH_2
N
C
H
O
mp. 129–132 °C

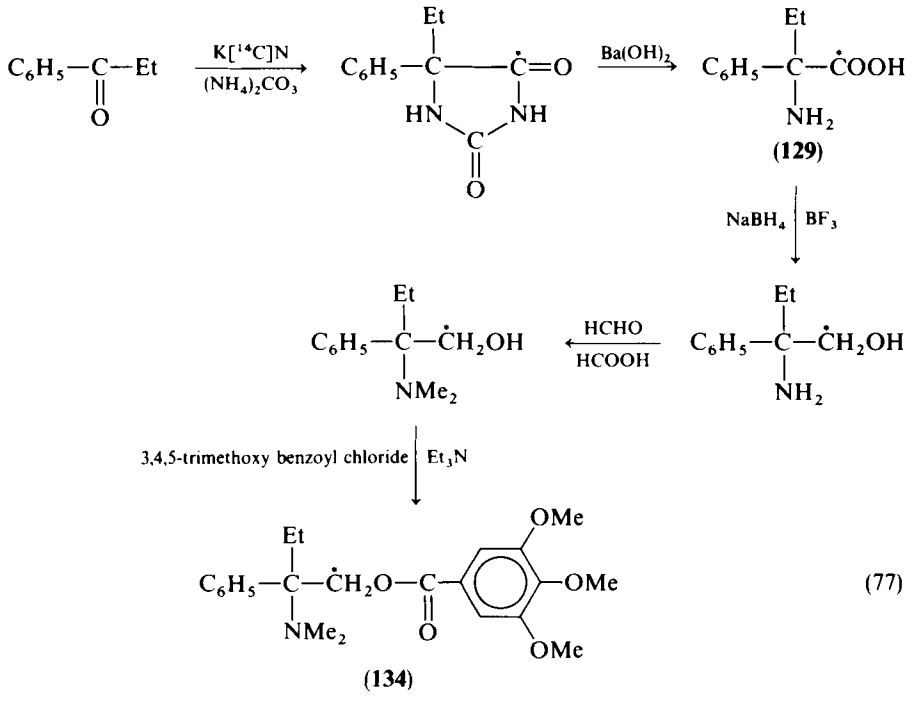

D_2/Pd-C 10%, RT in ethylene
glycol monoethyl ether or
T_2/Pd-C (190 Ci)


Cl
R
CH
H_2C
CH_2
N
C
H
O
+
(127)
(127a)

(76)


HCl/H_2O 100 °C,
2.5 h in sealed ampoule


(126)a,b
(a) R = D
(b) R = T
separation by column
chromatography
R
CH
H_2C
CH_2
H_2N
COOH
+
Cl
(128)
(126)



(77)

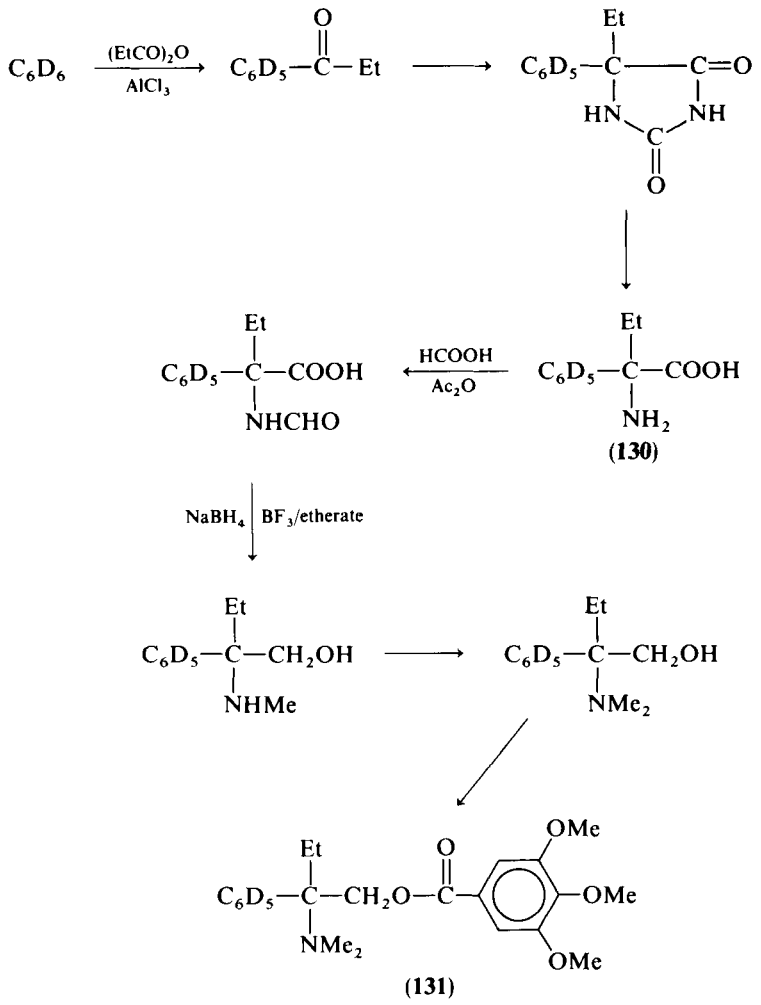
31.6% overall radiochem. yield,
'Ċ' denotes ^{14}C label, sp. act. 2.50 μCi mg^{-1}

14. Synthesis of (±) [2-^{14}C]mevalonolactone (**137**)

This widely used substrate in biosynthesis of terpenoids has been obtained by condensation of 1-trimethylsilyloxy-3-butanone (**138**) and trimethylsilyl[2-^{14}C]acetate (**139**) (equation 81) in high chemical and radiochemical yields. The overall recovery of radioactivity as based on [2-^{14}C]acetic acid was 66.7%[130]. **139** has been prepared in excellent yields (94–97%) by reacting [2-^{14}C]acetic acid with *N*-trimethylsilylimidazole[130].

15. Synthesis of 5-bromopentanoic-[5-^{14}C] acid (**140**) *and ^{14}C-labelled prostaglandins*

This acid (**140**) has been obtained in a five-step synthetic[131] (equation 82) and applied for synthesis of prostaglandins labelled in metabolically stable positions (equation 83). The *ortho* ester **141** prepared from 4-bromobutyronitrile (**142**) has been converted to its Grignard reagent and carboxylated with $^{14}CO_2$ or $^{13}CO_2$ to give the acid **143** which, after reduction with lithium aluminum hydride, yielded the alcohol **144**. The desired product **140** has been obtained in a one-step reaction (involving deprotection of **144** and conversion of the alcohol to the bromide) of **144** with 48% hydrobromic acid in concentrated sulphuric acid[132,133]. **140** in turn has been converted first to the Wittig salt **145** and then to the ylide **146**. The ^{14}C-labelled ylide **146** has been condensed with lactols **148a,b** to give **149**, which after Jones chromium trioxide-acetone oxida-



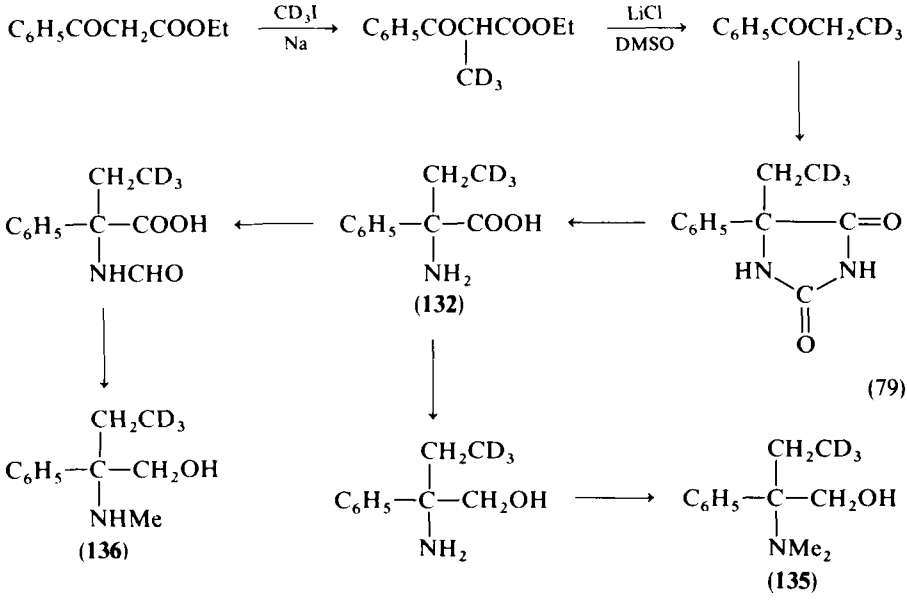
(78)

tion[134a,134b] and removal of the tetrahydropyranyl (THP) protecting group[135] gave the ^{14}C-prostaglandins **150a,b** (equation 83).

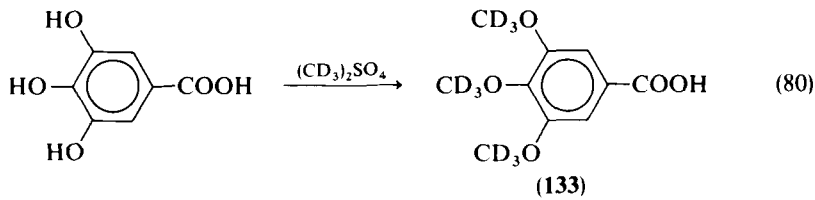
A structurally different prostaglandin, **150c**, ^{14}C- or ^{13}C-labelled at position 5 has also been prepared by a modification of the synthetic route of equation 83.

16. Synthesis of ^{14}C-labelled PD-113,926 and CI-930 of high specific activity

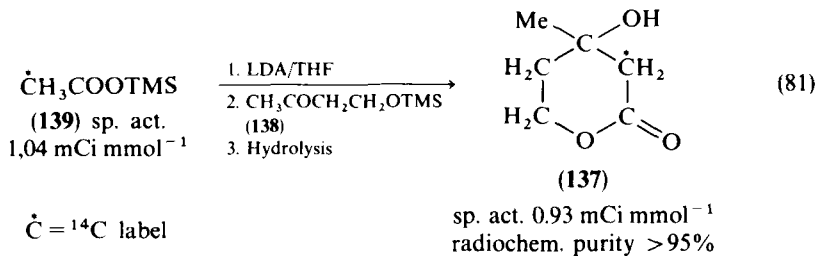
Carbon-14-labelled 4-(1*H*-imidazol-1-yl) α,α-di(methyl-$^{14}C_2$)-β-oxobenzenepropanoic acid methyl ester (**151**) and 4-(1-*H*-imidazol-1-yl)-β(methyl-^{14}C)-γ-oxobenzenebutanoic acid-β-^{14}C, **152**, have been prepared[136] in the course of syntheses of two ^{14}C-labelled potent cardiotonic agents[137] PD-113,926 (**153**) (equation 84) and CI-930 (**154**, equation 85).



(79)



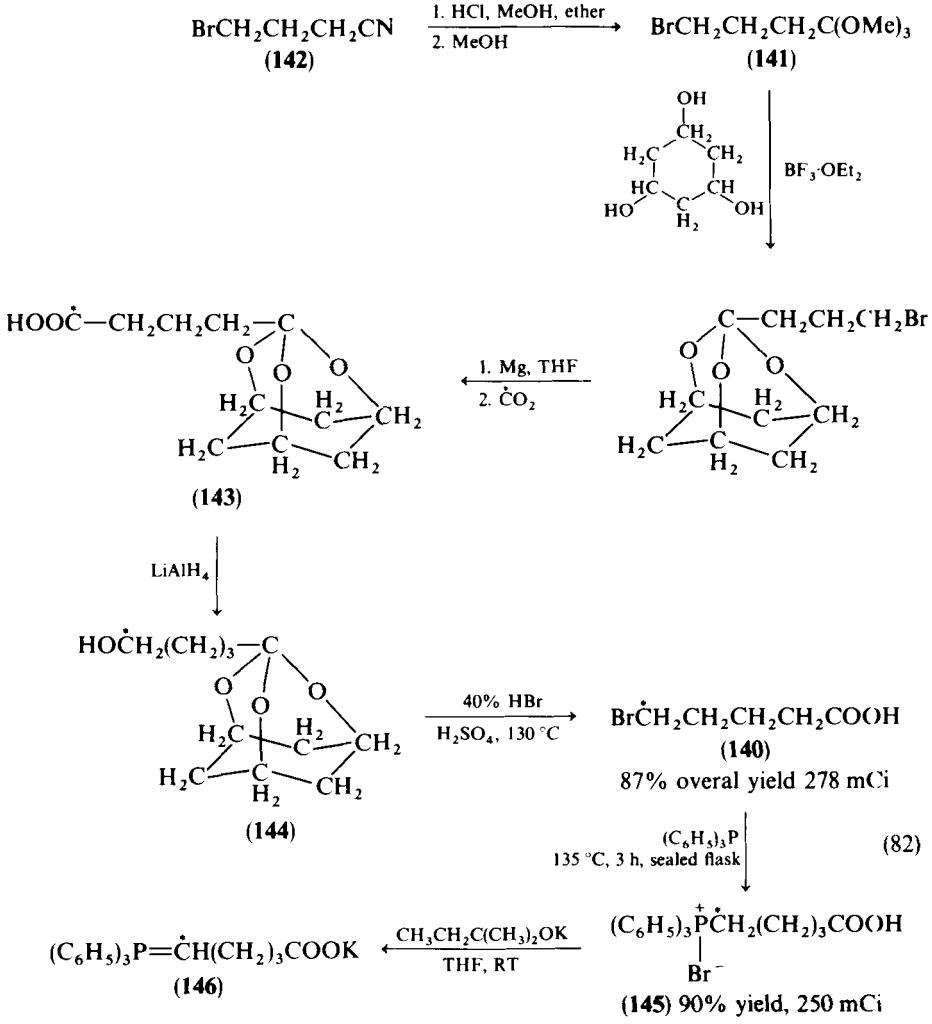
(80)



(81)

17. Synthesis of [^{14}C]flupirtine maleate (**155**)

This compound, ethyl 2-amino-6-{[(4-fluorophenyl)methyl]amino}-3-pyridinyl-[2,6-^{14}C]carbamate maleate, a centrally acting analgesic[138] agent (**155**), has been synthesized[139] in 6.3% overall yield and 99.8% radiochemical purity in a nine-step procedure starting with potassium cyanide-^{14}C and 1,3-dibromopropane (equation 86).

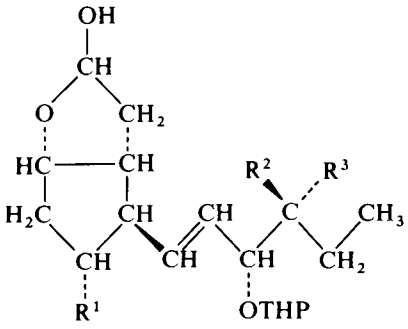


18. Synthesis of 3,6-dichloropicolinic acid 2,6-^{14}C (**156**)

This compound, an active herbicide, with a specific activity of 11.6 mCi mmol^{-1} has been synthesized in five steps from glutarimide-2,6-^{14}C (**157**) for environmental studies[140–142] (equation 87).

19. Synthesis and applications of 2-chloroethyl isocyanate (carbonyl-^{14}C) (**161**)

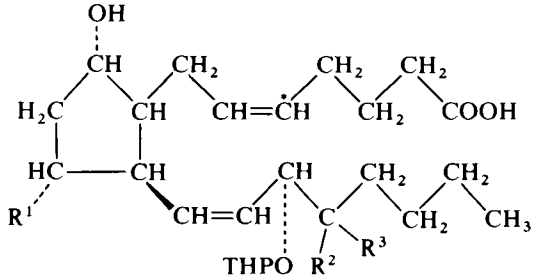
This has been synthesized[143a] under phase transfer conditions from 3-chloro[carboxyl-^{14}C]propionic acid (equation 88) and used to synthesize ^{14}C-labelled 2-chloroethyl tetrazinone (**162**) and two 2-chloroethyl nitrosoureas (**163a,b**) (equation 89) applied for metabolic studies.



+ potassium hydroxide + **146**

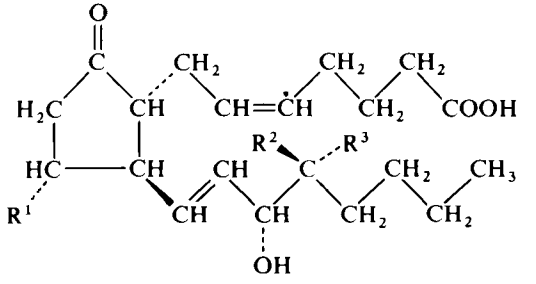
(**148a**) $R^1 = R^2 = R^3 = Me$
(**148b**) $R^1 = R^2 = H$, $R^3 = F$

THF | RT



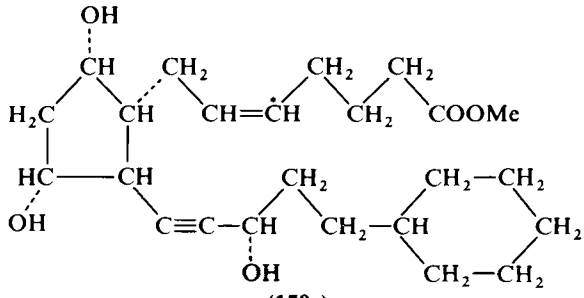
(**149a**) $R^1 = R^2 = R^3 = Me$
(**149b**) $R^1 = R^2 = H$, $R^3 = F$

1. Jones reagent, under nitrogen at 0 °C
2. THF/AcOH/H_2O

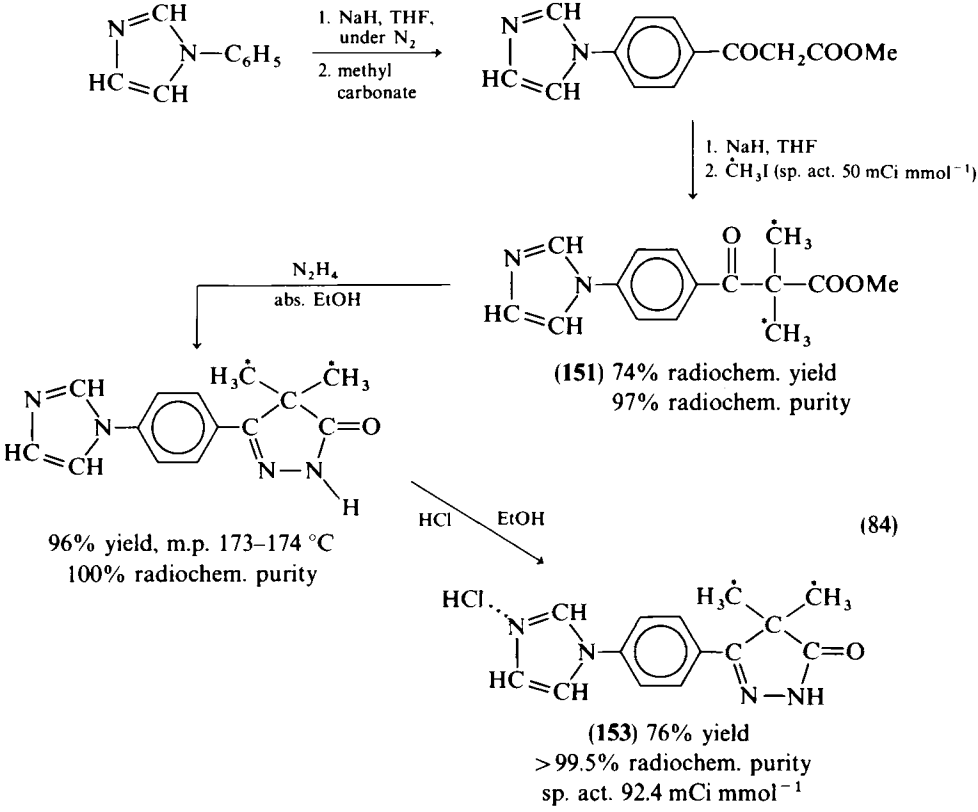


(83)

(**150a**) $R^1 = R^2 = R^3 = Me$
(**150b**) $R^1 = R^2 = H$, $R^3 = F$
overall yield 16.8 mCi (30%)
37% overall yield starting from **145** and lactol **148b**, radiochem. purity 97.8%



(150c)

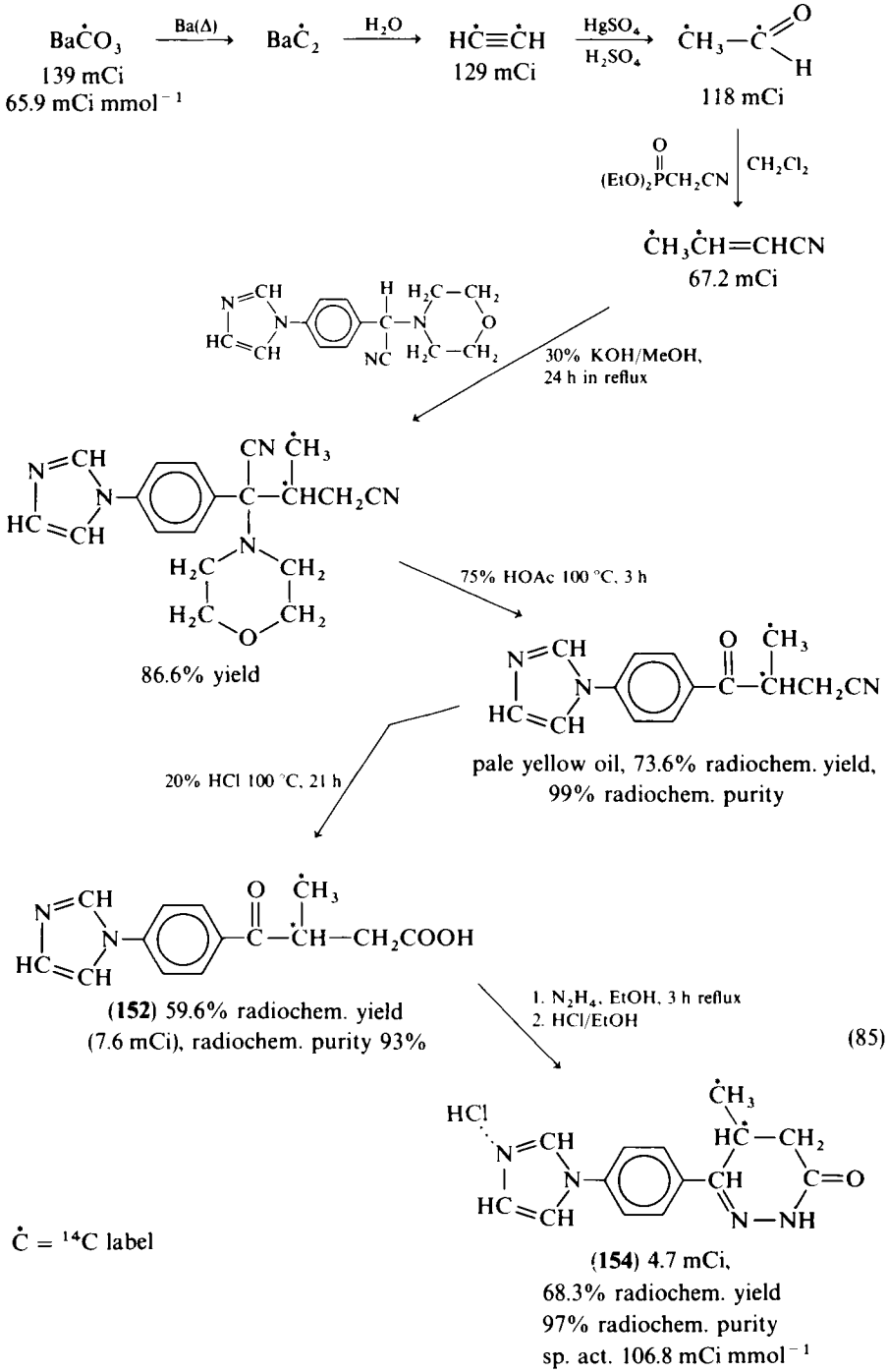


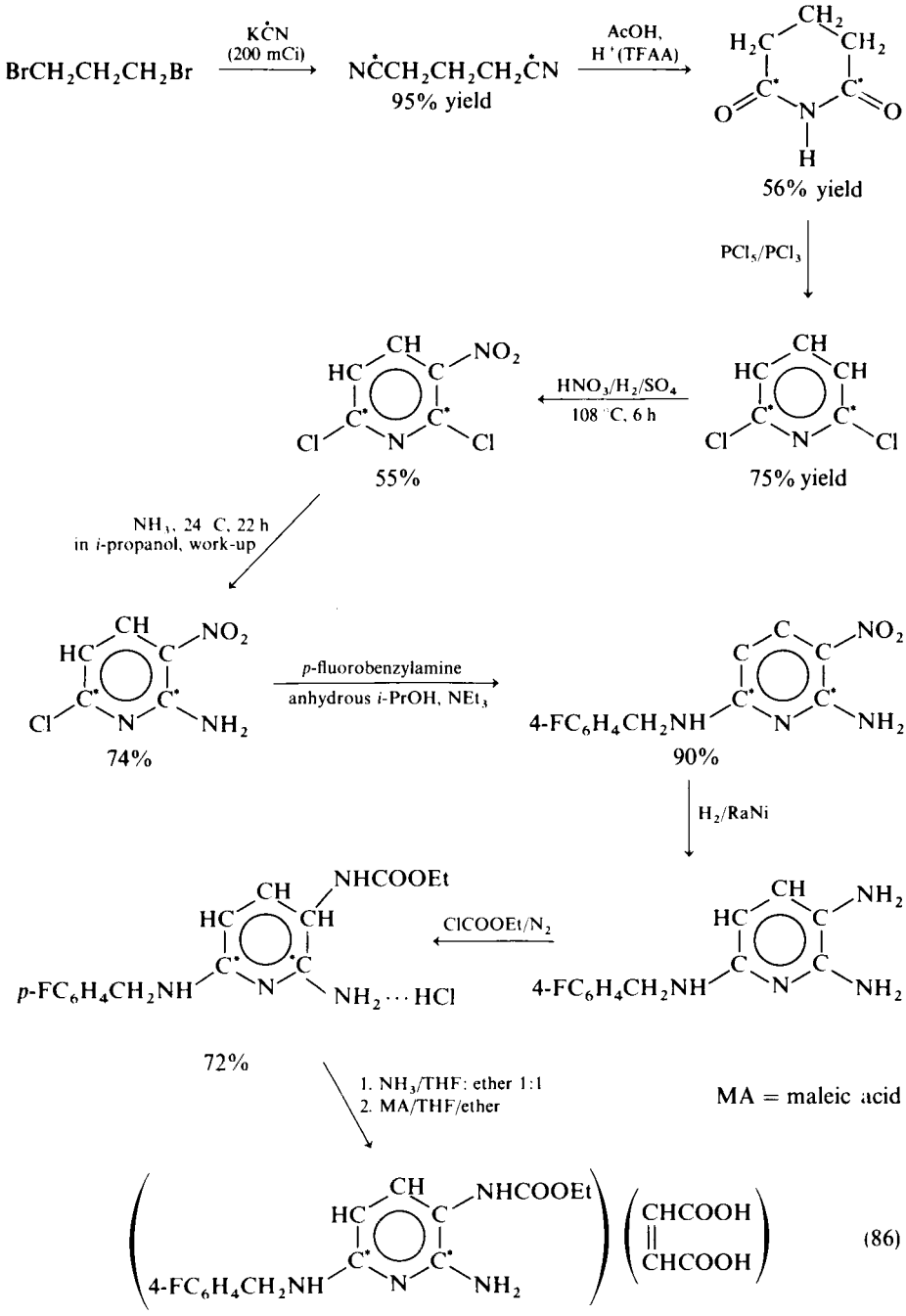
(151) 74% radiochem. yield
97% radiochem. purity

96% yield, m.p. 173–174 °C
100% radiochem. purity

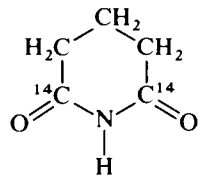
(84)

(153) 76% yield
>99.5% radiochem. purity
sp. act. 92.4 mCi mmol^{-1}


BaĊO3
139 mCi
65.9 mCi mmol−1
Ba(Δ)
BaĊ2
H2O
HĊ≡ĊH
129 mCi
HgSO4
H2SO4
ĊH3—Ċ(=O)—H
118 mCi
(EtO)2PCH2CN
CH2Cl2
ĊH3ĊH=CHCN
67.2 mCi
30% KOH/MeOH,
24 h in reflux
86.6% yield
75% HOAc 100 °C, 3 h
pale yellow oil, 73.6% radiochem. yield,
99% radiochem. purity
20% HCl 100 °C, 21 h
(152) 59.6% radiochem. yield
(7.6 mCi), radiochem. purity 93%
1. N2H4, EtOH, 3 h reflux
2. HCl/EtOH
(85)
Ċ = 14C label
(154) 4.7 mCi,
68.3% radiochem. yield
97% radiochem. purity
sp. act. 106.8 mCi mmol−1

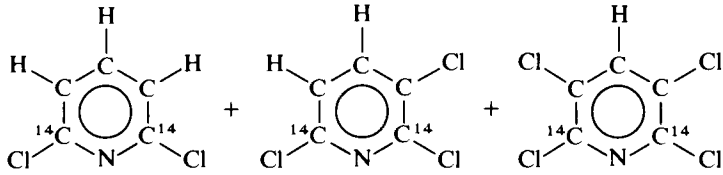


(**155**) 76% yield, 5.4 mCi white solid, m.p. 181–183 °C



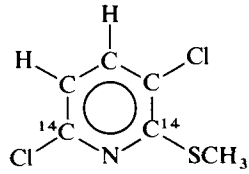
(**157**) 3 mmol, 64.3 mCi

$PhPOCl_2$, PCl_5 ↓ (87a)



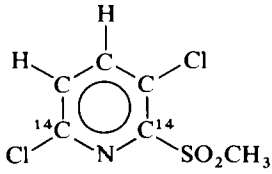
3.7% (**158**) 47.9%

158 + $NaSCH_3$ —DMF→ (87b)



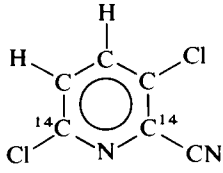
(**159**)

159 —HOCl→



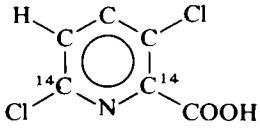
85–95%
97% radiochem. purity

NaCN, DMF ↓ (87c)



(**160**) 94%

H_2SO_4 ←



(**156**) 77% yield
99% radiochem. purity
sp. act. 11.64 mCi $mmol^{-1}$

$$(Na^{14}CN + ClCH_2CH_2OH) \xrightarrow{\text{Ref. 144a}} ClCH_2CH_2{}^{14}COOH$$

(**164**) 20 mmoles, 100 mCi

$$ClCH_2CH_2{}^{14}COOH \xrightarrow{PCl_3} ClCH_2CH_2{}^{14}COCl$$

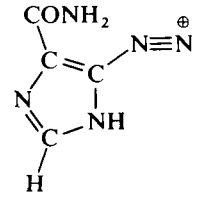
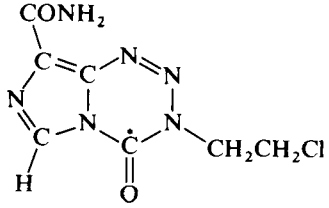
70%
5 mCi mmol^{-1}

$$ClCH_2CH_2{}^{14}COCl \xrightarrow{NaN_3} ClCH_2CH_2{}^{14}CON_3$$

96%

$$ClCH_2CH_2{}^{14}CON_3 \xrightarrow{\text{(Curtius react.)}} ClCH_2CH_2N{=}{}^{14}C{=}O \qquad (88)$$

(**161**) 96%

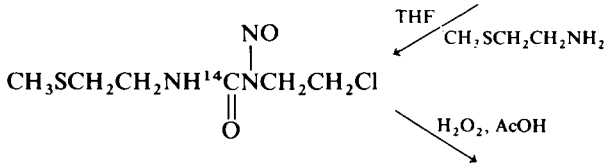
161 (50 mCi) +  →  (89a)

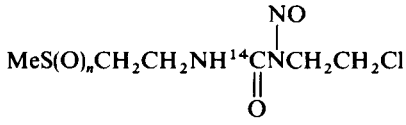
(**162**) 45% radiochem. yield
$\dot{C}$ = ^{14}C label

$$\textbf{161} \xrightarrow{4\text{-}O_2NC_6H_4OH} 4\text{-}O_2NC_6H_4O{}^{14}CNHCH_2CH_2Cl$$

78% radiochem. and chem. yield
sp. act. 18.5×10^7 Bq mmol^{-1}

$$4\text{-}O_2NC_6H_4O{}^{14}CNHCH_2CH_2Cl \xrightarrow{NOCl,\ Py,\ -20\,^\circ C} 4\text{-}O_2NC_6H_4O{}^{14}CN(NO)CH_2CH_2Cl$$

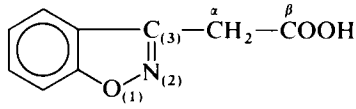
 (89b)



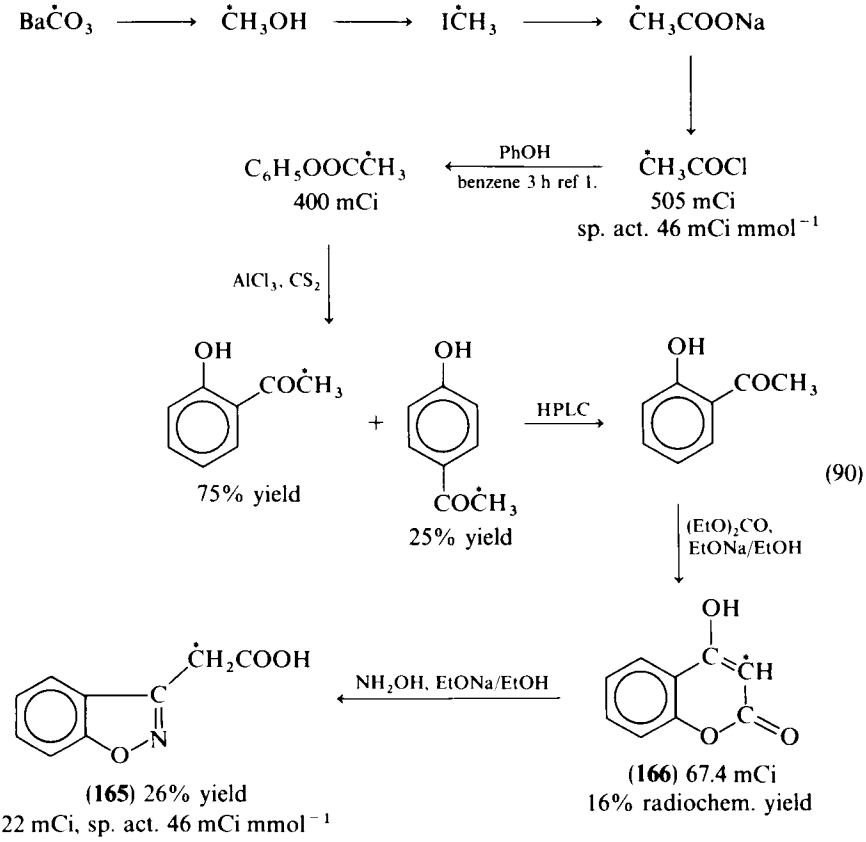
(**163a**) $n = 1$ (**163b**) $n = 2$

20. Syntheses of ^{14}C-labelled 1,2-benzisoxazole-3-acetic acid (**164**)

This acid, which has various industrial[143b] and pharmaceutical applications[144b-146], has been ^{14}C-labelled in α or β positions of the side chain according to equations 90 and 91. α-^{14}C acid (**165**) has been synthesized[147a] from 4-hydroxycumarin[3-^{14}C] (**166**) via Fries rearrangement of phenyl acetate[methyl-^{14}C] (equation 90).



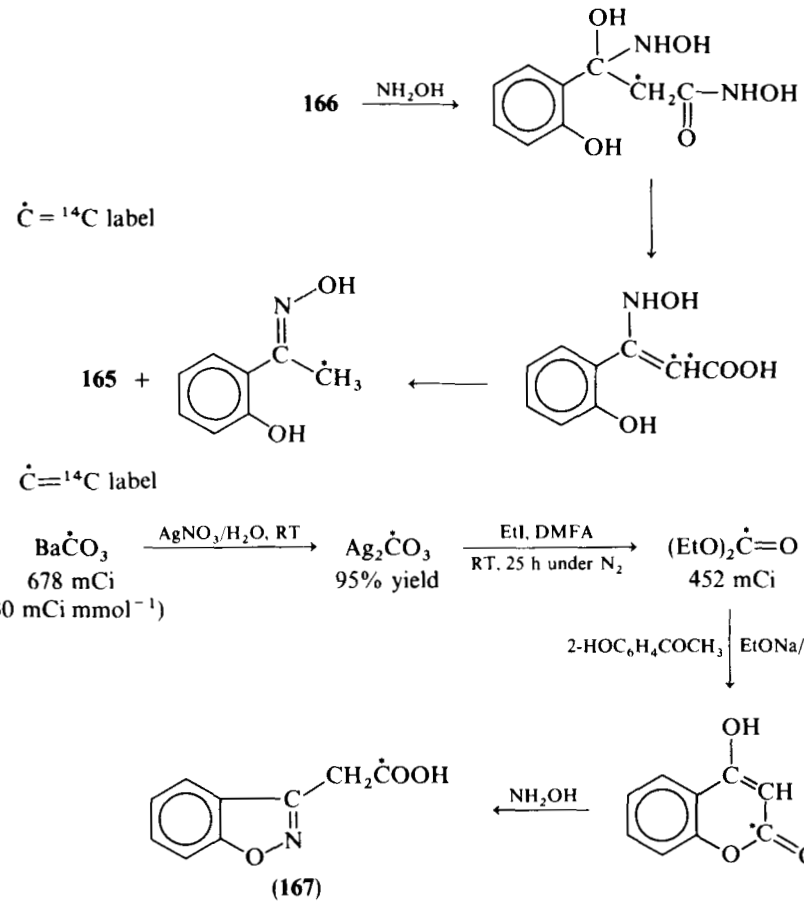
(**164**)



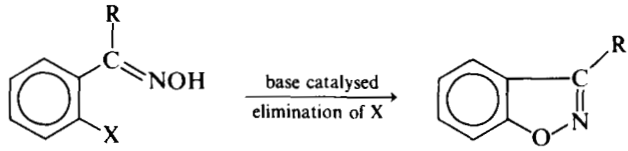
(90)

It has been suggested[147a] that the rearrangement of **166** proceeds according to equation 90a.

Beta-^{14}C acid **167** has been prepared from 4-hyroxycoumarin[2-^{14}C] obtained from ^{14}C-diethyl carbonate (equation 91). The positions of ^{14}C-label in **165** and **167** have been determined by mass spectrometry. The synthetic schemes of equations 90 and 91 were necessary, since in the classical method of benzisoxazole (**168**) synthesis (equation



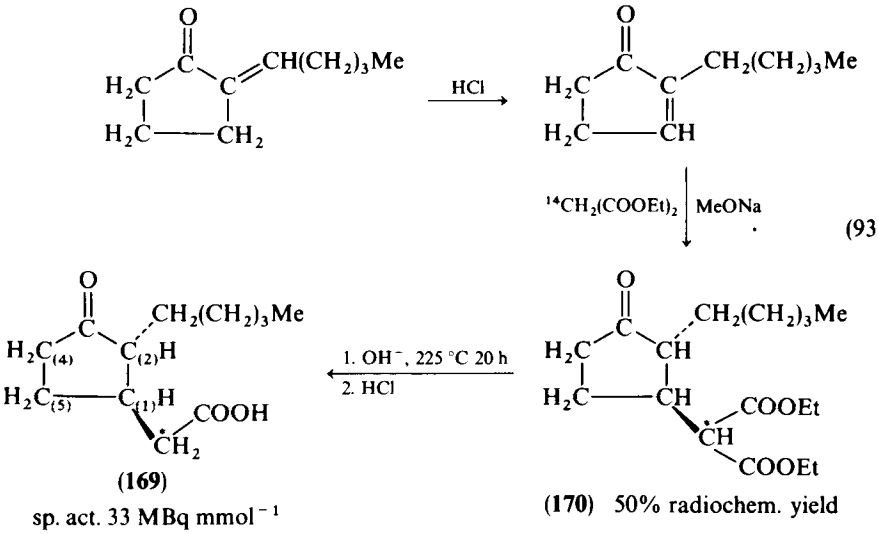
92) the decomposition of the benzisoxazole ring takes place when R contains a carboxylic acid group[143b].



(92)

21. Synthesis of [2-^{14}C](±)dihydrojasmonic acid, 3-oxo-2-pentylcyclopentylacetic acid (**169**)

This acid has been synthesized[147b,148] from 2-pentylcyclopent-2-enone and diethyl (2-^{14}C)malonate (equation 93), for plant growth regulator studies[147b].



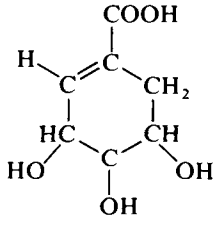
(93)

(169)
sp. act. 33 MBq mmol^{-1}

(170) 50% radiochem. yield

22. *Biopreparation of [^{14}C]-labelled shikimic acid*

Uniformly ^{14}C-labelled shikimic acid (**171**) has been synthesized recently[149a] (see also Reference 149b) in a facile and very efficient natural method based on photoassimilation of $^{14}CO_2$ by henbane leaves (*Hyoscyamus niger* L.) in the presence of the herbicide

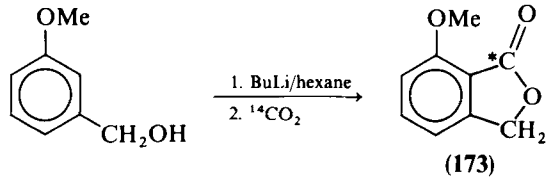


(171)

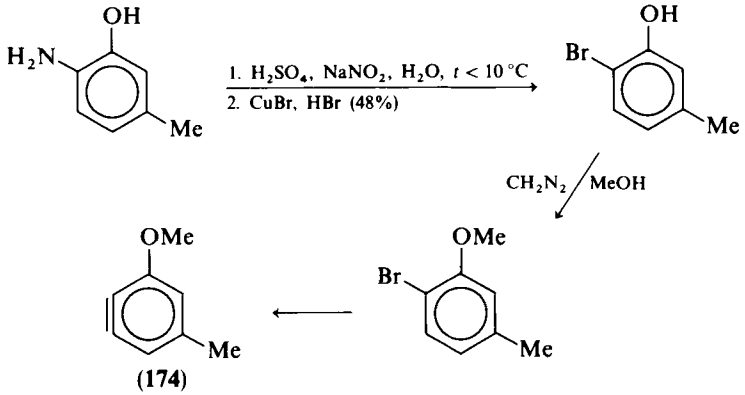
glyphosate[149a]. A flask containing *H. niger* leaves in potassium phosphate buffer (pH 5.5), glyphosate and $^{14}CO_2$ was irradiated for 24 hours with a 1000-W quartz halogen lamp. The leaves were extracted with refluxing methanol, the extracts purified by successive anion exchange, paper and thin-layer chromatography, yielding ^{14}C-labelled shikimic acid of 99.5% radiochemical purity. 13.2% of the total radioactivity of the acid was found in the carboxyl group, so it was assumed that the ^{14}C is uniformly distributed in the shikimic acid. This procedure is more efficient than others published previously[150–154].

23. *Synthesis of [C-9-^{14}C]-1,8-dihydroxy-3-carboxyanthraquinone*

[C-9-^{14}C]-rhein (**172**) is needed to study the mechanism of action, toxicology and metabolism of laxatives, since after oral administration only 17–20% of anthracene derivatives have been recovered in urine and faeces after 72 hours. It has been synthesized



(173) (94)



(174) (95)

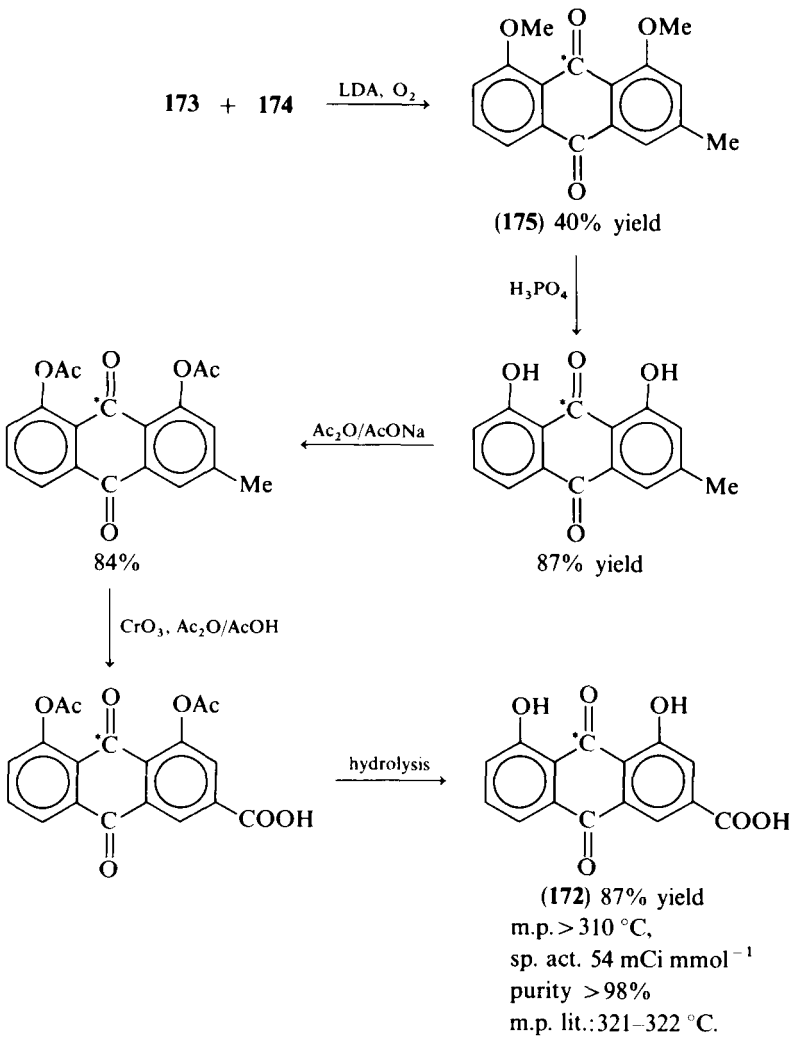
according to equations 94–96[155]. Phthalide **173** has been prepared[156] as shown in equation 94, and **174** as shown in equation 95. Nucleophilic addition reaction of 7-methoxyphthalide **173** to the aryne derivative **174** is regioselective[157]. After several additional steps the oxidation of the 1,8-diacetoxy derivative with CrO_3 in a mixture of acetic acid and acetic anhydride and hydrolysis of the acetyl groups gave **172** in much higher (70–90%) yield than the direct oxidation of the 3-methyl group of **175** with CrO_3 (3–7%).

24. Synthesis of (−)-, (+)- and (±)-[^{14}C]SK and F 94836

This compound possesses vasodilator activity and is used for the treatment of congestive heart failure. 2-Cyano-1-methyl-3-[4-(4-methyl-[6-^{14}C]-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]guanidine, SK and F 94836 (**176**)-racemate has been labelled with ^{14}C in the carbonyl group of the dihydropyridazinone heterocycle[158–160] according to equation 97 which resulted (**176**) in 24.6% overall radiochemical yield starting from K[^{14}C]CN. (−)- and (+)-[*N*-methyl-^{14}C]SK and F 94836 have been prepared according to equations 98a and b.

25. Synthesis of (R,S)-6H-6-[2-(dimethylamino)ethoxycarbonyl]-[6-^{14}C]dibenzo[b,d]pyran · HCl ([14C]FCE 20696, **180***)*

This new synthetic immunomodulating agent, showing protective activity in a broad range of viral infections in mice and hamsters[161,162], has been prepared[163,164] in a seven-step synthesis starting from 9-[9-^{14}C]fluorenone **181** (equation 99). Oxidation of **181** with H_2O_2 gave lactone **182**, which has been reduced subsequently to lactol **183** with diisobutylaluminium hydride (DIBAH). **183** with trimethylsilylcyanide (TMSCN) yielded nitrile **184** and, after hydrolysis, gave the 97% radiochemically pure acid **185**.

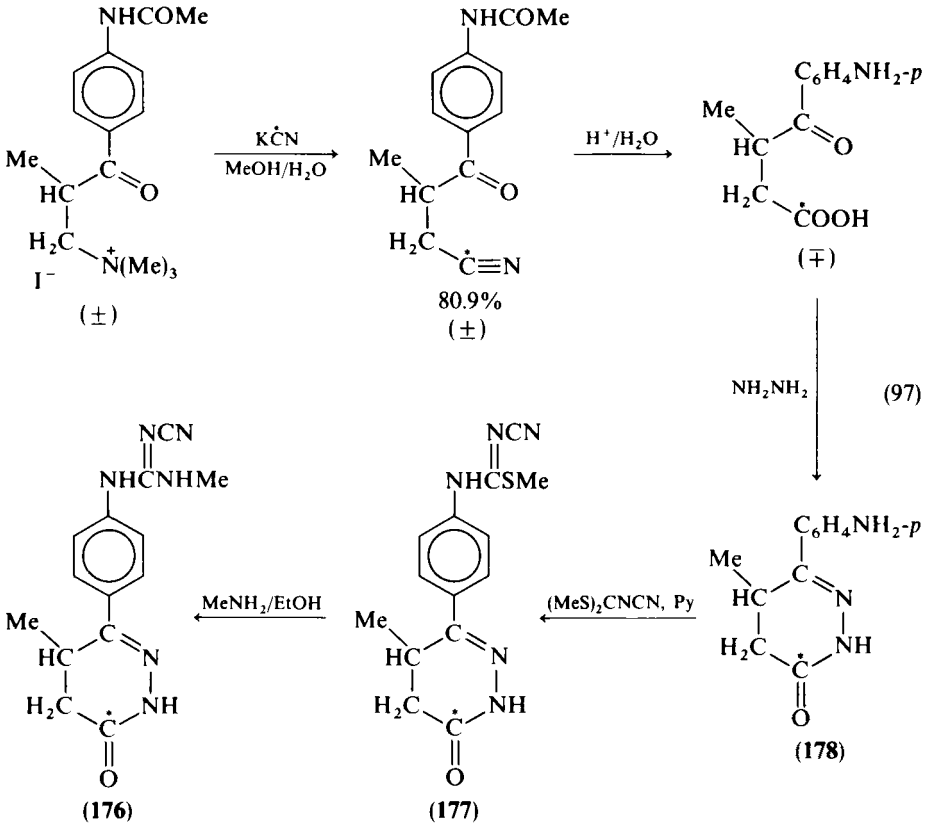


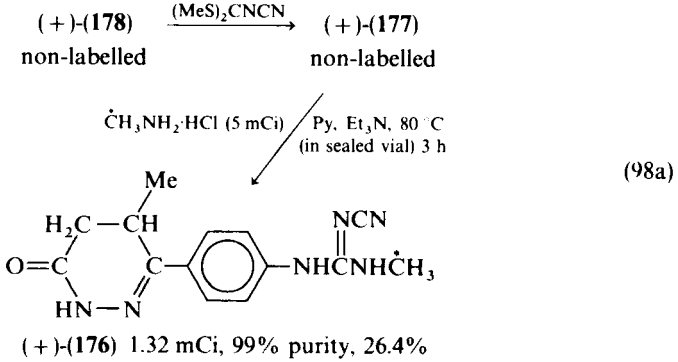
(96)

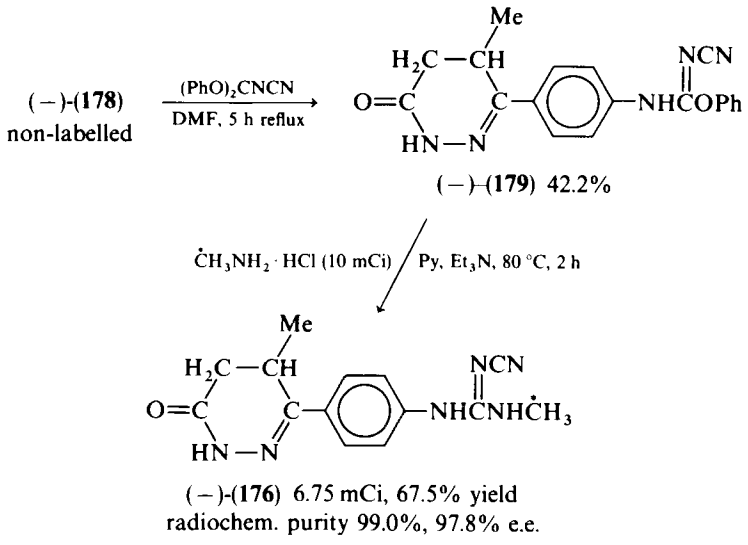
The acid chloride **186** gave with 2-*N*,*N*-dimethylaminoethanol **187**, which in turn has been converted to salt **180**. In view of the instability of **187** in humid atmosphere it is convenient to store the stable intermediate **185**. 97% purity by radio-TLC, 31% overall radiochem. yield from **181**.

*26. Synthesis of 2-(cyclopropylmethyl)-5,6-di-(methoxyphenyl)-3-oxo-(3-^{14}C)-1,2,4-triazine [**188**, (3-^{14}C)ST1118]*

This analgesic and antiaggregant compound has been prepared[165] with 99.5% radiochemical purity and 5.8 mCi mmol^{-1} specific activity by condensing (^{14}C)semicarbazide hydrochloride, obtained from (^{14}C) urea and hydrazine hydrate (equation 100) with 1,2-di-(4-methoxyphenyl)-ethane-1,2-dione (**189**), obtained as in equation 101,


NHCOMe
Me
HC
C
O
H2C
N(Me)3
I−
(±)
KĊN
MeOH/H2O
80.9%
(±)
H+/H2O
C6H4NH2-p
(∓)
NH2NH2
(97)
NCN
NHCNHMe
NHCSMe
MeNH2/EtOH
(MeS)2CNCN, Py
N
NH
(176)
(177)
(178)
(±)-[carbonyl-14C]SK
and F 94836
sp. act. 195.4 μCi mg−1
radiochemical purity
>97.0% by TLC


(+)-(178)
non-labelled
(MeS)2CNCN
(+)-(177)
non-labelled
ĊH3NH2·HCl (5 mCi)
Py, Et3N, 80 °C
(in sealed vial) 3 h
Me
H2C—CH
O=C
C
HN—N
NCN
NHCNHĊH3
(98a)
(+)-(176) 1.32 mCi, 99% purity, 26.4%



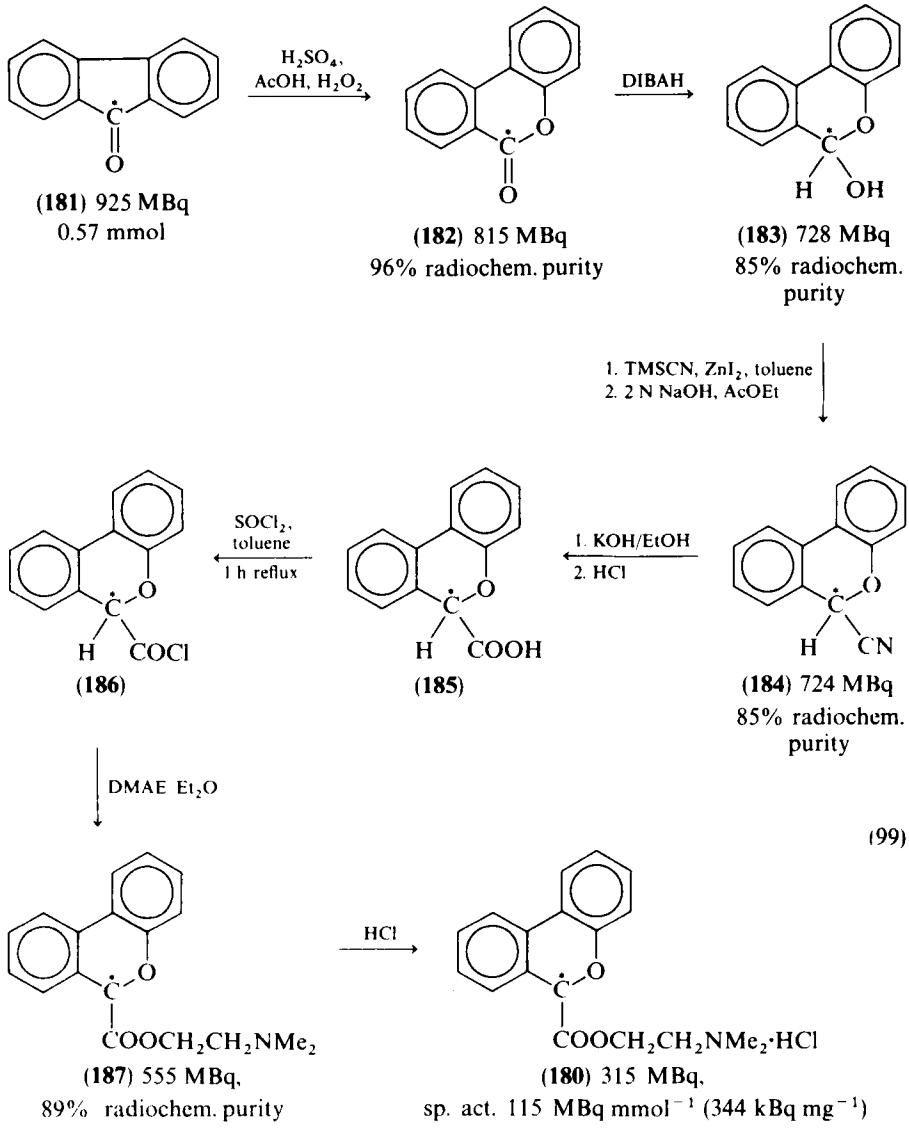
giving rise to 5,6-di-(4-methoxyphenyl)-3-oxo-(3-^{14}C)-1,2,4-triazine (**190**). Condensation of **190** with bromomethyl cyclopropane produced (3-^{14}C)ST-1118 (**188**) in 37.2% overall yield based on urea (equation 102). **188** has been used for pharmacokinetic studies with animals.

27. Synthesis of 3-amino-4-[3-(3-[2,6-^{14}C]-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole hydrochloride (**191**)

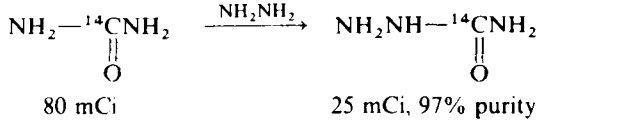
This is a potent histamine H_2-receptor antagonist (inhibitor of gastric secretion), and a drug used for the treatment of peptic ulcers[166,167]. It has been ^{14}C-labelled[168] by treatment of 3-(3-2,6-^{14}C-piperidino-methylphenoxy)propylamine (**192**) with 3-amino-4-methoxy-1,2,5-thiadiazole-1-oxide (**193**), extrusion of the sulphur from the thiadiazole ring of **194** and its re-insertion using N,N'-thiobis phthalimide to yield **195**, and in turn **191** (equation 103). Attempts to reduce **194** to the thiadiazole **195** have been unsuccessful.

28. Synthesis of ^{14}C- and ^{2}H-labelled dibucaine

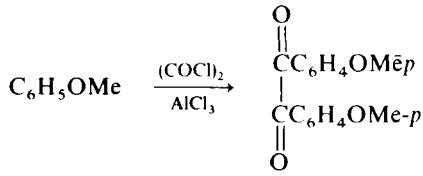
a. [^{14}C]Dibucaine, 2-butoxy-*N*-[2-(diethylamino)ethyl]-4-quinoline carboxamide (**196**) is an extremely potent local anaesthetic. It has been labelled with ^{14}C in the heterocyclic ring[169] in a five-step synthesis starting with isatin (**197**) and acetic anhydride-2-^{14}C (equation 104) to study its percutaneous absorption and metabolism[170]. *N*-Acetylisatin-^{14}C (**198**) with sodium hydroxide solution[171] gave 2-hydroxyquinoline-4-carboxylic acid-^{14}C (**199**). Thermal decarboxylation of **199** at 350–360 °C yielded 2-hydroxyquinoline (**200**) with retention of all radioactivity. The hydroxy acid **199** has been heated with phosphorus pentachloride to obtain the acid chloride **201** which, condensed with *N*,*N*-diethylethylenediamine, produced 2-chloro-*N*-[2-(diethylamino)ethyl]-4-quinoline carboxamide-^{14}C (**202**), which in turn, with sodium n-butoxide, yielded ^{14}C-dibucaine **196**. The overall chemical yield based on isatin was 25%; the radiochemical yield from acetic anhydride-2-^{14}C was 12%.


H2SO4, AcOH, H2O2
DIBAH
1. TMSCN, ZnI2, toluene
2. 2 N NaOH, AcOEt
SOCl2, toluene
1 h reflux
1. KOH/EtOH
2. HCl
DMAE Et2O
HCl
(181) 925 MBq
0.57 mmol
(182) 815 MBq
96% radiochem. purity
(183) 728 MBq
85% radiochem. purity
(184) 724 MBq
85% radiochem. purity
(185)
(186)
(187) 555 MBq,
89% radiochem. purity
(180) 315 MBq,
sp. act. 115 MBq mmol⁻¹ (344 kBq mg⁻¹)

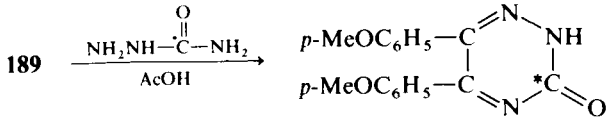
(99)


NH2NH2
80 mCi
25 mCi, 97% purity

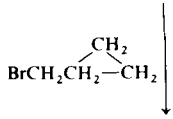
(100)



(189) (101)

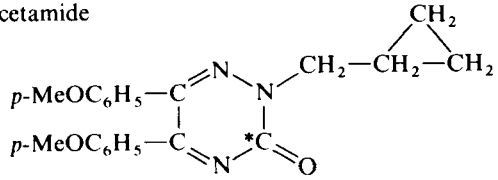


(190) m.p. 270 °C
71.6% yield, 97.3% radiochem. purity

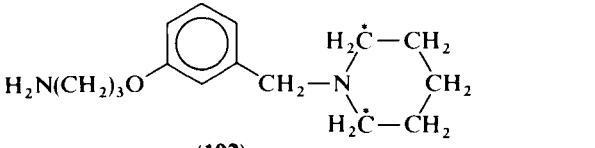


(102)

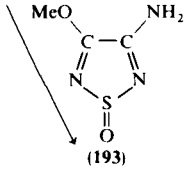
DMA = dimethyl acetamide



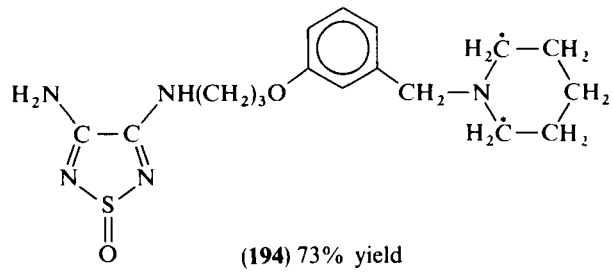
(188) 73.7% yield, m.p. 114 °C



(192)

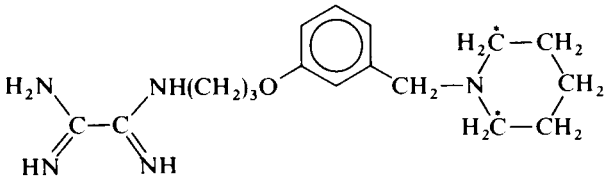


(193)



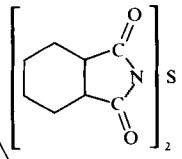
(**194**) 73% yield

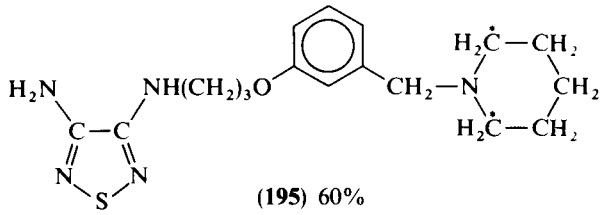
excess HCl/EtOH



97% yield

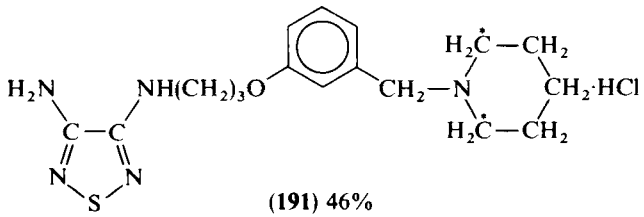
1. CH_2Cl_2, Et_3N
2. 20% KOH





(**195**) 60%

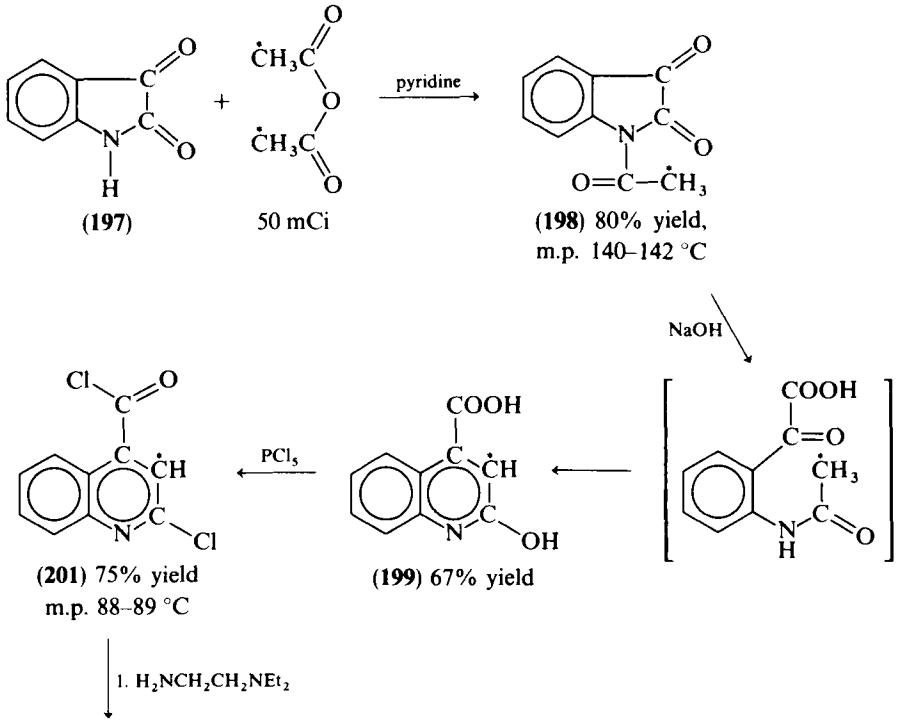
conc. HCl / *i*-propyl alcohol, RT, 10 min



(**191**) 46%

98% radiochem. purity sp. act. 43.9 μCi mg^{-1}

(103)



(197) 50 mCi

(198) 80% yield, m.p. 140–142 °C

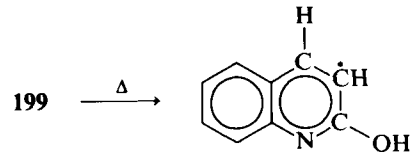
(201) 75% yield m.p. 88–89 °C

(199) 67% yield

(202) 80% yield, m.p. 72–73 °C

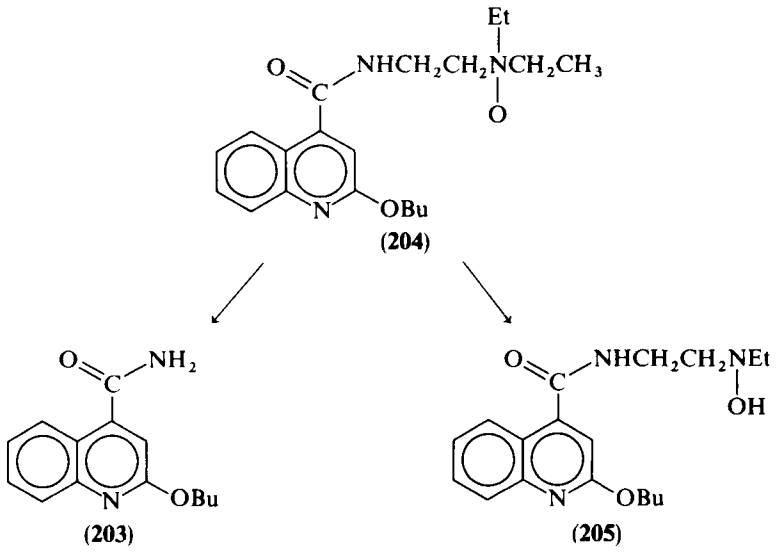
(196) 78% yield, m.p. 63–64 °C 6.05 mCi

(104)



(200)

^{14}C dibucaine undergoes considerable radiolysis on storage yielding 2-butoxyquinoline-4-carboxamide (**203**) as a major decomposition product and four minor by-products. A sample of **196** stored at -5 °C for two years contained 30% of unchanged dibucaine only. It has been suggested that the radiolysis of **196** involves the formation of N-oxide **204** detected also as one of the radiolysis by-products. However, the compound **205** which is produced in the course of thermal decomposition (at 160–165 °C) of dibucaine, proceeding with elimination of ethylene (equation 105), has not been found in the post-radiolysis mixture[169].

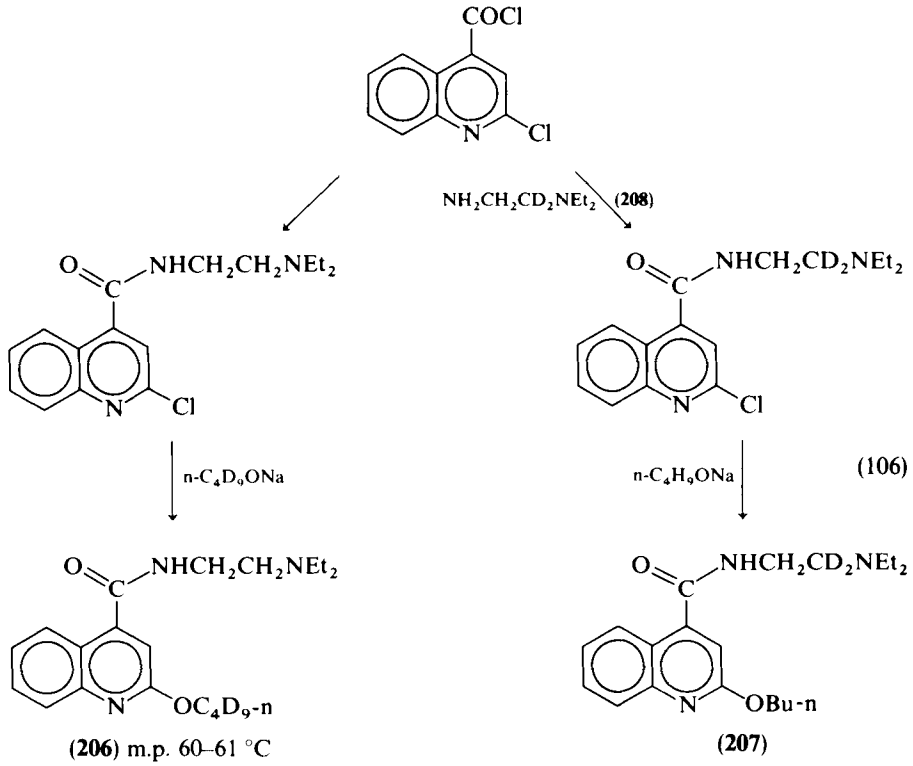


(105)

b. Synthesis of dibucaine-d_2 and dibucaine D_9, needed for the development of a sensitive GC-MS method of analysis of dibucaine in biological fluids, has been carried out[169] as shown in equation 106. Dibucaine-D_9 (**206**) has been synthesized by condensation of 2-chloro-*N*-[2-(diethylamino)ethyl]-4-quinoline carboxamide with sodium salt of n-butyl-D_9 alcohol. Dibucaine-D_2 (**207**) has been synthesized by condensation of 2-chloroquinoline carboxylic acid chloride with *N,N*-diethyl dideuterioethylenediamine (**208**) followed by reaction with sodium n-butoxide. **208** has been prepared as shown in equation 107.

29. Synthesis of heteroarotinoid ethyl(E)-4-[2-(3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-6-yl)-1-propenyl]benzoate-9,10,11,20-$^{14}C_4$ (**209**)

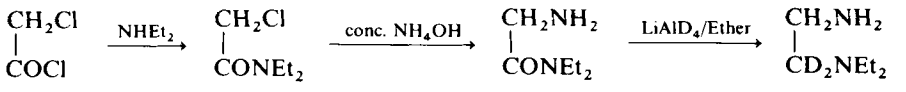
This compound, exhibiting excellent pharmacological activity[172] compared to the standard *trans*-retinoic acid **210** has been ^{14}C-labelled[173] in positions 9, 10, 11 and 20 as shown in equation 108 involving treatment of methyl 3-phenoxypropionate **211** with ^{14}C-methylmagnesium iodide, cyclization of **212** to 4,4-dimethylchroman-9,10-$^{14}C_2$ (**213**), acylation of **213** with $Me^{14}COCl$ producing 4,4-dimethylchrom-6-yl methyl ketone-9,10,11-$^{14}C_2$ (**214**), reduction of **214** with $LiAlH_4$, phosphorylation of the alcohol **215** to the phosphonium salt **216**, addition of n-butyllithium to **216**, generating the Wittig reagent which reacts *in situ* with ethyl 4-formylbenzoate-$^{14}COOEt$ (**217**) to give **209** with specific activity equal to 0.15 $\mu Ci\ mg^{-1}$ after purification. Compound **217** has been



(106)

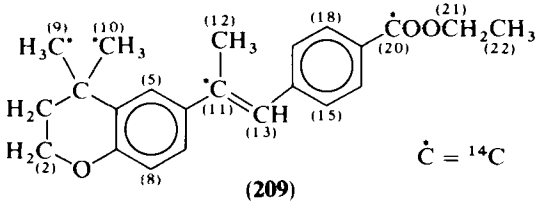
(206) m.p. 60–61 °C

(207)

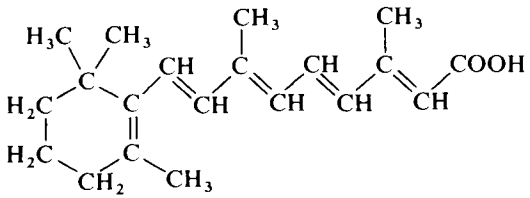


(208)

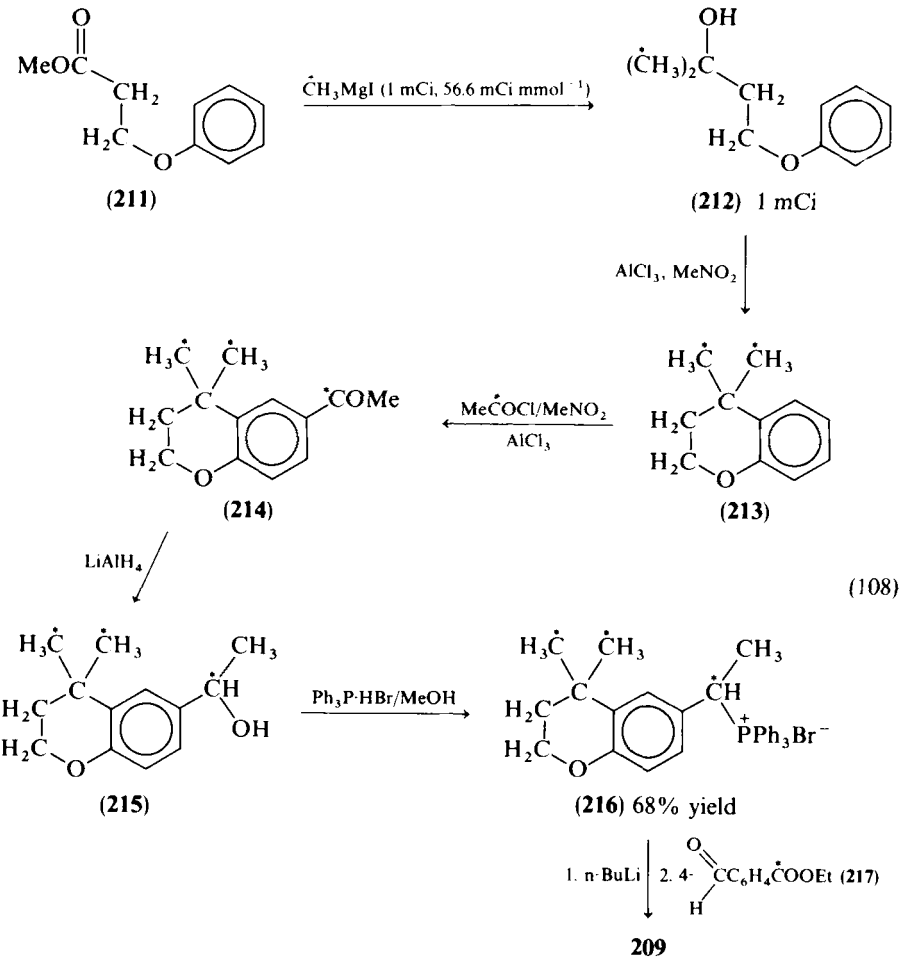
(107)



(209)

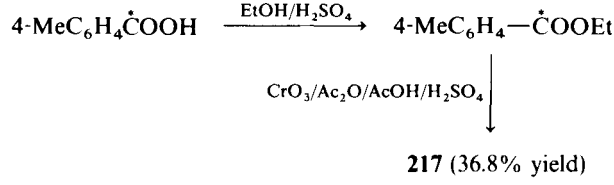


(210)



(108)

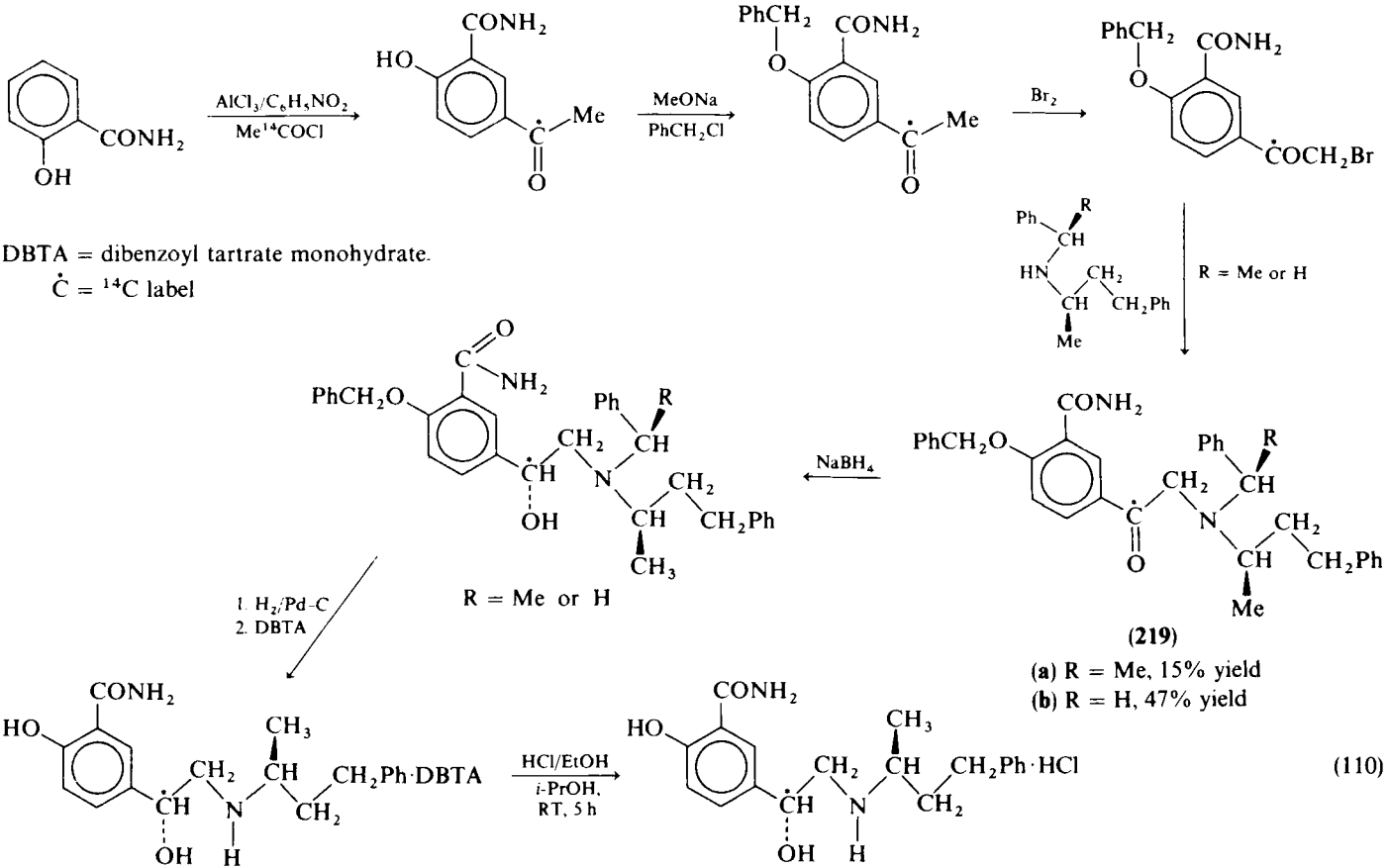
synthesized from commercial *p*-toluic acid-$^{14}C{=}O$, as shown in equation 109. The compound **209** is currently used for metabolic studies in animals[173].



(109)

30. Synthesis of ^{14}C-dilevalol

[1-^{14}C]-Dilevalol, 5-[(*R*)-[1-^{14}C]-1-hydroxy-2[((*R*))-1-methyl-3-phenylpropyl)-amino]-ethyl]-salicylamide hydrochloride (**218**), an antihypertensive agent[174,175], has been synthesized[176] from [1-^{14}C]-acetyl chloride in 7 steps (equation 110).



DBTA = dibenzoyl tartrate monohydrate.

Ċ = ^{14}C label

R = Me or H

(219)

(a) R = Me, 15% yield

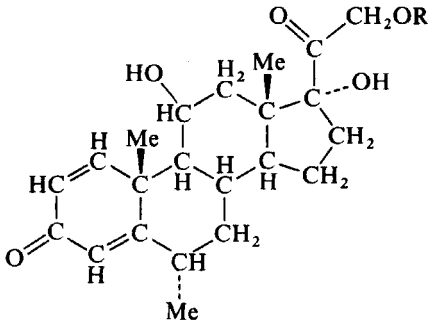
(b) R = H, 47% yield

(110)

(218) 70% yield, 99% radiochem. purity, m.p. 198.5–200 °C

31. Synthesis of ^{14}C- and tritium-labelled methylprednisolone

Methylprednisolone (**220**), showing a particular activity in treating acute bronchospasm when administered intravenously[177,178], has been initially tritium-labelled in the A-ring of the steroid portion of the molecule and with ^{14}C at both carboxylic carbons



(**220**) (**a**) R = H, methylprednisolone

(**b**) R = $-C(=O)-(CH_2)_2COONa$,

methylprednisolone hemisuccinate

(**c**) R = $-C(=O)-(CH_2)_6-C(=O)-N(Me)-(CH_2)_2SO_3Na$,

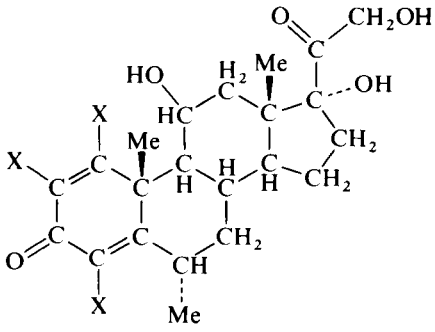
methylprednisolone suleptanate

of the suberic acid portion of the side chain[179] (equation 111). However, it appeared after administration of **221** to rats that these labelled positions are not metabolically stable. Therefore, a second pair of labelled compounds (**200c**) has been synthesized with tritium at $C_{(7)}$ in the B-ring of the steroid **223** (equation 112) and with ^{14}C exclusively at the carboxamide carbon in the side chain (**224**; equation 113). Drugs **223** and **224** showed excellent metabolic stability of both ^{3}H and ^{14}C labels, and should be suited for conducting absorption, distribution, biotransformation and excretion test studies in animals and men.

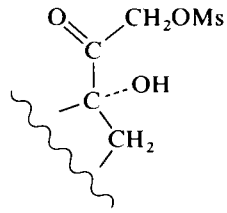
32. Synthesis of ^{14}C-labelled 5-substituted-4,6-dithianonanedioic acid derivatives

5-(2-Dodecylphenyl)-4,6-dithia[5-^{14}C]nonanedioic acid (**225a**) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithia[5-^{14}C]nonanedioic acid (**225b**) are ^{14}C-labelled leukotriene receptor antagonists *in vitro*, and also display *in vivo* significant activity in blocking LTD_4-induced bronchoconstriction[180]. They have been obtained[181] (equation 114) to investigate the possible contribution of metabolism (initiated by ω-oxidation) to the brevity of their pharmacologic action[182,183].

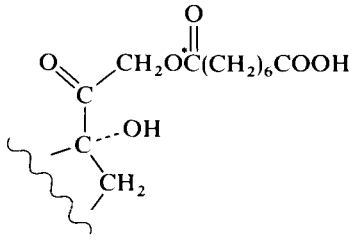
The specific activities of ^{14}C-SKF 102081 and of ^{14}C-SK 102922 synthesized in about 35% overall yield with radiochemical purity greater than 95% were 9.15 mCi mmol^{-1}



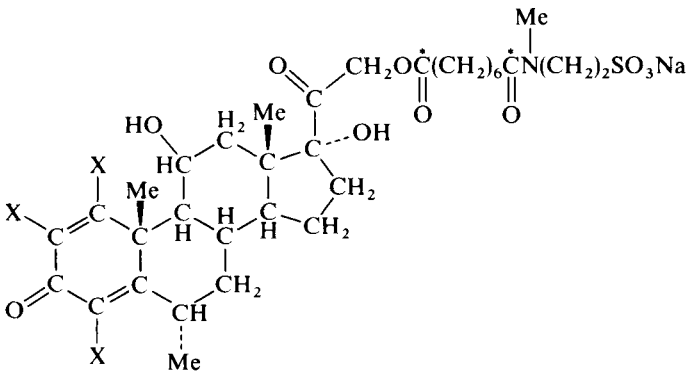
(a) X = ^{3}H or (b) X = ^{2}H



(222b)
99% yield, sp. act. 229 μCi mg^{-1}

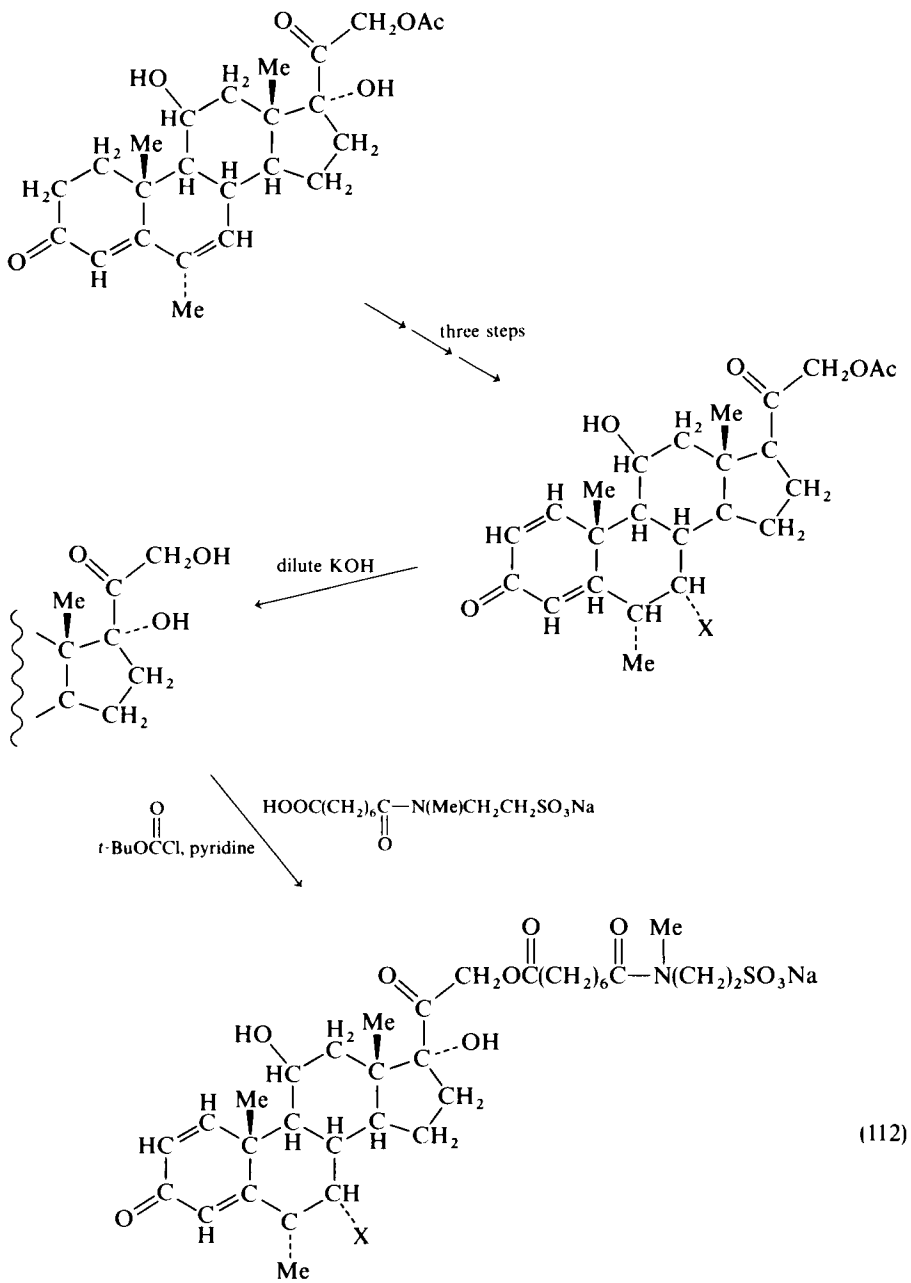


(a) 83% yield, sp. act. 193 μCi mg^{-1}
(b) 33.4% yield, sp. act. 97.3 μCi mg^{-1}



(111)

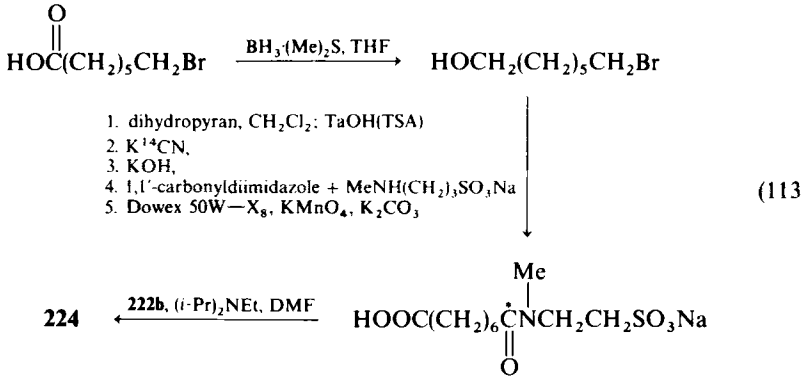
(221) (a) X = ^{3}H, $\dot{C}$ = ^{12}C, 43.6% yield,
sp. act. 143 μCi mg^{-1}, >99% radiochem. purity
(b) X = ^{2}H, $\dot{C}$ = ^{14}C, 62.6% yield,
sp. act. 76.3 μCi mg^{-1}, >99% radiochem. purity



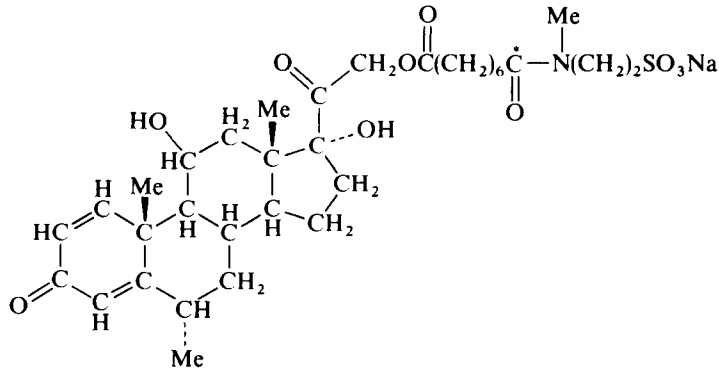
(112)

(223) **(a)** X = ^{2}H (88.6%)

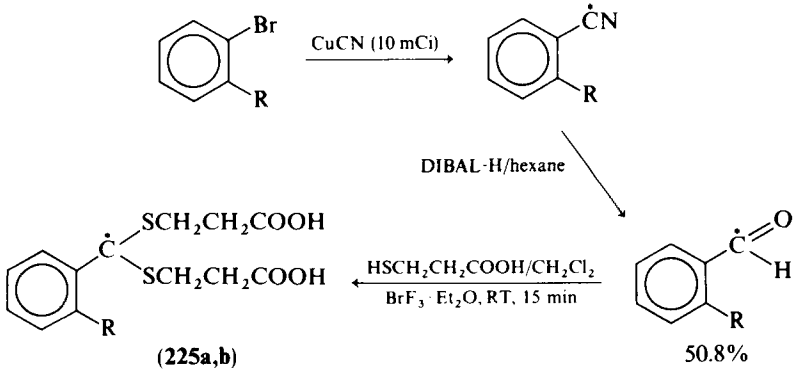
(b) X = ^{3}H (84.4% radiochem. yield) total activity 122 mCi sp. activity 844 μCi mg^{-1} 99% radiochem. pure



(113)



(**224**) 87% yield, sp. act. 78.1 μCi mg^{-1}, >98% radiochem. purity



(114)

(**a**) ^{14}C—SKF 102081, R = $C_{12}H_{25}$, 75.9% yield

(**b**) ^{14}C—SKF 102922, R = $(CH_2)_8C_6H_5$, 70.5% yield

and 11.57 mCi mmol^{-1}, respectively. The two starting aryl bromides have been prepared according to equation 115.

$$C_6H_5(CH_2)_7OH \xrightarrow[(C_6H_5)_3P,\ CH_2Cl_2]{CBr_4} C_6H_5(CH_2)_7Br \quad 94\% \qquad (115a)$$

$$RBr \xrightarrow[72\text{ h refl. under argon (for a), 24 h for b.}]{(C_6H_5)P,\ MeCN} R{-}\overset{+}{P}(C_6H_5)_3Br^- \quad 67\%$$

$$\downarrow \text{ 1. n-BuLi/THF; 2. 2-Bromobenzaldehyde}$$

$$\text{(a) R} = C_{12}H_{25},\ 93\%\text{ yield} \qquad \text{(b) R} = (CH_2)_8C_6H_5$$

$$\xleftarrow{H_2/[(C_6H_5)_3P]_3RhCl}$$

$$\text{(a) R}' = (CH_2)_{10}CH_3 \qquad \text{(b) R}' = (CH_2)_7C_6H_5 \quad 75\% \qquad (115)$$

33. *Synthesis of ^{14}C-labelled felbamate, 2-phenyl-1,3-propanediol-2-^{14}C dicarbamate* (**227**)

This new antiepileptic drug has been prepared[184] in 28% overall yield from phenylacetic-(methylene-^{14}C) acid in a procedure (equation 116) which involves carboxylation of phenylacetic acid, reduction of the 2-phenylmalonic acid to 2-phenyl-1,3-propanediol, conversion of the latter to its bis-chloroformate and carbamation to **227** in 32% overall radioyield.

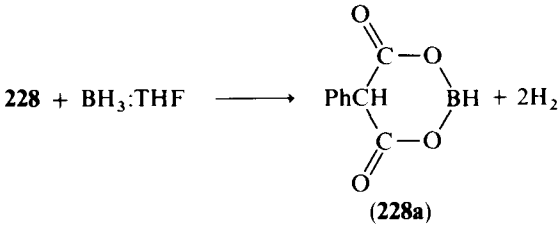
$$\underset{50\text{ mCi}}{Ph\dot{C}H_2COOH} \xrightarrow{n\text{-BuLi, }CO_2} \underset{(228)}{Ph\dot{C}H(COOH)_2} \xrightarrow[THF\text{ complex}]{\text{excess of } BH_3} \underset{(229)\ 72\%}{Ph\dot{C}H(CH_2OH)_2}$$

$$\downarrow COCl_2,\ \text{antipyrine}$$

$$Ph{-}\dot{C}H(CH_2O\overset{O}{\overset{\|}{C}}NH_2)_2 \xleftarrow{NH_3} Ph\dot{C}H(CH_2O\overset{O}{\overset{\|}{C}}Cl)_2$$

$$\underset{\text{sp. act. 6.09 mCi mmol}^{-1}}{(227)\ 72\%} \qquad (116)$$

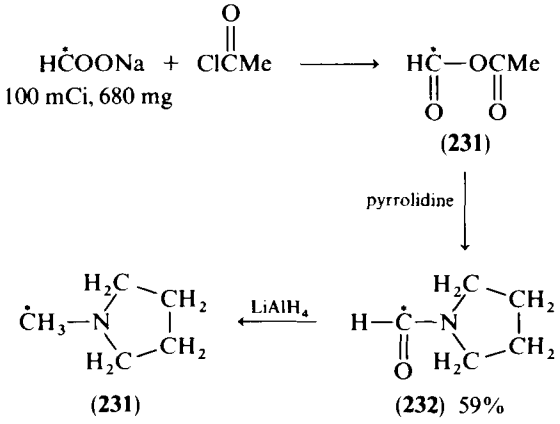
The low (25%) yield of the reduction of **228** with borane complexes[185] has been increased to 72% by decomposing the excess hydride and inert sterically hindered borylene phenylmalonate **228a** (equation 117) by methanol and repeating this procedure two or three times.



(117)

34. Synthesis of 7-[α-(2-aminothiazol-4-yl)-α-(z)-methoximinoacetamido]-3-(1-[^{14}C]methylpyrrolidino)-methyl-3-cephem-4-carboxylate sulphate (**230**)

This ^{14}C-labelled cephalosporin, showing high antipseudomonal activity, has been synthesized[186] for metabolism and pharmacokinetic studies according to equation 118 starting from [^{14}C]formate. Treatment of the mixed anhydride **231** with pyrrolidine gave N-formyl compound **232**[187].



35. Synthesis of ^{3}H- and ^{14}C-cisapride (**233, 234**)

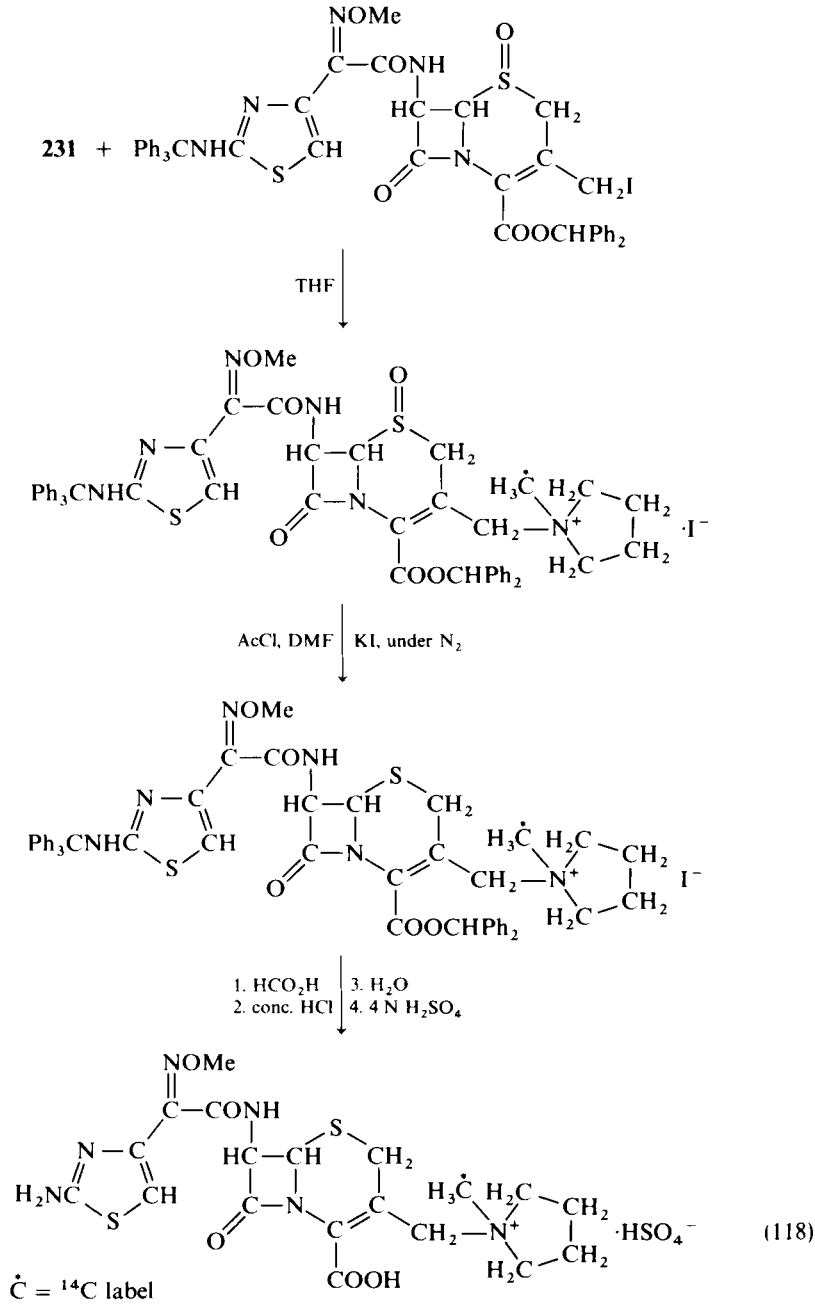
This gastrokinetic drug[188] has been tritiated[189] in the fluorophenyl moiety by means of reductive dehalogenation (equation 119) and by reductive amination of the piperidine ring (equation 120). [^{14}C]-Cisapride (**235**) has been labelled in the benzamide function by amidation of unlabelled **236** with 4-amino-5-chloro-2-methoxybenzene-[^{14}C]carboxylic acid, **237** (equation 121). **235** was applied for metabolic studies.

36. Synthesis of 4-[2-(di-n-propylamino)ethyl]-[2-^{14}C]-2(3H)-indolone (**238**)

This novel antianginal and antihypertensive drug[190] is a selective non-phenolic dopamine agonist, decreasing sympathetic neurotransmission. It has been obtained[191] as shown in equation 122. The ^{14}C label has been placed in the 4-ethylindole moiety to avoid possible metabolic loss of the radioisotope through N-dealkylation.

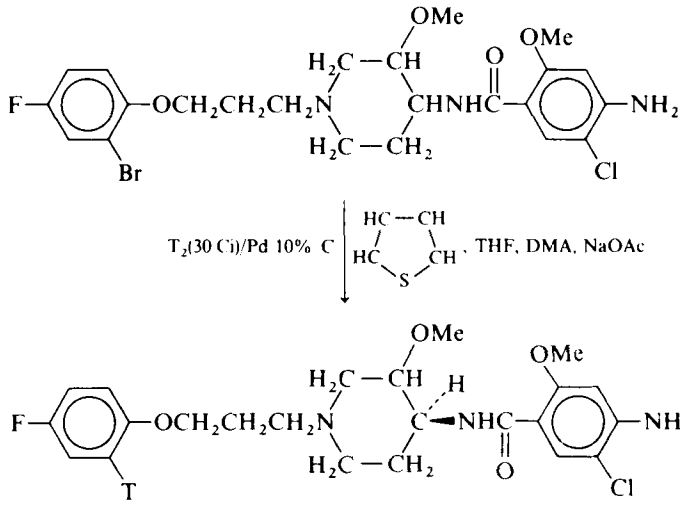
37. Synthesis of tritium-labelled 'CI-911' and ^{14}C-labelled 'CI-933'

Several pyrrolidine derivatives showing good cognition activity[192,193] including 1-(4-methoxybenzoyl)-5-oxo-2-pyrrolidine [1-^{14}C]propanoic acid, 'CI-933', and

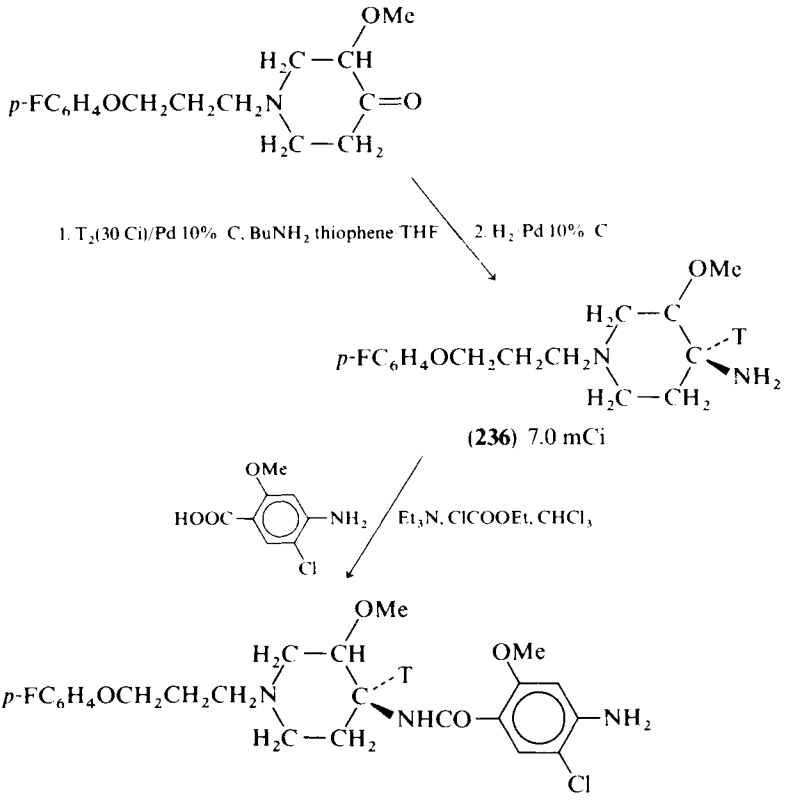


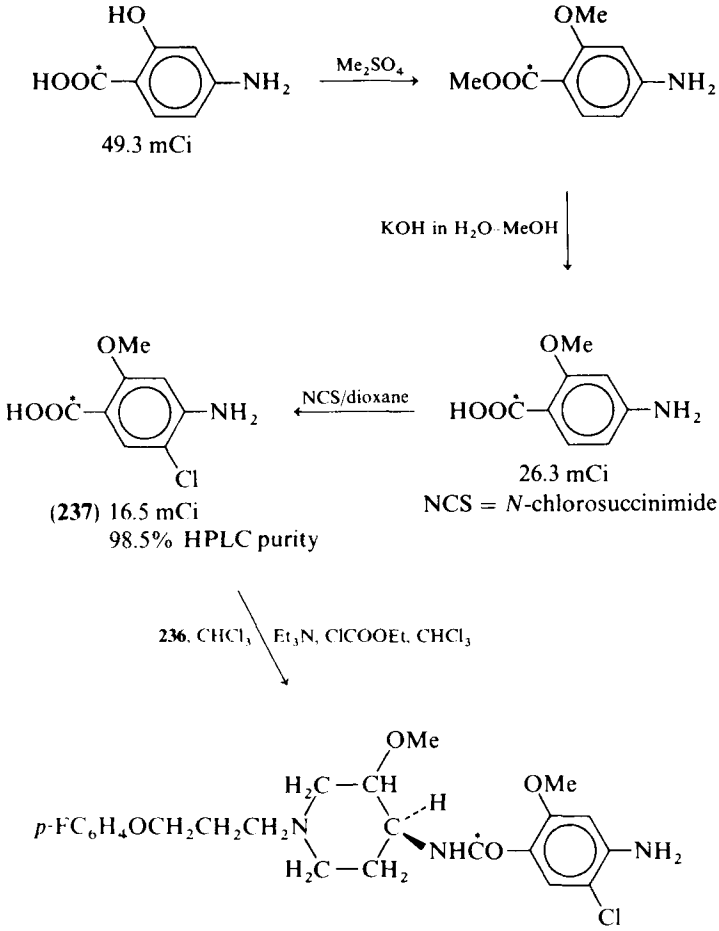
(118)

(230) 97.5% radiochem. purity
sp. act. 21.7 μCi mg^{-1}



(**233**) sp. act. 17.0 Ci mmol^{-1}, chem. and radiochem. yield 23%



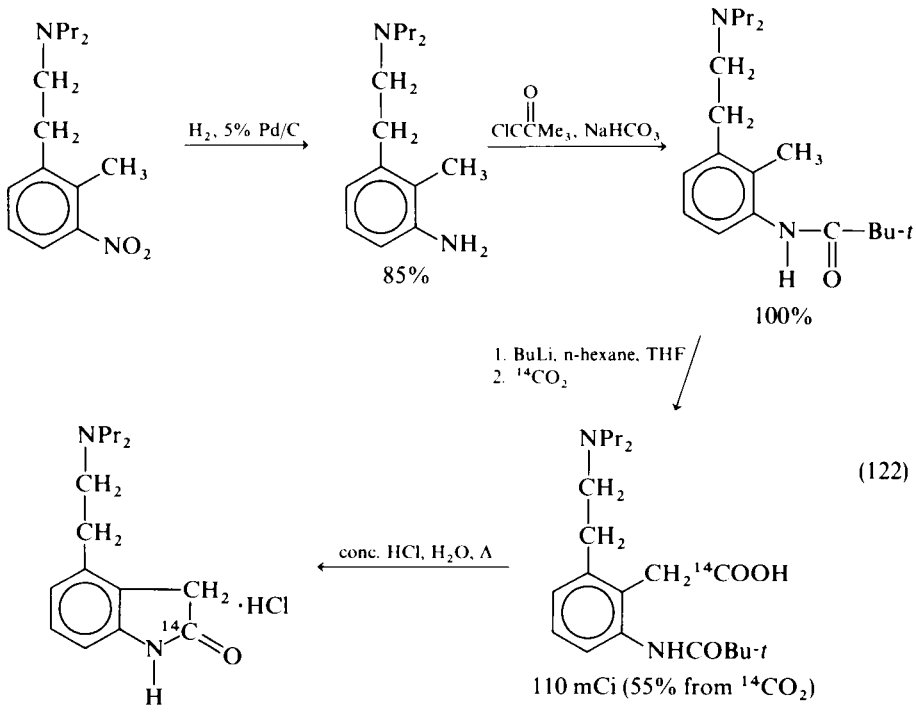


(121)

(**235**) sp. act. 7.6 mCi mmol^{-1}
HPLC purity 98.5%
76.5% chem. yield
77.0% radiochem. yield

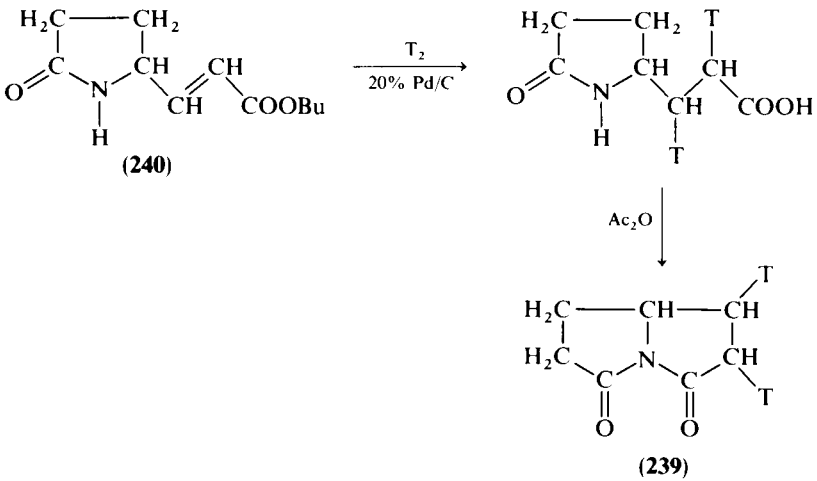
exhibiting good amnesia-reversal activity[194], have been radiolabelled for metabolic, binding and pharmacokinetic studies. 'CI-911' (**239**) has been tritium-labelled according to the reaction sequence given in equation 123. **240** was prepared starting from 5-(carboxyl)-2-pyrrolidinone (**241**), which was reduced in the first step (equation 124) to 5-(hydroxymethyl)-2-pyrrolidinone (**242**).

'CI-933' (**243**) has been obtained as shown in equation 125. The crude **243** contained initially 99% of the radioactivity, but repeated recrystallizations needed to remove chemical impurities lowered the final yield of the product in the last step to 37%.

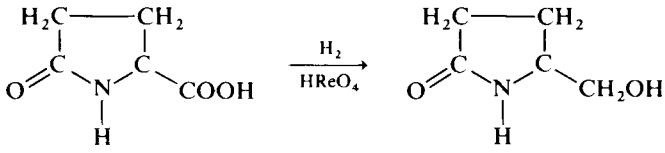


(122)

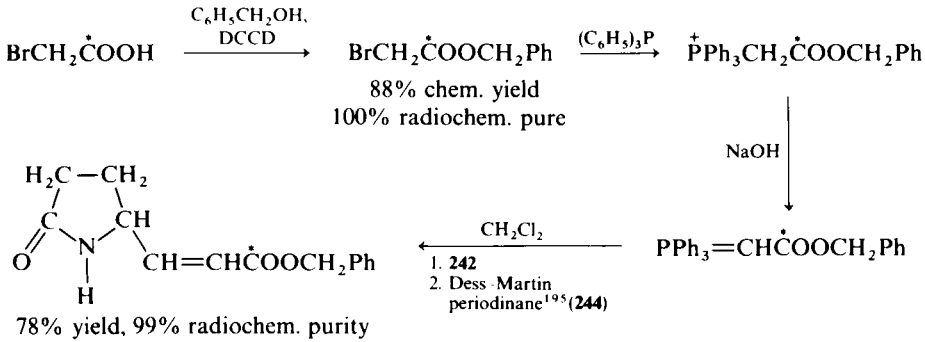
sp. act. 22.1 mCi mmol^{-1}
39.5% radiochem. yield from $Ba^{14}CO_3$,
98.6% chem. and radiochem. purity



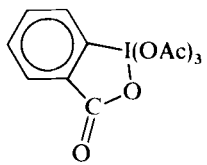
(123)



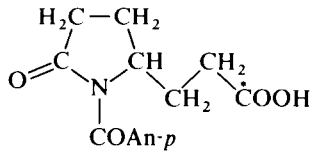
(241) (242) (124)



(125)



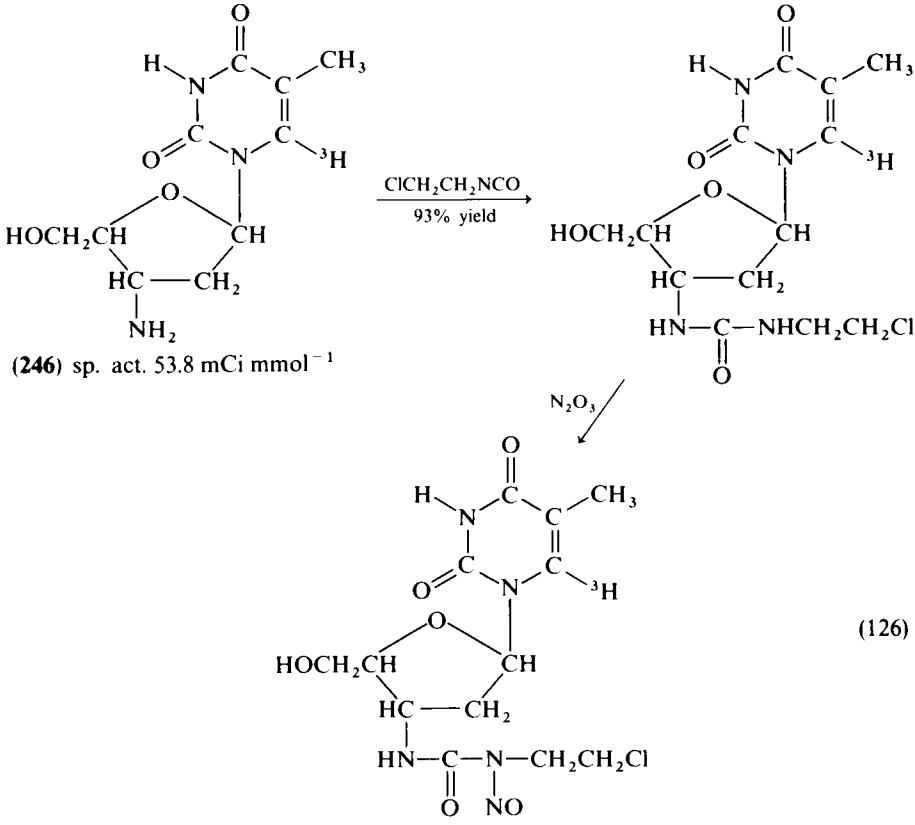
(244) 'periodinane'



(243) white solid, m.p. 128.0–129.5 °C
25.33 mCi, sp. act. 16.81 mCi mmol^{-1}
37% chem. yield
overall radiochem. yield 12.7%

38. Synthesis of 3′-CTNU labelled with ^{14}C in the alkylating moiety and with ^{3}H in the carbamoylating moiety

Both [^{3}H]- and [^{14}C]-labelled 3′-CTNU, the anticancer drugs possessing alkylating and carbamoylating moieties responsible for the alkylation of nucleic acids and proteins and the carbamoylation of proteins[196], have been synthesized[197] according to equations 126 and 127 to elucidate their cellular target site and to understand the molecular basis of their action[198].



(**246**) sp. act. 53.8 mCi mmol^{-1}

(**245**) 91% yield, sp. act. 54.6 mCi mmol^{-1}

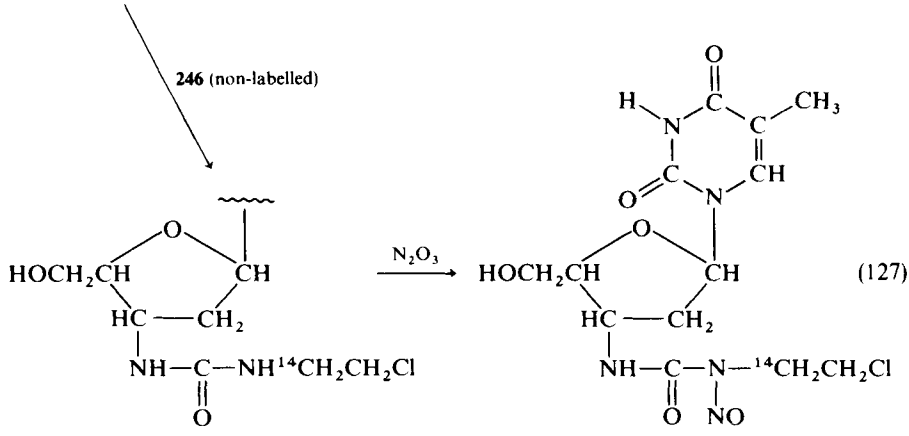
(126)

a. [6-^{3}H]3′-[3-(2-chloroethyl)-3-nitrosoureido]-3′-deoxythymidine *([^{3}H]3′-CTNU)*, (**245**-^{3}H) radiolabelled with ^{3}H in the carbamoylating moiety has been obtained in high yield according to equation 126.

b. The same compound ^{14}C-labelled in the alkylating moiety has been prepared starting from [2-^{14}C]ethanolamine hydrochloride to produce [1-^{14}C]-chloroethyl isocyanate in two steps, which has been converted subsequently to 3′-[3-(1-^{14}C]2-chloroethylureido)]-3′-deoxythymidine ([^{14}C]3′-ATdR), and nitrosated to yield 3′-[3-([1-^{14}C]2-chloroethyl)-3-nitrosoureido]-3′-deoxythymidine ([^{14}C]3′-CTNU) (equation 127).

$HOCH_2{}^{14}CH_2NH_2 \cdot HCl$ sp. act. 124 μCi mmol^{-1} $\xrightarrow[99\%\ \text{yield}]{SOCl_2}$ $ClCH_2{}^{14}CH_2NH_2 \cdot HCl$ $\xrightarrow{COCl_2}$

$ClCH_2{}^{14}CH_2NCO$

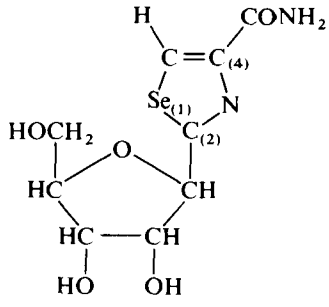


(127)

(**245**—^{14}C) ([^{14}C]3′—CTNU)
sp. act. 118 μCi mmol^{-1}
90% yield, chem. and radiochem. pure

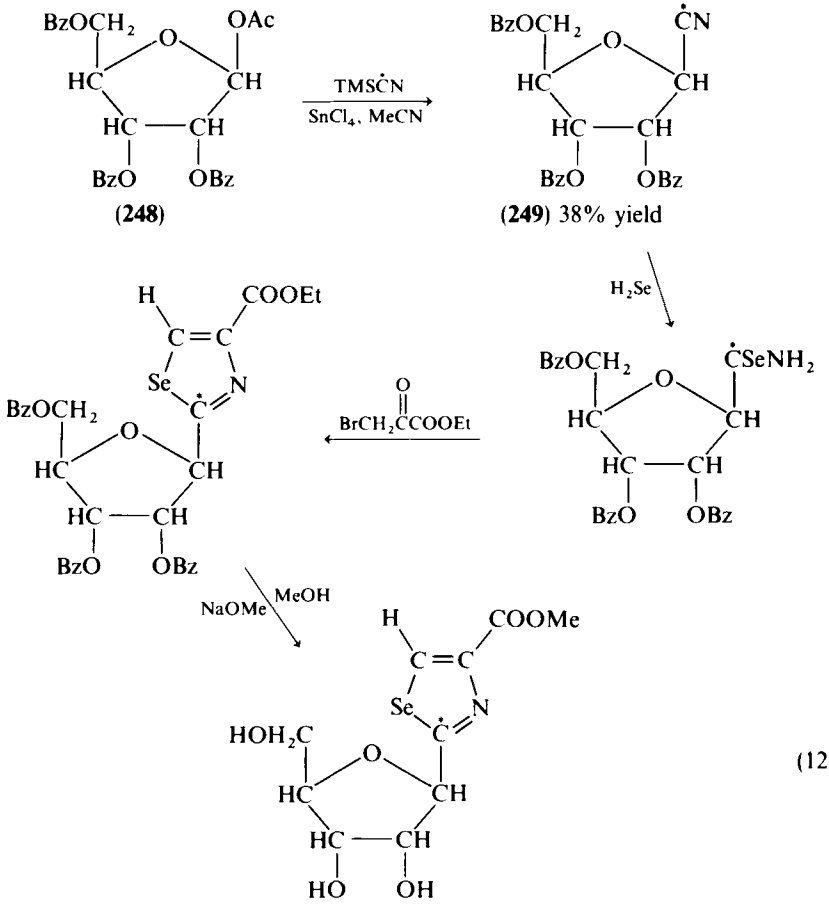
39. Synthesis of 2-β-D-ribofuranosyl-4-selenazolecarboxamide (**247**)

This compound, showing pronounced antitumor activity *in vivo*, has been ^{14}C-labelled at $C_{(2)}$ for pharmacokinetic and metabolic studies[199] according to equations 128 and 129. Reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**248**) with [^{14}C]cyanotrimethylsilane (equation 128) gave [1-^{14}C]allononitrile (**249**), which in several steps produced methyl β-D-ribofuranosyl-4-[2-^{14}C]selenazolcarboxylate (**250**), the precursor of **247**. **250** had 98% radiochemical purity, 98% chemical purity and 49 mCi mmol^{-1} specific activity.



(**247**)

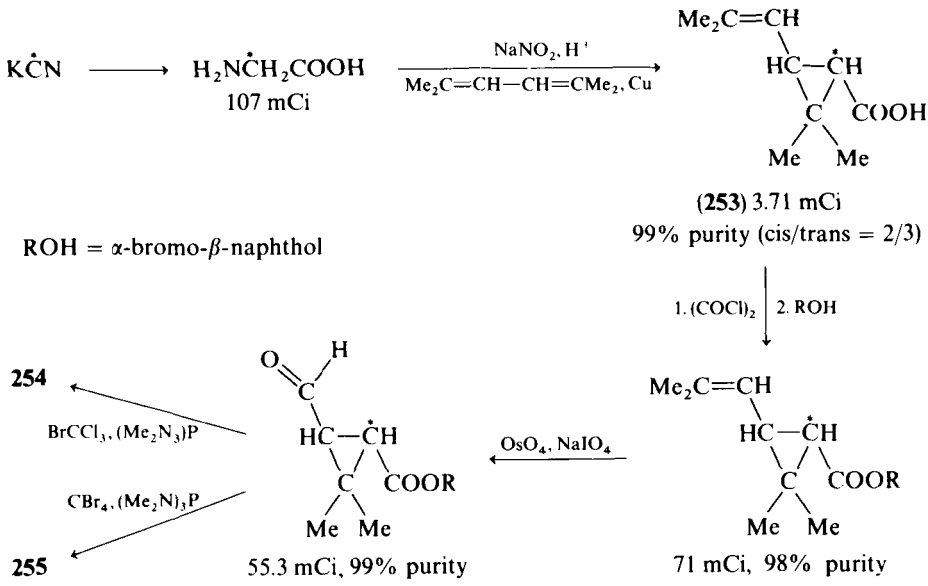
$$K^{14}CN \xrightarrow{Me_3SiCl} TMS^{14}CN\ (TMS\dot{C}N) \qquad (128)$$



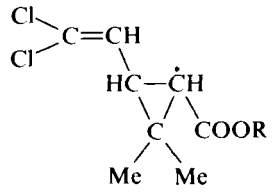
(129)

40. Synthesis of all stereoisomers of [1-^{14}C]-labelled DCV and DBV acids

The four optically active 3-(2,2-dichloroethenyl)-2,2-dimethyl[1-^{14}C]cyclopropanecarboxylic acids, [1-^{14}C]DCV (**251a–d**), and their dibromo analogues, [1-^{14}C]DBV (**252a–d**), provide high insecticidal activities, photostabilities and moderate mammalian toxicities[200]. They have been prepared efficiently from [1-^{14}C]chrysanthemic acid (**253**) to study the dependence of their metabolism in animals on their stereochemistry[201–203]. All ^{14}C-labelled compounds prepared according to equation 130 were found to behave in chemical reactions identical to the unlabelled materials (no kinetic isotope effects were noticed).



(130)

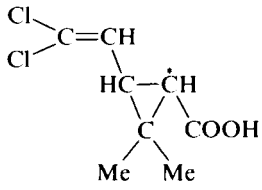


(**254**) 50.7 mCi, 99% purity

chiral-phase HPLC
different retention times of **254a–d**

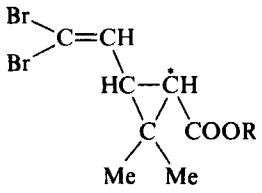
(1*R*)-*cis* (**254a**), 6.96 mCi 100% opt. pur.
(1*S*)-*cis* (**254b**), 6.83 mCi 99.7% opt. pur.
(1*R*)-*trans* (**254c**), 15.7 mCi, 100% opt. pur.
(1*S*)-*trans* (**254d**), 16.1 mCi, 99.2% opt. pur

KOH/MeOH



(**251a–d**)

(**251a**) 6.08 mCi, 98% purity
(**251b**) 6.57 mCi
(**251c**) 14.9 mCi
(**251d**) 16.0 mCi

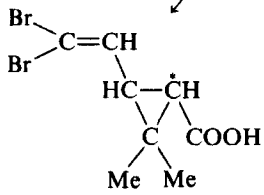


(255) 26.9 mCi, 99% purity

chiral-phase HPLC

(1*R*)-*cis* (**255a**), 4.65 mCi, 100% opt. pur.
(1*S*)-*cis* (**255b**), 4.0 mCi, 100% opt. pur.
(1*R*)-*trans* (**255c**), 7.78 mCi, 99.1% opt. pur.
(1*S*)-*trans* (**255d**), 7.68 mCi, 100% opt. pur.

35% NaOH/EtOH



(**252a–d**) 99% purity, 100% yield

(130)

$\dot{C}$ = ^{14}C label

41. Synthesis of ^{2}H-, ^{3}H-, ^{14}C- and ^{35}S-labelled captopril

Captopril (**256**), the orally active inhibitor of the angiotensin converting enzyme[204], has been isotopically labelled in the side chain[205] (equations 131 and 132). ^{2}H-, ^{3}H- and ^{14}C- have been incorporated into the proline ring according to equations 132 and 133[205].

An isotope effect was found in the IR spectrum when the side[206] chain carbonyl carbon was labelled with ^{14}C [$\omega_{(-^{14}C=O)} = 1520\ cm^{-1}$, $\omega_{(-^{12}CO)} = 1590\ cm^{-1}$ (strong band)]. This shift of about $70\ cm^{-1}$ is in good agreement with the theoretical value, $(\omega_{^{12}C} - \omega_{^{14}C}) = 67\ cm^{-1}$, calculated by the harmonic approximation model for the isolated carbonyl group frequency shift.

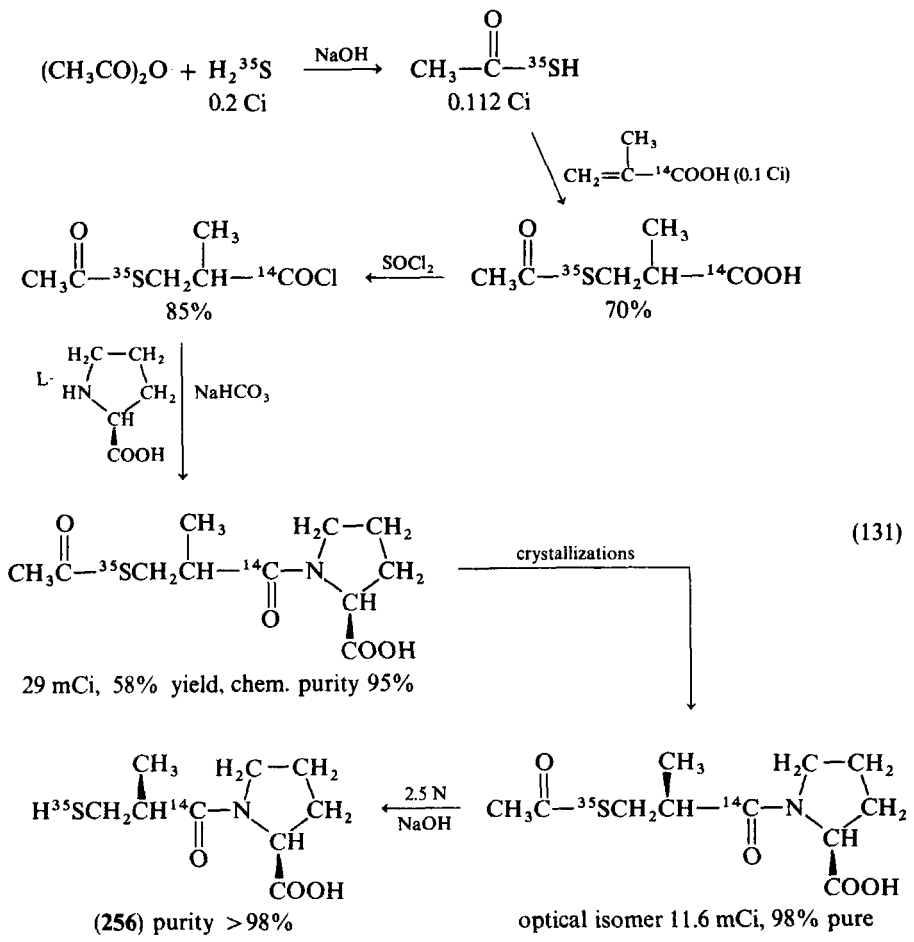
In the scheme of equation 132, thiobenzoic acid has been condensed (to minimize polymerization) with an ether solution of methacrylic (1-^{14}C) acid in hexane. The optical isomers of **257** have been resolved by crystallization of the dehydroabietylamine salt of **257** from isopropanol–water (9:1 V/V) solvent, followed by conversion to the acid chloride, which coupled with ^{14}C-labelled L-proline to give after hydrolysis captopril **259**.

In equation 133 the optically resolved, commercially available acid is converted to acid chloride, which is then coupled with ^{2}H-, ^{3}H- or ^{14}C-L-proline and the product **260** is hydrolyzed to the proline-labelled captopril **261**.

The radiation-induced polymerization of methacrylic acid has been minimized by keeping it in solution, and by condensing it with the thio acid as soon as possible. Solid ^{14}C-captopril (sp. act. 5 $\mu Ci\ mg^{-1}$) decomposed at $-20°C$ at the rate of 6% per year. Compounds with higher activities have been stored as the acetylthio- or benzoylthio-derivatives.

42. Synthesis of 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one

This compound (**262**) labelled with carbon-14 in the quinonoid ring and in the phenyl ring has been synthesized by Prakash and coworkers[207] to study its inhibitory action of the leukotriene biosynthesis and possible therapeutic applications for treating asthma, respiratory allergies, inflammation and certain skin diseases[208a].



(131)

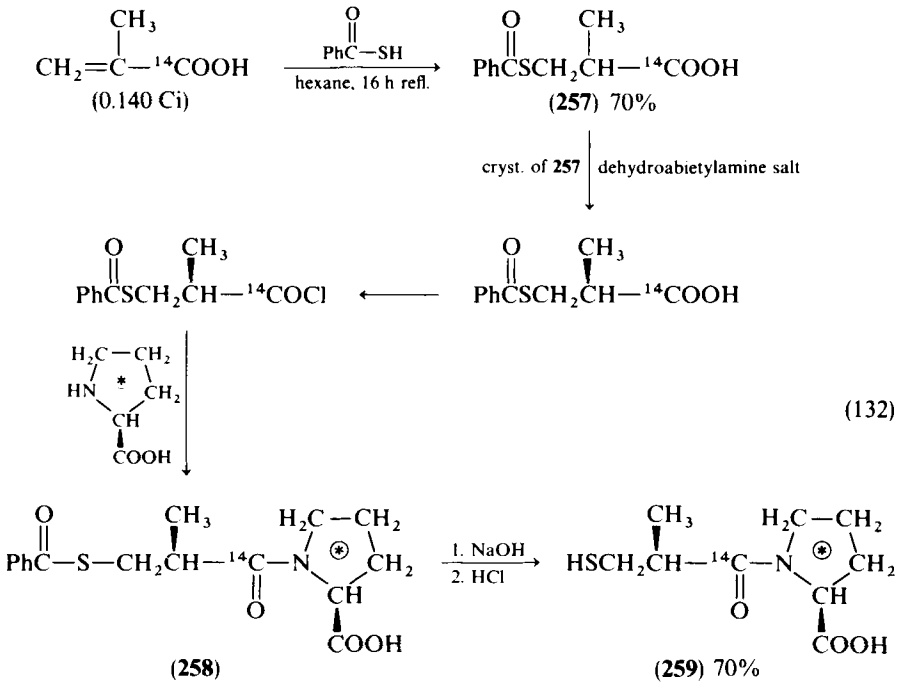
E. Syntheses of Carboxylic Acid Derivatives Labelled with ^{15}N, ^{18}O, ^{37}Cl, ^{75}Se, ^{82}Br, ^{123}I, ^{125}I, ^{99m}Tc and ^{111}In

1. Synthesis of [^{15}N]16-doxyl stearic acid (**264**)

The synthetic procedure of Keana[208b] (equation 134) for obtaining [^{15}N]16-doxyl stearate ester (**263**), a fatty acid spin label 'FASL', has been improved[209] (equation 135) by increasing the overall yield of 2-amino-2-methylpropanol[210] (**265**) with respect to [^{15}N]glycine to about 60% and by reducing the reaction volume, giving an overall yield of 50%.

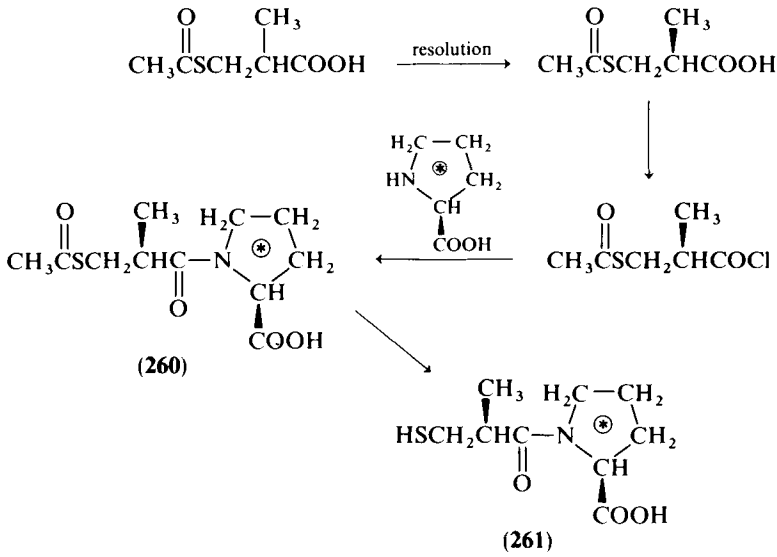
2. Synthesis of ^{15}N-labelled methotrexates

a. Synthesis of methotrexate-1-^{15}N and methotrexate-4-$^{15}NH_2$. Methotrexate **266** labelled at the ring $N_{(1)}$-nitrogen and in the 4-amino group with ^{15}N, needed to measure

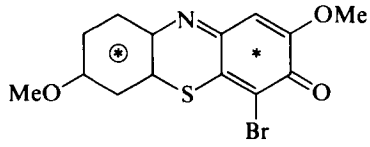


(132)

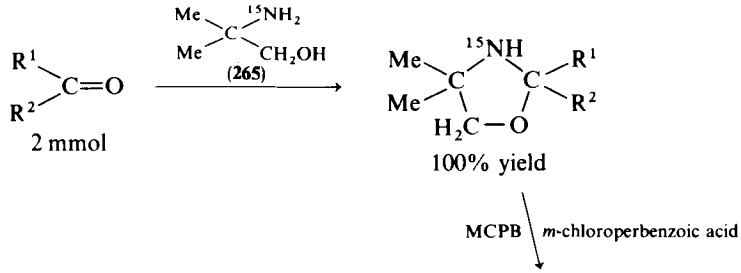
⊛ denotes isotopically ring-labelled proline



(133)



(262) ⊛ = U—^{14}C

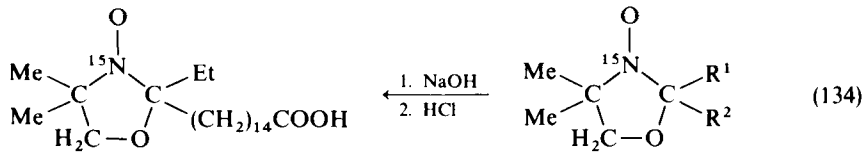


2 mmol

(265)

100% yield

MCPB *m*-chloroperbenzoic acid

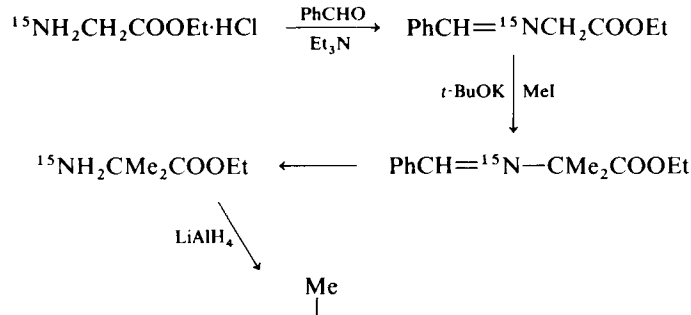


1. NaOH
2. HCl

(134)

(264) [^{15}N]16-Doxyl stearic acid[211a]

(263) R^1 = Et, R^2 = $(CH_2)_{14}COOMe$ yellow liquid

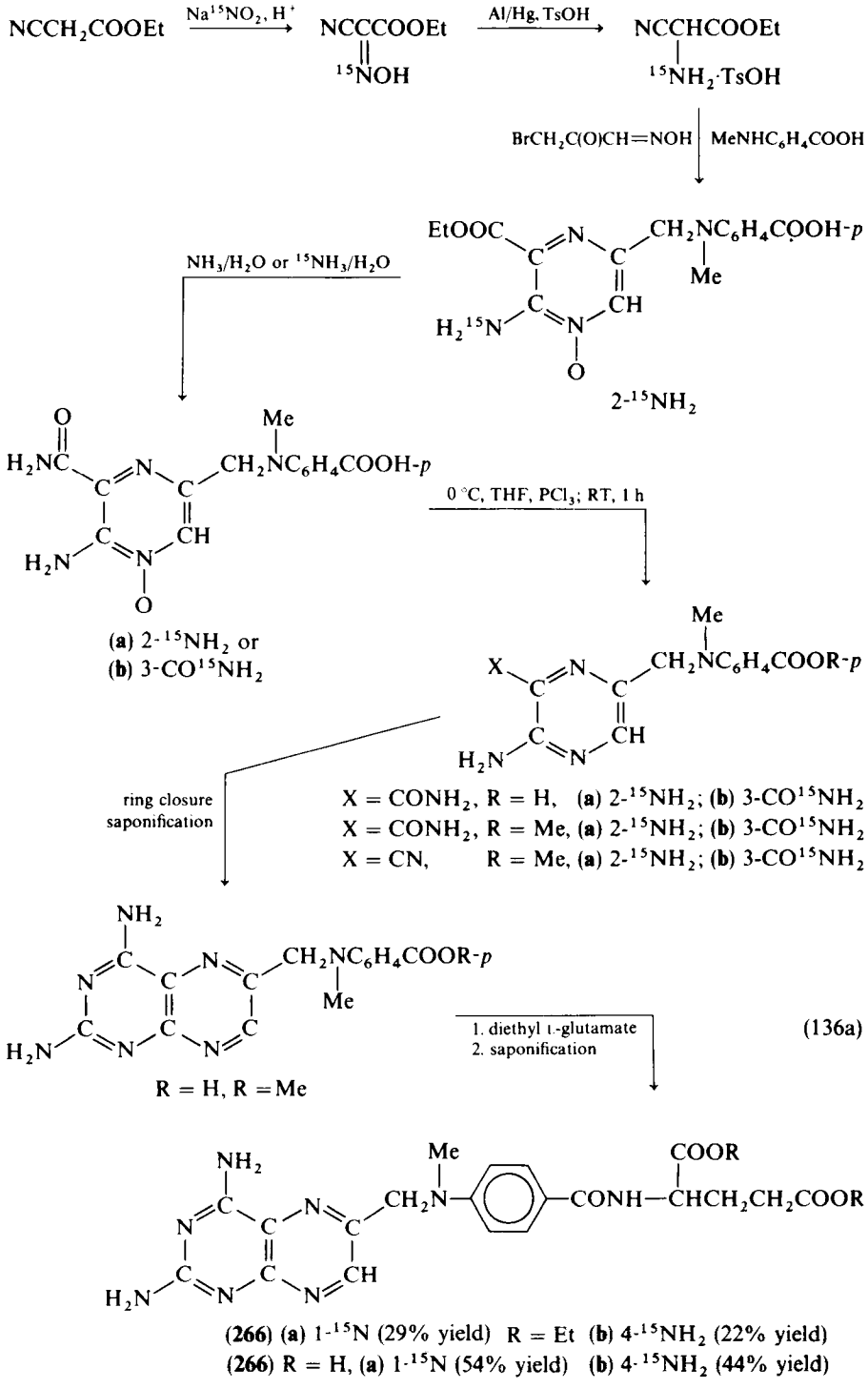


(135)

(265) 60% yield

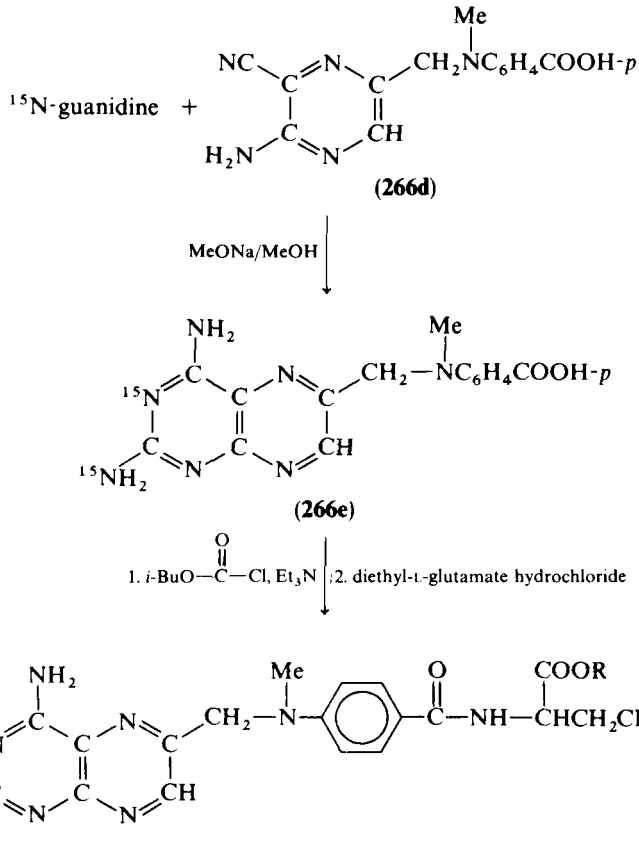
the NMR shift between methotrexate and its complex with dihydrofoliate reductase enzyme, has been synthesized[211b,212] as shown in equation 136a.

b. Synthesis of methotrexate-3-^{15}N-2-$^{15}NH_2$. Methotrexate bearing ^{15}N-labels at the ring N-3 and 2-NH_2 positions (**266c**), needed also for ^{15}N-NMR study of the complex


NCCH2COOEt
Na15NO2, H+
NCCCOOEt
15NOH
Al/Hg, TsOH
NCCHCOOEt
15NH2·TsOH
BrCH2C(O)CH=NOH
MeNHC6H4COOH
EtOOC
CH2NC6H4COOH-p
Me
H2 15N
CH
O
2-15NH2
NH3/H2O or 15NH3/H2O
O
H2NC
Me
CH2NC6H4COOH-p
H2N
(a) 2-15NH2 or
(b) 3-CO15NH2
0 °C, THF, PCl3; RT, 1 h
X
CH2NC6H4COOR-p
X = CONH2, R = H, (a) 2-15NH2; (b) 3-CO15NH2
X = CONH2, R = Me, (a) 2-15NH2; (b) 3-CO15NH2
X = CN, R = Me, (a) 2-15NH2; (b) 3-CO15NH2
ring closure
saponification
NH2
CH2NC6H4COOR-p
Me
H2N
R = H, R = Me
1. diethyl L-glutamate
2. saponification
(136a)
COOR
CH2N
CONH—CHCH2CH2COOR
(266) (a) 1-15N (29% yield) R = Et (b) 4-15NH2 (22% yield)
(266) R = H, (a) 1-15N (54% yield) (b) 4-15NH2 (44% yield)

$$KSC^{15}N \xrightarrow{\text{three steps}} \begin{matrix} {}^{15}NH_2 \\ \diagdown \\ C{=}{}^{15}NH\cdot HCl \\ \diagup \\ {}^{15}NH_2 \end{matrix} \qquad (136b)$$

formed between dihydrofoliate reductase and its inhibitors, has been prepared[211c] by condensing triply ^{15}N-labelled guanidine, obtained from commercially available $KSC^{15}N$ as shown in equation 136b, with 4-[*N*(2-amino-3-cyano-5-pyrazinyl-methyl)-*N*-methylamino]benzoic acid (**266d**), subsequent coupling of doubly ^{15}N-labelled intermediate acid **266e** with diethyl L-glutamate and followed by alkaline hydrolysis of the methotrexate-3-^{15}N-2-$^{15}NH_2$ diethyl ester (**266f**) (equation 136c).

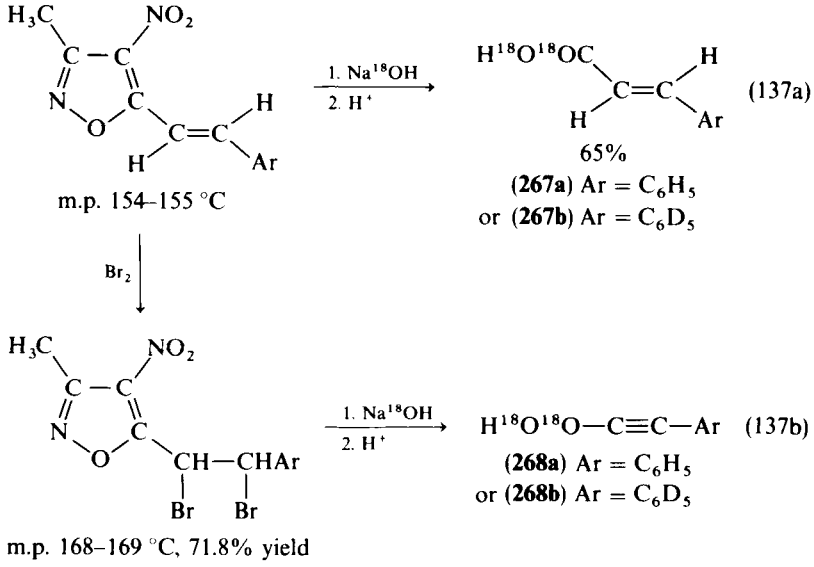


(136c)

3. Synthesis of carboxyl oxygen-18 bilabelled and deuterium labelled 3-phenyl-2-propenoic and 3-phenyl-2-propynoic acids

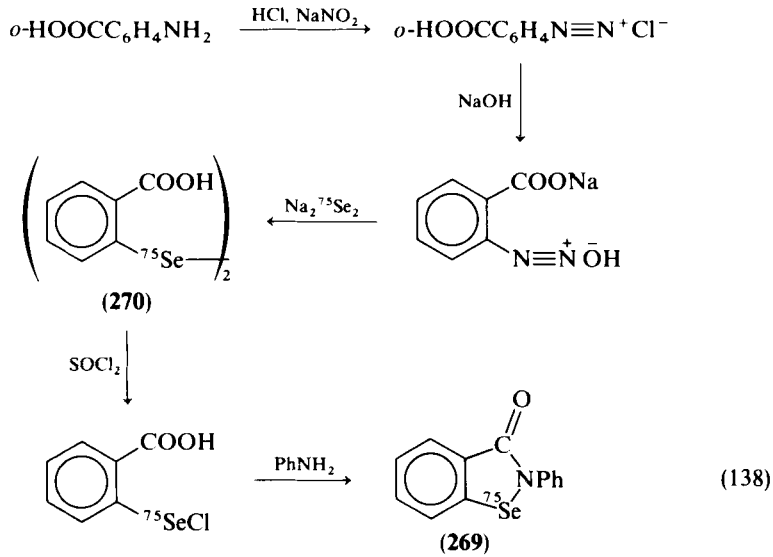
^{18}O-labelled carboxylic acids have usually been obtained[213] from $C^{18}O_2$, or by hydrolysis and ^{18}O-exchange reaction[214] with $H_2{}^{18}O$. Recently[215–217] doubly ^{18}O-

labelled coumaric acid[216] ($HOC_6H_4CH{=}CHC^{18}O_2H$), 3-[$^2H_5$]-phenyl-2-propenoic and 3-phenyl-2-propenoic (cinnamic) acids (**267**) have been prepared by alkaline hydrolysis of styrylisoxazoles (equation 137a). Using dibromo compounds as intermediates in the isoxazole synthesis, 3-phenyl-2-propynoic (phenylpropiolic) and 3-[$^2H_5$]-phenyl-2-propynoic ^{18}O-bilabelled acids (**268**) have also been prepared (equation 137b).



(137a)

(137b)



(138)

The starting styrylisoxazoles have been obtained[218] by condensing 3,5-dimethyl-4-nitroisoxazole with benzaldehyde or with [$^2H_5$]-benzaldehyde. $Na^{18}OH$ has been prepared by addition of Na to $H_2{}^{18}O$. The mass spectra of acids **267a** and **267b** showed signals at $m/e = 151, 152$ and $m/e = 156, 157$, respectively ($M^+ - 1$ and M^+ of the acids). Similarly, peaks in mass spectra of **268a** and **b** appeared at $m/e = 150(M^+)$ and at $m/e = 155(M^+)$.

4. *Synthesis of ^{75}Se-2-phenyl-1,2-benzisoselenazol-3(2H)-one (^{75}Se-PZ51, 'Ebselen', **269**)*

This new organoselenium drug with extremely low toxicity and showing *in vivo* anti-inflammatory properties[219,220] has been prepared[221] in 40% radiochemical yield from elemental ^{75}Se as shown by equation 138. ^{75}Se-selenium with sodium borohydride and NaOH yielded $Na_2{}^{75}Se_2$, which was used in the synthesis of ^{75}Se-diselenosalicylic acid (**270**).

5. *Synthesis of [$^{37}Cl_2$]chloramphenicol* (**271**)

This antibiotic, possessing especially bone marrow toxic properties[222], has been prepared[223,224] according to equation 139 in over 95% isotopic purity. Pure **271** was used as internal standard in the isotope-dilution GC/MS method to determine chloramphenicol in biological samples[225].

$$Na^{37}Cl + H_2O_2 \xrightarrow{H_2SO_4} {}^{37}Cl_2 \xrightarrow{EtOCCHN_2} \underset{\textbf{(272)}}{EtOCCH^{37}Cl_2} \qquad (139)$$

$$\textbf{272} + p\text{-}O_2NC_6H_4CH(OH)CH(NH_2)CH_2OH \xrightarrow{EtOH} \underset{\textbf{(271)}\ 36\%\ \text{(overall)}}{p\text{-}O_2NC_6H_4CH(OH)CH(CH_2OH)NHCCH^{37}Cl_2}$$

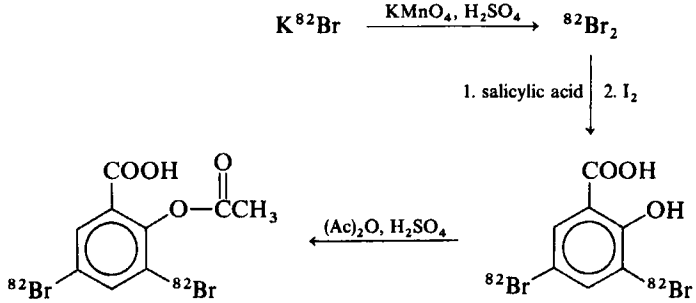
6. *Synthesis of acetyl-3,5-Br-82-dibromosalicylic acid* (**273**)

This compound (dibromoaspirin), which acetylates hemoglobin *in vitro*, has been ^{82}Br ($T_{1/2} = 35.34$ h, $E_{(\beta^-)} = 0.444$ MeV, $E_\gamma = 0.777$ MeV, 83.6%)[226,227] labelled (equation 140) for biodistribution and pharmacological studies[228] since aspirin is an anti-inflammatory and anti-prostaglandin agent.

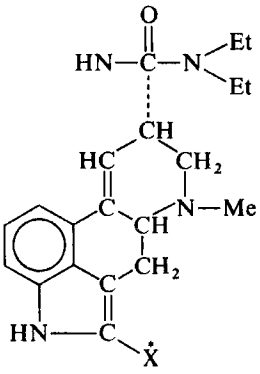
The distribution of bromine-82 activity after injection of **273** to mice and rabbits in blood, lungs, heart, kidneys, liver and spleen (4%) has been studied[228].

7. *Synthesis of ^{123}I-radioiodinated derivatives of lisuride and amphetamine*

Radiohalogenated derivatives of Lisuride (**274**) have been prepared in 60% yield[229] by electrophilic substitution at the indole moiety of lisuride, using *in situ* oxidation (H_2O_2–AcOH) of NCA radiobromide or radioiodide. ^{123}I is commercially available,



(273) 0.4 mCi (8%) (140)



(274)

while $^{75-76}Br$ have been produced by irradiating As–Cu targets with 28 MeV–^{3}He particles. The yield of ^{123}I-*N*-isopropyl-*p*-iodoamphetamine (IAMP) has been highly improved (above 95%)[230] by adding $SnCl_2$ to the reaction mixture containing Cu(II) in acetic acid solution [generating Cu(I) *in situ*], and using a $^{123}I^-$ solution. The yields in previous labelling methods did not exceed 60%[231, 232].

8. Synthesis of ^{125}I-labelled 14-iodo-9-tetradecynoic acid

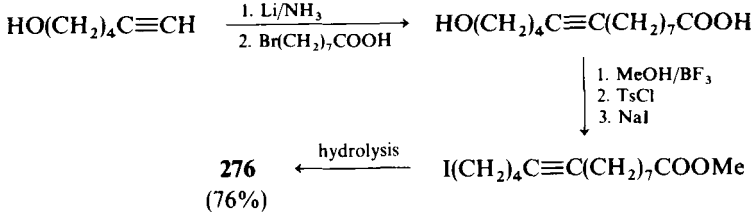
Fatty acids radioiodinated with γ-emitting ^{123}I ($T_{1/2}$ = 13.3 h) or with ^{131}I ($T_{1/2}$ = 8.05 d) have been used to detect abnormalities in regional myocardial perfusion[233,234]. $^{125}I(CH_2)_{15}COOH$ has also been applied to evaluate the myocardial uptake in rats[235,236]. 14-^{125}I-iodo-9-tetradecynoic acid (**275**), a potential suicide inhibitor of

$$\underset{\textbf{(276)}}{I(CH_2)_4C{\equiv}C(CH_2)_7COOH} \xrightarrow{Na^{125}I,\ MeCOEt} \underset{\textbf{(275)}}{^{125}I(CH_2)_4C{\equiv}C(CH_2)_7COOH} \quad (141)$$

95%, radiochem. purity >97%,
final sp. act. 0.78 μCi mg^{-1},
^{125}I ($T_{1/2}$ = 60 d, *K*, E_γ = 0.035 MeV)

acyl-CoA dehydrogenase or enoyl-CoA isomerase, has been obtained by an exchange method (equation 141) and applied for tissue distribution study in dogs[236].

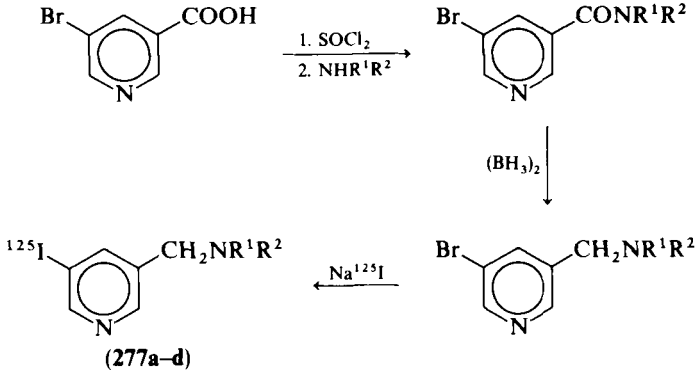
Unlabelled **276** has been prepared in a six-step synthesis (equation 142).



(142)

9. *Synthesis of radioiodinated nicotine analogues*

^{125}I-labelled nicotine analogues **227a–d** have been synthesized by halogen exchange (equation 143) and used as brain and adrenal medulla imaging agents[237]. Compound **277d** showed the highest brain-to-blood and adrenal-to-blood ratios and also the highest uptake in both the brain and the adrenal (at 2 min post-administration).



(277a–d)
(143)

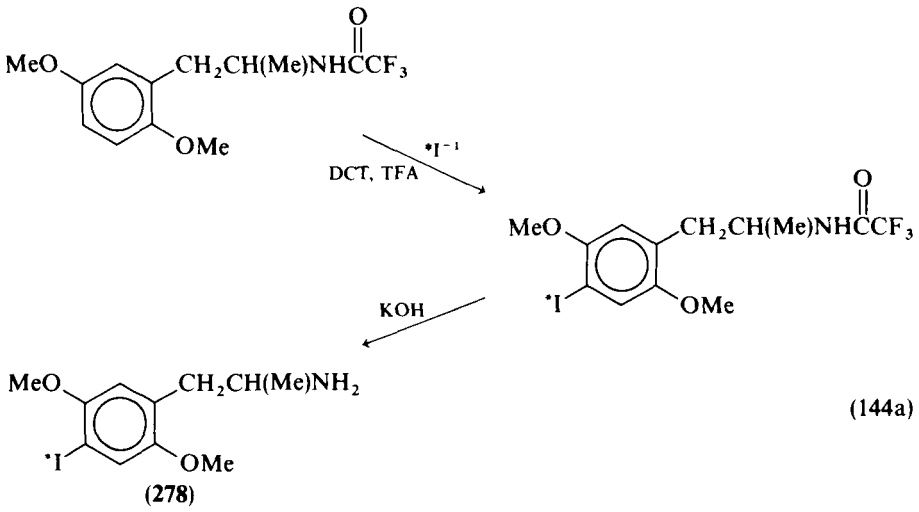
(**a**) R^1 = Me, R^2 = n-Pr, yield 0.7 mCi (70%), sp. act. 0.17 Ci mmol^{-1}
(**b**) R^1 = R^2 = Et, yield 0.47 mCi (46.6%), sp. act. 0.113 Ci mmol^{-1}
(**c**) R^1 = H, R^2 = *i*-Pr, yield 0.75 mCi (75%), sp. act. 0.172 Ci mmol^{-1}
(**d**) R^1 = R^2 = *i*-Pr, yield 0.60 mCi (66%), sp. act. 0.179 Ci mmol^{-1}

10. *Synthesis of ^{125}I- and ^{123}I-labelled 2,5-dimethoxy-4-iodophenylisopropylamine (DOI)* (**278**)

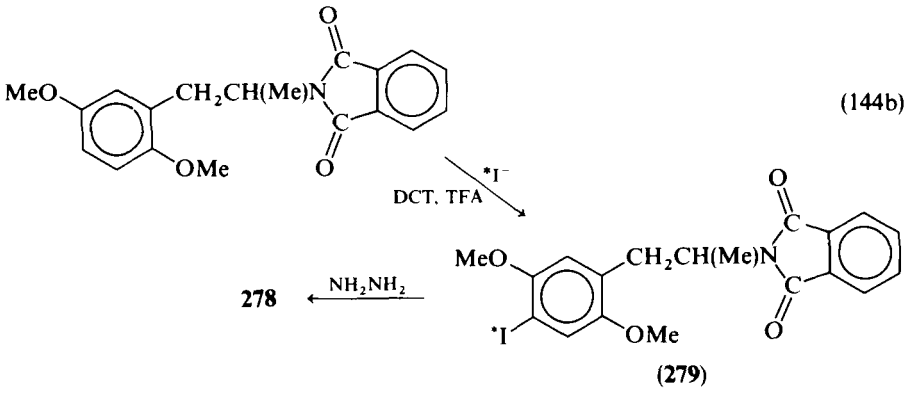
(*R*)- and (*S*)-DOI, extremely potent psychoactive agents in humans, have been ^{125}I- and ^{123}I-labelled according to the three routes (equations 144a, b, c)[238]. ^{125}I- and ^{123}I-labelled products have had average specific activities of 1100 Ci mmol^{-1} and > 20,000 Ci mmol^{-1}, respectively[238].

11. *Synthesis of [^{125}I]-3-Me IVDU* (**280**)

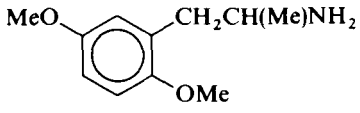
^{125}I-(*E*)-5-(2-Iodovinyl)-$N_{(3)}$-methyl-2′-deoxy-uridine (**280**) has been synthesized[239] for the non-invasive diagnosis of *Herpes Simplex Encephalitis*[240]. $N_{(3)}$-methyl substitu-



(144a)



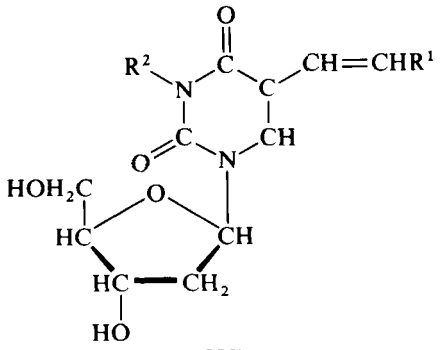
(144b)



278 (94 ± 6% yield) (144c)

*I = no-carrier-added ^{125}I-iodide or ^{123}I-iodide in 0.1 N NaOH;
DCT = dichloramine-T; TFA = trifluoroacetic acid; CAT = chloramine-T

tion increases the lipophilicity of IVDU, enhances its diffusion across the blood brain barrier and thus should increase the probability that it will be metabolically trapped in infected cells. **280a** was synthesized either by $N_{(3)}$-methylation of **280b** and/or by iodination of **280c**. In vitro studies have indicated that the extent of metabolic trapping of **280a**-[^{125}I] by kidney cells infected by virus (HSV-1 TK$^+$) is less than the trapping of [^{125}I]-**280b**.

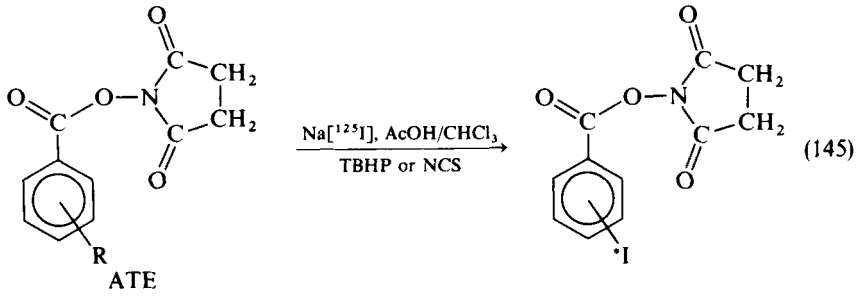


(280)

(**280a**) R^2 = Me, R^1 = I, ^{125}I
(**280b**) R^2 = H, R^1 = I, ^{125}I
(**280c**) R^2 = Me, R^1 = COOH

12. Radioiodination and astatination of ATE compounds

N-Succinimidyl-3-(trimethylstannyl)benzoate ('*m*-MeATE') and *N*-succinimidyl-4-(tri-n-butylstannyl)benzoate ('*p*-BuATE'), required to investigate the relative inertness towards dehalogenation *in vivo* of *meta* versus *para* aryl iodide residues, were synthesized[241] by reacting the corresponding bromobenzoic acids with BuLi and subsequent reactions with the appropriate trialkyltin chloride, followed by reaction with *N*-hydroxysuccinimide and dicyclohexyl carbodiimide. The iodination of *m*-MeATE and *m*-BuATE has been carried out using *t*-butylhydroperoxide (TBHP) or *N*-chlorosuccinimide (NCS) as the oxidants (equation 145). Yields of *N*-succinimidyl-3-[^{125}I]iodobenzoate higher than 85% were obtained using *m*-MeATE and NCS.



(145)

ATE

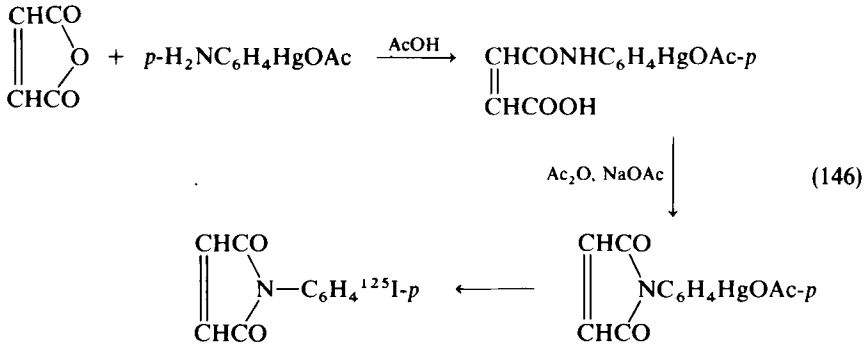
p-BuATE, R = 4-Bu_3Sn
m-BuATE, R = 3-Bu_3Sn
m-MeATE, R = 3-Me_3Sn

Subsequent bio-observations have shown that *meta* isomer of iodobenzoic acid, '*m*-[^{125}I]IBA', is more inert toward dehalogenation *in vivo* than *p*-[^{131}I]IBA. The antibodies have also been astatinated with ^{211}At ($T_{1/2}$ = 7.21 h) produced in ^{209}Bi(α, 2n)→^{211}At nuclear reaction. Subsequent chemical reaction of ^{211}At in $CHCl_3$ with TBHP and *m*-BuATE gave *N*-succinimidyl-3-^{211}At astatobenzoate (**281**) in 70–75% yield. Reaction of **281** with the antibody 81C6 followed by Sephadex G-25 column purification produced the ^{211}At-labelled monoclonal antibody 81C6IgG (IgG = immunoglobuline), which concentrates preferentially in tumor cells. Tumor-to-tissue ratios for blood, liver, kidney, muscle and brain were 2.1, 7.1, 9.0. 26.4 and 87.6, respectively. High

linear energy transfer of α-particles emitted by ^{211}At (E_α = 5.868 MeV) combined with tumor specificity of the monoclonal antibody can thus be utilized for radiotherapy.

13. Synthesis of N-(p-[^{125}I]iodophenyl)maleimide (IPM, 282)

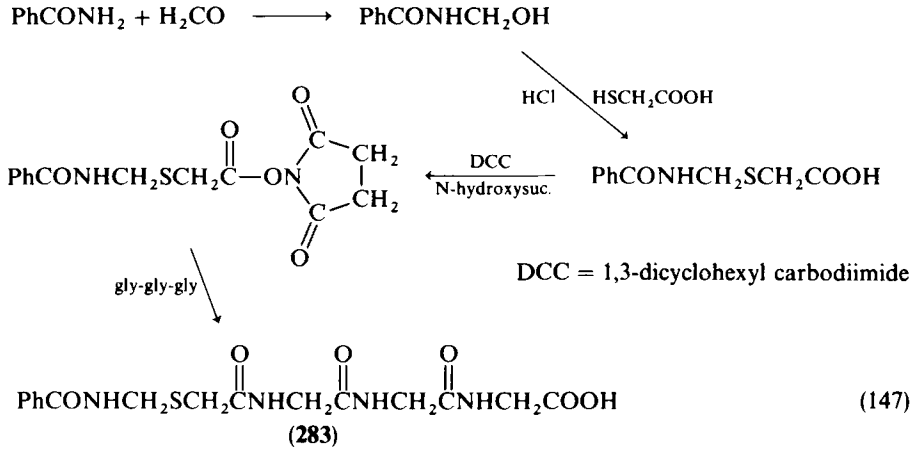
N-substituted maleimides react with protein thiols to form a thioether linkage under mild conditions[242]. **282** has thus been prepared via Na[^{125}I] or [^{125}I]Cl as shown in equation 146[243], and applied for diagnosis and radioimmunotherapy of cancer. Tumor and thyroid uptake of IPM by mice have also been investigated.



(146)

14. Synthesis of ^{99m}Tc-MAG$_3$

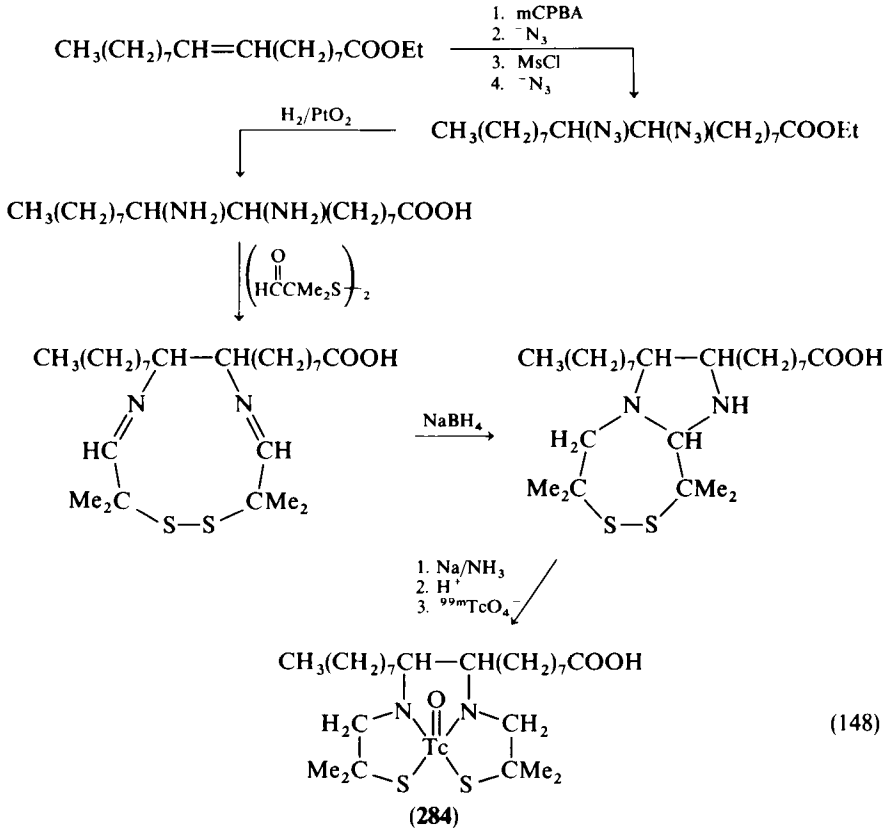
Benzyl, benzoyl and benzamidomethyl groups have been used[244–246] to prevent the rapid oxidation of the thiol function during chemical synthesis and storage of MAG_3 used for preparation of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) applied in routine renal function studies (as substitute for ^{131}I-Hippuran). Benzamidomethylmercaptoacetylglycylglycylglycine (**283**) has been obtained as illustrated in equation 147. The labelled ^{99m}Tc-MAG_3 has been prepared from the ligand with $^{99m}TcO_4^-$. The highest rate of incorporation from ^{99m}Tc-tartrate to ^{99m}Tc-MAG_3 has been achieved when benzoyl is used as protective group for the MAG_3 molecule.



(147)

15. Synthesis of ^{99m}Technetium fatty acid

A novel ^{99m}technetium fatty acid, the highly lipid soluble ^{99m}Tc complex **284**, a useful radioimaging agent for the myocardium, has been synthesized[247–249] as shown in equation 148. Characterization of the proposed structure **284** for the complex is under investigation[247].



(148)

(284)

16. Synthesis of Iodofenin-^{99m}Tc

3-Iodo-2,4,6-trimethylphenyl-carbamoylmethyl-iminodiacetic acid (**285**), an efficient complexing agent for ^{99m}Tc, has been synthesized[250] via **286** and **287** in 63% yield. The ^{99m}Tc transporter, iodofenin-^{99m}Tc, showing almost no renal excretion, has been prepared subsequently from **285** with $Na^{99m}TcO_4$.

17. Synthesis of the Br-Me$_2$HBED-protein complex radiolabelled with In-111

N-(2-Hydroxy-3,5-methylbenzyl)-*N'*-(2-hydroxy-5-bromoacetamidobenzyl)-ethylenediamine-*N*,*N'*-diacetic acid (**288**), designated 'Br-Me$_2$HBED', is used for radiolabelling of antibodies[251]. The bromoacetamide moiety in this compound is used to bind the chelating group to proteins[252]. The 'Br-Me$_2$HBED-protein complex' has been radiolabelled subsequently by treating it with In-111 citrate (over 83%). *In vivo*, the

In-111-IgA localized in the liver. The biodistribution and degradation of **288** has been investigated and compared with other ligands[251].

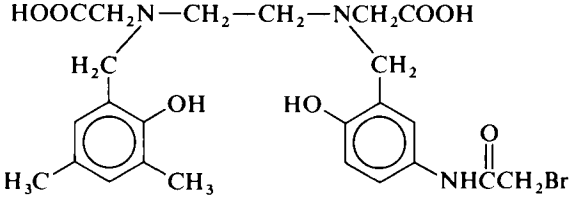
III. SYNTHESES AND APPLICATIONS OF CARBOXYLIC ACIDS LABELLED WITH ISOTOPES OF HYDROGEN

A. Deuterium-labelled Carboxylic Acids

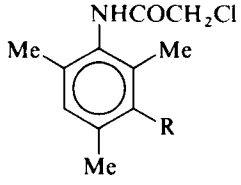
1. *Synthesis of short-chain 2-^{2}H-, 2,3-$^2H_2$- and 2,2-$^2H_2$-labelled carboxylic acids*

Short-chain deuterated carboxylic acids have been synthesized as standards for mechanistic studies of acyl-CoA dehydrogenases[253,254], particularly for the identification of enzymically deuterated products obtained via extensive proton/deuteron exchange reactions taking place in the course of 'half' reactions between enzyme and substrate carried out in D_2O in the absence of electron acceptor and leading only to formation of 'enzyme–substrate complex'. No dehydrogenation of the substrate occurs in these conditions, but deuterium–hydrogen exchange with D_2O is observed.

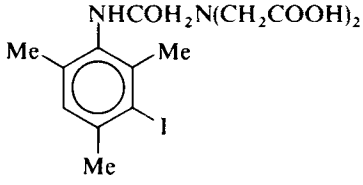
Carboxylic acids, monodeuterated in the 2-position, have been synthesized by decarboxylating the carboxyl corresponding deuterated-2-alkylmalonic acids (equation 149). Hexanoic-, pentanoic, 3-methylbutanoic-, 2-methylbutanoic-, butanoic-, and 2-methylpropanoic-2-^{2}H-acids have been prepared according to equation 149. Sodium [$^2H_1$]acetate with exceptional (>99%) isotopic purity was obtained in the mild debromination of bromoacetic acid with an excess of zinc dust in D_2O room temperature[254b].



(288)



(286) R = H
(287) R = I



(285) m.p. 222–224 °C

$$R^1R^2C(COOK)_2 \xrightarrow{^2H_3O^+} R^1R^2C(COO^2H)_2 \xrightarrow{\Delta} R^1R^2C^2HCOOH \quad (149)$$

2,3-Dideuteration has been achieved by catalytic deuteration of the corresponding 2,3-unsaturated carboxylic acids with sodium borodeuteride[255] (equation 150). Hexanoic-, pentanoic-, 3-methylbutanoic-, 2-methylbutanoic- and butanoic-2,3-$^2H_2$-acids have been thus synthesized.

$$R^1R^2C{=}CR^3COOH \xrightarrow[DCl]{NaBD_4,\ D_2PtCl_6,\ MeO^2D} R^1R^2C^2D{-}CR^3DCOOH \quad (150)$$

$$RCH_2COONa \xrightarrow[2.\ D_3O^+]{1.\ NaO^2H \text{ in } {}^2H_2O} RC^2H_2COOH \qquad (151)$$

Alkyl -2,-2-$^2H_2$ carboxylic acids have been obtained using H/D exchange of the carboxylate sodium salt in $NaOD/D_2O$ solutions[254] (equation 151). Hexanoic-, pentanoic- and 3-methylbutanoic-2,2-$^2H_2$-acids have been synthesized by Hine and coworkers[254a]. The first five aliphatic carboxylic acids have been deuterated in the α-position also by H/D exchange taking place between $NaOD/D_2O$ and sodium salts of these acids at elevated temperatures[255–261]. Acetic-2-$^2H_3$-acid, propionic-2-$^2H_2$-acid, butanoic-2-$^2H_2$-acid, pentanoic-2-$^2H_2$-acid and hexanoic-2-$^2H_2$-acid have been synthesized and applied for isotope exchange studies and for a kinetic isotope effect study of the mechanism of permanganate and manganate oxidation of α-deuteriated sodium carboxylates[256–261] (see Section IV).

2. *Synthesis of ω-$^2H_3$ aliphatic carboxylic acids*

Two general methods of synthesis of ω-$^2H_3$ aliphatic acids and alcohols have been proposed by Bouloussa and coworkers[262] (equations 152 and 153). ω-deuteriated acids

$$MeOOC(CH_2)_nCOOMe \xrightarrow{Ba(OH)_2} HOOC(CH_2)COOMe \xrightarrow{SOCl_2}$$

(291)

$$ClCO(CH_2)_nCOOMe \xrightarrow{H_2(Pd)} HCO(CH_2)_nCOOMe \xrightarrow{Ph_3P^+CH_3Br^-}$$

$$CH_2{=}CH(CH_2)_nCOOMe \xrightarrow[2.\ CH_3SO_2Cl\ 3.\ LiAlD_4]{1.\ LiAlD_4} CH_2{=}CH(CH_2)_nCD_3 \xrightarrow{KMnO_4}$$

$$CD_3(CH_2)_nCOOH \qquad (152)$$

(289)

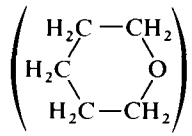
$$MeOOC(CH_2)_nCOOMe \longrightarrow ClCO(CH_2)_nCOOMe \xrightarrow{NaBH_4}$$

$$HOCH_2(CH_2)_nCOOMe \longrightarrow THP{-}O{-}(CH_2)_{n+1}COOMe \xrightarrow[2.\ CH_3SO_2Cl\ 3.\ LiAlD_4]{1.\ LiAlD_4}$$

tetrahydropyranyl ether

$$THP{-}O{-}(CH_2)_{n+1}CD_3 \xrightarrow{H_3O^+} HO(CH_2)_{n+1}CD_3 \qquad (153)$$

(290)



tetrahydropyran, THP

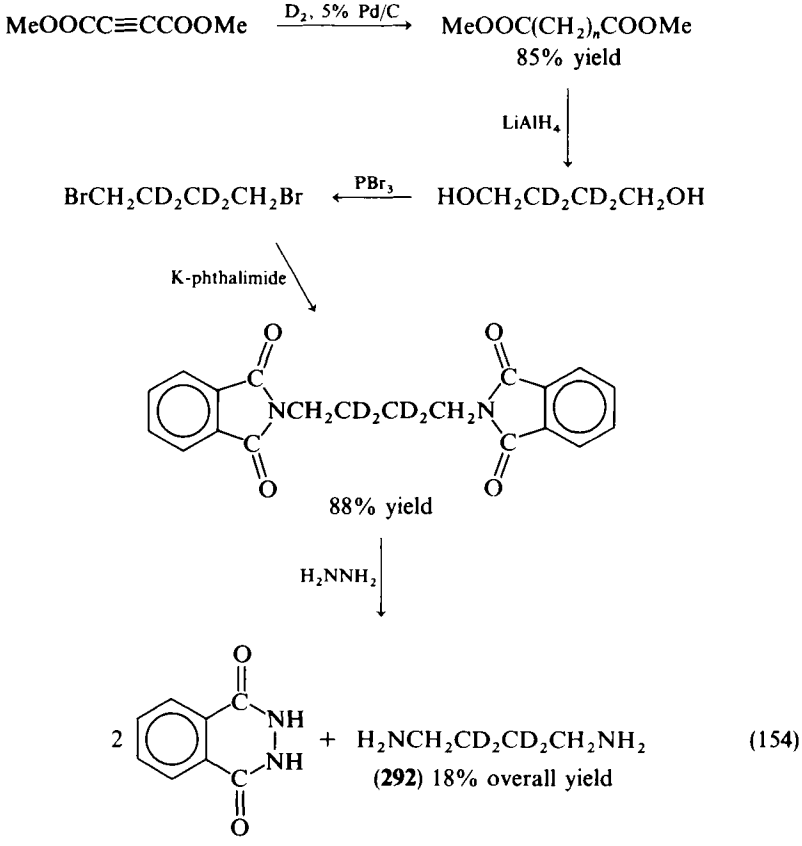
can be obtained from alcohols **290**. In both cases the first synthetic step involves hydrolysis of the diester to the acid-ester **291**, which was converted subsequently into the aldehyde ester and then to a vinyl ester. The latter was reduced to vinyl alcohol (1-$^2H_2$) and then by way of the mesylate derivative to the ω-$^2H_3$ 1-alkene, which by

oxidation yields the ω-$^2H_3$ acid (**289**). In equation 153 the hydroxyl group has been protected as the tetrahydropyranyl ether. Reduction of the ester group as in equation 152 yields ω-$^3H_3$ alcohol.

The methods of equations 152 and 153 have been applied to prepare (16-$^2H_3$) hexadecanoic acid in 83% yield and hexanol (6-$^2H_3$).

3. Synthesis of dimethyl succinate-2,2,3,3-D_4

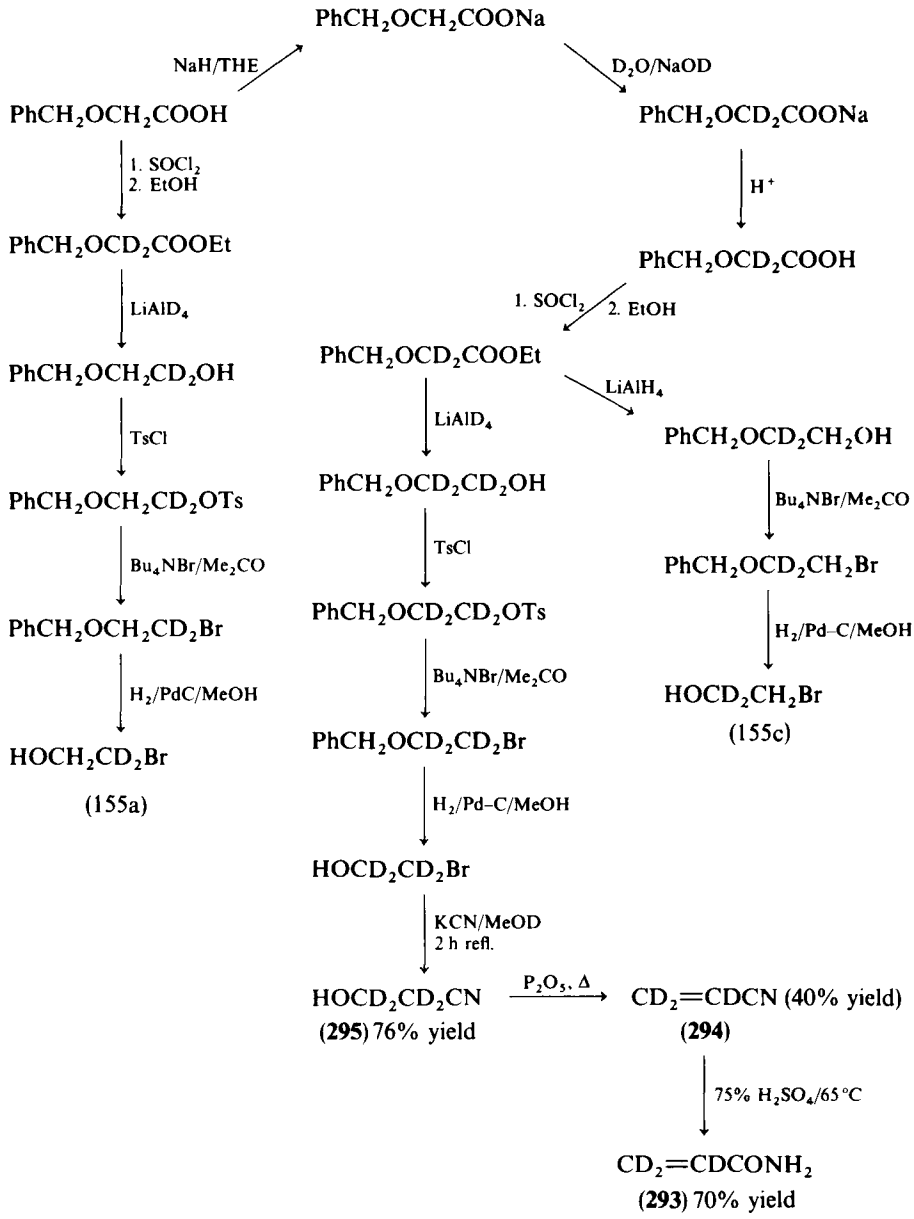
This diester has been obtained[263] starting from acetylene dicarboxylate in the course of the synthesis of 1,4-butanediamine-2,2,3,3-D_4 (**292**, equation 154) needed to study deuterium isotope effects in the thermal decomposition of explosives[264,265]. $H_2NCD_2CH_2CH_2CD_2NH_2$ has been obtained analogously in 66% yield[263,266].



(154)

4. Synthesis of [$^2H_4$]-2-bromoethanol, [1-$^2H_2$]-2-bromoethanol, [2-$^2H_2$]-2-bromoethanol, [$^2H_3$]-acrylonitrile and [$^2H_3$]-acrylamide from 2-benzyloxyacetic acid

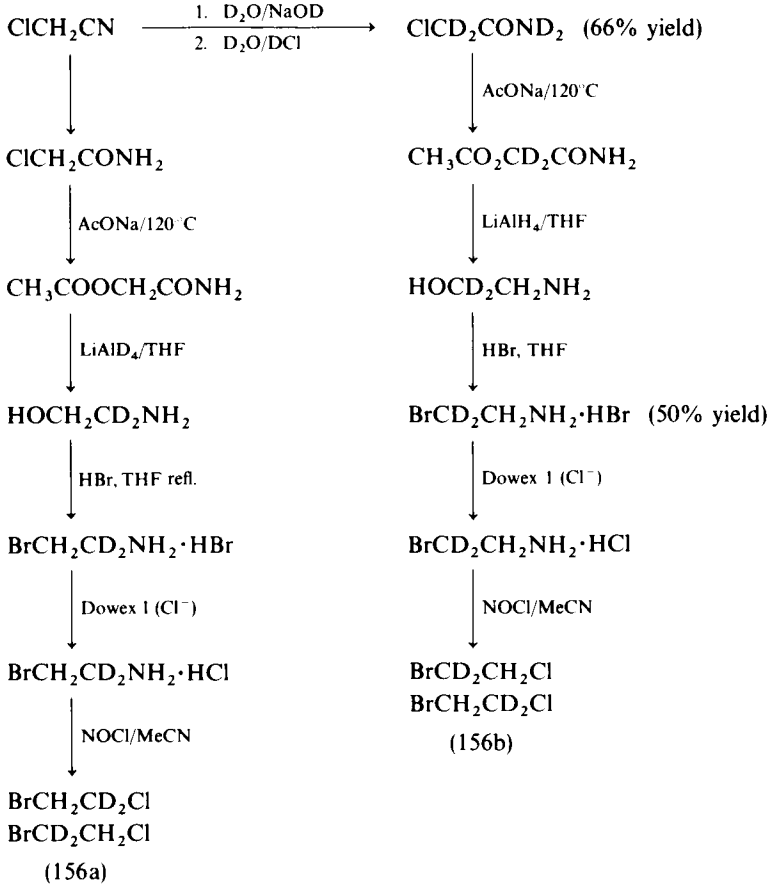
Several C_2 or C_3 deuterium-labelled compounds have been required for *in vivo* studies of the metabolism of low-molecular-weight carcinogens such as ethylene oxide,



acrylamide and 1,2-dichloroethane. These were synthesized according to equations 155a,b,c, and have been used subsequently for preparation of labelled analogues of the adducts formed between the carcinogens and cysteine sulphhydryl groups of proteins. The latter were used as internal standards in the gas chromatographic and mass spectrometric determinations of the unlabelled adducts found in proteins from populations exposed to the respective carcinogens[266–270]. For instance, acrylamide (**293**) exposure may be monitored by GC-MS determinations of its cysteine adduct in proteins

[*S*-(2-carbox-amidoethyl)cysteine] using the [$^2H_3$]-labelled analogue as internal standard[269]. [$^2H_3$]Acrylonitrile (**294**) has been obtained from [2,3-$^2H_4$]-3-hydroxypropionitrile (**295**) and hydrolysed subsequently to [$^2H_3$]-**293**.

Difficulties have been experienced in preparing isotopically pure [1-$^2H_2$]- and [2-$^2H_2$]-1-bromo-2-chloroethane from chloroacetonitrile (equations 156a,b) because some randomization of the halogens has been taking place in the last reaction steps. Significant amounts of 1,2-dibromoethane and 1,2-dichloroethane have also been obtained.

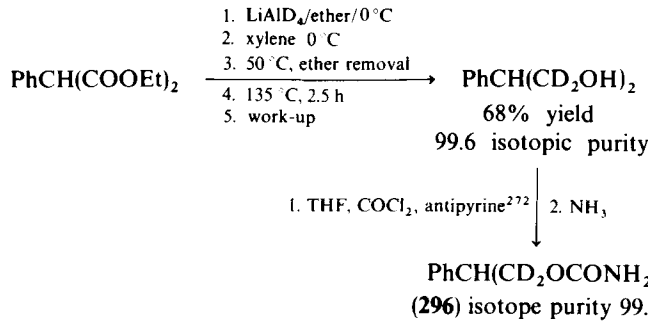


5. Synthesis of deuterium-labelled felbamate

2-Phenyl-1,3-propanediol-1,1,3,3-D_4 dicarbamate ('Felbamate-D_4', **296**), a new antiepileptic drug, has been synthesized for clinical pharmacodynamic studies (equation 157)[271], with 44% overall yield.

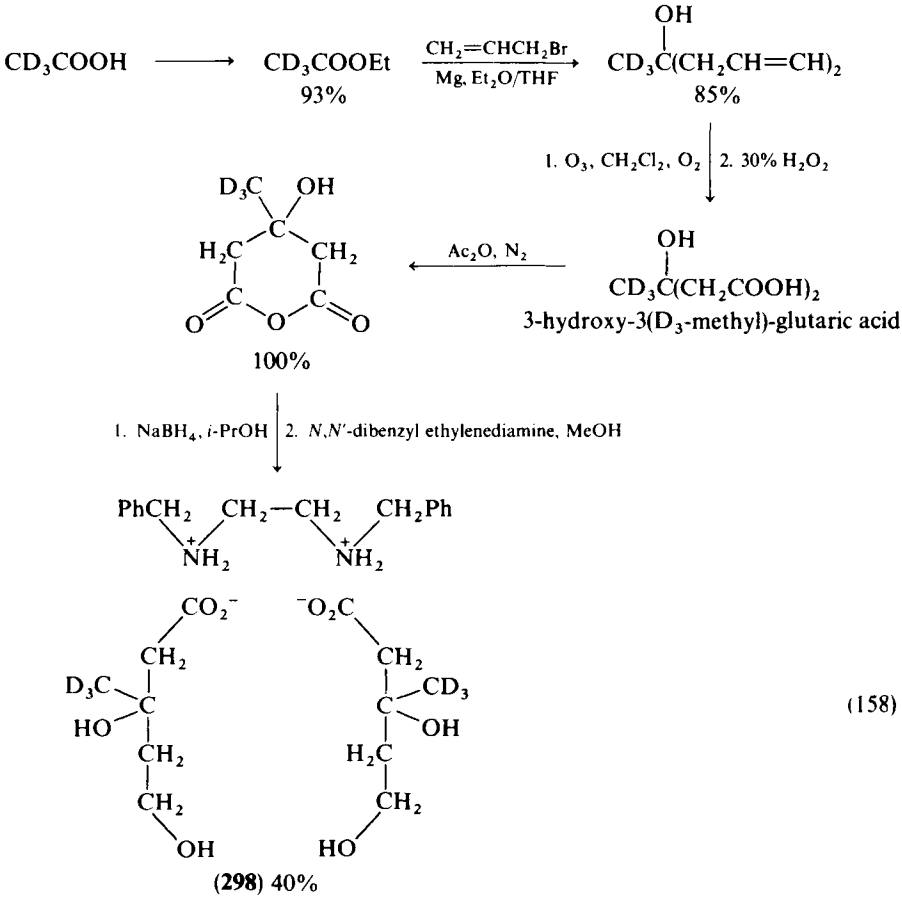
6. Synthesis of 3'-D_3-mevalonic acid

There are several reports concerning syntheses of mevalonic acid labelled with isotopic carbon and isotopic hydrogen[273–276]. This acid with 100% atom deuterium content in



(157)

the 3′-CD_3 group has also been synthesized from acetic acid-D_5, according to equation 158[277]. The product (reverting easily to lactone) was the crystalline salt *N,N′*-dibenzyl-ethylenediammonium bis(3,5-dihydroxy-3-(D_3-methyl)-pentanoate (**298**). It was shown by mass spectroscopy and ^1H NMR to be 100 atom% deuterium labelled. FAB mass

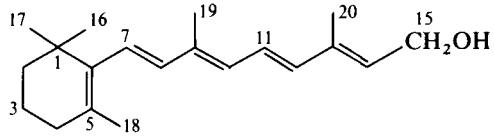


(158)

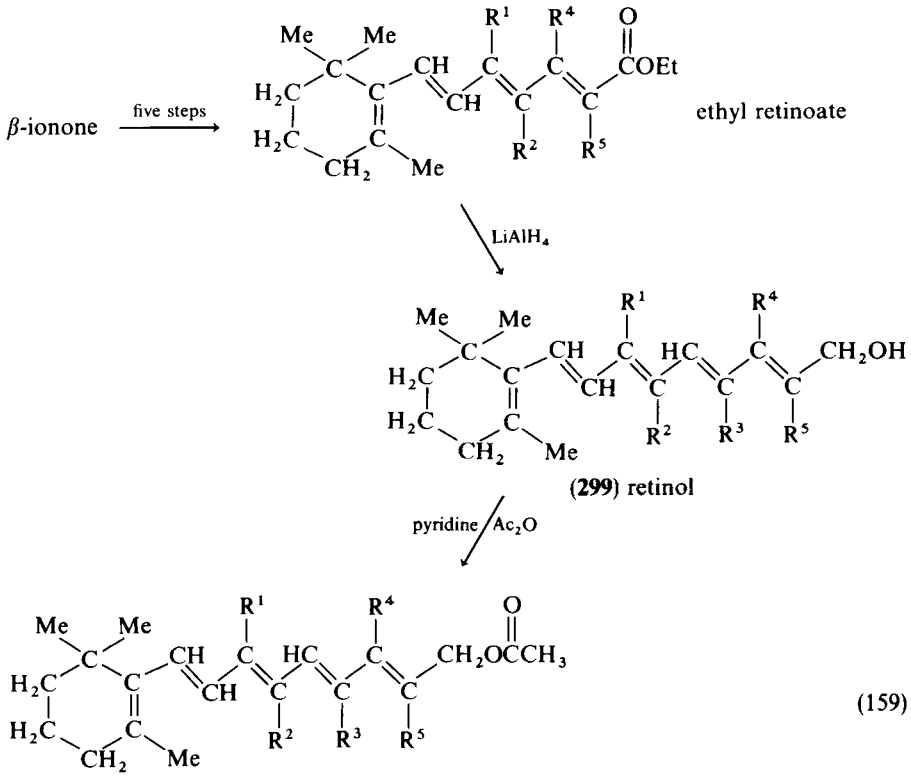
spectrum showed a negative ion of mass 150 (corresponding to labelled mevalonate) and a positive ion of mass 241 ($C_{16}H_{21}N_2^+$). The synthesis of **298** has been carried out to study the biosynthesis of triterpenoids in *Euphorbia lathyris latex*.

7. Syntheses of tri-, tetra- and penta-deuterated forms of vitamin A

Compounds **299** containing ^{13}C and deuterium in chemically and metabolically stable positions were required to study the metabolism of vitamin A in humans[278]. The



(**299**) numbering system of vitamin A



(159)

(**300**) retinyl acetate

(**300a**) 20,20,20-$^2H_3$-retinoic acid ethyl ester (R^1 = Me, R^4-C^2H_3)
(**300b**) 14,20,20,20-$^2H_4$-retinoic acid ethyl ester (R^1 = Me, R^4 = C^2H_3, R^5 = ^2H)
(**300c**) 12,14,20,20,20-$^2H_5$-retinyl acetate (R^1 = Me, R^3 = ^2H, R^4 = C^2H_3, R^5 = ^2H)
(**300d**) 10,19,19,19-$^2H_4$-retinyl acetate (R^1 = C^2H_3, R^2 = ^2H, R^4 = Me)

polydeuterated compounds **300a–d** have been synthesized[279] by a modified Wittig–Horner method[280–282], involving base catalysed incorporation of deuterium from D_2O or $(CD_3)_2CO$ into the appropriate intermediates (equation 159). 10,19,19,19-$^2H_4$-vitamin A (**300d**, >98% $^2H_4$) has been found to be the most useful for biological studies. The pentadeuteriated retinyl acetate **300c** had the following deuterium incorporation as shown by mass spectrometry: $^2H_0$ 0.1%, $^2H_1$ 3.8%, $^2H_2$ 11.3%, $^2H_3$ 18.3%, $^2H_4$ 27.0%, $^2H_5$ 39.5%.

10,19,19,19-$^2H_4$-Retinyl acetate (**300d**) has been obtained by using tri-deuteriated β-ionone[283] as the starting material. The final product contained more than 98% of $^2H_4$ species, as determined by NMR and GLC-MS.

8. Synthesis of $^2H_4$-labelled (±)-prostaglandin D_2 (PGD$_2$, 302)

Deuterated analogues of eicosanoids[284], biologically active C_{20} carboxylic acids, are indispensable tools in tracer studies concerning biochemical transformations and metabolism, and in facilitating mass spectrometric ultratrace analysis of endogeneous unlabelled fatty acids in biological materials. A new deuteriated phosphonate reagent (**301**), dimethyl 3,4,5,6-[$^2H_4$]-2-oxoheptylphosphonate, was prepared as shown in equation 160 and has been used[285,286] in a thirteen-step synthesis of 16,17,18,19-[$^2H_4$]-prostaglandin D_2 (**302**, equation 161).

$$\mathrm{Me(CH{=}CH)_2COOEt} \xrightarrow{(\mathrm{MeO})_2\mathrm{P\text{-}CH_2}^-\mathrm{Li}^+} \mathrm{Me(CH{=}CH)_2C(O)CH_2P(O)(OMe)_2} \xrightarrow{(\mathrm{Ph_3P})_3\mathrm{RhCl},\ ^2H_2} \mathrm{CH_3(CH^2H)_4C(O)CH_2P(O)(OMe)_2} \quad (160)$$

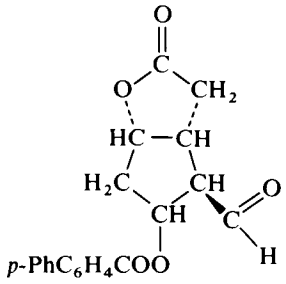
(301)

The required 15*S*-**305** has been isolated by fractional crystallization of the mixture of *R/S* **305** and then transformed into the key silyloxy compound **306** by regiocontrolled monosilylation of the diol **305b**. Reduction of the fully protected lactone **306b** with diisobutylaluminium hydride (DIBAH), Wittig olefination of the intermediate lactol followed by protection of the carboxylic acid with CH_2N_2 and of the hydroxyl group with *t*-butyldimethylchlorosilane produced[287] **307**, which after deprotection[288] yielded PGD_2 (**302**) (isotopic composition: 4% $^2H_2$, 24% $^2H_3$, 62% $^2H_4$, 10% $^2H_5$, less than 0.2% $^2H_6$).

Deuteriated *methyl 9,15-octadecadienoate-6,7-D_2* and methyl *9,12,15-octadecatrienoate-6,7-$^2H_2$* geometric isomers were obtained by Wittig coupling between methyl 9-oxononanoate-6,7-$^2H_2$ and 6-nonenyltriphenylphosphonium bromide[289].

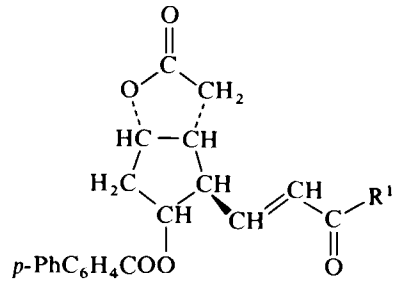
9. Regioselective deuterium labelling of aromatic acids

[*o*-^{2}H]-benzoic acid, sodium [*o*-^{2}H]-benzoate and [*o*-^{2}H]-anisic acid have been synthesized[290,291] with 90–98% regiospecificity from the unlabelled substrates by H/D exchange with D_2O in the presence of Group VIII metal trichlorides, such as $RhCl_3$, $RhCl_3 \cdot 3H_2O$, $RuCl_3$, $IrCl_3 \cdot 3H_2O$ and in the presence of $Ru(acac)_3$, $Rh(NO_3)_3$ and $Ru(Ph_3P)_3Cl_2$. Other Group VIII metal compounds such as $FeSO_4$, $CoCl_2$, $NiCl_2$,



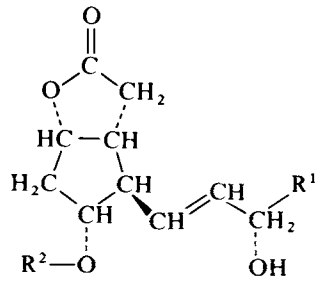
(303) 'Corey aldehyde'

301/NaH



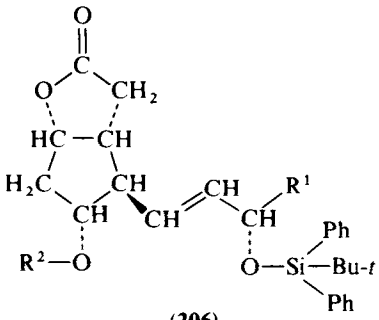
(304) $R^1 = Me(CH^2H)_4^-$

1. $BH_4^-/CeCl_3$
2. separation of 15*S*- and 15*R*-305



15*S*-(305) (a) $R^2 = p\text{-}PhC_6H_4CO$
(b) $R^2 = H$

$ClSi(t\text{-}Bu)Ph_2$

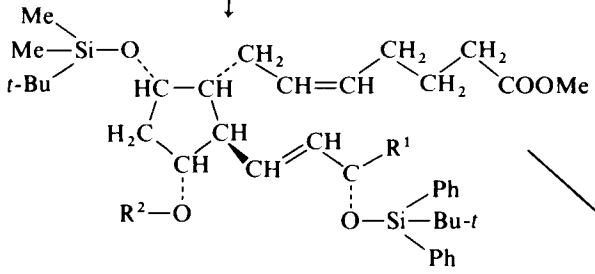


(306)

(a) $R^2 = H$
(b) $R^2 = THP$ (after protection with 3,4-dihydropyran)

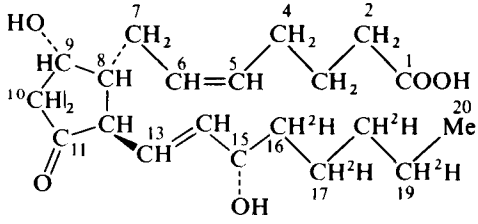
CH_2N_2 | $ClSi(t\text{-}Bu)Me_2$ | DIBAH/−78 °C, $Ph_3P{=}CH(CH_2)_3COO^-$

(161)



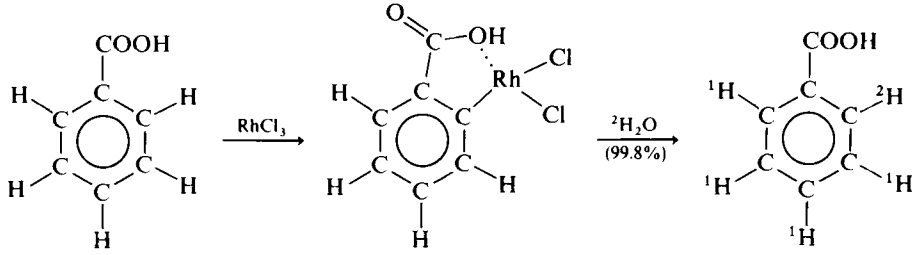
(307) (a) $R^2 = THP$
(b) $R^2 = H$

1. Δ (MeCN, 14–20d)
2. $OH^-/H_2O/MeOH$
3. pyridinium chlorochromate
4. $HF/H_2O/MeCN$



(302) 16,17,18,19-[$^2H_4$]-PGD$_2$

$PdCl_2$, $PtCl_2$, $Rh(Ac)_2$, $Fe(acac)_3$, $Rh(acac)_3$ and $Pd(acac)_2$ were found to be inactive or decomposed rapidly under the reaction conditions. Only about 5% of non-specific H/D exchange has been observed using K_2PtCl_4 and $PtCl_4$. The highly regioselective $RhCl_3$- catalysed deuteration of aromatic carboxylates (equation 162) probably involves a cyclometalation process[292–294], preceded by complex formation (i.e. coordination of the rhodium species with the non-bonding electrons of the carboxyl group[295]).

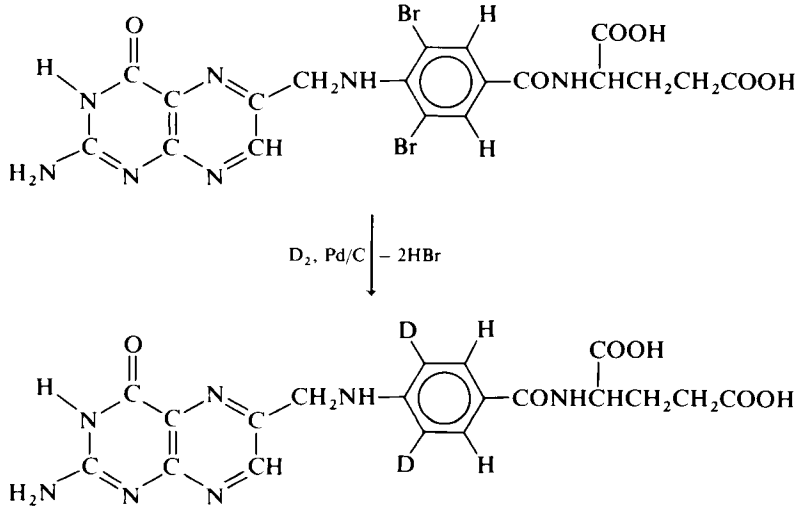


(162)

[$^2H_5$]-benzoic acid and sodium [$^2H_5$]-benzoate used in this study have been obtained via heterogeneous platinum black catalysed exchange of sodium benzoate with excess deuterium oxide[296]. Homogeneous H/D and H/T exchanges are discussed[297] in Section IV.

10. Synthesis of deuterium-labelled folic acid

This acid (**308**), labelled specifically in the metabolically and chemically stable 3′,5′-positions, has been obtained[298] (equation 163) for use in human metabolic studies by catalytic dehalogenation of 3′,5′-dibromofoliate with deuterium gas (66 hours at RT). Using longer reaction times increases the reduction of folic acid to dihydrofolate[299,300].

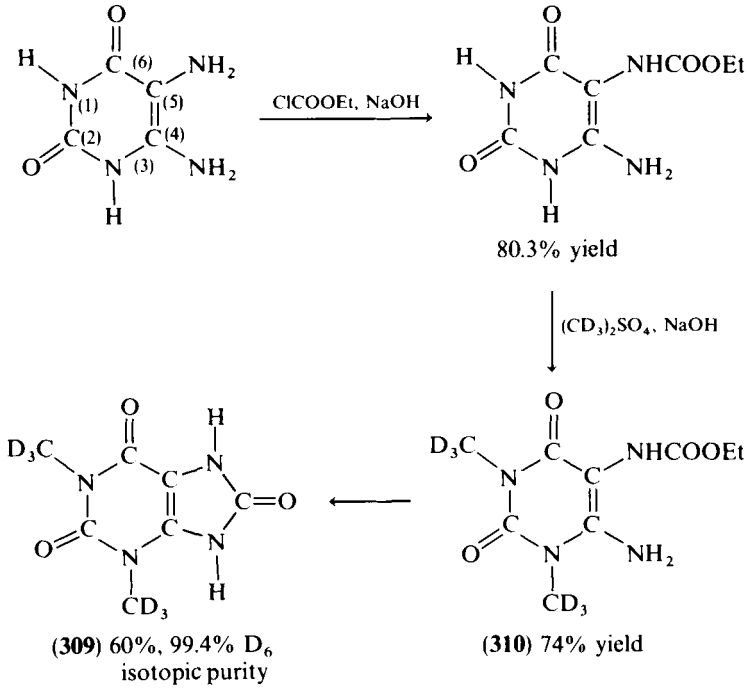


(163)

(308)

11. Synthesis of deuterium-labelled 1,3-dimethyluric acid

1,3-Di(trideuteriomethyl)uric acid (**309**), an analytical internal standard for use in GC-MS-SIM determinations of DMU in human blood and urine, has been synthesized[301] in 60% yield by methylation of 4-amino-5-carbethoxyaminouracil with di(trideuteriomethyl)sulphate followed by cyclization of the dimethylated intermediate **310** by heating (equation 164).



(164)

12. Synthesis of N-(1H-2-oxo-4-pyrimidinyl)-(2-$^2H_2$)-glycine

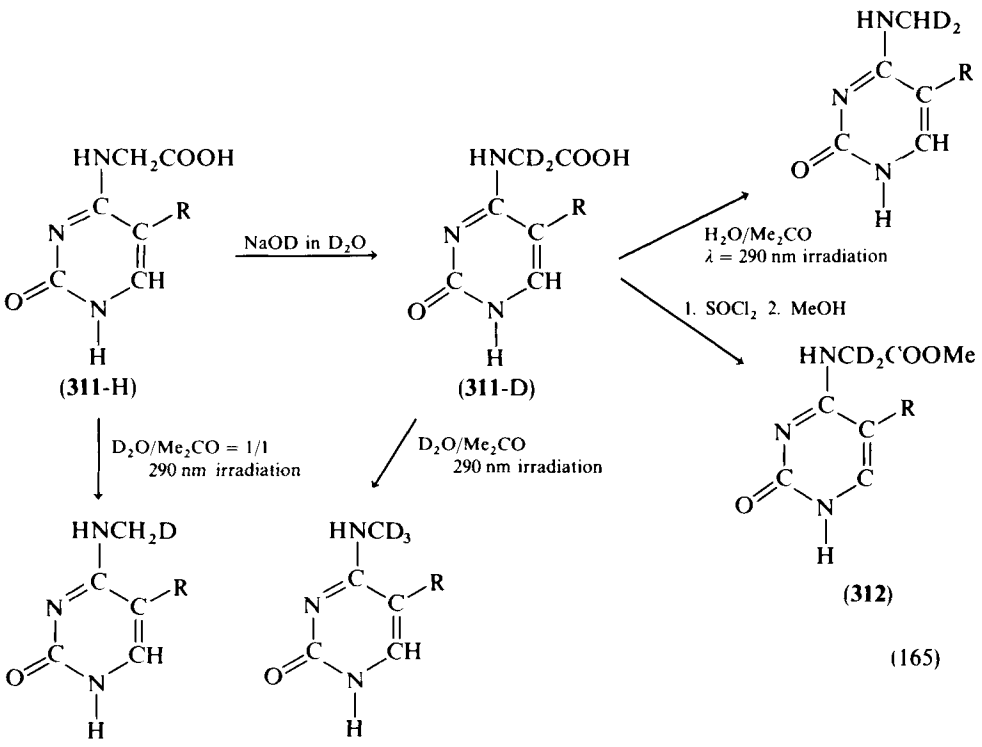
Compound **311**-D has been prepared[302] as an intermediate in the course of the synthesis of mono-, di- and trideuteriated 4-*N*-methylcytosines[302-305] by direct D/H exchange from **311**-H (equation 165).

13. Syntheses of 4'[^{2}H]-uridine and its derivatives

Deuterium has been introduced[306] at the $C'_{(4)}$ position of uridine and its derivatives by B_2D_6 (equation 166). Tritium can be introduced at the $C_{(4)}$ position of pyrimidine in a similar manner. The products were used for mechanistic studies[307,308] of drugs, such as the antitumor antibiotic bleomycin and other DNA-interacting molecules.

14. Synthesis of 2,4-diphenyl-5-ethoxycarbonyl-1-heptadeuteriated isopropyl-2-imidazoline (**315**)

This compound has been prepared[309] in 6% overall yield from heptadeuteriated isopropyl alcohol in six steps given in equation 167 to elucidate the mass fragmentation



(165)

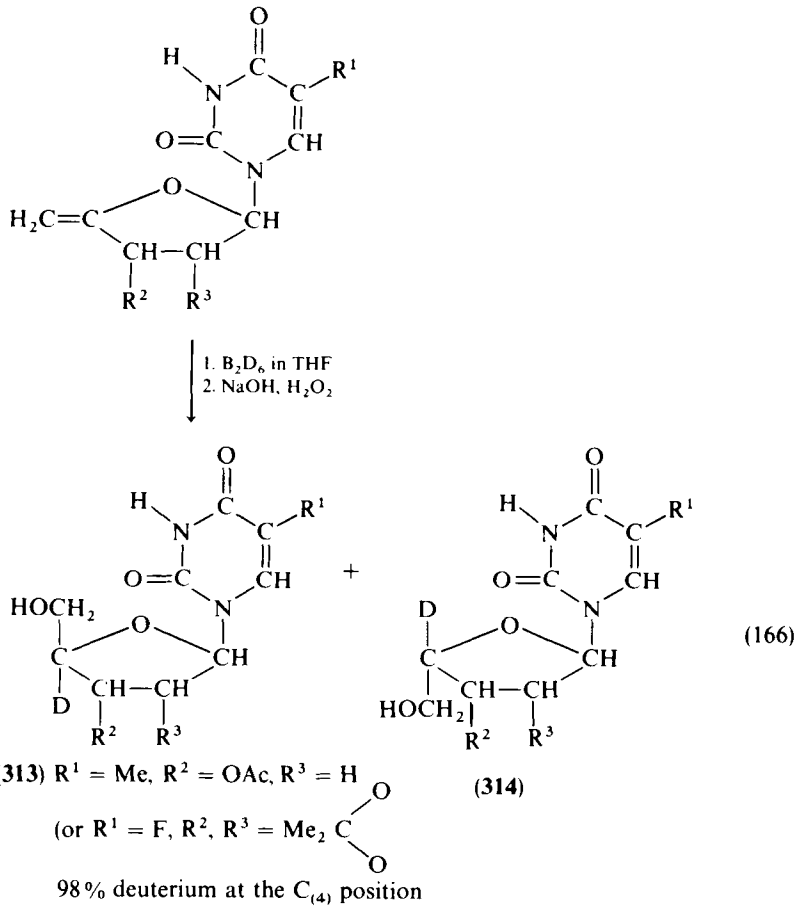
of unlabelled **315**. Ethyl 2-bromo cinnamate (**316**), obtained as shown in equation 167a, has been condensed in the last step with isopropyl benzamidine **317** to give **315**.

15. Synthesis of deuterium-labelled 4-diisopropylamino-2-(2-pyridyl)-2-phenylbutyramide ('disopyramide', 318)

This antiarrhythmic agent[310], radiolabelled[311] with ^{14}C and multilabelled[312] with ^{13}C and ^{15}N, has also been deuteriated[313] in the aromatic ring by H/D exchange. No deuterium exchange has been observed at low (25–90 °C) temperatures, but at 120–130 °C both phenyl and pirydyl protons of **318** were exchanged in $^2H_2SO_4$ (98% of deuterium). No deuterium exchange has been observed with deuteriated trifluoroacetic acid at 100–125°C, although nitrile formation took place. At 150°C substantial decomposition of **318** occurred.

16. Deuteration of 4-haloprolines and 2- or 7-bromocholesterols

The stereochemistry of Pd-catalyzed reductive debromination and deiodination of 4-haloprolines (**319**) and of 7-α-bromocholesterol acetate (**320**) with deuterium gas ($^2H_2$) under low pressure using ^2H NMR has been investigated[314a]. The tosylation of prolines increased the difference between $\delta H_{(4)}$-*trans* and $\delta H_{(4)}$-*cis* enough to be used in a ^2H NMR study of *N*-tosyl-4-deuterio-L-proline methyl ester formed upon reductive diodination of *N*-tosyl-4-*cis*-iodo-L-proline methyl ester. The reactions have been found to be stereoselective but not stereospecific. The stereochemistry of 4-tritio-L-proline, prepared



(313) R^1 = Me, R^2 = OAc, R^3 = H
(or R^1 = F, R^2, R^3 = Me_2C with O, O)
98% deuterium at the $C_{(4)}$ position

(314)

(166)

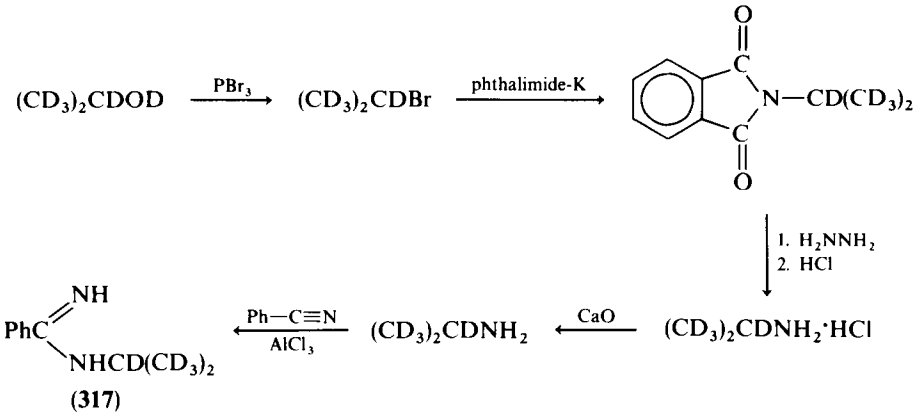
by reductive deiodination of 4-iodo-L-proline, has been studied[314b] and the 4-*cis*-^{3}H/(4-*trans*-^{3}H) ratio was found to be 1:5.

B. Tritium-labelled Carboxylic Acid Derivatives

1. Synthesis of tritium-labelled jasmonic acid, ethyl dihydrojasmonate and itaconic acid

These compounds (**322, 323** and **321**), which are important plant growth[315] regulators, were needed for physiological experiments. They have been tritium labelled[315] with palladium black activated with tritium gas without a tritium atmosphere at room temperature (3–4 hours) in solvents in which the substance to be labelled is soluble (Ethanol for **321** and **322** and ether for **323**). The labelling positions in **321–323** have not been investigated[315].

Radiograms of tritium-labelled **322** and **323** had shown that they are of very high radiochemical purity and need no purification. Lower specific activities in the case of compounds **321** and **322** are probably due to ethanol(hydroxylic solvent), which



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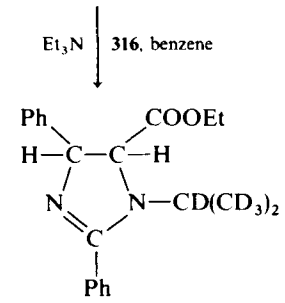
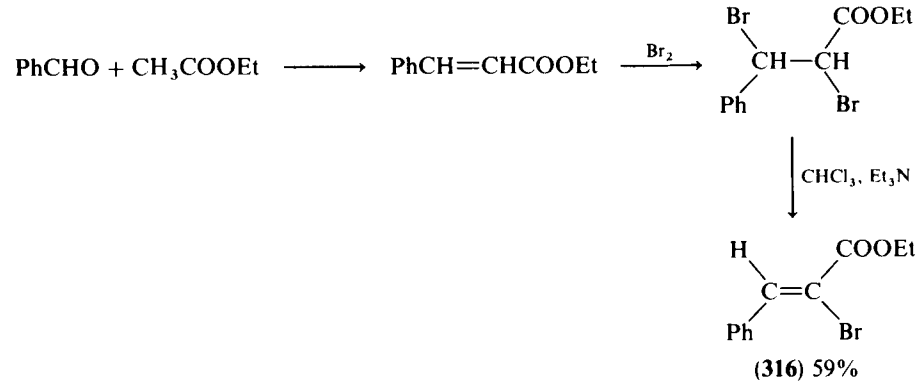
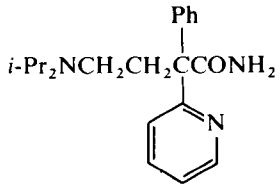


(315) 33%

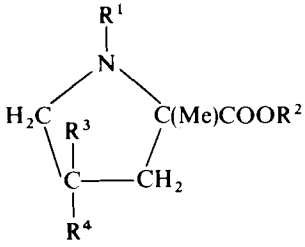


(316) 59%

(167a)

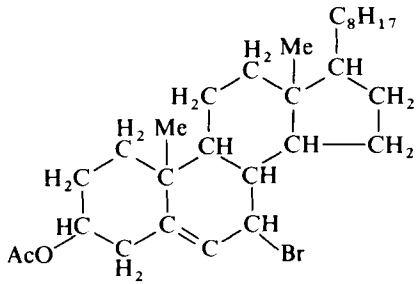


(318)

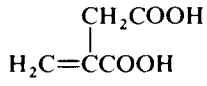


(319)

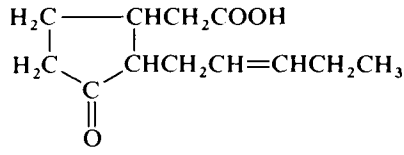
(a) $R^1 = R^2 = R^3 = H$, $R^4 = Br$
(b) $R^1 = R^2 = R^4 = H$, $R^3 = Br$
(c) $R^1 = Ts$, $R^2 = Me$, $R^3 = H$, $R^4 = Br$
(d) $R^1 = Ts$, $R^2 = Me$, $R^3 = Br$, $R^4 = H$
(e) $R^1 = Ts$, $R^2 = Me$, $R^3 = H$, $R^4 = I$
(f) $R^1 = TS$, $R^2 = Me$, $R^3 = I$, $R^4 = H$



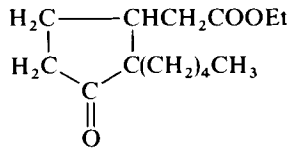
(320)



(321) itaconic acid
sp. acta. 3.1 GBq $mmol^{-1}$



(322) jasmonic acid sp. act.
7.0 GBq $mmol^{-1}$

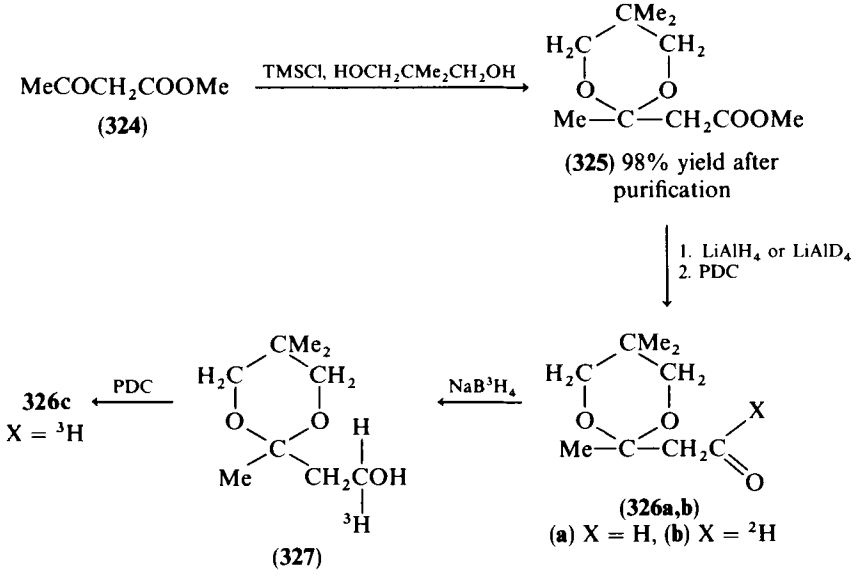


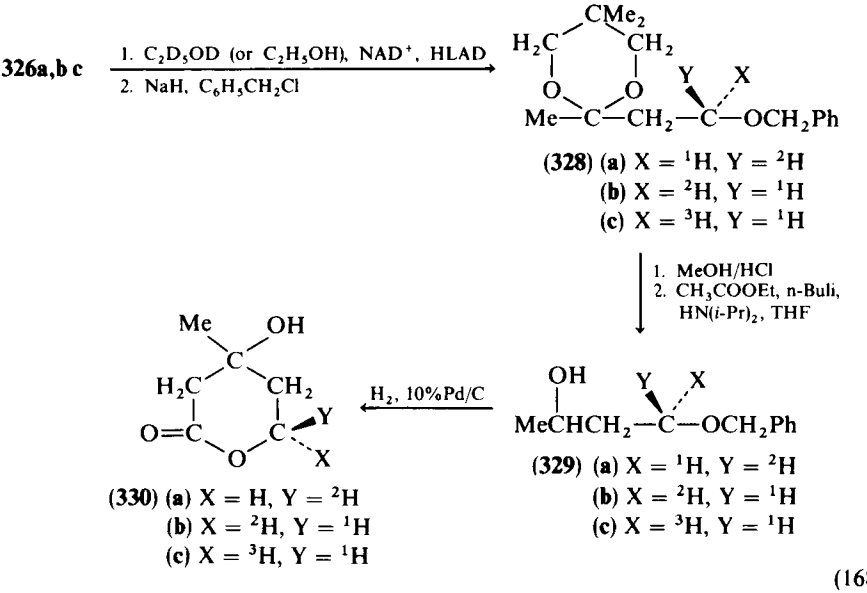
(323) ethyl dihydrojasmonate
sp. act. 34.1 GBq $mmol^{-1}$

exchanges its hydrogens with tritium gas adsorbed on the catalyst reducing its specific activity. The biological behaviour and melting points of the tritiated compounds are identical with those of the unlabelled compounds[315].

2. Stereospecific labelling of mevalonolactone with ^2H and ^3H at the $C_{(5)}$ position

The syntheses of (3*RS*) (5*R*) [5-^{2}H]-, (3*RS*) (5*S*) [5-^{2}H]- and (3*RS*) 5*S*) [5-^{1}H]-mevalonolactones have been achieved[316,317] by combining chemical reactions with an



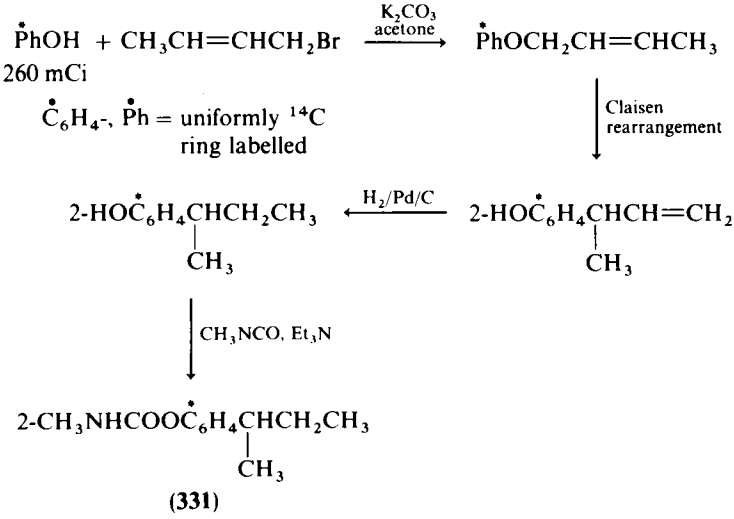


(168)

effective enzymic reduction system[318] eliminating the need to prepare NAD^2H or NAD^3H (equation 168). Commercially available methyl acetoacetate **324** has been converted[319] to 2,5,5-trimethyl-2-carbomethoxyl-1,3-dioxane (**325**), which in turn has been first reduced with $LiAlH_4$ or $LiAlD_4$ and then oxidized with pyridinium dichromate (PDC) to give the aldehyde **326a** or **326b**. **326c** has been prepared by reducing **326a** with NaB^3H_4 to [1-^{3}H]-2-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethanol (**327**) and its subsequent reoxidation with PDC. **326a,b,c** have been reduced enzymatically with horse liver alcohol dehydrogenase (HLAD) to the corresponding chiral alcohols, **328a–c**. Deprotection of **328a–c** and subsequent condensation of the resulting ketone with ethyl acetate and LDA gave **329a**, **329b** and **329c**, each in 93% yield. Debenzylation of **329a–c** by hydrogenolysis on a palladium catalyst produced (3*RS*) (5*R*) [5-^{2}H]-mevalonolactone (**330a**), (3*RS*) (5*S*) [5-^{2}H]-mevalonolactone (**330b**) and (3*RS*) 5*S*) [5-^{3}H]-mevalonolactone (**330c**) in 86% yields. The structures of all intermediates had been assigned by IR and (^{1}H-NMR) analyses and by mass spectrometry. Specific activity of **330c** was 20.5 μCi μmol^{-1}.

3. Synthesis of ^{14}C- and ^{3}H-labelled 2-sec-butylphenyl N-methyl carbamate (BPMC)

This carbamate-type insecticide (**331**) has been ^{14}C and tritium labelled at metabolically stable positions (for a study of its metabolic fate)[320,321] as shown in equations 169 and 170. [^{3}H]BPMC, 2-(1-methyl[2,3-^{3}H]propyl)phenyl methyl carbamate (**332**), was prepared following equation 170 and had specific activity 58 Ci mmol^{-1} and radio purity higher than 98%.



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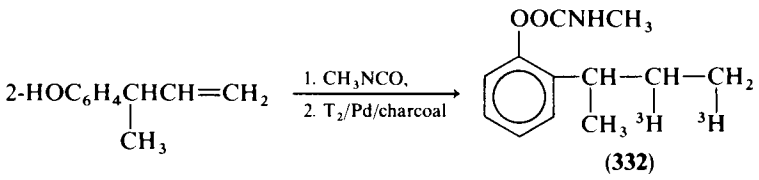
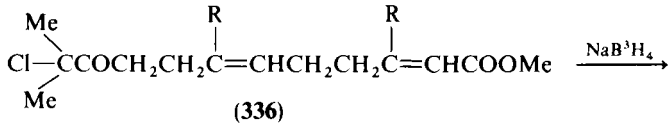


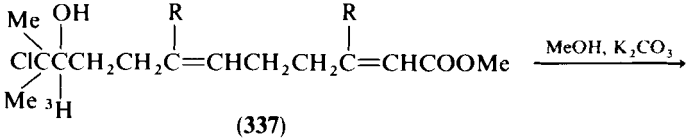
(170)

4. Synthesis of (10R, S)-[10-^{3}H]juvenile hormone and its conversion to methyl (2E, 6E)-[10-^{3}H]farnesoate and to (2E, 6E)-[10-^{3}H]farnesol]

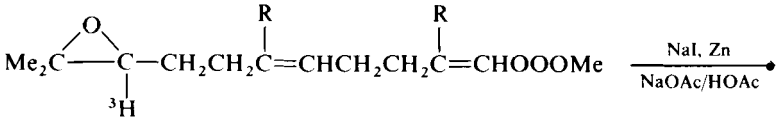
These compounds, **333**, **334** and **335**, have been prepared[322] according to equation 171. Methyl (2*E*, 6*E*)-11-chloro-3,7-diethyl-11-methyl-10-oxo-2,6-tridecadienoate (**336**), prepared by Anderson and coworkers[323], was reduced to the corresponding chlorohydrine (**337**) and then transformed to the [10-^{3}H]juvenile hormone **333**. Reduction of **333** yielded methyl[10-^{3}H]farnesoate **334** and further reduction gave [10-^{3}H]farnesol [(2*E*, G*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-ol], **335**. Similar reactions provided racemic **338**-*cis*- and **338**-*trans*-[10-^{3}H]JHO[322].



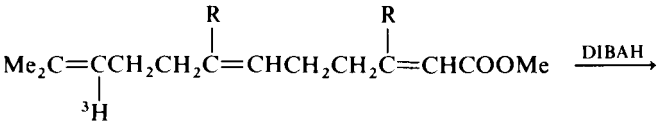
(**336**)



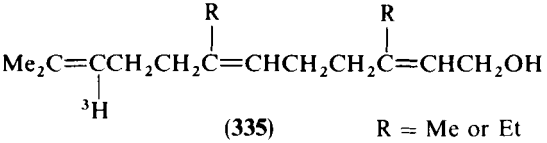
(**337**)



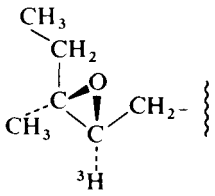
(**333**) 54%, sp. act. 1.4 Ci mmol^{-1}



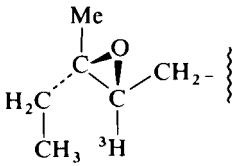
(**334**) 40% yield, sp. act. 1.7 Ci mmol^{-1}
98% radiochem. purity



(**335**) R = Me or Et (171)



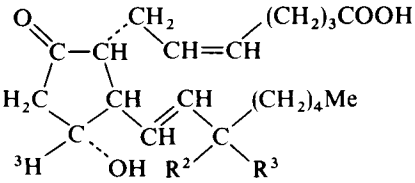
(**338**)-*cis* JHO



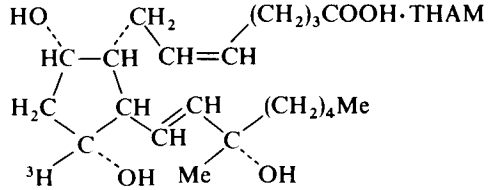
(**338**)-*trans* JHO

5. Synthesis of tritium-labelled arbaprostil and related 15-methyl prostaglandins

Arbaprostil, 15(*R*)-15-methyl prostaglandin E_2 (**339**), a gastric and duodenal cytoprotective antiulcer agent[325], also inhibits gastric secretion and is chemically related to the tris-(hydroxymethyl)aminomethane (THAM) salt **340**; a potential antifertility agent has been labelled[324] with tritium at the C-11 position (equation 172).



(**339**) (**a**) R^2 = OH, R^3 = Me, R^1 = ^3H (at $C_{(11)}$) or R^1 = ^1H
(**b**) R^2 = Me, R^3 = OH, R^1 = ^3H (at $C_{(11)}$) or R^1 = ^1H



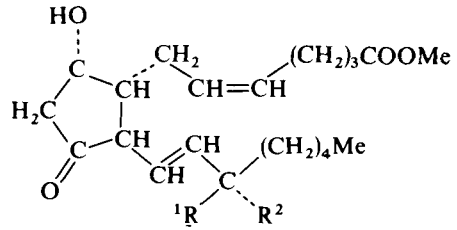
(**340**) THAM = 2-Amino-2-(hydroxymethyl)-1,3-propanediol

Reduction of 15(*R*)-15-methyl-PGD_2 methyl ester (**341a**) with sodium borotritide yielded **342a**, which on selective sililation at the $C_{(11)}$ hydroxy group gave 15 (*R*)-15-methyl- [11β-^{3}H]PGF_{2a} methyl ester 11-trimethylsilyl ether (**344a**). Oxidation of **344a** provided 15(*R*)-15-methyl-[11β-^{3}H]PGE_2 methyl ester 11-trimethylsilyl ether (**345a**) which on mild desilylation with citric acid gave 15(*R*)-15-methyl-[11β-^{3}H]PGE_2 methyl ester (**346a**). Hydrolysis of the PGE_2 ester with esterase derived from the coral *P. homomalla*, without causing dehydration of the acid- and base-sensitive β-hydroxy-ketones, produced 15(*R*)-15-methyl-[11β-^{3}H]PGE_2 ([11-^{3}H]Arbaprostil, **339a**) of 1.95 Ci mmol^{-1} specific activity. Synthesis of **339b** (specific activity 6.25 mCi mg^{-1}) from **342b** and from **341b** was analogous. All tritium-labelled intermediates decomposed at a rate of about 2.3% per month in 25 mCi ml^{-1} ethanol solution at -20 °C, but only at 0.18% per month in 0.3 mCi ml^{-1} solution.

6. Synthesis of isotopically labelled retinoids

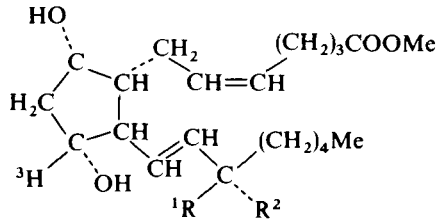
a. Retinyl acetate (**347**) has been tritium labelled at the $C_{(11)}$ and $C_{(12)}$ positions[326] by partial reduction of oxenin (**348**) with tritium gas followed by acetylation of the hydroxenin(11,12-$^3H_2$) obtained and its rearrangement. Alkaline hydrolysis of **347** yielded retinol **349** (very unstable under β-self-radiolysis conditions) which has been transformed into esters (**350a–c**) or has been oxidized to the all *trans* retinoic acid[11,12-$^3H_2$- (**351**) (equation 173).

b. Synthesis of ^{14}C-labelled retinoic acid. 13-*Cis* retinoic acid has been labelled with ^{14}C in the 6 and 7 positions[327]. In metabolic studies this acid[328] remained largely intact, and hence 13-*cis retinoic acid* (**352**) labelled with ^{14}C at the $C_{(14)}$ position has been

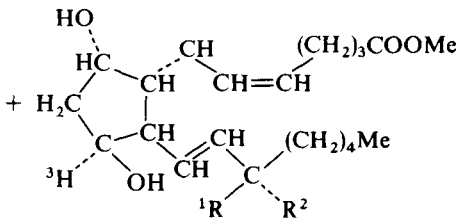


NaB^3H_4

(**341**) (**a**) $R^1 = OH$, $R^2 = Me$
(**b**) $R^1 = Me$, $R^2 = OH$



(**342**) (**a**) $R^1 = OH$, $R^2 = Me$, 44% total radiochem. yield sp. act. 1.95 Ci mmol^{-1}
(**b**) $R^1 = Me$, $R^2 = OH$

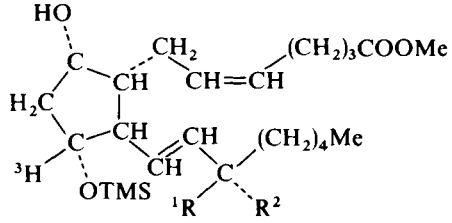


(**343a**) $R_1 = OH$, $R^2 = Me$
(**343b**) $R^1 = Me$, $R^2 = OH$

342 —(1. KOH 2. THAM, MeCN/DMSO)→ **340**

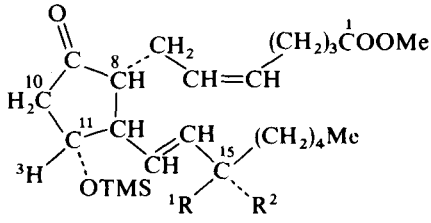
65.8% yield based on **342B**.
sp. act. 393 mCi mmol^{-1}

TMSDEA = *N*-trimethylsilyldiethylamine



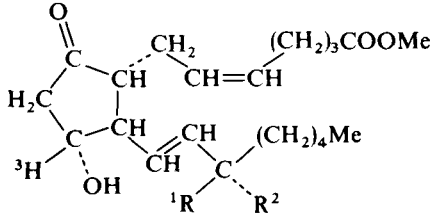
(**344**) (**a**) $R^1 = OH$, $R^2 = Me$
(**b**) $R^1 = Me$, $R^2 = OH$

CrO_3, Py, CH_2Cl_2



(**345a**) $R^1 = OH$, $R^2 = Me$
(**345b**) $R^1 = Me$, $R^2 = OH$

citric acid

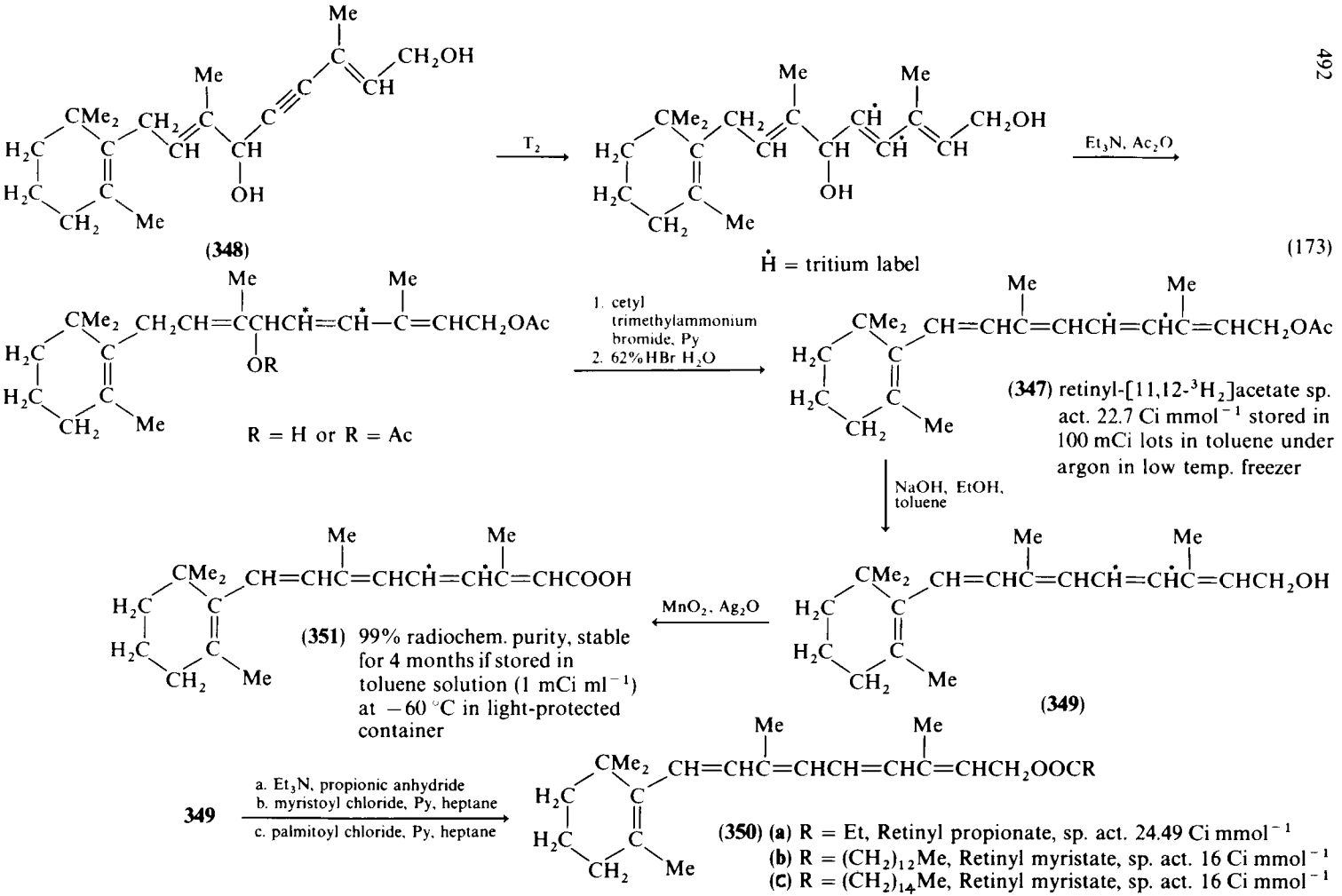


(**346a**) $R^1 = OH$, $R^2 = Me$
(**346b**) $R^1 = Me$, $R^2 = OH$

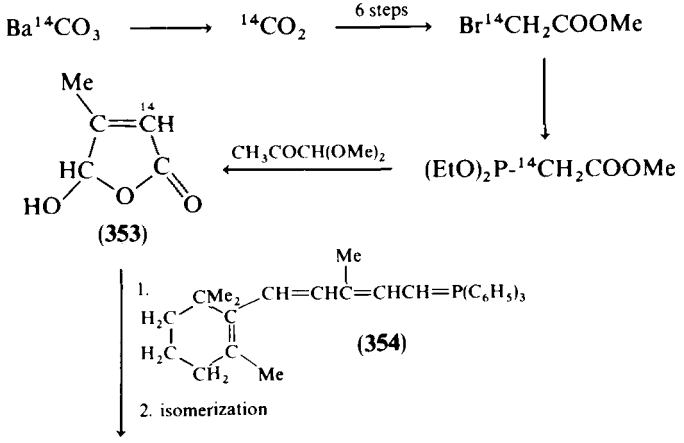
339a,b

Carol P homomalla esterase, H_2O/Me_2CO

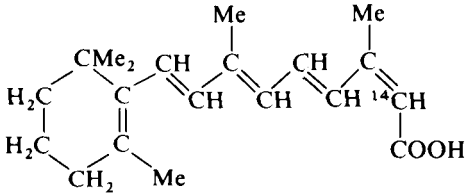
(172)


(348)
T2
Ḣ = tritium label
Et3N, Ac2O
R = H or R = Ac
1. cetyl trimethylammonium bromide, Py
2. 62% HBr H2O
(347) retinyl-[11,12-3H2]acetate sp. act. 22.7 Ci mmol−1 stored in 100 mCi lots in toluene under argon in low temp. freezer
NaOH, EtOH, toluene
(349)
MnO2, Ag2O
(351) 99% radiochem. purity, stable for 4 months if stored in toluene solution (1 mCi ml−1) at −60 °C in light-protected container
349
a. Et3N, propionic anhydride
b. myristoyl chloride, Py, heptane
c. palmitoyl chloride, Py, heptane
(350) (a) R = Et, Retinyl propionate, sp. act. 24.49 Ci mmol−1
(b) R = (CH2)12Me, Retinyl myristate, sp. act. 16 Ci mmol−1
(c) R = (CH2)14Me, Retinyl myristate, sp. act. 16 Ci mmol−1

(173)



(174)



(352) sp. act. 537 mCi mmol^{-1}

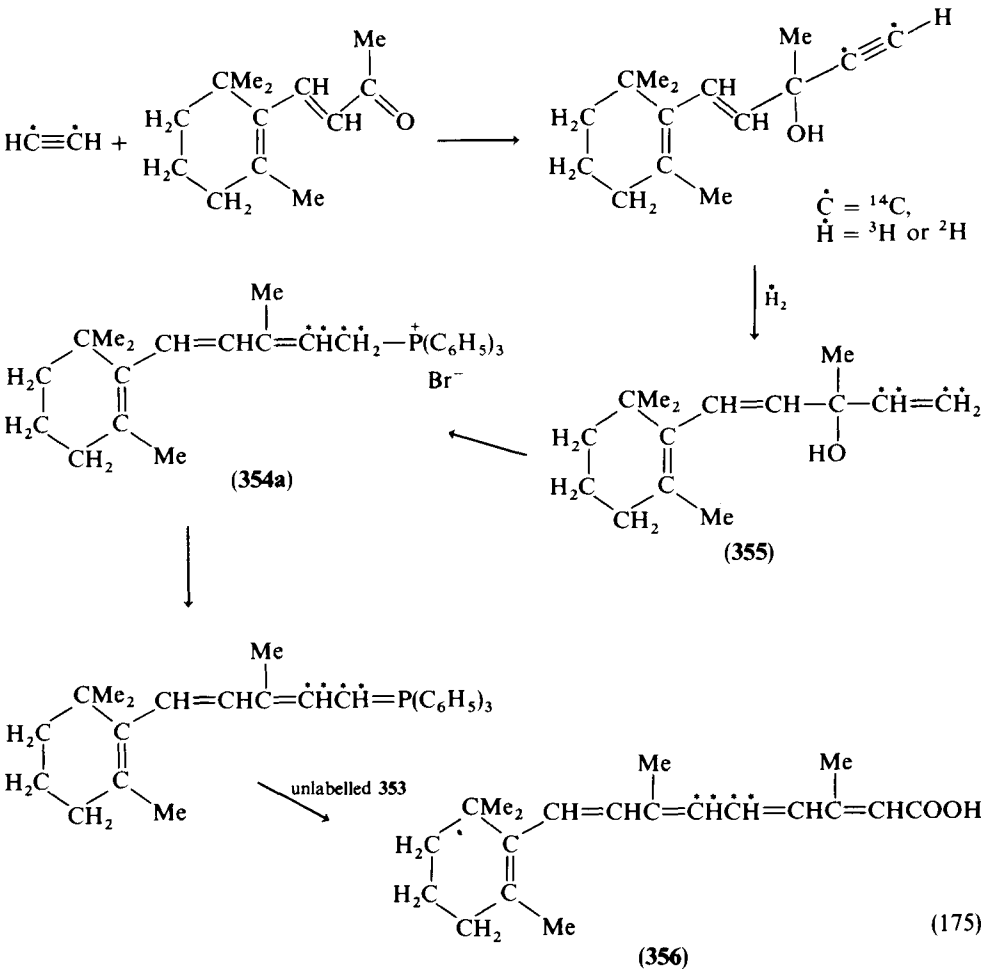
synthesized also (equation 174). The ^{14}C-labelled butenolide (**353**) has been prepared as shown and in the last step the Wittig reagent **354** gave the ^{14}C-acid **352**.

The phosphonium salt **354a** was prepared either using ^{14}C-labelled acetylene (equation 175) and/or tritium or deuterium to produce the labelled olefin **355**, which has been utilized in the synthesis of D/T and ^{14}C-labelled all-*trans* retinoic acid[329,330] (**356**, equation 175).

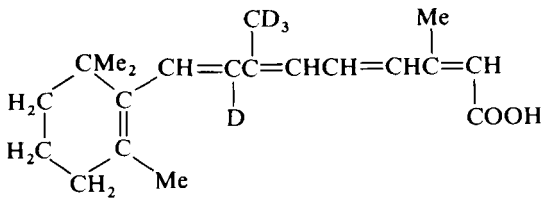
c. Deuterium-labelled 13-cis Retinoic-(8,9,9,9-methyl)-$^2H_4$ acid (**357**) and *4-oxo-13-cis retinoic-8,9,19-*$^{13}C_3$*-acid* (**358**) have also been prepared[327] starting with perdeuterated acetone, $(CD_3)_2C{=}O$, or with acetone-1,2,3-$^{13}C_3$, $(\overset{*}{C}H_3)_2\overset{*}{C}{=}O$, and with the aldehyde **359** in the first condensation step.

7. Synthesis of tritiated and deuteriated homovanillic acids (HVA)

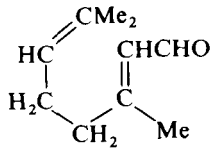
4-Hydroxy-3-methoxyphenylacetic acid (**360**) has been tritiated[331] and deuteriated[331,332] by T/H or D/H exchange of all aromatic hydrogens and the methylene hydrogens with T_2O or with D_2O, catalyzed by sulphuric acid (equation 176). The protons of the methoxy-methyl group of HVA did not exchange with D_2O in the above experimental conditions. The specific activity of the product **360** is limited only by the specific activity of the tritiated water. This allowed the reinvestigation of the possible routes of elimination of HVA involved in the test studies with deuterated HVA[332,333]. No back H/T exchange has been found between HVA tritiated in stable positions and 0.1 N HCl at room temperature. Limited tritium exchange occurs between tritiated HVA and 0.1 N NaOH at room temperature involving only the tritons on the α-carbon, but this will not be significant under physiological conditions.



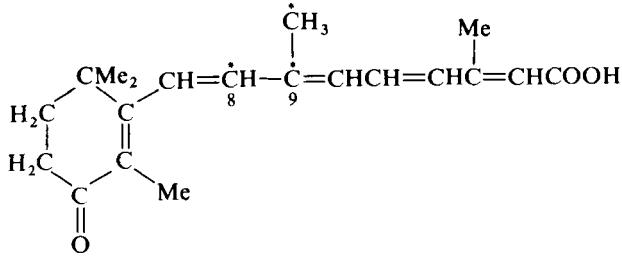
(175)



(357) 94% D_4

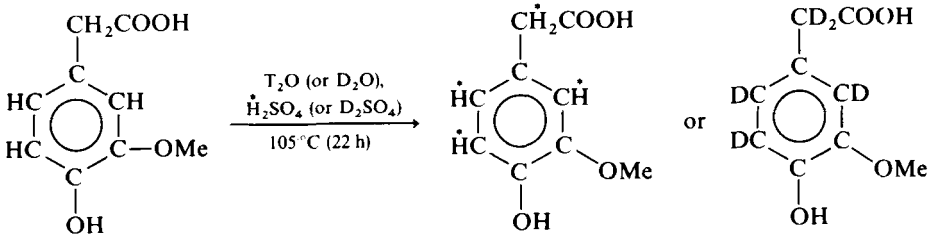


(359)



(358) 99% (^{13}C)

$\dot{C} = {}^{13}C$



HVA

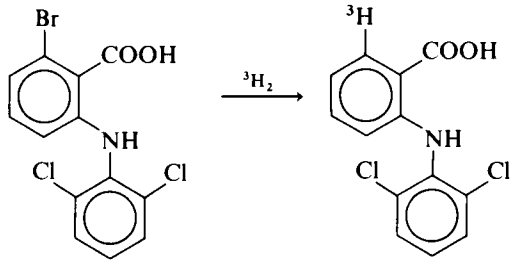
(360) sp. act. 25.2 mCi $mmol^{-1}$ 50% yield, based

(176)

8. *Tritium labelling by selective debromination*

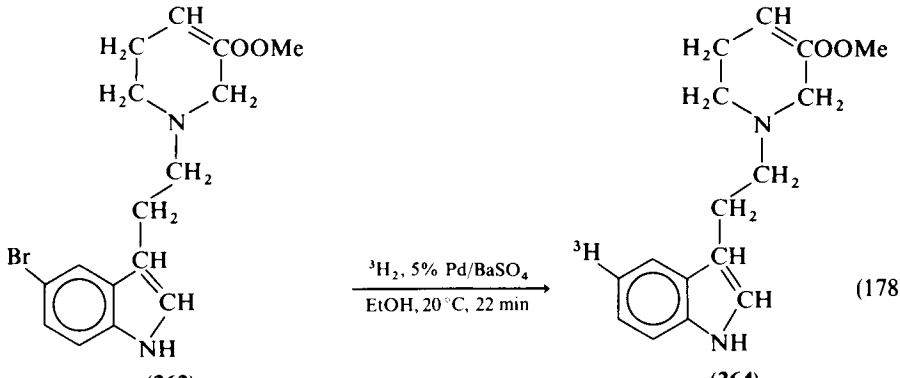
Several important drugs containing chlorine (for instance, diclofenac **361**) have been labelled with tritium (specific activities up to 10–28 Ci $mmol^{-1}$) by selective catalytic debromination even in the presence of chlorine in the molecule[333–336] since the ease of dehalogenation is related inversely to the carbon–halogen bond strength. Thus [^{3}H]Diclofenac **361** sodium has been prepared[337] by selective reduction of **362** with ^3H gas (8 Ci) in the presence of 5% $Pd/BaSO_4$ (equation 177).

361 was stored at −196 °C in liquid N_2 as its Na salt. Similarly compound **363** has been hydrogenated with $^3H_2$ gas (equation 178) to **364**. The latter compound has been stored at −196 °C in ethanol.



(177)

(362) (361) 54.8% sp. act. 9.7 Ci mmol^{-1} TLC purity 97.9%



(178)

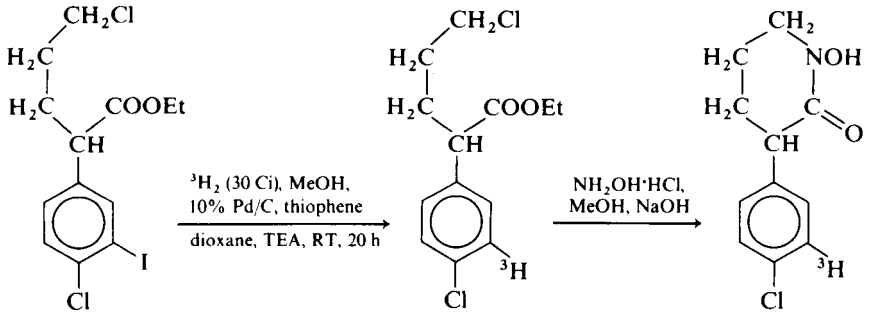
(363) (364) [^{3}H]CGP 22848, 15% sp. act. 24 Ci mmol^{-1}

9. Synthesis of 1-hydroxy-3-[3-^{3}H]-(4-chlorophenyl)-2-piperidone (**365**)

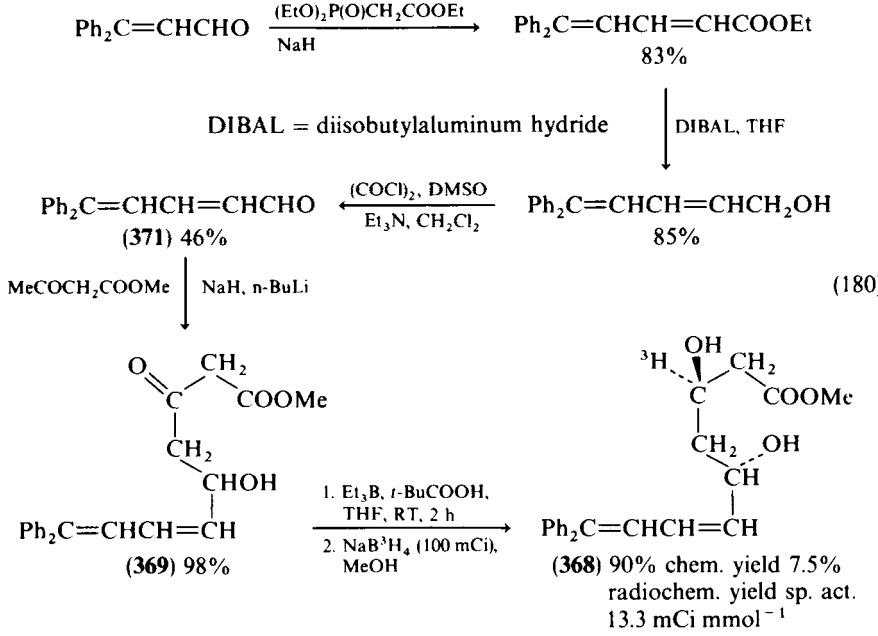
This potential topical anti-inflammatory agent has been tritium labelled[338,339] on the benzene ring in a position neighbouring the chlorine atom by selective iodine–tritium replacement (equation 179) of the iodinated precursor **366**. The tritium–iodine exchange reaction has been carried out in mild conditions[340] to avoid replacement of the chlorine. Ethyl-5-chloro-[2-([3-^{3}H]-4-chlorophenyl)] pentanoate (**367**) has been cyclized to hydroxamic acid **365** in the presence of hydroxylamine in very good chemical yield and radiochemical purity.

10. Synthesis of tritium-labelled (3R, 5S)-3,5-dihydroxy-9,9-diphenyl-6,8-nonadienoate (**368**)

This inhibitor of cholesterol biosynthesis (CoA reductase inhibitor), halting and reversing[341] atherosclerosis, has been tritium labelled at $C_{(3)}$ (equation 180) in order to investigate tissue selectivity and the relation between structure and tissue distribution of the drug. Diastereoselective introduction of the tritium label to **368** has been achieved



(179)

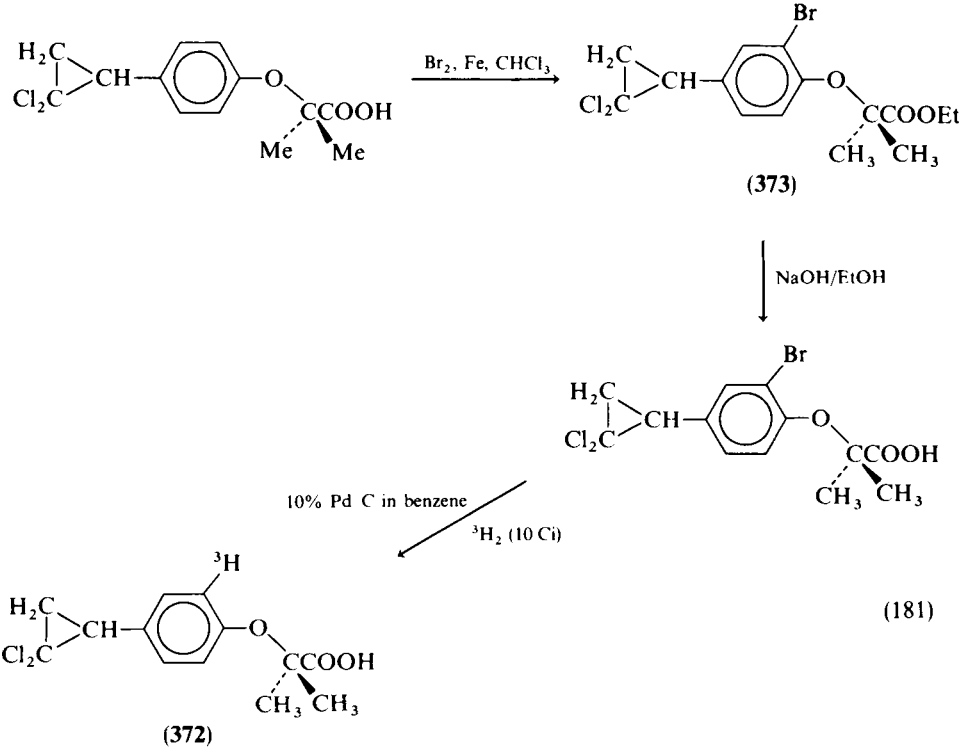


(180)

by reduction with tritium-labelled sodium borohydride of the complex formed in anhydrous THF by adding to (*E*)-5-hydroxy-9,9-diphenyl-3-oxo-6,8 nonadienoic acid (**369**) triethylborane and a catalytic amount of pivalic acid under nitrogen. The reduction of **369** gave the product **368** in 95% radiochemical purity. The method outlined by equation **180** may be applicable to the preparation of other radiolabelled HMG (Gonadotropin)–CoA reductase inhibitors possessing a 3,5-dihydroxy acid moiety.

11. Synthesis of tritiated ciprofibrate and cadralazine

[^{3}H]ciprofibrate (2-[2-^{3}*H*-4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid (**372**), a novel hypolipidemic agent[342], has been prepared[343] according to equation 181 which involves bromination of ciprofibrate[343b], rapid hydrolysis of ester **373** to **374** and its catalytic tritiodehalogenation to **372** having specific activity of 8.0 Ci mmol^{-1}, in 93–95% yield. After 3 years of storage in ethanol at − 20 °C the radiochemical purity of **372** decreased from 95% to 84%.

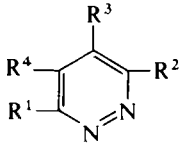


(373)

(372)

(181)

Catalytic dehalogenation has also been employed for synthesis of [^{3}H]cadralazine[344,345] (**374**) which is of potential use in hypertension and exhibits prolonged duration of action[344]. Cadralazine labelled in the side chain has been obtained by reduction of the ketone **375** with sodium borotritide[345] (equation 182).



R^1 = N(Et)CH_2CHOHCH_3
R^2 = NHNHCOOEt
R^3 = H, R^4 = ^{3}H or ^{1}H

(**374**) sp. act. 18 Ci mmol^{-1}
of (4(5)-[^{3}H] Cadralazine)

Ketone **375**: $R^1 = N(Et)CH_2COCH_3$, $R^2 = NHNHCOOEt$, $R^3 = H$ ('ISF 3623')

↓ (sodium bororitide (1 Ci))

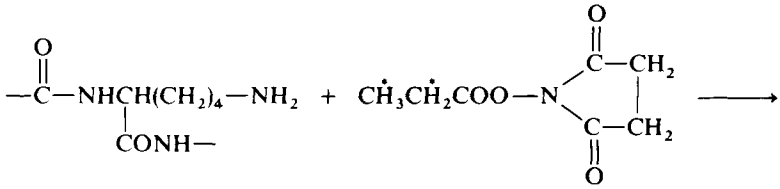
(182)

3-(*N*-Ethyl-*N*-(2-[^{3}H]-2-hydroxypropylamino)-6-(2'-ethoxycarbonyl)hydrazino)pyridazine

sp. act 18 Ci mmol^{-1}, radiochem. purity 95%.

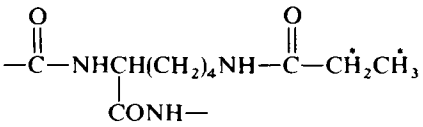
12. Synthesis of N-succinimidyl[2,3-^{3}H]propionate (NSP, **376***)*

[2,3-^{3}H]NSP is used for labelling and detection of sub-microgram quantities of proteins. It has been obtained[346] from *N*-hydroxysuccinimide with [2,3-^{3}H]propionic acid and has been applied to introduce a tritium label into the epsilon amino group of lysine in proteins (equation 182a). Thiol reagents (often used to stabilize some proteins) have to be absent when labelling with **376**.



(376)

(182a)

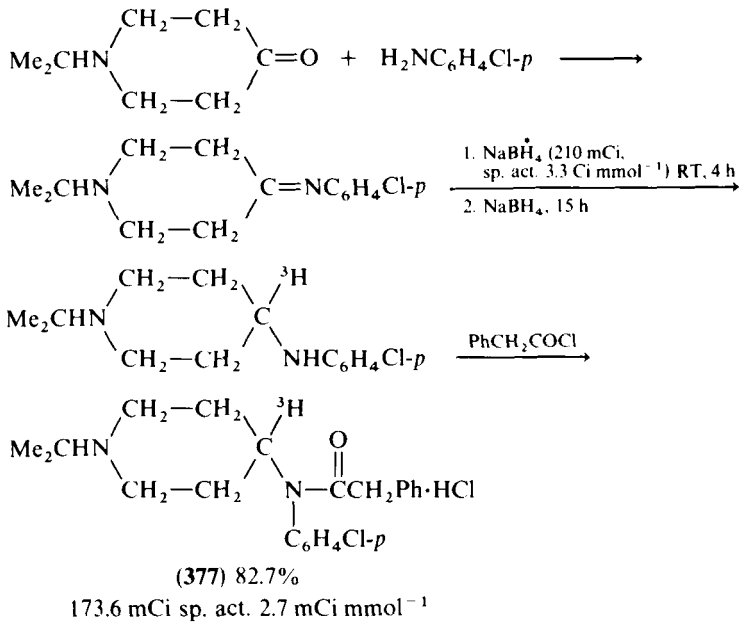


13. Synthesis of ^{3}H-lorcainide monohydrochloride (R 15 889)

This compound, *N*-(4-chlorophenyl)-*N*-[1-(1-methyl ethyl)-4-piperidinyl-4-^{3}H]benzeneacetamide monohydrochloride (**377**), a new orally administered potent and long-lasting antiarrhythmic drug, has been tritium labelled[347] in the 4-position (which is minimally subjected to metabolic attack) of the piperidine ring in a two-step reaction[348,349] (equation 183) utilizing tritiated borohydride[348], and isolated as the radiochemically pure monohydrochloride salt used subsequently for various pharmacokinetic and biotransformation studies.

14. Synthesis of tritium-labelled Ropivacaine

(*S*)-*N*-(2,6-Dimethylphenyl)-1-propyl-[4,5-^{3}H]piperidine-2-carboxamide (Ropivacaine) hydro-chloride monohydrate [(*S*)-**378**], exhibiting local anaesthetic properties[350], has been labelled exclusively in the piperidine ring[351] by tritiation of racemic *N*-(2,6-



(183)

(**377**) 82.7%
173.6 mCi sp. act. 2.7 mCi mmol^{-1}

dimethylphenyl)-1,2,3,6-tetrahydropyridine-2-carboxamide (**379**) followed by alkylation with 1-iodopropane and resolution of the racemic mixture **378** into labelled enantiomers by preferential crystallization with added carrier (equation 184). Specific activity of (*S*)-**378** was 1.83 Ci mmol^{-1}, radiochemical purity 98% and enantiomeric purity 100%. (*R*)-**378** of 97% enantiomeric purity has also been isolated (specific activity 866 mCi mmol^{-1} in radiochemical purity $\geqslant$99%).

15. Synthesis of tritiated functionalized congeners of 1,3-dipropylxanthine

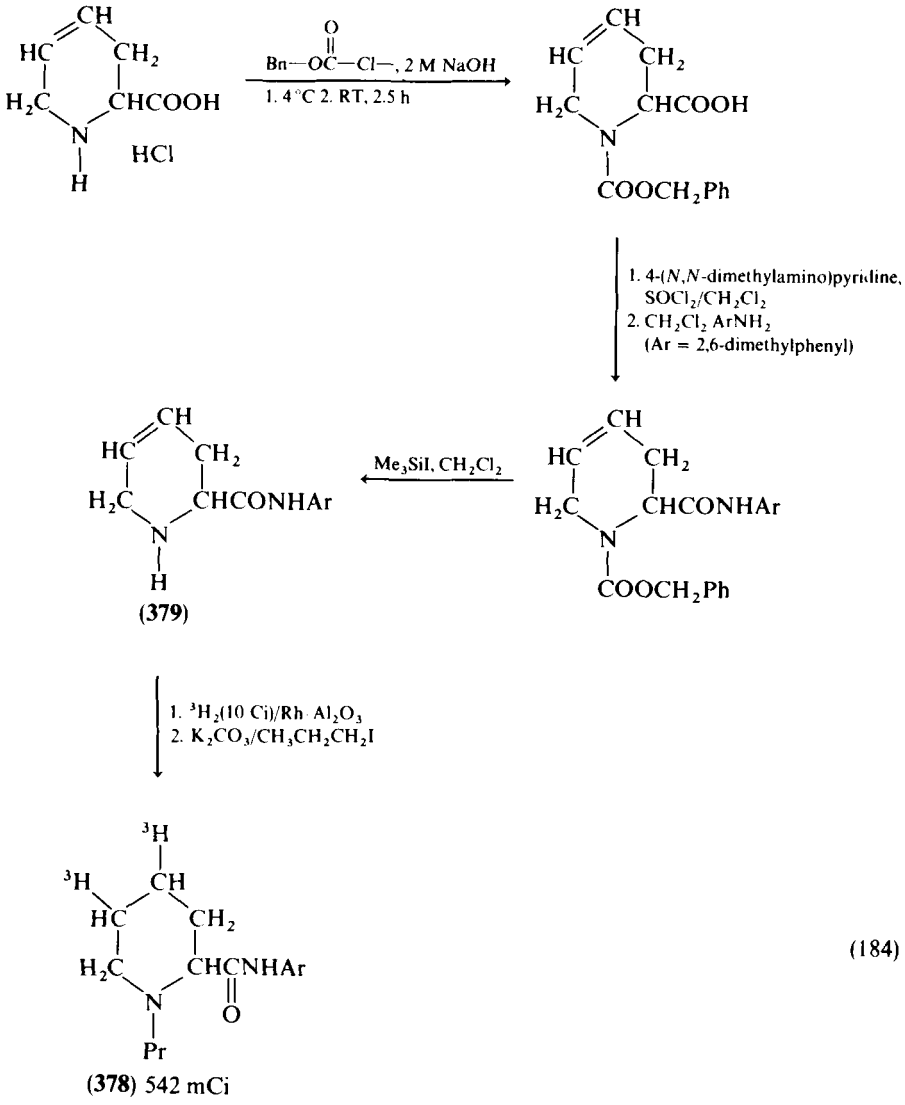
Two potent ligands **380** and **381** for adenosine receptors have been tritium labelled in four positions of the n-propyl groups by catalytic reduction of 1,3-diallyl precursors[352]. Both are structurally related to 1,3-dipropyl-8-phenylxanthine (equation 185). Bindings of both radioligands were studied in membrane preparations of rat brain and were found to satisfy essential criteria for the identification of membrane bound receptors. The diallyl precursors **382** and **383** bound much more weakly to adenosine receptors.

16. Synthesis of [^{3}H]MTP-cephalin (CGP-19835)

Tritium-labelled MTP-cephalin (**384**), showing biological response modifying activities, has been synthesized[353] by direct coupling of highly-tritiated muramyl dipeptide with alanyl-cephalin (equation 186). **384** has prophylactic and therapeutic activities[354]. [^{3}H]MDP (**385**) has been synthesized earlier[355].

17. Synthesis of [^{3}H]-Carbamazepine

10-[^{3}H]-5*H*-dibenz[*b*, *f*]azepine-5-carboxamide (**386**), the active substance of Tegretol^R (used in the treatment of epilepsy and trigeminal neuralgia), has been prepared[356]



(379)

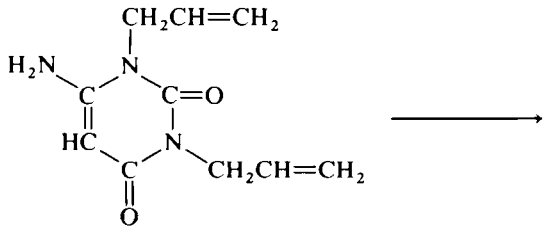
(378) 542 mCi

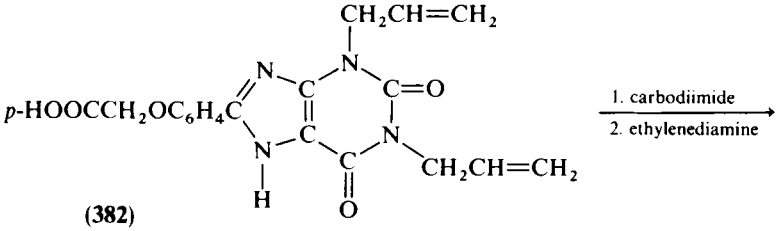
(184)

from its 10-bromo analogue by selective reduction with tritium gas (equation 187), to study the interaction of this drug at the level of the receptor.

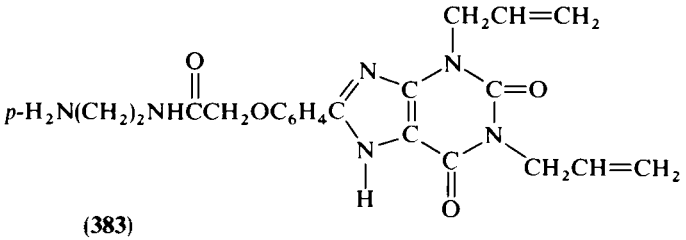
18. Synthesis of perdeuterio-^{15}N-(1-oxyl-2,2,6,6-tetramethyl-4-piperidinyl)maleimide

An improved synthesis (equation 188) of this ^{15}N and ^{2}H isotopically labelled spin label **387** was devised to increase the resolution and sensitivity of EPR measurements[357]. The ^{15}N- and ^{2}H-labelled acid **388**[358] has been cyclized to give **387**.

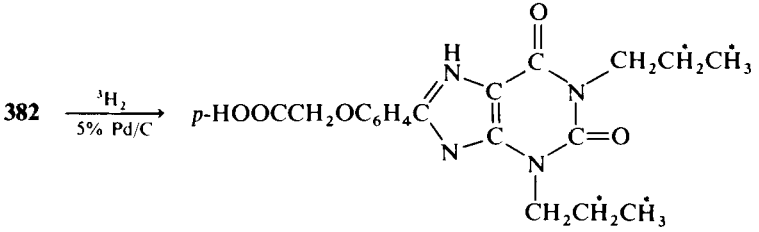




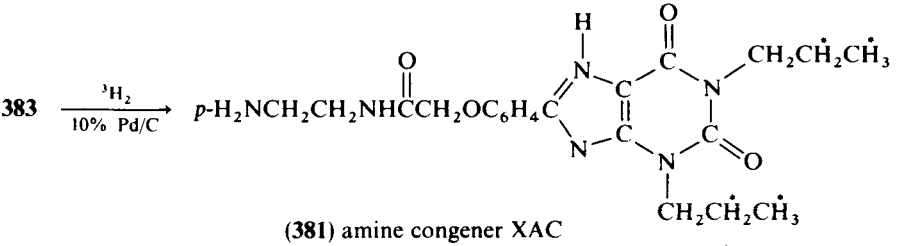
(382)



(383)

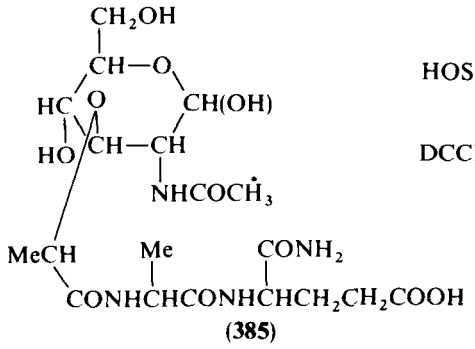


(380) carboxylic congener, sp. act. 149 Ci mmol^{-1}



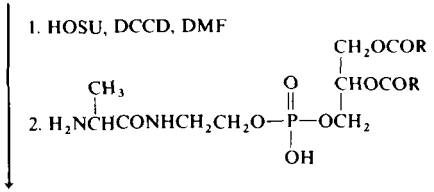
(381) amine congener XAC
sp. act. 103 Ci mmol^{-1}

$\dot{H}$ = tritium label

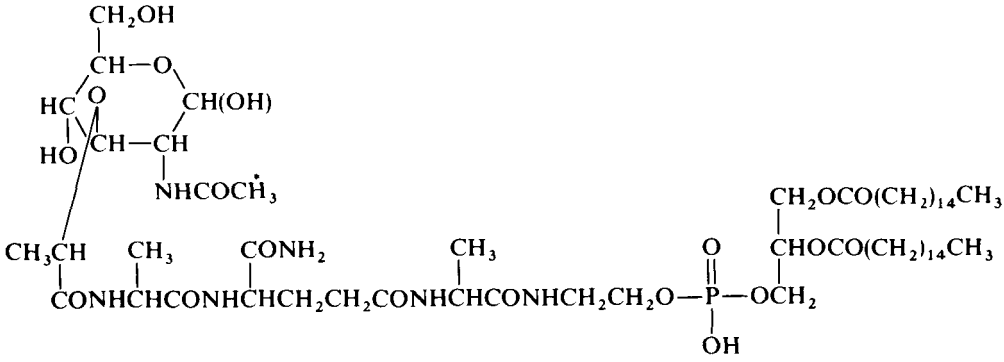


HOSU = *N*-hydroxysuccinimide used for activation of γ-carboxyl group
DCCD = 1,3-dicyclohexylcarbodiimide

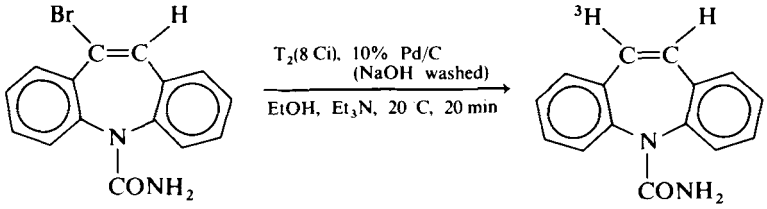
(385)



(186)

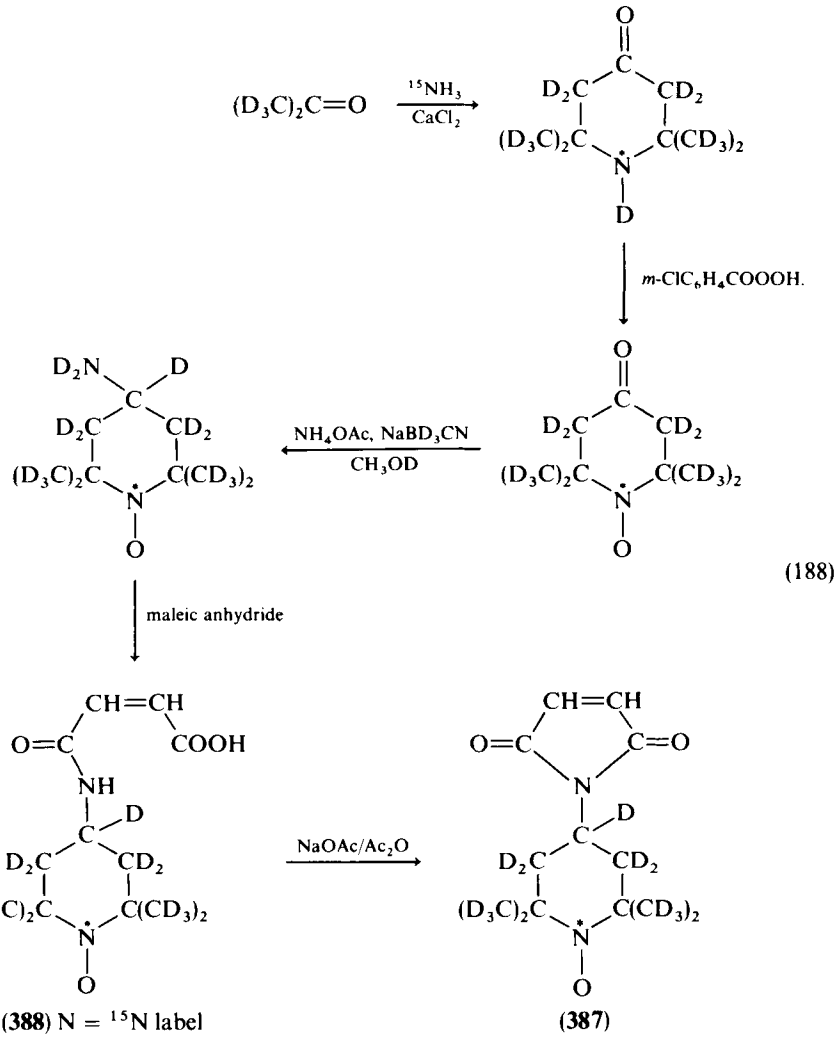


(384) sp. act. 22 Ci mmol^{-1}, 8% yield, radiochem. purity 96–98%



(187)

(386)



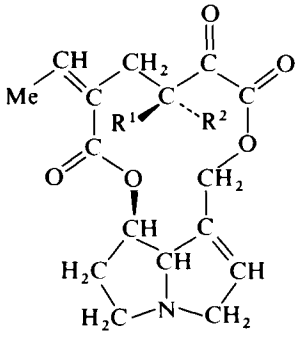
(188)

19. Synthesis of [^{14}C]senecionine, [^{14}C]isosenecionine and [^{14}C]senecic acids[359]

[18-^{14}C]senecionine (**389a**) and [18-^{14}C]isosenecionine (**389b**) (hepatotoxic pyrrolizidine alkaloids occurring in plant species of the genus *Senecio*) have been obtained from the keto esters (**390**) with [^{14}C]MeMgI. Hydrolysis of **389** gave the senecic acids **391** (equation 189).

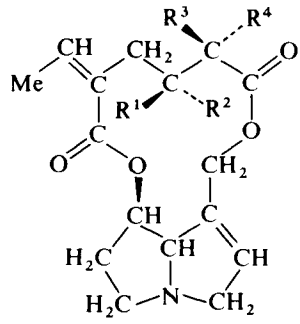
20. Synthesis of ^{3}H-putrescine and biosynthesis of ^{3}H-jacobine

Tritiated jacobine (**392**) is one of the hepatoxic and carcinogenic pyrrolizidine alkaloids (PA's) found in *Senecio jacobaea* and other plants[360,361a]. Its direct radio-



(390a) R^1 = H, R^2 = Me
(390b) R^2 = H, R^1 = Me

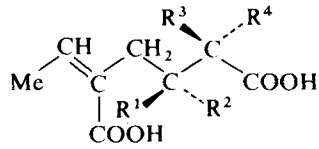
$^{14}CH_3MgI$



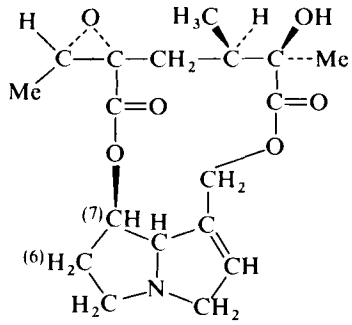
(389a) R^1 = H, R^2 = Me, R^3 = OH, R^4 = $^{14}CH_3$
(389b) R^1 = Me, R^2 = H, R^3 = $^{14}CH_3$, R^4 = OH

(189)

$Ba(OH)_2$



(391a) R^1 = H, R^2 = Me, R^3 = OH, R^4 = Me($^{14}CH_3$)
(391b) R^1 = Me, R^2 = H, R^3 = $^{14}CH_3$, R^4 = OH



(392) Jacobine

chemical synthesis is difficult because it contains several asymmetric carbon atoms. Catalytic tritium exchange is also unsuitable because it saturates the CH=CH double bond. However, biochemical synthesis of jacobine is facile, starting from tritiated putrescine (**393**), and yields radiolabelled jacobine and other PAs in *S. jacobaea* for use in animal metabolism studies.

[2,3-^{3}H or ^{2}H]-1,4-diaminobutane dihydrochloride, putrescine (**393**), has been obtained[361] from [2,3-^{3}H]-succinonitrile (equation 190).

$$CNCH_2CH_2CN \xrightarrow{\text{three steps}} NH_2CH_2C\dot{H}_2C\dot{H}_2CH_2NH_2 \qquad (190)$$

(**393**) 72% chem. yield
16% radiochem. yield
96% radiochem. purity
sp. act. 49 μCi mmol^{-1}

In the biosynthesis ^{3}H-putrescine · 2 HCl has been injected into *senecio jacobaea* plants, which were allowed to grow for three weeks, after which the plants were harvested, homogenized and extracted with methanol, and PAs were isolated from the extract[362]. Jacobine accounted for 31.2 ± 5% of the total alkaloid radioactivity, and was purified to more than 99% purity by preparative HPLC. 99% of the incorporated tritium resided in the necine base portion (carbons number 2, 6 and 7[363]) of the molecule.

21. Synthesis of 3-methyl-15-phenyl-[carboxyl-^{14}C]-pentadecanoic acid (**394**)

This acid was needed for a study of the myocardic metabolism of fatty acids, possessing a β-methyl side chain which stops its β-oxidation in mitochondria and allows a longer experimental time in animal studies[364]. It has been obtained[365] (equation 191) in the reaction of Na^{14}CN with the mesylate compound **395** to yield **396** and hydrolysis of the latter to the **394**-^{14}C-acid (specific activity 1.92 mCi mmol^{-1}, radiochemical purity 99.5%). The mesylate **395** has been prepared[365] in five steps starting from PhC≡CH.

$$\underset{\textbf{(395)}}{Ph(CH_2)_{12}\overset{Me}{\overset{|}{C}}HCH_2O-\overset{O}{\overset{\|}{S}}(=O)-Me} \xrightarrow{Na^{14}CN/DMSO} \underset{\textbf{(396)}\ 92\%}{Ph(CH_2)_{12}\overset{Me}{\overset{|}{C}}HCH_2{}^{14}CN} \xrightarrow{NaOH} \underset{\textbf{(394)}\ 93\%}{Ph(CH_2)_{12}\overset{Me}{\overset{|}{C}}HCH_2{}^{14}COOH} \qquad (191)$$

IV. EXCHANGE, TRACER AND ISOTOPE EFFECT STUDIES WITH ISOTOPICALLY LABELLED CARBOXYLIC ACID DERIVATIVES

The development of new syntheses of isotopically labelled carboxylic acid derivatives has been stimulated mainly by their pharmacological and medical applications. The number of publications aimed at elucidations of pure chemical problems (not of immediate application) is rather limited. Exchange reactions important for the atomic industry have been the subject of more considerable study[374].

A. Isotopic Exchange and Isotopic Tracer Studies

Several deuterium-labelled carboxylic acid derivatives have been obtained by the isotope exchange method. Deuterium exchange studies often precede also tritium exchange studies, since the extent of deuteration is easily assessed by ^1H NMR and does not necessitate radiation protection procedures and presents no danger of internal contamination encountered in syntheses employing tritiated water of very high specific activity.

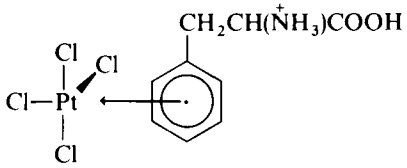
1. Deuterium and tritium exchange studies with phenylalanine and phenylglycine

^{14}C- and/or ^3H-labelled phenylalanine of high specific activity are used in the syntheses of biologically active peptides and other substances[366]. K_2PtCl_4 is an efficient and very useful homogeneous catalyst for deuterium and tritium exchange of the aromatic hydrogens of phenylalanine[367–369], tyrosine[370] and phenylglycine[371]. Using tritiated water of 1 Ci total activity, tritium-labelled chemically and radiochemically pure phenylalanine samples with specific activity of 10 mCi $mmol^{-1}$ were obtained. In the absence of the catalyst no deuterium exchange was observed under the experimental conditions applied. The specific activity of tritiated benzoic acid obtained by oxidation of tritium-labelled phenylalanine was the same as that of the substrate. In the course of deuteration the NMR signals corresponding to $—CH_2—$ and —CH— hydrogens remained constant while the signal of the C_6H_5 group was disappearing with increasing exchange time. The exchange of the aromatic hydrogens proceeds according to an electrophilic substitution mechanism. This has been documented by investigating the effect of ring substituents on the rate of the aromatic H/T exchange. Mechanistic conclusions have also been drawn by analysis of composite H/D and H/T exchange kinetic curves[297,370].

Electron-donating groups, *p*-OH, *p*-MeO- and *p*-EtO-, accelerate the ring deuterium exchange reaction while the electron-withdrawing *p*-NO_2 group retards it strongly. The 3,5-hydrogens of the aromatic ring of tyrosine exchange with D_2O/DCl in the presence of K_2PtCl_4 at a much faster rate than do the 2,6-*ortho*-hydrogens. D/H or T/H exchange between phenylglycine of natural isotopic composition and D_2O or T_2O proceeded relatively fast at 80–130°C when the exchange in the α-position of the aliphatic chain was also rapid. At 373 K, almost complete replacement of aromatic hydrogens with deuterium was found after 72 hours in the presence of K_2PtCl_4. The temperature dependence of the initial rate of disappearance of NMR signals of aromatic hydrogens in the 3,5-positions has an activation energy of 21.4 kcal mol^{-1}.

The above H/D and H/T exchange results have been rationalized[297] by assuming that, similar to what was postulated in the case of deuterium exchange between alkylbenzenes and D_2O[372,373], the H/D and H/T exchanges with the amino acids are preceded by reversible formation of 'inner' centrosymmetric complexes **397** of $(PtCl_4)^{2-}$ with the amino acid through the aromatic ring which, in the course of further approach of platinum(II) to the benzene ring is transformed into a more stable platinum(II) periferal 'outer' π-complex **398**. Not all aromatic hydrogen atoms are equivalent in complex **398**. Hydrogens located in 2,6-*ortho*-positions undergo H/D exchange at a slower rate than hydrogens in 3,5-*meta* positions and especially in the *p*-position, which is the most accessible for electrophilic attack by D_3O^+. The deactivation of *ortho*-ring positions is probably caused mainly by steric hindrance.

In a subsequent step a bond is probably formed between the Pt(II) atom possessing an empty orbital and an electron-rich carbon of the benzene ring of phenyl alanine, with simultaneous abstraction of a ring hydrogen atom by platinum(II) or its oxidation. Attack of D_3O^+ at this 'C—Pt' bond leads to reconstruction of the benzene ring and



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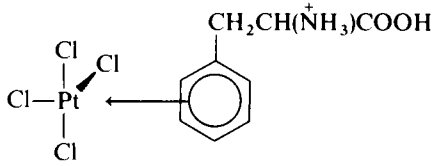
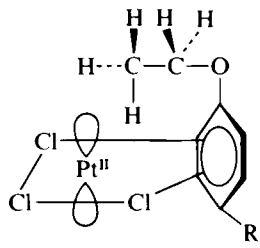


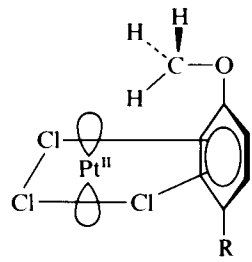
(398)

to deuterium and tritium exchange. It has also been suggested that the rate of H/D exchange proceeds faster in the presence of homogeneous chloroplatinate(II) because the formation of the π-complex increases the concentration of free 'activated chloride ions' near the reaction centre that play the role of a base, accepting protons from the electron-rich positions of the aromatic ring attacked by the D_3O^+ species. Solvated Cl^- ions and D_2O molecules have smaller ability to accept expelled ring protons than do the platinum complexed chloride ions.

A two-step 'π-σ' conversion mechanism involving a 'terminal abstraction π-complex process' (**399a,b**), followed by formation of intermediate linear structures **400a,b** and attack of D_3O^+ leading to H/D and H/T exchanges, has been proposed[297] to explain the deuteration of the methoxy group and of the methyl group of the ethoxy group of *para*-substituted phenylalanines[367,297] (equation 192). The higher rate of deuterium exchange of the terminal methyl hydrogens in the *p*-ethoxy substituent than of *p*-methoxy hydrogens is probably caused by better overlap of the platinum d-orbitals with hydrogen in structure **399a** than in structure **399b**.



(**399a**) R = $CH_2CH(\overset{+}{N}H_3)COOH$



(**399b**)

$$p\text{-}EtOC_6H_4CH_2(\overset{+}{N}H_3)COOH + D_2O \underset{}{\overset{K_2PtCl_4}{\rightleftharpoons}} [\textbf{399a} \text{ (or } \textbf{399b})] \dashrightarrow [\text{or } p\text{-}MeOC_6H_4CH_2CH(\overset{+}{N}H_3)COOH]$$

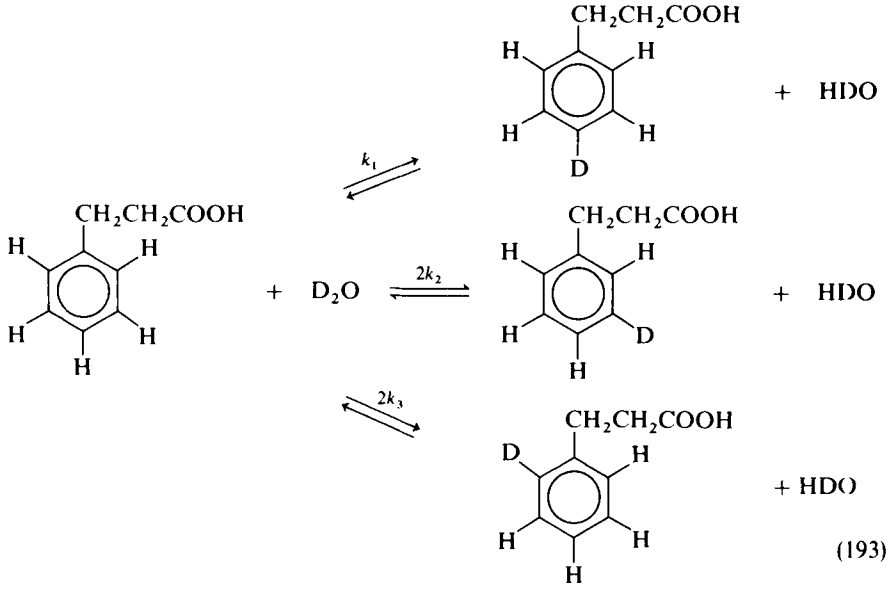
$$\left[\begin{matrix} H \\ | \\ PtCl_2SCH_2CH_2OC_6H_4R \end{matrix}\ (\textbf{400a})\right] \underset{}{\overset{D_3O^+}{\rightleftharpoons}} (PtCl_4)^{2-} + p\text{-}DCH_2CH_2OC_6H_4R \text{ (or } p\text{-}DCH_2OC_6H_4R)$$

$$\left[\left(\begin{matrix} H \\ | \\ \text{or } PtCl_2SCH_2OC_6H_4R \end{matrix}\right)\ (\textbf{400b})\right] \qquad (192)$$

S = Cl or D_2O

2. Deuteriation of β-phenylpropionic acid in the presence of homogeneous K_2PtCl_4 catalyst

The deuteration of the β-phenylpropionic acid with large excess of D_2O acidified with DCl in the presence of K_2PtCl_4 has been investigated[375] in the 100–130°C temperature interval. The decrease in the natural logarithm of the composite (^1H) NMR integration signal of the ring hydrogens with time of H/D exchange and the corresponding McKay plots, $-\ln(1-F)$ vs time, have been analysed and interpreted in terms of rate constants defined by equation 193.



(193)

The pseudo-unimolecular rate constant for the most reactive ring hydrogens deduced from the analysis of the decay diagram of the ^1H NMR integration equals 6.85×10^{-2} [h^{-1}] at 100°C. The Arrhenius activation energy for this process equals 24.7 kcal mol^{-1}. This value corresponds to the dependence of the rate constant k_1 on temperature characterizing deuterium exchange with the most accessible hydrogen in the electron-rich *p*-position of the ring. The exchange of *o*-hydrogens ($2k_3$) is the slowest, probably due to steric hindrance. The second exchange process corresponds to the two *meta*-hydrogens ($2k_2$). The precision of the NMR determinations is not good enough to estimate the activation energy precisely by simple analysis of the composite decay curves. Further NMR investigations of the deuterium exchange between perdeuterated β-phenylpropionic acid, $C_6D_5CD_2CD_2COOD$ and H_2O catalysed by Pt(II) should provide data permitting one to evaluate activation energies for all three exchanges shown in equation 193. Deuteration of benzoic acid[375a] and phenylacetic acid[375b] has also been investigated.

3. Tritium exchange between α-tritiated propionate and aqueous potassium and sodium hydroxide.

a. Deuterium and tritium exchange with acetates. The kinetics of deuterium and tritium exchange between deuteriated and tritiated potassium and sodium acetates and aqueous

potassium and sodium hydroxides as well as between acetates of natural isotopic composition and tritiated or deuterated water has been investigated both at low and high concentrations of bases[376–382] (equation 194).

$$CH_2{}^3HCOOK + H_2O \underset{\longleftarrow}{\overset{\text{KOH (or NaOH)}}{\longrightarrow}} CH_3COOK + {}^3HHO \qquad (194)$$

In diluted KOD solutions the deuterium exchange of potassium acetate catalysed by DO^- depends on the concentration of alkali raised up to first power. The activation energy of this exchange was[376,377] 22 ± 2 kcal mol^{-1}. This value resembles the activation energy of the oxidation of acetate with alkaline permanganate[381,382] which is 24 kcal mol^{-1} (i.e. 100.5 kJ mol^{-1}). The tritium exchange between sodium (2-^{3}H)acetate and concentrated water solutions of sodium hydroxide, both in pyrex and in copper reactions vessels[381,382], proceeds also with an Arrhenius activation energy of 100.55 kJ mol^{-1}, but the rate of tritium exchange was found to be proportional to between the second and third power of the 'analytical' concentration of sodium hydroxide in the 2–13 mol dm^{-3} concentration range. This coincidence of activation energies suggests that the strong bases facilitate the oxidation of acetate with permanganate by ionizing the C—H bond of the methyl group. The anion $[CH_2COONa]^-$ should be oxidized more readily by permanganate than the tetracoordinated carbon of the neutral methyl group of acetate[382].

b. Tritium exchange of α-tritiated potassium and sodium propionates. Aliphatic substitution on the α-carbon of acetate slows the exchange rate several-fold[383,255]. To synthesize CH_3CD_2COOH by an exchange technique it was necessary to heat potassium propionate in D_2O containing OD^- in a stainless steel bomb at 150°C during 24 h, remove the D_2O diluted with H_2O, add fresh D_2O and repeat the H/D exchange reaction five times[255]. The detailed knowledge of the H/D and H/T exchanges of α-tritiated and α-deuteriated propionates with sodium and potassium hydroxides has been needed to interpret correctly the ^{14}C and ^3H kinetic isotope effects observed in the oxidation of ^{14}C-, ^3H- and ^2H-labelled propionates with alkaline manganate and permanganate (see Section IV.B). The available data[255], though very instructive for preparation of deuterium- and tritium-labelled propionates, were insufficient for testing the permanganate and manganate oxidation mechanisms of aliphatic carboxylates. More detailed data have been obtained by studying tritium exchange between α-tritiated potassium and sodium propionates and water solutions of potassium and sodium hydroxides[384,385]. Equations 195–199 were used to describe the tritium exchange[386,385].

$$CH_3C\dot{H}_2COOK + H_2O \underset{\frac{1}{2}\beta x R}{\overset{\frac{1}{2}\alpha y R}{\rightleftharpoons}} CH_3CH_2COOK + \dot{H}_2O \qquad (195)$$

$$\frac{dx}{dt} = \left(\frac{R}{2a}\right)(\alpha y - \beta x) \qquad (196)$$

$$-\ln(1 - F) = \rho t \qquad (197)$$

$$\rho = R[(\alpha a + \beta b)/2ab] \cong \alpha R/2b \text{ when } b \ll a \qquad (198)$$

$$\log(\alpha k_{0t}) = \log(\alpha k_t) - 2A_t z_A z_B \sqrt{I}/(1 + \sqrt{I}) \qquad (199)$$

$$A_t = 1.82525 \times 10^6/(\varepsilon_t \cdot T)^{3/2} \qquad (199a)$$

where R is the rate (expressed in gmol min^{-1}) with which H exchanges at equilibrium between α-hydrogens of propionate and labile hydrogens of water, $a = [H_2O]$ and

$b = [CH_3CH_2COOK]$ are the total concentrations of labile hydrogens and of potassium priopionate, respectively, $x = [\overset{*}{H}_2O]/([\overset{*}{H}_2O] + [H_2O])$ and $y = [P\overset{*}{P}]/([\overset{*}{P}P] + [PP])$ are fractions of tritium-labelled species, H_2O including water derived from potassium hydroxide, and potassium propionate (PP), α and β are tritium isotope effects,

$$F = (x_t - x_0)/(x_\infty - x_0) = (A_t - A_0)/(A_\infty - A_0)$$

is the degree of exchange, A_0, A_t and A_∞ are specific activities at time $t = 0$, t and $t = \infty$, $\alpha k = (\alpha R/b)$ are tritium exchange rate constants expressed in min^{-1}, αk_0 are the corresponding rate constants for the infinitely dilute solution, $I = \frac{1}{2}\sum C_i z_i^2$ [mol dm^{-3}] stands for all ions in the solution, z_A and z_B are charges of the reacting ions, ε_t is the dielectric constant at given reaction temperature and T is absolute temperature.

The following results have been deduced from the kinetic experimental data: At a given concentration of KOH the rate of tritium exchange, αR, depends on the concentration of potassium propionate raised to the first power. At a given concentration of potassium propionate the tritium exchange rate constants, αk, depend on the concentration of KOH raised to a power which changes depending on the concentration range of the alkali. This strong deviation from the straight line plot is partially caused by the simultaneous increase in the ionic strength of the medium, I, which accelerates reactions taking place between ions of the same charge. The repulsion between two negatively charged reactants, $CH_3CH_2COO^-$ and HO^-, is decreasing with addition of potassium chloride to the exchange solution. The exchange rate constants, αk_0, extrapolated to zero ionic strength with the use of equation 199, continue to depend on C_{KOH} raised to a power which increases with increasing molar concentration of KOH. At 172.8 °C the power x in the expression $\alpha k_0 = \alpha k_0'(C_{KOH})^x$ equals 1.16 in the 0.084–0.42 molar concentration range of KOH. The dependence of αk_0 on the KOH concentration is especially pronounced in the 5–10 M KOH concentration range, where $x = 2.65$ both at 130.1 and 100.65 °C. In 5.2 molar KOH and in the temperature range of 100–150 °C the correlation coefficients of the linear Arrhenius plots of the rate constants given in equations 200 and 201 are 0.99988 and 0.99967, respectively.

$$\ln(\alpha k) = 24.906 - 11918/T \tag{200}$$

$$\ln(\alpha k_0) = 19.962 - 10813/T \tag{201}$$

$$\alpha k = 6.56 \times 10^{10} e^{-23675/RT} \tag{200a}$$

$$\alpha k_0 = 4.67 \times 10^{8} e^{-21480/RT} \tag{201a}$$

The exchange of α-hydrogen of potassium propionate proceeds in diluted aqueous KOH solutions with an activation energy higher by about 3 kcal mol^{-1}, than in concentrated KOH solutions.

The detritiation of a carbon acid, involving formation of a carbanion intermediate[387], can be schematically depicted by equations 202–204.

(a) Ionization of the R—T bond:

$$RT + HO^- \underset{k_2^T}{\overset{k_1^T}{\rightleftharpoons}} R^- \cdot TOH \tag{202}$$

(b) Replacement of the solvating tritiated water molecule with ordinary water, H_2O, and/or internal rotation of the TOH and formation of $R^- \cdot HOT$ isomer:

$$R^- \cdot TOH + HOH \overset{k_3^{TH}}{\rightleftharpoons} R^- \cdot HOH + TOH \tag{203}$$

(c) Collapse of the $R^- \cdot HOH$ intermediate, formation of the RH molecule and regeneration of the catalyst:

$$R^- \cdot HOH \underset{}{\overset{k_2^H}{\rightleftharpoons}} RH + HO^- \tag{204}$$

At tracer concentration levels of tritium and when ionization of the R—T bond is the rate-determining step, i.e. $k_2^T < k_3^{TH} \cdot [HOH]$, the rate law simplifies to equation 205:

$$d[RT]/dt = k_1^T([RT]_{equil.} - [RT])[HO^-] \tag{205}$$

When the exchange system undergoes internal return, $k_2^T > k_3^{TH}[HOH]$, the rate law is given by equation 206:

$$d[RT]/dt = \frac{k_1^T}{k_2^T} \cdot k_3^{TH}([RT]_e - [RT])[HO^-][HOH] \tag{206}$$

In all tritium and deuterium exchange reactions with C—H acids reviewed previously[387] the rate of C–H hydrogen exchange with labile hydrogens of water, catalysed by bases, depends on the concentration of the hydroxide anion raised to the first power. In diluted KOD solution[376] only, deuterium exchange of potassium acetate catalysed by DO^- depends on the concentration of alkali raised to the first power. In acetate[381,382] and in propionate tritium exchange, in concentrated alkalis (5–13 molar solutions) the rate of tritium exchange depends on the concentration of alkali raised to nearly the third power.

Ionization of C—H acids by 'free hydroxide ion' should proceed at a higher rate than the ionization of the C—H bond with hydroxide ion fully solvated by water molecules. One frequently assumes that $HO^-(H_2O)_3$ is the stable species in solution and predictions are made that when there are not enough solvent molecules to completely hydrate the HO^- ions, a sharp rise in the activity of base should occur[388–391]. However, it is hard to imagine the approach of voluminous hydrated $OH(H_2O)_n^-$ ion to the α-hydrogen of propionate, abstracting a slightly polarized but covalently bound tritium or protium from the $C_{(\alpha)}$—H bond. It seems much more likely that only highly energetic free hydroxide ions which have lost at least one water molecule from their first solvation sphere are the kinetically active species abstracting tritium.

A gross correlation of the type given in equation 207 has been found[389,390] between tritium exchange rate constants (αk_0), the stoichiometric concentration of the hydroxide ion $C_{(HO^-)}$ and the concentration of free water $C_{(H_2O)}$ in the 1–5 M KOH concentration range. The linear correlation between $\lg_{10}(\alpha k)$ and the basicity H_2^- scale[391] constructed for concentrated solutions of KOH was observed only up to 3–4 M of KOH.

$$\alpha k_0 = \text{const} \cdot (C_{(HO^-)}/C^n_{(H_2O)}) \tag{207}$$

In spite of the lack of ideal agreement between the available kinetic tritium exchange data and the present theoretical treatment of reactions in concentrated solutions, it is obvious that detailed tritium (and deuterium) exchange studies with aliphatic carboxylates open new possibilities for experimental investigation of the structure of concentrated solutions, of the intimate interaction of concentrated alkalis with aliphatic carboxylates and of reactions in general in concentrated alkalis by the method originated by Yagil and coworkers[389–391a].

Oxygen-18 exchange studies of aqua- and oxo-ions including carboxylate ions have been reviewed by Gamsjäger and Murmann[391b]. Kinetic data for the ^{18}O-exchange between carboxylic acids and water have been tabulated and discussed. The ^{18}O exchange is assumed to go through formation of tetrahedral intermediates $RC(OH)_3H^+$, $RC(OH)_3$, $RC(OH)_2O^-$, which decompose yielding ^{18}O-labelled carboxylates or acids.

4. Room temperature oxidation and degradation of propionic [3-^{14}C] acid and lactic [1-^{14}C] acid by hexavalent chromium in acid medium

Oxidation of propionic acid [3-^{14}C] with CrO_3 in acidic medium at room temperature has been studied[392]. Earlier results[393–397] concerning oxidation of propionic acid with Cr(VI) in sulphuric acid indicated that the oxidation of EtCOOH proceeds exclusively as shown in equation 208:

$$CH_3CH_2{}^{14}COOH \xrightarrow{2\ CrO_3,\ H_2SO_4} CH_3COOH + {}^{14}CO_2 + 2Cr^{3+} \qquad (208)$$

Complete oxidation of aliphatic acids occurs in the Van Slyke–Folch mixture containing CrO_3,H_3PO_4 and oleum at elevated temperatures[398,399] (equation 209):

$$^{14}CH_3CH_2COOH \longrightarrow {}^{14}CO_2 + 2CO_2 + 3H_2O \qquad (209)$$

Carbon dioxide collected in the course of oxidative degradation of propionic acid (3-^{14}C) with potassium dichromate in 16 N sulphuric acid and with CrO_3 in 65% H_2SO_4 was found to be radioactive. Quantitative correlation of specific activities of the gases collected in separate 'degradation' and complete 'wet' oxidation experiments showed that Cr(VI) oxidizes about 10% of the propionic acid molecules completely to carbon dioxide in sulphuric acid medium at 20 °C, while the oxidative degradation of propionic acid (3-^{14}C) proceeds probably according to equation 210 involving a common fast reacting intermediate, which decomposes in two different ways with two different probabilities. The contribution of the oxidation of $^{14}CH_3COOH$ with CrO_3 to the total amount of $^{14}CO_2$ produced is negligible at room temperature.

The oxidation of propionic acid with CrO_3 was found to be[396,397] first-order in each of both reactants, and second-order dependent on hydrogen ions in aqueous sulphuric acid medium[396,397].

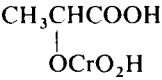
Chromium trioxide is not well soluble in sulphuric acid but is readily soluble in 85% H_3PO_4. The parameters illustrated in equation 210 have therefore been redetermined in orthophosphoric acid medium. The rate of oxidative degradation of propionic acid (3-^{14}C) with the CrO_3H^+ species in 85% H_3PO_4 has first-order dependence each on chromium trioxide concentration and on propionic acid (up to about 1 mol dm^{-3}).

$$^{14}CH_3CH_2COOH + CrO_3 \xrightarrow{k_1} \left[\begin{matrix}\text{intermediate}\\ \text{compound}\end{matrix}\right] \begin{matrix} \xrightarrow{k_2} CO_2 + {}^{14}CH_3COOH \\ \xrightarrow{k_3} {}^{14}CO_2 + 2CO_2 \end{matrix} \qquad (210)$$

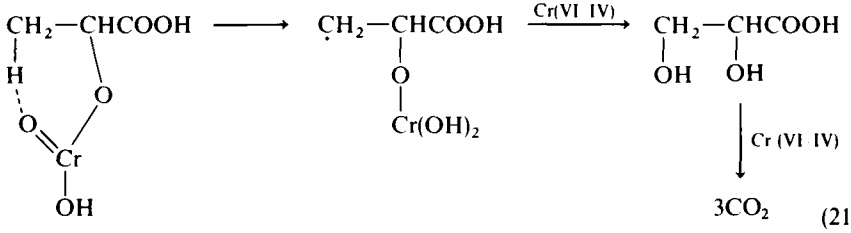
The Arrhenius temperature dependence in the 20–70 °C temperature interval of the rate constant k_1 calculated from equation 210 is given in equation 211:

$$k_1 = 7.42 \times 10^6 e^{-(16110/RT)}[\text{dm}^3\ \text{mol}^{-1}\ \text{s}^{-1}] \qquad (211)$$

^{14}C, T and D kinetic isotope effects have not yet been determined for the oxidation of labelled propionic acids but chemical reasoning suggests that the bimolecular oxidation of the methylene group of the propionic acid with partly or fully protonated chromium trioxide derived electron-deficient species, such as $HCrO_3^+$ or $H_3CrO_4^+$ (free or forming pairs of the type $CrO_3H^+H_2PO_4^-$) or a complex species like $HOCrO_2{-}O{-}PO_3H_2$ and formation of the mono-ester of chromic acid



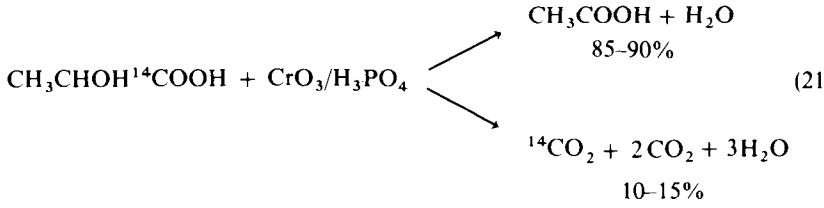
is the rate-determining step[400,401]. The negative entropy of activation implies a cyclic structure for the transition complex within which the methylene hydrogen transfer proceeds with lowered activation energy. The rearrangement schemes of the ester leading to acetic acid formation have been reviewed[397,400]. It is possible that the side reaction (k_3) in equation 210 occurs by internal oxidation of the ester with Cr(IV) and oxidation of the intermediate radical to a hydroxyacid, which in turn through a series of further fast oxidation steps is oxidized to carbon dioxide (equation 212). Cr(IV) usually causes cleavage and side reactions in alcohol oxidations[403].



(212)

Breaking of the $C_{(3)}$—$C_{(2)}$ bond may occur already in the first step of the mono-ester internal rearrangement. Attack of Cr(VI) at the double bond formed in the course of enolization of the keto acid postulated as one of the intermediates[404,405] may also contribute to the oxidation side process of propionic acid.

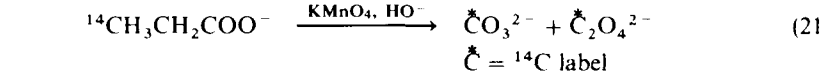
The suggestion that the complete oxidation of 10–15% of the propionic acid molecules to carbon dioxide is the result of a side branched reaction as indicated in equation 210 is supported by the recent[406] study of the fast room-temperature oxidation of lactic (1-^{14}C) acid with CrO_3/H_3PO_4 solution or with CrO_3/H_2SO_4 mixtures (equation 213).



(213)

5. Oxidation of propionic acid (3-^{14}C) with alkaline permanganate

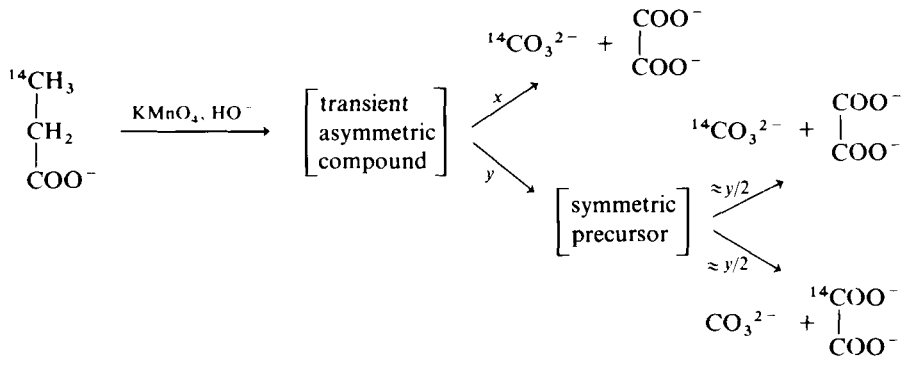
The problem of the distribution of the radioactive carbon between oxalates and carbonates (the products of propionate ion oxidation with permanganate in alkaline medium) has been reinvestigated using methyl-^{14}C-propionate[407] (equation 214).



(214)

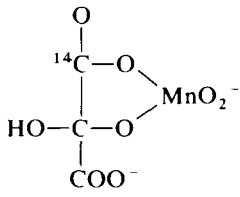
The distribution of ^{11}C between the oxidation products of $CH_3CH_2{}^{11}COOH$ depended on the alkalinity of the oxidizing medium[408]. Mechanistic studies with ^{11}C-labelled compounds are complicated by experimental difficulties caused by the short (20.34 min) half-life of carbon-11. Nevertheless, a preferential rupture of the $C_{(3)}$—$C_{(2)}$ bond in propionate (1-^{11}C) in highly concentrated alkaline solutions of NaOH (and KOH) was noted and explained by the formation of the symmetrical intermediate which decomposes

in two different modes and has been confirmed by oxidation experiments with propionate (3-^{14}C). The ratio R of the $C_{(3)}$—$C_{(2)}$ to $C_{(2)}$—$C_{(1)}$ bond rupture was calculated directly using the relation $R = (A_{oPA}/A_{oxal}) - 1$, where A_o is the specific activity of propionic acid (3-^{14}C) and A_{oxal} is the specific activity of oxalate; the ratio was also determined experimentally[384]. The latter results indicated that it is impossible to achieve 90% cleavage of the α–β carbon bond in the propionate by simply increasing the alkalinity of the oxidizing solution. In 12 N KOH 26.4% of the ^{14}C-label appeared in the oxalate and 73.6% in the carbonate. In very concentrated NaOH solutions a 100 °C cleavage at the β-position of propionate occurs 3 to 3.5 times more frequently than cleavage of



(215)

the bond between the α-carbon and the carboxyl group. In fused potassium hydroxide the $C_{(3)}$—$C_{(2)}$ to $C_{(2)}$—COOH bond rupture ratio was the same as in concentrated NaOH. These results have been rationalized by assuming that the oxidative degradation of propionate to oxalate and carbonate proceeds according to equation 215. The asymmetric compound may have, for instance, a structure like **401**, and the symmetric precursor a structure like **402**.



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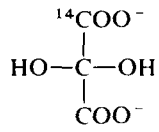

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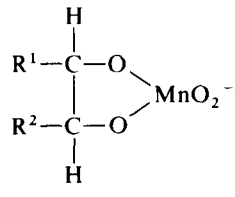


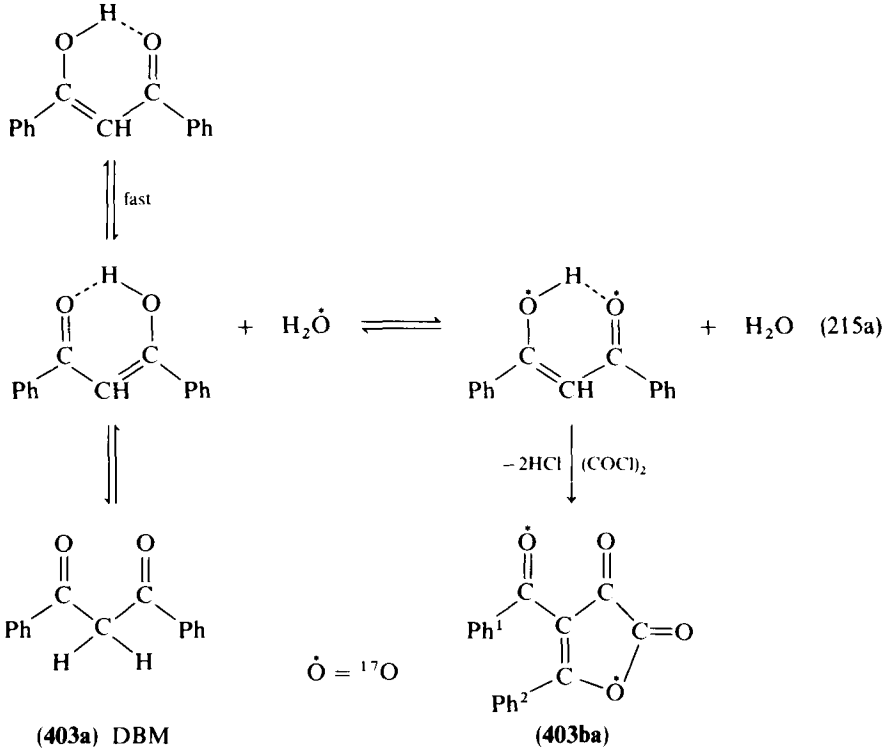
(403)

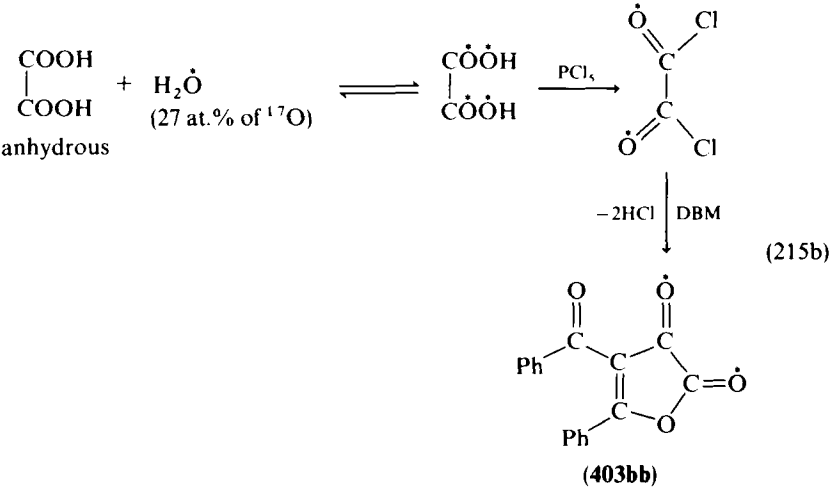
The ^{14}C kinetic isotope effect introduces an uncertainty of less than 10% and thus the symmetrical precursor should oxidize with nearly equal probability to $^{14}CO_3^{2-}$ + $C_2O_4^{2-}$ or to CO_3^{2-} + ^-OOC—$^{14}COO^-$. The cleavage of the chain may take place already at the stage of oxidation of propionic acid presented by the structure **403** postulated frequently in organic oxidation studies[409].

6. *^{17}O-study of furan-2,3-dione rearrangements*

Novel furan-2,3-dione rearrangements have been investigated by oxygen-17 labelling[463]. The label has been introduced into dibenzoylmethane (DBM, **403a**) by isotope exchange reaction involving hydration of the two carbonyl groups with $H_2{}^{17}O$ in methanol (equation 215a).

DBM exists predominantly in its enolic form. The rate of interconversion of the two possible enols is high enough to give only one signal (δ = 250 ppm) in the ^{17}O NMR spectrum. The ^{17}O-label was introduced also into both exocyclic carbonyl oxygens (equation 215b). Both 4-benzoyl-5-phenylfuran-2,3-diones **403ba** and **403bb** have been used to show that the furandione rearrangement of the unstable adduct **403c**, formed by

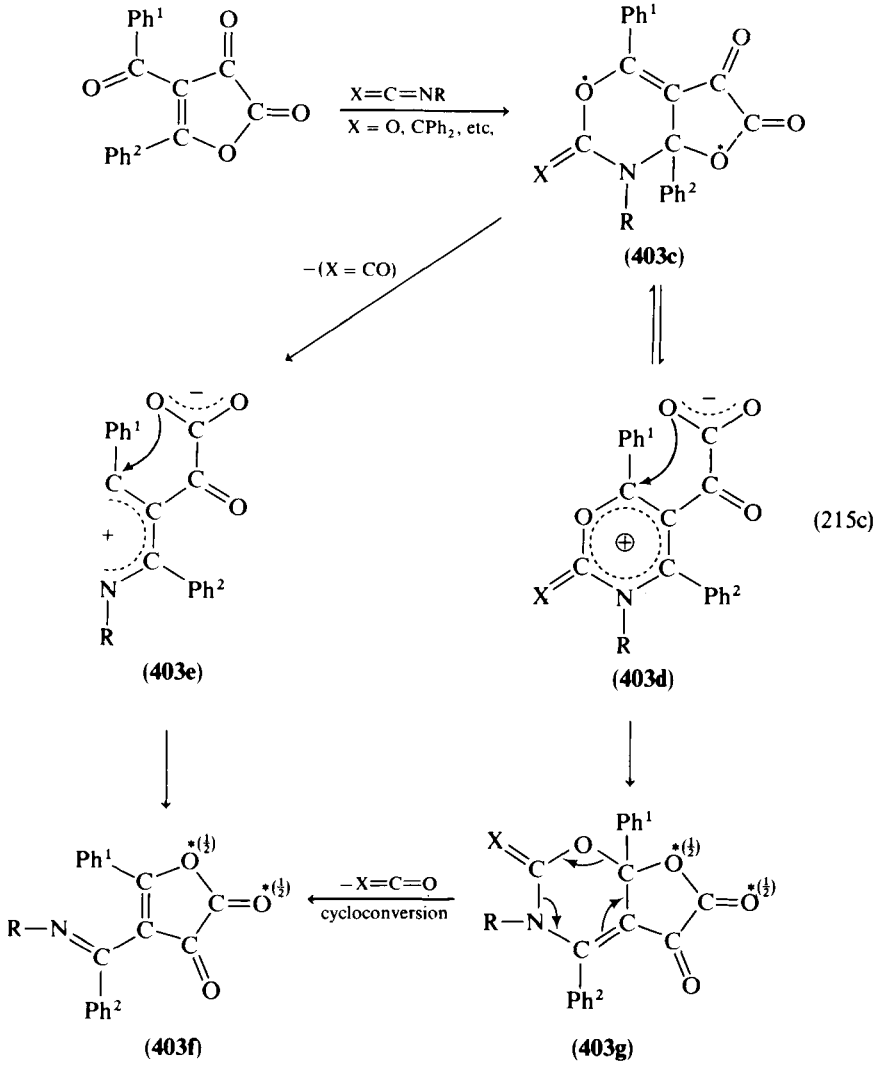




formal (4 + 1) or (4 + 2) cycloaddition of aryl isocyanides or heterocumulenes[4c,3] to **403b**, proceeds via opening of the furan ring with formation of an oxo carboxylic side chain **403d** or **403e**. The latter undergo free rotation around the single bond to give the heterocyclic systems by relactonization at the former benzoyl carbon leading to the exchange of the two phenyl groups in **403b** (equation 215c). Reactions involving carbodiimides, isocyanates and ketene imines have been investigated.

When **403ba** reacted with $Ph_2C{=}C{=}NTo\text{-}p$, the ^{17}O-labelled product **403h** was obtained. Starting from **403bb** and $Ph_2C{=}C{=}NTol\text{-}p$, **403i** has been obtained in agreement with the proposed mechanism of equation 215c.

Analogous reactions of **403ba** and **403bb** with PhN=C=O gave **403j** and **403k**.



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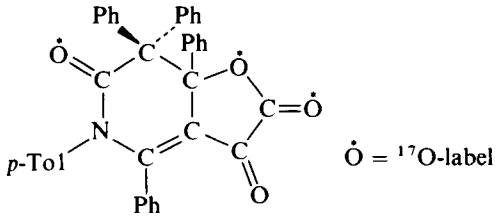
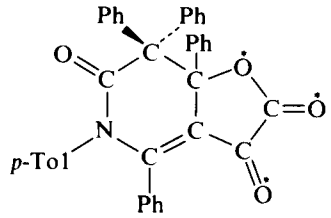


(403h)



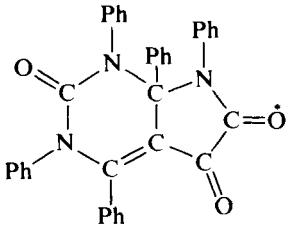
(403i)

B. Isotope Effect Studies with Labelled Carboxylic Acids and Carboxylic Acid Derivatives

1. Carbon-14 kinetic isotope effect studies of the mechanism of the bromodecarboxylation of substituted cinnamic acid dibromides

This reaction has been studied recently[110,410] by the kinetic isotope effect (KIE) methodology[411,412]. Carbon-14 isotope effects ($k/k_{(\alpha)}$) in the bromodecarboxylation of α-^{14}C-labelled *p*-methoxy aryl compound at 25 °C, ^{14}C-KIE in the bromodecarboxylation of α-labelled unsubstituted and *p*-nitrocinnamic acid dibromides at 70 °C as well as ^{14}C-KIE ($k/k_{(\beta)}$) in the bromodecarboxylation of β-labelled cinnamic acid dibromide at 70 °C were found to be 1.020 ± 0.005, 1.044 ± 0.003 and 1.068 ± 0.004, respectively, for the α-labelled acids and 1.035 ± 0.002 or β-labelled unsubstituted compound. ^{14}C-KIE in the bromodecarboxylation of carboxyl-^{14}C labelled compounds are studied and isotope effect calculations will be carried out. The occurrence of both α- and β-carbon-14 isotope effects indicates that there are bonding changes at both α- and β-positions in the rate-determining steps of bromodecarboxylation of the cinnamic acid dibromides. The results rule out the stepwise mechanism[413,414] of bromodecarboxylation for all three compounds and indicate that the loss of carbon dioxide must be concerted with the loss of the β-bromine for all compounds investigated (equation 216).

The dependence of the $k/k_{(\alpha)}$ values on the nature of the aryl substituent R shows additionally that the bonding change at the α-carbon is much greater for compounds with electron-withdrawing groups than for those with electron-donating groups. The largest $k/k_{(\alpha)} = 1.068$ for $R = NO_2$ has been interpreted as showing that $C_{(\alpha)}—COO^-$ bond rupture in the activated complex leads to $C_{(\beta)}—Br$ bond rupture in this case while the reverse sequence of events takes place with the *p*-methoxy compound, in which the positive charge at the β-carbon is better delocalized. Structures **404** and **405** have been suggested for the activated complexes in bromodecarboxylation reactions proceeding according to a concerted mechanism (equation 216).



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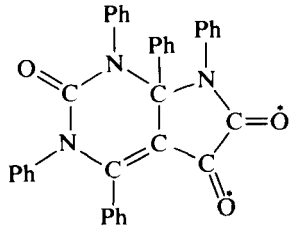
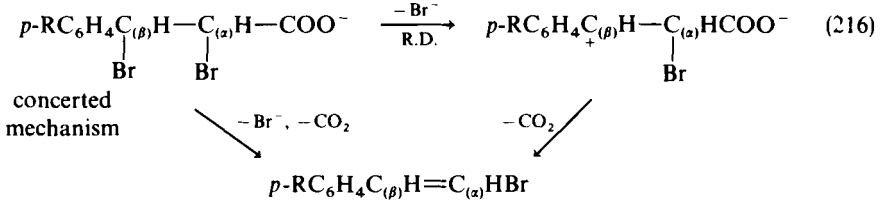


(403k)

'stepwise mechanism'



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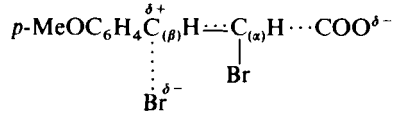

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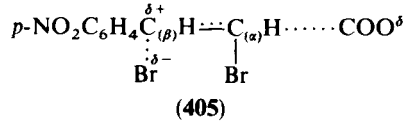


(405)

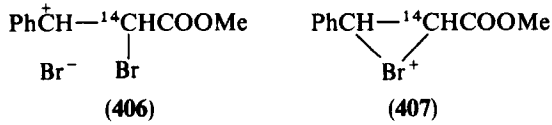
2. Carbon-14 isotope effects and mechanism in the bromination of methyl cinnamate [1-^{14}C]

Ropp, Raaen and Weinberg have found[415] that the products of partials and complete Br_2 additions to [α-^{14}C]- and [β-^{14}C]-labelled methyl cinnamates (equations 216a and b) had the same specific activities and no carbon-14 kinetic isotope effect was observed.

$$PhCH{=}{}^{14}CHCOOMe + Br_2 \xrightarrow[CCl_4]{25\,^\circ C} PhCHBr{-}{}^{14}CHBrCOOMe \quad (216a)$$

$$Ph^{14}CH{=}CHCOOMe + Br_2 \xrightarrow[CCl_4]{25\,^\circ C} Ph^{14}CHBr{-}CHBrCOOMe \quad (216b)$$

Carbon-14 kinetic isotope effect in the reaction 216a has been re-examined recently[416] with more precise instruments. The results showed that there is a small $(k/k_{(\alpha)})$-^{14}C isotope effect equal to 1.008 ± 0.003 and the earlier conclusion[415] is incorrect. This small but measurable ^{14}C-KIE indicates that there are bonding changes at the α-carbon of the methyl cinnamate (1-^{14}C) ester in the rate-determining step of the bromination. Structures **406** and **407** have been proposed for the transition state.



(406) (407)

3. *Carbon-14 kinetic isotope effect in the decarbonylation of lactic acid [1-^{14}C]*

^{14}C and ^{13}C kinetic isotope effects in the decarbonylations of carboxylic acids (equations 217 and 218) have been studied extensively in several laboratories and have been reviewed[1,417–428]. Reasonably good agreement has been found between ^{13}C and ^{14}C kinetic isotope effects determined at 0 °C and below this temperature. However,

$$H^{12}COOH \xrightarrow[95.6\%\ H_2SO_4]{k_{(^{12}C)}} {}^{12}CO + H_2O$$

$$H^{14}COOH \xrightarrow[95.6\%\ H_2SO_4]{k_{(^{14}C)}} {}^{14}CO + H_2O \qquad (217)$$

$$k_{(^{12}C)}/k_{(^{14}C)} = 1.118 - 1.132 \text{ at } 0\ ^\circ C$$
$$1{,}087 - 1.101 \text{ at } 24.75\ ^\circ C$$
$$k_{(^{12}C)}/k_{(^{13}C)} = 1.0664 \pm 0.0009 \text{ at } 0\ ^\circ C$$
$$1.0720 \pm 0.0011 \text{ at } -15\ ^\circ C$$
$$1.0799 \text{ at } -30\ ^\circ C$$
$$(1.0767 \text{ at } -26.0\ ^\circ C)$$

$$\begin{array}{l} {}^{14}COOH \\ | \\ {}^{12}COOH \end{array} \xrightarrow[H_2SO_4]{k_{(^{12}C)}} {}^{12}CO + {}^{14}CO_2 + H_2O$$

$$\begin{array}{l} {}^{14}COOH \\ | \\ {}^{12}COOH \end{array} \xrightarrow[H_2SO_4]{k_{(^{14}C)}} {}^{14}CO + {}^{12}CO_2 + H_2O \qquad (218)$$

$$k_{(^{12}C)}/k_{(\overset{*}{C})} = 1.067 \pm 0.0035 \quad (\text{for } \overset{*}{C}={}^{14}C) \text{ at } 80,\ 1\ ^\circ C$$
$$1.0325 \pm 0.0015 \quad (\text{for } \overset{*}{C}={}^{13}C) \text{ at } 80,\ 1\ ^\circ C$$
$$1.032 \pm 0.003 \quad (\text{for } \overset{*}{C}={}^{13}C) \text{ at } 100\ ^\circ C$$
$$1.055 \pm 0.003 \quad (\text{for } \overset{*}{C}={}^{14}C) \text{ at } 103\ ^\circ C$$
$$1.027 \pm 0.0022 \quad (\text{for } \overset{*}{C}={}^{13}C) \text{ at } 103\ ^\circ C$$

observed effects at higher temperatures are not in close agreement with the theoretically predicted values based on the assumption that one carbon–oxygen bond is almost completely broken in the transition state. It has been suggested that probably all the bonds in formic and oxalic acid are altered significantly during activation leading to decarbonylation reaction.

$$CH_3CHOH^{12}COOH \xrightarrow[H_2SO_4]{k_{(^{12}C)}} CH_3CHO + {}^{12}CO + H_2O$$

$$CH_3CHOH^{14}COOH \xrightarrow[H_2SO_4]{k_{(^{14}C)}} CH_3CHO + {}^{14}CO + H_2O \qquad (219)$$

Our group studied the ^{14}C kinetic isotope effect in the decarbonylation of lactic acid [1-^{14}C] (equation 219)[429,430] in the temperature interval 20–90°C so far. Values of the $k_{(^{12}C)}/k_{(^{14}C)}$ ratio were 1.133–1.123 at 20–40 °C and are in satisfactory agreement with data calculated under the assumption that one carbon–oxygen stretching vibration is lost in the rate-determining step (calculated ^{14}C-KIEs are 1.1208 at 20 °C, 1.1168 at 30 °C and 1.11306 at 40.30 °C, respectively). This fit in experimental and theoretical values indicates that the reaction involves the steps given in equation 220.

$$CH_3CH(OH)^{14}COOH + H_2SO_4 \rightleftharpoons HSO_4^- + CH_3CH(OH)^{14}C(=O)\overset{+}{O}H_2$$

$$CH_3CH(OH)^{14}C(=O)\overset{+}{O}H_2 + H_2SO_4 \xrightarrow{\text{R.D. step}} H_2O \cdot H_2SO_4 + CH_3CH(OH)^{14}\overset{+}{C}{=}O$$

$$CH_3CH(OH)^{14}\overset{+}{C}{=}O + H_2SO_4 \longrightarrow {}^{14}CO + AcH + AcH\text{-polymers} \qquad (220)$$

The $k_{(^{12}C)}/k_{(^{14}C)}$ values at 50–90 °C deviate from the theoretical values calculated[419,430] with the use of equation 221[386]:

$$k_{(^{12}C)}/k_{(^{14}C)} = \sinh(u_{(^{12}C)}/2)/\sinh(u_{(^{14}C)}/2) \qquad (221)$$

where sinh denotes the hyperbolic sine; $u_i = hc\omega_i/kT$, where h is Planck's constant, c is velocity of light, ω_i are the frequencies corresponding to the isotopic carbon–oxygen bonds broken competitively in the decarbonylation, k is Boltzmann's constant and T is the absolute temperature. This discrepancy may be caused by side reactions (equation 222 and papers to appear) taking place in sulphuric acid at higher temperatures and changing possibly also the isotopic composition of the unreacted ^{14}C-labelled lactic acid undergoing decarbonylation. The abnormal temperature dependence of the ^{14}C separation observed in the decarbonylation of (1-^{14}C)lactic acid in concentrated sulphuric acid at higher temperatures has been corroborated by the recent study[430a] of the ^{13}C kinetic isotope effects in the decarbonylation of lactic acid containing carbon-13 at the natural abundance level.

$$2\ CH_3CHCOOH \underset{\rightleftharpoons}{\overset{H_2SO_4}{}} CH_3CH(-O-C(=O)-)-C(=O)-O-CHCH_3 \qquad (222)$$

(OH)

4. Carbon-14 kinetic isotope effects in the oxidation of α- and β-^{14}C-labelled propionates

Modern liquid scintillation counters permit one to determine very precisely specific activities of crystalline organic compounds which are soluble in dioxane or in toluene and do not extinguish scintillations, but not of liquid acids. Therefore, the labelled propionic acids had to be transformed into crystalline[431,432], *p*-bromophenacyl esters (**408**), *p*-phenylphenacyl esters (**409**) or *p*-toluide derivatives (**410**)[431,432].

$CH_3{}^{14}CH_2COOCH_2\overset{\overset{O}{\|}}{C}C_6H_4Br\text{-}p$, m.p. 63.0–63.3 °C
(408)

${}^{14}CH_3CH_2COOCH_2\overset{\overset{O}{\|}}{C}C_6H_4C_6H_5\text{-}p$, m.p. 102.0 ± 0, 1 °C
(409)

${}^{14}CH_3CH_2CONHC_6H_4CH_3\text{-}p$, $CH_3{}^{14}CH_2CONHC_6H_4CH_3\text{-}p$, m.p. 125.5–126 °C
(410a) **(410b)**

p-Bromophenacyl esters have been used[433,434] for determination of the radioactivity of ^{14}C-labelled formic[433] and acetic acid[434]. In the case of propionic acid we preferred **409** rather than the skin-irritating **408**. However, the *p*-toluide[435] appeared to have the best counting properties, was easy to purify and hence was chosen by us for precise determinations of the specific activities R_0 and R_r of the starting and recovered unreacted propionates at partial oxidations denoted by f (equation 223).

$$\begin{array}{l}\overset{\beta}{C}H_3\overset{\alpha}{C}H_2COO^- \\ (\text{or } \overset{\beta}{C}H_3\overset{\alpha}{C}H_2COO^-)\end{array} \xrightarrow[\substack{\text{HO}^-,\ 100\ ^\circ\text{C} \\ \text{partial preset} \\ \text{oxidation}}]{KMnO_4} \begin{array}{l}\overset{\beta}{C}H_3\overset{\alpha}{C}H_2COO^- + {}^{14}\text{C-carbonates and} \\ \text{unreacted} \qquad\qquad {}^{14}\text{C-oxalates} \\ (\text{or } \overset{\beta}{C}H_3\overset{\alpha}{C}H_2COO^-)\end{array} \tag{223}$$

$k_{(^{12}C)}/\overset{\alpha}{k}_{(^{14}C)}$ and $k_{(^{12}C)}/\overset{\beta}{k}_{(^{14}C)}$ values have been calculated by equation 224[436b,436c]. The degree of oxidation f was controlled by using a predetermined amount of $KMnO_4$. Specific activities R_0 and R_r were determined with a scintillation counter.

The carbon-14 KIE of propionate [2-^{14}C] with permanganate was found to be $k_{(^{12}C)}/\overset{\alpha}{k}_{(^{14}C)} = 1.046 \pm 0.003$ at 100 °C. The ^{14}C-KIE in the oxidation of propionate [3-^{14}C] with permanganate at 100.5 °C was found to be practically negligible and

$$k_{(^{12}C)}/k_{(^{14}C)} = \ln\left[\frac{(1-f)(R_0+1)}{(R_r+1)}\right] \Big/ \left[\ln\frac{R_r(1-f)(R_0+1)}{R_0(R_r+1)}\right] \tag{224}$$

equal to $k_{(^{12}C)}/\overset{\beta}{k}_{(^{14}C)} = 1.006 \pm 0.003$.

These results indicate that in the rate-determining step of the oxidation there is C_α—H bond weakening and practically no bonding change at the β-carbon. These data fit

$$\begin{array}{l}\overset{\beta}{C}H_3\overset{\alpha}{C}H_2COO^- \longrightarrow \overset{\beta}{C}H_3\overset{\alpha}{C}HCOO^- \longrightarrow {}^-OO\overset{\beta}{C}-\overset{\alpha}{C}(=O)-COO^- \\ \qquad\qquad\qquad\

equation 225, in which X denotes a free radical center, an oxygen derivative or a carbocation centre in the case of $\overset{\alpha}{H}^-$ transfer to the oxidizer. The intermediate products are oxidized by permanganate at a much faster rate than unsubstituted propionate in the same experimental conditions.

5. Tritium isotope effect in the alkaline permanganate and manganate oxidation of α-tritiated propionate

A substantial ^{14}C KIE described above pointed to the possibility of a large kinetic tritium isotope effect in the oxidation of α-tritiated propionate. Tritium and deuterium KIE had to be determined before the final interpretation of ^{14}C KIE data, since the carbon isotope effect is sensitive both to the degree of transfer of hydrogen from $C_{(2)}$—H to the oxygen atom of the oxidizer and to changes of other bonds to $C_{(2)}$ including changes of deformation force constants at $C_{(2)}$. The position of hydrogen in the transition state can be mapped more exactly by investigating tritium and deuterium kinetic isotope effects in the oxidation of $CH_3CT_2COO^-$, $CH_3CHTCOO^-$, $CH_3CD_2COO^-$ and $CH_3CHDCOO^-$ with permanganate and manganate in alkaline medium, which permit one to evaluate directly the k_H/k_T and k_H/k_D ratios.

The complete elucidation of the mechanism requires one also to study secondary deuterium and tritium isotope effects in the oxidation of $CD_3CH_2COO^-$ and perdeuteriated propionate, $CD_3CD_2COO^-$. As a start, the tritium isotope effect[436,437] in the oxidation of propionate singly labelled with tritium in the α-position, $CH_3CHTCOO^-$, was undertaken. In the competitive physical-chemical method of study of KIE of tritium (equations 226) one determines at tracer concentration of tritium-labelled propionate the fractionation factor η (equation 227) by measuring the specific activity of water vapour A_t over the reacting solution at different degrees of oxidation of propionate, f (corrected for vapour pressure isotope effect, VPIE, if necessary)[436c].

$$\begin{aligned}
&CH_3CH_2COONa + \text{oxidant} \xrightarrow{2k_{HH}} CH_3\underset{\displaystyle X}{\underset{|}{C}}HCOONa + H_2O \\
&CH_3CHTCOONa + \text{oxidant} \xrightarrow{k_{TH}} CH_3\underset{\displaystyle X}{\underset{|}{C}}HCOONa + HTO \qquad (226) \\
&CH_3CHTCOONa + \text{oxidant} \xrightarrow{k_{HT}} CH_3\underset{\displaystyle X}{\underset{|}{C}}TCOONa + H_2O
\end{aligned}$$

$$\eta = k/\overset{*}{k} = 2k_{HH}/(k_{TH} + k_{HT}) = \ln(1 - f)/\ln(1 - A_t/A_\infty) \qquad (227)$$

The value of the primary tritium isotope effect, estimated by using relation 228, depends on the magnitude of the secondary tritium isotope effect $s = k_{HT}/k_{HH}$.

$$k_{HH}/k_{TH} = \eta/(2 - \eta s) \qquad (228)$$

Recently it has been assumed[438] that $s = k_{HD}/k_{HH} = 1$ within $\pm 10\%$ error at 298 K. Within this approximation all $\eta \geqslant 2$ should be rejected, since already in the case $k_{HH}/k_{TH} = \eta/(2\text{-}\eta) = \infty$ when $\eta = 2$.

In earlier careful studies[439,440] the average value $k_{HH}/k_{HD} = s^{-1} = 1.097 \pm 0.060$ was found at 25 ± 1 °C. The exact value of k_{HH}/k_{HT} can be deduced from the experimental factor η which falls in the range 2.042 ± 0.024 (at 93 °C) to 2.211 ± 0.05 (at 27 °C) with

$KMnO_4$ in 3 M NaOH, and in the range 2.04 ± 0.04 (at 93 °C) to 2.17 ± 0.05 (at 53 °C) with K_2MnO_4, using also the experimental tritium kinetic isotope effect in the oxidation of CH_3CT_2COONa (equation 229). Accepting at present that $k_{HH}/k_{HT} = s^{-1} = 1.15$ and taking $\eta = 2.2$ and 2.05, we obtain for k_{HH}/k_{TH} the values 25.3 and 9.43, respectively. Obviously the determination of the fractionation factor η alone cannot serve as a reliable method of estimating the primary kinetic tritium isotope effect. Nonetheless, the kinetic tritium fractionation factor estimated by measuring the tritium specific activity of water vapour over the reacting solution fully confirms the conclusion drawn from the ^{14}C isotope effect studies, that the α-C—H bond is substantially weakened in the transition state of the rate-controlling step, and suggests additionally the possibility of large tunnelling in the investigated hydrogen transfer process.

$$CH_3CT_2COONa \xrightarrow[\text{oxidant}]{2k_{TT}} CH_3\underset{\displaystyle X}{\overset{\displaystyle |}{C}}TCOONa + HTO \qquad (229)$$

6. Deuterium isotope effect in the oxidation of sodium propionate (2-$^2H_2$) with permanganate and with manganate

To evaluate strictly the primary and secondary tritium isotope effects in the reaction set (equations 226) the k_{HH}/k_{TT} ratio in the reaction in equation 229 has to be measured also. We have chosen the oxidation of α,α-dideuteriopropionate with alkaline permanganate (equations 230 and 230a) and with alkaline manganate (equations 231 and 231a)

$$CH_3\overset{*}{C}D_2COO^- + 4MnO_4^- = \overset{*}{C}_2O_4^{2-} + \overset{*}{C}O_3^{2-} + 4MnO_2 + \overset{*}{H}O^- + 2\overset{*}{H}_2O$$

$\overset{*}{C}$ = ^{14}C-label, $\overset{*}{H}$ = deuterium enriched (230)

$$\ln\left[\left(1 - \frac{x}{a}\right)\Big/\left(1 - \frac{4x}{b}\right)\right] = (4a - b)k_{DD}t \qquad (230a)$$

$$CH_3CD_2COO^- + 6MnO_4^{2-} + 2H_2O = C_2O_4^{2-} + CO_3^{2-} + 6MnO_2 + 9OH^- \qquad (231)$$

$$\ln\left[\left(1 - \frac{x}{a}\right)\Big/\left(1 - \frac{6x}{b}\right)\right] = (6a - b)k_{DD}t \qquad (231a)$$

as the second step in our investigation program[256,257,260], where a is the initial concentration of propionate, b is the initial concentration of permanganate or manganate, x/a is the degree of oxidation of propionate, while x, $4x$ and $6x$ represent the concentrations of propionate, permanganate and manganate, respectively, that have reacted at the same time.

$$CH_3\overset{*}{C}H_2COONa + NaOD/D_2O \rightleftharpoons CH_3\overset{*}{C}D_2COONa + NaO\overset{*}{H}/\overset{*}{H}_2O \qquad (232)$$

Sodium α,α-dideuteriopropionate has been obtained in six successive isotopic exchanges at elevated temperatures[256,257] (equation 232) between sodium propionate and NaOD in D_2O. The NMR ^1H spectrum of the deuterated propionate showed complete deuteration at $C_{(2)}$. Similarly [2-^{14}C], (2-$^2H_2$)-propionate has been prepared from [2-^{14}C]propionate for future study of the effect of deuteration on the ^{14}C KIE in the oxidation of [2-^{14}C]propionate. Theoretical calculations of ^{14}C KIE in this process suggest the possibility of assessing the contribution of tunnelling to the observed KIE by combining precise experiments and calculations[448] for $CH_3\,{}^{14}C^2H_2COO^-$ and for $CH_3\,{}^{14}CH_2COO^-$.

All the oxidations were carried out to more than 10% of the reaction to eliminate any effect of traces of isotopic impurities noted in experiments carried out at low fractions of oxidations[256]. These preliminary experiments showed that the deuterium isotope effect, k_{HH}/k_{DD}, in the oxidation of sodium α,α-dideuteriopropionate with manganate is much larger than with permanganate. The k_{HH}/k_{DD} ratios were, for both reactions (230 and 231), higher than the calculated isotope effects corresponding to (C—H/C—D) bond rupture governed by the difference in the zero-point energy values of the corresponding isotopic bonds[441]. The KIE increase with increasing concentration of sodium hydroxide. In more concentrated NaOH solutions MnO_4^{2-} is more stable and the disproportionation of manganate into permanganate and manganese dioxide is diminished (equation 233).

$$3MnO_4^{2-} + 2H_2O = 2MnO_4^- + MnO_2 + 4HO^- \quad (233)$$

In neutral and acidic solutions manganate disproportionates fast to manganese dioxide and permanganate[442–444].

a. Oxidation with manganate. The temperature dependence of the primary deuterium isotope effect in the oxidation of sodium propionate (2-$^2H_2$) with manganate at 40–93.5 °C has been investigated in 3 M NaOH. The mean values of bimolecular rate constants k_{HH} and k_{DD}, calculated from equation 231a, and their ratios are presented in Table 1.

The data for k_{HH} in Table 1 give the Arrhenius plot of ln k_{HH} versus $1/T$ for which the correlation coefficient is 0.99996, the slope is 8.14942 corresponding to 16.189 kcal mol^{-1} and the intercept is 19.6852 corresponding to 3.5414×10^8 min^{-1}. The Arrhenius plot of ln k_{DD} versus $1/T$ has correlation coefficient 0.99984, slope 9.27355 corresponding to 18.4215 kcal mol^{-1} and intercept is 20.517402 corresponding to 8.1394×10^8 min^{-1}. Thus in the semiclassical isotope effect equation

$$k_{HH}/k_{DD} = (A_{HH}/A_{DD})\exp[(E_a^D - E_a^H)/RT]$$

valid over a short range of temperature, we have an activation energy difference $\Delta E = (E_a^D - E_a^H) = 2.233$ kcal mol^{-1} which is larger than the difference between the zero-point energy of the C$^\alpha$—H and C$^\alpha$—D bonds (1.15 kcal mol^{-1}) and $A_{HH}/A_{DD} = 0.4351$ which is beyond the limits ($0.5 < A_H/A_D < \sqrt{2}$) predicted by the transition state theory in the absence of tunnelling. Values of A_H/A_D smaller than 0.5 and differences of activation energies larger than the appropriate differences of the zero-point energy demonstrate tunnelling. The k_{HH}/k_{DD} ratios in Table 1 are much larger than the ZPEC

TABLE 1. Oxidation of sodium propionate (2-$^1H_2$) and sodium propionate (2-$^2H_2$) with manganate in 3.0 MNaOH aqueous solutions

Temp. (°C)	k_{HH} (dm^3 mol^{-1} min^{-1})	k^α_{DD} (dm^3 mol^{-1} min^{-1})	k_{HH}/k^α_{DD}
93.5	78.9×10^{-3}	8.23×10^{-3}	9.587
70.5	17.91×10^{-3}	1.604×10^{-3}	11.16
49.5	37.21×10^{-4}	2.76×10^{-4}	13.48
39.6	17.36×10^{-4}	1.043×10^{-4}	16.64
30.0	83.2×10^{-5}	4.06×10^{-5}	20.5[a]

[a] Value determined later and not included in calculations of kinetic parameters[256].

TABLE 2. Deuterium isotope effects calculated for hydrogen transfer from α-carbon of sodium propionate to oxygen of manganate

Temp. (°C)	Z.P.E.C[a]	Q_H/Q_D[b]	$k_{(C-H)}/k_{(C-D)}$[c]
25	6.7814	3.0075	20.395
39.6	6.2019	2.4931	15.4620
49.5	5.8643	2.2638	13.2756
70.5	5.2637	1.9426	10.225
93.5	4.7433	1.7278	8.1955

[a] Zero-point energy contributions to the deuterium KIE were calculated with the sinh approximation, ZPEC = $[\sinh(u_{(C-H)}/2)/\sinh(u_{(C-D)}/2]$ taking $\omega_{C-H} = 2985\ cm^{-1}$, $\omega_{C-D} = 2191.68\ cm^{-1}$, $u = hc\omega/kT$, where h is Planck's constant, k is Boltzmann's constant, c is the velocity of light and T is absolute temperature.
[b] The tunnel corrections Q_H and Q_D to the reaction velocity constants were calculated with the use of the Bell equation[441].
[c] These kinetic deuterium isotope effects were obtained by multiplying the ZPEC factors by the Q_H/Q_D ratios at each temperature.

values given in Table 2. However, the semiclassical ZPEC values multiplied by the tunnel corrections Q_H/Q_D estimated with the use of the Bell equation[441] reproduce quite well the k_{HH}/k_{DD} ratios found experimentally.

b. Oxidation with permanganate. Basic (diluted) and neutral solutions are suitable to study deuterium isotope effects[257,260] in the oxidation of sodium propionate (2-$^2H_2$) with permanganate, since manganate ions disproportionate rapidly[422-444] in such conditions into permanganate and manganese dioxide (equation 233) and the KIE corresponds entirely to the oxidation of propionate with permanganate. The effect of the increase in the ionic strength of the solution on the rate constants k, calculated from equation 230a, is taken into account quite well[260] by the approximate equation 199. The experimental data are given in Tables 3–5.

TABLE 3. Oxidation of sodium propionate (2-$^1H_2$) and (2-$^2H_2$) in 0.48 M NaOH aqueous solutions (all rate constants are given in $dm^3\ mol^{-1}\ min^{-1}$)

Temp. (°C)	k_{HH}[a]	k^{α}_{DD}[a]	k_{HH}/k^{α}_{DD}	k_{oHH}	k^{α}_{oDD}	k_{oHH}/k^{α}_{oDD}
81	3.16×10^{-2}	4.02×10^{-3}	7.861	8.43×10^{-3}	1.08×10^{-3}	7.81
70.4	1.42×10^{-2}	1.732×10^{-3}	8.199	3.93×10^{-3}	4.81×10^{-4}	8.17
50.1	2.684×10^{-3}	2.85×10^{-4}	9.418	7.93×10^{-4}	8.45×10^{-5}	9.38
39.6	1.071×10^{-3}	9.78×10^{-5}	10.951	3.257×10^{-4}	2.98×10^{-5}	10.93
30.0	4.174×10^{-4}	3.415×10^{-5}	12.223	1.300×10^{-4}	1.07×10^{-5}	12.14

[a] Calculated from equation 230a.

TABLE 4. Oxidation of sodium propionate (2-$^1H_2$) and (2-$^2H_2$) with permanganate in 0.24 M NaOH aqueous solutions (all rate constants are given in $dm^3\ mol^{-1}\ min^{-1}$)

Temp. (°C)	k_{HH}[a]	k^{α}_{DD}[a]	k_{HH}/k^{α}_{DD}	k_{oHH}	k^{α}_{oDD}	k_{oHH}/k^{α}_{oDD}
81.2	3.19×10^{-2}	3.732×10^{-3}	8.548	9.31×10^{-3}	1.14×10^{-3}	8.17
70.5	1.381×10^{-2}	1.581×10^{-3}	8.735	4.29×10^{-3}	4.99×10^{-4}	8.60
50.5	2.680×10^{-3}	2.646×10^{-4}	10.129	8.66×10^{-4}	8.66×10^{-4}	10.37
39.6	9.11×10^{-4}	8.06×10^{-5}	11.303	3.07×10^{-4}	$2.58_8 \times 10^{-5}$	11.86
30.5	4.10×10^{-4}	3.39×10^{-5}	12.094	1.340×10^{-4}	$1.15_8 \times 10^{-5}$	11.57

[a] Calculated from equation 230a.

TABLE 5. Rate constants of the oxidation of sodium propionate (2-$^1H_2$) and (2-$^2H_2$) with permanganate in water solutions (all rate constants are given in $dm^3\ mol^{-1}\ min^{-1}$)

Temp. (°C)	k_{HH}[a]	k^{α}_{DD}[a]	k_{HH}/k^{α}_{DD}	k_{oHH}	k^{α}_{oDD}	k_{oHH}/k^{α}_{oDD}
95.75	$7.71_4 \times 10^{-2}$	$1.098_4 \times 10^{-2}$	7.023	2.496×10^{-2}	3.597×10^{-3}	6.94
81.25	2.756×10^{-2}	3.655×10^{-3}	7.540	9.32×10^{-3}	1.232×10^{-3}	7.56
70.1	1.131×10^{-2}	1.40×10^{-3}	8.079	4.02×10^{-3}	4.93×10^{-4}	8.15
70.8	—	1.492×10^{-3}	—	—	5.24×10^{-4}	—
60.2	4.88×10^{-3}	5.656×10^{-4}	8.628	1.764×10^{-3}	2.036×10^{-4}	8.664
50.2	1.903×10^{-3}	2.133×10^{-4}	8.922	7.402×10^{-4}	7.79×10^{-5}	9.50

[a] Calculated from equation 230a.

TABLE 6. Deuterium isotope effect on the activation parameters in the permanganate oxidation of sodium propionate (2-$^2H_2$) in water solutions

Activation parameter[a]	Concentration of sodium hydroxide		
	0.000 M	0.24 M	0.48 M
$A_{HH,\ Arrh}$ ($dm^3\ mol^{-1}\ s^{-1}$)	2.59×10^8	1.30×10^8	7.24×10^7
$(A_{HH}/A_{DD})_{Arrh}$	1.062	0.930	0.531
$Q_{HH,\ Arrh}$ (kcal mol^{-1})	19.063	18.463	18.046
$(Q_{DD} - Q_{HH})_{Arrh}$ (kcal mol^{-1})	1.388	1.545	1.876
$A_{oHH,\ Arrh}$ ($dm^3\ mol^{-1}\ s^{-1}$)	2.9×10^7	1.89×10^7	7.75×10^6
$(A_{oHH}/A_{oDD})_{Arrh}$	0.71	0.76	0.53
Q_{oHH} (kcal mol^{-1})	18.34	17.958	17.399
$(Q_{oDD} - Q_{oHH})_{Arrh}$ (kcal mol^{-1})	1.666	1.674	1.872
$\Delta S^{\neq}_{HH}$ (e.u.)	−26.633	−27.169	−29.291
$\Delta S^{\neq}_{DD} - \Delta S^{\neq}_{HH}$ (e.u.)	0.687	0.553	1.355
$\Delta H^{\neq}_{HH}$ (kcal mol^{-1})	17.597	17.388	16.717
$\Delta H^{\neq}_{DD} - \Delta H^{\neq}_{HH}$ (kcal mol^{-1})	1.666	1.674	1.903

[a] Explanation of abbreviations used in Table 6 are given in the text.

Activation parameters calculated from the data presented in Tables 3–5 as well as enthalpies $\Delta H^{\neq}$ and entropies $\Delta S^{\neq}$ of activation calculated with the aid of the absolute rate theory are collected in Table 6. These data clearly indicate that in all three solutions the KIE are smaller than in the case of oxidation in 3 M NaOH. The tunnelling in water and at low concentrations of alkali is less pronounced, approaching the classical limits. Direct comparison of the experimental with the theoretical deuterium isotope effects[256] will be possible only after further study. In the oxidation in concentrated sodium hydroxide solutions the contribution of tunnelling to the observed DKIE is very large. Table 6 also shows that $\Delta S^{\neq}$ values are more positive in diluted than in concentrated NaOH solutions. The entropies of activation for the oxidation of propionate (2-$^2H_2$) are more favourable than for propionate (2-$^1H_2$), and $\Delta S^{\neq}_{DD} - \Delta S^{\neq}_{HH}$ has positive values. The activation enthalpy difference in water is larger than the corresponding difference in the free energy of activation.

The possible mechanisms, intermediates and activated complexes in oxidations of organic compounds have been reviewed by Stewart[442,443] and Freeman[444] as well as in other volumes[445–447] although permanganate oxidation of propionate[408] has not been included in these reviews probably because of its apparent complexity.

Isotope effect studies with (2-$^2H_2$)-, (2-^{3}H)- and (2-^{14}C)-propionates indicated that, after the attack of the permanganate ion at the ethyl group of propionate, encounter complexes are formed and the transfer of hydrogen from the α-carbon to the oxygen of the oxidizer within these complexes determines the rate of oxidation. The observed distribution of carbon-14 of (1-^{14}C)- and (3-^{14}C)-labelled propionates takes place in the subsequent fast oxidation reactions of intermediates[449].

Large negative entropies of activation (presented in Table 6, and an even larger negative value $\Delta S^{\neq}_{HH} \cong -42.564$ e.u. found in the oxidation of propionate with doubly charged manganate ion in 3 M NaOH) show that the structure of the transition state is more ordered than the initial structure of the reactants, pointing to cyclic transition states and/or solvations. Entropies of activation for the dideuteriopropionate are slightly greater than for the diprotiopropionate.

The C—H bond scission in the rate-controlling step is accompanied by a considerable tunnel effect in the case of oxidation with doubly charged manganate ions in 3 M NaOH which does not disappear completely in the oxidation with singly charged permanganate ion even in neutral water solution. Steric compression in the transition state making the energy barrier higher and narrower is considered as the main reason of large tunnelling observed in sterically hindered proton transfers from carbon acids to organic bases[450]. The presence of the negatively charged carboxylate group, adjacent to the reaction center, in propionate increases the potential energy barrier by steric and electronic repulsions, which are probably responsible for the relatively large tunnelling observed especially in the oxidation of propionate with manganate (and also permanganate) in sodium hydroxide solutions.

7. Kinetic deuterium isotope effect in the oxidation of sodium butyrate (2-$^2H_2$) with manganate

a. Introduction. Hydrocarbons are insoluble or nearly insoluble in aqueous bases and kinetic studies with alkanes have been carried out in acidic or neutral media only[451–457]. However, aliphatic carboxylic acids provide the opportunity to study the interaction of the oxidizers with aliphatic chains also in basic solutions. Carboxylates are deuterated easily at $C_{(2)}$, by direct H/D exchange and permit one to determine the points of attack by the oxidizer [Mn(VII,VI,V)] on the aliphatic chain. The results of such determinations with short-chain carboxylates and manganate are presented in this and the next two sections.

b. α,α-*Dideuteriobutyrate.* This has been obtained[258] in threefold successive hydrogen/deuterium exchanges between $CH_3CH_2CH_2COO^-$ and D_2O catalysed by NaOD. The sodium butyrate was obtained using sodium deuteriooxide. The NMR ^1H spectrum showed complete deuteration of the sodium salt of butyrate at the $C_{(2)}$ position.

c. The second-order rate constants k_{HH} and d^{α}_{DD} expressed in $dm^3\ mol^{-1}\ min^{-1}$, corresponding to oxidation of normal sodium butyrate and of (2-$^2H_2$) butyrate, with manganate, both in 3 M NaOH solutions, proceeding according to equation 234, were calculated with the aid of equation 234a:

$$CH_3CH_2CH_2COO^- + 9MnO_4^{2-} + 3H_2O = 2CO_3^{2-} + C_2O_4^{2-} + 9MnO_2 + 13HO^- \quad (234)$$

$$\ln\left(1 - \frac{x}{a}\right)\Big/\left(1 - \frac{9x}{b}\right) = (9a - b)kt \quad (234a)$$

where x/a is the degree of oxidation of butyrate, a is the initial concentration of sodium butyrate, b is the initial concentration of potassium manganate and t is the time. The Arrhenius dependences of k_{HH} and k_{DD} are given by equations 235 and 236.

$$\ln \bar{k}_{HH} = 22.35293 - 9220.56/T, \text{ correlation coefficient } 0.999984 \quad (235)$$

$$\ln \bar{k}^{\alpha}_{DD} = 21.89667 - 9332.24/T, \text{ correlation coefficient } 0.999933 \quad (236)$$

$$Q_{DD} - Q_{HH} = (18.538 - 18.316)\ \text{kcal mol}^{-1} = 0.222\ \text{kcal mol}^{-1}$$

The k_{HH}/k_{DD} and $k_{\alpha HH}/k^{\alpha}_{\alpha DD}$ ratios using equation 199 are given in Table 7. The values indicate that, as in propionate (2-$^2H_2$), the rupture of the C—H bond in sodium butyrate proceeds also with a large primary deuterium isotope effect. The rupture of the β-C—H bond initiates the oxidation of the $CH_3CH_2CD_2COONa$ isotopic isomer with manganate in 3 M NaOH. Equations 237 and 238 define the rate constants corresponding to rate-determining steps in the oxidation of butyrate with manganate, where X is a radical centre, an oxygen of the oxidizer, $OMn(OH)O_2^{2-}$, or a carbonium ion (in the case of hydride abstraction).

$$CH_3CH_2CH_2COO^- \xrightarrow{k_{\alpha HH}} CH_3CH_2\underset{X}{C}HCOO^- \qquad CH_3\underset{X}{C}HCH_2COO^- \quad (237)$$

($k_{\beta HH}$)

$$CH_3CH_2CD_2COO^- \xrightarrow{k_{\alpha DD}} CH_3CH_2\underset{X}{C}DCOO^{-1} \qquad CH_3\underset{X}{C}HCD_2COO^- \quad (238)$$

($k'_{\beta HH}$)

Equation 239 gives the relation between the $k_{\alpha HH}/k_{\alpha DD}$ ratios presented in Table 7 and the rate constants shown by equations 237 and 238.

$$k_{\alpha HH}/k_{\alpha DD} = (k_{\alpha HH} + k_{\beta HH})/(k_{\alpha DD} + k'_{\beta HH}) \quad (239)$$

TABLE 7. The effect of deuteriation at $C_{(2)}$ on k_{HH} values

Temperature (°C)	$(k_{HH}/k^{\alpha}_{DD})_{exp.}$	k_{oHH}/k^{α}_{oDD}
60.40	2.196	2.184
70.24	2.194	2.196
92.85	2.165	2.16
100.1	2.108	2.114

Assuming in the first approximation that α and β methylene groups in $CH_3CH_2CH_2COO^-$ are attacked and react at an equal rate, and the abstraction of β-hydrogens from $C_{\gamma}H_3C_{\beta}H_2C_{\alpha}D_2COO^-$ is not effected by the deuteration of the α-hydrogens, that is, $k_{\alpha HH} \cong k_{\beta HH} \cong k'_{\beta HH}$, we obtain the simplified relation (equation 240) if the $k_{\alpha HH}/k_{\alpha DD}$ ratio expressing the primary kinetic deuterium isotope effect is very large [as found before in the oxidation of (2-$^2H_2$)propionate].

$$(k_{oHH}/k_{oDD}) \cong 2/(1 + k_{\alpha DD}/k_{\alpha HH}) \cong 2 \tag{240}$$

The values in Table 7 indicate that the above assumptions are reasonable and the $k'_{\beta HH}/k_{\beta HH}$ ratio is in the range 0.9–1.0. In addition, the Arrhenius temperature dependences (equations 235 and 236) give nearly the same energies of activation (Q_{oHH} and Q_{oDD}) and enthalpies of activation ($\Delta H^{\neq}_{oHH}$ and $\Delta H^{\neq}_{oDD}$). The rate-determining bond-breaking steps are followed by subsequent, much faster oxidation reactions, yielding carbonate and oxalate. Specific activities of carbon in carbonates and in oxalates were within $\pm 3\%$ of comparable values. These preliminary[258] data indicate that a highly symmetrical intermediate is formed which subsequently splits into oxalate and carbonate, producing a nearly statistical ^{14}C distribution between the final products.

8. Deuterium kinetic isotope effect in the oxidation of sodium valerate (2-$^2H_2$) with manganate

The results presented above imply that in the oxidation of α,α-dideuteriovalerate with manganate in 3 M NaOH the k_{HH}/k^{α}_{DD} ratio should be 1.5 at room temperature. $CH_3(CH_2)_2CD_2COONa$ has been synthesized[261] and both normal and (2-D_2) sodium valerate have been oxidized. The oxidation reaction proceeds according to equation (241).

$$C_4H_9COONa + 11.5K_2MnO_4 + 4H_2O = 2CO_3^{2-} + 1.5C_2O_4^{2-} + 11.5\,MnO_2 + 17\,HO^- \tag{241}$$

The Arrhenius temperature dependence of k_{HH} and k_{DD} calculated by equation 242 is presented in equation 243 and 244

$$\ln\left(1 - \frac{x}{a}\right)\Big/\left(1 - \frac{12x}{b}\right) = (12a - b)kt \tag{242}$$

$$\ln \bar{k}_{HH} = 20.85294 - 8529.66/T,\ R = 0.999934 \tag{243}$$

$$\ln \bar{k}^{\alpha}_{DD} = 20.48351 - 8534.77/T,\ R = 0.99965 \tag{244}$$

where R is the correlation

$$Q^{\alpha}_{DD} - Q_{HH} = (16.954 - 16.944)\ \text{kcal mol}^{-1} = 0.010\ \text{kcal mol}^{-1}$$

$$(A_{HH}/A_{DD})_{Arrh} = (1.897 \times 10^{7}/1.311 \times 10^{7}) = 1.447$$

The experimental k_{HH}/k^{α}_{DD} ratios and the ratio of k_{oHH} and k_{oDD} values are presented in Table 8.

Previous studies with sodium salts of acetic, propionic and butyric acids have shown[381,382,385,437,258] that the terminal methyl groups are quite resistant towards the oxidation with $KMnO_4$ or K_2MnO_4 and only attack at the methylene groups leads to the oxidation and degradation of the aliphatic chain. Hence equation 245 relates the experimentally determined k_{HH}/k^{α}_{DD} ratios to the rate constants shown in equations 246 and 247.

$$(k_{oHH})k^{\alpha}_{oDD})_{exp} = (k_{\alpha HH} + k_{\beta HH} + k_{\gamma HH})/(k_{\alpha DD} + k'_{\beta HH} + k'_{\gamma HH}) \tag{245}$$

$$\begin{array}{l} \\ \\ \text{CH}_3\text{C}_\gamma\text{H}_2\text{C}_\beta\text{H}_2\text{C}_\alpha\text{H}_2\text{COONa} \\ \\ \\ \end{array} \begin{array}{l} \xrightarrow{k_{\alpha HH}} \\ \xrightarrow{k_{\beta HH}} \\ \xrightarrow{k_{\gamma HH}} \\ \\ \end{array} \begin{array}{l} \text{CH}_3\text{CH}_2\text{CH}_2\text{CHCOONa} \\ \qquad\qquad\quad \vert \\ \qquad\qquad\quad \text{X} \\ \text{CH}_3\text{CH}_2\text{CHCH}_2\text{COONa} \\ \qquad\quad \vert \\ \qquad\quad \text{X} \\ \text{CH}_3\text{CHCH}_2\text{CH}_2\text{COONa} \\ \quad \vert \\ \quad \text{X} \end{array} \tag{246}$$

$$\begin{array}{l} \\ \\ \text{CH}_3\text{C}_\gamma\text{H}_2\text{C}_\beta\text{H}_2\text{C}_\alpha\text{D}_2\text{COONa} \\ \\ \\ \end{array} \begin{array}{l} \xrightarrow{k_{\alpha DD}} \\ \xrightarrow{k'_{\beta HH}} \\ \xrightarrow{k'_{\gamma HH}} \\ \\ \end{array} \begin{array}{l} \text{CH}_3\text{CH}_2\text{CH}_2\text{CDCOONa} \\ \qquad\qquad\quad \vert \\ \qquad\qquad\quad \text{X} \\ \text{CH}_3\text{CH}_2\text{CHCD}_2\text{COONa} \\ \qquad\quad \vert \\ \qquad\quad \text{X} \\ \text{CH}_3\text{CHCH}_2\text{CD}_2\text{COONa} \\ \quad \vert \\ \quad \text{X} \end{array} \tag{247}$$

Assuming again that $k_{\alpha HH} \cong k_{\beta HH} = k_{\gamma HH} = k'_{\gamma HH}$ we obtain the simple relation (equation 248) which gives the calculated values shown in Table 9.

$$(k_{oHH}/k_{oDD})_{exp} = \frac{3}{1 + (k'_{\beta HH}/k_{\alpha HH}) + (k_{\alpha DD}/k_{\alpha HH})} \tag{248}$$

A comparison of the experimental ratios k_{HH}/k^{α}_{DD} (Table 8) and the values of k_{oHH}/k^{α}_{oDD} (Table 9) leads to the conclusion that the three methylene groups in valerate[261] are kinetically equivalent or nearly equivalent in the reaction and that there is a very large primary kinetic deuterium isotope effect in the rupture of the C—D bonds in valerate. This would make it very worthwhile to study the oxidation of perdeuterated valerate.

Deuterium isotope effects in the hydroxylation of perdeuteriated cyclohexane catalysed by iron porphyrin complexes[458], in the hydroxylation of pentane-D_4,

TABLE 8. The effect of α-deuteration of sodium valerate on the rate constants for oxidation with manganate in 3 M aqueous NaOH

Temp. (°C)	60.23	70.4	80.60	92.83
k_{HH}/k^{α}_{DD}	1.461	1.481	1.468	1.425
k_{oHH}/k^{α}_{oDD}	1.461	1.486	1.454	1.418

$CH_3CD_2CH_2CD_2CH_3$, using 'iodosobenzene and mn(TTTPP)OAc[459] and in the hydroxylation of D_{12}-cyclohexane by $KHSO_5$, catalysed by manganese porphyrin complexes and other metalloporphyrins[460], were found to be 12.9 ± 1, 3.5 and 2.0 ± 0.2, respectively.

9. Kinetic deuterium isotope effect in the oxidation of sodium caproate (2-$^2H_2$) with manganate

Sodium (2-D_2) caproate has been synthesized in three successive exchange reactions between $CH_3(CH_2)_4COONa$ and excess of D_2O catalysed by NaOD at 190–200 °C[259]. It was used[259] to investigate the effect of α-deuteration on the oxidation rate with K_2MnO_4 in 3 M NaOH. Natural sodium caproate reacts with K_2MnO_4 at 50–93°C 1.30 ± 0.03 times faster than sodium caproate (2-$^2H_2$), in agreement with the expectations based on previous results obtained with other acids.

The Arrhenius temperature dependences of the rate constants calculated by equation 249 corresponding to equation 250 are given in equations 251 and 252.

$$\ln\left[\left(1-\frac{x}{a}\right)\Big/\left(1-\frac{14x}{b}\right)\right] = (14a-b)kt \tag{249}$$

$$CH_3(CH_2)_4COONa + 14K_2MnO_4 + 5H_2O = 2C_2O_4Na_2 + 2Na_2CO_3 + 14MnO_2 + 21HO^- \tag{250}$$

(where x/a is the degree of oxidation of sodium caproate, a is its initial concentration, b is the initial concentration of potassium manganate and t is the time),

$$\ln \bar{k}_{HH} = 20.26838 - 8289.11/T, \text{ correlation coefficient } 0.99973 \tag{251}$$

$$\ln \bar{k}^{\alpha}_{DD} = 19.97864 - 8281.88/T \text{ correlation coefficient } 0.99951 \tag{252}$$

$$Q_{DD} - Q_{HH} = (16.452 - 16.466) \text{ kcal mol}^{-1} = -0.014 \text{ kcal mol}^{-1}$$

$$A_{HH}/A_{DD} = (10.575 \times 10^6/7.915 \times 10^6) = 1.336$$

Equation 253 expresses the $(k_{oHH}/k^{\alpha}_{oDD})_{exp.}$ ratios in terms of the rate constants per methylene groups α–δ illustrated by equations 254 and 255. In equations 254 and 255 X is a radical centre, a compound of the Mn(V or IV), —O—Mn(HO)—O$^-$ or a carbonium ion.

TABLE 9. k_{oHH}/k_{oDD} ratios calculated from equation 248 taking $k_{\alpha HH}/k'_{\beta HH} = 1.05$ and $(k_{\alpha DD}/k_{\alpha HH})^{-1}$ primary isotope effects[256]

Temp. (°C)	30	39.6	49.5	70.5	93.8
$k_{\alpha HH}/k_{\alpha DD}$	20.4	16.644	13.482	11.166	9.584
$(k_{oHH}/k_{oDD})_{calc.}$	1.499	1.491	1.480_4	1.469	1.459

$$(k_{oHH}/k^{\alpha}_{oDD})_{exp.} = \frac{k_{\alpha HH} + k_{\beta HH} + k_{\gamma HH} + k_{\delta HH}}{k_{\alpha DD} + k'_{\beta HH} + k'_{\gamma HH} + k'_{\gamma HH}} \tag{253}$$

$$CH_3C_\delta H_2C_\gamma H_2C_\beta H_2C_\alpha H_2COONa \xrightarrow{k_{\alpha HH}} CH_3CH_2CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}HCOONa$$

$$\xrightarrow{k_{\beta HH}} CH_3CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}HCH_2COONa$$

$$\xrightarrow{k_{\gamma HH}} CH_3CH_2\underset{\displaystyle X}{\underset{|}{C}}HCH_2CH_2COONa$$

$$\xrightarrow{k_{\delta HH}} CH_3\underset{\displaystyle X}{\underset{|}{C}}HCH_2CH_2CH_2COONa \tag{254}$$

$$CH_3C_\delta H_2C_\gamma H_2C_\beta H_2C_\alpha D_2COONa \xrightarrow{k_{\alpha DD}} CH_3CH_2CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}DCOONa$$

$$\xrightarrow{k'_{\beta HH}} CH_3CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}HCD_2COONa$$

$$\xrightarrow{k'_{\gamma HH}} CH_3CH_2\underset{\displaystyle X}{\underset{|}{C}}HCH_2CD_2COONa$$

$$\xrightarrow{k'_{\delta HH}} CH_3\underset{\displaystyle X}{\underset{|}{C}}HCH_2CH_2CD_2COONa \tag{255}$$

Neglecting in the first approximation the secondary deuterium isotope effects, i.e. assuming that $k_{\alpha HH} = k'_{\beta HH} = k_{\gamma HH} = k'_{\gamma HH} = k_{\beta HH} = k'_{\delta HH} = k_{\delta HH}$ we obtain the simple relation in equation 256.

$$(k_{oHH}/k^{\alpha}_{oDD})_{exp.} \cong \frac{4}{3 + (k_{\alpha DD}/k_{\alpha HH})} \cong \frac{4}{3} = 1.33 \tag{256}$$

This expression indicates that when the primary deuterium kinetic isotope effect in the rupture of C_α—D versus C_α—H bonds in caproate is very large and $k_{\alpha DD}/k_{\alpha HH} = 0$, then $(k_{oHH}/$ and $k^{\alpha}_{oDD})_{calc.} = 1.33$. If there is no tunnelling and the primary deuterium isotope effect is caused solely by the zero-point energy differences of the C_α—D/C_α—H oscillators, then $k_{C-D}/k_{C-H} = 1/6 = 0.1667$ and $(k_{oHH}/k^{\alpha}_{oDD})_{calc.} = (4/3.1667) = 1.263$. Experimental k_{oHH}/k^{α}_{oDD} ratios are in the range 1.285–1.33. They indicate therefore that the D-KIE in the oxidation $CD_3(CD_2)_4COONa$ should be larger than the deuterium isotope effects determined only by the zero-point energy differences. The reasonable conclusion that all methylene groups in caproate react at the same rate should be corroborated by additional isotope effect studies.

A straightforward linear relation, $k = k_{ethane} + (n - 2)k_{(CH_2)}$, has been

found[451,455,457] in the oxidation of homologous series of straight-chain paraffins with CrO_3 and Mn(VII) in acidic media, particularly for larger values of *n*. However, some departures have been noted[454,455,256] (and explanations suggested) in propane and butane oxidations. Kinetic isotope effects depend drastically on the number of equivalent reactive sites in the molecule and can be used for unambiguous determination of kinetically equivalent sites in the case of lower alkyl groups, for instance, by measuring the k_{HH}/k^{α}_{DD} ratio; isotopic labelling changes only negligibly the structure of the aliphatic alkyl group and its interaction with solvents and reactants in comparison with the changes caused by the introduction of a new functional group or even by altering the number of methylene groups. Deuteriation changes mainly the reactivity of the carbon–hydrogen bond chiefly by a zero-point energy effect, and tunnel effects in favourable cases.

10. General remarks

The examples presented in Section IV.B clearly show once again that heavy atom isotope effects in combination with hydrogen isotope effects are universal and powerful research techniques for the elucidation of the mechanisms of complex gas-phase reactions[461,462], complex solution-phase reactions[408,256,463] and solid-phase reactions[264,265].

Isotope effects have been used for direct identification of the rate-controlling steps and associated covalent bond ruptures taking place in the slowest chemical reaction occurring in complicated reaction sequences found in condensed-phase (including solid state) processes. The presence of the polar group in carboxylic acids and in carboxylates makes them soluble in basic media and permits one to investigate the reactions of hydrocarbon moieties with various reactants, and particularly with oxidants, in neutral and basic solutions. Tracer and isotope effect studies with aliphatic carboxylic acids provide a rich ground of studies for present and future generations of organic and inorganic physical chemists.

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CHAPTER 10

The chemistry of lactones and lactams

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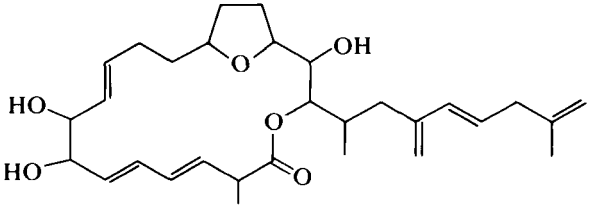
I. INTRODUCTION

Since the publication in 1979 of the previous review[1] in this series, progress in the chemistry of lactones and lactams has been rapid and a vast amount of work has been reported. Entirely new synthetic procedures have been devised, such as free-radical coupling and organometallic reactions, and much attention has been paid to asymmetric transformations leading to optically active, naturally occurring compounds. Enzyme-catalyzed reactions, which are just beginning to be explored, are of great promise in this respect. (See also chapter by G. G. Haraldsson in this volume.)

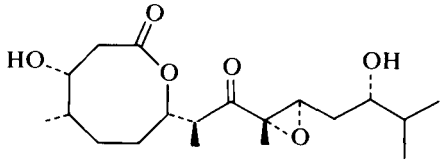
The present survey has been written as a sequel to the previous account[1] with an emphasis on very recent work. Review articles are cited wherever possible. The author had to be severely selective so that whole areas had to be omitted. This applies particularly to substances of medicinal interest, such as tumour-inhibiting α-methylene-γ-lactones, which have been reviewed extensively [2a–f], and β-lactam antibiotics.

II. LACTONES

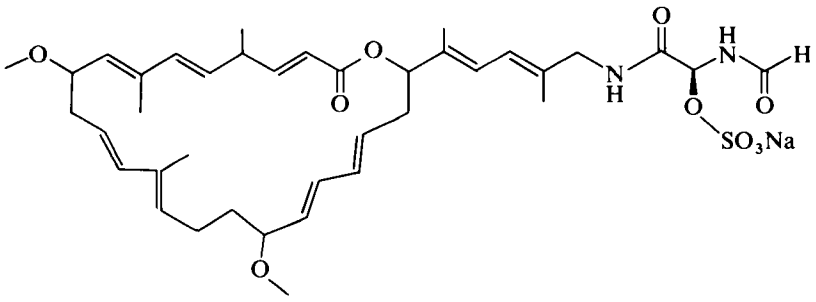
Interest has focused recently on the synthesis of macrocyclic lactones because the macrolide antibiotics belong to this class. The synthesis, chemistry and biological properties of the macrolides, of which more than one hundred are now known, have been reviewed repeatedly[3a–g]; here we will only mention six recently described compounds, the 19-membered lactone Amphidinolide E[4], Octalactin A[5], isolated from the marine bacterium *Streptomyces* sp., the 24-membered ring macrolide Iejimalide C from marine organisms[6], which exhibits antineoplastic activity, and the cytotoxic 26- and 27-membered macrocyclic lactones Amphidinolide H and G, isolated from microalgae[7].



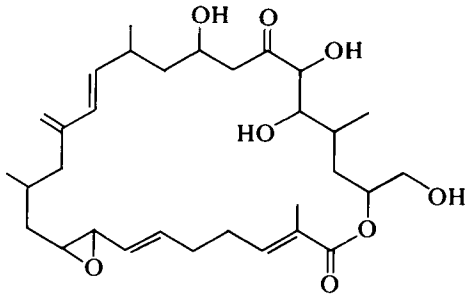
Amphidinolide E



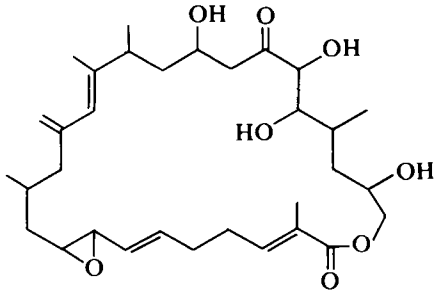
Octalactin A



Iejimalide C



Amphidinolide H

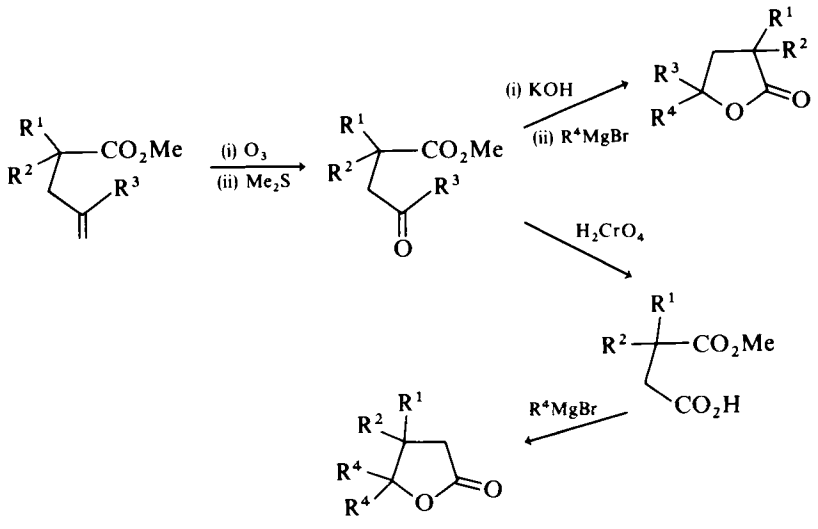


Amphidinolide G

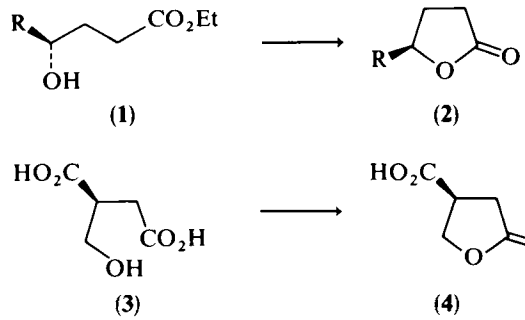
A. General Methods of Synthesis

1. From hydroxy acids and their synthetic equivalents

A general method for making various γ-lactones from esters of γ,δ-unsaturated acids is shown in equation 1[8]. Cyclization of the chiral hydroxy esters (**1**: R = Me, Et or n-C_8H_{17}) with acetic acid yields optically pure γ-lactones (**2**)[9]. (*S*)-(−)Paraconic acid (**4**) results from treatment of chiral (hydroxyethyl)succinic acid (**3**) with dilute hydrochloric acid[10].



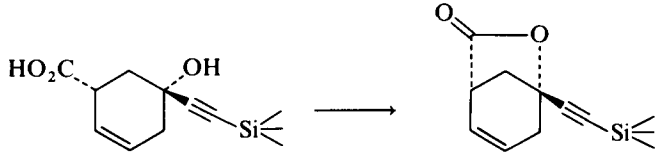
(1)



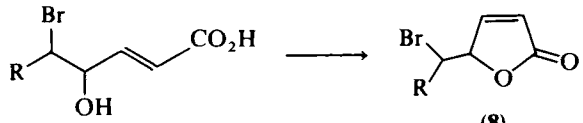
(1) (2)

(3) (4)

Lactonization under neutral conditions is exemplified by the conversion of the hydroxy ester (**5**) into the γ-lactone (**6**) in the presence of molybdenyl acetylacetonate[11]. Photolactonization of the *trans*-hydroxy acids (**7**; R = H or Me) results in the butenolides **8**; the corresponding methyl esters cyclize less readily[12].

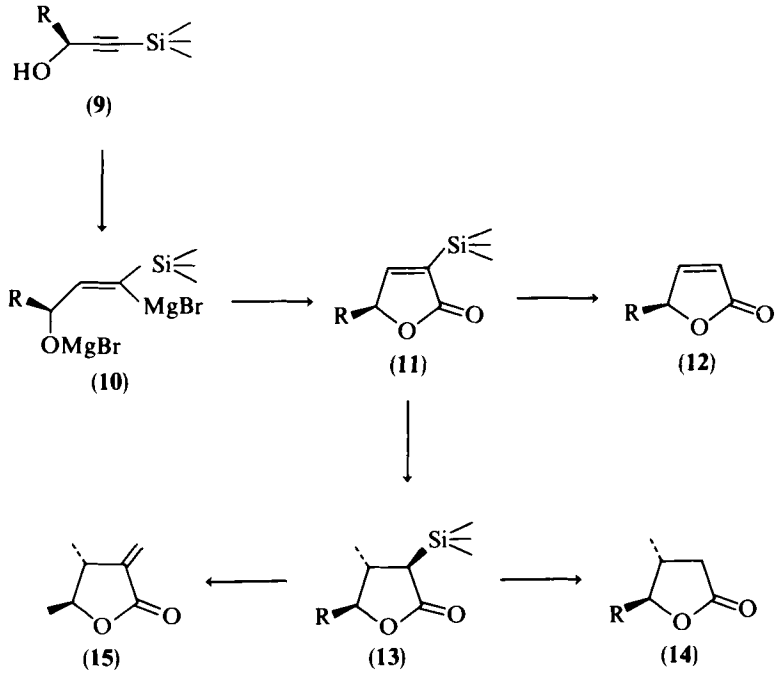


(5) (6)



(7) (8)

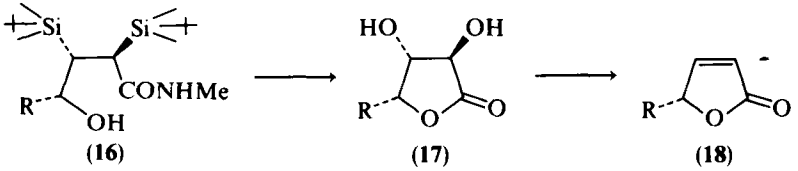
The synthesis and reactions of chiral α-trimethylsilyl-α,β-unsaturated butenolides are shown in Scheme 1[13]: the optically active propargyl alcohols (**9**) are converted into the magnesium derivatives (**10**) by the action of isobutylmagnesium bromide, catalysed by Cp_2TiCl_2. Treatment of **10** with carbon dioxide and subsequent acidification yields the trimethylsilylbutenolides **11**, which can be transformed into butenolides **12** by the action of aqueous tetrabutylammonium fluoride. A methyl group is introduced by reaction with lithium dimethylcuprate to give **13**. The latter can be converted into the *trans*-disubstituted butyrolactone **14** by aqueous ammonium fluoride, and into the methylene-γ-lactone **15** by treatment with formaldehyde.



R = Me, n-C_5H_{11} or CH_2OCH_2Ph

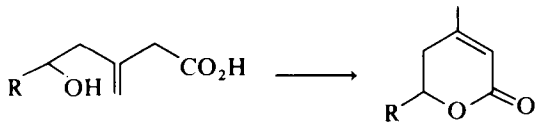
SCHEME 1

The chiral amides **16** (R = Bu, n-C_8H_{17} or n-$C_{13}H_{27}$) cyclize to the dihydroxylactones **17** in the presence of hydrochloric acid; subsequent treatment with a mixture of triiodoimidazole, triphenylphosphine and zinc in toluene gives the (*R*)-butenolides **18** in optical yields of 85–89% (equation 2)[14].

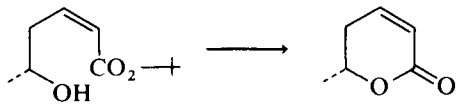


(2)

The hydroxy acids **19** are converted into the unsaturated δ-lactones **20** by the action of dilute hydrochloric acid[15]; the *t*-butyl ester **21** gives parasorbic acid (**22**) on acidic

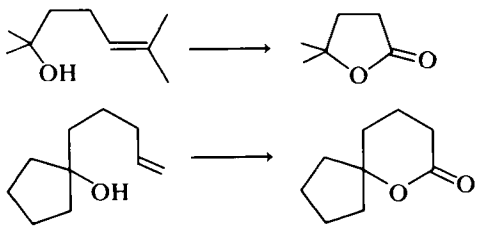


(**19**) (**20**)



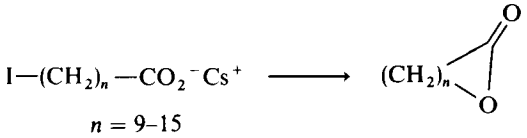
(**21**) (**22**)

hydrolysis[16]. ω-Hydroxyalkylalkenes are converted into γ- or δ-lactones with the loss of one or more carbon atoms by treatment with potassium permanganate and copper(II) sulphate in methylene chloride in the presence of a catalytic amount of water (equation 3)[17].

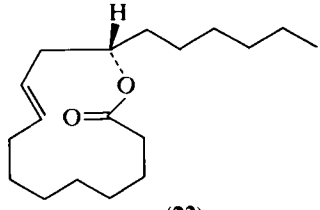


(3)

A simple high-yield synthesis of macrocyclic lactones of ring size 11–17 from the caesium salts of ω-iodoalkanoic acids is shown in equation 4. The method has been used for preparation of the 13-membered lactone **23** of ricinelaidic acid[18].



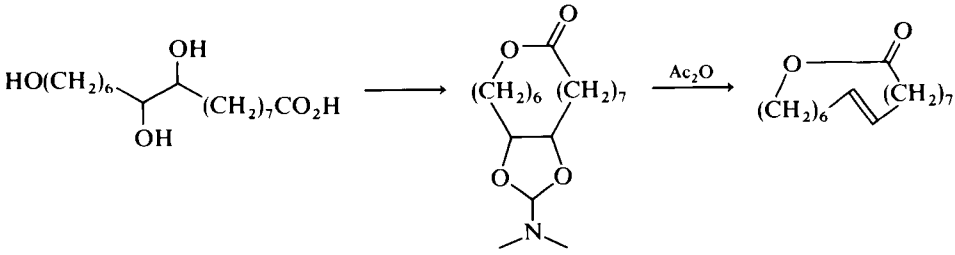
$n = 9$–15 (4)



(**23**)

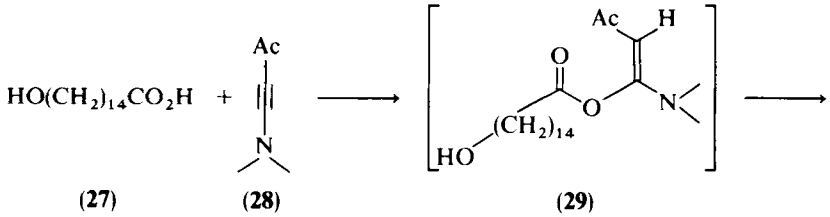
Potassium salts of ω-bromo acids cyclize in toluene by solid–liquid phase-transfer catalysis by tetrabutylammonium bromide to form 7-, 13-, 16- and 17-membered lactones in 70–95% yields; the 9-membered ring was obtained in only 26% yield[19]. Heating

threo-aleuritic acid (**24**) with the hindered dimethylformamide dineopentylacetal affords the acetal **25**, which is readily converted into *trans*-Δ^9-isoambrettolide (**26**), a 17-membered ring lactone[20].



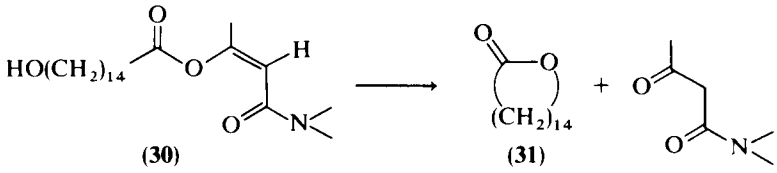
(**24**) (**25**) (**26**)

15-Hydroxypentadecanoic acid (**27**) reacts with the 'push–pull' acetylene **28** to yield the enol ester **30** via the transient adduct **29**. The enol ester readily cyclizes to the 16-macrolide **31** in the presence of the Lewis acid 10-camphorsulphonic acid (equation 5)[21]. Lactonization of ω-hydroxyalkanoic acids **32** (n = 5, 7, 10, 11, 12 or 14) has been



(**27**) (**28**) (**29**)

(5)

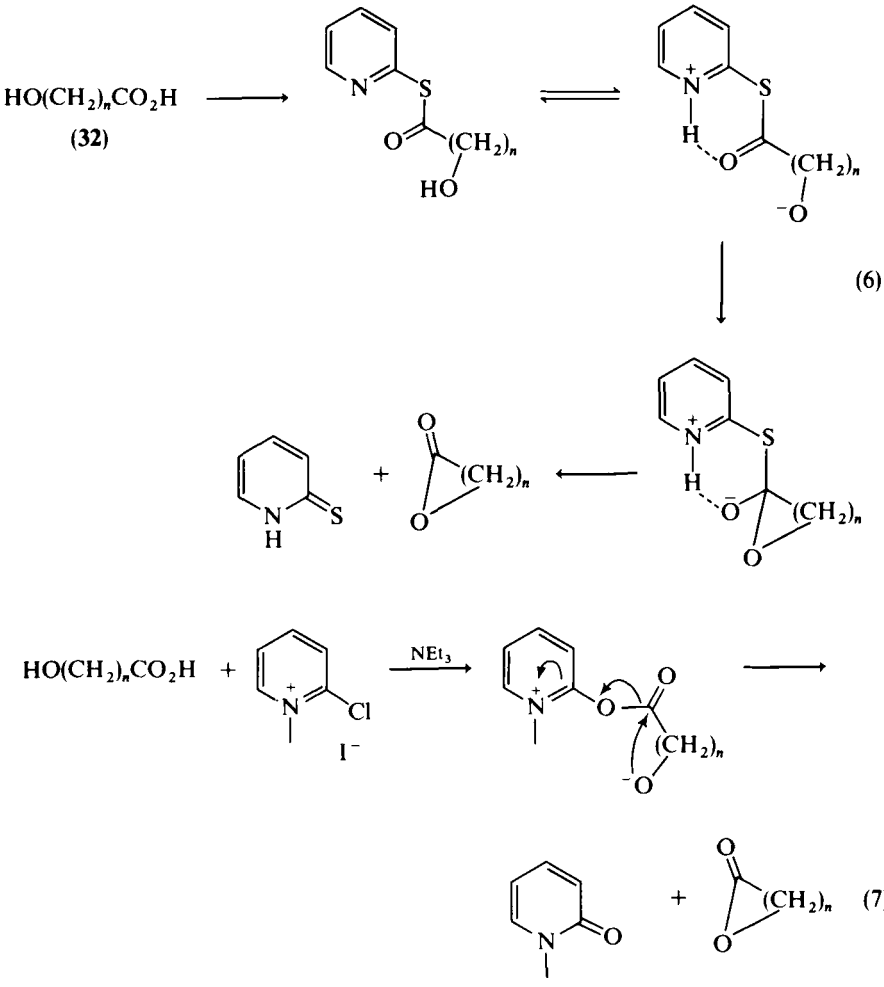


(**30**) (**31**)

achieved by Corey and Nicolaou[22] by treating the acids with di-α-pyridyl disulphide in refluxing xylene, which causes simultaneous activation of both the hydroxyl and carboxyl groups. The lactones (except for the nine-membered ring) are produced in good yields (equation 6).

A modification of this method was introduced by Mukaiyama[23]. It involves the use of 2-chloro-1-methylpyridinium iodide in acetonitrile or methylene chloride; lactonization occurs rapidly at moderate temperatures (equation 7). The trimethylsilyl derivatives **33** (n = 11, 12, 14 or 15) of hydroxy acids are converted into macrocyclic lactones in up to 94% yields in refluxing toluene in the presence of dipropylboryl trifluoromethanesulphonate, $Pr_2BO_3SCF_3$[24].

Optically active γ- and δ-lactones have been synthesized from acetoxy dicarboxylic acid chlorides and the chiral auxiliary (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine. The resulting diamides **34** furnished the lactone derivatives **35** with better than 70% e.e. (equation



(6)

(7)

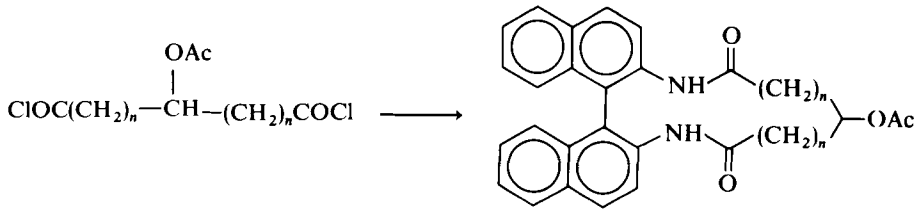
$$\equiv SiO(CH_2)_nCO_2Si\equiv$$

(33)

8). The reactions show that enantiotropic groups remote from a prochiral centre are effectively discriminated[25].

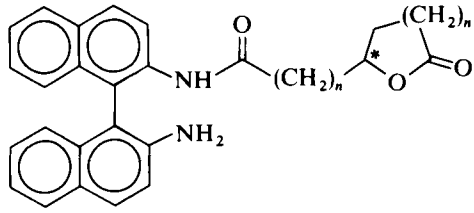
Tin-mediated template-driven lactonization occurs when ω-hydroxy acids containing 11–15 methylene groups are treated with dibutyltin oxide. It is suggested that the intermediate **36** is converted into the template-held tin compound **37**, which collapses to the macrolide by expulsion of dibutyltin oxide (equation 9)[26].

A similar principle operates in the formation of the macrocyclic polylactones **39** (n = 1–5) when a mixture of propiolactone and the distannoxane **38** is heated in chloroform. The reaction may involve insertion of several molecules of the β-lactone



(34)

(i) KOH
(ii) CF_3CO_2H (8)



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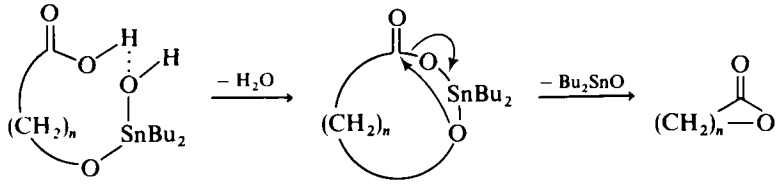
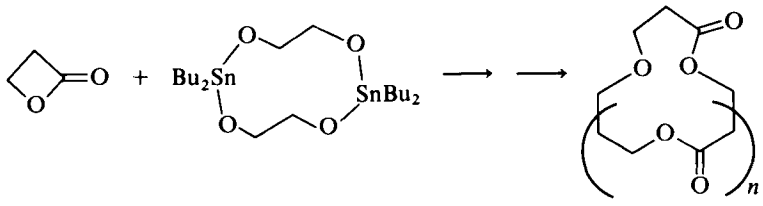


(9)

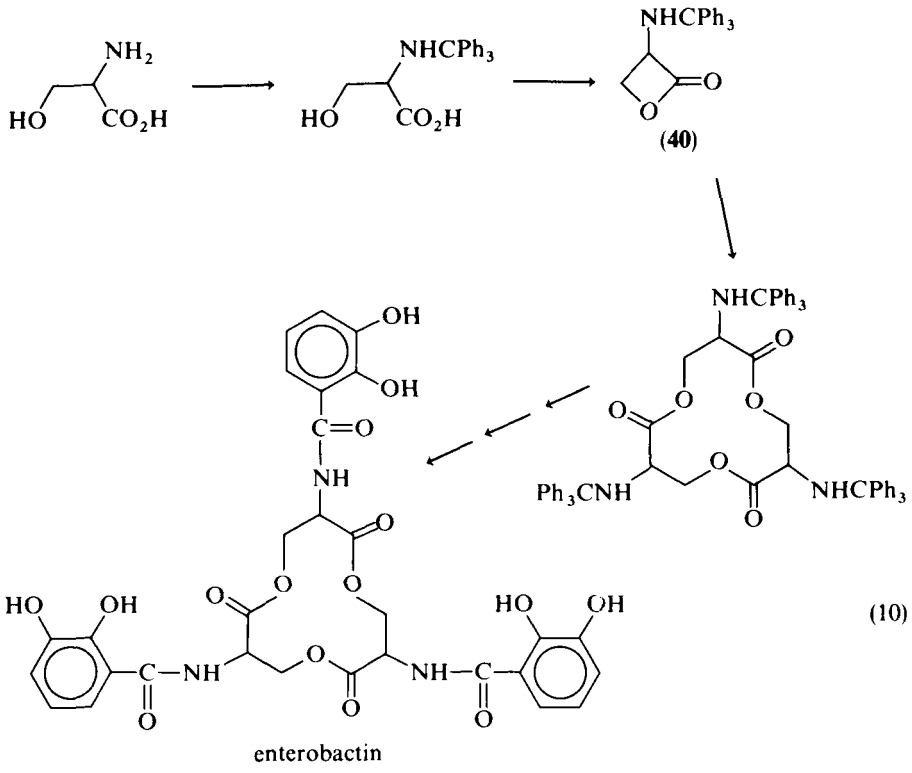
(36) (37)



(38) (39)

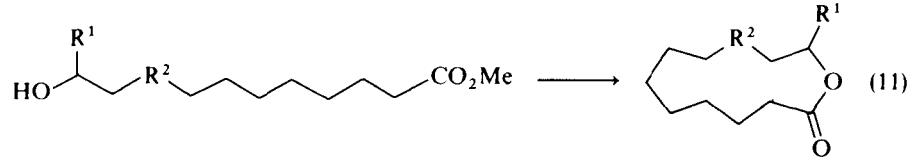
into the tin–oxygen bonds, followed by expulsion of the macrolide[27]. The method was used for the synthesis of enterobactin from L-serine by sequential tritylation, ring-closure to the β-lactone **40** by the combined action of *N*,*N*′-diisopropylcarbodiimide and 4-(dimethylamino)pyridine, reaction with **38**, removal of the protecting group, triacylation with *p*-nitrophenyl 2,3-di(benzyloxy)benzoate and, finally, debenzylation by hydrogenolysis (equation 10)[28].

Asymmetric transformations catalysed by enzymes in organic solvents[29] have recently been applied to the preparation of optically active lactones from racemic starting



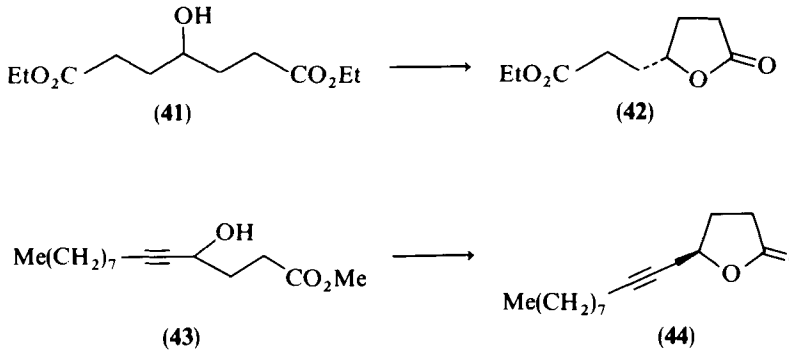
enterobactin

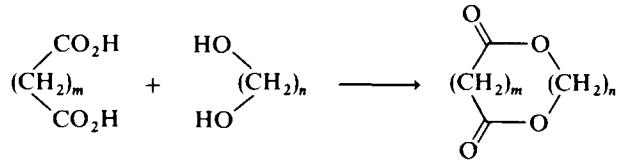
materials. Pork pancreatic lipase converts ω-hydroxy esters into thirteen-membered macrolides in moderate yields but with high e.e. (equation 11)[30]. Similarly, macrocyclic lactones have been obtained from the methyl esters of ω-hydroxy acids of chain lengths 13–16 by the action of the lipase in benzene[31]. The lactonization of 15-hydroxypentadecanoic acid and of 16-hydroxyhexadecanoic acid in toluene or light petroleum in yields of up to 30% is catalysed by *Mucor javanicus* L46 and *M. miehei*[32]. Treatment of the racemic hydroxy diester **41** with porcine pancreatic lipase in toluene affords the optically pure (*S*)-butanolide **42**, whereas the lipase from *Pseudomonas fluorescens* gives the (*R*)-enantiomer in only 32% enantiomeric excess[33].



H	CH_2CH_2
Me	CH_2CH_2
n-C_6H_{13}	CH_2CH_2
n-C_6H_{13}	(*E*)-CH=CH
n-C_6H_{13}	(*Z*)-CH=CH

The Japanese beetle pheromone (*R*)-**44** was obtained by means of lipase-catalysed enantioselective lactonization of the racemic hydroxy ester **43**[34]. The action of porcine pancreatic lipase on the methyl esters of ω-, δ- and ε-hydroxy acids causes oligomerization; in contrast, the δ-methyl-δ-hydroxy ester **45** yields the δ-lactone **46**[35]. Treatment of mixtures of α,ω-dicarboxylic acids and α,ω-diols with pork pancreatic lipase or *Pseudomonas* sp. in cyclohexane or carbon tetrachloride yields macrocyclic dilactones (equation 12); the best yields were for 24- to 28-membered rings[36].



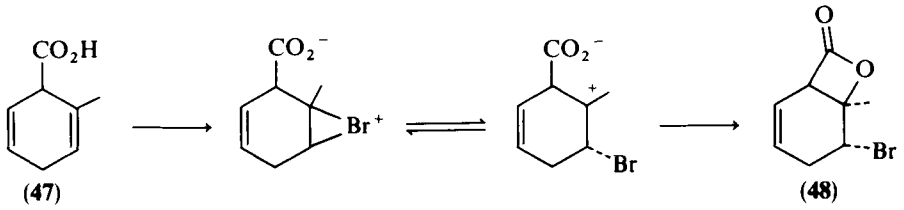


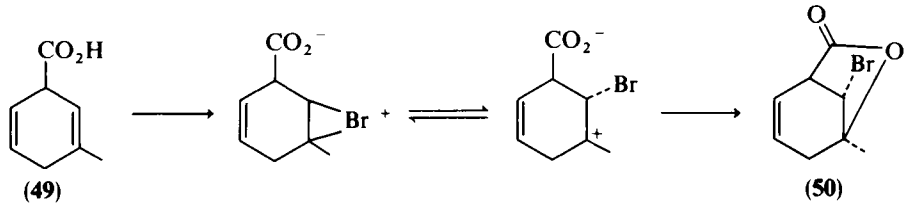
(12)

2. *From unsaturated acids and their synthetic equivalents*[37]

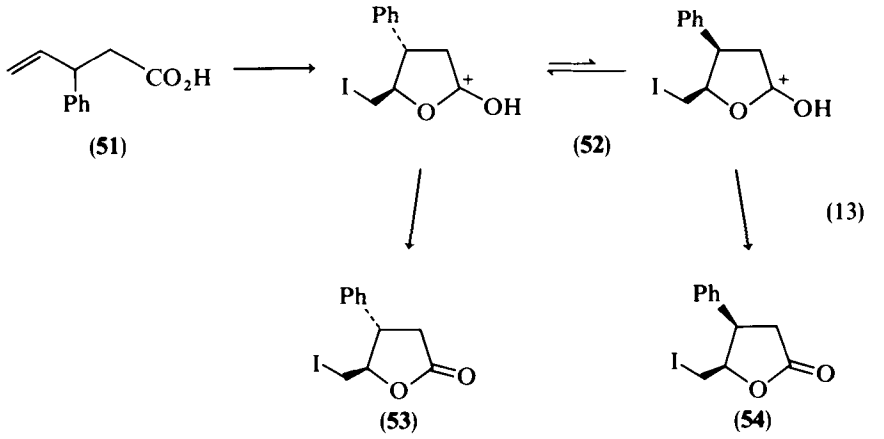
The formation of β- or γ-lactones by the action of bromine on methyl-substituted 1,4-dihydrobenzoic acids depends on the position of the methyl group, compound **47** yielding the β-lactone **48** and the isomer **49** giving the γ-lactone **50**. Thus lactonization occurs at the more substituted double bond and at the more substituted carbon atom. This is explained by the direction of the opening of the intermediate brominium ion, which has more carbonium character at the more substituted carbon atom (see Scheme 2)[38].

Iodolactonization of the unsaturated acid **51** in acetonitrile in the absence of a base proceeds with high diastereoselectivity to yield a 20:1 mixture of *trans*- and *cis*-substituted γ-lactones (**53** and **54**, respectively). Under these conditions there is a high concentration of the protonated intermediate **52**, which equilibrates to give the more stable *trans*-isomer, whereas under the usual basic conditions a kinetically controlled mixture of *cis*- and *trans*-compounds is produced (equation 13)[39].



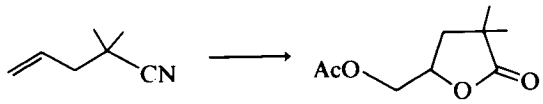


SCHEME 2

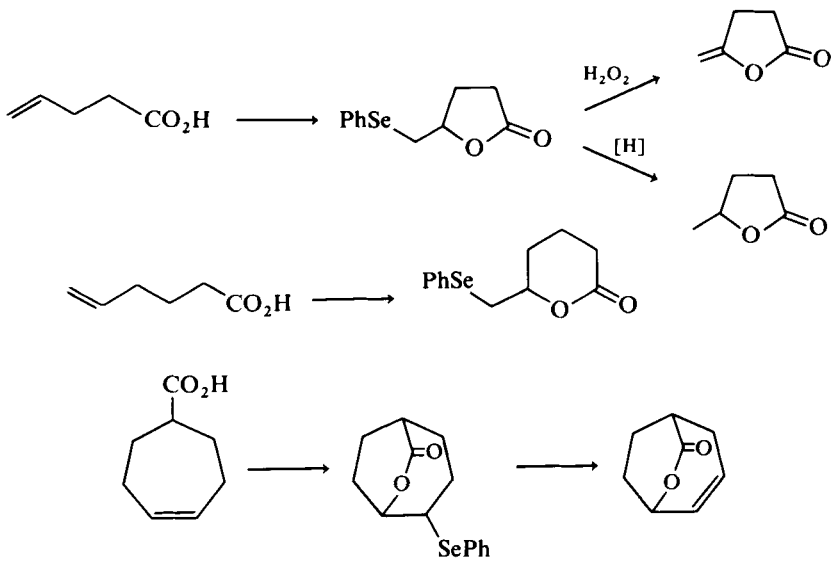


(13)

Halolactonization of unsaturated acids can be carried out using *N*-bromo- or *N*-iodo-succinimide[40]. The nitrile **55** reacts with the tervalent iodine compound $PhI(OAc)_2$ in a mixture of acetic and tetrafluoroboric acids to give the lactone **56**[41]. An

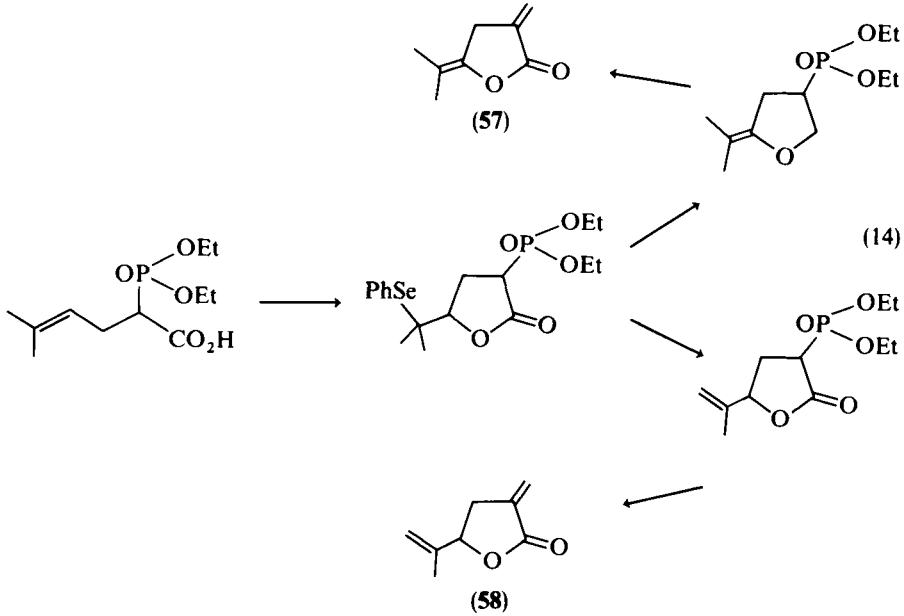


alternative to halolactonization, which is usually carried out in water under basic conditions, is selenolactonization with phenylselenyl chloride. The reaction proceeds in dichloromethane at low temperatures in the absence or presence of bases. The formation of five-membered rings is preferred to that of four- and six-membered rings, and six- and



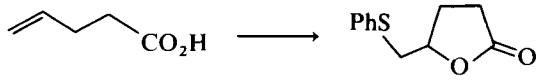
SCHEME 3

seven-membered rings are favoured over seven- and eight-membered rings. The presence of the phenylseleno group offers valuable synthetic possibilities: thus oxidation with hydrogen peroxide, followed by elimination, yields unsaturated lactones and the phenylseleno group can be removed reductively by treatment with Raney nickel or tributyltin hydride in the presence of AIBN (Scheme 3)[42]. An example of the application of the



method to the preparation of the methylenebutanolides **57** and **58** from a phosphonic ester derivative is shown in equation 14; in each case the final step is a Wittig–Horner reaction with formaldehyde[43].

Phenylsulphenyl cations PhS^+, generated electrochemically from diphenyl disulphide, react with unsaturated acids to give phenylthio-substituted lactones (equation 15)[44]. The reaction has been applied to the synthesis of δ-lactones (equation 16)[45].



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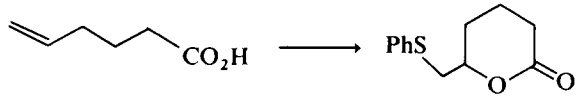
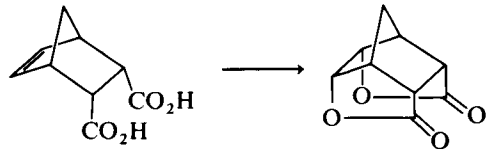
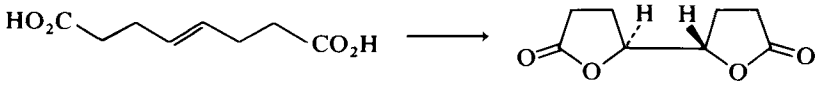


(16)

Olefinic dicarboxylic acids are converted into dilactones on treatment with [hydroxy(tosyloxy)iodo]benzene, PhI(OH)OTos[46], or lead tetraacetate[47] or via diacyl hypoiodites, generated by the action of iodine and silver acetate on their silver salts[48]; thus 5-norbornene-*endo*-2,3-dicarboxylic acid (**59**) yields the bislactone **60**, and the acid **61** forms **62**[48].

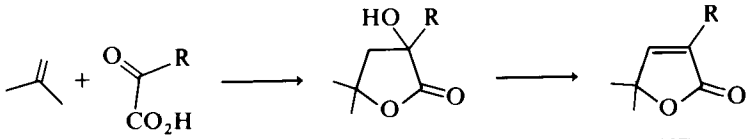


(**59**) (**60**)



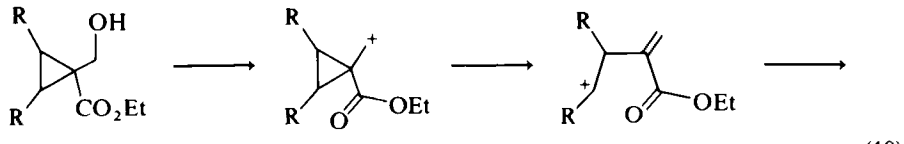
(**61**) (**62**)

2-Methylpropene reacts with α-keto acids **63** (R = Me, Et or Ph) in the presence of titanium tetrachloride to yield hydroxylactones **64**, which are readily dehydrated to the butenolides **65** (equation 17)[49].



(**63**) (**64**) (**65**) (17)

The acid-catalysed ring-opening of esters of (hydroxymethyl)cyclopropanecarboxylic acids results in the formation of α-methylenebutanolides (equation 18)[50]. Bicyclic acids containing a fused cyclopropane ring afford cycloalkano-γ-lactones in a related process, which involves a rearrangement of primary to secondary carbonium ions (equation 19)[51].



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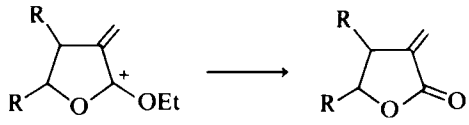
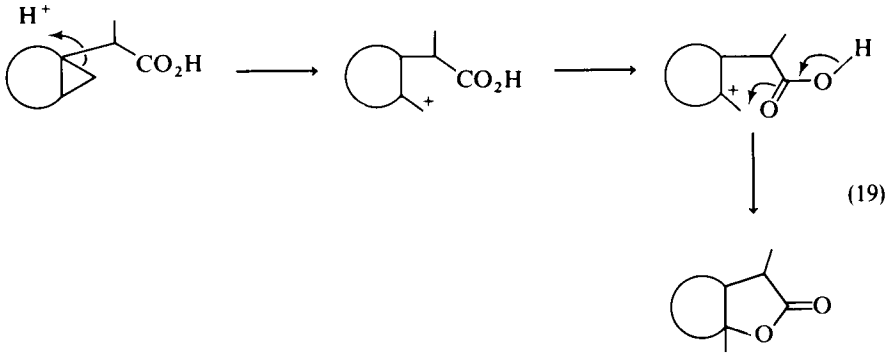
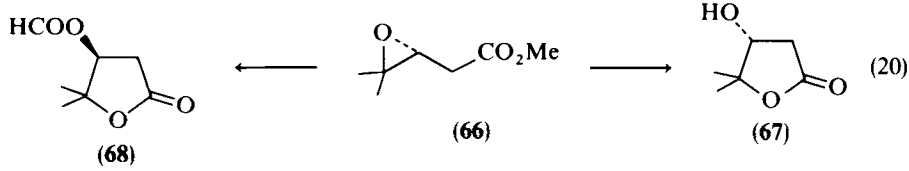




(19)

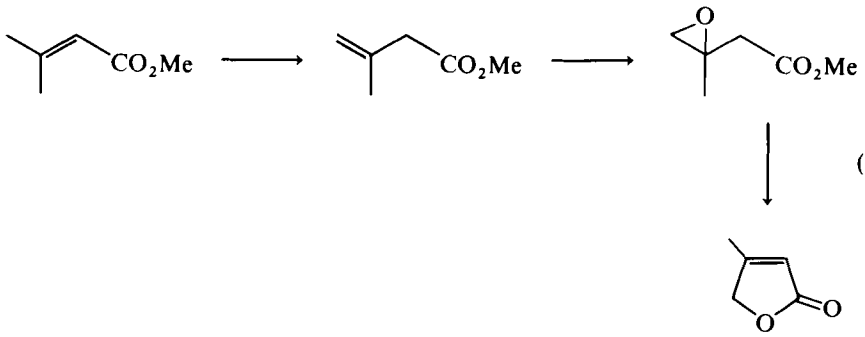
Kinetic resolution of racemic β,γ-epoxy esters with pig liver esterase, followed by acid-catalysed cyclization, yields optically active hydroxy-γ-lactones. The ester **66**, for example, is converted into the (*R*)-enantiomer **67** with retention of configuration by the action of hydrochloric acid, while formic acid yields the (*S*)-lactone **68** with inversion of configuration (equation 20)[52].



(20)

(68) **(66)** **(67)**

'Deconjugative epoxidation' of α,β-unsaturated esters by sequential treatment with LDA and hydrogen peroxide yields epoxides, which form butenolides by the action of acetic acid (equation 21)[53]. The LDA-mediated 'deconjugative alkylation' of the ester **69** by dodec-1-ynal yields an intermediate hydroxy ester, which on dehydration affords the dienoate **70** [R = $HC{\equiv}C{-}(CH_2)_9$]. Selective epoxidation by *m*-chloroperbenzoic acid gives the oxiran **71**, which is converted into litsenolide A_2 by acid-catalysed lactonization (equation 22)[54]. Allene carboxylic acids react with dimethyldioxirane to yield hydroxyoxolactones by way of transient bisepoxides (equation 23)[55].



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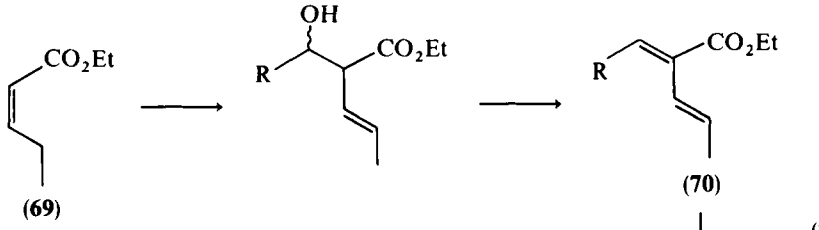
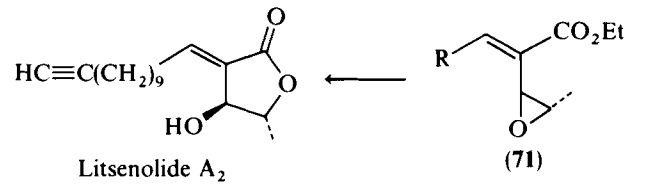
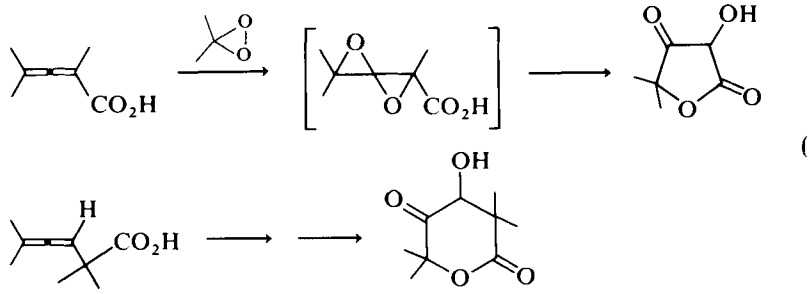


(69) (70)

(22)



Litsenolide A_2 (71)

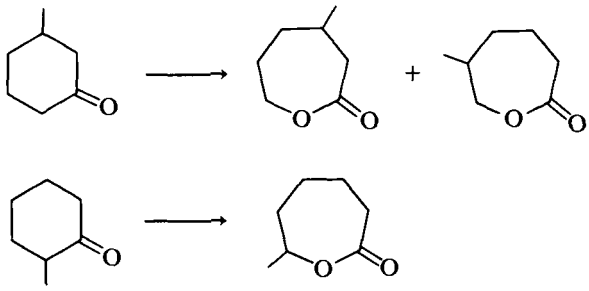


(23)

3. *From cyclic ketones*

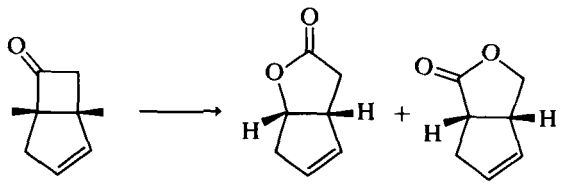
The Baeyer–Villiger oxidation[56] of cyclic ketones is a reliable method for making lactones of all ring sizes. A convenient modification of the original method, which employed hydrogen peroxide, is to treat a solution of the ketone in dichloromethane with a mixture of wet alumina and 'oxone', a stable 2:1:1 composite of potassium hydrogen monopersulphate, potassium hydrogen sulphate and potassium sulphate.

Yields of *ca* 80% are achieved in the oxidation of cyclopentanone and of cyclohexanone by this procedure to give hexanolide and heptanolide, respectively. 3-Methylcyclohexanone yields a mixture of two ε-lactones, while 2-methylcyclohexanone gives only one product (equation 24)[57]. The method is claimed to be much more convenient than the use of an oxidant supported on alumina[58].



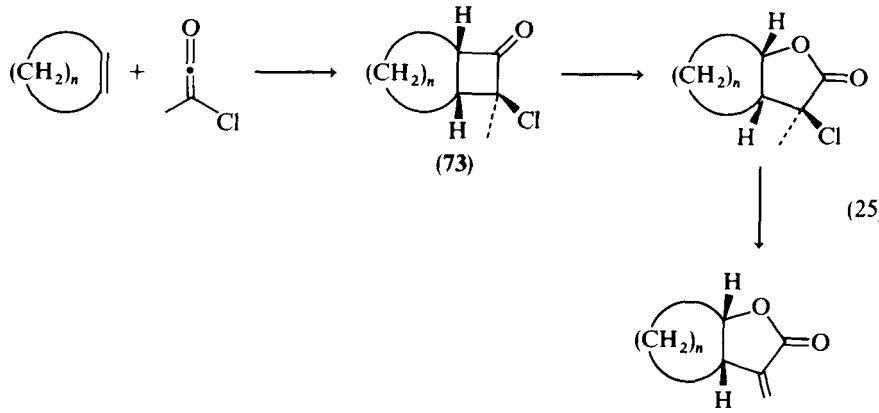
(24)

The conversion of cyclic ketones into lactones has also been carried out by reaction with oxygen in the presence of a mixture of bis(dipivaloylmethanato)nickel(II) and isovaleraldehyde in 1,2-dichloroethane[59]. Oxidative ring-expansion of the bicycloheptenone **72** to yield a mixture of isomeric lactones is effected by the biocatalytic fungus *Curvularia lunata*[60].



(72)

Oxidation of the bicyclic 2-chloroketones **73** (n = 3, 4 or 6), prepared by cycloaddition of methylchloroketene to cycloalkenes, with *m*-chloroperbenzoic acid or hydrogen peroxide in acetic acid results in chlorolactones, which are converted into α-methylenelactones by the action of DBU (equation 25)[61].

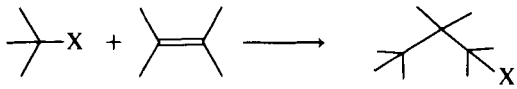


(73)

(25)

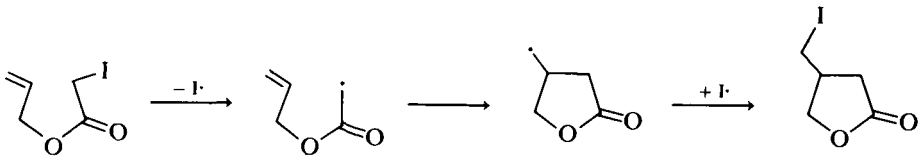
4. By free-radical reactions

The formation of lactones by free-radical cyclizations of suitably constituted esters is a rapidly developing field in lactone synthesis. Many reactions proceed by 'atom transfer addition', of C—X, where X is usually halogen, to a double bond (equation 26)[62–64].



(26)

The intramolecular version of this reaction applied to the formation of a γ-lactone is shown in equation 27, where the initiator is $Bu_3Sn\cdot$, generated from tributyltin hydride in the presence of AIBN, or photochemically from hexabutyldistannane[65]. The γ-lactone of equation 27 is accompanied by the macrocyclic bislactone **74** and the trislactone **75**[66].



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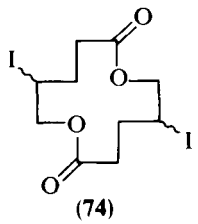

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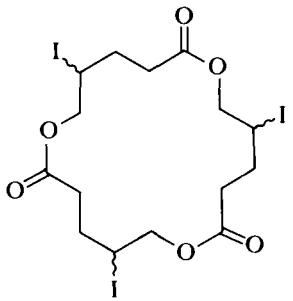
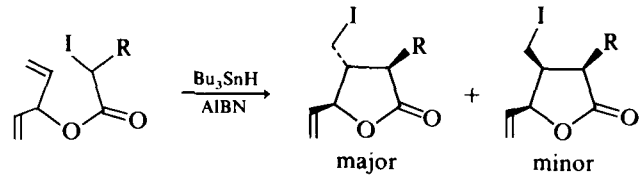


(75)

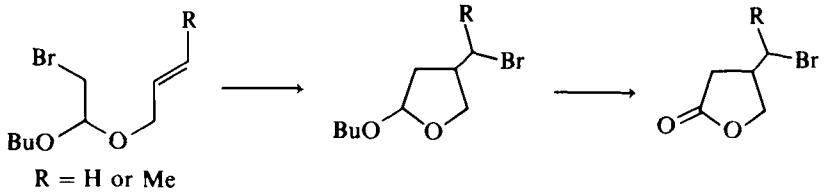
α-Iodo esters of penta-1,4-dien-3-ol cyclize stereoselectively to vinyllactones (equation 28)[67]. In the presence of a free-radical initiator, bromoacetals cyclize to tetrahydrofurans, which are converted into γ-lactones by Jones oxidation (equation 29)[68].

The acetylenic ester **76** (R = H) gives the methylenebutanolide **77** (R = H); the trimethylsilyl analogue (**77**; R = Me_3Si) can be rearranged to the butenolide **78**[69]. The chiral radical **79**, generated from the corresponding bromo compound by the action of tris(trimethylsilyl)silane in the presence of AIBN, cyclized to the unsaturated 14-membered keto lactone **80** (R = Me), which was converted into natural (*S*)-(−)-zearalenone (**80**; R = H)[70].

Copper(I) salts promote the cyclization of allyl trichloroacetate to the lactone **81** by intramolecular transfer of chlorine[71]. Free-radical cyclizations of thio and seleno esters have recently been reported. The acetylenic selenocarbonate **82** yields an α-methylene-butyrolactone (equation 30)[72], while homoallylic xanthates **83** and **85** form the thionolactones **84**[73] and **86**[74], respectively. The latter can be converted into lactones by the action of *m*-chloroperbenzoic acid[75]. An analogous free-radical reaction of the cyclooctadienyl derivative **87** results in the bicyclic thiolactone 88[74].



(28)



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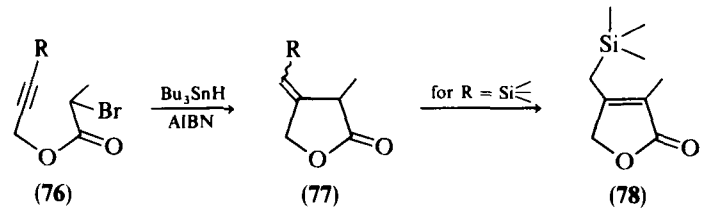
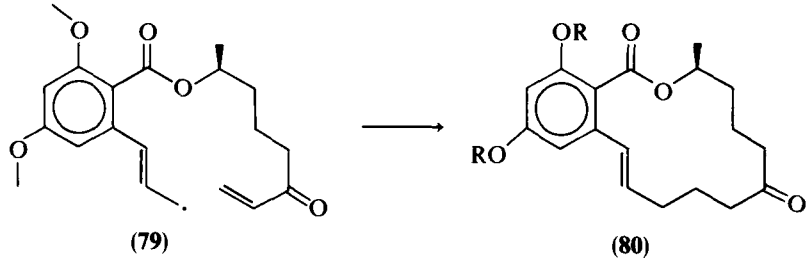
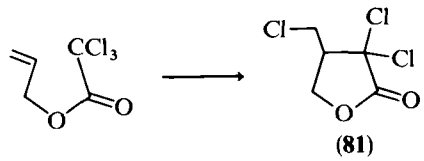
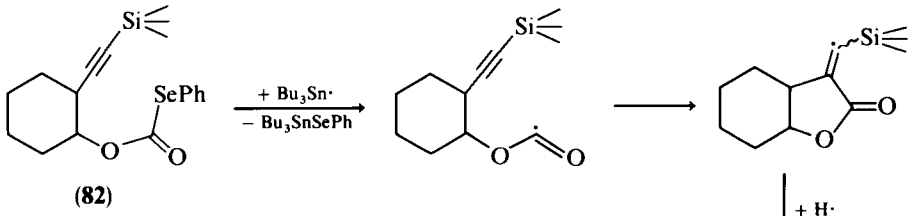






In the presence of tributyltin hydride/AIBN and under conditions of high dilution the esters **89** undergo intramolecular macrocyclization to form 10- to 15-membered lactones in 50–80% yields (equation 31)[76]. Under similar conditions, acyl radicals, generated from the phenylseleno esters **90** (n = 6, 7, 9, 11 or 15), give keto lactones **91** in fair yields[77].

Photolysis of the propargyl esters **92** (R^1, R^2 = H or alkyl) in a mixture of methanol and 2-propanol in the presence of benzophenone and collidine results in the formation of butenolides in a chain reaction from ketyl radicals by electron transfer (equation 32)[78].



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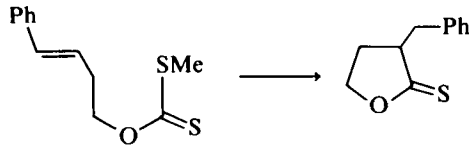

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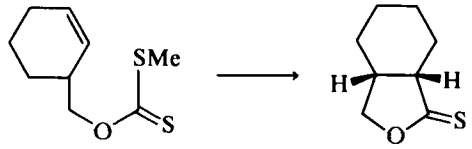

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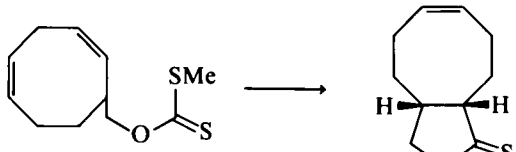

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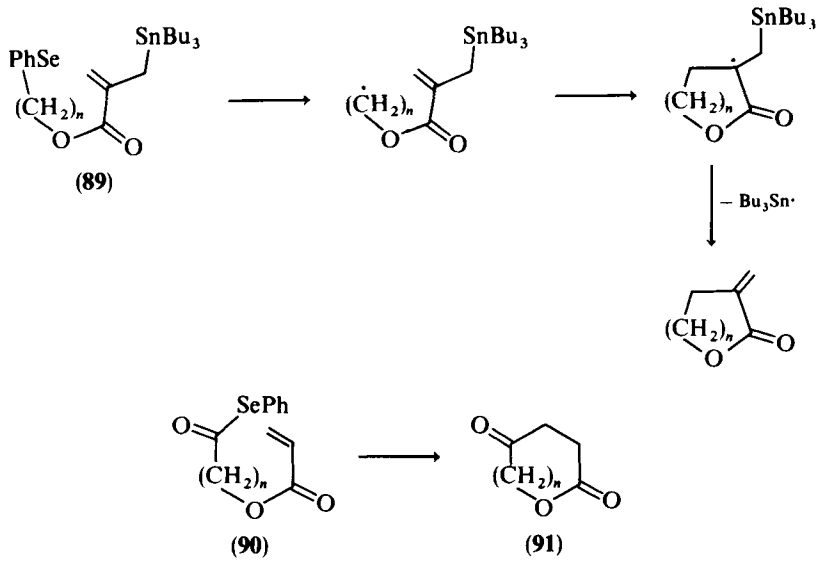
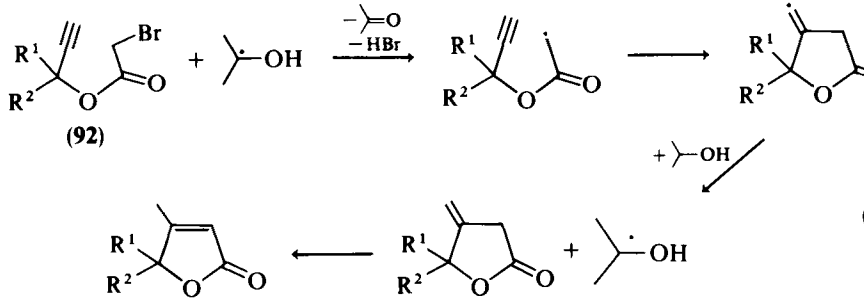
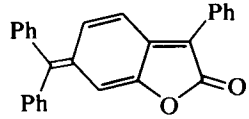




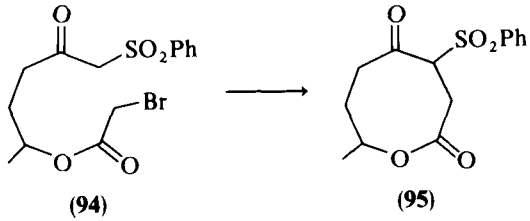
5. *Miscellaneous syntheses*

The deep-purple product of the pyrolysis[79] of benzilic acid has been shown by X-ray analysis to be the quinodimethane derivative **93**[80]. Intramolecular alkylation of the

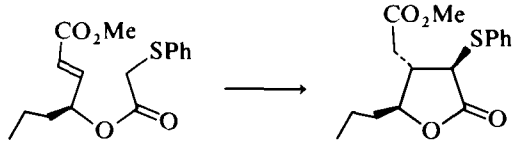


(93)

β-keto sulphone **94** yields the eight-membered keto lactone **95**; lactones containing rings of nine and ten atoms were obtained by analogous reactions[81]. An example of a general diastereoselective synthesis of butanolides by the intramolecular Michael addition of chiral phenylthio acetates of γ-hydroxy-α,β-unsaturated esters is shown in equation 33[82].

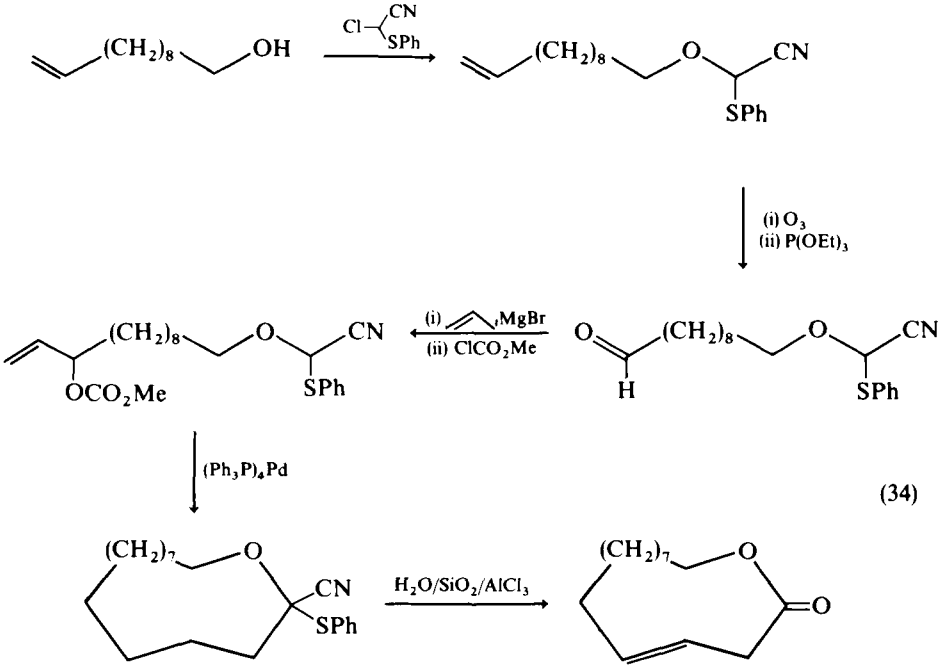


(94) (95)



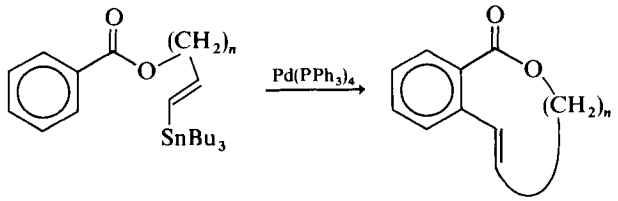
(33)

In a synthesis of macrolides based on a new principle, a synthetic equivalent of the carbonyl group of the lactone, namely phenylthiochloroacetonitrile, is inserted between the termini of an acyclic precursor (equation 34)[83]. Palladium-catalysed cyclizations



(34)

leading to macrolides are exemplified by the formation of lactones of ring size 10, 12, 14 and 15 by intramolecular Pd(0)-catalysed coupling of organostannanes (equation 35)[84]. Similarly, the stannanes **96** (n = 5–8) are converted into the methylene lactones **97** in *ca* 55% yields under conditions of high dilution[85] and into the oxo-macrolides **98** (n = 4–8) by palladium-catalysed carbonylation[86].



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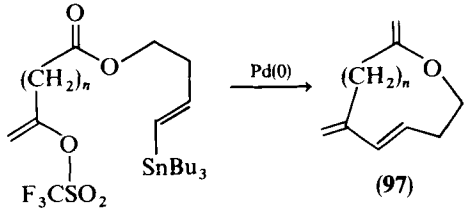
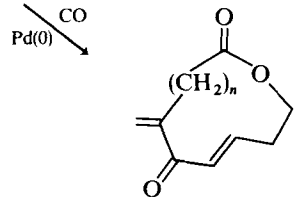


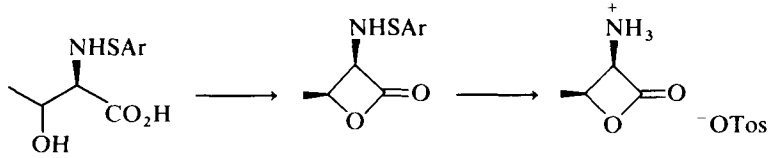
(96) (97)



(98)

6. *Synthesis of β-lactones*[87]

The conversion of β-hydroxy acids into β-lactones is exemplified by the cyclization of *N*-[(*o*-nitrophenyl)sulphenyl]-L-threonine (**99**; Ar = o-$O_2NC_6H_4$) by the action of *p*-bromobenzenesulphonyl chloride in pyridine; deprotection of the product by means of thiophenol in the presence of toluene-*p*-sulphonic acid gave the salt **100** (equation 36)[88]. Hydroxy acids are dehydrated under Mitsunobu conditions[89], i.e. with triphenyl-

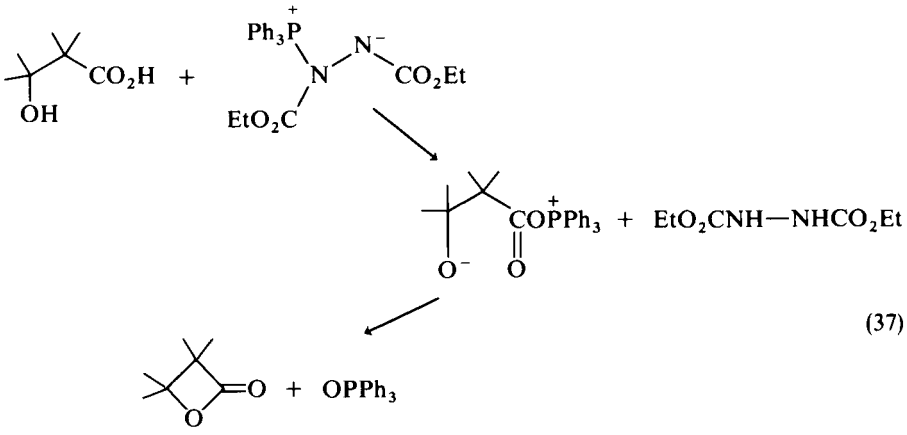


(36)

(99) (100)

phosphine and diethyl azodicarboxylate. The reaction usually involves activation of the carboxyl group if the acids contain bulky substituents (equation 37)[90]. In the case of the deuterium-labelled L-serine derivative **101** (R = benzyl), activation of the carboxyl group would lead to the β-lactone **102**, formed with retention of configuration at the carbon atom bearing the hydroxyl group, whereas activation of the hydroxyl group would lead to inversion to yield **103**, which is what was observed (Scheme 4)[91].

Hydroxy acids can be dehydrated to β-lactones by using triphenylphosphine in conjunction with the polymeric reagent **104**. The spent reagent may be reconstituted by



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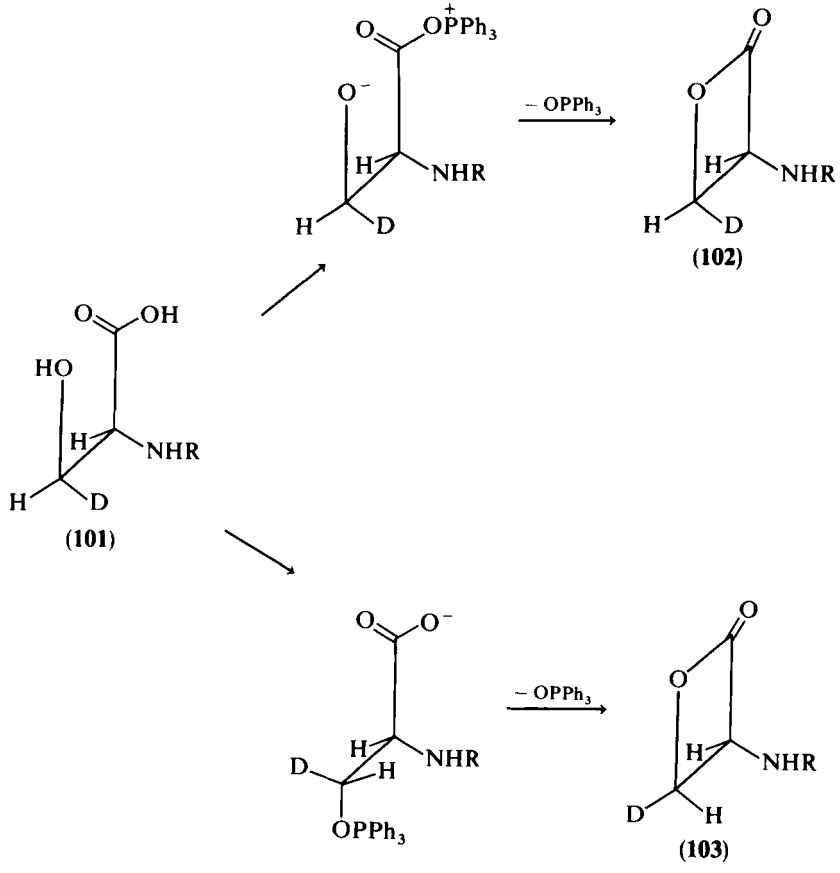
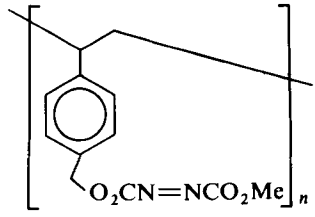
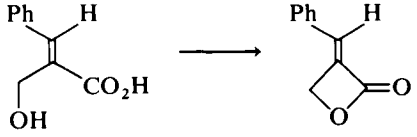


SCHEME 4

treatment with NBS in pyridine[92]. Dehydration of α-benzylidene-β-hydroxypropionic acid (**105**) by the combined action of methanesulphonyl chloride and sodium carbonate in dichloromethane at room temperature results in α-benzylidenepropiolactone (**106**)[93].

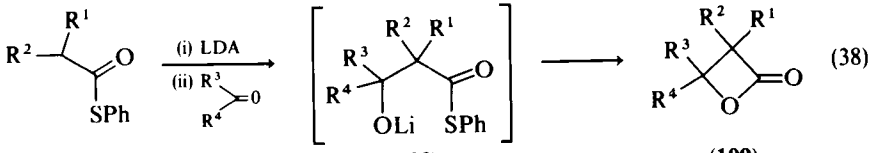


(**104**)



(**105**) (**106**)

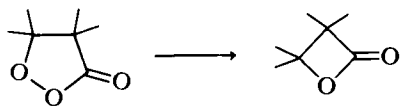
The reaction of lithium enolates of thiol esters **107** with aldehydes or ketones yields transient adducts **108**, which cyclize spontaneously to β-lactones **109** (R^1–R^4 = H or alkyl) (equation 38)[94].



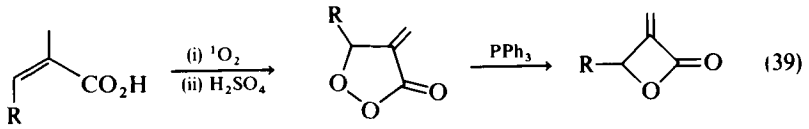
(38)

(**107**) (**108**) (**109**)

Tetramethyl-β-propiolactone (**111**) is obtained by deoxygenation of the 'peroxylactone' **110** with triphenylphosphine[95]. The reaction was used to prepare a series of α-methylene-β-lactones from unsaturated acids by sensitized photooxygenation, as shown in equation 39. The products polymerize above 60°C[96].



(**110**) (**111**)

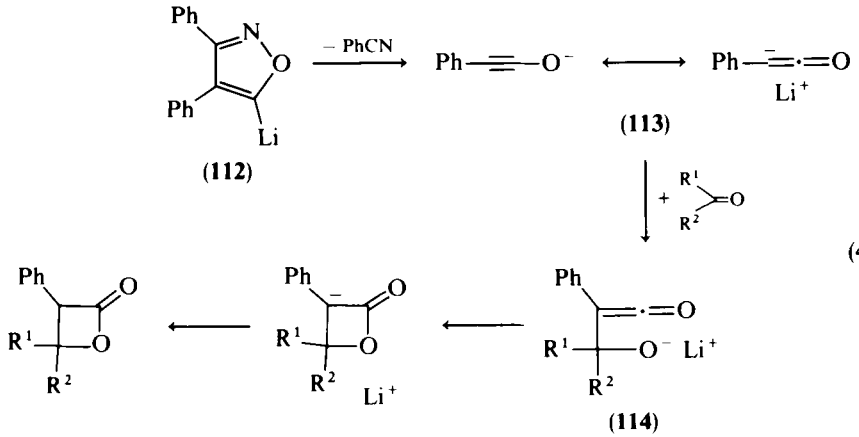


(39)

R = Me, Et or Pr^i

The formation of β-lactones by way of ynolate anions has been reported by two groups. Treatment of 3,4-diphenylisoxazole with butyllithium gives the lithio derivative

112, which fragments to benzonitrile and the lithium ynolate **113** already at $-60°C$. Reaction of the latter with a ketone gives an adduct **114**, which cyclizes spontaneously. Addition of acetic acid furnishes the β-lactone (equation 40)[97]. The lithium compound **113** was also obtained by a carbon analogue of the Hofmann reaction (equation 41); treatment with cyclohexanone gave the spiro-lactone **115**[98].



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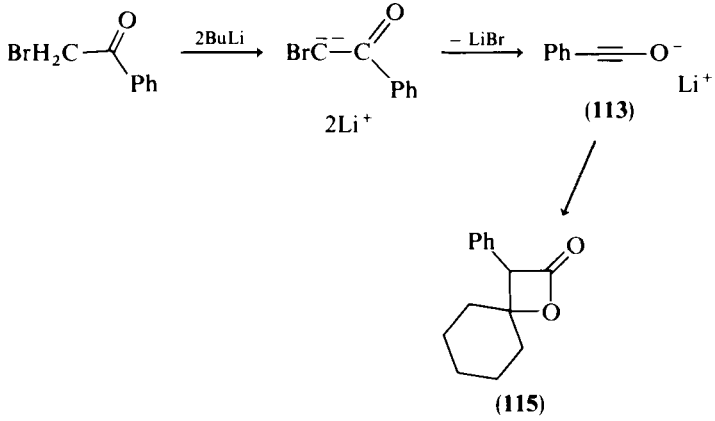
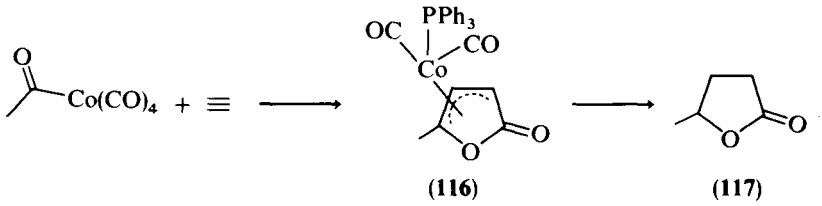


(41)

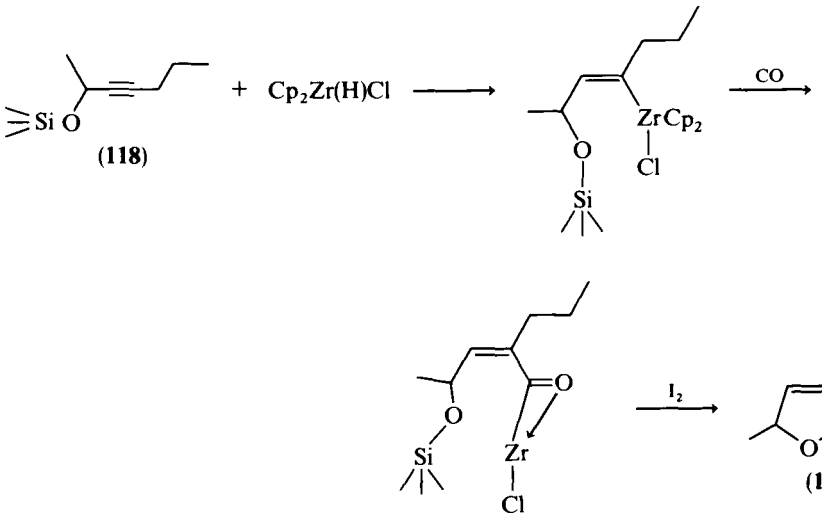
7. Synthesis of β-, γ- and δ-lactones by organometallic reactions

There have been many reports on the formation of lactones by the use of organometallic reagents since Heck's pioneering work on the reaction of acetylcobalt tetracarbonyl with acetylene in the presence of triphenylphosphine, which resulted in the complex **116**. Hydrogenation gave γ-valerolactone (**117**)[99].



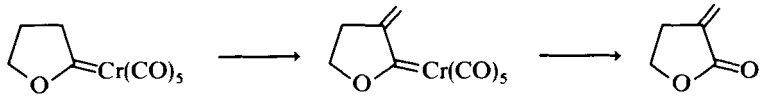
(116) (117)

Hydrozirconation of the protected acetylenic alcohol **118**, followed by carbonylation and addition of iodine, afforded the butenolide **119** (equation 42)[100]. The key step in



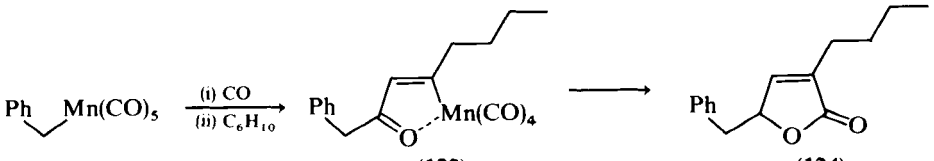
(118) (42) (119)

the sequence is insertion of carbon monoxide into the carbon–metal bond. The chromium carbonyl carbene complex **120** reacts with chloromethyl methyl ether, a synthetic equivalent of formaldehyde, to yield **121**, which is converted into the methylene-butanolide **122** by oxidation with cerium(IV) ammonium nitrate[101].



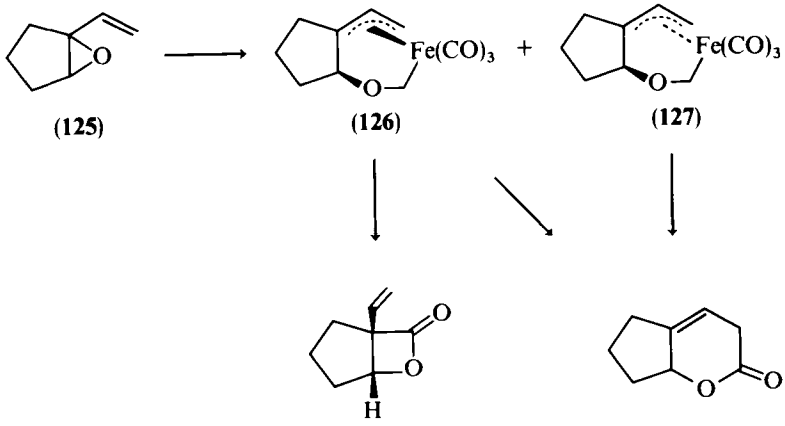
(120) (121) (122)

The high-pressure reaction of benzylmanganese pentacarbonyl with carbon monoxide, followed by treatment with hex-1-yne, gives the manganese complex **123**, which affords the butenolide **124** by hydride reduction[102]. Vinyloxirans react with diiron enneacarbo-



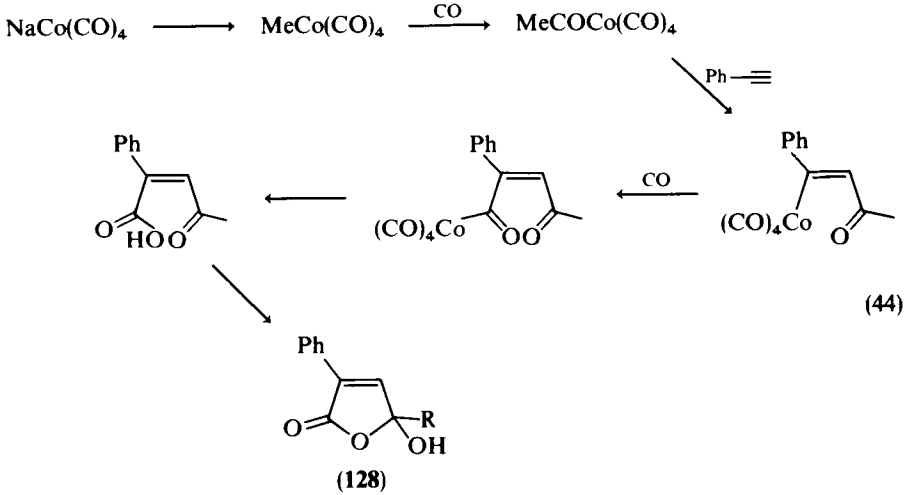
(123) (124)

nyl under the influence of ultrasound to yield air-stable π-allyltricarbonyliron lactone complexes, which are oxidized by cerium(IV) salts to β- and δ-lactones[103]. The oxiran **125**, for example, yields a mixture of the *cis*- and *trans*-complexes **126** and **127** in the ratio 6:1. Oxidation of the former gives a mixture of β- and δ-lactones, whereas the latter affords only the δ-lactone (equation 43)[104].



(125) (126) (127) (43)

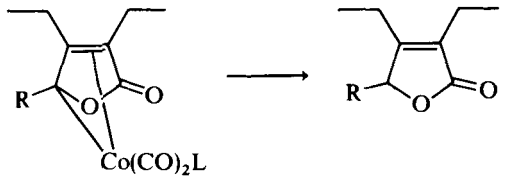
Treatment of dicobalt octacarbonyl with benzene/aqueous sodium hydroxide in the presence of the phase-transfer catalyst cetyltrimethylammonium bromide generates $NaCo(CO)_4$, which reacts with a mixture of carbon monoxide, phenylacetylene and methyl iodide to yield γ-hydroxy-γ-methyl-α-phenyl-α,β-butenolide (**128**; R = Me) (equation 44)[105]. The benzyl analogue (**128**; R = CH_2Ph) is obtained by an analogous reaction with carbon monoxide, phenylacetylene and benzyl bromide in the presence of the chelating agent $N(CH_2CH_2OCH_2CH_2OCH_3)_3$[106].



(44)

(128)

The combined action of acyl chlorides and hex-3-yne on sodium cobalt tetracarbonyl results in the complexes **129** (L = ligand), which are transformed into the butenolides

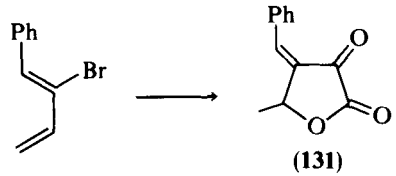


(129) (130)

130 (R = Me, Et, Ph, $PhCH_2$) by hydrochloric acid[107]. 'Cyclocarbonylation' of unsaturated bromo alcohols by nickel dicarbonyl bis(triphenylphosphine) affords γ- or δ-lactones (equation 45)[108]. The oxolactone **131** is formed by the nickel(II) cyanide-catalysed carbonylation of 2-bromo-1-phenylbuta-1,3-diene[109].

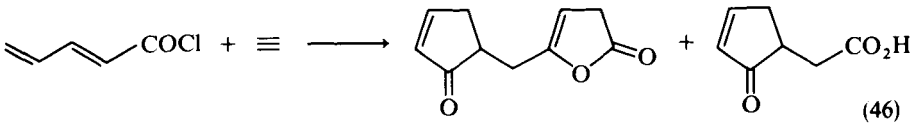
(45)

$n = 1$ or 2

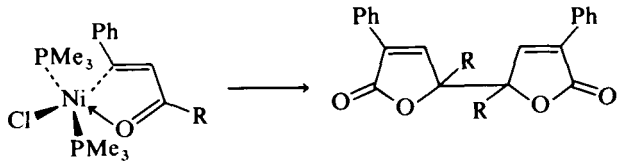


(131)

The action of nickel tetracarbonyl on a mixture of penta-2,4-dienoyl chloride and acetylene yields the lactone **132**, together with a derivative of cyclopentenone (equation 46)[110]. Dibutenolides are formed by carbonylation of the nickel complexes **133** (R = Me, neopentyl or CH_2SiMe_3) (equation 47)[111].

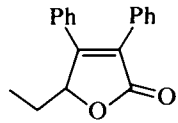


(132) (46)



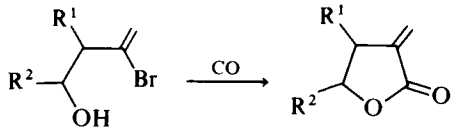
(133) (47)

The high-pressure reaction of carbon monoxide with a mixture of ethylene and diphenylacetylene in ethanol, catalysed by tetrarhodium dodecacarbonyl, leads to the butenolide **134**[112]. Methylenebutanolides **136** (R^1 = H or Me; R^2 = Me or Et) are

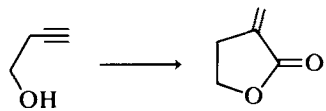


(134)

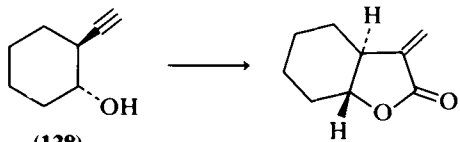
formed when the olefinic bromo alcohols **135** are carbonylated in the presence of palladium(0) tetrakis(triphenylphosphine)[113]; the acetylenic alcohols **137** and **138** react analogously[114]. Also, β- and γ-lactones have been obtained from a variety of halogen-substituted alcohols by palladium-catalysed carbonylation (equation 48)[115].



(135) (136)



(137)



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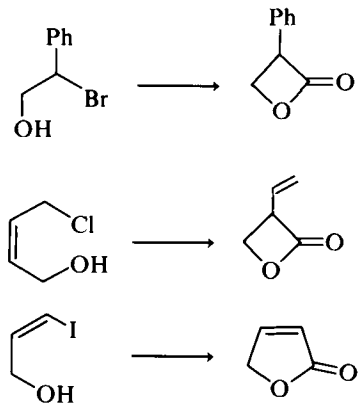
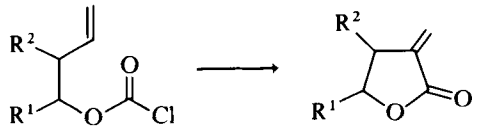


(48)

Homoallylic chloroformates are converted into α-methylenebutanolides in the presence of various zero-valent palladium compounds (equation 49)[116]. The palladium(II)-catalysed dicarbonylation of buta-3-en-1-ols in methanol in the presence of propylene oxide and triethyl orthoacetate gives good yields of the esters **139**[117].



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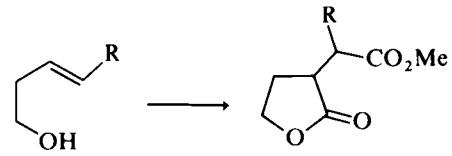
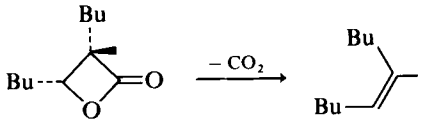


R = H or alkyl (**139**)

B. Reactions of Lactones

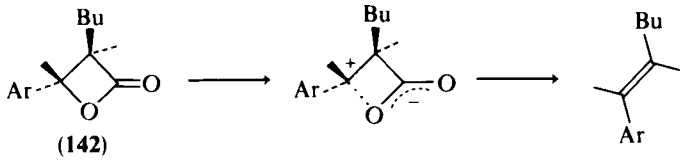
1. Reactions of β-lactones

β-Lactones decompose smoothly into carbon dioxide and olefins on heating. The reaction is completely stereospecific: the (*Z*)-lactone **140**, for instance, gives only the (*Z*)-olefin **141**[118].



(**140**) (**141**)

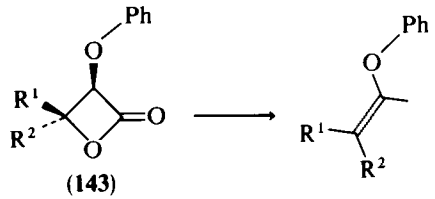
The rates of decomposition of compound **142** (Ar = *p*-$MeOC_6H_4$), determined as a function of pressure, indicate that the decarboxylation occurs in two steps via the zwitterionic intermediate shown in equation 50[119]. Pyrolysis of β-lactones has been used



(**142**) (50)

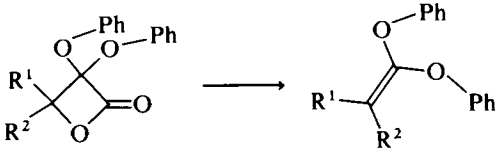
to prepare all kinds of olefins. The phenoxy compounds **143** decompose at 150 °C to yield phenyl enol ethers[120]; in the presence of silica gel decarboxylation occurs at 30 °C[121]. Ketene diphenyl acetals **145** are obtained from the β-lactones **144** (R^1, R^2 = Me or Ph)[122].

The preparation of the *trans*-olefins **147** from the hydroxy acids **146** is shown in equation 51[123]. A synthesis of benzo[*b*]furans from β-phenoxy acids proceeds via

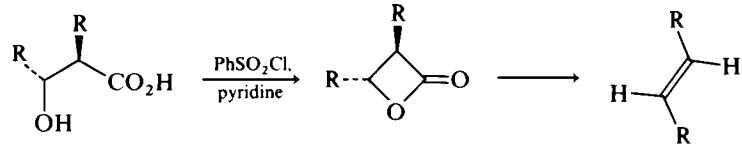


(143)

R^1, R^2 = Me or Ph



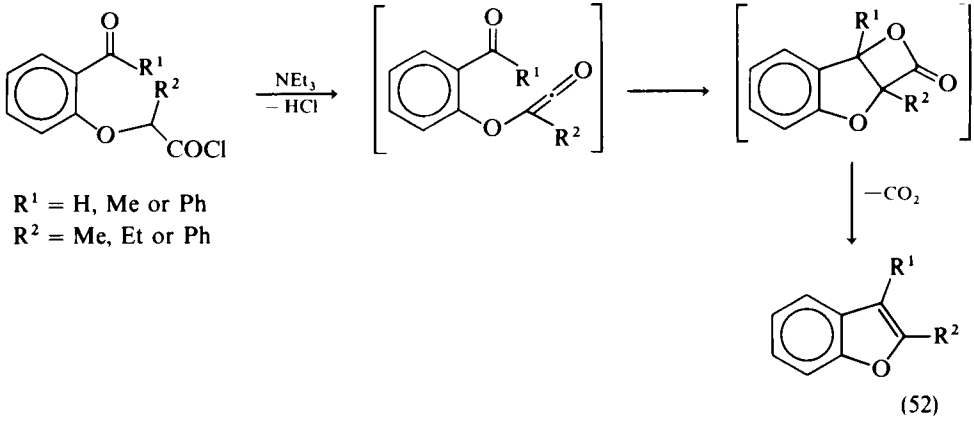
(144) (145)



(146) (147) (51)

R = *t*-Bu or 1-Ad

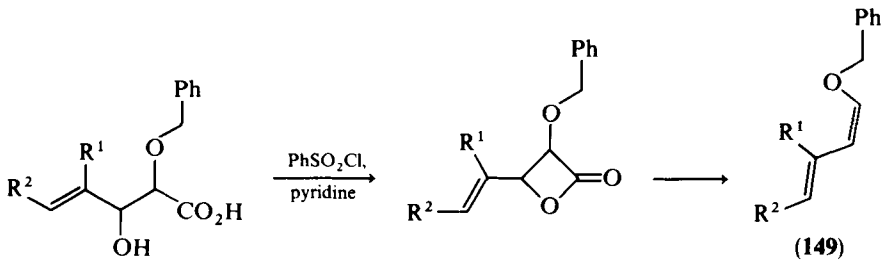
transient ketenes and transient β-lactones (equation 52)[124]. The key step, the cycloaddition of a ketene to a carbonyl compound, is discussed in Reference 1, p. 498.



R^1 = H, Me or Ph
R^2 = Me, Et or Ph

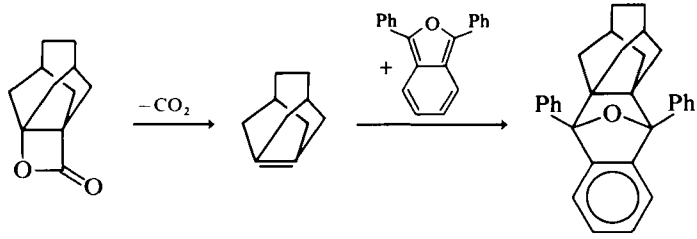
(52)

A method for the conversion of the hydroxy acids **148** into butadienes **149** is outlined in equation 53[125]. Pyrolysis of the β-lactone **150** generates the highly unstable pyramidalized alkene **151**, which was trapped as the cycloadduct **152** by an *in situ* reaction with 1,3-diphenylisobenzofuran (equation 54)[126].



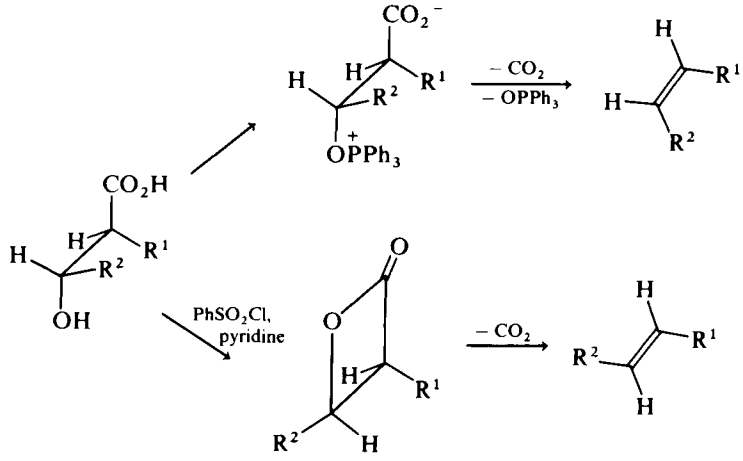
(53)

R^1, R^2 = Me, H or Ph



(54)

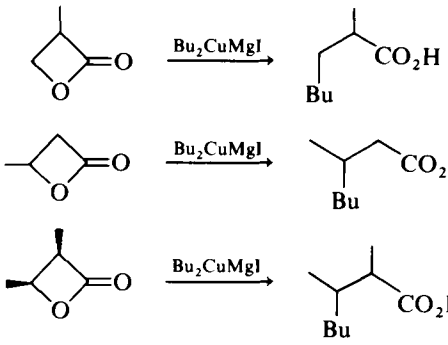
threo-3-Hydroxy carboxylic acids can be converted into either *Z*- or *E*-alkenes at will[127]. The former are obtained by the action of the adduct of triphenylphosphine to diethyl azodicarboxylate, while the latter are prepared by way of *β*-lactones (Scheme 5).



R^1 = Ph or OPh,
R^2 = Me, Et or Pr

SCHEME 5

Nucleophilic ring-opening of β-lactones can occur either with alkyl–oxygen fission by attack of the nucleophile at the cyclic oxygen atom or with acyl–oxygen fission by attack at the carbonyl group[128]. 'Soft' nucleophiles such as organometallic compounds react by alkyl–oxygen fission, 'hard' nucleophiles by acyl–oxygen fission. Thus dibutylcopper magnesium iodide [from butylmagnesium bromide and copper(I) iodide] reacts with β-lactones to yield carboxylic acids (equation 55)[129].



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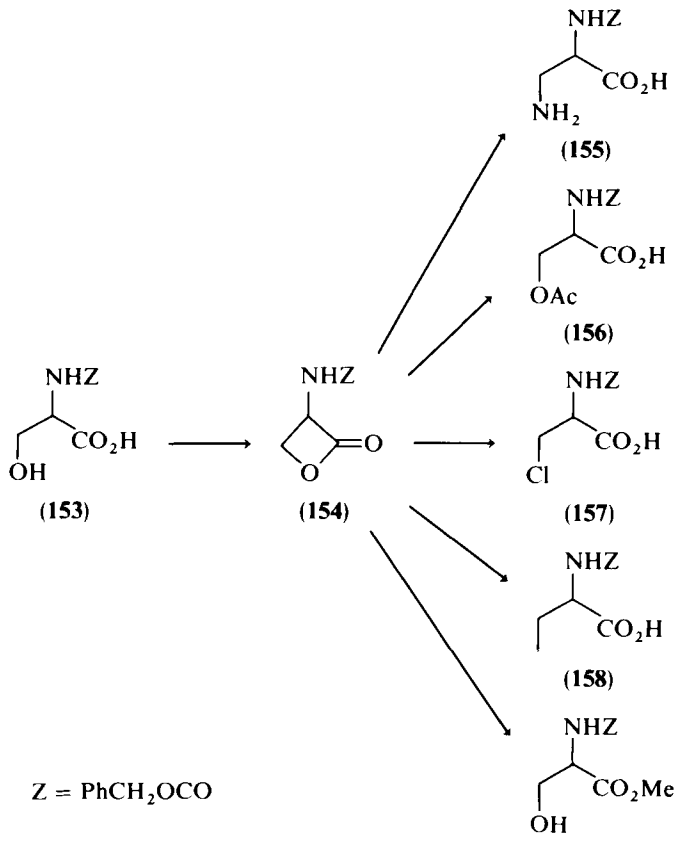
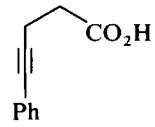
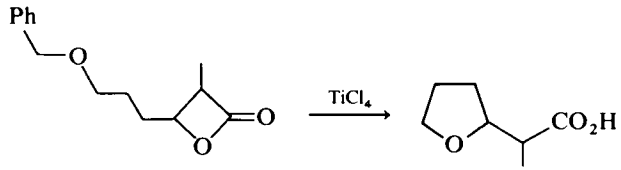


SCHEME 6

The *N*-protected serine **153** was converted into the lactone **154** without racemization; treatment of the latter with the soft nucleophiles ammonia, sodium acetate and magnesium chloride gave the β-substituted alanines **155–157**, respectively[130], and lithium dimethylcuprate afforded the acid **158**[131]. The hard reagent sodium methoxide, on the other hand, yielded the ester **159** (Scheme 6)[130]. Similarly, the reaction of β-propiolactone with lithium phenylacetylide led to the acid **160**[132]. α-Tetrahydrofurylpropionic acid **162** is produced by intramolecular nucleophilic attack in the lactone **161**[133].

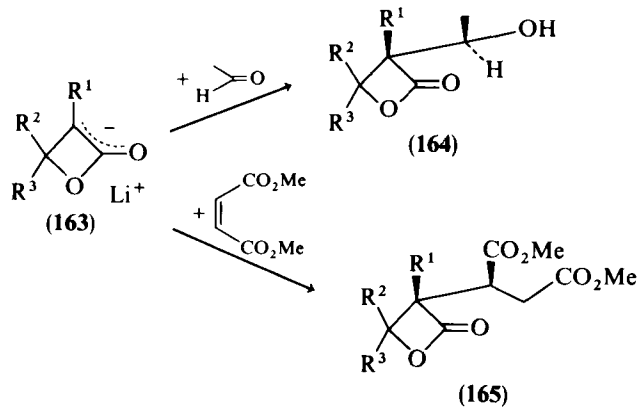


(160)



(161) **(162)**

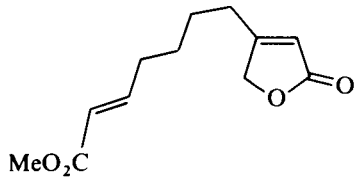
The lithium salts **163** (R^1–R^3 = alkyl or Ph) derived from β-lactones undergo highly stereoselective additions to acetaldehyde to form the alcohols **164**[134]; similarly, Michael addition of the enolates **163** to dimethyl maleate proceeds with stereocontrol of both newly formed chiral centres to yield predominantly the diastereomers **165** (equation 56)[135].



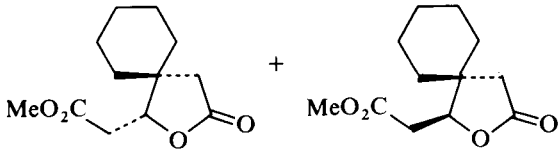
(163) **(164)** **(165)** (56)

2. *Reactions of other lactones*

The chemistry of γ-lactones has been reviewed[136]. 'Electroreductive cyclization' of the γ-butenolide **166** in the presence of diethyl malonate as a proton source yields a

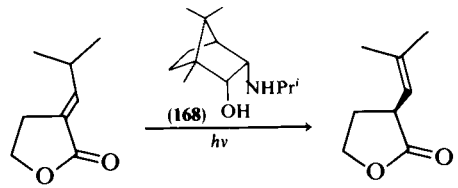


(166)



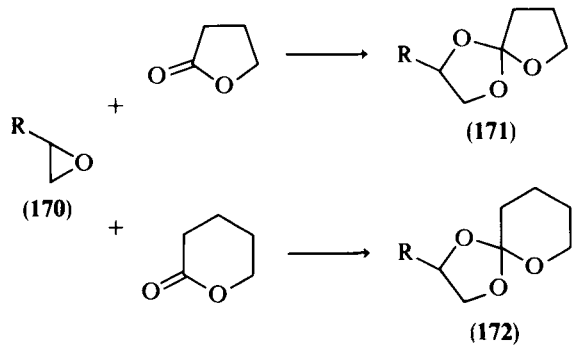
(57)

mixture of spiro compounds (equation 57)[137]. Photodeconjugation of the α-alkylidene-γ-lactone **167** by irradiation in the presence of the chiral cyclic inductor **168** derived from (+)-camphor gives the optically active lactone **169** in 43% e.e.[138]. The reaction



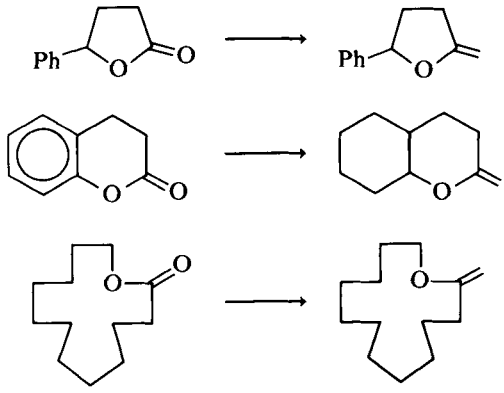
(167) (169)

of epoxides **170** (R = Me or $ClCH_2$ with γ-butyrolactone in the presence of 2-cyano-1-(4-methoxybenzyl)pyridinium hexafluoroantimonate leads to the spiro compounds **171**; the homologues **172** are produced from δ-valerolactone[139].



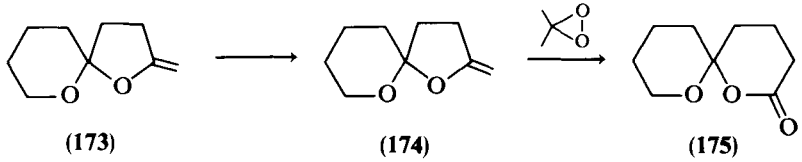
(170) (171) (172)

The carbonyl groups of simple lactones are transformed into methylene groups by means of methylenetitanocene, $Cp_2Ti{=}CH_2$ (equation 58)[140,141]. The spiro-lactone **173**



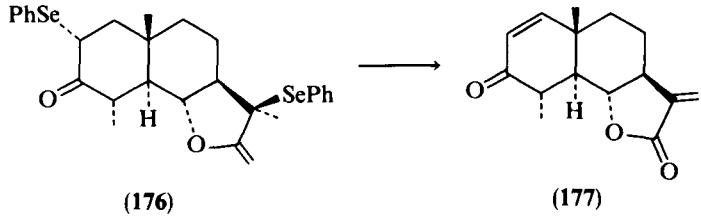
(58)

was similarly converted into the methylene compound **174**, which underwent oxidative ring expansion to the spiro-δ-lactone **175** by the action of dimethyldioxiran, followed by camphorsulphonic acid[142].

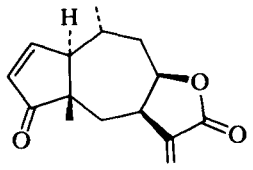


(173) **(174)** **(175)**

Methods for the conversion of γ-lactones into α-methylene-γ-lactones are exemplified by the reaction of ozone with the di(phenylseleno) compound **176** to yield (±)-tuberiferine (**177**)[143], by the synthesis of (±)-helenalin (**178**) from the corresponding lactone by treatment of its lithium derivative with formaldehyde, followed by dehydration[144], and by a procedure, in which the lactone is treated with LDA, followed by Eschenmoser's salt, methylenedimethylammonium iodide[145]. The resulting Mannich base is transformed into the methylenelactone by methylation, followed by treatment with sodium hydrogen carbonate or DBU (equation 59)[146].



(176) **(177)**



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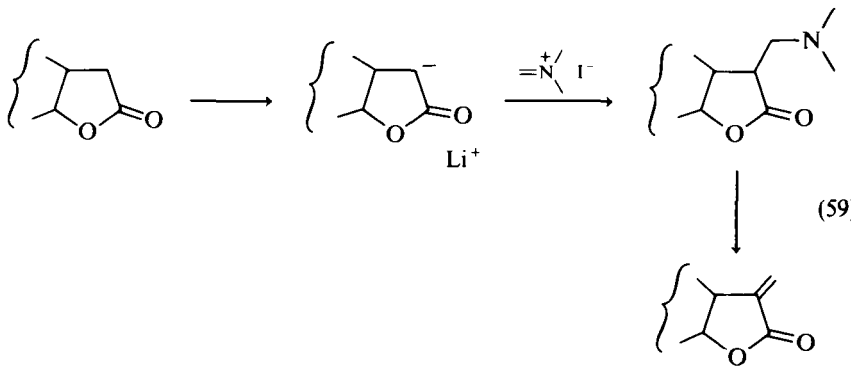
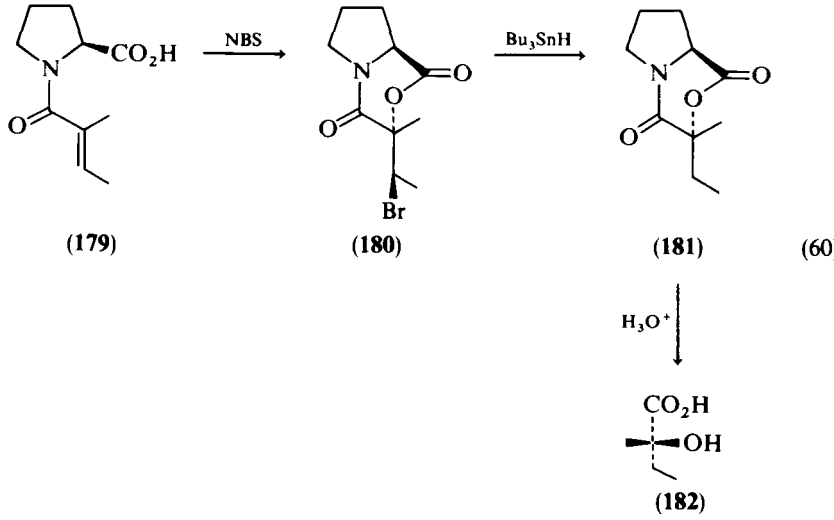


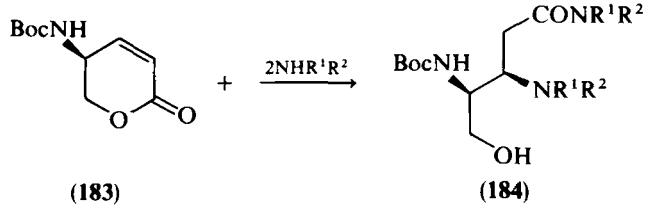
(59)

A method for the synthesis of chiral α-hydroxy acids via lactones is described in the following example. The amide **179**, prepared from (*S*)-proline and tiglyl chloride, underwent bromolactonization to yield the lactone **180**, which was reduced to **181**. Hydrolysis of the latter gave almost optically pure (*R*)-2-hydroxy-2-methylbutanoic acid (**182**) (equation 60)[147]. Addition of amines, e.g. benzylamine, butylamine, dimethylamine,



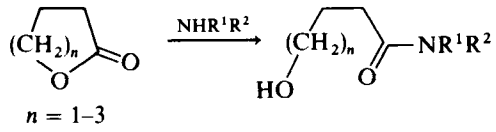
(60)

pyrrolidine etc., to the chiral unsaturated δ-lactone **183** occurs with high diastereoselectivity to yield the (*R*, *S*)-amides **184**[148].



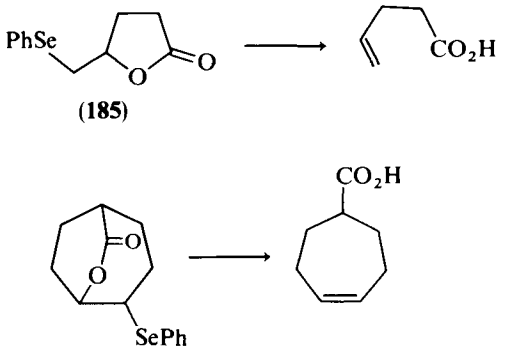
Boc = Bu^{t}OCO

Aminolysis of lactones is not a general reaction but it succeeds with dialkylaluminium amides[149]. It was recently reported that 5-, 6- and 7-membered lactones react with primary or secondary amines in the presence of aluminium chloride to yield amides of ω-hydroxyalkanoic acids (equation 61)[150]. The phenylselenoalkyllactones **185** and **186**



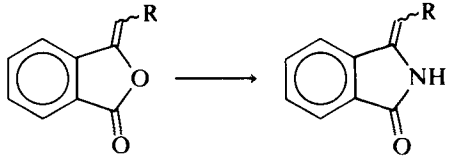
(61)

(and their sulphur analogues) are converted into unsaturated acids by the action of sodium in liquid ammonia (equation 62)[151]. This amounts to a reversal of the seleno-lactonization reaction.



(62)

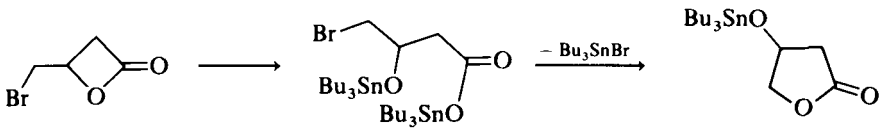
The alkylidenephthalides **187** (R = H, Pr or Ph) are converted into the lactams **188** by reaction with the titanium isocyanate complex $3THF \cdot Mg_2Cl_2OTiNCO$[152]. Ring-expansion occurs when bromomethyl-β- or -γ-lactones are treated with hexabutylditin oxide, $Bu_3SnOSnBu_3$. The lactone **189** gave solely the *cis* product **190** in this reaction (equation 63)[153]. The trifluoromethanesulphonates **191** and **192** derived from sugar



γ-lactones undergo ring-contraction to the ester **193**, accompanied by a little of the epimer **194**, by the action of methanolic potassium carbonate (equation 64)[154]. The lactone **195** yields solely the oxetan **196**[155].

3-Tosyl-2-pyrone (**197**) adds to electron-rich olefins in a Diels–Alder reaction with inverse electron-demand. 1,3-Dioxalene, for instance, gave the adduct **198**, which was transformed into the cyclohexene derivative **199** by the action of sodium methoxide (equation 65)[156].

The Claisen rearrangement of allyl vinyl ethers, which constitutes a method for



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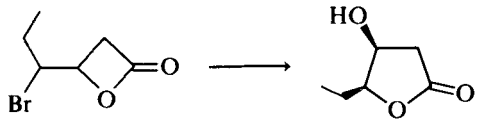
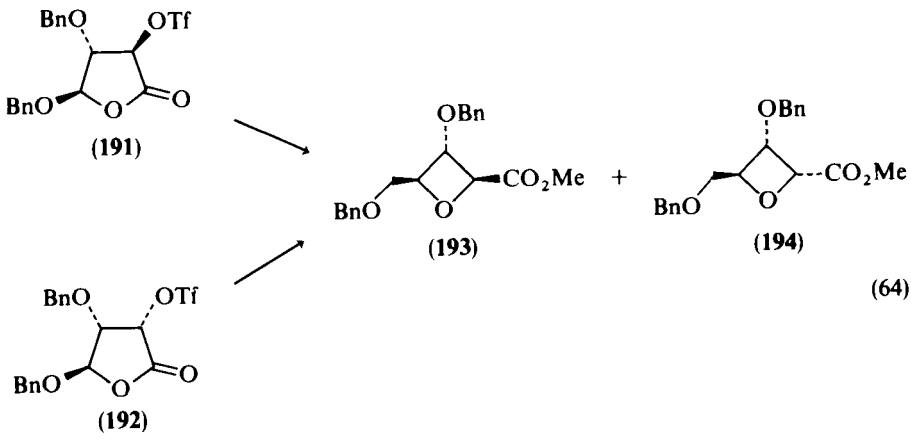
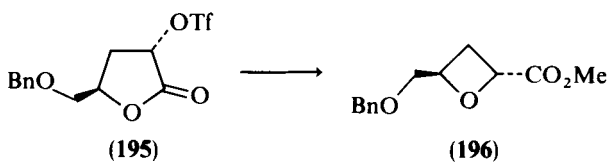


(189) (190)

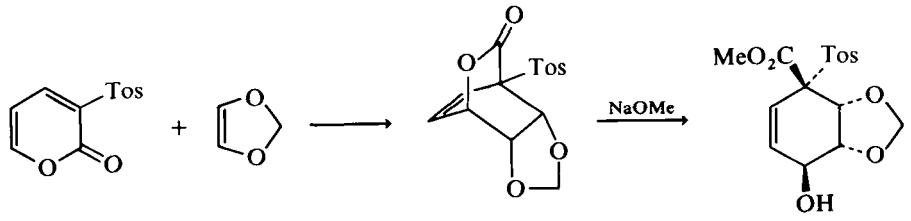


(64)

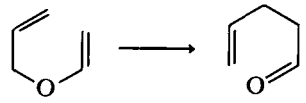
Bn = $PhCH_2$
Tf = F_3CSO_2



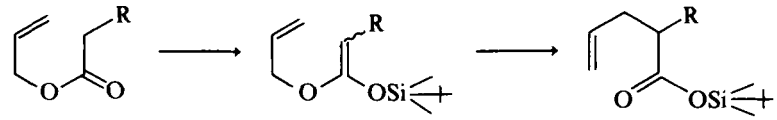
(195) (196)



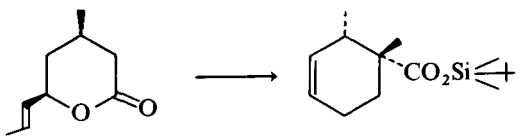
(197) (198) (199) (65)

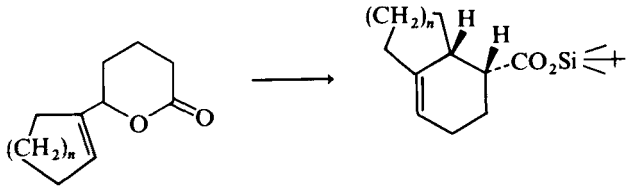
 (66)

carbon–carbon bond formation, takes place at elevated temperatures (equation 66). Allyl esters of simple carboxylic acids are converted into ester enolates by the action of LDA, followed by *t*-butyldimethylsilyl chloride; these enolates rearrange at or below room temperature (equation 67)[157]. When this reaction is applied to unsaturated lactones with

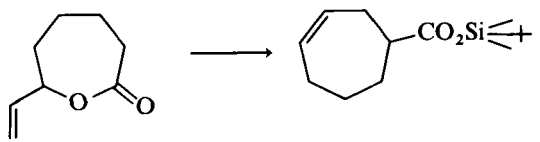
 (67)

an appropriately placed external or internal double bond, carbocyclic compounds are produced. Cyclohexenes were obtained from vinyl-δ-lactones (equation 68), cycloalkenyl-δ-lactones gave bicyclic products (equation 69) and the vinyl-ε-lactone **200** yielded the cycloheptene **201** (equation 70)[158].

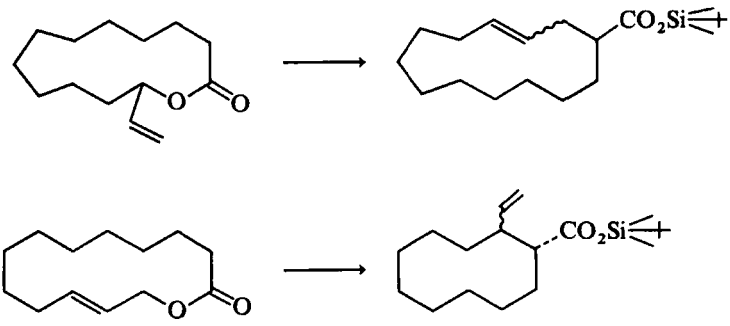
 (68)

 (69)

$n = 1$ or 2

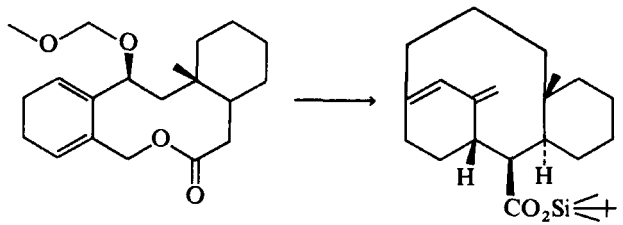
 (70)

(200) (201)

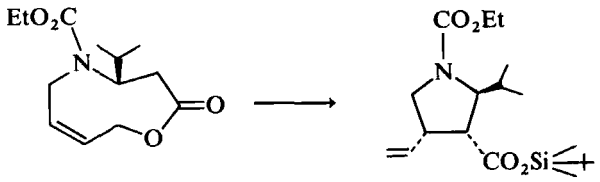


(71)

The formation of medium-ring cycloalkenes as mixtures of (*Z*)- and (*E*)-isomers is illustrated in equation 71[159]. The ten-membered lactone **202** afforded a single product **203**, which contains the taxane ring system[160]. The application of the lactone enolate Claisen rearrangement to the preparation of an optically pure pyrrolidine derivative is shown in equation 72[161].



(202) **(203)**



(72)

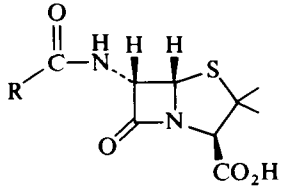
III. LACTAMS

A. β-Lactams

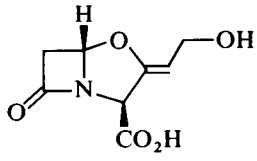
The chemistry of β-lactams (azetidin-2-ones) has developed enormously since the discovery of the antibiotic properties of penicillin. There is such a vast literature on this subject that only a brief outline of recent progress can be given here. The reader is referred to the excellent general account of syntheses, physical properties and reactions of azetidinones by Davies and Storr in *Comprehensive Heterocyclic Chemistry*[162] and to the reviews cited in this section.

In the penicillins (**204**) the azetidinone ring is fused to a thiazolidine ring; penicillin G is the phenylacetyl derivative (**204**; R = $PhCH_2$). Clavulanic acid (**205**) contains an oxazolidine ring and thienamycin (**206**), a member of the carbapenem class[163], a

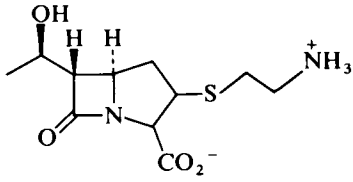
pyrroline ring. Fused four- and six-membered rings are present in the cephams (**207**) and recently synthesized oxygen analogues, such as Latamoxef (**208**)[164,165]. Monocyclic β-lactam antibiotics[166] are represented by the norcardicins (**209**) and monobactams (**210**; X = H or OMe, Y = H or Me).



(**204**)



(**205**)



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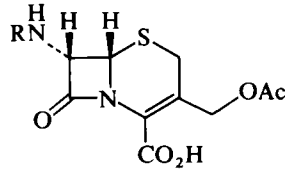
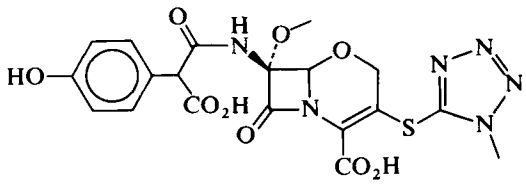
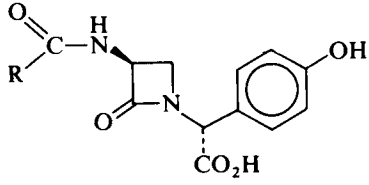


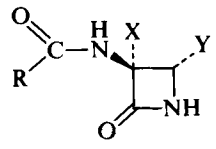
(**207**)



(**208**)



(**209**)



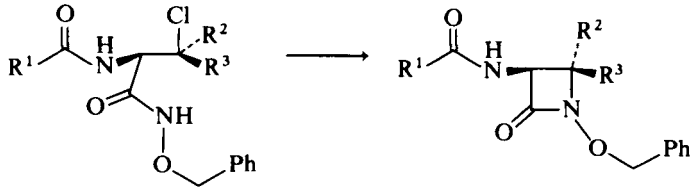
(**210**)

General reviews on β-lactam antibiotics are a three-volume work[167] on their chemistry and biology, a very readable account by Dürckheimer and others[168], a report of the proceedings of an international symposium[169], the regular surveys in Annual Reports[170a–e] and others[171–174]. Asymmetric syntheses of azetidinones have recently been reviewed[175]. More specialized reviews are on enantioselective syntheses of carbapenem antibiotics[176], preparative routes to chiral hydroxyethylazetidinones[177], applications of organometallic reagents[178], cleavage and rearrangements of β-lactams[179] and the stereochemistry of electrophilic substitutions in this system[180].

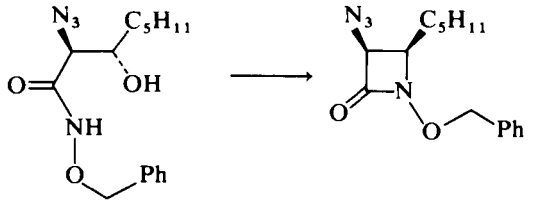
1. Synthesis of β-lactams

a. Cyclizations. The cyclization of β-amino acids to β-lactams (equation 73) is promoted by various phosphorus compounds, such as $EtOP(O)Cl_2$ and $PhPOCl_2$[181,182]. Derivatives of hydroxamic acids cyclize under basic conditions (equation 74)[183]. The α-azido-β-hydroxy amide **211** is converted into the (*Z*)-azetidinone **212** on treatment with triphenylphosphine/diethyl azodicarboxylate by activation of the hydroxyl group[184].

(73)

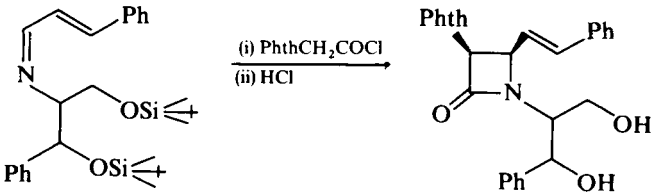


(74)



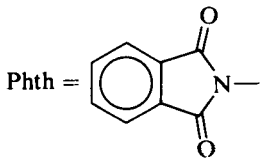
(211) **(212)**

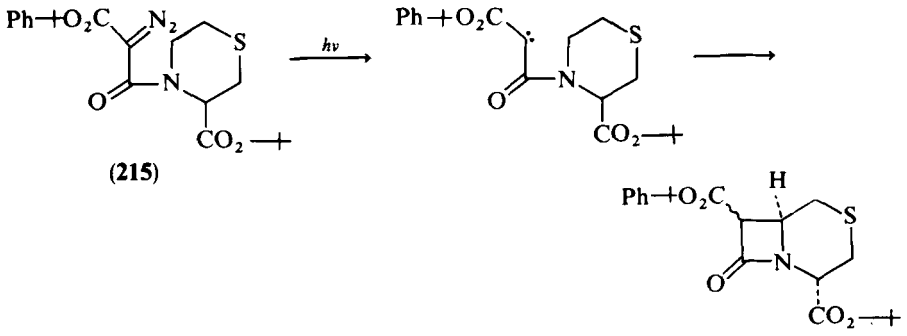
The formation of the styrylazetidinone **214** from the chiral (1*S*,2*S*)-1-aza-1,3-butadiene **213** and phthalimidoacetyl chloride (equation 75) is highly diastereoselective[185,186].



(213) **(214)**

(75)

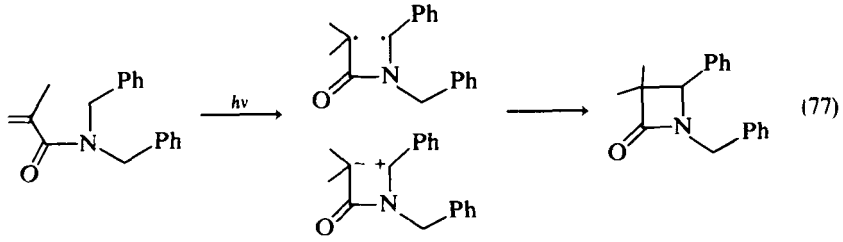




(215)

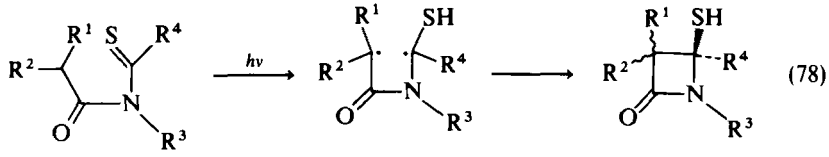
(76)

Irradiation of the diazo amide **215** yields a mixture of (*Z*)- and (*E*)-products by insertion of the derived carbene into a carbon–hydrogen bond (equation 76)[187]. A variety of other photocyclization reactions resulting in the formation of the C(3)—C(4) bond of azetidinone has been described. The photochemical ring-closure of *N*,*N*-dibenzylmethacrylamide is thought to be a Norrish type II reaction, which proceeds by way of a diradical or the corresponding zwitterion (equation 77)[188].



(77)

Irradiation of the monothioimides **216** yields the thiols **217** as mixtures of geometrical isomers, which were isolated as the *S*-benzoyl derivatives (equation 78)[189,190]. Bicyclic azetidinones have been obtained by analogous reactions: *N*-(thiobenzoyl)methacrylamides **218** (R = Me, Et, Ph or $PhCH_2$) give thietan-fused β-lactams (equation 79)[191,192] and irradiation of the tetrahydrothiazine derivative **219** affords the cepham analogue **220**[193].

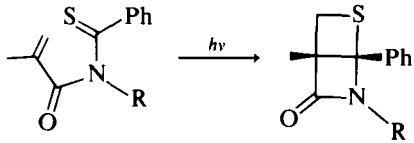


(216) (217)

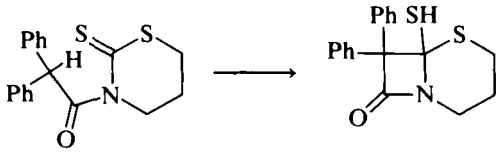
(78)

R^1 = H, OMe or Ph
R^2 = H or Me
R^3,R^4 = Me or Ph

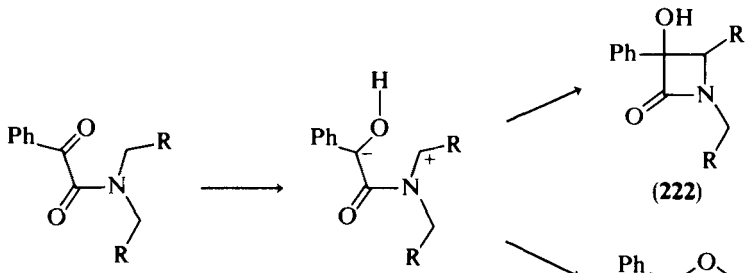
A study of the photochemistry of α-oxoamides **221** has shown that the reaction yields β-lactams **222** and/or oxazolidin-2-ones **223**. Radical-stabilizing groups, e.g. R = Ph,



(218) (79)



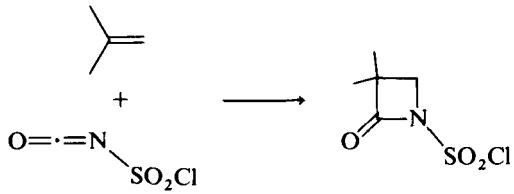
(219) (220)



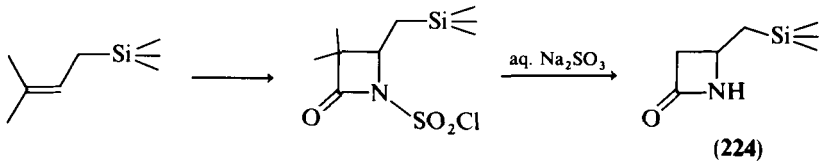
(221) (222) (223) (80)

favour lactams, whereas others, e.g. R = Me, cause the formation of oxazolidinones (equation 80)[194].

b. From olefins or imines. The reaction of chlorosulphonyl isocyanate with olefins to yield azetidinones (equation 81)[195] has been applied to the preparation of the trimethylsilyl derivative **224** (equation 82); the allene **225** similarly yields a mixture of alkylidene-β-lactams (equation 83)[196].

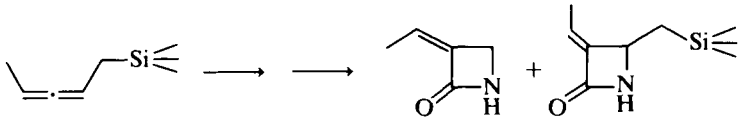


(81)



(82)

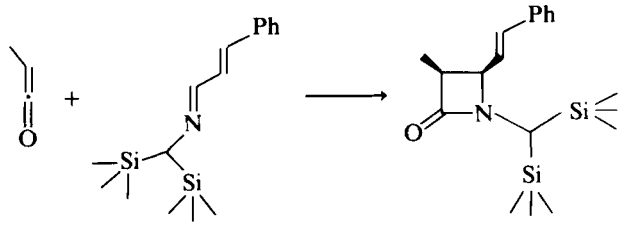
(224)

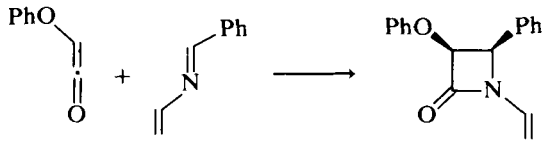


(83)

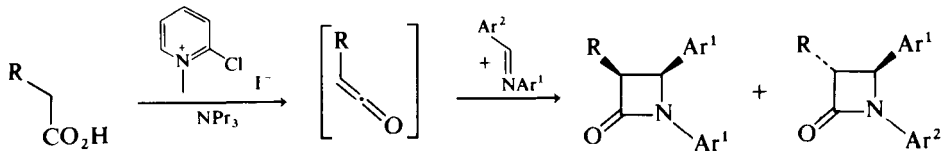
(225)

β-Lactams are obtained by the Staudinger reaction of ketenes with imines[197]. The formation of *cis*-3,4-disubstituted azetidin-2-ones from 1-azabuta-1,3-dienes[198] and 2-azabutadienes[199] is shown:





Three recent applications of the Staudinger synthesis are as follows. Dehydration of the acids **226** (R = phenoxy, phthalimido, vinyl, azido or methoxymethyloxy) with Mukaiyama's reagent in the presence of aromatic Schiff's bases gives mixtures of *cis*- and *trans*-azetidinones, in which the former predominate (equation 84)[200]. 1-(4-Methoxy-

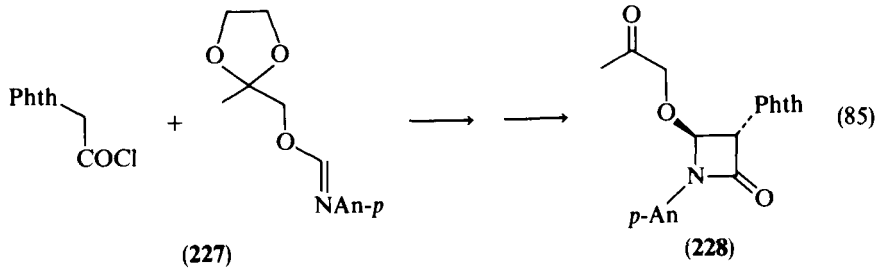


(226)

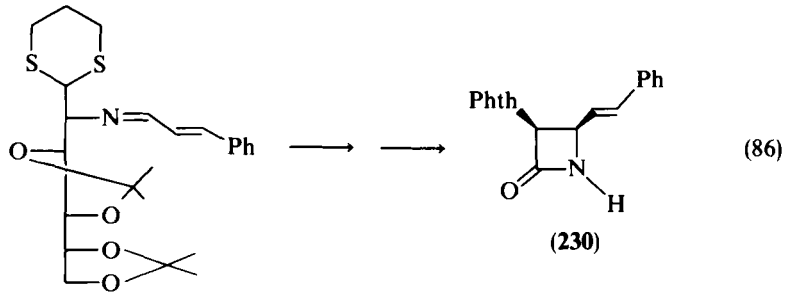
(84)

phenyl)-4-(2-oxopropyloxy)-3-phthalimido-azetidin-2-one (**228**), a useful intermediate for oxacephalosporin synthesis, is produced from the imidate **227** (equation 85)[201].

The chiral Schiff's base **229**, prepared from cinnamaldehyde and 3,4;5,6-di-O-isopropylidene-D-glucosamine propanedithioacetal, reacts with phthalimidoacetyl chloride in



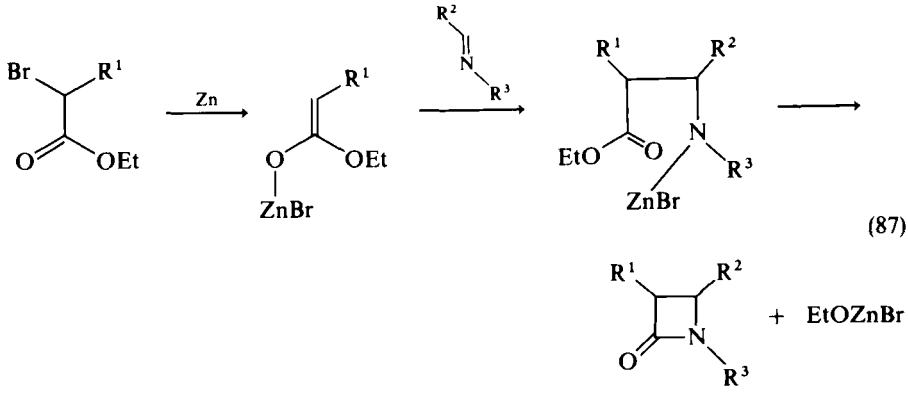
(227) (228) (85)



(229) (230) (86)

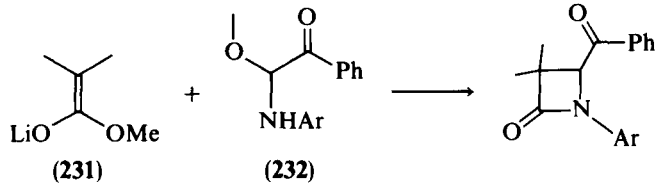
the presence of triethylamine to yield a *cis*-azetidinone with complete diastereoselectivity. The chiral auxiliary group is readily removed by β-elimination, giving **230** (equation 86)[202].

Gilman and Speeter found in 1943[203] that Reformatsky reagents add to imines to yield β-lactams. The reaction probably involves an acyclic intermediate (equation 87).

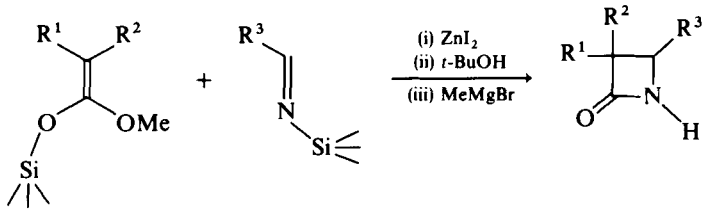


(87)

This ester enolate–imine synthesis has been extensively reviewed[204a–c]. A modification of the original procedure is treatment of a mixture of an α-bromo ester and an imine with zinc in the presence of trimethylsilyl chloride[205]. The reaction of the lithium enolate **231**, prepared from methyl isobutyrate and LDA, with the masked imines **232** at room temperature affords 4-benzoylazetidin-2-ones in good yields (equation 88)[206]. A 'one-pot' synthesis of *N*-unsubstituted β-lactams is shown in equation 89[207].

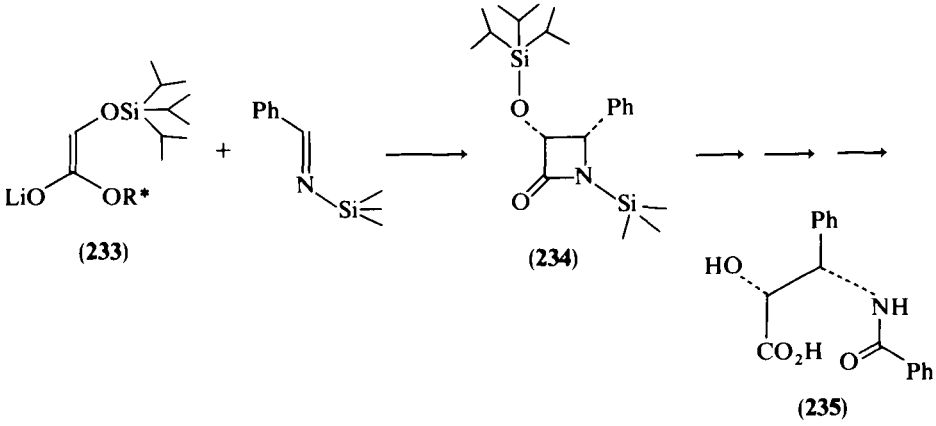


(88)



(89)

The ester enolate **233**, where R* is the chiral auxiliary group (−)-*trans*-2-phenyl-1-cyclohexyl, forms the optically active product **234** with benzylidene(trimethylsilyl)amine. Desilylation with tetramethylammonium fluoride, followed by successive treatment with hydrochloric acid (which opens the β-lactam ring) and benzoyl chloride, yields *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine **235**, a key intermediate for the introduction of the C-13 side chain of the anti-cancer agent taxol (equation 90)[208]. The ynolate **113** reacts with a variety of aromatic Schiff's bases to afford 1:2 adducts **236** (equation 91)[209].



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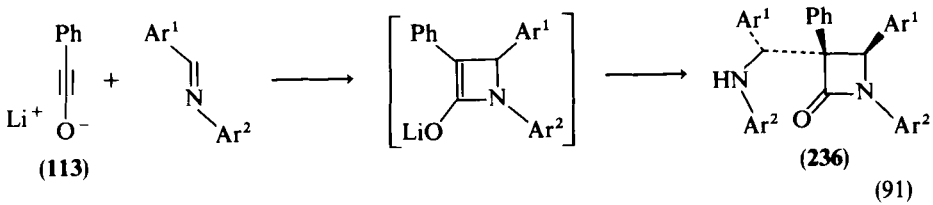
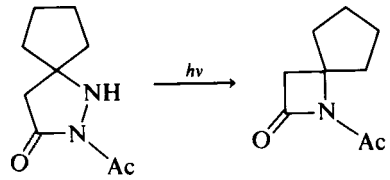


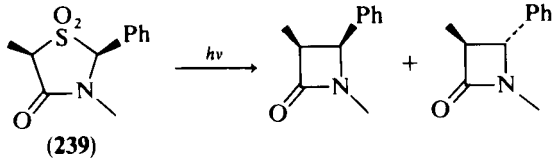
(91)

c. By ring-contraction. The spiro-β-lactone **238** is formed by photolytic ring-contraction of the pyrazolidinone **237**[210]. A mixture of *cis*- and *trans*-azetidinones is produced by the photo-extrusion of sulphur dioxide from the thiazolidinone SS-dioxide **239**

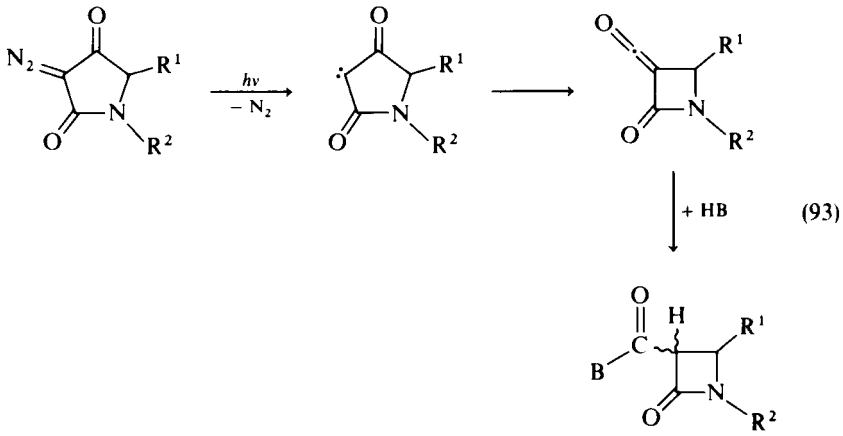


(237) **(238)**

(equation 92)[211]. Irradiation of 3-diazopyrrolidine-2,4-diones generates carbenes, which undergo Wolff rearrangement, resulting in ring-contraction. Derivatives of 3-carboxyazetidin-2-one are isolated when the reaction is carried out in the presence of nucleophiles (equation 93)[212].



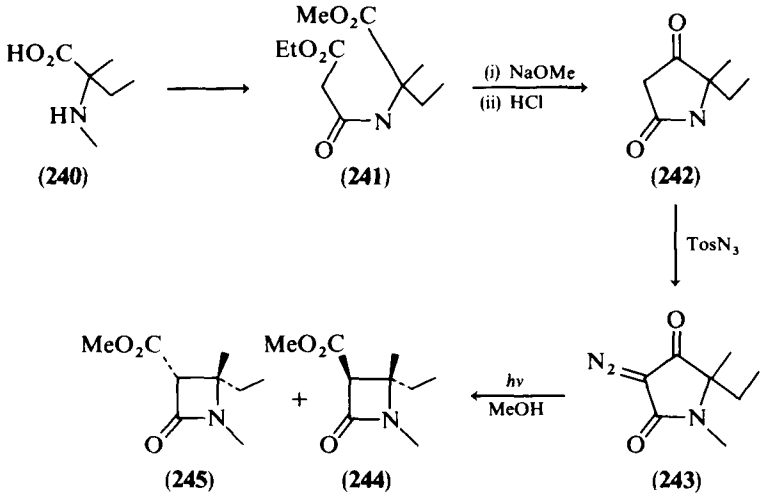
(239) (92)

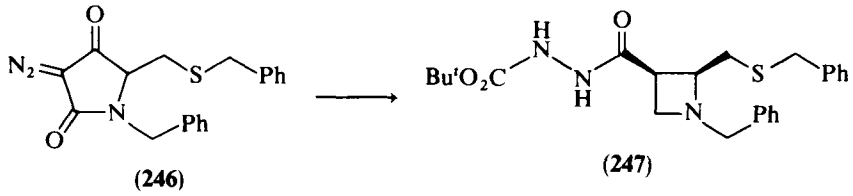


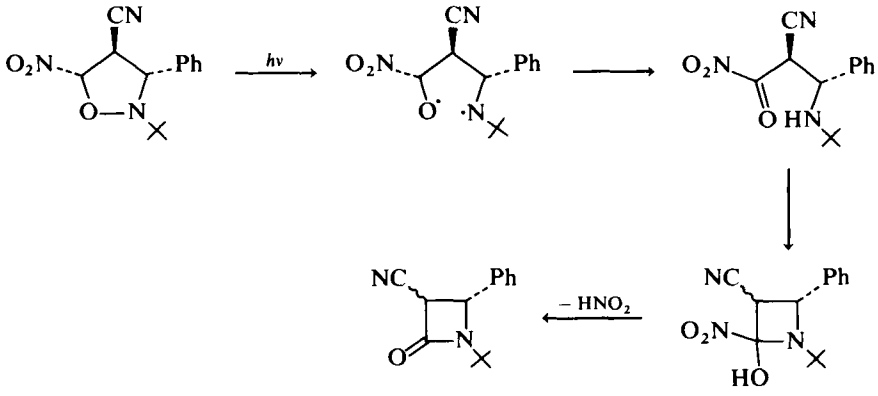
(93)

An example of this reaction is outlined in equation 94: the amide **241**, derived from the amino acid **240**, was converted into the pyrrolidinedione **242** by Dieckmann cyclization, followed by hydrolysis and decarboxylation. Diazo group transfer by means of tosyl azide gave **243**, which was irradiated in methanol, when a mixture of about equal amounts of the β-lactams **244** and **245** was isolated in 95% yield[212].

The hydrazide **247**, accompanied by the *trans*-isomer, was prepared analogously by irradiation of the diazo compound **246** in the presence of t-BuO_2CNHNH_2[213]. A remarkable photochemical ring-contraction of an isoxazolidine to an azetidinone, together with a suggested mechanism, is depicted in equation 95[214].

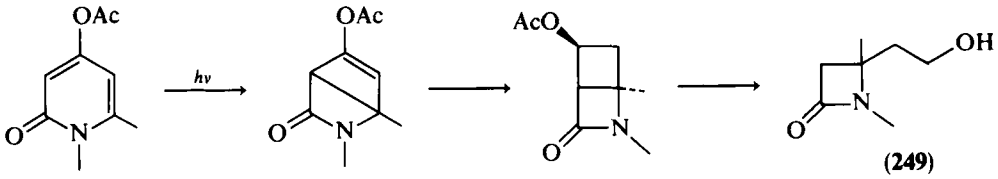






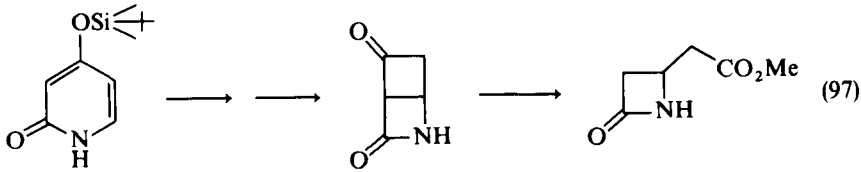
(95)

Irradiation of 2-pyridones gives Dewar-pyridones ('photo-pyridones') which can be converted into β-lactones by opening of the carbocyclic ring. Photo-4-acetoxy-1,6-dimethyl-2-pyridone (**248**) was transformed into the (hydroxyethyl)azetidinone **249** by sequential hydrogenation and treatment with sodium borohydride (equation 96)[215]. The pyridone **250** was irradiated and the protecting group was removed; the resulting bicyclic ketone **251** reacted with methanol to afford the ester **252** (equation 97)[216]. Fission of the cyclobutene ring of photopyridones **253** by ozonolysis has been reported in-



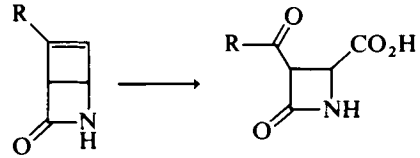
(248) (249)

(96)

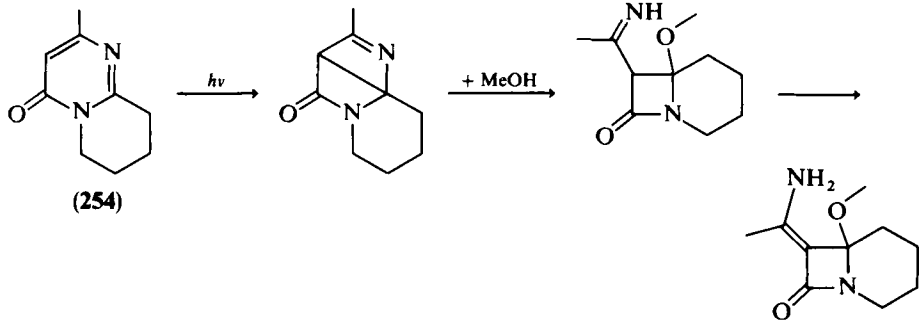


(250) (251) (252)

(97)



(253)



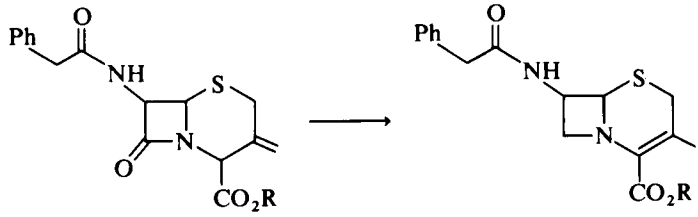
(254) (255)

(98)

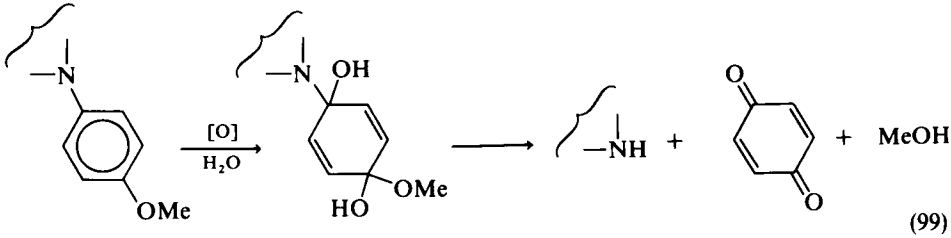
dependently by two groups[217,218]. Photolysis of 4-methyl-1,2-cyclohexano-6-pyrimidone (**254**) in methanol gives the bicyclic azetidinone **255** (equation 98)[219].

2. *Reactions of β-lactams*

The X-ray crystal structure of the 3-*exo*-methylenecephalosporin **256** has been determined; it isomerises to the *endo*-compound in the presence of triethylamine[220]. *p*-Methoxyphenyl groups attached to the nitrogen atoms of azetidinones are removed oxidatively by the action of ceric ammonium nitrate (equation 99)[221].

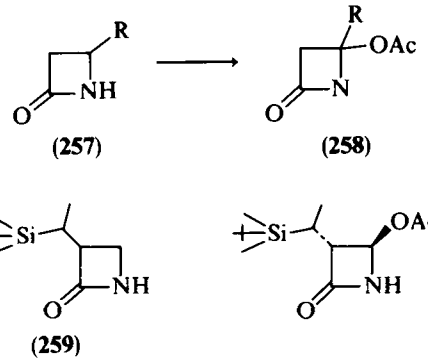


(256) R = $CH_2C_6H_4NO_2$-*p*



(99)

Peracetic acid reacts with the β-lactams **257** (R = H or Me) in the presence of bis(triphenylphosphine)ruthenium dichloride to yield 4-acetoxy derivatives (**258**); the introduction of the acetoxy group into the silyl compound **259** proceeds with high diastereoselectivity (equation 100)[222]. The acetoxy substituent in **258** (R = H) is replaced

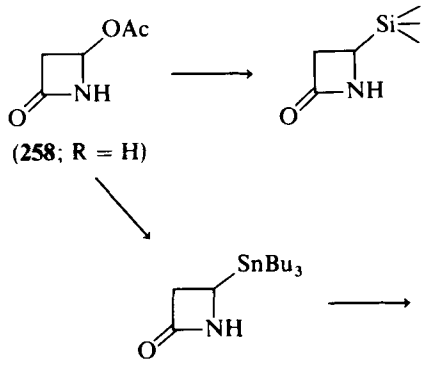


(257) (258) (259) (100)

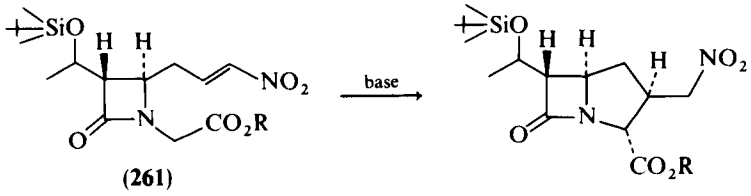
by the trimethylsilyl group by the action of lithium trimethylsilane/copper(I) chloride. Replacement by tributylstannyl, followed by reaction with phenylacetyl chloride in the presence of tetrakis(triphenylphosphine)palladium, gives the 4-phenylacetyl derivative **260** (equation 101)[223].

A new carbapenem synthesis (equation 102) involves an intramolecular Michael addition in the nitro olefin **261**[224]. The diazo compound **262** cyclizes to the carbapenem **263** under the influence of dirhodium tetraacetate. The reaction proceeds by intramolecular attack of a carbene on the nitrogen atom (equation 103)[225].

The 4-(ω-aminoalkyl)azetidinones **264** (*n* = 1 or 2) act as trinucleophiles towards the vinyl triketo ester **265**, yielding the tricyclic compounds **267**: the primary amino groups add at the β-position of the vinyl groups and also at the central carbonyl group; in the third stage the lactam nitrogen atom adds to the iminium ions **266** formed from the intermediate carbinolamines (equation 104)[226]. The spiro-β-lactam oxadiazoline **269**, obtained from the imine **268** by ketene cycloaddition, fragments into nitrogen, acetone

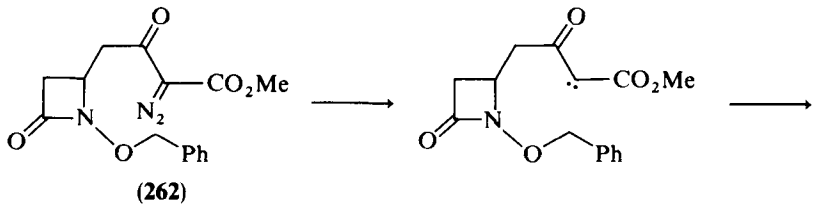


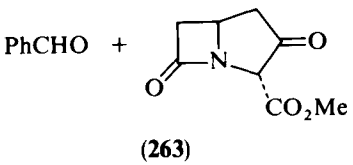
(101)



(102)

R = $CH_2C_6H_4NO_2$-*p*

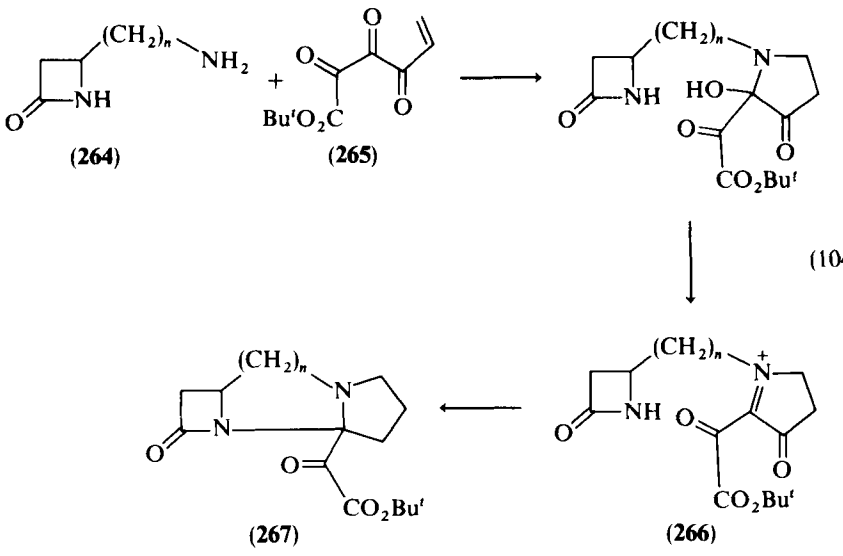


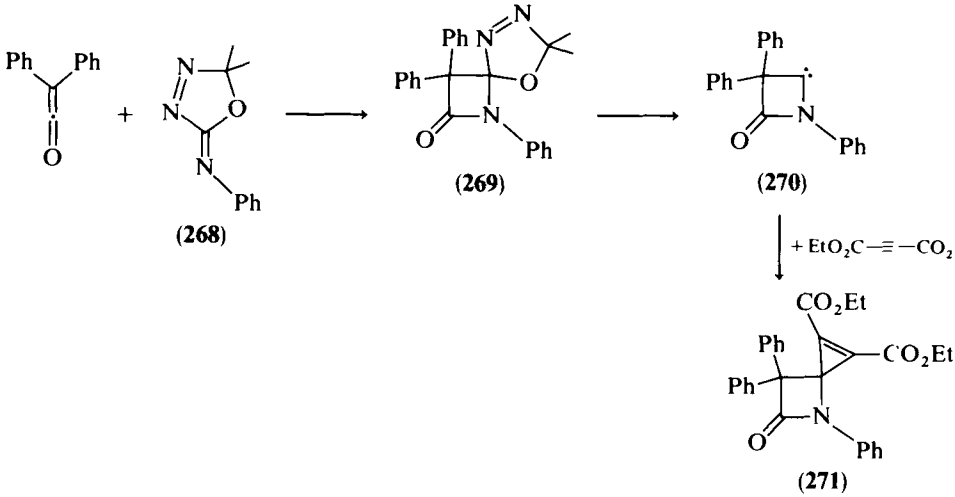


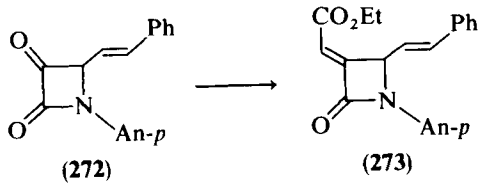
(103)

and the carbene **270**, which can be trapped as the spiro-cyclopropene **271** in the presence of diethyl acetylenedicarboxylate (equation 105)[227].

The azetidine-2,3-dione **272** is converted into the (ethoxycarbonylmethylene) compound **273** by reaction with ethyl bromoacetate in the presence of zinc and trimethylsilyl chloride, followed by desilylation and dehydration[228].

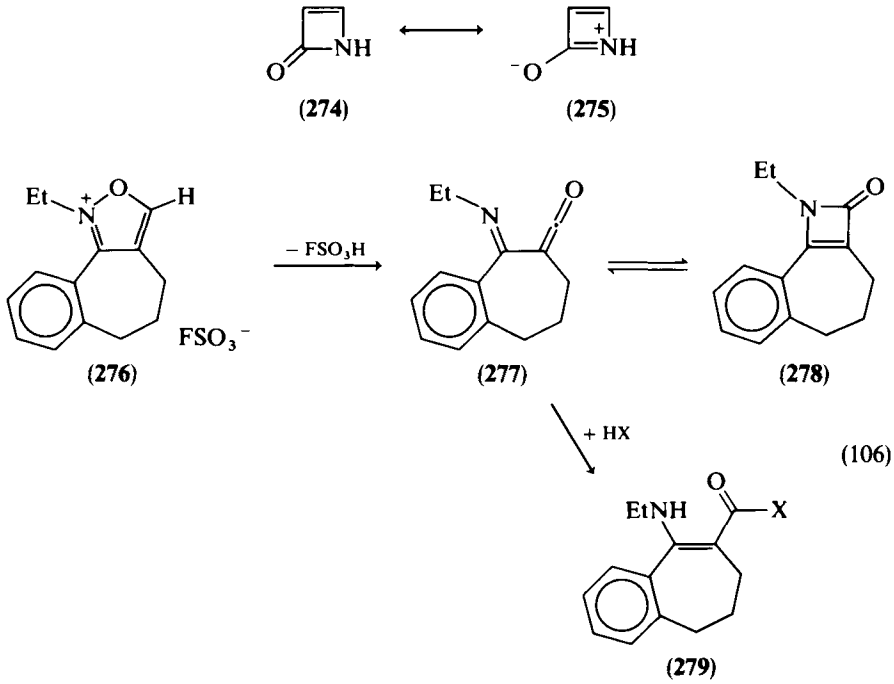

(CH2)n
NH2
NH
O
Bu^tO2C
(264)
(265)
HO
CO2Bu^t
(104)
(266)
(267)


Ph
Ph
N
O
Ph
(268)
(269)
(270)
+ EtO2C—≡—CO2Et
CO2Et
(271)
(105)


Ph
An-p
(272)
CO2Et
(273)

3. Azetin-2-ones

The planar azetinone ring system **274** is destabilized by resonance with the anti-aromatic canonical form **275**, which contains 4 π-electrons. Experiments designed to produce an azetinone which is distorted by fusion to a seven-membered ring met with some success. Treatment of the tricyclic isoxazolium salt **276** with the hindered base ethyldiisopropylamine produced a yellow solution absorbing in the 1800 cm^{-1} region, whose colour persisted for about 4 min. When the deprotonation was carried out in the presence of nucleophiles HX the benzocycloheptene derivatives **279** were isolated. These results were attributed to the formation of the ketene **277**, which is in equilibrium with the yellow azetinone **278**. Solutions of the corresponding *N*-*t*-butyl and *N*-1-adamantyl compounds were stable for up to 20 min at room temperature (equation 106)[229].



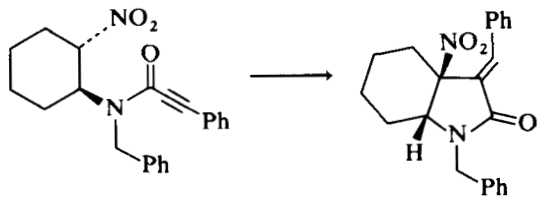
(106)

B. Other Lactams

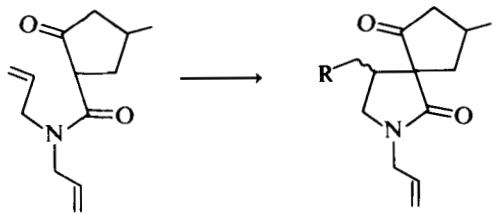
1. Syntheses

Amines react with ammonium salts in the presence of dicyanogen to yield amides but the reaction is restricted to intramolecular condensations. β- and ε-lactams are formed at rates comparable to those for γ- and δ-lactones[230].

A stereospecific synthesis of an α-methylene-γ-lactam by internal Michael addition, catalysed by Triton B, is shown in equation 107[231]. The *N*,*N*-diallyl-β-ketoamide **280** is converted into the γ-lactone **281** (R = I) by the action of sodium hydride, followed by *N*-iodosuccinimide[232]. A similar result is obtained when manganese(III) acetate is used, compound **281** (R = H) being formed[233].

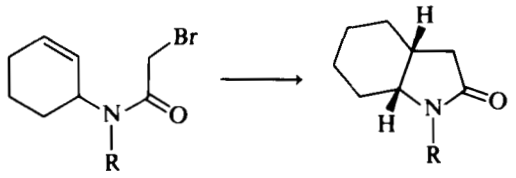


(107)

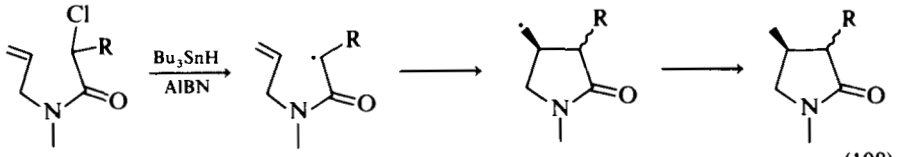


(280) (281)

The free-radical cyclization *N*-alkyl-*N*-bromoacetylcyclohex-3-enylamines (**282**), induced by tributyltin hydride and AIBN, yields solely the *cis*-fused lactams **283**[234,235]. γ-Lactams are produced from *N*-allyl-α-carbamoyl radicals as indicated in equation 108; more *trans*- than *cis*-isomers are produced in this reaction[236].

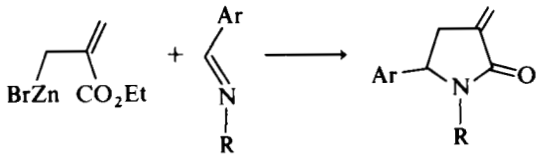


(282) (283)

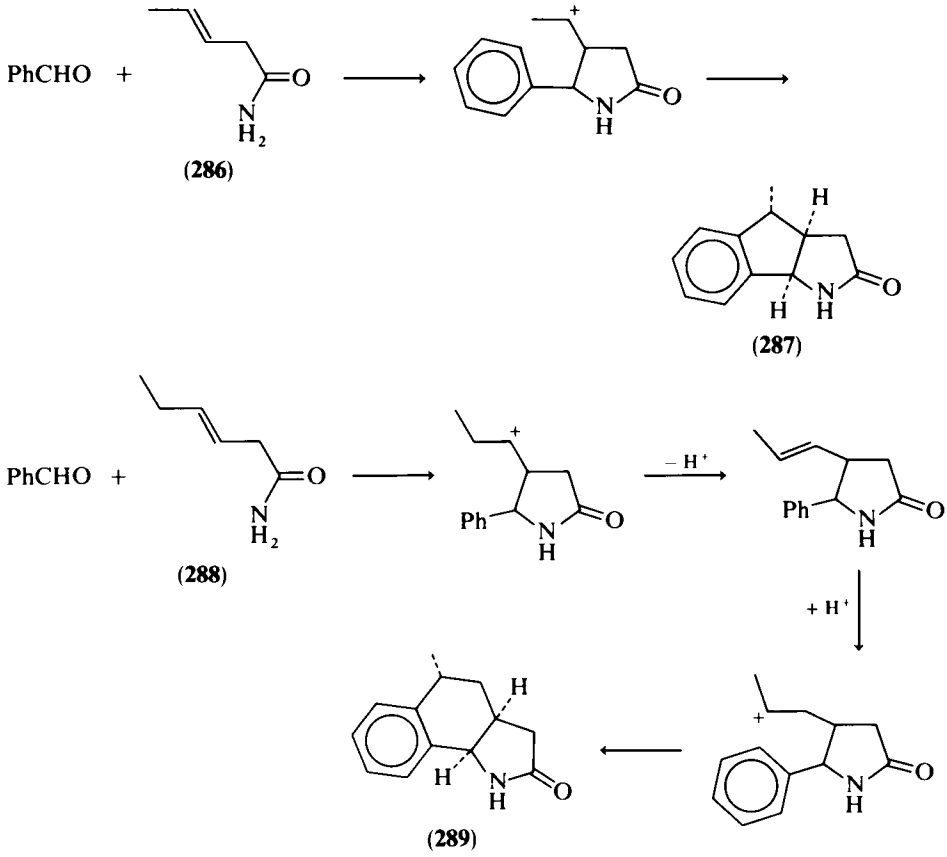


R = Me or Ph (108)

The action of the zinc derivative **284** of ethyl α-bromomethylmethacrylate on Schiff's bases **285** (R = alkyl or aryl) results in the formation of α-methylene-γ-lactams (equation 109)[237]. The amide **286** of pent-3-enoic acid reacts with benzaldehyde in polyphosphoric



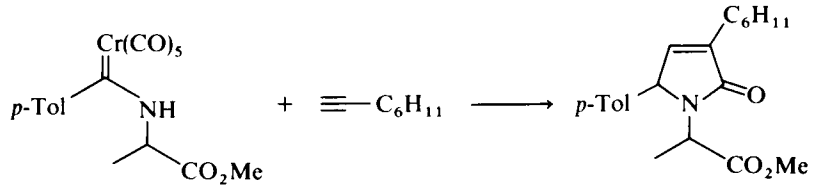
(284) (285) (109)



SCHEME 7

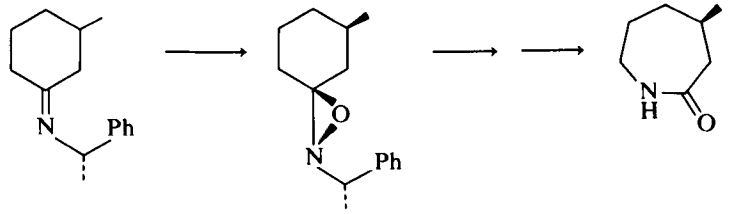
acid at 30 °C to yield the *cis*-fused tricyclic lactam **287**. The homologue **288** affords the analogue **289**, which contains a central six-membered ring. The authors propose that the reactions involve intermediate carbonium ions, which cyclize by attack on the benzene rings (Scheme 7)[238]. Treatment of the chromium carbene complex **290**, derived from alanine, with oct-1-yne produces the unsaturated γ-lactam **291**[239].

Two methods for the ring-expansion of cyclohexanones to seven-membered lactams, which are alternatives to the Beckmann and Schmidt reactions, have been described. In



(290) (291)

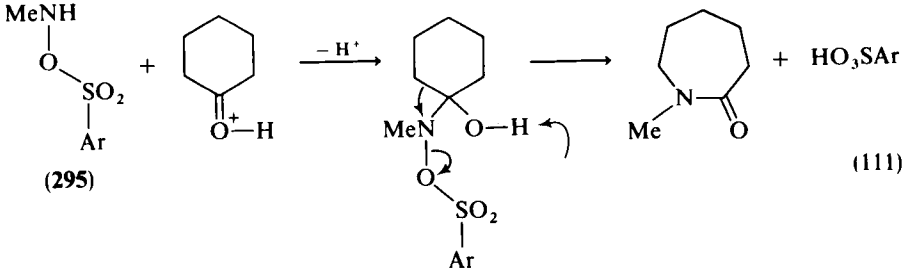
the first, the imine **292**, prepared from (*R*)-(+)-3-methylhexanone and (*R*)-α-methylbenzylamine, is oxidized with (+)-monoperoxycamphoric acid to give a mixture of diastereomeric oxaziridines containing more than 90% of **293**. Photolysis of the latter, followed by reductive debenzylation with sodium in liquid ammonia, gave the chiral ε-lactam **294** (equation 110)[240].



(110)

(292) **(293)** **(294)**

N-(*p*-Nitrobenzenesulphonyloxy)methylamine (**295**) reacts with cyclohexanone under acidic conditions to form an adduct which rearranges spontaneously to *N*-methylcaprolactam (**296**) (equation 111). The process can be extended to the preparation of *N*-methyl derivatives of medium and macrocyclic lactams from cyclic ketones[241].

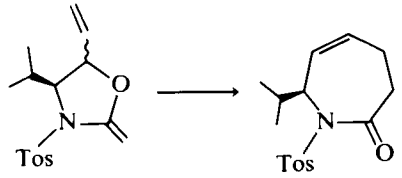


(111)

(295)

$Ar = p\text{-}O_2NC_6H_4$

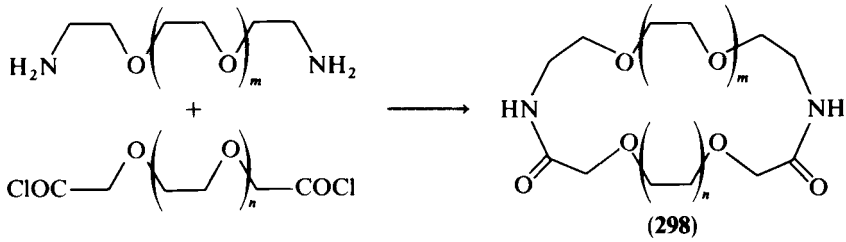
The Claisen rearrangement (see equation 66) of the methyleneoxazolidine **296** results in the unsaturated ε-lactam **297** (equation 112)[242].



(112)

(296) **(297)**

The synthesis of macrocyclic lactams has been reviewed[243,244]; 12- and 24-membered dilactams are formed from α,ω-diamines and the chlorides of α,ω-dicarboxylic acids[245]. The condensation of diamines with diacyl chlorides in the presence of triethylamine under conditions of high dilution affords macrocyclic polyoxadilactams, e.g. **298** ($m = 2$, $n = 1$) and **298** ($m = n = 2$)[246]. The bicyclic dilactam **299** was obtained in good yield by acid–amine condensation in the presence of diphenylphosphoryl azide (equation 113)[247].



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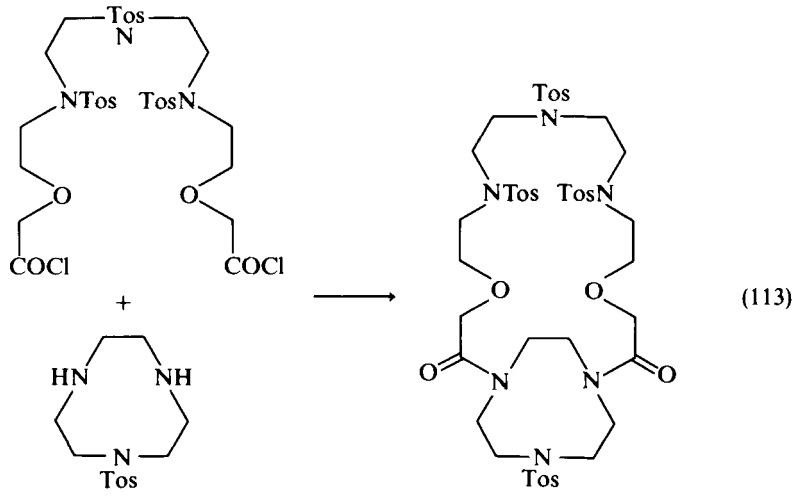
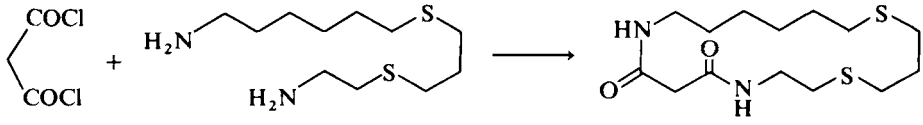


(113)

(299)

The X-ray structure of 1,5-dithia-8,12-diazacyclotetradecane-9,11-dione (**301**), prepared from malonyl chloride and the diamine **300**, has been reported[248]. The dioxadiamine **302** condenses with the dimethyl ester **303** at 8 kbar to afford the macrocycle **304**[249]; a similar high-pressure reaction of **302** with dimethyl adipate gave the dilactam **305**[250].

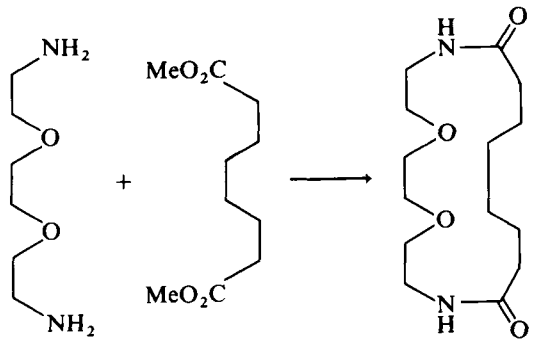


(300) (301)

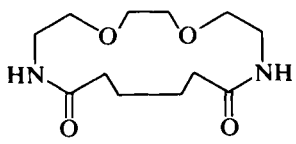
2. Reactions

Diverse lactams have been converted into thiolactams by the combined action of P_4S_{10} and sodium carbonate in THF at room temperature[251]. Diastereoselective Michael addition of lithium dimethylcuprate to the lactam **306** yields **307**[252].

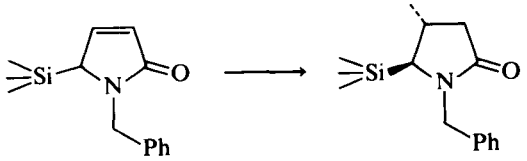
A detailed review on the cyclopropanation of lactams and the synthetic uses of the products has appeared[253]. The bicylic α,β-unsaturated lactams **308** (R = H or Me), for instance, react with trimethylsulphoxonium ylid **309** to give either *endo*- or *exo*-adducts.



(302) (303) (304)



(305)



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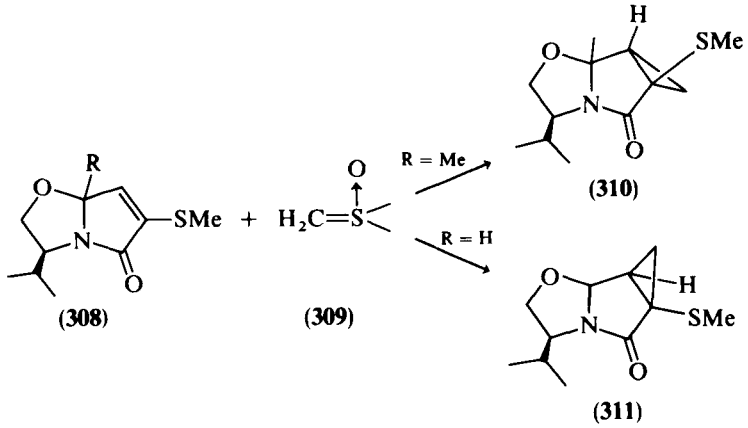
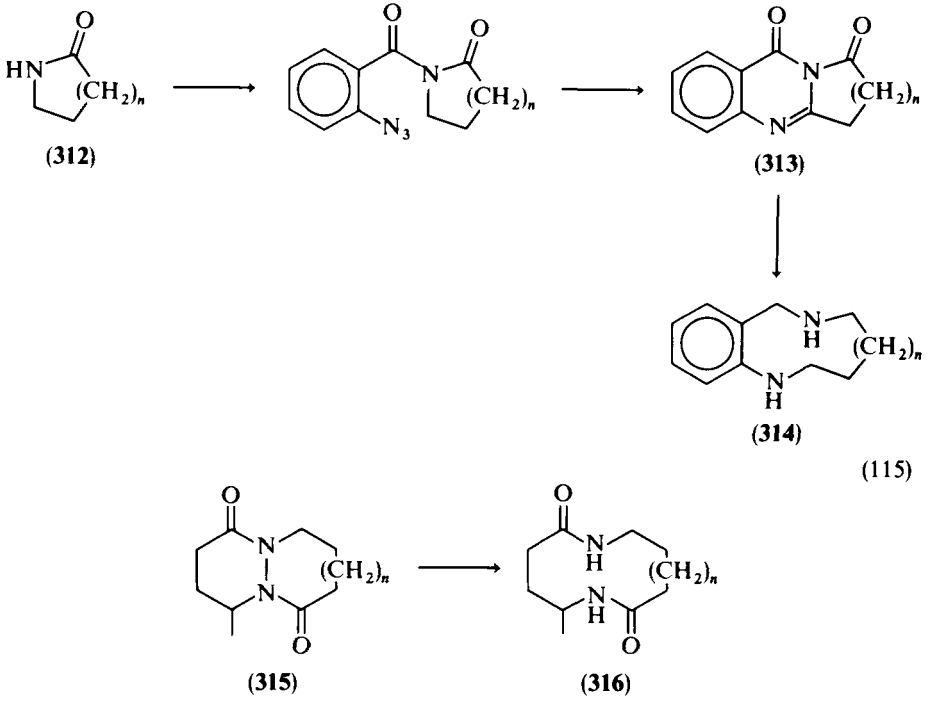


(308) (309) (310) (311)

(114)

310 or **311**, respectively, depending on the presence or absence of the angular methyl group (equation 114).

Macrocyclic diamines **314** (n = 3, 4, 5 or 9) have been obtained in high yields from the lactams **312** by the sequence shown in equation 115. The lactams are condensed with *o*-azidobenzoyl chloride and the products are treated with tributylphosphine, when an intramolecular aza-Wittig reaction takes place to give the tricyclic quinazolinones **313**. The latter afford the diamines on reductive cleavage with the $BH_3 \cdot THF$ complex[254]. Bicyclic diacylhydrazines **315** (n = 1–3) suffer fission of the nitrogen–nitrogen bond by the action of sodium in liquid ammonia to afford the macrocyclic dilactams **316** in yields of 83–88%[255].



(115)

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CHAPTER 11

The synthetic uses of carboxylic acids and their derivatives

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I. INTRODUCTION

The synthesis of complex, polyfunctional organic molecules, in a stereocontrolled manner, is surely one of the wonders of modern chemistry. The beauty and elegance of the methodologies devised and reported in the literature, especially by the world's major synthetic groups, often leaves one totally spellbound upon first reading.

A cursory glance at almost any modern synthetic sequence will convince the reader of the central importance of carboxylic acid derivatives as sources of chiral starting materials, as key intermediates and as target molecules. The reader is referred to the excellent *Art in Organic Synthesis* by Arnand, Bindra and Ranganathan[1] which chronicles key syntheses that have been successfully completed over the last few decades. This work amply indicates the central role of acid derivatives in synthetic organic chemistry.

An excellent review[2] on the synthesis of natural pheromones has shown the importance of naturally occurring, optically active, carboxylic starting materials such as α-amino acids, tartaric and citronellic acid. The review has also shown the importance of acid-derived functional group interconversions, of lactonization as a key synthetic step, of fractional crystallization of acids/bases for enantiomeric separation and of the many carbon–carbon bond-forming reactions which are possible with acid derivatives. Many other workers have espoused the use of other acid derivatives as synthetic substrates, such as glutamic acid[3] and sugar lactones[4], and have extolled the virtues of carboxylic acid derivatives in all aspects of synthetic chemistry.

Thus, carboxylic acids and their derivatives are probably the most versatile tools available to the synthetic organic chemist. Conversions to amines, aldehydes, alcohols, ethers, halides and hydrocarbons may be readily performed. In some cases a carbon atom is lost giving 'nor functionalities'. In addition, interconversion between the different acid derivatives is easy to achieve. α-Functionalization of carboxylic acid derivatives may also be performed readily as may decarboxylation and decarbonylation. However, the major synthetic importance of acids and their derivatives arises from the ease by which they may be used in carbon–carbon bond-forming reactions and in the preparation of heterocycles.

In this review all the above-mentioned, useful synthetic processes will be discussed in detail with examples taken mainly from the chemical literature since 1980.

The present work does not cover the use of acyl silanes in synthesis and the reader is referred to the reviews of Ager[5], Bullman Page and coworkers[6] and Ricci and

Degl'Innocenti[7]. Similarly, as regards the chemistry of selenium, tellurium and tin analogues of carboxylic acid derivatives the reader is referred to leading references in the literature[8–12]. Nor does this chapter cover the chemistry of *ortho* esters which have been reviewed elsewhere[13], or the chemistry of ketenes (which may be derived from acids) which have been the subject of a volume in the 'Functional Groups' series[14] and numerous reviews[15–17].

Preparations of acid derivatives themselves have been covered in great detail elsewhere, in *The Chemistry of the Functional Group* series, and the reader is referred to these works for details[18–21]. However, a brief discussion of acid derivative interconversions is presented in Section II.G, for completeness of the present work.

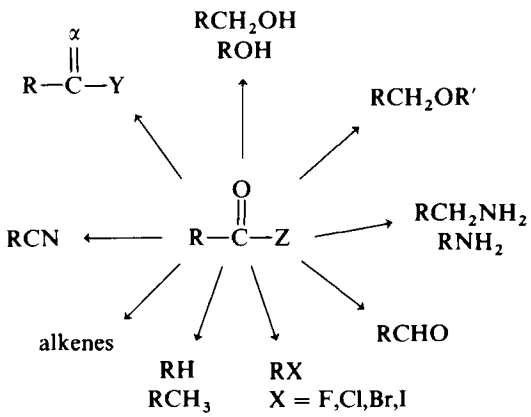
This review covers the chemical literature up to the beginning of 1991.

II. FUNCTIONAL GROUP INTERCONVERSION OF CARBOXYLIC ACID DERIVATIVES

Carboxylic acids and their derivatives are very versatile compounds that may have their functional groups transformed into a wide range of other functionalities, as shown in equation 1. All these functional group interconversions are discussed in this section. Some of these processes involve loss of a single carbon atom in which case 'nor' functionalities are formed. The synthetic usefulness of acid derivatives in the production of lactones and lactams is briefly mentioned in Section II.G, where these functionalities are formed by reduction, and is covered in detail in Section V since synthetic target molecules containing these functional groups are so important and widespread in organic chemistry. It should be noted that acid derivatives may be converted into ketones, but that this reaction is considered in Section IV since it is a carbon–carbon bond-forming reaction. Alcohols are also produced by reaction of organometallic reagents with acid derivatives in carbon–carbon bond-forming reactions and these too are covered in Section IV.

A. Formation of Alcohols and Ethers

Reduction of carboxylic acid derivatives to alcohol and ether functionalities may be brought about by a wide range of reducing reagents. These reactions are discussed here.

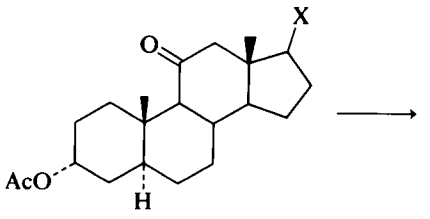


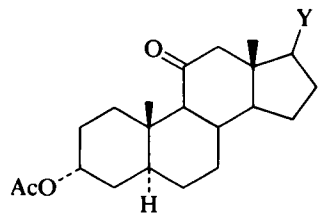
(1)

Reaction of carboxylic acids using mild conditions with lithium aluminium hydride produces primary alcohols, via aldehydes which are themselves difficult to isolate in many instances (however, see Section II.B). Sodium borohydride may also be employed if used in combination with activators such as *N,N*-dimethylchloromethyleniminium chloride[22]. In this case, reduction of the acid group may be performed selectively in the presence of other reducible groups such as esters, halides, olefins and nitriles (equation 2)[23]. The carboxylic acid group in an N-protected α-amino acid was reduced to an alcohol, at 0°C, by use of borane in THF[24]. Catalytic hydrogenation at low temperatures and pressures, with a ruthenium catalyst, has also been used to prepare alcohols from carboxylic acids[25].

$$RCO_2H \xrightarrow{Cl^-NMe_2=CHCl} RCOOC(H)=\overset{+}{N}Me_2\ Cl^- \xrightarrow{NaBH_4} RCH_2OH \qquad (2)$$

'Nor' alcohols may be obtained, in excellent yield, via radical decarboxylation of carboxylic acids. The reaction involves the formation of a thiohydroxamate ester followed by its reaction with a trisphenylsulphide of a Group Va metal (especially antimony) in the presence of air[26,27]. This reaction has been used for the conversion of steroidal acids into alcohols (equation 3)[28].





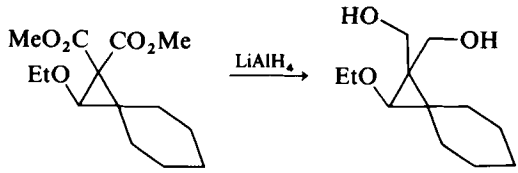
(3)

X = CO_2H, $CH(CH_3)CO_2H$, $CH(CH_2)_2CO_2H$ (with CH_3) Y = OH, $CH(CH_3)OH$, $CH(CH_2)_2OH$ (with CH_3)

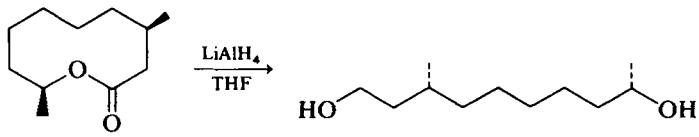
Reduction of esters and lactones with lithium aluminium hydride[29,30], lithium borohydride[31,32], sodium borohydride with activators[33–36] and a wide variety of other reducing reagents[22,25,37–39] gives alcohols as products. For example, alkoxy-substituted ethyl cyclopropane carboxylates are reduced, in excellent yields, to the corresponding alcohols (equations 4 and 5)[30,40]. In some cases, reduction may be performed selectively in the presence of other reducible functional groups such as halogens and nitro groups[31]. By the lithium aluminium hydride reduction of chiral lactones diols were readily formed. This methodology has been used to prepare long-chain diols with remote chiral centres without the need of resolution (equation 6)[41].

Lithium aluminium hydride (LAH) and lithium borohydride reduction of ortho esters gives an allylic alcohol as major product with, in most cases, a small amount of the

(4)

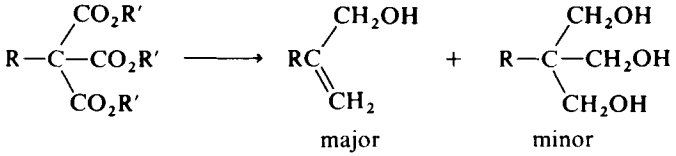


(5)



(6)

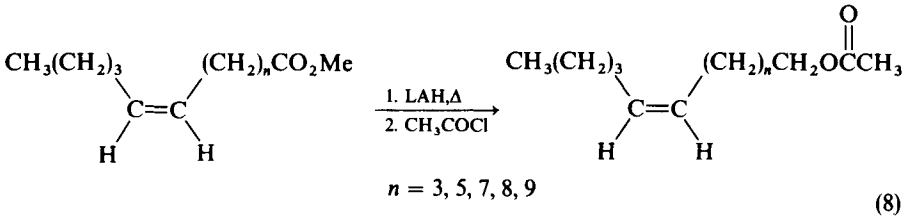
expected triol (equation 7)[42]. The allylic alcohol has been shown to be formed by reduction of a decarboxylated intermediate.



(7)

In general, esters are inert towards reduction by sodium borohydride (without activators), except when neighbouring group participation assists the process or in the case of a few aromatic, heterocyclic esters.

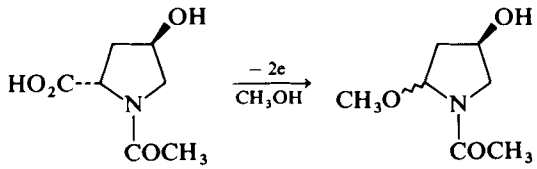
The reduction of an ester to an alcohol, followed by acetylation, is often the last step in the synthesis of lepidopteran, and other, pheromones. This conversion can be performed either stepwise[43,44] or in a single step (e.g. equation 8)[45].



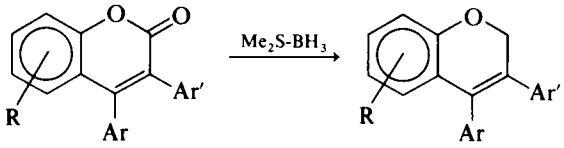
$n = 3, 5, 7, 8, 9$

(8)

Hydride transfer reductions of esters in the presence of boron trifluoride-etherate results in the production of ethers[46]. The same transformation may also be performed by using trichlorosilane and UV light. Electrochemical decarboxylation of hydroxyproline derivatives also produces ethers (equation 9)[47]. 3,4-Diarylcoumarins and 3,4,5-



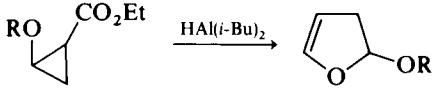
(9)



(10)

triarylfuranones (lactones) are also reduced to the ether level by the use of dimethyl sulphide-borane complex, as exemplified in equation 10[48].

Attempts to produce cyclopropane carboxaldehydes by reduction of the corresponding esters have resulted in ring-expanded ethers as shown in equation 11[30].



(11)

Thiol esters (RCOSR') are converted to sulphides with Raney nickel whilst thiono esters (RCSOR') produce ethers with the same reagent[49].

Acyl halides are reduced to primary alcohols by LAH. Other hydride transfer reagents, such as $NaBH_4$, may also be employed[50].

Chain shortening of acyl halides leads to excellent yields of nor-alcohols via a radical chain reaction in the presence of dimethyl sulphide (equation 12)[51].

$$RCH_2COX \longrightarrow [RCH_2OOH] \xrightarrow{Me_2S} RCH_2OH \qquad (12)$$

LAH reduction of anhydrides also produces alcohols. With cyclic anhydrides, either diols or lactones are formed depending upon the reaction conditions. In the first laboratory synthesis of the first lignans to be found in humans, and animals, an anhydride was identified as the key intermediate. Upon reduction with sodium borohydride in DMF the anhydride yielded one lignan (a lactone) as shown in equation 13 whilst reduction with LAH afforded another lignan (a diol) as shown in equation 14[52].

(13)

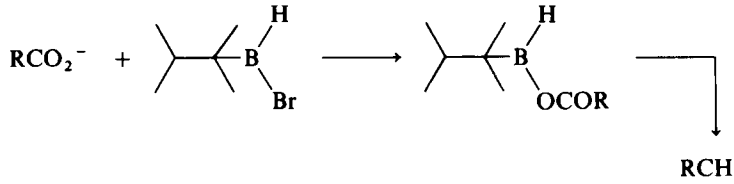
(14)

B. Formation of Aldehydes

While reduction of carboxylic acid derivatives usually leads to primary alcohols as the major products, the methodology for halting the reduction at the aldehyde stage is also well established and this has been reviewed recently by Cha[53].

Carboxylic acids may be reduced to aldehydes, via imines, by reaction with lithium in either ammonia or a simple primary amine, followed by hydrolysis.

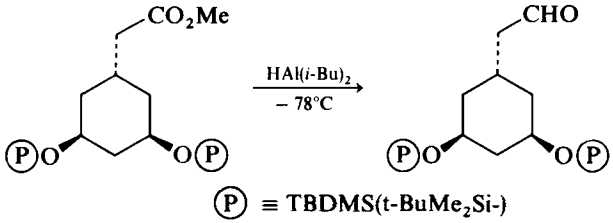
The use of boron-containing reagents for the conversion of carboxylic acids, and their salts, into aldehydes has received much attention[54–61]. Sodium and lithium salts of acids[56,57], and acids themselves[55,60], react with two equivalents of thexylborane–dimethyl sulphide complex to give extremely high yields of aldehydes at room temperature (equation 15). A similar reaction also takes place if 9-borabicyclo[3.3.1]nonane (9-BBN) is used as reducing agent[58,69].



(15)

Complex aluminium hydrides in pyridine with *N,N*-dimethylchloromethyleniminium chloride[62] or in refluxing THF[63] also produce excellent yields of aldehydes. Aldehydes may also be formed by reaction of an acid with a Grignard reagent with a titanium-containing catalyst followed by hydrolysis[64].

Esters may be readily reduced to aldehydes by use of either diaminoaluminium hydride or by diisobutylaluminium hydride at low temperatures (equation 16)[65]. For example, the protected methyl 3,5-dihydroxy-1-cyclohexane acetate was reduced to the aldehyde *en route* to 2,4-dioxaadamantane, as shown in the equation. A patent has been filed for the hydrogenation of esters to aldehydes using either yttrium or zirconium oxides as catalyst[66].



(16)

Acid chlorides have been reduced to aldehydes using $LiAlH(OBu\text{-}t)_3$ at $-78°C$[67], with tributyltin hydride[68,69], by catalytic hydrogenation (Rosenmund reduction)[70,71], by chromium or tungsten hydrides[72] and with both sodium and complex copper borohydrides in a polar aprotic solvent[73–76]. The latter reaction may be catalysed by metal ions, in which case non-acyl halides present in the molecule being reduced are unaffected[77]. Polymer-supported hydrides have also been used to prepare aldehydes by reduction of acyl chlorides[78,79].

Nor-aldehydes are produced from acyl chlorides via a radical reaction involving treatment with TsCl in pyridine (equation 17)[51].

$$RCH_2COCl \longrightarrow RCH_2OOH \xrightarrow[Py]{TsCl} RCHO \qquad (17)$$

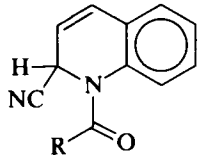
In a synthetically very useful reaction, acyl halides have been converted into nor-aldehydes by initial conversion into acylcobalt salophens followed by sunlamp irradiation with nitrogen monoxide, in dichloromethane, and hydrolytic work-up, as shown in equation 18[80,81].

Disubstituted amides may be reduced to the aldehyde level by the use of lithium

$$RCH_2COCl \longrightarrow RCH_2CO{-}Co(salophen) \xrightarrow[2.\ H_2O]{1.\ h\nu,\ NO} RCHO \qquad (18)$$

aluminium hydride although it is very difficult to stop the reaction at this stage. Alcohols are nearly always produced as by-products and this reaction has been reviewed previously in an earlier volume of the present series[67].

A special group of amides, Reissert compounds, may easily be converted into aldehydes simply by treatment with sulphuric acid, as shown in equation 19[82]. (Reissert compounds are produced by reaction of a carboxylic acid with quinoline and cyanide ion.)



$\xrightarrow{H_2SO_4}$ RCHO (19)

Other special classes of amides such a 1-acylimidazoles and acylsulphonylhydrazides ($RCONHNHSO_2R'$), where the aldehyde produced has no α-hydrogen atoms, may also be converted into aldehydes by LAH and bases, respectively[83]. Also, the Sonn–Muller procedure may be used for the conversion of *N*-phenyl arylamides into aldehydes by treatment of the amide with phosphorus pentachloride followed by hydrolysis (equation 20).

$$ArCONHPh \xrightarrow[2.\ H_3O^+]{1.\ PCl_5} ArCHO \qquad (20)$$

C. Formation of Amines

The formations of amines from carboxylic acid derivatives include the classical Curtius and Schmidt reactions and the Hofmann rearrangement and the hydride reduction of amides.

In the Schmidt reaction the acid is reacted with hydrazoic acid to give an intermediate isocyanate, which upon hydrolysis yields the amine as shown in equation 21[84]. A similar functional group transformation may be performed in 51–86% yield, in a single pot, by reaction of aromatic or heteroaromatic acids with thionyl chloride followed by hydroxylamine-*O*-sulphonic acid in dry toluene under reflux[85].

$$RCO_2H + HN_3 \longrightarrow \xrightarrow{H^+} RNH_2 \qquad (21)$$

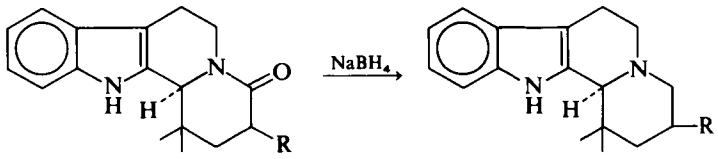
Hofmann rearrangement of unsubstituted amides gives amines, again via the isocyanate[86–88]. The intermediate may be isolated if the reaction is performed under phase-transfer conditions[89]. Similarly, the Curtius rearrangement of acyl azides and the Lossen rearrangement of RCONHOCOR also produce amines via the isocyanate upon hydrolysis[88,90]. Using the Hofmann rearrangement, N-protected 2,3- and 2,4-diaminobutyric acids, needed for solid-phase peptide synthesis, have been prepared from N-protected asparagine and glutamine, respectively[86].

In general, the reduction of a wide structural variety of amides with hydride transfer reagents[32], borane[91,92] or by catalytic hydrogenation also produces amines (note the exception of disubstituted amides with $LiAlH_4$ as discussed in Section II.B). In this

reaction no carbon atoms are lost, as shown in the preparation of muscimol[92,93] (a potent, toxic GABA neurotransmitter agonist) by reduction of an isoxazole amide (equation 22).

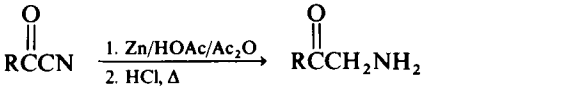
(22)

Disubstituted amides may be reduced to amines with trichlorosilane[94]. Lactams may be similarly reduced with sodium borohydride; tertiary δ-lactams have thus been converted into tertiary cyclic amines (equation 23)[95].



(23)

Acyl nitrile may be readily converted into the corresponding α-aminoketones by reduction followed by hydrolysis as shown in equation 24[96]. The reduction is chemoselective since it can be performed in the presence of olefins, esters and ketones.



(24)

D. Formation of Halides

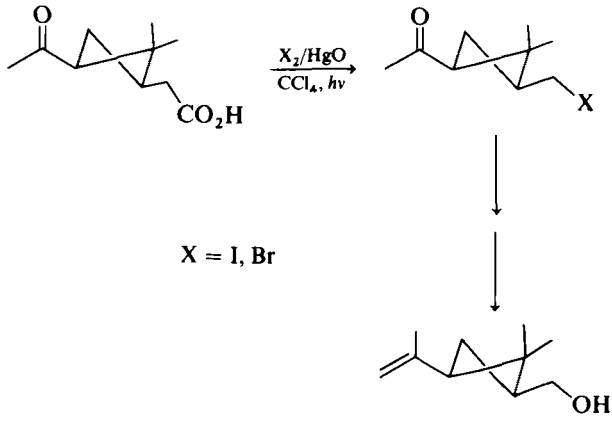
There are very few ways to prepare a halide from an acid in good yields. The classical Hunsdiecker method is one well-used exception although some others of limited applicability are also available, and will be discussed.

Halides with one carbon atom fewer than the starting acid may be formed by the Hunsdiecker reaction of bromine with silver salts of carboxylic acids. Except where the acid is unsaturated, the reaction is of widespread applicability. In a short, stereoselective synthesis of a sex pheromone of the citrus mealybug, *Planococcus citri* (Risso), (+)-*cis* pinonic acid [prepared by oxidation of (+)-α-pinene] was halodecarboxylated using the Cristol–Firth variation of the Hunsdiecker reaction (equation 25)[97]. In more recent years, thallium salts have been employed since these are more readily prepared and much more easily purified than the silver salts[98]. A radical reaction, involving organoantimony compounds, has been used to form nor alkyl iodides from acids[28].

Alkyl fluorides have been produced, in 54–84% yield, by treating acids with xenon fluoride and HF (equation 26)[99]. This method was unsuccessful in the presence of hydroxyl groups and so could not be used for the fluorodecarboxylation of cholic acid.

If acyl halides, with no α-H atoms, are heated with either Wilkinson's catalyst $[RhCl(Ph_3)_3]$[100,101] or palladium[102], then alkyl halides are formed in reasonable yields. Alkyl halides (Cl, Br, I) are also obtainable from acyl halides by treatment with iodoform, with amine catalysis[103].

Arylmethyl acyl halides have been used to prepare arylmethyl halides via cobalt salophens by irradiation in the presence of bromotrichloromethane[81]. This reaction



(25)

$$RCO_2H \xrightarrow[20°C]{XeF_2,\ HF} RF \tag{26}$$

proceeds in a very similar fashion to the classical Hunsdiecker reaction, as discussed above.

E. Formation of Nitriles and Isonitriles

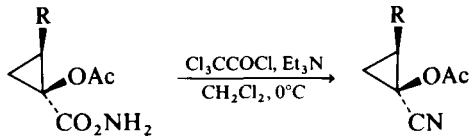
The conversions of acid derivatives into nitriles are discussed below.

Carboxylic acids may be converted into nitriles simply by heating their ammonium salts, by heating the acid with BrCN or ClCN to about 300°C or by heating with ammonia followed by treatment with ethyl polyphosphate[104]. Nitriles are also produced by heating acyl halides, which may be prepared in the same pot from the acid by reaction with thionyl chloride, with sulphamide (equation 27)[105].

$$RCO_2H \xrightarrow{SOCl_2} RCOCl \xrightarrow[\Delta]{(NH_2)_2SO_2} RCN \tag{27}$$

N-Alkylated or *N*,*N*-dialkylated amides may be converted into nitriles under forcing conditions using PCl_5. This reaction is known as the von Braun reaction. A milder process using phosphorus oxychloride has been used to perform the same conversion, in excellent yield[106].

Unsubstituted amides, upon treatment with phosphorus pentoxide, and many other dehydrating agents, such as cyanuric chloride[107], *N*,*N*-dimethylchloromethyleniminium chloride[108] and trimethylsilylpolyphosphate[109] are converted into nitriles. Mild conditions for this transformation are now well established[110,111] and a trichloroacetyl chloride/triethylamine combination was recently used to form the 1-acetoxycyclopropanecarbonitrile (equation 28)[112].



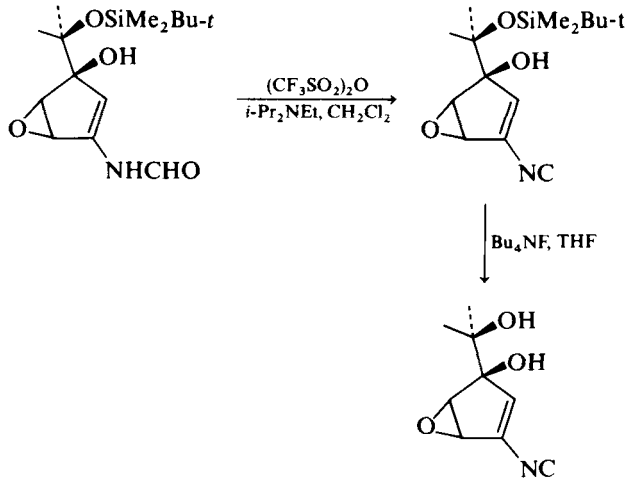
(28)

R = H, CH_3

Both amides and thioamides may be used to prepare nitriles under phase-transfer conditions in yields in excess of 60%[113], whilst thioamides are converted into nitriles by reaction with 2,4-dichloro-5-nitropyrimidine[114].

Formamides may be converted into isonitriles by reaction with trifluoromethanesulphonic acid at −78°C, in high yield, as exemplified in equation 29[115]. The formamide may be conjugated to an olefin and such a reaction has been employed for the preparation of isonitrin B, a metabolite produced by fungi of the genus *Trichoderma* (equation 30)[116,117].

$$\text{RNHCHO} \xrightarrow{(CF_3SO_2)_2O} \text{R}-\overset{+}{\text{N}}\equiv\overset{-}{\text{C}} \qquad (29)$$



(30)

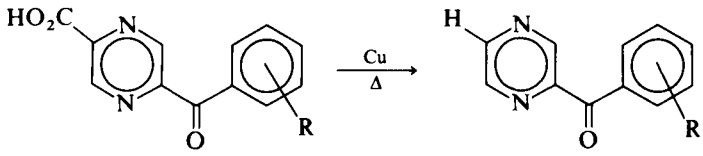
F. Decarboxylations and Decarbonylations

This section covers the decarbonylation and decarboxylation reactions that do not result in a new carbon–carbon bond being formed. Such reactions are often of key importance in synthetic sequence, since they allow the use of the activating qualities of the acid group and then allow it to be removed. Both replacement of the carboxyl group by a hydrogen atom and the production of alkenes in a β-type elimination process are covered.

Decarboxylations with the introduction of nor functionalities have been discussed in Sections II.A–E.

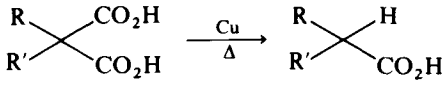
1. Replacement by hydrogen (RCOX → RH)

Aromatic acids, upon heating with copper quinoline, are readily decarboxylated to yield aromatic hydrocarbons. 2-Pyrazinyl ketones, important synthetic building blocks that are hard to prepare by other means, have been formed by decarboxylation of 5-aroyl-2-pyrazine carboxylic acids by pyrolysis over copper (equation 31)[118]. A similar decarboxylation has also been performed in the preparation of hexaazatriphenylene (a useful polynuclear ligand) from its hexacarboxylic acid derivative[119]. 5-substituted-2-furoic acids are decarboxylated rapidly, simply by warming in chloroform with TFA catalysis[120].



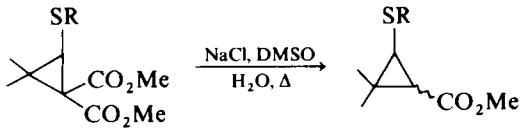
(31)

Decarboxylation of alkylated or arylated malonic acids, by heating at 60–80°C with copper in acetonitrile, gives a nearly quantitative yield of the monoacid (equation 32)[121]. In addition, cadmium salts of aromatic acids, or any salt in the presence of cadmium ions, readily disproportionate upon heating, to give a hydrocarbon and an aromatic diacid[122].



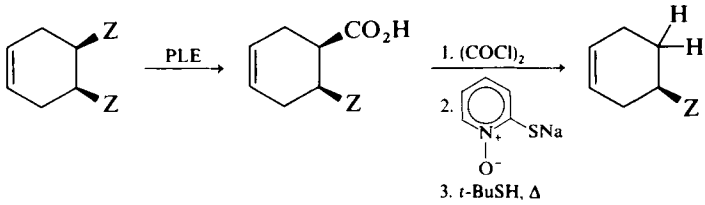
(32)

Decarboxylation of most simple aliphatic acids, to form alkanes, is usually a more difficult process than for aromatic acids. However, the reaction occurs readily in the presence of electron-withdrawing groups such as cyano, nitro, aryl, keto and trihalo in the α-position[123]. If substituents allow decarboxylation to occur via an enol, with a six-membered transition state, then the reaction is particularly facile, such as with a β-keto substituent. In this case, the reaction is particularly useful in synthesis and is readily performed simply by warming the acid, or ester, in wet DMSO containing sodium chloride (equation 33), or other salts[124–12], or in the gas phase[130,131]. Although these latter decarboxylations are carried out in the gas phase, they may be performed on a large scale and are thus synthetically useful.



(33)

Enantioselective decarboxylation of a diester has been performed in high enantiomeric excess by (i) hydrolysis of the diester to the ester acid, with pig liver esterase[132], (ii) activation of the acid and (iii) decarboxylation, as shown in equation 34[133].

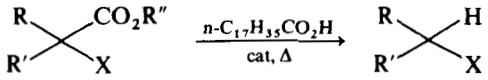


(34)

$Z \equiv CO_2Me$

Malonic esters and β-ketoesters are readily decarboxylated by initial transesterification to the corresponding acid, catalysed by onium ions (equation 35)[134] and by many other methods. The extremely important synthetic aspects of these reactions have been reviewed by Krapcho[125,126].

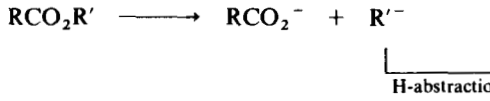
Palmitic acid has been converted into pentadecane, in 85% yield, by treatment of an organoantimony compound, formed via a radical reaction, with oxygen-free HCl[28].



(35)

$X \equiv COCH_3$, CO_2Et, CO_2Me, etc.

Aliphatic acids that are hard to decarboxylate by other means may usually be decarboxylated by conversion to the 9-hydroxy-10-chlorodihydrophenanthrene ester, or the 9-hydroxy-10-phenylthiodihydrophenanthrene ester, followed by treatment with tributyltin hydride[135,136]. It is also possible to convert the alcohol portion of an ester into a hydrocarbon by reduction with potassium in *t*-butylamine in the presence of 18-crown-6 at room temperature (equation 36)[137]. This reaction has been performed on a series of diesters of sterols and related compounds. The reaction is regioselective since unhindered esters tend to give alcohols whilst hindered esters give hydrocarbons as shown in equation 37[138].



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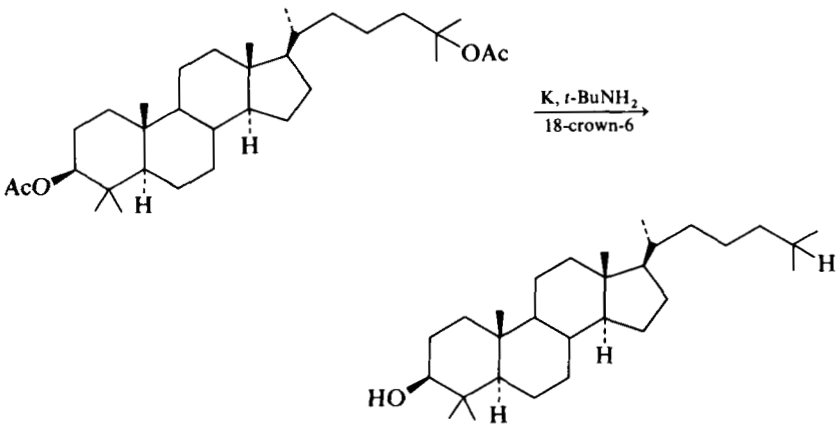
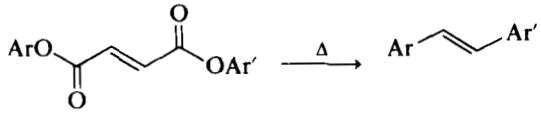


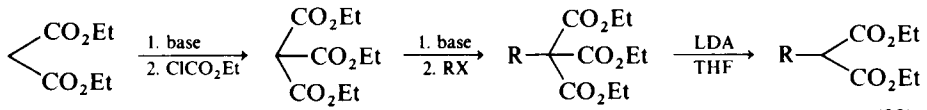
(37)

Both symmetrical and unsymmetrical stilbenes may be prepared, in reasonable yields, from their corresponding aryl cinnamates by decarboxylative pyrolysis in a sealed tube at 320°C (equation 38)[139].



(38)

Decarboxylation of alkyl-1,1,1-tricarboxylic esters to alkyl-1,1-dicarboxylate esters occurs readily at low temperatures by use of either sodium ethoxide or LDA in THF[142]. Since a third carboalkoxy group may be readily introduced into a malonate, this



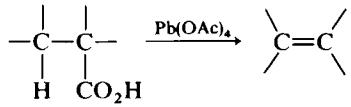
(39)

decarboxylation process serves as a means by which controlled mono alkylation may be performed in malonic acid synthesis, as exemplified by equation 39.

Primary or secondary acyl halides produce good yields of hydrocarbons, by dehalocarbonylation, upon heating with tripropylsilane in the presence of *t*-butylperoxide[140].

2. *Formation of alkenes [C(X)—C(COY) → C=C]*

Carboxylic acids with β-H atoms undergo facile oxidative decarboxylation to give alkenes in the presence of lead tetraacetate (equation 40)[141]. Many side reactions are possible, including rearrangements and cyclizations, and these should be carefully considered before this reaction is used synthetically. Good yields of the expected alkene are usually obtained with tertiary carboxylic acids or with γ-ketoacids. Many other oxidizing agents may be used including Ag(II), Mn(III) and Pd(II)[142-144]. $Pd(OAc)_2$ also converts allylic β-keto esters into α,β-unsaturated ketones, as shown in equation 41[144].



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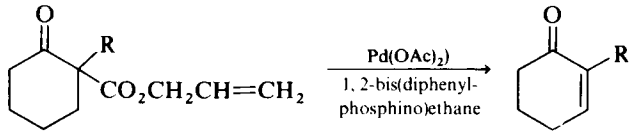
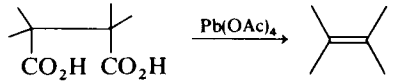


(41)

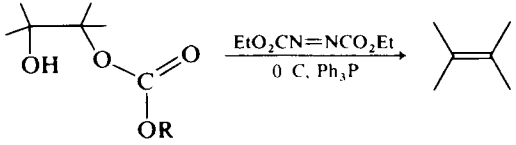
Oxidative decarboxylation of 1,2-diacid groups with lead tetraacetate also leads to alkenes (equation 42). This reaction is stereoselective but it is not stereospecific, and it may be brought about by using other oxidizing reagents such as rhodium complexes[141].



(42)

β-Hydroxyacids may be converted into alkenes under very mild conditions using diethyl azodicarboxylate (equation 43)[145]. The same reaction also occurs for β-lactams, presumably via the β-amino acid[146,147].

Other reagents may also be used for this conversion[148-150]. For example, β-hydroxyacids are converted stereospecifically into alkenes by catalysis with tungsten tetrachloride in basic acetonitrile (equation 44)[150].



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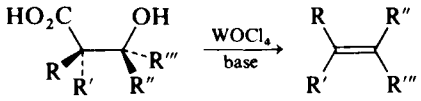
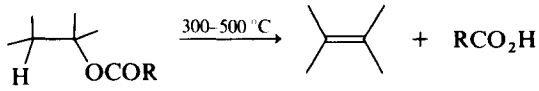


(44)

Esters with β-H atoms undergo thermal elimination producing a carboxylic acid and an alkene (equation 45). This reaction is usually performed in the gas phase. By this method, allylic acetates have been usefully converted into dienes[151].



(45)

β-Lactones are stereospecifically decarboxylated, to yield alkenes, by heating in non-acidic solvents[152]. The presence of acids in the reaction medium causes configurational scrambling.

G. Interconversion Between Carboxylic Acid Derivatives

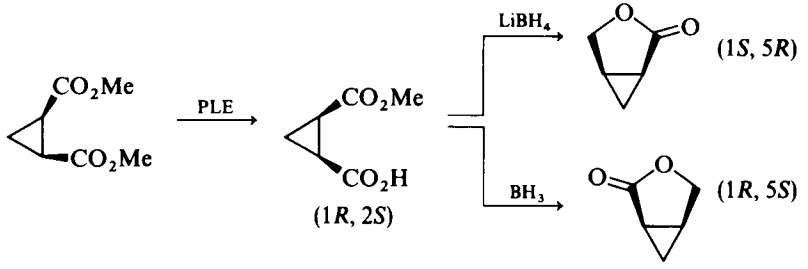
The interconversion between carboxylic acid derivatives is very important in the use of these types of compounds in organic synthesis. In most instances the procedures are simple and occur in high yields. Interconversion between acid derivatives allows access to all functional group interconversions discussed in Section II.A–F and all the carbon–carbon and C-Y bond formations discussed in the rest of this chapter. This ease of interconversion is also of use in purification procedures where it may be easier to purify a compound with a particular acid derivative functional group but better from a synthetic point of view to have a different functional group present for reaction. For example, carboxylic acids are usually very easy to purify by recrystallization; acyl halides are often much more difficult to obtain in a pure state.

Interconversions (especially acid $\leftrightarrow$ ester) are also important in the area of protecting groups. Carboxylic acids are usually protected as esters which are removed at a later step of the synthetic sequence. This field has been reviewed by Haslam[153].

The general discussion herein is necessarily brief and the reader is referred to the excellent reviews of Euranto[154], Beckwith[18], Ansell[19] and Ogliaruso and Wolfe[20,21] for more detailed coverage of the preparations of acid derivatives. The preparation of lactone and lactam target molecules is such an important synthetic use of acid derivatives that this subject is considered, in the present review, as the synthesis of heterocycles which are covered in Section V.

Carboxylic acids may be produced by simple hydrolysis of any of the other acid derivatives. Acyl halides[155] are more easily hydrolysed than anhydrides[156] and esters[157–160], which are more readily hydrolysed than amides[161,162]. Hydrolysis either under phase-transfer conditions[163] or using ultrasound[157] tends to both speed up the reactions and produce higher yields. Hydrolysis of esters (especially diesters) with pig liver esterases (PLE) is now widely accepted as a means of exerting stereochemical control in the process[132,164]. For example, *meso*-dimethyl cyclopropane-1,2-dicarboxylate is hydrolysed, by PLE, into the (−)-(1*R*, 2*S*) mono acid derivative as shown in equation 46. This compound may then be reduced to produce either one or other of the γ-lactones in an enantioselective fashion. Such reactions are difficult if enzymes are not employed; this field has been reviewed recently[165].

Iodotrimethylsilane has been used as a versatile dealkylating agent of esters, under neutral conditions: the intermediate silyl ethers are easily hydrolysed into acids. The synthetic utility of this overall process is shown in the deprotection of the *t*-butyl ester



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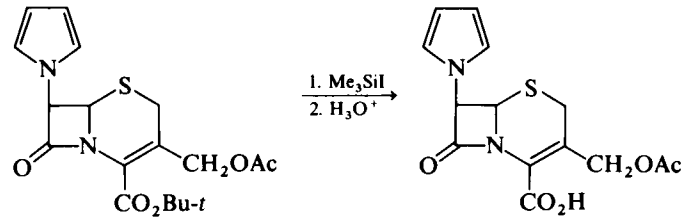

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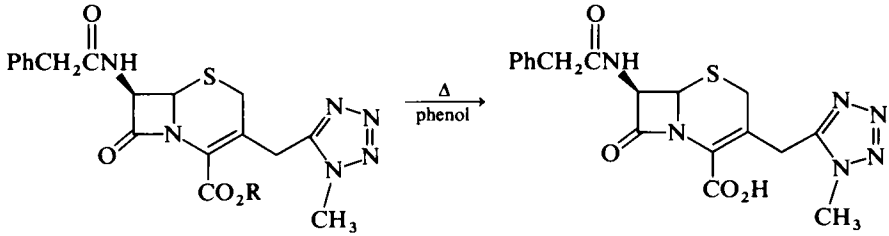


(48)

of the 7-pyrrolocephalosporin derivative shown in equation 47. Attempted deprotection by normal methods failed due to the instability of the functional groups present to acidic conditions[166]. The reaction is selective since the acetate group present was left untouched. Another, rather unusual, ester to acid deprotection reaction involves the gentle heating of the ester with phenol, as exemplified in equation 48. This procedure has been used recently in a β-lactam antibiotic synthesis[167]. Esters may also be reductively cleaved to give carboxylates[168].

Esterification of acids with alcohols[153,169], alkenes[170–173] and alkyl halides[174], and of acid salts with alkylating agents[175] and transesterification mediated by iodotrimethylsilane[166], are all well-established routes by which acids may be converted into esters.

Cyclic anhydrides may be converted into lactones by reaction with Zn/HOAc, hydrogen/catalyst, sodium borohydride or lithium aluminium hydride; the latter reagent sometimes gives diols[176–178] and it is possible to selectively react with only one of the carbonyl groups, to give a hydroxylactone[177,178]. β-Ethylthio- and β-phenylthioacrylic acids have been converted into γ- and δ-lactones by reaction with carbonyl compounds and epoxides, respectively[179,180].

Acyl iodides, which are highly reactive acylating agents, and an excellent source of an acyl synthon, may be readily prepared from acid derivatives by treatment with diiodosilane[181].

Amides may be made by reaction of esters with ammonia or amines with catalysis[182]. High yields of amides are produced from acids if they are first converted into mixed sulphonic–carboxylic anhydrides, under phase-transfer conditions[183] followed by refluxing with an amine (equation 49) or via acyl chlorides followed by treatment with hexamethyldisilazane[184]. A potentially useful and novel preparation of amides is the reaction of titanium(IV)- or zirconium(IV)-complexed carboxylates with amines[185]. Amides have also been formed in high yield, at 0°C, by desulphurization of thioamides with nitrogen tetroxide[186].

$$RCO_2H + R'SO_2Cl \longrightarrow RCOOSO_2R' \begin{cases} \xrightarrow{R''NH_2} RCONHR'' \\ \xrightarrow{R''OH} RCO_2R'' \end{cases} \quad (49)$$

Dehydration of acids with phosphorus pentoxide and other reagent gives anhydrides[20,187], which may also be produced by reaction of carboxylates with acyl halides under phase-transfer conditions[188]. In the latter case unsymmetrical anhydrides may be prepared, whilst the former case is generally only useful for symmetrical anhydrides. Both cyclic and acyclic anhydrides may be formed in many different ways by dehydration of carboxylic acids. One modern method involves the use of trimethylsilylethoxyacetylene in an inert solvent[189].

Thiolesters are the most easily prepared from acid derivatives by treatment of acyl halides with thiols, or by successive treatment of an ester with LDA, chlorotrimethylsilane and hydrogen sulphide[190]. Thioacids may be prepared by reaction of esters, acyl halides or anhydrides with hydrogen sulphide[191] and thiolactams may be synthesized from lactams by treatment with phosphorus pentasulphide[192].

III. α-FUNCTIONALIZATION OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

α-Functionalized acid derivatives are often required for carbon–carbon bond-forming reactions and the synthesis of heterocyclic compounds as discussed in Sections IV and V below. These derivatives are often key intermediates obtained from other acid derivatives and are sometimes the targets of synthesis. This important aspect of the uses of acid derivatives is covered in this section.

Functionalization in the α-position is facilitated by the relative ease by which the hydrogens on a carbon atom adjacent to the acid derivative grouping may be removed. This facility is significantly increased if two or more acid-derived groups are attached to a single carbon atom that bears at least one hydrogen atom. Out of two or three acid-derived groups at least one may be removed by a decarbonylation/decarboxylation reaction (see Section II.F), making the α-functionalization processes potentially even more useful.

α-Halogenation of acids is commonly performed using the Hell–Volhard–Zellinskii reaction, involving bromine or chlorine in the presence of a phosphorus trihalide (equation 50)[193,194].

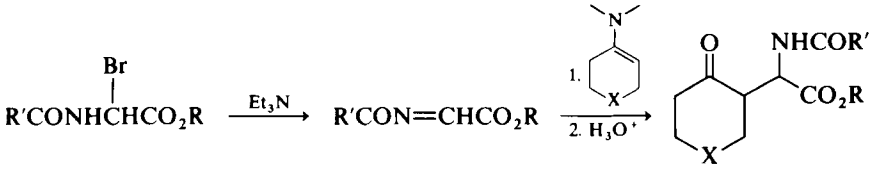
$$RCH_2CO_2H + X_2 \xrightarrow{PX_3} \underset{\displaystyle X}{RCHCO_2H} \quad (50)$$

Iodine may be introduced by using a modification of the above procedure using iodine with chorosulphonic acid as the catalyst[195,196], or by refluxing a carboxylic acid with iodine and a copper salt[197].

α-Halogenation may also be performed by reaction of an acid derivative with a base followed by a source of positive halogen such as *N*-halosuccinimides. In one such method, fluorine has been successfully introduced by reaction of acids with LDA followed by acetyl hypofluorite (CH_3COOF)[198].

α-Haloesters may be prepared by α-halogenation of an acid, followed by esterification[193,199]. α-Bromoesters may also be prepared by reaction of malonic ester analogues with bromine, initiated by irradiation with a mercury lamp[200].

α-Haloesters are very useful in synthesis, for example, in the Reformatsky reaction and the Darzens condensation (Section IV), in the preparation of *O*-silyl ketene acetals[199], in the preparation of acyliminoesters (which are used to prepare unnatural α-amino acid derivatives, equation 51)[201], in a novel stereocontrolled, electrochemical synthesis of β-lactams[202], in the Blaise reaction (equation 52)[203] and in the Arbuzov reaction where a phosphonoacetate group is produced (equation 53)[204]. These organophosphorus compounds may be used to form α-alkylated acrylate esters by reaction with formaldehyde.



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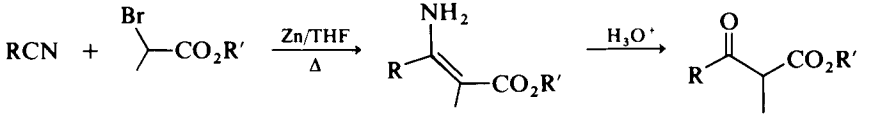

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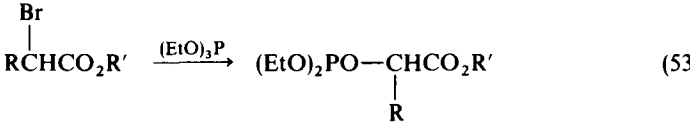
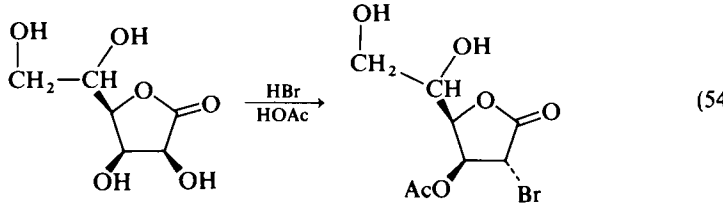


(53)

α-Bromolactones, derived from L-ascorbic acid, have been prepared from the corresponding hydroxy compounds as depicted in equation 54[205–207]. Such compounds are

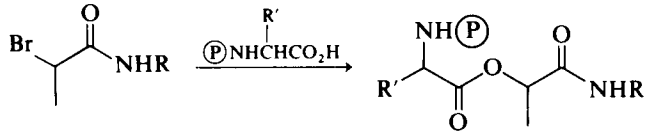


(54)

easily purified and characterized and have been used for the synthesis of some novel furanone chirons (i.e., chiral synthons), useful in natural product synthesis[207].

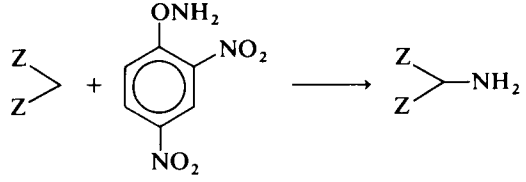
α-Haloamides may be synthesized by reaction of α-anions of amides with electrophilic halogen sources. These products are useful in a variety of synthetic sequences and have been used in base-induced reactions which give a series of linear and cyclic polyfunctional products[208].

Both primary and secondary α-bromoamides react with a range of α-aminoacids to form esters in the presence of silver oxide, in acetonitrile, as shown in equation 55[209]. The chiral centre in the α-bromoamide remains unchanged whilst the chiral centre from the amino acid is epimerized.



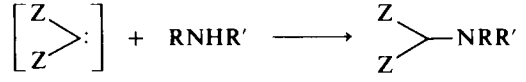
(55)

α-Amination of malonates has been performed by the reaction shown in equation 56 using *O*-(2,4-dinitrophenyl)hydroxylamine[210]. Such products are especially useful for the preparation of unnatural amino acids and heterocyclic compounds.



(56)

β-Hydroxy-α-amino acids may be prepared by reaction of 2,3-epoxyacids with diethylamine in the presence of tetraisopropoxytitanium[211,212]. This reaction also occurs with the corresponding amides[211]. Both mono- and disubstituted α-amino malonates have been prepared by insertion of bis(methoxycarbonyl)carbene into the N—H bond of a primary or secondary amine, in the presence of copper(II) acetylacetonate (equation 57)[213].



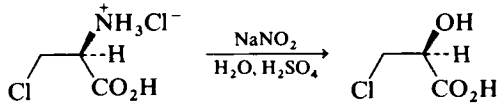
(57)

β-Hydroxy-α-azidoesters may be prepared from 2,3-epoxyesters by reaction with hydrazoic acid. The reaction occurs with almost exclusive C-2 ring opening and no epimerization of either potential chiral centre is observed[212]. These azidoesters may be readily converted into β-hydroxy-α-amino acids of biological interest and other compounds and are thus important synthetic intermediates.

α-Amino acids may be converted into α-hydroxyacids by aqueous sodium nitrite, in sulphuric acid. In this fashion, pure enantiomers of β-chlorolactic acid (a useful three-carbon chiron with three different functionalities) has been prepared in reasonable yield (equation 58)[214].

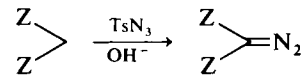
α-Hydroxyesters, and hence acids, may be prepared by several other methods involving direct functionalization. These methods include hydroxylation of ester enolates with molybdenum pentoxide/pyridine/HMPT[215] and reduction of α-ketoesters[216,217].

Malonates have also been α-diazotized in a diazotransfer reaction involving reaction



(58)

with tosyl azide, and other azides, under phase-transfer conditions as depicted in equation 59[218]. Such diazotized compounds may then be used in carbon–carbon bond-forming reactions, using carbene methodology. For example, such compounds with a silyl enol ether[219] give a cyclopropane (equation 60) which may be converted into a wide range of 4-oxoalkanoic acid derivatives by ring-opening reactions. A similar reaction occurs, albeit in lower yield, if the silyl enol ether is replaced by an alkene[220].



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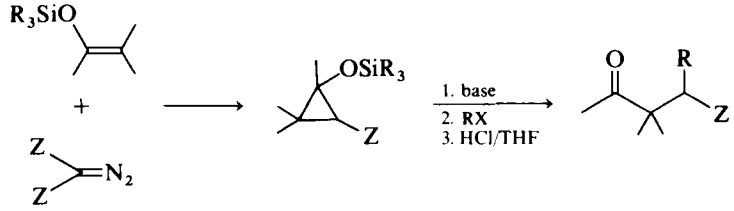
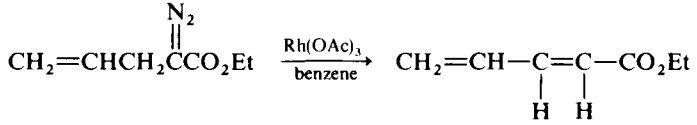


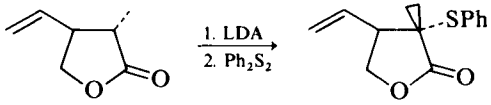
(60)

Decomposition of α-diazoesters, catalysed by rhodium(II) carboxylates, stereospecifically produces *cis* enoates (equation 61)[221].



(61)

α-Sulphenylation of esters is an important reaction that has been reviewed by Trost[222]. α-Thio groups may be introduced into esters and lactones by reaction with a base followed by a disulphide (equation 62)[223].



(62)

β-Ketoesters may be converted into β-ketosulphones by α-sulphenylation and S-oxidation followed by hydrolysis and decarboxylation of the acid group. Diphenylthio esters may be readily converted into α-ketoesters by reaction with iodine, followed by acidic work-up (equation 63). α-Ketoesters are useful synthetic intermediates and have been used in the synthesis of α,β-dehydro amino acids and peptides[224–226]

Seleno groups are often introduced at the α-position of carboxylic derivatives and then subsequently eliminated, via oxidation, in order to generate an α,β-unsaturated compound[227]. Active hydrogen-containing compounds such as malonates may be

$$RCH_2CO_2Et \xrightarrow[Ph_2S_2]{\text{base}} RC(SPh)_2CO_2Et \xrightarrow[2.\ CF_3CO_2H/H_2O]{1.\ I_2,\ MeOH} RC(=O)CO_2Me \qquad (63)$$

α-nitrosated by reaction with nitrous acid or alkyl nitrites. If tautomerizable hydrogens are present then oximes are formed[228].

IV. CARBON–CARBON BOND FORMATION USING CARBOXYLIC ACIDS AND THEIR DERIVATIVES

The stereocontrolled construction of complex organic molecules relies absolutely upon the formation of new carbon–carbon bonds in a controlled fashion, whilst building up the molecular framework. Carboxylic acid derived functional groups play a pivotal role in these constructions.

This subject is divided into new carbon–carbon bond formations (i) at the carbonyl group, (ii) at the α-position and (iii) at the β-position and remote locations.

The first section deals with acylations, reactions with organometallic compounds and other reactions. The second part covers alkylations, condensations with aldehydes and ketones and other acid derivatives, and other reactions. The last section deals mainly with Michael-type reactions of α,β-unsaturated acid derivatives with a few other relevant processes.

A. Carbon–Carbon Bond Formation at the Carbonyl Group

Carbon–carbon bond-forming reactions at the carbonyl carbon are further subdivided into four subjects, namely acylations, reactions with organometallic reagents, acyloin-type reactions and others, with some unavoidable overlap.

1. Acylation reactions

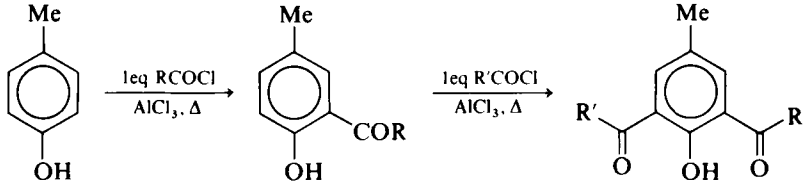
Acylations involve carbon–carbon bond formation at the carbonyl group of an acid derivative and occur at both aliphatic and aromatic carbon atoms. The formation, from acyl halides with silver salts or Lewis acids and amides by deamination, and reactions of acylium ions, has recently been reviewed[229]. In aromatic acylations, a Lewis acid catalyst is usually required. Cyclizations, involving C—C bond formation between the carbon atom of a carbonyl group and an aromatic carbon atom, are considered as aromatic acylations in the present work. Reactions of α-anions of acid derivatives with other carboxylic acid derivatives could be considered as acylations or as C—C bond formation at the α-position. In this review the latter approach will be used (see Section IV.B).

Aromatic acylations are historically important in the formation of aromatic ketones. The most common reaction is the Friedel–Crafts acylation of an aromatic compound with an acyl halide in the presence of a Lewis acid catalyst (equation 64). For example, thiophenes and 2-acylthiophenes have been acylated with long-chain acyl halides to give 2-acyl- or 2,5-diacylthiophenes, respectively[230]. These products were then desulphurized and unsaturated; long-chain fatty acids and alcohols, with 20–32 carbon atoms, were produced. The Friedel–Crafts reaction is of very wide scope, is usually prevented by the presence of electron-withdrawing groups and has been reviewed by March[231]. The acyl halide may be replaced by acids or anhydrides; however, it should be noted that the use of esters usually produces Friedel–Crafts alkylation.

A related reaction is the Fries rearrangement, where an aryl ester is heated with a Lewis acid to give either *ortho*- or *para*-phenolic ketones. For example, *para*-cresol

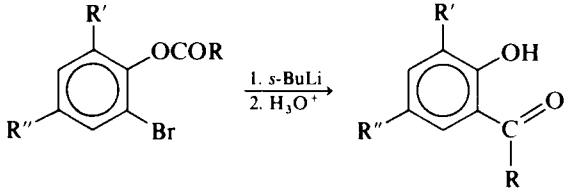
$$ArH + RCOX \xrightarrow{\text{catalyst}} ArC(=O)R \qquad (64)$$

undergoes monoacylation, via the O-acylated adduct (ester), when reacted with one equivalent of either acetyl or benzoyl chloride with aluminium trichloride catalysis. A second acylation may be performed, using a different acyl chloride if necessary, by adding a second equivalent of acyl halide, as shown in equation 65[232].



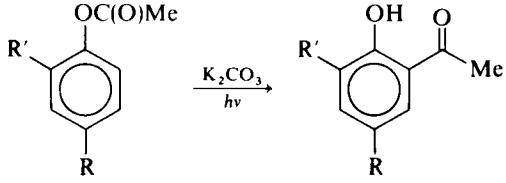
(65)

The high temperatures required for Fries rearrangement often cause alkyl groups to either migrate or be eliminated. This problem has been overcome, in one instance, by using titanium tetrachloride in place of $AlCl_3$ as the catalyst[233]. A reaction similar to the Fries rearrangement has also been carried out involving promotion of the process by *ortho*-lithiation as shown in equation 66[234].



(66)

The Fries rearrangement initiated photochemically[235–237] has been successfully used for the preparation of *o*-hydroxyacetophenones from substituted phenyl acetates using potassium carbonate as the catalyst, in 80–90% yield, as shown in equation 67. This reaction produced only very poor yields when attempted by the standard aluminium chloride catalysed procedure[237].

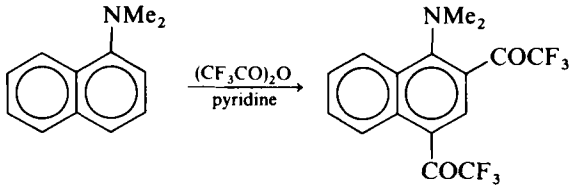


(67)

$R' \equiv H, CH_3$

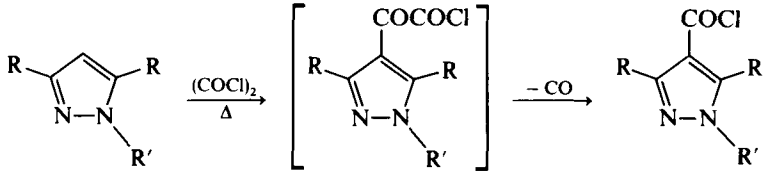
$R \equiv H, CH_3, OCH_3, Cl$

Acylation of aromatic compounds that are highly activated towards electrophilic substitution may be performed by reaction of the aromatic compound with an anhydride in the presence of pyridine, at room temperature, in nearly quantitative yield (equation 68)[238]. This is a much milder alternative to the Friedel–Crafts procedure.



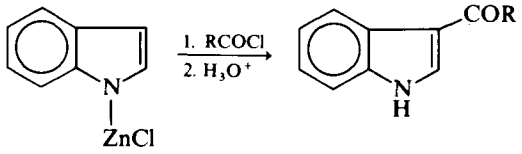
(68)

Pyrazoles have been directly acylated with oxalyl chloride which, following decarbonylation, gave a pyrazole acid chloride (equation 69)[239].



(69)

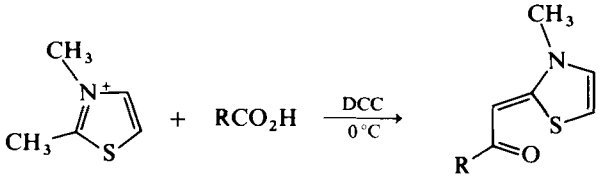
Cyclopent[*b*]indolones are important synthetic targets that require 3-acylindoles as precursors. These may be prepared in very good yields by reaction of an acyl halide with the zinc salt of indole (prepared from the Grignard reagent and zinc chloride) followed by hydrolysis (equation 70)[240].



(70)

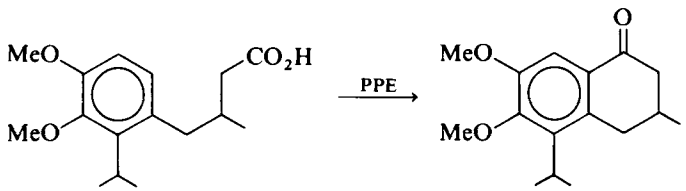
3-Acylindoles may also be prepared by Friedel–Crafts acylation of N-protected indoles (a rather lengthy procedure)[241] and by reaction of acyl halides by the requisite Grignard reagent (which tends to give diacylation and low yields). These and other methods have been reviewed[242].

Aromatic 2-acylmethylidene-3-methylthiazolines, compounds that possess anti-inflammatory and analgesic properties, may be synthesized in one-pot by acylation of thiazolium salts by activated carboxylic acids (equation 71)[243],



(71)

Cyclization, causing formation of a new C—C bond at an aromatic carbon atom, is a very powerful reaction which may be performed by intramolecular acylation. Thus, polyphosphate ester (PPE) catalysed cyclization was used to give a tetralone in high yield (equation 72)[244]. The product was subsequently aromatized and underwent phenolic coupling to give a binaphthyl backbone used in the synthesis of gossypol. A similar reaction was used to prepare 9-oxoacridan-4-carboxylic acids (equation 73)[245–248].



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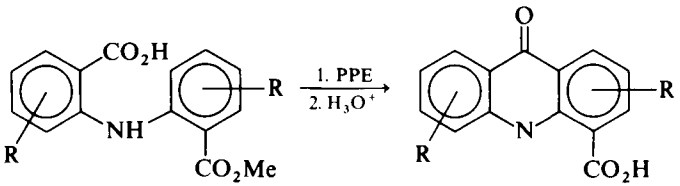
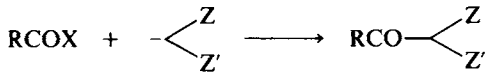


(73)

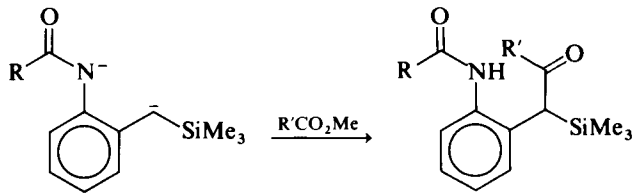
Acylation of carbanions is an important C—C bond-forming reaction that occurs at the carbonyl group of an acid derivative. The control of C-acylation versus O-acylation in enolates has recently been reviewed[249]. The most common reaction is of an anion of a diactivated compound of type ZCH_2Z' (Z and Z' may be an acid derivative or CHO, CN, NO_2, SO_2R etc.) with an acyl halide, as depicted in equation 74. The product of the reaction actually contains three activating groups and further reaction often ensues.



(74)

Carbanions may also be formed from monoactivated substrates (e.g. $RCOCH_3$). In these cases stronger bases are required to form the anion. Low temperatures are also often necessary in order to ensure that C-alkylation occurs in preference to O-alkylations[250].

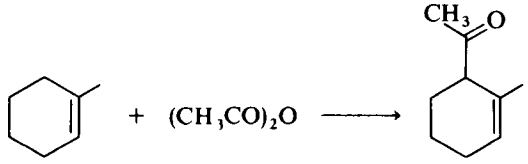
The dilithium salts of 2-trimethylsilylmethylanilides are acylated by esters, in basic media at low temperatures, to initially give side-chain acylation (equation 75)[251]. In a subsequent step, ring closure and deoxysilylation gives 2-substituted indoles.



(75)

Either allylic or vinylic ketones may be formed by reaction of acyl halides, or anhydrides, with alkenes in the presence of a strong base such as LDA (equation 76)[252].

Ketones with α-H atoms may be readily acylated by reaction with esters, via their α-carbanions as shown in equation 77, to form β-diketones. If the ester is a formate then a β-ketoaldehyde is produced. If unsymmetrical ketones are used then they usually react at the least substituted side, as expected.



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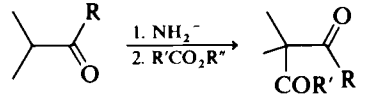
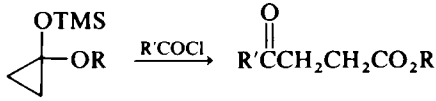


(77)

Similar acylations occur with α-carbanions formed from a variety of compounds including nitriles, sulphoxides and sulphones. For example, imides react with the anion of dimethyl sulphone to give ω-amido-β-ketosulphones, which are useful synthetic intermediates[253]. The sulphur functionalities may be later usefully removed by reductive desulphurization. Dianions, for example of ketones, react at the least acidic site in the first instance. Thus, with two equivalents of ester, 1,3,5-triketones may be produced.

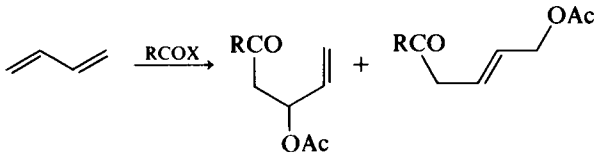
Acylation of 1-alkoxy-1-siloxycyclopropanes yields ring-opened γ-ketoesters with various catalysts (equation 78)[254].



(78)

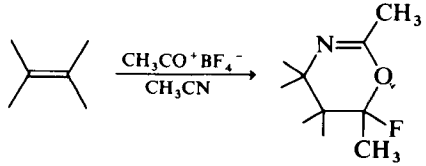
Acylation of alkenes and alkynes is a very important means by which new C—C bonds are formed. These reactions have recently been reviewed[229].

Trisubstituted alkenes react with alkyl acylium salts to give α,β-unsaturated ketones in reasonable yields[255], whilst butadiene may be stereoselectively acylated to produce *trans* ketones[256,257]. However, in the presence of acetic anhydride, this latter reaction produces unsaturated ketone acetates as shown in equation 79[258].



(79)

Alkenes react with $CH_3CO^+BF_4^-$ in acetonitrile to give, unexpectedly, oxazines (equation 80) via acylation[259,260]. 2-Methylpropene has been converted, regioselectively, into 1,3,6,8-tetraalkyl-2,7-naphthyridines by reaction with 4 equivalents of an acylium salt, followed by treatment with liquid ammonia in a one-pot process (equation 81)[261–263].



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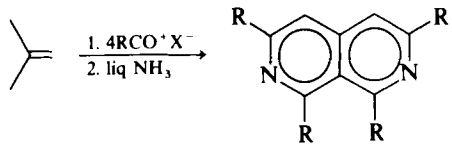
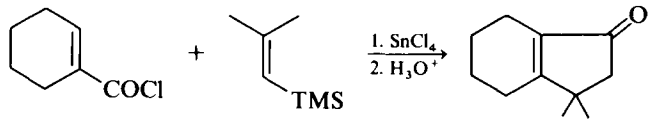


(81)

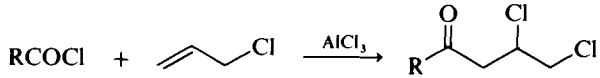
Vinyl silanes react with α,β-unsaturated acyl halides, in the presence of tin(IV) chloride, to give bicyclic ketones upon acidic work-up (equation 82)[264]. This methodology has been used in the synthesis of naturally occurring ketofurans[265].



(82)

Allylic halides are acylated by acyl halides, in the presence of aluminium chloride, to give overall addition to the double bond (equation 83)[266]. The products were used to produce synthetically useful, 1,4-dicarbonyl compounds in several more steps.

Alkenynes complexed to transition metals react with acylium salts at the alkene site. Good yields of alkynyl ketones are produced by this process, in the presence of nucleophiles (equation 84)[267,268].



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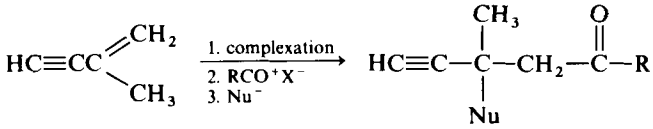
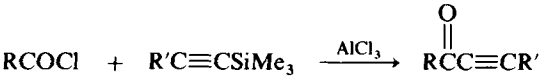
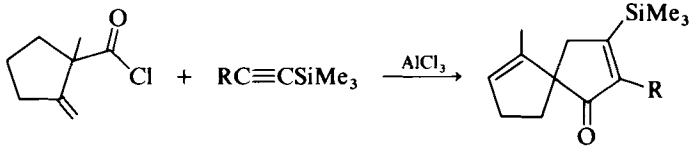


(84)

Acyl halides react with trimethylsilylalkynes, with aluminium trichloride catalysis, to give acylation as shown in equation 85. If the acyl chloride possesses α,α-disubstitution and it is β,γ-unsaturated, then cyclopentenones are formed and a rather surprising, but useful, synthetic route to spiro[4.4]-nona-2,6-dienones is produced as exemplified in equation 86[269].



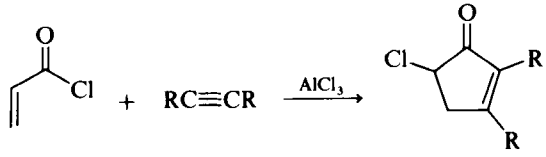
(85)



(86)

α,β-Unsaturated acyl chlorides react with alkynes, with Lewis acid catalysis, to give chlorocyclopent-2-enones as shown in equation 87[270]. Further processing, with silver

perchlorate and triethylamine, to remove the halogen from the product was used in order to create an exocyclic double bond. This compound was then used to prepare the antibiotic methylenomycin B in 47% yield[270].



(87)

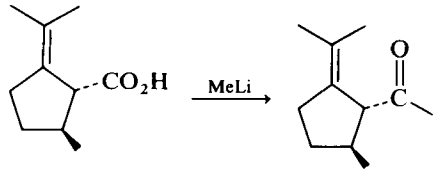
2. Reactions of acid derivatives with organometallic reagents

Carboxylic acids and their derivatives usually react with a wide range of organometallic reagents to give ketones and aldehydes. These and similar reactions involve new carbon–carbon bond formation at the carbonyl group and are discussed below.

Carboxylic acids react with Grignard reagents, in the presence of dichlorotriphenylphosphorane, to give ketones (equation 88)[271,272].

$$RCO_2H + R'MgX \longrightarrow RCOR' \qquad (88)$$

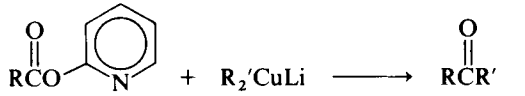
In the synthesis of Prelog–Djerassi lactone, Hacini and Santelli have reacted (−)-*trans*-pulegenic acid with methyllithium to give the methyl ketone in a highly stereocontrolled fashion as shown in equation 89[273].



(89)

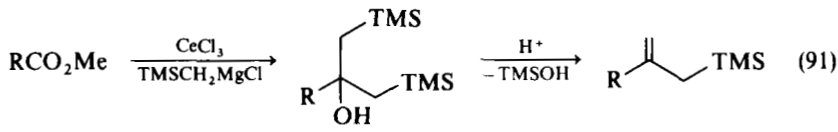
Lithium formate reacts with Grignard reagents to give aldehydes in excellent yields. Reduction and halogenation completes a neat overall homologation of the original alkyl halide from which the Grignard reagent was prepared[274]. Lithium carboxylates react with organolithium compounds to give ketones, upon aqueous work-up[275,276].

In most instances, esters react with Grignard reagents to give tertiary alcohols whilst thioesters react with lithium dialkylcopper reagents to give good yields of ketones[277,278]. 2-Pyridyl esters, which may contain bromo, ester and keto functionalities, react with lithium dialkylcuprates, at − 78°C, to give very high yields of ketones (equation 90)[277]. This and other reactions of 2-pyridylesters have been reviewed[279].



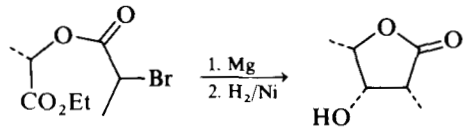
(90)

Esters react with trimethylsilylmethylmagnesium chloride, in the presence of cerium(III) chloride, to give a tertiary alcohol which spontaneously deoxysilylates to an allyl silane (equation 91)[280–282]. Allyl silanes are very useful in annulation and other synthetic reactions[283], and this preparation is of wide synthetic utility since it may be performed with acetals and halogens present in the reacting molecules. A similar process also occurs if the ester is replaced by an acyl halide[284].



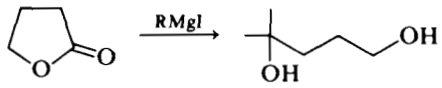
(91)

Stereocontrolled C—C bond-forming ring closure of a lactone has been performed by reaction of an ester with an internal Grignard reagent, formed at the α-position to the carbonyl group of the eventual lactone (equation 92)[285].



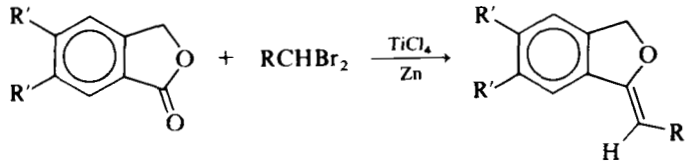
(92)

γ-Lactones also react with Grignard reagents to give 1,4-diols upon acid work-up (equation 93)[286].

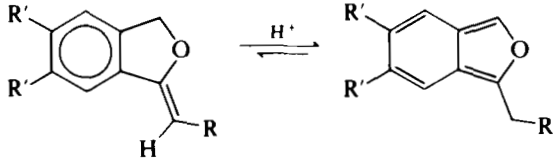


(93)

Phthalides react with 1,1-dibromoalkanes to give enol ethers, in the presence of zinc metal and titanium tetrachloride, in THF with TMEDA (equation 94). This reaction has been shown to proceed via organotitanium species[287]. The products are benzylidene phthalans, which under acid catalysis are equilibrated to give isobenzofurans (equation 95); these are useful as dienes in Diels–Alder reactions.

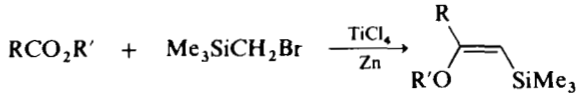


(94)



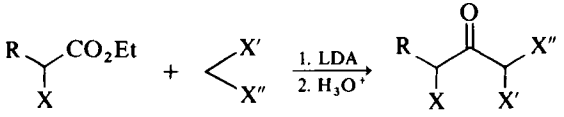
(95)

Under similar conditions esters and thiolesters react with (trimethylsilyl)bromomethane to give (*Z*)-alkenylsilanes as the major products, via the intermediacy of low-valent titanium complexes (equation 96)[288].



(96)

Dihalomethanes react with α-haloesters, at −78°C with LDA in THF, to give α,α,α′-trihaloketones in a regiospecific manner (equation 97)[289]. Such products are useful in a wide range of reactions including the Favorskii rearrangement[290] and the synthesis of polyhalogenated alcohols[291].



(97)

X, X′, X″ ≡ halogens

Ester homologation may be performed in reasonable yield by reaction of dibromomethyllithium (prepared *in situ*) with esters, in the presence of tetramethylpiperidine. The lithium alkynolate produced is then quenched with the requisite alcohol in acid solution (equation 98)[292].

$$RCO_2R' \longrightarrow RC{\equiv}COLi \xrightarrow[H^+]{R'OH} RCH_2CO_2R' \qquad (98)$$

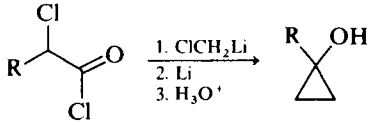
Grignard reagents react with dialkyl oxalates to give α-ketoesters at −80°C and this methodology has been utilized for the preparation of esters of 2-oxo-3-alkenoic acids. These esters are key intermediates in some synthetic routes to cephalosporins[293]. This method is advantageous over those previously reported since it is a simple, one-pot, reproducible procedure that uses commercially available materials.

Acyl halides react under mild conditions with a wide variety of lithium dialkylcopper reagents to give excellent yields of ketones (equation 99). If oxygen is not excluded then esters are also produced, which in some cases are the major products. This reaction has been much used in the synthesis of natural products[294,295]. The acyl halide used may have a wide range of structures and may contain such functional groups as esters, iodides, ketones, nitriles and nitro groups.

$$RCOX + R'_2CuLi \longrightarrow RCOR' \qquad (99)$$

Other organometallic reagents may be used to prepare ketones from acyl halides including organocadmium reagents[296], organomercury reagents[297] and alkyl organosilanes in the presence of palladium catalysts[298–300]. The reaction of acyl halides with Grignard reagents usually produces tertiary alcohols. However, in the presence of metal halides and at low temperature, ketones may be isolated in good yields[301,302].

Acyl halides react with organolithiums to give geminal haloalcohols, which easily give cyclopropanols if the lithium reagent has an α-halogen atom (equation 100)[303–305]. Such products are synthetically very important since they are easily transformed into homoenolate derivatives.

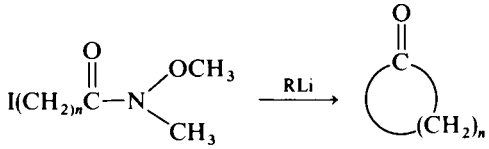


(100)

The reaction of most amides with Grignard reagents gives low yields of a mixture of ketones, alcohols and amines. However, disubstituted formamides react cleanly with Grignard reagents to give tertiary amines as depicted in equation 101[306], which is known as the Bouveault reaction.

$$R_2NCHO + 2MgXR' \longrightarrow R_2NCHR'_2 \qquad (101)$$

Disubstituted amides react with organolithium compounds to give excellent yields of ketones[307–309]. ω-Iodoalkanamides are cyclized internally to give cyclic ketones by reaction with the internal organolithium centre (equation 102)[310]. The organometallic reagent is formed by reaction with *t*-BuLi in THF at low temperature. Ketones with four- to seven-membered rings were formed in good yields but attempts to produce larger rings resulted in failure.



(102)

$n = 3, 4, 5, 6$

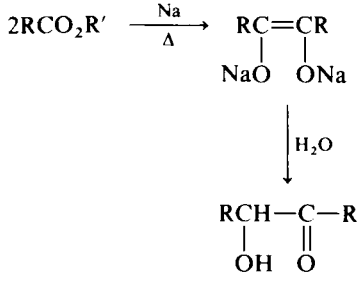
Some acid derivatives also react with alkynylboranes to give α,β-alkynylketones as shown in equation 103[311].

$$(R'C{\equiv}C)_3B + 3RCOX \longrightarrow 3RCOC{\equiv}CR' \qquad (103)$$

3. Acyloin reaction

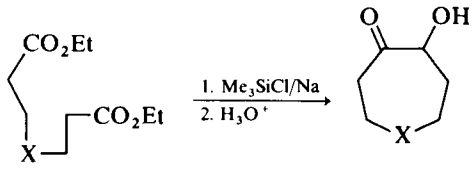
The acyloin reaction of carboxylic acid esters is especially useful for the preparation of large carbocyclic ring systems.

Esters heated in xylene with sodium undergo the acyloin reaction—a dimerization involving C—C bond formation to produce an α-hydroxyketone (also known as an acyloin) as shown in equation 104[312]. If the two esters are part of the same molecule then a cyclic product is formed by intramolecular reaction, which has been used to obtain 10- to 20-membered rings in yields in excess of 60%. This reaction is one of the best methods of preparing such ring systems. Synthetic genius combined with the acyloin reaction has been used to prepare both a 34-membered ring and a catenane with two interlocking 34-membered rings[312]. Much improved yields of acyloins have been obtained by use of a potassium–graphite intercalation compound (C_8K) in the place of sodium metal[313].



(104)

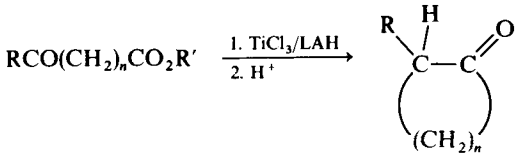
Acyloins are also formed under milder conditions if the above reaction is carried out in the presence of trimethylchlorosilane. Indeed some acyloins may only be prepared by this latter method (for example ethyl acetate → acetoin). This modified method has also been used for the preparation of seven-membered heterocyclic compounds as shown in equation 105[314]. Use of ultrasonic irradiation improves the yield of acyloins in the modified reaction and also makes the preparation easier[315].



(105)

X = S,NR

In a reaction related to the acyloin reaction, ketoesters have been reduced by LAH to give good yields of cyclic ketones via a radical process involving titanium trichloride, after hydrolysis (equation 106)[316].



(106)

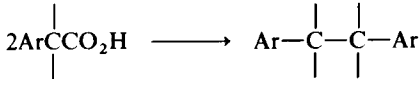
4. Miscellaneous reactions

There are several miscellaneous C—C bond-forming reactions which occur at the carbonyl group of acid derivatives that do not fit into the other sub-divisions. It should be noted that acyl radical cyclizations involving selenoacids are not covered here. The reader is referred to a recent paper by Crich and coworkers (and references therein) for details of this type of carbon–carbon bond-forming reaction[317].

Wurtz-type coupling of acyl chlorides in the presence of pyrophoric lead, lithium or samarium iodide yields α-diketones (equation 107)[318,319]. Ultrasonic irradiation allows the reaction to be performed under milder conditions and gives higher yields[319]. Attempted Reformatsky reactions with 2-iodomethyl-2-propenoates have been unsuccessful, but these substrates undergo Wurtz-type coupling very readily[320,321].

$$2RCOCl \xrightarrow{SmI_2} RCOCOR \qquad (107)$$

Kolbe electrolysis of carboxylates leads to carbon–carbon bond formation at the α-position, by dimerization, of two acid molecules after decarboxylation has occurred in both. This reaction has been reviewed in detail by Schafer[322]. The reaction does not occur with aromatic acids nor with acids with α-branching. In addition, side reactions caused by hydrogen abstraction processes and polymerization are likely to affect yields in most cases. A similar process has been performed by Fristad and Klang, non-electrolytically, using a mixture of sodium persulphate and silver nitrate, as shown in equation 108[323].



(108)

Decarboxylative acylation of α-amino acids, in basic acetic anhydride (the Dakin–West reaction), is a means by which the corresponding α-acetylaminoalkylmethylketones may be prepared as shown in equation 109. This reaction has also been shown to occur for non-amino acids such as phenylacetic acid and the reaction has recently been reviewed in detail[324].

$$\underset{\underset{R}{|}}{NH_2CHCO_2H} \xrightarrow[\text{base}]{Ac_2O} \underset{\underset{R}{|}}{AcNHCHCOCH_3} \qquad (109)$$

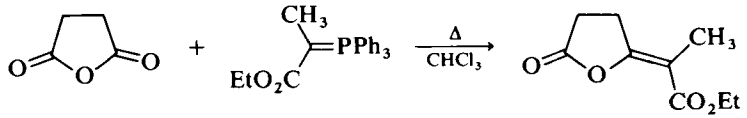
Acid chlorides react with diazomethane to give the next homologous carboxylic acid, after Wolfe rearrangement of the intermediate diazoketone (equation 110). This reaction is known as the Arndt–Eistert synthesis. Other diazonium compounds also undergo a similar reaction[325] and the rearrangement step of this process has been reviewed previously[326].

$$RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[Ag_2O]{H_2O} RCH_2CO_2H \qquad (110)$$

Esters and lactones react with carbon tetrachloride, in the presence of triphenylphosphine under reflux, to give novel 2,2-dichlorovinyl ethers. These ethers may be hydrolysed to the corresponding α,α-dichloroketones as shown in equation 111[327].

$$RCO_2R' \xrightarrow[Ph_3P]{CCl_4} \underset{\underset{CCl_2}{\|}}{RCOR'} \xrightarrow{H_3O^+} \underset{\underset{O}{\|}}{RCCHCl_2} \qquad (111)$$

Esters, thiolesters, lactones and anhydrides also react with ylids[328–331] and these reactions have been reviewed recently[332]. In one such reaction, succinic anhydride was reacted with (1-ethoxycarbonylethylidene)triphenylphosphorane to give an enol lactone in 64% yield (equation 112)[328,329]. The product was then converted into a 2,2-disubstituted-cyclopentan-1,3-dione; these compounds are important in the synthesis of natural products such as sterols, tricothecenes and prostaglandins. In another reaction, a thiolester was reacted with a ylid, containing a β-lactam moiety, to give a key penicillin intermediate (equation 113)[333].



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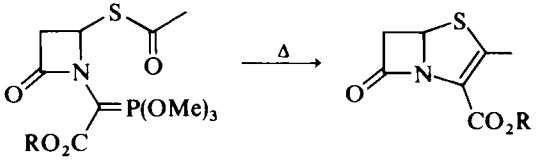
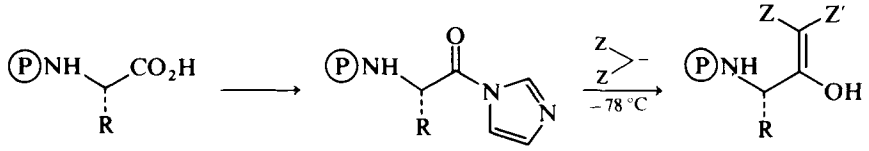


(113)

In another example of the above methodology, aromatic acid chlorides were reacted with ethoxycarbonylmethylenetriphenylphosphorane to give acetylenic, chain extended acid derivatives on flash vacuum pyrolysis (equation 114)[330,331]. The ester produced may then be used as starting material and the reaction repeated to give conjugated di- and triacetylenic esters[330]. At any stage in this process the ester grouping can be removed to produce a terminal alkyne. This is a powerful method for preparing terminal alkynes, and terminal alkynes with several other conjugated alkyne functionalities.

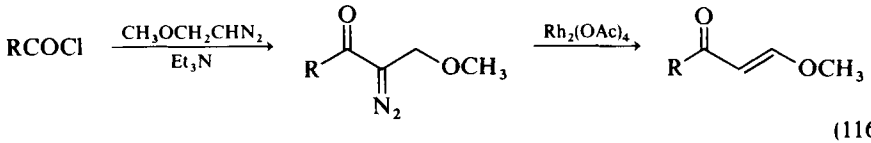
$$RCOCl \xrightarrow[2.\ FVP]{1.\ Ph_3P{=}CHCO_2Et} RC{\equiv}CCO_2Et \xrightarrow{FVP} RC{\equiv}CH \qquad (114)$$

In an investigation of enzyme–substrate interactions, the terminal carboxylic acid group of an N-protected dipeptide has been converted to a dipeptide enol with C—C bond formation at the carbonyl carbon atom[334]. In this reaction the acid group was first activated by reaction with 1,1'-carbonyldiimidazole and then this was reacted with the anion of a diactivated methylene-containing compound at −78°C, as shown in equation 115. The hydroxyl group could be replaced by SR, OR and NR_2. Chiral centres present in the dipeptide were unaffected by the reaction conditions.



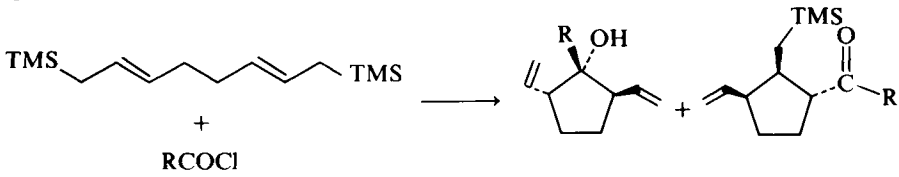
(115)

β-Methoxyenones (which are useful in many synthetic applications) have been formed by a two-carbon extension of acyl halides[335]. The acyl halide was added to a mixture of freshly prepared 1-diazo-2-methoxyethane and triethylamine in ether. The diazoketone produced was then converted into the enone by stirring with rhodium acetate (equation 116).



(116)

Acid chlorides react with 1,8-bis(trimethylsilyl)-2,6-octadiene, at low temperature with titanium tetrachloride catalysis, to yield 2,5-divinylcyclopentanols and vinylcyclopentyl ketones in a stereocontrolled manner (equation 117)[336]. If nitromethane is added as a cosolvent, then only the cyclopentanols are produced[337]. If the acid chloride possesses an ω-ester group, then the ester and alcohol functionalities, in the product, react to give spirolactones.



(117)

Acyl halides also react with copper(I) cyanide[338] and other cyanides[339–341] to produce acyl cyanides (equation 118). The reaction gives improved yields if performed under phase-transfer conditions[342] or with ultrasonic irradiation[343].

$$RCOCl \xrightarrow{CN^-} RCOCN \qquad (118)$$

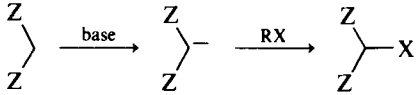
B. Carbon–Carbon Bond Formation α to the Carbonyl Group

Carbon–carbon bond formation at the α-position of acid derivatives is a very common reaction. Such bond formations may be divided into alkylations, condensations with

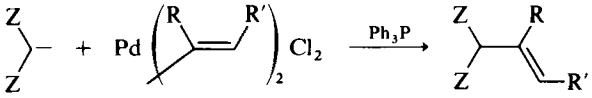
either aldehydes and ketones or with the other acid derivatives, radical- and carbene-mediated cyclizations and miscellaneous reactions.

1. Alkylations

Carboxylic acid derivatives require strong bases in order to form α-anions, which may then be readily alkylated. Acid derivatives with a second activating group attached in the α-position are more readily alkylated, via the enolate anion which is easy to produce with a wide variety of bases (equation 119). Alkylation may be performed with a wide range of alkylating agents including alkyl halides[204,344,345], sulphates[42] and palladium complexes with triphenylphosphine (equation 120)[346–349]. Both dialkylation and *O*-alkylation (favoured by aprotic solvents such as DMSO) are possible side reactions as is saponification if one of the activating groups is an ester. Alkylations of dianions may be performed in which case the first alkyl group is introduced at the more acidic position.

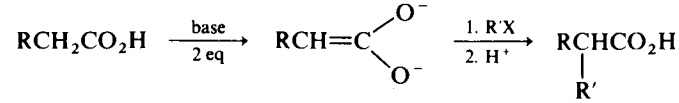


(119)



(120)

Carboxylic acid dianions may be readily alkylated at the more reactive, α-site to produce α-alkylated acids (equation 121)[350,351]. This reaction has been reviewed by Petragnani and Yonashiro[352]. The reaction is commonly followed by decarboxylation which in case of keto acids, yields a ketone. Thus, acetoacetate has been used as a source of an acetone enolate synthon[351].

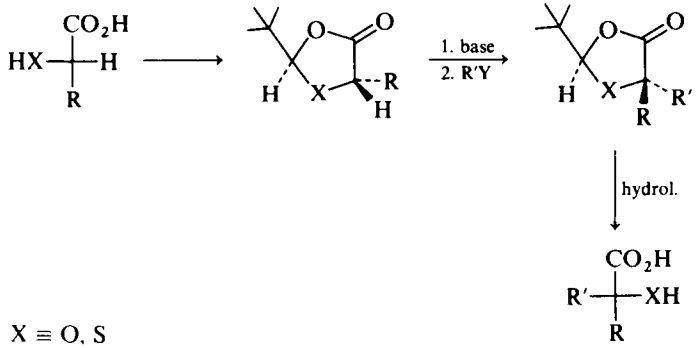


(121)

It is often very useful to be able to alkylate a readily available chiral α-heterosubstituted carboxylic acid in an enantiospecific manner, as a means of using the chiral centre and at the same time building-up the rest of the target carbon skeleton. Such a reaction has been devised by Seebach and coworkers[353]. In this process α-hydroxy- and α-mercaptocarboxylic acids were first reacted with pivalaldehyde, to produce a 1,3-dioxolanone or 1,3-oxathiolanone. This was followed by reaction with base and alkylation by an alkyl halide and then subsequent hydrolysis to regenerate the hydroxyl or thiol group (equation 122). The product was obtained in greater than 95% enantiomeric excess. Similar reactions with other electrophiles were also successful.

Carboxylic acid dianions have also been alkylated by reaction with aziridines to give novel γ-amino substituted acids in good yields[354]. Methoxybenzoic acids have also been alkylated in a reductive process by reaction with lithium in ammonia followed by treatment with an alkyl halide. The product formed in this one-pot reaction is an alkylated cyclohexa-2,5-diene carboxylic acid[355].

Dimerization and trimerization of alkylbromocyanoacetates (a self-alkylation reaction) has been used for the synthesis of highly substituted cyclopropanes and dialkyl-(*E*)-2,3-dicyanobutendioates (equation 123)[200]. The latter products are potentially very useful for the synthesis of a wide range of heterocyclic compounds.



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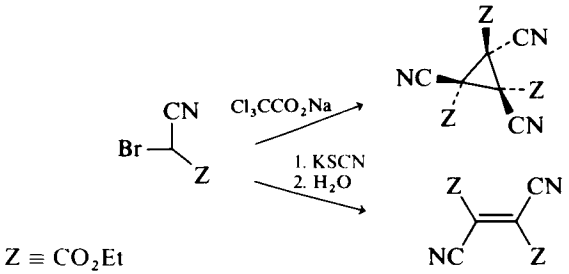
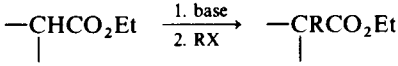


(123)

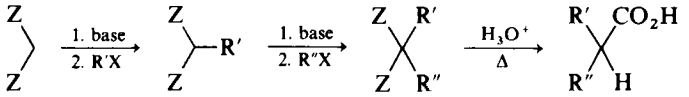
The alkylation of esters proceeds by removal of an α-hydrogen atom by a strong base such as an alkoxide, amide ion or hydride, in a non-protic solvent, followed by treatment with an alkylating agent (equation 124)[30,148,356–362]. Side reactions such as reduction of the ester to an alcohol (as discussed in Section II.A) or Claisen condensation (if the anion is not 100% formed before the alkylating agent is added) sometimes plague this procedure.



(124)

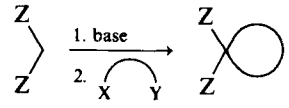
Dianions of β-hydroxyesters are also readily alkylated in the α-position[363] and the stereoselectivity of this process has been reviewed[364]. Such a reaction has been used for the introduction of an alkyl group prior to lactone-forming ring closure[365].

Controlled, step-wise dialkylation may be performed. Equation 125 shows a typical malonic ester synthesis including hydrolysis and decarboxylation to give an α,α-

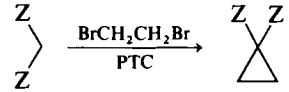


(125)

dialkylated acid. Acetoacetic ester synthesis and cyanoacetic ester syntheses give ketones ($CH_3COCHRR'$) and nitriles (RR'CHCN), respectively. Alkylation of malonate derivatives with a range of α,ω-dihalides produces cyclic compounds with three- to seven-membered rings readily (equation 126)[366,367], and medium- and large-sized rings may be closed using high dilution techniques[368]. Alkylation of a malonate derivative with 1,2-dihaloethanes, with potassium carbonate under solid–liquid phase-transfer condi-



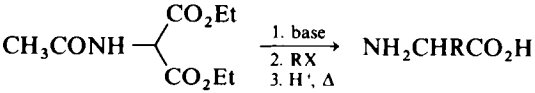
X,Y ≡ halogens (126)



Z ≡ CO_2R (127)

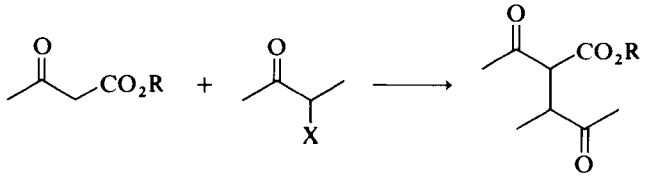
tions (PTC) using a quaternary ammonium catalyst, gives cyclopropanes in 73–91% yield (equation 127)[345,369].

The Sorensen method of amino acid synthesis uses a modification of the malonic ester synthesis. In this modification an N-protected malonic ester is alkylated, hydrolysed and decarboxylated to give an α-amino acid, as shown in equation 128.



(128)

Alkylation of β-ketoesters with α-haloketones has been used as an efficient synthesis of 1,4-diketones containing an ester functionality (equation 129)[370].



(129)

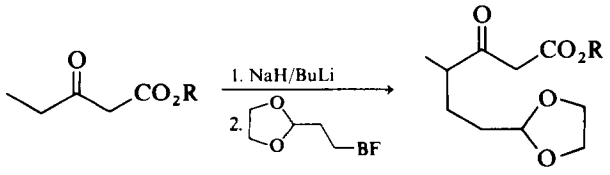
X ≡ halogen

Alkylation of β-ketoesters with ω-substituted alkyl halides is an efficient method for the synthesis of cyclic products[371–374]. In one such sequence, the dianion of a β-ketoester reacted with 2-(2-bromoethyl)-1,3-dioxolane, the ω-substituent in this case being a masked aldehyde. Upon regeneration of the aldehyde functionality, a condensation reaction occurred to give the cyclohexanone as shown in equation 130[371].

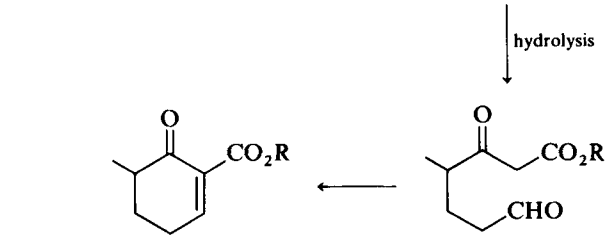
A thirteen-membered ring was formed by intramolecular alkylation, at the α-position, of a β-ketoester in 74% yield (equation 131)[372].

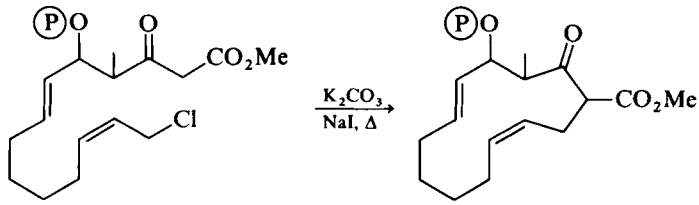
A medium-sized ring has also been synthesized by a different route involving alkylation of a β-ketoester. In this case, ethyl cyclohexanone-2-carboxylate was treated with 1,4-diiodobutane in the presence of sodium hydride. The adduct, upon treatment with radical initiators, gave a 10-membered ring as the major product (equation 132)[373]. Similar reactions have also been performed that produce 5-, 6-, 12-, 13- and 14-membered rings[375]. A similar process with anionic ring expansion has also been reported[374].

Carbon–carbon bond formation at the α-position of a lactone is an important reaction which has been reviewed previously[352]. The ene-reaction has recently become very useful in the stereocontrolled closure of five-membered rings and this has been used in conjunction with lactone alkylation. In one such synthetic sequence, alkylation of a lactone was one step in the construction of a molecule that would potentially undergo



(130)





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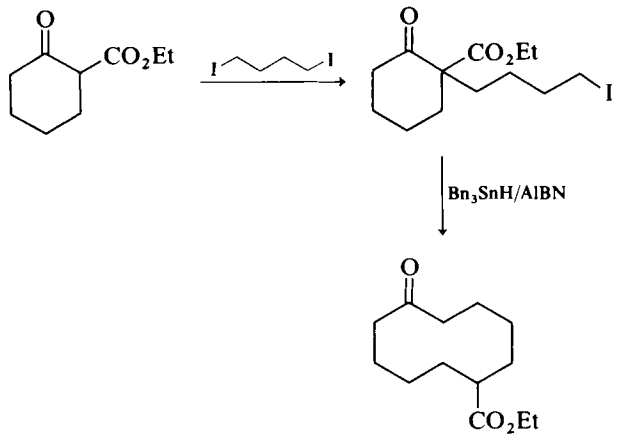
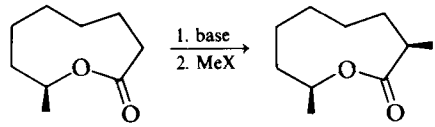


(132)

an ene-reaction[376]. The alkylation step was simply performed by reaction of the lactone with LDA in THF/HMPT at $-78°C$ followed by addition of an alkyl iodide; 88% yield was realized. In another sequence involving the synthesis of lignans, a lactone was similarly reacted with LDA followed by a substituted benzyl bromide, to give an excellent yield of alkylated product[377].

It has also been found that in medium-sized lactones (eight- to twelve-membered) a single chiral centre at a remote position causes highly stereoselective formation of a new chiral centre adjacent to the carbonyl group (equation 133); this effect falls off as the

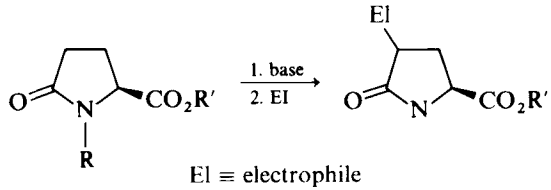


(133)

X ≡ halogen

distance between the enolate and the controlling asymmetric centre increases[227]. Such stereocontrol is caused by the conformational properties of the particular lactone being alkylated.

Lactams may be alkylated at the α-position by reaction with a strong base, such as LDA or hexamethyldisilazide, followed by treatment with an alkyl halide. Baldwin and coworkers have used this methodology in their synthesis of unnatural amino acids from protected pyroglutamates (equation 134)[378]. The same reaction has been used for



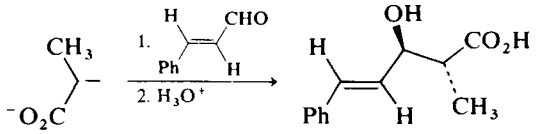
(134)

El ≡ electrophile

alkylating five- to nine-membered lactams[379]. It is noteworthy that α-alkylated seven- to nine-membered lactams are quite hard to cyclize directly and so ring closure followed by α-alkylation is an important synthetic sequence. α,α-Dialkylation of lactams has also been performed. In this reaction, good diastereoselectivity was obtained by reacting bicyclic lactams, derived from (*S*)-valinol and levulinic acid, with a base followed by an alkylating agent in two cycles[380].

2. Acid derivative condensations with aldehydes and ketones

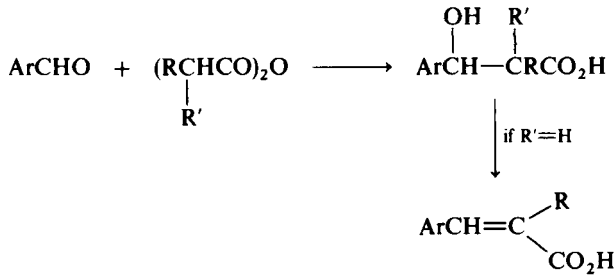
Carboxylic acid dianions react with α,β-unsaturated aldehydes in a regiospecific fashion to give 1,2-addition and formation of a β-hydroxy carboxylic acid which retains the double bond[381]. Ketones give 1,2- or 1,4-addition depending critically upon the reaction conditions and the exact nature of the substituent groups. This methodology has been used in a synthesis of the aggregation pheromone of the elm bark beetle, *Scolytus multistriatus*, with the key step being shown in equation 135[382].



(135)

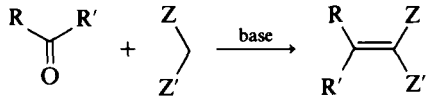
Anhydrides may be condensed with aromatic aldehydes in the presence of the corresponding carboxylate anion to give either an α,β-unsaturated acid or a β-hydroxyacid (equation 136). This is the Perkin reaction and dehydration generally occurs if the anhydride has two α-hydrogen atoms. In some instances the β-hydroxyacid decarboxylates under the reaction conditions to give an alkene. An important variant of the Perkin reaction is the heterocycle producing, Erlenmeyer azlactone synthesis; this is covered in Section V.

Condensation between compounds of type ZCH_2Z' (where Z and Z' are electron-withdrawing groups and at least one of them is an acid derivative) and aldehydes or



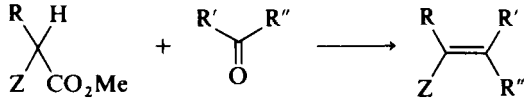
(136)

ketones (usually without α-hydrogen atoms) is known as the Knoevenagel condensation (equation 137). The reaction is rarely of synthetic utility with aliphatic aldehydes[383]. A modification of the reaction using pyridine as solvent, under high pressure at 190°C, has allowed the preparation of α,β-unsaturated acids from malonic acid and aliphatic



(137)

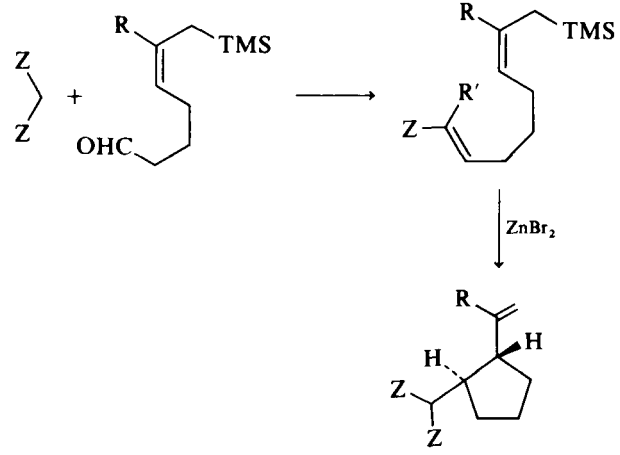
aldehydes[383]. Decarboxylation of the initial product usually occurs under the reaction conditions[384] but this is not so in all cases[385]. If the acid derivative being condensed is of the form ZCHRZ', then the initially produced alcohol may be isolated or water may be subsequently eliminated after decarboxylation as exemplified in equation 138[386]



(138)

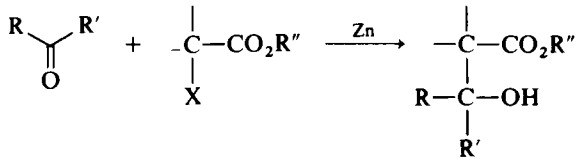
$Z = CO_2R$

The Knoevenagel condensation reaction has been used in tandem with hetero-Diels–Alder reactions[387], ene-reactions (equation 139)[384,388–393] and allylsilane cyclization and related imine cyclization reactions[394–396] to prepare a wide variety of heterocyclic and carbocyclic compounds. In the ene reaction the *trans* cyclopentane is formed diastereoselectively on treatment of the initial adduct with a Lewis acid[384].



(139)

In the Reformatsky reaction[321], an α-haloester reacts with an aldehyde or a ketone, in the presence of zinc or tin dusts or other metals, to form a β-hydroxyester (equation 140)[397–401]. The reaction occurs faster and in higher yield upon ultrasonic irradiation[402].



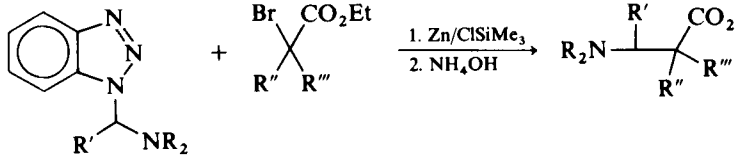
(140)

Ito and coworkers have used Reformatsky methodology to stereoselectively prepare key intermediates for 1β-methylcarbapenem synthesis[398,400]. The diastereoselectivity of this reaction is dependant on the bulk of the C-4 oxazolidone ring substituents and the temperature of reaction. Best results were obtained in boiling THF with 4,4-dialkyl-substitution.

Under Reformatsky conditions 2-chloromethyl-2-propenoates are inert and the corresponding iodo compounds undergo Wurtz-type coupling. However, the corresponding bromo compounds undergo Reformatsky-type, metal-induced carbon–carbon bond formation with a wide range of electrophilic reagents. The preparation of α-methylene-γ-lactones using this methodology has been reviewed by Hoffman and Rabe[403]. The same conditions may also be used to stereoselectively react with carbohydrate derived ketones[404,405].

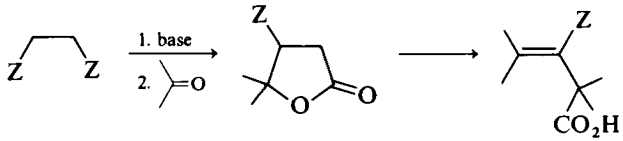
A wide range of natural products, especially steroids and alkaloids, have been synthesized by reactions of carbonyl compounds with alkyl 2-bromomethyl-2-propenoates under the above-specified, modified Reformatsky conditions and these syntheses have been reviewed recently[321].

In another variation of Reformatsky conditions, 3-dialkylamino esters and 3-benzyloxycarbonylamino esters have been prepared by reaction of ethyl 2-bromoalkanoates with 1-dialkyamino- and 1-benzyloxycarbonylamino-1-(1-bentotriazolyl)alkanes in the presence of zinc and Me_3SiCl (equation 141)[406].



(141)

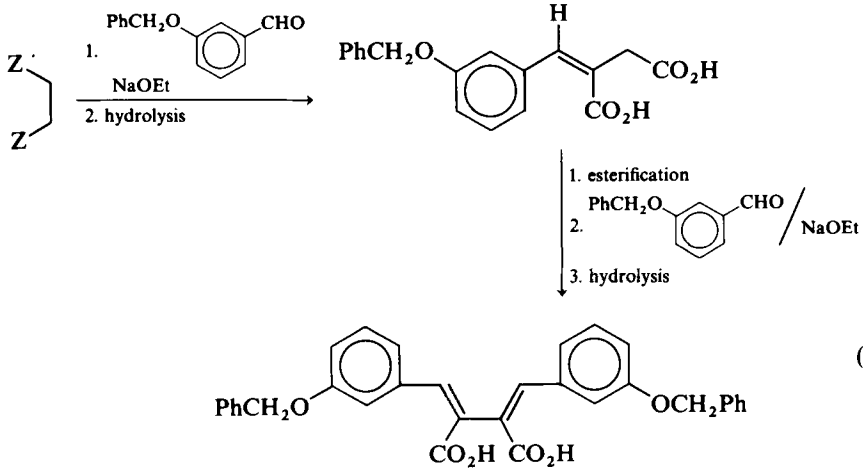
If the ester in a Reformatsky-type reaction is a succinate or similar diester, then the reaction sequence is known as the Stobbe condensation. In this case, one ester group is always lost in the product molecule since the reaction proceeds through a lactone intermediate (equation 142). This reaction has has been used in the synthesis of aryltetralin lignans[407,408]. The lactone intermediate may be isolated under controlled conditions.



(142)

$Z \equiv CO_2R$

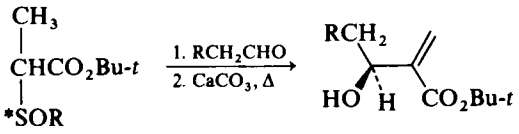
In a synthesis of the first lignan discovered in humans and animals, Kirk and coworkers[52] performed a double Stobbe condensation by reacting diethyl succinate with 3-benzyloxybenzaldehyde in the presence of sodium ethoxide, followed by hydrolysis, esterification and then repeating the reaction sequence once more (equation 143). The resultant bis-(3′-benzyloxybenzylidene)-succinic acid was then further processed to give the lignans.



(143)

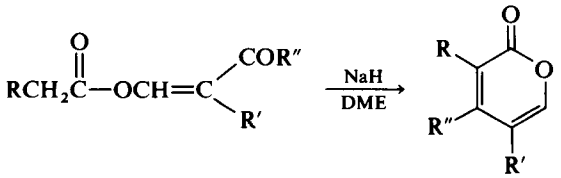
α-Anions of esters react with aldehydes or ketones to yield the same products as are produced in the Reformatsky reaction and this reaction has been used for the preparation of some non-proteinogenic amino acids[409,410]. Decarboxylation often, but not always[411], occurs to give an α,β-unsaturated ester, if the product has an α-hydrogen atom.

Aldehydes react with *in situ* generated ester α-anions, which contains a chiral α-sulphoxide moiety, to give asymmetrically induced β-hydroxyesters after desulphurization (equation 144)[412].



(144)

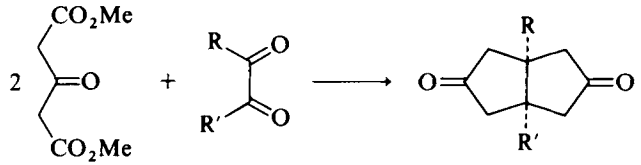
Ester α-anions also react intramolecularly with α,β-unsaturated ketones to give cyclic unsaturated lactones, as exemplified in equation 145[413]. Similarly, intramolecular reactions occur with remote aldehydic groups to give macrolides[414].



(145)

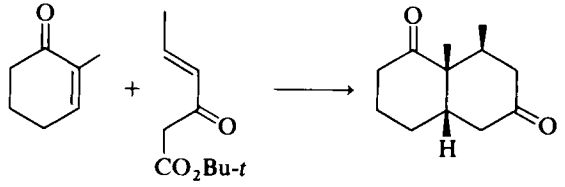
O-alkyllactic acid anions have been reacted with aldehydes to stereoselectively give either the *erythro* or the *threo* diastereomer of the α-alkyl-α,β-dihydroxy carboxylic acid, after hydrolysis of the resultant ether[415,416]. The best yields were obtained when the aldehyde was highly volatile and hence could be used in excess, and then easily removed from the product by distillation.

β-Ketoacids react with aldehydes to produce a carbon–carbon bond at the α-position in buffer at pH 7 with concomitant loss of carbon dioxide to give β-hydroxyketones[417]. In their approach to the synthesis of polyquinanes, Cook and coworkers have used dimethyl β-ketoglutarate to stereospecifically produce bicyclo compounds upon reaction with 1,2-diones, and similar compounds, in buffers at ambient temperatures (equation 146)[418–421].



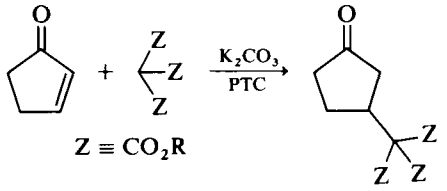
(146)

Michael addition of β-ketoester anions to enones produces carbocyclic rings if there is γ-unsaturation in the ketoester. This reaction is base catalysed and has been performed using caesium carbonate, starting with a cyclic enone to give a dicarbonyl *cis*-decalin (equation 147)[422,423].



(147)

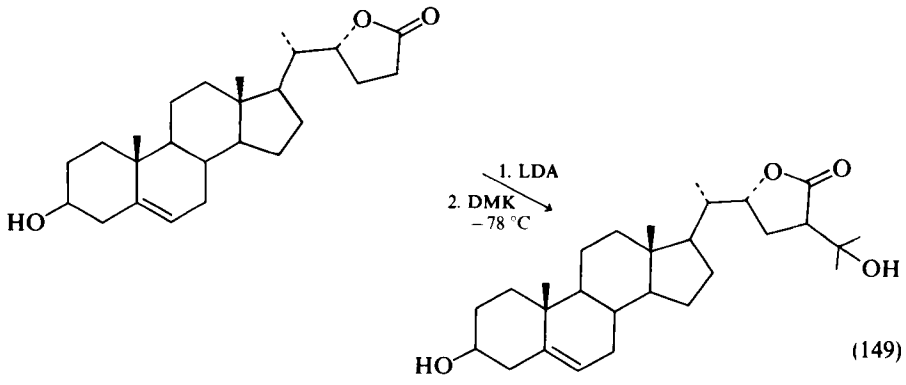
Triethyl methanetricarboxylate has been used in a Michael addition process with unsaturated aldehydes, ketones and nitriles. The reaction occurs under solid–liquid phase-transfer conditions using a quaternary ammonium catalyst and proceeds in high yield (equation 148)[424]. The high acidity of the product eliminates the possibility of a second addition of the Michael acceptor molecule.



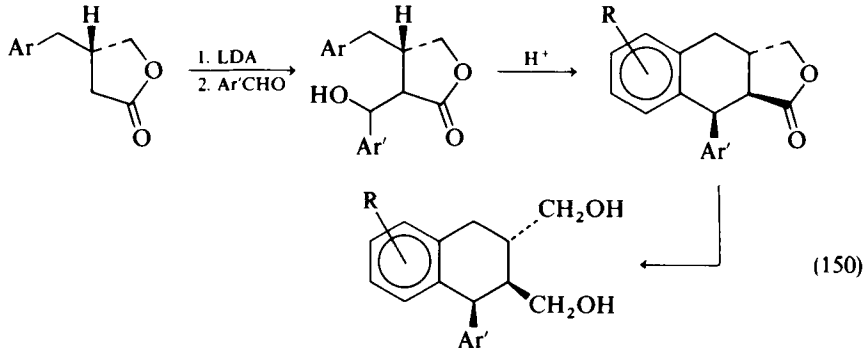
(148)

Lactones and α-anions formed on reaction of lactones with LDA react with aldehydes or ketones. This reaction has been utilized in the synthesis of the highly oxygenated side-chain of depresosterol (equation 149)[254].

In addition, aryl aldehydes may be condensed with α-anions of benzyl substituted lactones to give alcohols. These products are readily cyclized to give isolariciresinols (lignans) upon reduction of the lactone ring (equation 150)[425–428]. The use of this methodology in the synthesis of lignans has been recently reviewed by Ward[377].

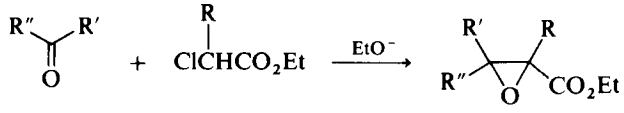


(149)



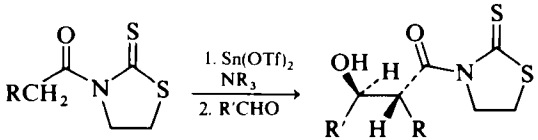
(150)

Anions formed by reaction of α-chloroesters with bases like sodium ethoxide react with aldehydes and ketones to produce α,β-epoxyesters (glycidyl esters)[429]. This reaction is known as the Darzens condensation and is exemplified in equation 151. Dianions of α-chloro acids undergo a similar reaction[430]. The product epoxy acid derivatives may be readily converted into aldehydes by acid catalysed decarboxylation.



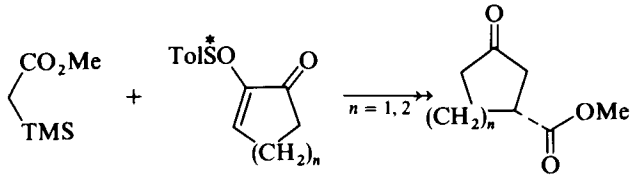
(151)

Chiral tin enolates, formed from amide-containing heterocycles such as 3-amino substituted butanoylthiazolidine-2-thiones, readily react with aldehydes to give diastereoselective products as shown in equation 152[431]. This reaction has been successfully used for the synthesis of (±)thienamycin.



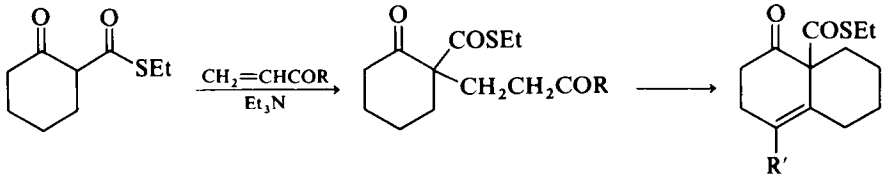
(152)

α-Trimethylsilyl ester enolates react with α,β-unsaturated ketones, by 1,4-addition, to form new C—C bonds adjacent to the ester group. If the unsaturated ketone is a chiral vinylic sulphoxide then asymmetric induction occurs to give greater than 95% enantiomeric excess of the final 1,5-dicarbonyl product, after desulphurization (equation 153)[432].



(153)

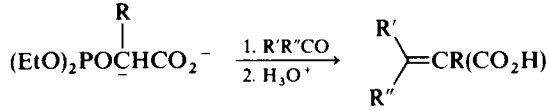
β-Keto-thiolester anions undergo Michael addition with conjugated enones. The products may be readily cyclized to give useful angularly substituted bicyclic compounds (equation 154)[433]. Under high pressure, malonate anions also undergo 1,4-addition in a similar manner, even with sterically hindered cyclic enones[434,435]



R ≡ Me, Et R′ ≡ H, Me

(154)

As part of the synthesis of manicone and related compounds, phosphorus ylids containing α-carboxylate groups have been reacted with aldehydes and ketones in up to 90% yields, giving α,β-unsaturated acids (equation 155)[436].

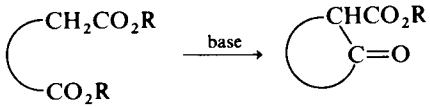


(155)

3. *Acid derivative condensations with acid derivatives*

Esters which possess α-hydrogen atoms undergo self-condensation in the presence of a strong base resulting in the formation of an α-acylated ester. This reaction may be intermolecular (Claisen condensation, equation 156) or intramolecular (Dieckmann condensation, equation 157).

(156)

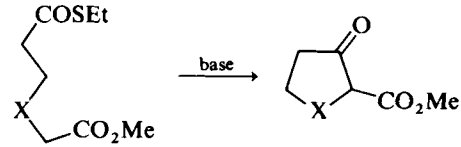


(157)

Mixed Claisen condensations are possible between two different esters but this method is usually only of synthetic utility if one of the esters does not possess α-hydrogen atoms. For example, formates allow the introduction of an α-formyl into an ester, equation 158.

$$RCH_2CO_2R' + HCO_2R'' \xrightarrow{\text{base}} \underset{\displaystyle CHO}{\overset{\displaystyle |}{RCHCO_2R'}} \qquad (158)$$

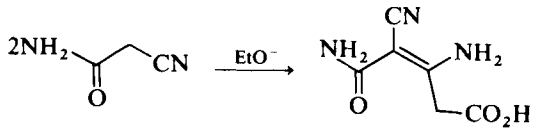
Dieckmann condensations are most successful for five- to seven-membered rings[329,437]. However, large rings may be closed using high dilutions. Dieckmann condensation of unsymmetrical diesters has been performed using solid-phase supported reagent chemistry[437,438]. Dieckmann cyclization of a half-thiol diester occurred regioselectively to give five-membered homo- and heterocyclic compounds, as shown in equation 159[437].



(159)

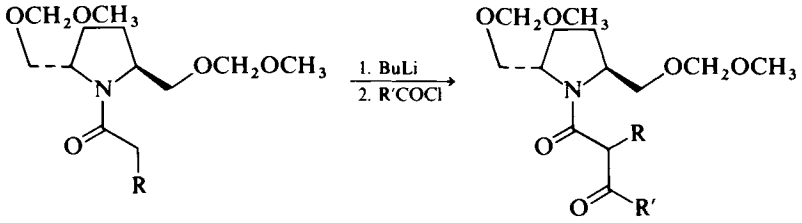
$$X \equiv CH_2, S, NCO_2Et$$

Amides with α-nitrile groups undergo self-condensation upon treatment with sodium ethoxide to give a product with a rather surprising structure (equation 160)[439], which was further processed to produce pyridazine derivatives.



(160)

Lithium ester enolates react with acid chlorides, at low temperatures in THF, to give α-acylation[440]. The α-anions formed by the reaction of chiral amides with BuLi are also readily acylated, in an asymmetric fashion by acid chlorides (equation 161)[441].



(161)

Carboxylic acid dianions, formed by reaction of LDA with a carboxylate salt, react with esters or acid halides to give C-acylation at the more reactive site[442]. The product is a β-ketoacid which may be readily decarboxylated to produce a ketone (equation 162). If the acylating agent used is a formate then the initially formed α-formylcarboxylate usually decarboxylates to give an aldehyde. This latter reaction is an alternative to the reduction methods for preparing aldehydes discussed in section II.B.

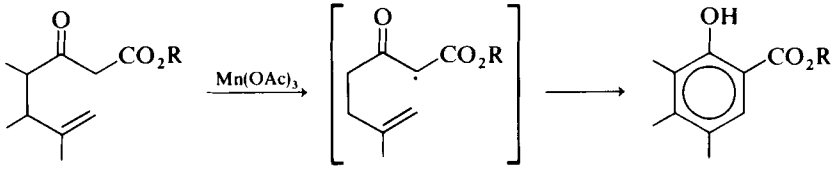
Malonates are readily acylated to form methanetricarboxylic esters (which are useful

$$RCH_2CO_2^- \xrightarrow[2.\ R'CO_2Me]{1.\ LDA} \underset{\displaystyle COR'}{\overset{|}{RCHCO_2^-}} \xrightarrow{-CO_2} RCH_2COR' \qquad (162)$$

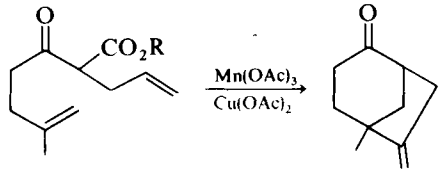
for the preparation of multidentate ligands and as a synthetic intermediate) by replacement of an active hydrogen atom by an acyl group from acid chlorides, in the presence of magnesium oxide[443] or magnesium chloride/triethylamine[444].

4. *Radical- and carbene-mediated cyclizations*

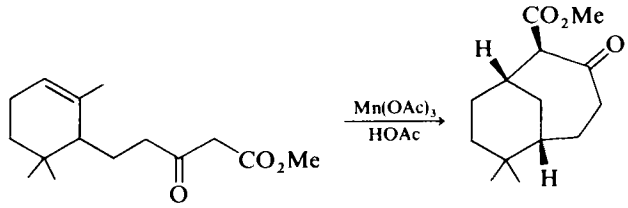
Oxidation of β-ketoesters by manganese(III) acetate yields an α-radical, which in the presence of the appropriate intramolecular alkene functionality yields aromatic esters (equation 163)[445,446], bicyclic compounds (equations 164 and 165)[10] and seven- and eight-membered carbocyclic rings (equation 166)[447,448].



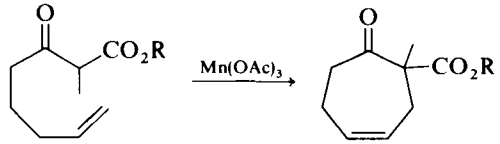
(163)



(164)



(165)

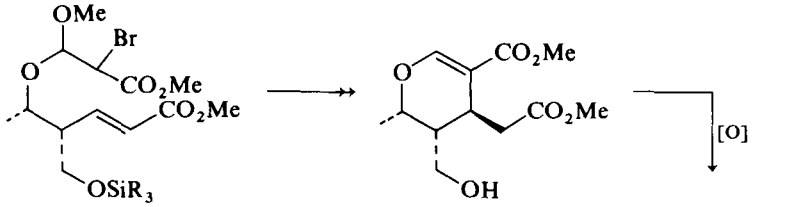


(166)

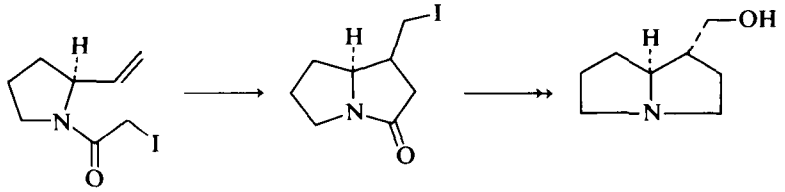
(−)-Methyl elenolate has been synthesized via a key step involving radicals generated at the α-position of an ester functionality as shown in equation 167[449].

Amides with α-iodo substituents form α-radicals upon reaction with ethyl iodide and n-butyltin radicals (formed by sun-lamp irradiation). These radicals will cyclize if correctly oriented intramolecular double bonds are present. Using this methodology the natural product trachelanthamidine has been prepared in good yield (equation 168)[450].

α-Iodo- and α-bromoesters are diastereoselectively cyclized using chromium acetate in

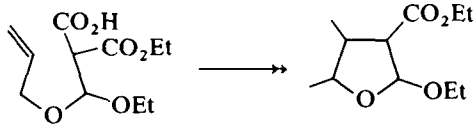


(167)



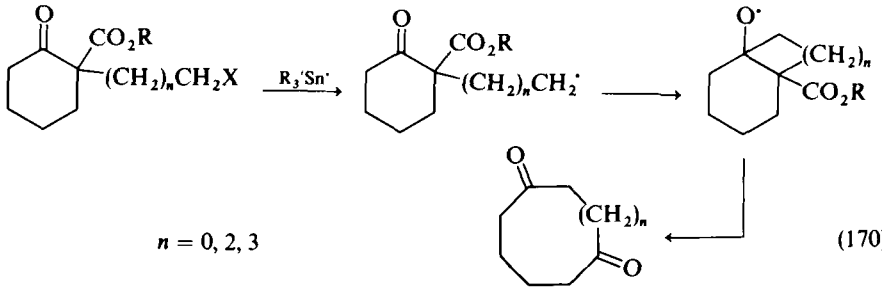
(168)

the presence of intramolecular olefins, upon irradiation. A similar radical process also occurs in the Kolbe electrolysis of double-bond-containing substituted malonates (equation 169) giving a tetrahydrofuran product[451].



(169)

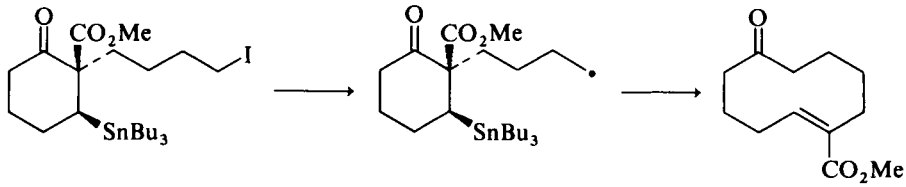
α-(n-haloalkyl)-cyclic-β-ketoesters (with five-, six- and seven-membered rings) undergo very efficient radical-mediated 1-, 3- or 4-carbon ring expansion upon treatment with a source of tri-n-butyltin radicals. The yields of these reactions were reasonable but some alkyl halides were simply reduced to alkanes (equation 170)[373,452]. A similar methodology has also been used by Baldwin and coworkers to form a cepham by one-carbon ring expansion of a penam[453].



$n = 0, 2, 3$

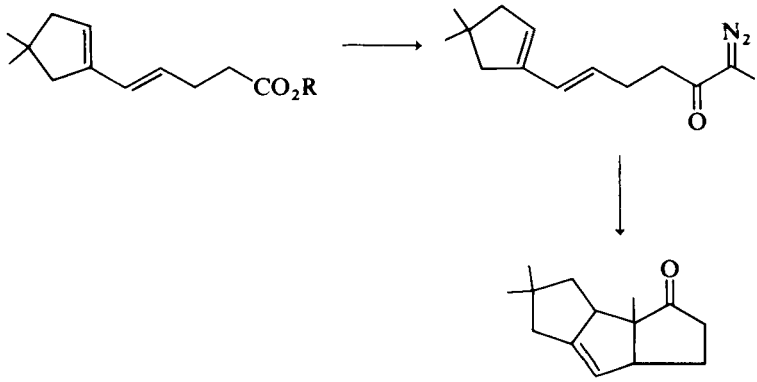
(170)

In further studies, α-(n-alkyl radical)-β-stannyl-cyclic-β-ketoesters were cyclized to form 10-membered rings as shown in equation 171[454–456]. No reduction of the halide to the alkane was evident in this case.

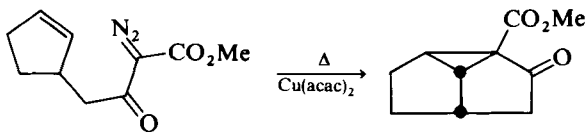


(171)

Esters containing two conjugated double bonds, starting at the γ-position have been converted into tricyclic ketones, such as hirsutene, by initial formation of an α-diazoketone followed by carbene-mediated cyclization as shown in equation 172[457]. Other ketone functionalities present in the molecule are unaffected and thus diketones have also been prepared in this way[458]. In earlier work, Vandewalle and coworkers have constructed a novel tricyclic-β-ketoester, via an α-diazo-β-ketoester as shown in equation 173, which was subsequently transformed stereoselectively, with a range of nucleophiles and electrophiles, into other *cis*-bicyclo[3.3.0]octanes[459].



(172)

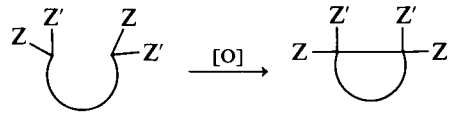


(173)

5. Other

Several other ways of forming new C—C bonds at the α-position of an acid derivative are discussed in this section.

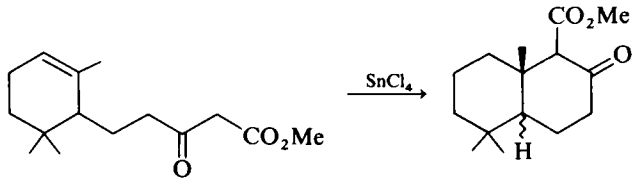
Oxidative coupling of acid derivatives of the type ZCH_2Z', such as ketoesters, occurs upon reaction with iodine, silver oxide and other reagents. This reaction has been successfully employed in the synthesis of carbocyclic rings (equation 174)[460]. Similarly dianions of several acids have been oxidatively self-coupled or cross-coupled[461].



(174)

Carbon–carbon bond formation in the α-position may be performed by reaction of an acid derivative with an alkene to give cyclic compounds. Several methods may be employed, including the use of α-seleno derivatives[462] and Lewis acid catalysts[448]. In addition, these processes may be performed using radicals and carbenes as intermediates. These latter reactions have been covered in Section IV.B.4 above.

Using the first of these methods, acid catalysed cyclization of α-phenylseleno-β-ketoesters has been used to produce both cyclo- and bicyclo-products. The second method, using tin tetrachloride cyclization of β-ketoesters with correctly placed remote double bonds, gives six-membered rings as shown in equation 175 (this should be contrasted with the radical route which gives seven-membered rings as products). Sodium malonates react with the α,β-double bond of allenic sulphoxides to give unsaturated diesters (equation 176)[463],



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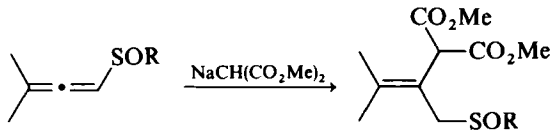
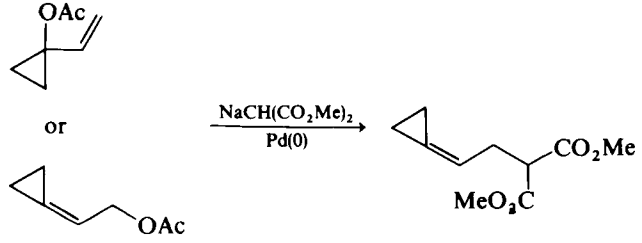


(176)

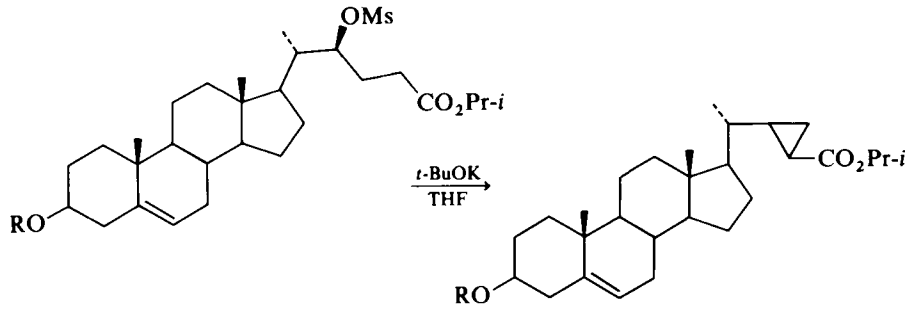
Decomposition of aryldiazonium salts, by titanium(III) ions, in the presence of maleic acids and their derivatives produces 2-arylsuccinic acid derivatives in good yields[464].

Dimethyl malonate anion gives nucleophilic substitution with acetoxy cyclopropane derivatives to yield new C—C bonds. For example, the unsaturated cyclopropane acetates shown in equation 177 react with sodium dimethyl malonate, with palladium(0) catalysis, under reflux in THF to give the same product by either S_N2' or S_N2 displacement as appropriate[465]. Such nucleophilic displacements of cyclopropanes are rare with other nucleophiles.



(177)

A steroid ester α-anion has been used in a nucleophilic displacement of a γ-mesylate to produce demethylgorgosterol, a cyclopropyl containing steroid, as shown in equation 178[254,466].

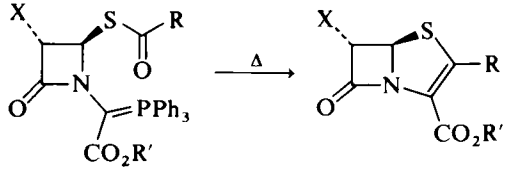


(178)

A similar reaction where an ω-tosylate was nucleophilically displaced gave rise to five- and six-membered carbocyclic rings in a highly stereoselective fashion. The stereoselectivity has been attributed to the stringent conformational requirements in the transition state[467–469].

Intramolecular cyclization by nucleophilic substitution of a wide range of leaving groups, including halogens, mesylates and tosylates, by β-ketoester anions gave five-membered lactones through C—C bond formation[470].

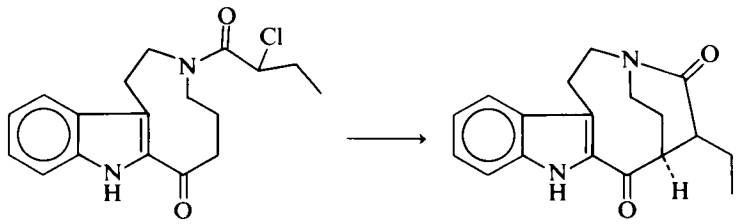
In the synthesis of penem derivatives from azetidinone derivatives, the five-membered ring can be closed in many ways. One route is cyclization of the thiolester with a carboxylic ester ylid to give new bond formation between the carbon atom of the carbonyl group, in the thiolester, and the α-carbon atom of the carboxylic ester, as exemplified in equation 179[471].



(179)

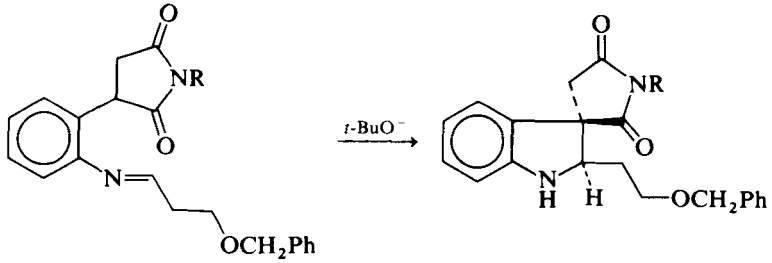
β-Lactams may be formed from α-halo substituted acetamides by two electrochemical reduction methods[202]. These involve C—C bond formation at the α-position, by nucleophilic substitution of the halogen by the generated anion. This reaction joins C(3) to C(4) in the product lactam. The reaction gives high yields and proceeds in the presence of many groups that may be required to further elucidate natural product, β-lactam structures.

Intramolecular nucleophilic substitution of a chlorine atom in a α-chloro amide, by a ketone enolate, causes cyclization and this has been used in the synthesis of some alkaloid ring systems (equation 180)[472]. The product of this reaction is a key intermediate for the synthesis of *Strychnos*, *Aspidosperma*, *Schizozygane* and *Eburnamine* alkaloids.



(180)

Cyclization of an imine by reaction with an internal amide α-anion occurs in high yield upon treatment of the imine with *t*-BuOLi in *t*-BuOH/THF at 5 °C, to give an indoline with *cis*-stereochemistry (equation 181)[473]. This methodology has been applied to the synthesis of the *Aspidosperma* ring system.



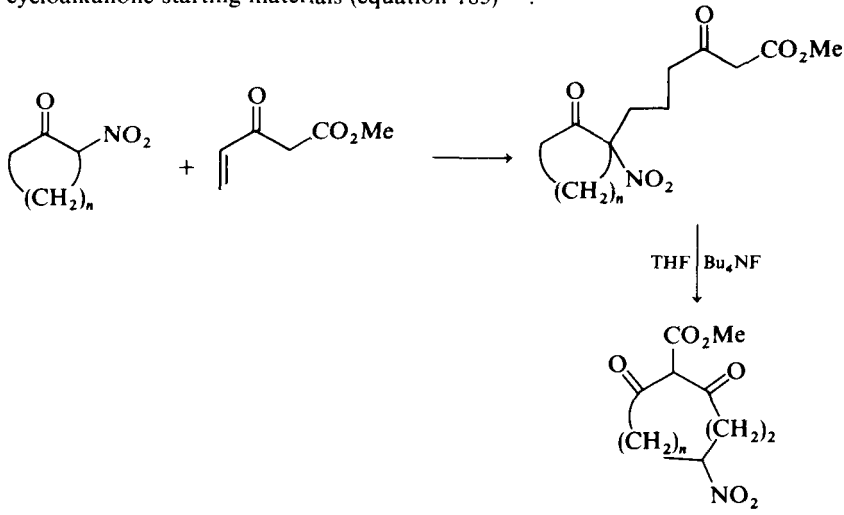
(181)

R ≡ $SiMe_2tBu$

As part of a recent synthesis of the potent insecticide deltamethrin, a γ-alkoxy-α,β-unsaturated lactone has been converted into a bicyclic compound by C—C bond formation at both the α- and β-positions upon treatment with $Me_2\bar{C}\overset{+}{S}Ph_2$ in DMF at − 78 °C (equation 182)[474].

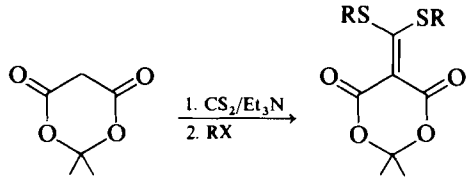
(182)

Cyclic α-nitro ketone anions have been reacted with γ,δ-unsaturated-β-ketoesters to give adducts. These, in the presence of tetrabutylammonium fluoride, undergo a high yielding ring expansion by four carbon atoms (the 'Carbon Zip' reaction). The reaction is essentially a condensation between an ester and a ketone. Using this methodology 11-, 12- and 16-membered rings have been synthesized from 7-, 8- and 12-membered cycloalkanone starting materials (equation 183)[475].



(183)

Finally, cyclic 1,3-diesters and diamides, like Meldrum's acid, may be condensed with carbon disulphide, in the presence of triethylamine, to give a bisalkythioylidene derivative, after alkylation, as shown in equation 184[476].



(184)

C. Carbon–Carbon Bond Formation at Remote Positions

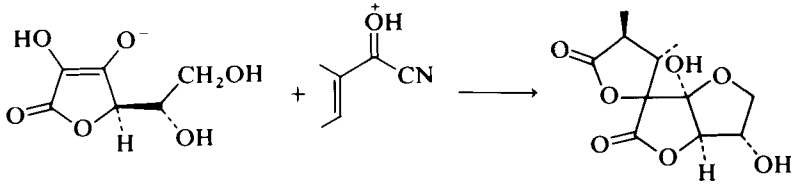
Carbon–carbon bond formation at the β-position and more remote positions is a very useful means by which target molecules may be constructed. For β-attacks the Michael reaction is the most common and is of widespread applicability. For the more remote positions, specialized functionalities are usually required.

In the Michael reaction, carbanions react with α,β-unsaturated carboxylic acid derived functionalities, to give addition products. Such a reaction results in a C—C bond being formed at the β-carbon atom of the acid derived group. The reaction may be both diastereoselective and enantioselective depending upon the reaction conditions employed[477,478].

1. β-Bond formation by Michael reaction

Michael reactions are extremely important C—C bond-forming processes. Michael Induced Ring Closure (MIRC) reactions are important methods of cyclization and have been the subject of two recent excellent reviews[10,479]. Another review[480], of Michael additions of organolithium compounds, is an excellent source of information on the relatively sparse work concerning Michael reactions of amides and thioamides.

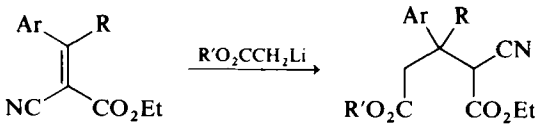
α,β-Unsaturated acids are rarely used in Michael reactions. However, the synthesis of the novel glycoside piptoside, a major component from the extraction of the bitter vine *Piptocalyx moorie* Oliv., has been accomplished by Michael addition of ascorbic acid to tigloyl cyanide in aqueous solution (equation 185)[481]. Under the conditions



(185)

employed the adduct cyclized to give a furanose ring, and then ketolizes and spontaneously lactonizes to give 25% yield of the required product. This reaction is, unfortunately, not of general synthetic utility—vitamin C does not give adducts with unsaturated acids, esters or acyl halides under these conditions.

α,β-Unsaturated esters react with a wide range of carbanionic species to give C—C bond formation at their β-positions. Thus lithium ester enolates have been added to ethyl 2-cyano-2-alkanoates to give glutarates in high yield (equation 186)[482–484]. Homologation to higher 2-alkenoates has been performed by reaction of Grignard

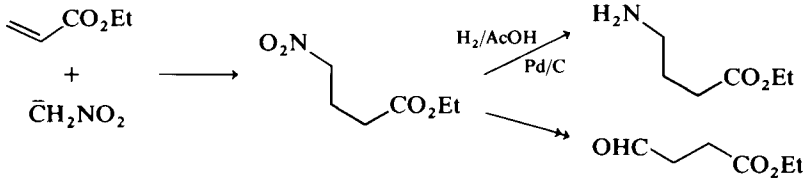


(186)

reagents with ethyl crotonate[485] and α,β-acetylenic esters undergo stereocontrolled Michael addition with organocuprates[39].

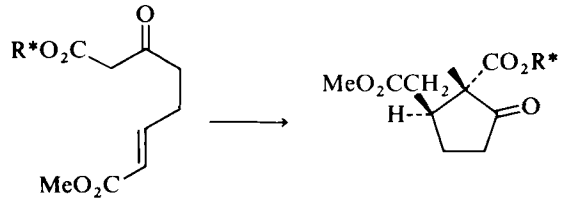
Addition of organomanganese(II) reagents to β-monosubstituted alkylidenemalonic esters gives conjugate addition products in good yields (equation 187)[486]. Michael addition of nitromethane anions to α,β-unsaturated esters has been used to prepare a range of γ-nitroesters, which may be readily converted into γ-amino acids[487] or γ-ketoesters[488] by simple procedures (equation 188).

(187)



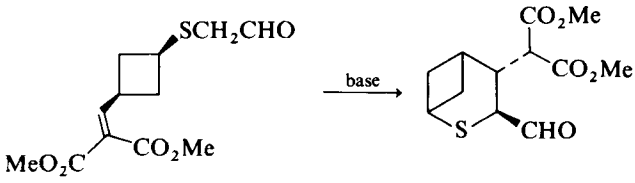
(188)

Ring-closure reactions have been performed by Michael reaction of a β-ketoester enolate with an internal α,β-unsaturated ester to give a highly stereoselective synthesis of substituted cyclopentanones (equation 189) which are very useful synthetic intermediates[489,490]. In the synthesis of thromboxane A_2 analogues, a bicyclic sulphide has been formed by Michael addition of an aldehyde enolate to an α,β-unsaturated diester (equation 190)[385].



(189)

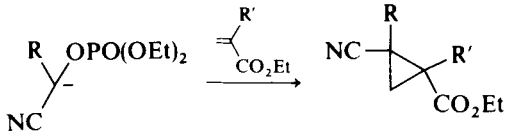
R* ≡ chiral group



(190)

Michael-induced ring-closure reactions have been performed using α,β-unsaturated esters as the Michael acceptors. These reactions involve conjugated nucleophilic addition to the acceptor followed by ring closure of the resulting enolate by displacement of a leaving group. MIRC reactions have been classified as type I and type II. In type I MIRC reactions the Michael acceptor and the leaving group are in one molecule and the nucleophile is introduced. In type II reactions the nucleophile and the leaving group are in the same molecule and the acceptor is a separate entity.

Type II MIRC reactions, with acid derivatives, have especially been used for the formation of cyclopropanes (equation 191)[491–494]. On the other hand, type I reactions have usually been used for larger rings (equation 192)[495–501].



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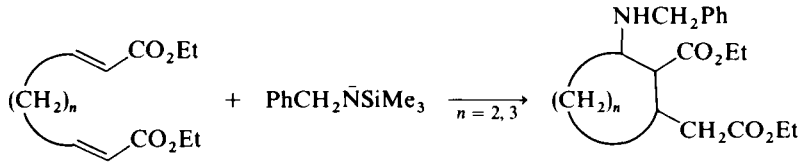
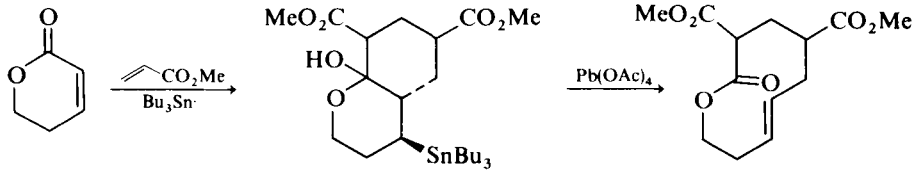


(192)

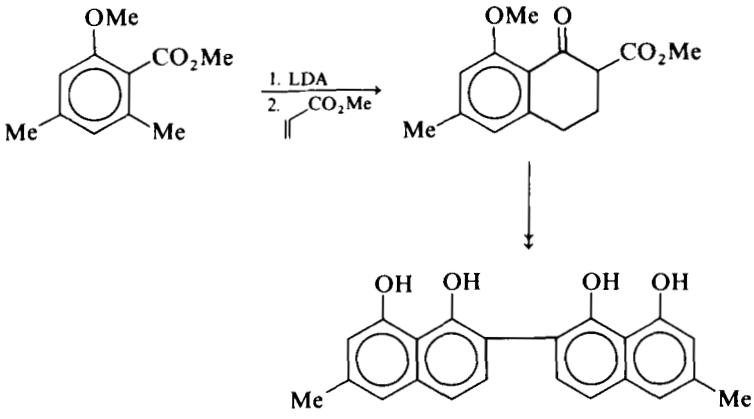
In addition, multiple Michael-initiated ring closures have also been used effectively, for example, in the synthesis of a 10-membered lactone as shown in equation 193[502]. Tandem Michael reaction–Dieckmann condensation reactions have also been used, very successfully, as the key steps in the synthesis of several natural products[503–505]. In one example, the carbon skeleton of diospynol has been prepared by reaction of a substituted benzylic anion with methyl acrylate (equation 194).



(193)

α,β-Unsaturated lactones also undergo facile Michael reactions with carbanions to give synthetically useful products. In one such reaction, *trans*-3,4-dibenzyl-substituted butyrolactones have been synthesized by tandem conjugate addition of anions of aryldiphenylmethane to butenolide, followed by anionic trapping with a benzyl bromide (equation 195)[506]. In another reaction of this type, Michael addition of lithium dimethylcuprates to 10- to 13-membered-α,β-unsaturated macrolides has occurred in a stereocontrolled fashion when methyl substituents are present adjacent to the ring oxygen atom (equation 196)[227].

α,β-Unsaturated amides have been relatively rarely used as Michael acceptors and only a few reports are available in the recently published literature[480]. Organolithium compounds have been reacted with unsaturated *N*-phenylamides to give cleanly 1,4-addition products[507]. Stereocontrolled addition of dialkylorganocuprates to unsaturated lactams has been achieved by the presence of an exocyclic chiral centre[508].



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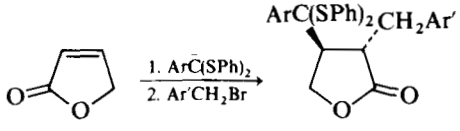

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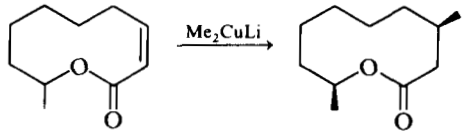
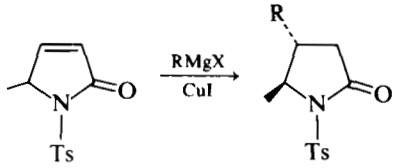


(196)

N-Tosylated α,β-unsaturated amides and lactams however do undergo conjugate addition with organocopper reagents. With lactams, stereochemical control can be achieved and this methodology has been used for the preparation of *trans*-β,γ-dialkyl-γ-lactams (equation 197).

On the other hand, thioamides react to give both 1,2- and 1,4-addition products, the actual outcome being very sensitive to the reaction conditions[509].

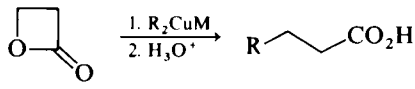


(197)

2. *β-Bond formation by other reactions*

Other means for C—C bond formation at the β-position in carboxylic derivatives include direct substitution, condensation with aldehydes and by a radical-mediated process. These reactions are discussed below.

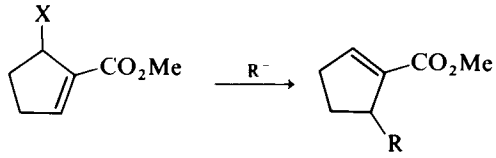
β-Lactones undergo regioselective S_N2 ring opening with 'soft' organometallic reagents, such as organocuprates and Grignard reagents in the presence of copper(I) salts, to give 3-substituted propionic acids in good yields (equation 198)[510]. In direct contrast,



(198)

organolithium reagents give mixtures of α,β-unsaturated ketones and diols, via reaction at the carbonyl group[511],

Cyclopentenes with conjugated ester groups and correctly placed leaving groups undergo S_N2' substitution of the leaving group with a wide variety of organocuprates and Grignard reagents in the presence of copper(I) salts (equation 199)[512,513]. The stereochemistry of the reaction may be controlled in some instances.



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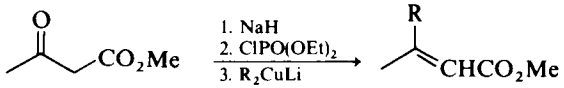
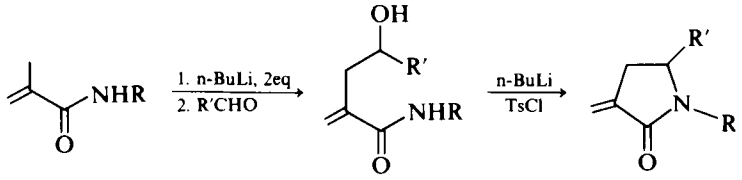


(200)

β-Ketoesters may be converted into α,β-unsaturated esters by formation of an intermediate phosphorylated enol ether which is substituted by organolithium cuprates to give new C—C bond formation at the β-position (equation 200)[514,515]. The products are extremely useful synthetic intermediates.

Dianions of N-monosubstituted α,β-unsaturated amides react with aldehydes to give hydroxyamides, which were further reacted with n-BuLi and TsCl to give 3-methylene-2-pyrrolidinones (equation 201)[516]. In a similar fashion, dianions of α,β-unsaturated acids were condensed with aldehydes to give lactones[286,517] upon cyclization of the first-formed hydroxy acid (equation 202).



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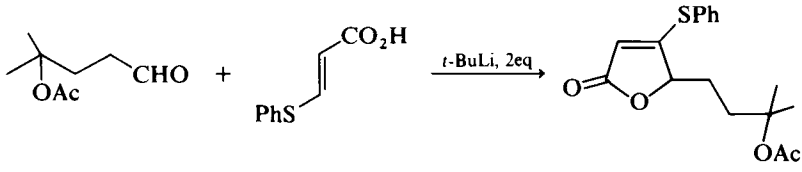
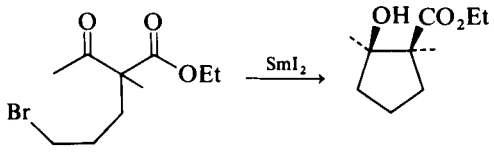


(202)

β-Ketoamides and acids may be intramolecularly cyclized using samarium dioxide, if they possess a primary δ-bromine substituent. The product formed is a β-hydroxycyclopentanecarboxylate and stereochemical control is exerted over two adjacent chiral centres (equation 203)[518]. The same substrates with δ,ε-unsaturation also undergo



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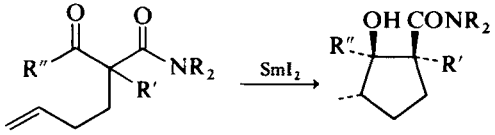
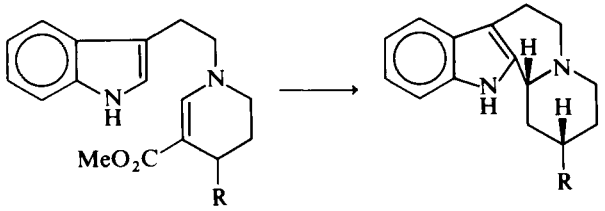


(204)

stereocontrolled cyclization. In this case the stereochemistry of three adjacent chiral centres is controlled (equation 204)[519].

In-depth studies[520,521] of the stereochemical course of the alkaline, decarboxylative cyclization of substituted 1-[2-(3-indoyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines to substituted indolo[3,3-*a*]quinolizidines has shown that there is a preponderance of *cis* C(12b)H-C(2)H product for C(4)-monosubstituted precursors (equation 205). For C(5)-monosubstituted compounds a *trans* C(12b)H-C(3)H product is formed (equation 206) whilst for 4,5-disubstituted precursors both *cis* and *trans* products may be formed depending upon the exact substitution pattern in the starting material.



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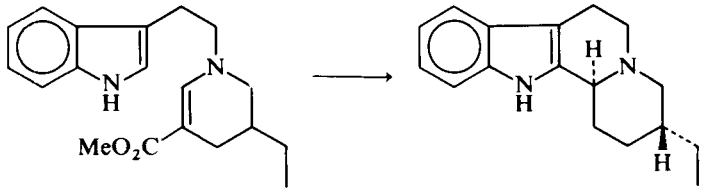


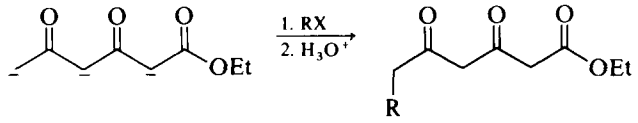
(206)

3. Positionally more remote bond-formation reactions

Carbon–carbon bond formation at more remote positions requires specific functional group orientations within a reacting molecule. Reactions of compounds with the requisite structures are discussed below.

Alkylation at a remote position may be performed in several ways. Alkylation of anions of α,β-unsaturated esters usually occurs at the α-position, but if a removable blocking group is introduced then the γ-alkylation reaction may predominate[522].

Monoalkylation of β-ketoester dianions[515] or trianions of 3,5-dioxohexanoates, and the corresponding amides, gives 4- and 6-alkylated products (equation 207)[523]. In addition, alkylation of dianions of furan-2-carboxylic acids gives products that are alkylated at the remote 5-position (equation 208)[524].



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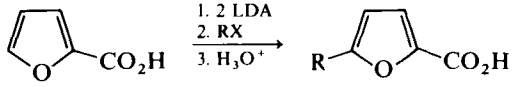
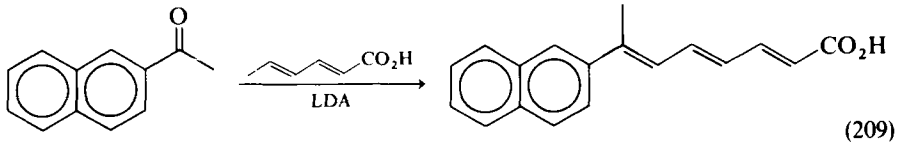


(208)

Condensations of polyenolates of unsaturated carboxylic acids have been used in the synthesis of retinoic acids[525]. Thus, ketones react with polyunsaturated acids to give products with extended conjugation, upon dehydration (equation 209). Extended conjugated systems may also be formed by iodine-mediated oxidative coupling of diene- and triene-diolates of unsaturated carboxylic esters[526]. Such a process has been used for the synthesis of dicarboxylic acids as shown in equation 210.



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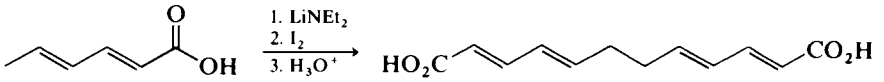
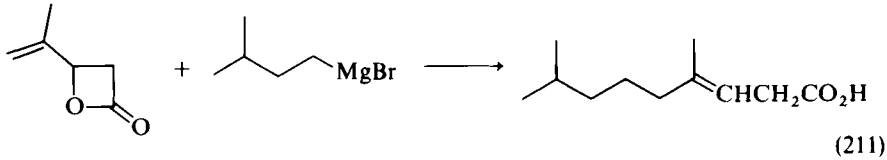


(210)

Fujisawa and coworkers exploited remote C—C bond-forming reactions in β-propiolactones[527–530]. β-Vinyl-β-propiolactone was reacted with organocuprates and Grignard reagents, with copper(I) salts, to give ring opening by a S_N2' pathway (equation 211)[527,528,530]. Similar reactions with the β-ethynyl-substituted lactone gave allenes (equation 212).



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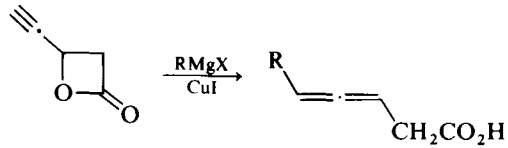
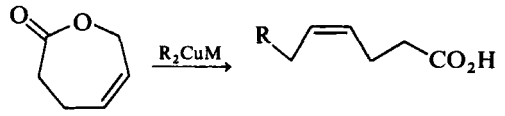


(212)

The same workers found that (*Z*)-4-hexenolide, rather surprisingly, gave S_N2 ring opening to produce (*Z*)-4-alkenoic acids (equation 213). These products are very useful in the synthetic perfume and flavour industries and in the synthesis of some natural products[531].

Allylsilanes have been reacted with 4-alkenyl-4-butanolides, activated by trimethyl-



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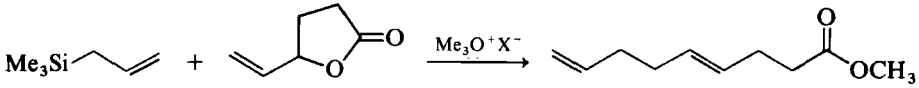


(214)

oxonium salts, to give C—C bond formation at a remote position. The product ester possesses a terminal double bond and has three more carbon atoms than the starting material (equation 214)[532]. A similar reaction occurs with a 4-hexenolide by attack of the allylsilane on the cyclic double bond.

V. PREPARATION OF HETEROCYCLIC COMPOUNDS BY C—Y BOND FORMATION

One of the key uses of carboxylic acid derivatives in organic synthesis is the preparation of heterocyclic compounds. These are either key intermediates in organic syntheses or are the target molecules of a particular reaction sequence. Lactones and lactams are particularly important in this regard. The reader is referred to the more in-depth coverage of lactones and lactams in the chapter by G. V. Boyd in the present volume.

This section covers the synthesis of heterocyclic compounds by carbon–heteroatom bond formation, while formation of heterocycles by C—C bond-forming reactions has been covered in Section IV.

A. Lactones

Synthesis of polyfunctional compounds with controlled stereochemistry is one of the fine arts of modern science and the synthesis of macrolides is probably the pinnacle of these achievements.

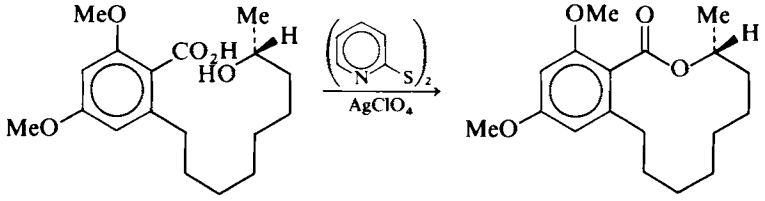
Lactones exhibit many useful properties especially in the field of pharmaceutical synthesis. They are a very prevalent structural feature in natural products and are key intermediates in many synthetic sequences. Hence many lactones have been given names, such as Corey lactone, reflecting the scientist who introduced the compound as a key intermediate. Much interest and effort was exerted in the development of strategies for the synthesis of these heterocycles and there have been many reviews concerning the synthetic utility of lactones, for example of halolactones[533] and of the synthesis of target lactones, such as macrolide antibiotics[534].

Lactones may be readily prepared from ω-hydroxy or ω-halo acids or related compounds, by halolactonization of acids and by ring-opening lactonization of cyclopropanes, as discussed below.

1. From ω-hydroxy acid derivatives

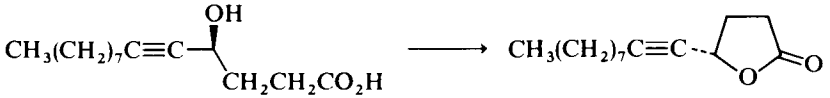
The most common method of lactone formation is carbon–heteroatom bond formation, by intramolecular reaction of an ω-hydroxyl group with the carbonyl group of the acid-derived moiety[535–538]. Steliou and Poupart have also used this method to produce macrolides (with 9–17 ring atoms) in high yields under very mild conditions[537]. The

acid group is often activated, because of the unfavourable entropic factors and possibilities of polymerization. This may be done, for example, by preparation of the thioester[254,539,540]. Thus, the 2-thiopyridyl ester has been used to prepare the 12-membered lactone in the macrolide (*R*)-lasiodiplodin, a fungal metabolite of *Botrysdiplodia threbromae*, in 49% yield (equation 215)[541] and the 14-membered lactone in erythromycin[540].



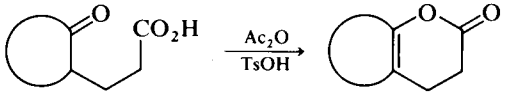
(215)

Activation of the hydroxyl group has also been used to facilitate lactonization, for example by conversion into a tosylate[254,542]. This procedure has been used for the key lactonization step in the synthesis of the Japanese beetle pheromone, (*R*, *Z*)-(−)-5-(1-decenyl)-2-oxotetrahydrofuran (equation 216)[542]. In a similar process, *p*-toluenesulphonic acid catalysed condensation of 1,5-dihydroxynaphthalene with ethyl 2-oxocyclohexanecarboxylate gave a 1:1 adduct which spontaneously lactonized, producing the tetracyclic ravidomycin skeleton[543].



(216)

For six-membered lactones and spirolactones, ring closure may be brought about via the enol of a γ-keto acid derivative with acid catalysis (equation 217)[544] or using triphenylphosphine (equation 218)[545].



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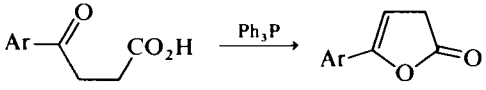
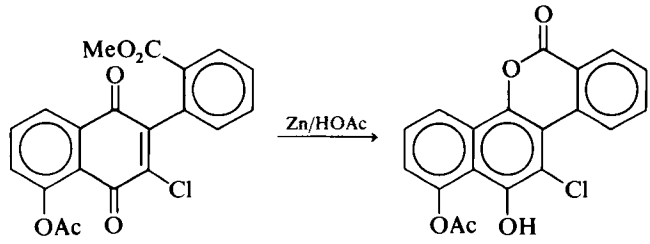


(218)

The ω-hydroxyl group may also be formed *in situ* by reaction with zinc. This method has been employed in the synthesis of the lactone ring in the tetracyclic ravidomycin family of anti-tumor agents (equation 219)[546]. Other reductions of a ketoacid with Selectride[547] or borohydride[548] and of an acid-ester with sodium in ammonia (equation 220)[549,550] or borane (equation 221)[550] also yield useful lactones. It should be noted that in the reductions of the acid-esters, borane gave the product with opposite regiochemistry to that obtained by the use of sodium in liquid ammonia.

Substituted 7-aryl-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines have been successfully prepared from anions of 6-methyl-5-pyrimidinecarboxylates by condensation with aromatic aldehydes. The key lactone ring closure occurs by reaction of the *in situ* generated alkoxide ion with the adjacent ester group, as shown in equation 222[551].



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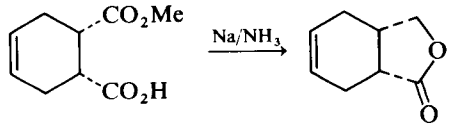

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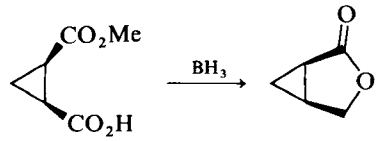

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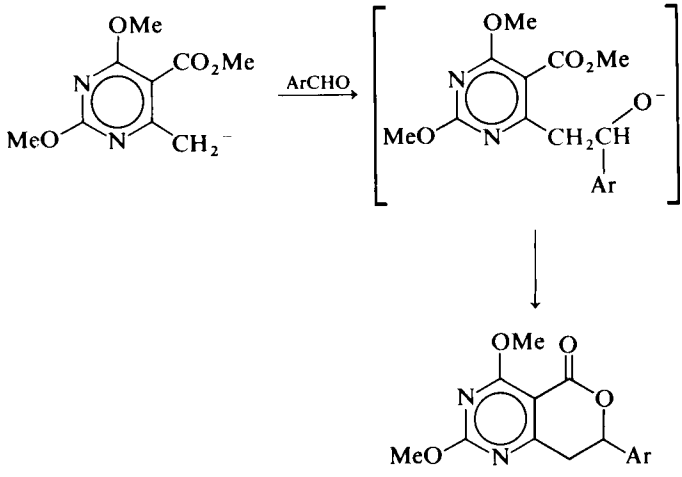
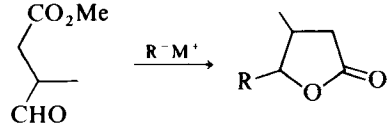


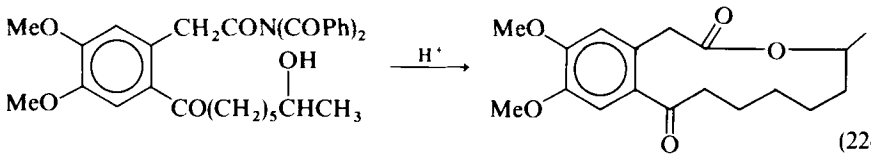
(222)

Alkoxide ions from the reaction of β-formyl esters with organometallic reagents also gave lactonization. In this case, stereoselectivity is controlled by the coordinating effects of the metal ions with the two carbonyl groups (equation 223)[552].



(223)

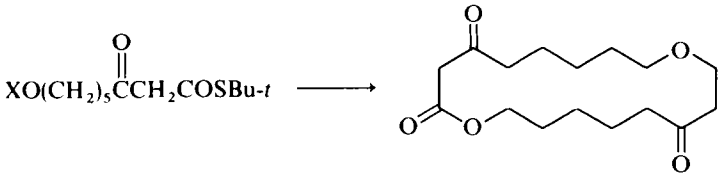
Triamides, formed from the corresponding oxazole by photooxygenation, undergo acid catalysed lactonization to give, for example, the 12-membered lactone in (±)-di-*O*-methylcurvularin, a metabolite of the fungal species *Curvalaria (equation 224)*[553].



(224)

The synthesis of nine-membered lactones from hydroxyacids (or their equivalent) usually gives low yields. However, excellent yields were obtained with an allylic alcohol with a more rigid carbon chain. The rigidity serves to reduce the unfavourable entropic factors of the ring-closure process[554].

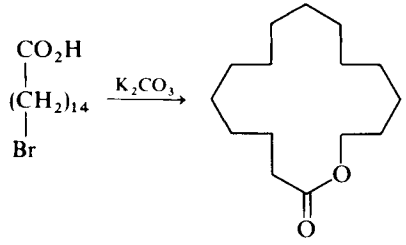
The above-described lactonizations often produce dilactones as side products, however these are sometimes the target molecules of a synthetic sequence. Yields of dilactones may be enhanced by activation of both the acid-derived group and the hydroxy group. Such a reaction has been performed using a thioester with an internal silyl ether (equation 225)[555].



(225)

2. *From ω-halo acid derivatives*

Treatment of ω-haloacids with potassium carbonate and other bases, especially using solid–liquid phase-transfer conditions and high dilution techniques, is a simple alternative method to prepare medium- and large-ring lactones[556,557]. Using this method, exaltolide, a component of the root oil of *Archangelica officianalis*, Syn. which is useful in the perfume industry, has been prepared in 78% yield (equation 226)[557]. Other ring sizes have also been prepared in a similar fashion[556].



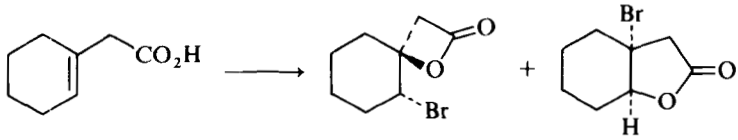
(226)

3. *By halolactonization*

Halolactonizations of carboxylic acids are highly regio- and stereoselective processes that are extremely important in the synthesis of natural products and their key intermediates. These reactions have recently been reviewed[558]. Such reactions are performed by treatment of unsaturated acids or carboxylate salts[559] with sources of

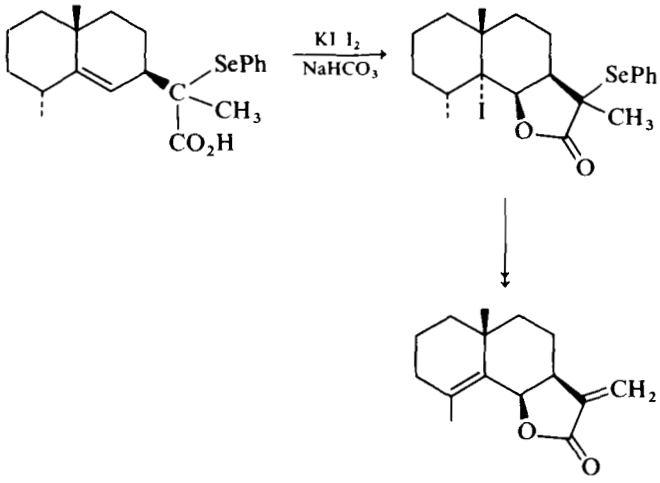
electrophilic halogens. These sources include bromine or iodine with thallium(I) carbonate[560], *N*-bromosaccharin[561], chloramine-T[562], an iodine(I) perchlorate–collidine complex[563] and a mixture of iodine, potassium iodide and potassium bicarbonate[133,564,565]. The lactonization process may also be brought about by a source of electrophilic selenium[566].

Regiocontrol of the reaction often depends on the reaction conditions employed. Thus bromolactonization of the unsaturated acid in equation 227, using bromine and thallium(I) carbonate, gave the γ-lactone, whilst use of NBS in DMF gave the β-lactone exclusively[567].



(227)

Using halolactonization, the lactone ring of the sesquiterpene (±)-frullanolide has been readily synthesized in excellent yield (equation 228)[568]. Similarly, halo aldehydic lactones of the Corey-type, key intermediates in the synthesis of prostaglandins, may be synthesized in excellent yields (equation 299)[569].



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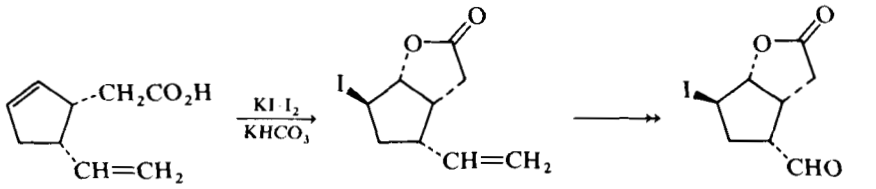
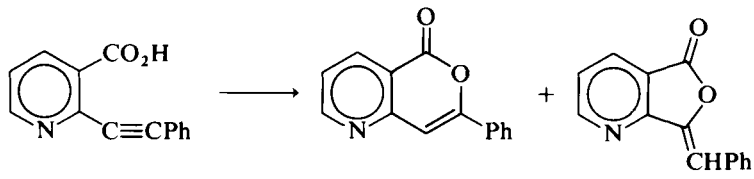


(229)

Lactonization of 2-phenylethynylnicotinic acid, catalysed by mercuric acetate, leads to a mixture of two bicyclic pyridine derivatives with ring structures that are often found in natural products (equation 230)[570]. The regioselectivity favoured the pyrano- over

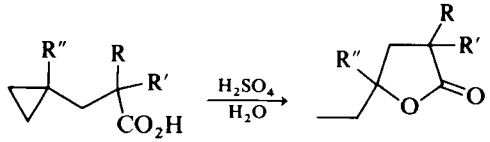


(230)

the furano-product. With the 3-carbamoyl derivative, an equivalent reaction can be performed which, in this case, gives only the five-membered lactam.

4. *From cyclopropanes*

Cyclopropanes with carboxyl substituents undergo electrocyclic ring opening followed by cyclization to give lactones. This reaction sequence is important in the synthesis of furan- (equation 231) and pyran-derivatives (equation 232)[571,572]. Ring opening occurs at the most hindered site, thus controlling the regioselectivity of the reaction.



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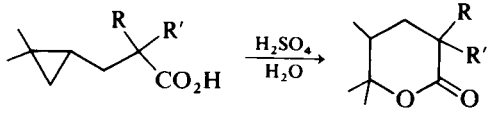
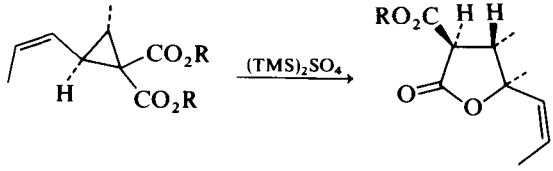


(232)

Vinylcyclopropanes with geminal diester groups also undergo ring opening followed by lactonization to give γ-butyrolactones in the presence of bis(trimethylsilyl)sulphate (equation 233)[573]. Some stereocontrol is exhibited in the generation of the new, third chiral centre. Acid catalysed reaction of equivalent trialkylsiloxy substituted compounds produces α,β-unsaturated lactones[219].



(233)

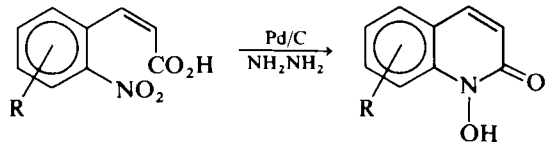
B. Lactams

Lactams are extremely important sub-units in natural product syntheses and their methods of formation are discussed below. In particular, β-lactams are important in penicillin and cephalosporin chemistry and these functionalities have thus received much attention; some of this work has been reviewed[574].

Lactams may be formed by intramolecular reaction of ω-(*N*-substituted) acids, by reaction of activated acids with imines and by other methods, including the novel 'Zip reaction'.

β-, γ- and δ-amino esters may be cyclized to give lactams in excellent yields, by intramolecular reaction[575–578]. For example, β-hydroxyamides, formed from tartaric acid, have been cyclized to give β-lactams[579,580].

Hydroxylactams have been synthesized by reductive cyclization of aromatic nitro compounds containing a β-alkoxycarbonyl group. Reagents such as Pd/charcoal/hydrazine or ammonium sulphide or zinc with acetic acid may be used for this reduction process (equation 234). However, if the nitro group is reduced to the amine, for example with Pd/charcoal/cyclohexane, then no hydroxyl group remains in the product (equation 235)[581].



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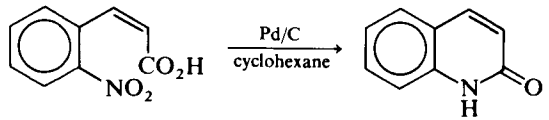
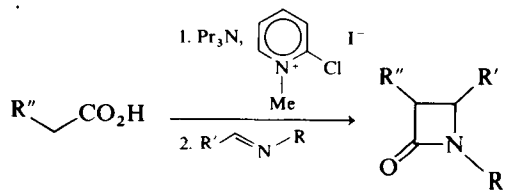


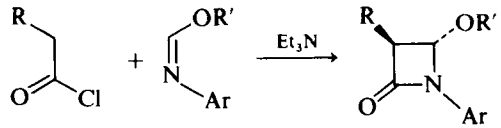
(235)

The usual method for forming β-lactams is by reaction of activated acid derivatives (or acids previously treated *in situ* with an activating agent) with imines, as exemplified in equation 236[582–587].



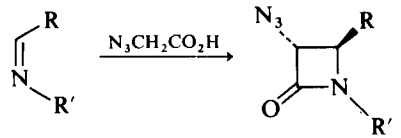
(236)

The acid chloride–imidate route is a popular method, involving formation of β-lactam with a 4-alkoxy substituent (equation 237)[585,587]. This substituent is usefully located for further reactions that may be used to build up the molecular framework of the required target molecule.



(237)

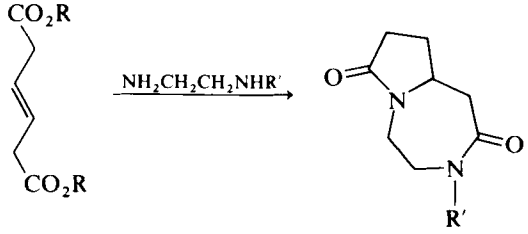
The reaction of activated azidoacetic acid derivatives with an imine, or a cyclic imine, is also a common route, employed for the synthesis of α-azido-β-lactams (Bose reaction) which are key intermediates in the synthesis of β-lactam-containing alkaloids and sugars



(238)

(equation 238)[586]. Stereocontrol of the reaction depends upon the reaction conditions used.

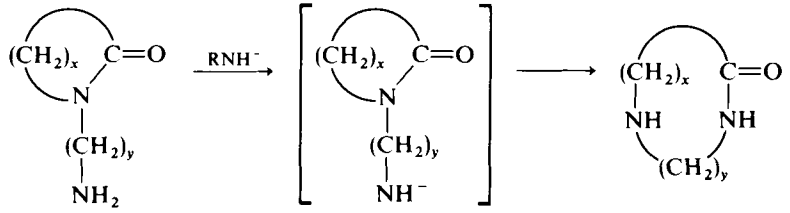
Five-membered lactams have been synthesized from *trans*-3-hexendioic esters by reaction with primary amines. Replacement of the amine with ethylenediamines has resulted in the formation of bicyclic compounds with two lactam moieties (equation 239)[588].



(239)

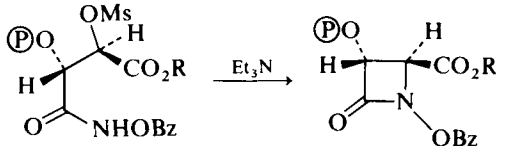
These products may easily be reduced to cyclic amines of importance in natural product synthesis.

A novel ring expansion reaction of lactams to larger lactams (the so-called Zip reaction) has been developed[589] based on the reaction of an aminolactam with a strong base followed by transamidation by reaction with the internal amide ion as exemplified in equation 240.



(240)

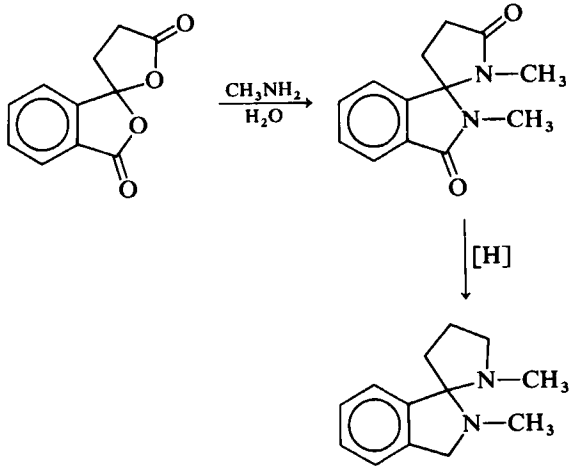
β-Lactams may also be formed by substitution of activated α-hydroxyesters by the nitrogen atom of a β-amido group (equation 241)[579],



(241)

Lactams have recently been prepared in a relatively simple process involving reaction of a lactone with a primary amine. In one striking example, the lactams in the spirodilactam-containing alkaloid, shihunine, were formed by reaction of a dilactone precursor with methylamine. The alkaloid product was then formed by reductive removal of the carbonyl groups (equation 242)[590].

Finally, a γ-hydroxyamide has been cyclized to a lactam by activation of the hydroxyl group and formation of the N-anion of the internal amide (equation 243)[516],



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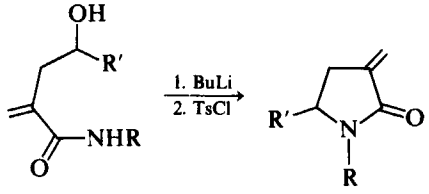
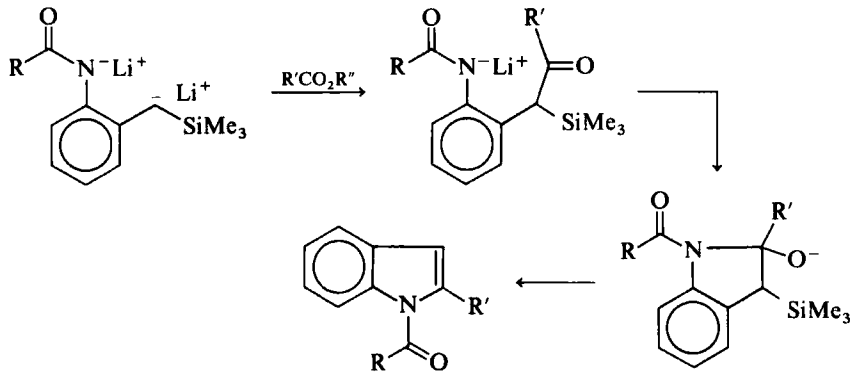


(243)

C. Other Heterocyclic Compounds

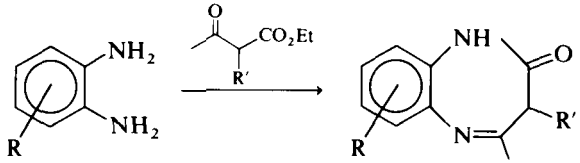
The synthesis of a great wealth of other heterocyclic compounds from acid derivative, by carbon–heteroatom bond formation in the key step, is also an important area of organic synthesis and especially of natural product work. Recent reviews have considered key synthetic intermediates of this type and the reader is referred to these sources for further information[229,591]. This section briefly reviews the formation of some N-, O- and S-containing heterocyclic compounds that have been the targets of recent synthetic pathways.



(244)

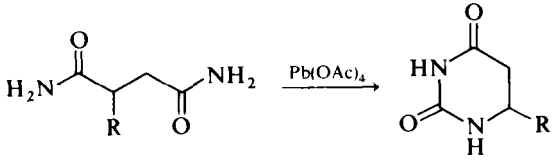
2-Substituted indoles are common sub-units of several classes of natural products. These may be synthesized rather elegantly from anilides. Acylation of the dilithium salts of 2-trimethylsilylanilides, at −10 to 0°C, with esters in basic media gives the expected C-acylated product which spontaneously cyclizes. This intramolecular cyclization occurs by reaction of the amide ion with the newly introduced carbonyl group. The product readily desiloxylates to give *N*-acyl 2-substituted indoles in good yields (equation 244)[251].

Benzodiazepines are found in some natural product molecules. These functionalities have been recently synthesized by reaction of *ortho*-diamino aromatic compounds with α-substituted β-ketoesters. The initially formed imine readily cyclizes to give the substituted benzodiazepine as shown in equation 245[592].



(245)

Dihydrouracils may be regioselectively prepared from substituted succinamides, in 90% yield, simply by oxidation with lead tetraacetate (equation 246)[593]. This reaction also occurs if an acetate group is present (equation 247). Using the products of this latter reaction, 6-substituted uracils may be readily prepared upon elimination of acetic acid[593].



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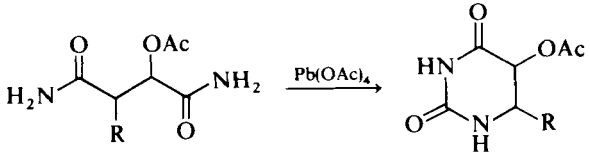
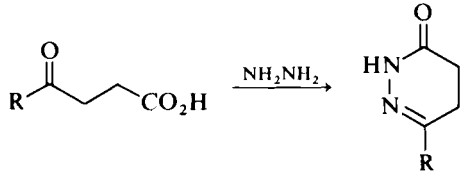


(247)

A series of novel dihydropyridazinones have been quantitatively prepared from γ-ketoacids upon reaction with hydrazine (equation 248)[594]. The product 4,5-dihydro-6-substituted-3(2*H*)-pyridazinones may be reduced, acylated with an ω-halo acyl halide and then reacted with sodium hydride to give novel bicyclic diacylhydrazines (equation 249). The latter may be ring opened (by N—N cleavage) to give macrolide dilactams by treatment with sodium in liquid ammonia.



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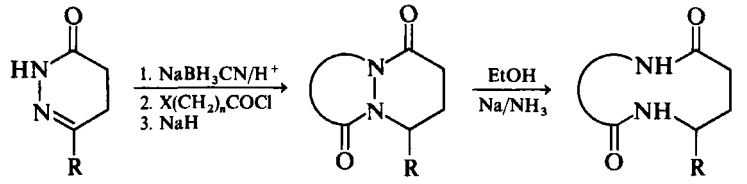
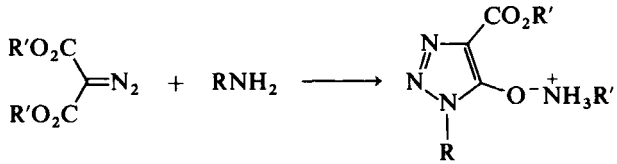
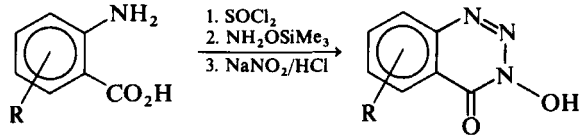


(249)

Triazine and triazole moieties are present in many important pesticides, and may readily be prepared from acid derivatives. Thus, alkylammonium salts of triazoles are formed in good yields by the reaction of primary amines with dimethyl diazomalonates (equation 250)[595]. Complex keto dihydro-1,2,3-benzotriazines may be obtained from substituted anthranilic acids by the reaction sequence shown in equation 251[596]. The products are useful in peptide synthesis since α-amino esters of these compounds suppress racemizations to a large degree.

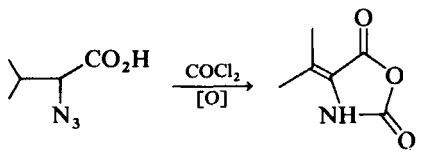


(250)

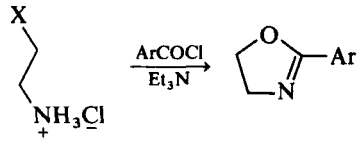


(251)

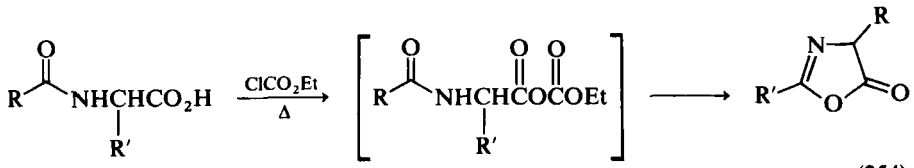
A wide variety of oxazolines, and related nitrogen and oxygen-containing five-membered rings, may be prepared readily from acid derivatives as shown in equations 252, 253 and 254.



(252)



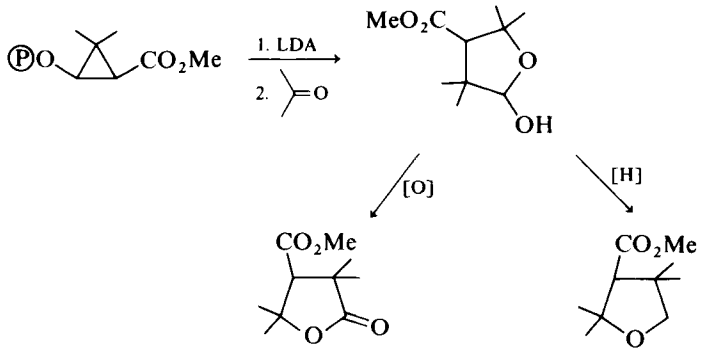
(253)



(254)

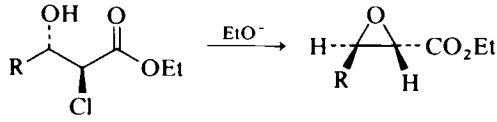
The first of these reactions is performed by treatment of an α-azidoacid derivative with phosgene and an oxidizing agent[597]. In the second, *N*-acylation of 2-haloethylamine hydrochloride using a substituted benzoyl chloride proceeds cleanly to the 2-aryloxazoline[598,599]. In a similar process, a β-amino alcohol gave a 2,4-disubstituted oxazoline upon activation of the hydroxyl group[600]. The last reaction, which may be brought about with either acetate/acetic anhydride or with ethyl chloroformate, is essentially the Erlenmeyer azlactone synthesis which has seen much use in amino acid synthesis[601].

γ-Lactols may be prepared by reaction of protected hydroxycyclopropanecarboxylic ester anions with ketones. The lactols may then be oxidized to lactones or reduced to tetrahydrofuran derivatives (equation 255)[602,603].



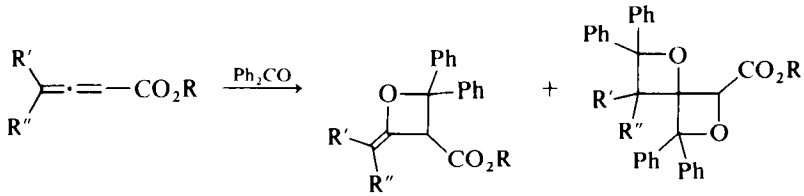
(255)

Glycidyl esters, which are important synthetic intermediates, were stereoselectively prepared from α-halo-β-hydroxyesters upon treatment with sodium ethoxide (equation 256)[604].



(256)

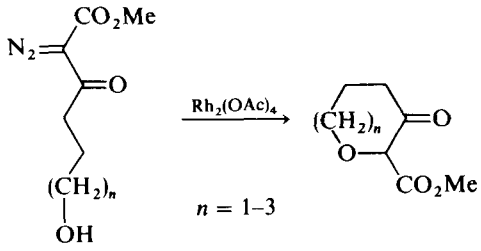
A recent report has indicated that photoaddition of benzophenone to allenic esters gives oxetanes and spirooxetanes, in excellent yields (equation 257)[605].



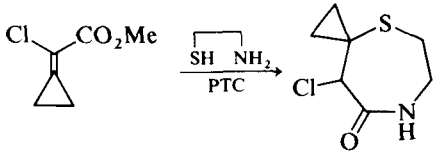
(257)

Cyclization of α-azido-ω-hydroxy-β-ketoesters, catalysed by rhodium(II) acetate, gives ethers with six-, seven- and eight-membered rings (equation 258)[606–608]. Thioethers have been synthesized in a similar fashion[609].

Reaction of methyl 2-chloro-2-cyclopropylidenacetate with various alcohols, thiols and amines has been used to form heterocyclic compounds. In one key reaction of this ester, a seven-membered lactam thioether has been produced by reaction with 2-aminoethanol under phase-transfer conditions (equation 259)[610].

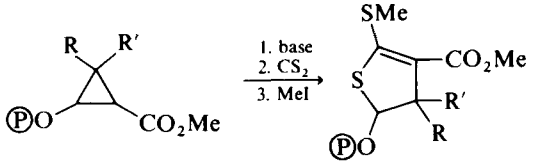


(258)



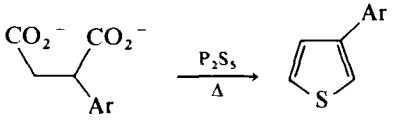
(259)

Reaction of the enolate anion of a hydroxyl-protected cyclopropanecarboxylate with carbon disulphide, followed by treatment with an alkylating agent, has provided a useful route to dihydrothiophene derivatives (equation 260)[602,611]. The product may be easily transformed into thiophene derivatives.



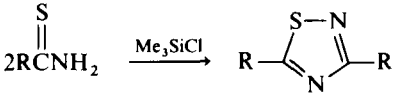
(260)

3-Arylthiophenes may be readily prepared under phase-transfer conditions, by heating 2-arylsuccinate salts with phosphorus pentasulphide (equation 261)[612].



(261)

Finally, an extremely useful synthesis of 3,5-disubstituted-1,2,4-thiadiazoles, present in some pesticide molecules, has been reported which simply requires the treatment of thioamides with chlorine, sulphuryl chloride or sulphur dichloride (equation 262). Yields are significantly improved in the presence of chlorotrimethylsilane[613].



(262)

VI. OTHER SYNTHETIC USES OF CARBOXYLIC ACID DERIVATIVES

Carboxylic acid derivatives are often used in organic synthesis for other reasons than are covered above. The electron-withdrawing abilities of acid derivatives makes them

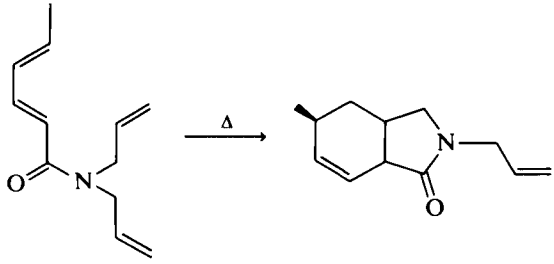
excellent controlling influences on the direction of aromatic substitution and Diels-Alder reactions. The ability of acid derived functional groups, especially amides, to complex metals and hence direct metallations in *ortho*-positions of aromatic rings is also of significant use. The stabilities of some imide anions makes them useful transfer agents for a variety of electrophilic synthons. The availability of enantiomerically pure acids, to prepare and separate diastereomeric ammonium salts, has been used for decades. Some aspects of these uses are discussed in this section.

A. In Diels–Alder Reactions

The Diels–Alder reaction is one of the cornerstones of modern organic synthesis. Electron-withdrawing, e.g. carboxyl-derived, functional groups present in the diene increase the rate of the cycloaddition and alter its regio- and diastereoselectivity. The rate increase is observed if either an electron-rich dienophile is used, or if the electron-withdrawing group is present in the dienophile and the diene is electron-rich[614]. Such choices of diene/dienophile, especially with acid-derived groups, have enhanced the synthetic usefulness of the Diels–Alder reaction. In addition, important target molecules may be synthesized with specific acid-derived groups present in the required locations for further synthetic operations. This important area of carboxylic acid chemistry requires a brief discussion.

The presence of carbomethoxy groups alters the diastereoselectivity of a Diels–Alder reaction. For example, 2-cycloalkenones usually give *endo* products with dienes, but if a carbomethoxy group is present at C-2 then *exo*-addition is either predominant or exclusive[615–618]. The regioselectivity is also affected by the presence of strong electron-withdrawing groups like esters[618].

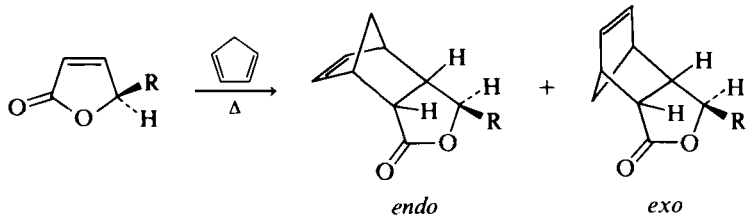
N-Dienyl amides and lactams are extremely useful dienes in the Diels–Alder synthesis of natural products[619]. Such usefulness has been extended by the N-alkylation of these amido compounds with an olefinic group present in the alkylating compound. This then gives a molecule which is able to perform intramolecular Diels-Alder reactions with the stereocontrolled formation of bicyclic compounds in a single step as exemplified in equation 263[620]. The inter- and intramolecular Diels–Alder chemistry of *N*-dienyl amides and lactams has recently been reviewed by Smith[619].



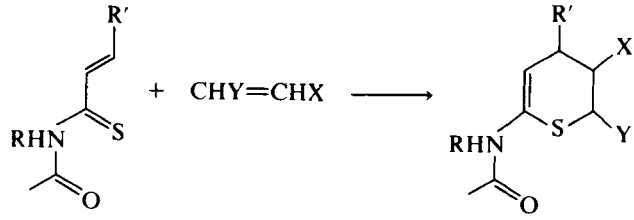
(263)

Chiral butenolides have also received attention in Diels–Alder reactions. Thus, these good dienophilic lactones have been reacted with a wide range of dienes. The selectivity of these cycloadditions has often been found to be kinetically controlled[621]. The reaction of chiral 2(5*H*)-furanones, a butenolide, with cyclopentadiene has been used to generate enantiomerically pure *endo* and *exo* adducts in very good yields (equation 264)[622].

Finally, thiopyran rings, which are present in some natural products with important pharmacological activity, may be easily synthesized by Diels–Alder reactions using acid derivatives[623]. This reaction may be performed both regio- and stereospecifically by



(264)



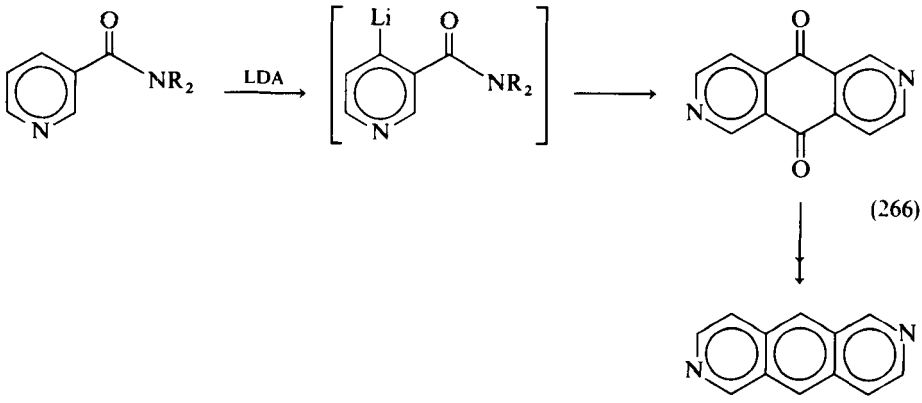
(265)

reaction of N-acylated α,β-unsaturated thioamides with dienophiles (equation 265)[624,625].

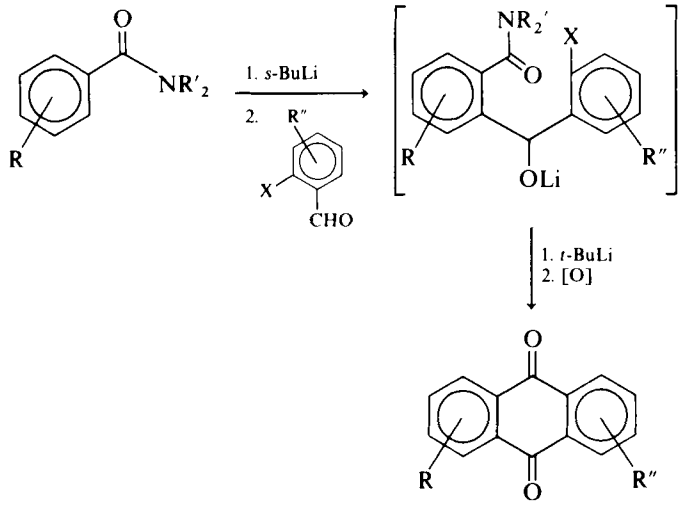
B. In Aromatic *Ortho* Reactions

Carboxyl-derived functional groups, especially amides, directly attached to aromatic rings have an important controlling influence on the course of metallation reactions. These processes are often the key step in the synthesis of condensed aromatic compounds. The presence of an acid derivative directs metallation to the *ortho*-position almost exclusively, often overcoming the electronic effects of ring substituents. This regiocontrol is due to the metal-coordinating abilities of the acid group and has been reviewed[626,627].

Two illustrative examples of this type of reaction follow: (i) A high yielding, convenient, regiocontrolled synthesis of pyrido[3,4-*g*]isoquinolines which occurs via an *ortho*-directed metallation process followed by dimerization, as shown in equation 266[628], and



(266)



(267)

(ii) a regioselective synthesis of substituted anthraquinones which are then useful in the preparation of natural products and dyes (equation 267)[629].

Another *ortho*-directed reaction involving acid derivatives is the *o*-hydroxylation which occurs on heating copper salts of aromatic acids in the presence of hydroxide ions and *o*-amination in the presence of ammonia[630].

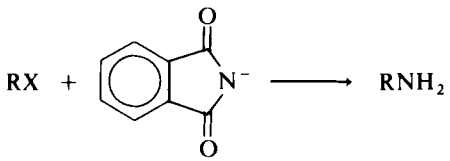
C. As Transfer Reagents

A few carboxylic acid derivatives, such as phthalimide and succinimide, have been used as transfer reagents for a whole range of electrophiles to nucleophilic centres in many synthetic organic operations.

Thus halogen cations are effectively transferred from *N*-bromo- and *N*-chlorosuccinimide. These reagents have been much used for electrophilic halogenations of sulphoxides[631] and at allylic positions[632], for example.

Transfer of sulphenyl sulphur-containing electrophilic species, to compounds with active methylene or methine groups, is also an important use of acid-derived transfer reagents. In this case phthalimides are most often the reagent of choice. Sulphenylation by this method followed by oxidation and elimination of a sulphinic acid moiety is an excellent synthetic route to unsaturated compounds.

It is also important to note that phthalimido anions have been used extensively in the Gabriel synthesis of amines, from alkyl halides (equation 268)[633] or from alcohols[634,635].



(268)

D. Resolution of Chiral Amines

Resolution of amines is a very important process in organic synthesis since often only one enantiomer of a synthetically prepared racemic mixture of an amine exhibits the sought after biological properties[2].

Carboxylic acids have been used in more than a thousand reported cases for the resolution of such racemic mixtures of amines. These have been reviewed by Newman[636] and by Jacques and coworkers[637]. The usual method of resolution consists of using a naturally occurring, optically active carboxylic acid to form a mixture of diastereomeric ammonium salts which are then separated by crystallization. The optically pure amine is then regenerated by basification. More recently, synthetic chiral acids, for example (*S*)-(+)-2-methyl-2-phenylbutanedioic acid, and its enantiomer, have been used since both enantiomers are usually available in contrast to most naturally occurring compounds[638].

VII. ACKNOWLEDGEMENTS

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CHAPTER 12

Vapour and gas-phase reactions of carboxylic acids and their derivatives

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I. INTRODUCTION

When the thermolysis of carboxylic acids and their derivatives was reviewed in this Series over ten years ago[1], emphasis was rightly placed on the use of gas-phase studies to elucidate reaction mechanisms. To this end, much data was analysed and interpreted in terms of linear free-energy relationships and the role of substituents around the reaction centre. It was anticipated that such studies would increase as a result of developments in gas-phase kinetic techniques. The present review confirms that this increase has in fact occurred and the work has been used to extend our knowledge of

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the transition states and reaction mechanisms of a wide variety of carboxylic acid derivatives. The title of the present review, however, enables a wider view of the gas-phase chemistry of these species to be covered than in the previous one. Although the majority of the work discussed here still necessarily involves thermolysis, it has been possible to include also laser-induced reactions which have been increasingly important both in providing deeper understanding of unimolecular reactions and energization processes at the molecular level and also in providing possible synthetic routes, less prone to interference from heterogeneous effects.

Heterogeneous reactions as such have been excluded, although many important industrial processes involving carboxylic acid derivatives in the gas phase which react over solid catalysts are known. The topics which have been included are very much the personal choice of the author and by no means represent a comprehensive coverage of the existing literature. Bimolecular reactions therefore are included only in respect of radical–molecule reactions and in particular of current work on the reactions of hydroxyl radicals with carboxylic acids or esters. These are particularly important in understanding the role of such species in the troposphere and in developing a systematic approach to the problems of environmental pollution. While the present review is concerned largely with experimental data acquisition and interpretation, the large quantity of data required by those workers developing models of atmospheric processes will in future lead to equal advances in the theoretical prediction of unknown rate data. A step in this direction is represented by some of the semi-empirical methods referred to in Section VII.

Reactions between ions and carboxylic acid derivatives have been much studied by mass-spectrometric techniques. Many studies relate to gas-phase acidities and basicities and provide complementary information to data acquired from solution phase studies. These are discussed together with other ion–molecule reactions in Section VIII.

It is hoped that by bringing together accounts of work which at first sight originate from quite disparate fields of chemical research, the common features become more apparent. Electronic substituent effects, for example, which are important in thermolysis, are equally important in the structure–reactivity relationships seen in the attack of OH radicals or in the processes of loss or gain of gas-phase protons. It is hoped also that the relatively few studies reported for derivatives other than esters will stimulate further work in this and other directions in future.

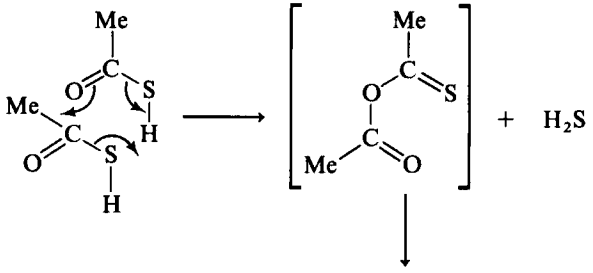
II. THE THERMOLYSIS OF CARBOXYLIC ACIDS

A. Saturated Carboxylic Acids

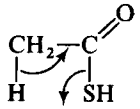
The thermolyses of simple aliphatic carboxylic acids were shown by Blake and coworkers[2–4] to be molecular processes leading to decarboxylation or dehydration. Decarboxylation was shown for acetic acid to involve a four-centred transition state. Dehydration involved a bimolecular six-centred process at lower temperatures and a unimolecular first-order process at higher temperatures. Taylor[5] has studied the thermolysis of diacetyl sulphide at around 600 K to give thioacetic acid in the thiono form, which is thought to equilibrate rapidly to the thiolo form. At these temperatures the acid decomposes rapidly to ketene, H_2S, COS, CH_3SH and methyl thioacetate. By analogy with acetic acid, formation of H_2S and ketene (analogous to dehydration) could proceed by the bimolecular mechanism (reaction 1), but no evidence for such a mechanism was found. The alternative process which, for acetic acid, is more important at higher temperatures involves a four-centred transition state. For thioacetic acid this could lead to reaction 2 or 3.

The observation of H_2S in the products, the non-appearance of thioketene and the

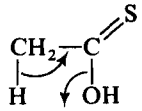
greater bond strength of C—O compared with C—S makes reaction 2 the more likely reaction.



(1)

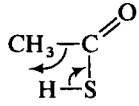


ketene + H_2S (2)



thioketene + H_2O (3)

The production of COS is likely to be accounted for by a process analogous to acetic acid also involving a four-centred transition state and production of methane, namely



$CH_4 + COS$ (4)

Overall, these are complex processes and the work so far reported is incomplete with some uncertainties about the role of surface and radical reactions. Some consideration should be given to the fact that since the value of E_a/RT is relatively low and the thioacetic acid (like the acetic acid molecule) contains only eight atoms, unimolecular processes such as reactions 2 and 4 would be expected to be in their 'fall-off' regions at accessible pressures (see Reference 6, p. 239).

It has been known for some time[7] that the α-fluorinated acetic acids decompose thermally in a different manner from acetic acid giving HF elimination and a carbonyl compound, CO, CO_2 and some minor products. Blake and Shraydeh[8] have investigated the thermolyses of the ethyl, isopropyl and *tert*-butyl esters of trifluoroacetic acid. At the temperatures used (311–413 °C), trifluoroacetic acid which is generated as a primary product decomposes further. Direct decarboxylation is relatively unimportant and the reaction products can be explained by HF elimination (reaction 5) followed by a series of radical steps such as reactions 6, 7, 8 and 9.

$$CF_3CO_2H \longrightarrow HF + {}^{\cdot}CF_2CO_2^{\cdot} \quad (5)$$

$${}^{\cdot}CF_2CO_2^{\cdot} \longrightarrow :CF_2 + CO_2 \quad (6)$$

$${}^{\cdot}CF_2CO_2^{\cdot} \longrightarrow CF_2O + CO \quad (7)$$

$$2{:}CF_2 \longrightarrow C_2F_4 \quad (8)$$

$$2C_2F_4 \longrightarrow C_4F_8 \quad (9)$$

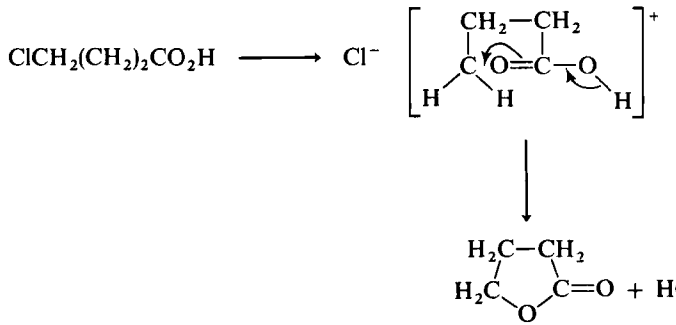
Earlier work[9] on the thermal decomposition of trifluoroacetic acid at 300–390 °C in silica and mild steel vessels showed that HF elimination and production of the biradical $\cdot CF_2CO_2^{\cdot}$ (reaction 5) was followed primarily by decomposition of the latter by step 6 in preference to step 7.

An important reaction of difluorocarbene was found to be its addition to trifluoroacetic acid to give difluoromethyl trifluoroacetate (step 10):

$$:CF_2 + CF_3CO_2H \longrightarrow CF_3CO_2CF_2H \qquad (10)$$

Pola[10] has studied the cw-CO_2 laser-induced SF_6-sensitized decompostition of trifluoroacetic acid. In contrast to the results of conventional thermolysis described above, no evidence for the occurrence of step 10 was found and the decomposition of the biradical by step 7 was found to be much more important than step 6 under conditions of the laser experiments. It was suggested that these experiments are less prone to heterogeneous effects than are conventional thermal studies. While this is likely to be true, there remain some puzzling features of the laser-induced experiments which merit further investigation. One of these is the fact that the ratio COF_2:C_2F_4 in the products decreases with increasing concentration of the SF_6 present. It is suggested that the relative importance of steps 6 and 7 ultimately generating these products could depend upon the energy content of a chemically activated biradical whose production in turn depends upon the concentration of SF_6* present. Such speculation could be tested experimentally by experiments in the presence of deactivators such as inert gases, which would not directly absorb the initial radiation. Relatively low concentrations of deactivators would be required to prevent preferential deactivation of SF_6* but it should be possible to detect whether such inert gases influence the COF_2:C_2F_4 ratio.

Hydrogen halide elimination also occurs from chlorinated and brominated carboxylic acids as was found by Chuchani and coworkers. In the case of 4-chlorobutyric (butanoic) acid, it was expected to be the primary product of thermolysis of the ethyl ester[11] in the temperature range 350–410 °C. Separate thermolysis of the acid in a vessel coated with carbon from allyl bromide thermolysis showed that it decomposes rapidly at these temperatures into butyrolactone and HCl. The observed rate parameters $\log_{10}(A/s^{-1}) = 12.28$ and $E_a = 172$ kJ mol^{-1} are consistent with a restricted transition state. This is likely to be similar to that proposed for the ester itself and so involve an intimate ion-pair in which assistance is provided from the neighbouring carboxyl group for the HCl elimination (reaction 11).



(11)

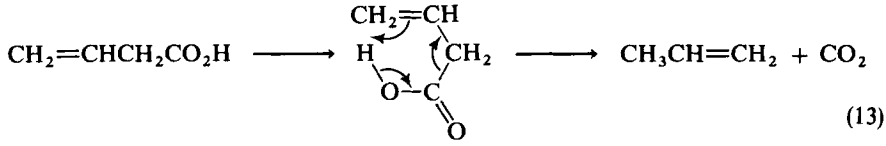
2-Chloropropionic (propanoic) acid has also been studied[12]. At temperatures of 320–370 °C in a seasoned vessel and in the presence of the free radical inhibitor cyclohexene, the thermolysis proceeds with a stoichiometry close to 3.0 as predicted by reaction 12.

$$CH_3CHCO_2H \longrightarrow HCl + CH_3CHO + CO \quad (12)$$
$$\quad\quad |$$
$$\quad\quad Cl$$

α-Propiolactone is not observed, as this is unstable at these temperatures and decomposes into acetaldehyde and CO. The mechanism is probably similar to that suggested above and involves an ion-pair transition state. By contrast, the methyl ester of this acid decomposes much more slowly to methyl acrylate and HCl by a normal four-centred elimination.

B. Unsaturated Carboxylic Acids

Unsaturated carboxylic acids with β, γ double bonds decompose to give alkenes and CO_2 via a six-membered transition state. For the parent molecule but-3-enoic acid this is represented by reaction 13.



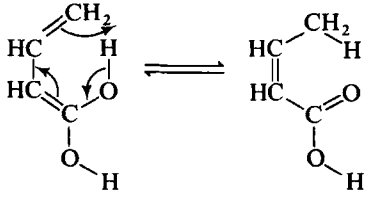
(13)

This transition state is analogous to that which occurs in the thermolysis of esters containing β-hydrogen atoms in the alkyl group and which is fully discussed in Section III.A.

Bigley and Clarke[13] have criticized the earlier kinetic data of Smith and Blau[14] for this reaction and redetermined activation parameters using a flow system. They found $\Delta H^{\neq} = 155$ kJ mol^{-1} and $\Delta S^{\neq} = 43.1$ J mol^{-1} K^{-1} at 658 K [equivalent to $E_a = 160.5$ kJ mol^{-1} and $\log_{10}(A/s^{-1}) = 11.3$]. These values are consistent with reaction 13.

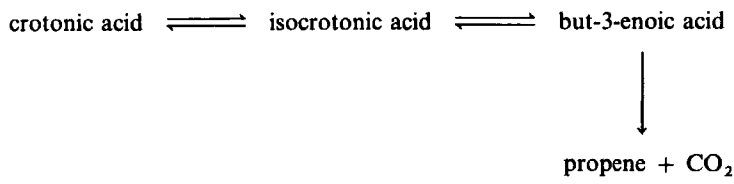
When α,β unsaturated acids are decomposed it was suggested[15] that they first undergo a slow isomerization to the β, γ acid, which then decomposes as in reaction 13.

Bigley and Clarke[13] have investigated this mechanism for but-3-enoic acid which exists in equilibrium with the *cis* and *trans* isomers of the corresponding α,β unsaturated carboxylic acid, namely isocrotonic and crotonic acids. From product measurements as a function of time for up to nine hours during the thermal decomposition of but-3-enoic acid at 593 K, it was found that isocrotonic acid is generated as a primary product which builds up to a maximum of 50% of the remaining acid mixture after about 15 minutes. It was suggested that but-3-enoic acid in the enol form can convert to isocrotonic acid by the 1,5 hydrogen shift in reaction 14. Starting with the stabler *trans*



(14)

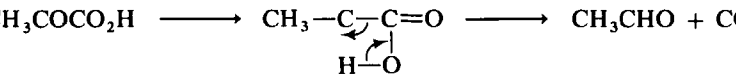
isomer, crotonic acid could convert to the *cis* isomer by normal *trans–cis* isomerization mechanisms. The whole series of reactions is then represented by equation 15. Since, in principle, other suitable α,β unsaturated acids could exist in *cis* and *trans* forms, similar considerations should also apply although none appear yet to have been investigated.



(15)

C. β-Ketoacids

Six-centred transition states can also account for the decomposition products of many β-ketoacids, which yield carbonyl compounds (aldehydes or ketones) and carbon dioxide. When such transition states are not possible, these products may be formed by four-centred transition states. Taylor[16] thus found for pyruvic acid that the reaction



(16)

could be represented by equation 16. The unimolecular first-order reaction at temperatures from 556.8 to 607.4 K was found to be described by the Arrhenius equation

$$\log_{10}(k/s^{-1}) = 13.53 - 172.6\ \text{kJ mol}^{-1}/2.303\,RT \qquad (17)$$

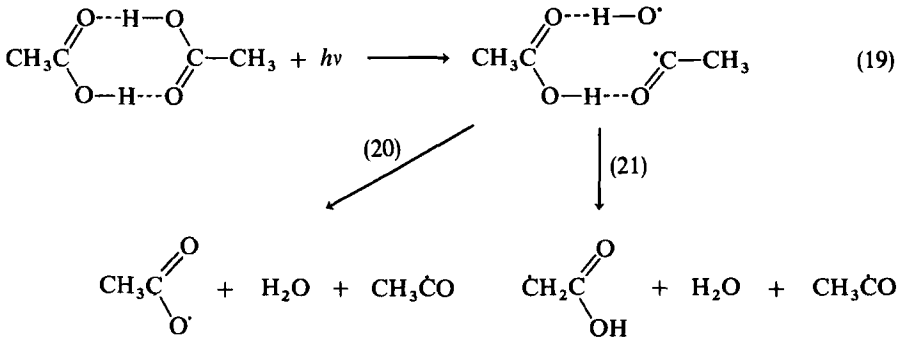
The A and E_a values found contrast with those of Yamamoto and Back[17] ($A = 10^{7.19}\ s^{-1}$, $E_a = 115.9\ \text{kJ mol}^{-1}$) which would appear to be anomalous. It was noted that this compound decomposes more slowly than oxalic acid (in which the CH_3 group of pyruvic acid is replaced by OH). The more electron-withdrawing OH group is able to stabilize, developing partial charge in the transition state. The phenyl group is also more inductively electron-withdrawing than methyl, and benzoylformic acid has been found recently[18] to undergo a comparable reaction to pyruvic acid which is 18 times faster at 600 K. The Arrhenius parameters are $\log_{10}(A/s^{-1}) = 15.3$, $E_a = 177.8\ \text{kJ mol}^{-1}$.

D. Photolysis of Carboxylic Acids

The UV photolysis of simple carboxylic acids and many other carbonyl compounds is due to the absorption of the C=O group and the n–π* transition[19]. Early work showed that the primary photolysis involved both molecular and radical processes. Molecular processes, such as producing CO or CO_2 from formic acid, probably occur by the same four-centred transition states postulated for the thermal decomposition. From work on the photolysis of formic and formic-d_1 acid in the absence and presence of radical scavengers (such as O_2 and C_2H_4), Gorden and Ausloos[20] identified reaction 18 as the most important of the primary photolytic processes producing free radicals.

$$HCO_2H + h\nu \longrightarrow HCO + OH \qquad (18)$$

An analogous process producing OH radicals is known to occur from work on the UV photolysis of acetic acid. These steps have been exploited by Singleton, Paraskevopoulos, Irwin and coworkers who used laser photolysis of carboxylic acids as a source of OH radicals[21–23]. Their work in connection with studies of relevance to atmospheric chemistry is reported later in more detail in Section VII. Vapour-phase photolysis of carboxylic acids is complicated not only by competing molecular and radical processes often leading to the same products, but also by the occurrence of comparable concentrations of both monomeric and dimeric species at low temperatures. At 296 K, for example, according to the equilibrium data of Halford[24] at a pressure of 13 torr HCO_2H is



approximately 67.5% associated into dimers[25]. Singleton, Paraskevopoulos and Irwin[26] have recently conducted measurements for the first time of quantum yields for the production of OH radicals from both the monomers and dimers of formic, acetic and propanoic acid vapours at 222 nm. Photolysis at this wavelength was by use of a pulsed KrCl excimer laser and the OH produced was monitored by time-resolved resonance absorption. The results show that OH production is largely from the monomers with very little produced from the dimers. To explain this observation it was suggested that the OH radical initially produced by C—OH bond fission from the dimer could hydrogen-bond to the carbonyl group producing a biradical. This is shown for the dimer of acetic acid in reaction 19. The biradical could then undergo one of two intramolecular H-abstractions from carboxylic hydrogen (20) or alkyl hydrogen (21). Kinetic evidence[21–23] appears to favour the former.

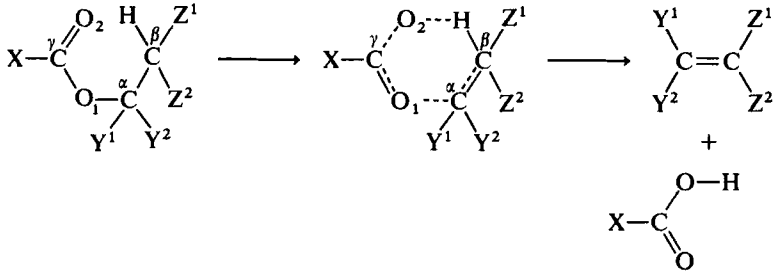
III. THE THERMOLYSIS OF CARBOXYLIC ACID ESTERS

The thermolysis of carboxylic acid esters is one of the most intensively studied areas of research in the history of gas-phase reactions. Many papers have been published since the Second World War and important contributions have been made by Maccoll[27,28], Smith and coworkers[29–33], Taylor and coworkers[34–36], Chuchani and coworkers[37–39] and others. Extensive reviews have also appeared, notably that of Smith and Kelly[40] dealing with structure–reactivity relationships and also the comprehensive review of this topic by Taylor published in this Series[1]. Particularly in view of the latter, it is not essential to cover many of the facets of ester thermolysis in detail, nor all of the detailed arguments in favour of the mechanism of ester thermolysis which is now broadly accepted. A summary of the major conclusions, however, will be given to enable the recent work to be considered and its context appreciated.

A. Esters with Non-vinylic β-Hydrogen Atoms

Carboxylic esters containing non-vinylic hydrogen atoms in the β-position undergo thermolysis via a six-centred cyclic transition state. The reaction may be represented as in equation 22. (The labelling applied to carbon atoms here and later in relation to this transition state follows the convention adopted by previous workers in this field.)

Experiments have shown that in the gas phase these are genuine unimolecular reactions, free from complications of either free-radical reactions or surface effects. It was shown by Maccoll[28] that in contrast to the four-centred elimination reactions undergone by alkyl halides, the thermolyses of esters proceeded by a much less polar transition state. Like alkyl halide thermolyses however, the rates are increased by the

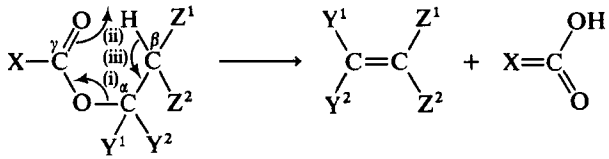


(22)

substitution of electron-releasing groups at the C^{α} carbon atom, although not to such a large extent.

The thermolyses of tertiary esters are faster than secondary, which in turn are faster than primary esters. This effect can be explained in the series: ethyl, isopropyl, *t*-butyl esters, by increasing electron donation stabilizing the incipient carbocation at the α-position. A purely concerted transition state in reaction 22 can be excluded from the observations of substituent effects at each of the three carbon atoms. Substitution of X, Y^1, Y^2, Z^1 and Z^2 by electron releasing or withdrawing groups and interpretation of consequent rate changes enables conclusions to be drawn concerning the extent of polarization of the bonds and charge creation at the 'ring' atoms. The rate enhancement produced by electron-supplying groups Y^1 or Y^2 is consistent with polarization of the C^{α}—O bond creating $C^{\alpha(\delta+)}$—$O^{(\delta-)}$ and this is also increased by increased electonegativity of X. Charges also develop on the carbonyl oxygen and β-hydrogen atoms. It is possible to regard the reaction as an internal elimination (E_i) involving an E2-like attack of the polarized carbonyl group on the acidic β-hydrogen. Another extreme possibility would be to regard polarization of the β-hydrogen as the dominant factor. The observed β-deuterium isotope effect has shown the involvement of the C^{β}—H bond in the transition state and the effect is close to the theoretical prediction for the complete loss of a C—H stretching vibration for primary esters.

It is clear from the the numerous studies of substituent effects and interpretation in terms of Hammett or Taft correlations that the transition state involves some quasi-heterolytic character and that the electronic changes involved in its production are not synchronous. As a result of his detailed review of work up to 1979, Taylor[1] in summarizing the mechanism of these reactions concluded that in producing the transition state, as shown in equation 23, the electron pair (i) has moved further than pair (ii), which in turn then moved further than pair (iii). As a consequence, substituent effects decrease in importance along the series $C^{\alpha} > C^{\gamma} > C^{\beta}$. This distinction becomes more pronounced for more reactive transition states, which are consequently described as more E1-like or more polar.



(23)

In addition to substituent effects which influence electronic changes, the picture is complicated by steric effects which can sometimes act in an opposite sense to electronic effects. The direction of elimination has also been much studied when alternative β-hydrogen atoms are involved. Frequently, since relatively high temperatures are

required to bring about thermolysis, energy differences are relatively unimportant and statistical factors operate, i.e., the relative number of available hydrogen atoms. It is not possible to generalize, however, as other factors may also be important. Although it has been shown that the elimination occurs preferentially with β-hydrogens located *cis* to the carbonyl group, steric factors (in determining the most favourable configuration for the transition state) may affect the *cis–trans* ratio of the alkene produced rather than its inherent thermodynamic stability. Product ratios are therefore generally governed by kinetic rather than thermodynamic control. Careful interpretation and experimental control is essential when attempting to unravel these inter-related effects. Although under genuine homogeneous conditions alkene isomerization is not usually important, it is known to be catalysed by certain surfaces[41,42] and must always be demonstrated to be absent before conclusions are drawn about reaction mechanism.

Recent work on the gas-phase thermolysis of carboxylic esters has largely been undertaken for the purpose of refinement of the mechanistic outline described above, although in some cases new reaction pathways have been discovered. A suitable classification of this work is based on the principal site of substitution in the esters involved.

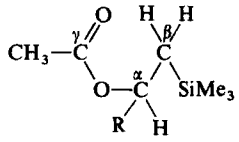
1. Substituent effects at the C^{α} atom

It is well established that electron-releasing groups increase the rate of reaction and electron-withdrawing groups generally decrease the rate of reaction when substituted at the C^{α} atom[43]. As part of a wider study of the effects of trialkyl metal substituents on ester thermolysis, Eaborn, Mahmoud and Taylor[34] studied the effects of electron-releasing substituents in the aryl ring of 1-aryl–2-trimethylsilyl ethyl acetates. The confirmation that the increase in reaction rate constant with increasing electron-releasing ability is primarily due to an electronic effect was provided by the excellent correlation found with the special 'electrophilic' substituent constants σ^{+}. (For an explanation see Reference 44.) The Hammett reaction constant ρ for the series studied was found to be -0.52 at 600 K. A negative value of ρ implies that the reaction is facilitated by increased electron density at the reaction centre which in this case supports the idea of increased stabilization of the incipient carbocation at C^{α}. The effect of the trimethylsilyl group at the C^{β} atom in this series of compounds can be assessed by comparison with similarly substituted 1-aryl ethyl acetates for which a more negative value of ρ (-0.66) was obtained. This could be the result of some stabilization of the C^{α} carbocation *via* hyperconjugation of the $SiMe_3$ group leading to a less polar transition state.

The kinetic results are listed in Table 1. Also shown in Table 1 are some recent results of Chuchani and coworkers[43] for a series of 2-substituted 2-propyl acetates. Rate constants are shown for three substituent groups relative to two-thirds of the rate constant for *t*-butyl acetate. It is seen that the tertiary butyl group produces a large increase in rate constant which is attributed to steric acceleration. The values for the electron-attracting groups CN and CH_3CO produce a diminution in rate, although the general conclusion of these workers is that such groups also exert primarily steric effects. This conclusion must be uncertain since it is based on a Taft correlation[44], but many of the E_s values for the appropriate substituents are unavailable.

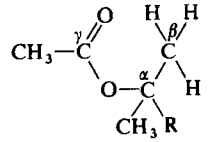
The effect of α-methylation in the series: ethyl, isopropyl, *t*-butyl acetates, has been mentioned previously and explained in terms of increasing stabilization of the incipient C^{α} carbocation. This effect has been found to be enhanced in the more polar transition states associated with thermolysis of the corresponding esters of trifluoro acetic acid[8]. In the case of the *t*-butyl trifluoroacetate, however, the transition state was found to be sufficiently polar for heterogeneous reaction to occur.

TABLE 1. Some kinetic results for esters with C$^{\alpha}$ substituents



1-aryl-2-trimethylsilyl ethyl acetates

R	$\log_{10}(A/s^{-1})$	E_{∞}/kJ mol^{-1}	k(600 K)/$k_{C_6H_5}$	Ref.
C_6H_5	12.52	156.8	1.000	
C_6H_4Me-p[a]	11.85	147.4	1.406	
C_4H_4Me-m	12.44	155.4	1.101	34
C_6H_4Cl-p	12.72	158.9	1.039	
C_6H_4Cl-m	12.62	160.7	0.575	



2-substituted, 2-propyl acetates

R	$\log_{10}(A/s^{-1})$	E_{∞}/kJ mol^{-1}	k(573 K)/k_{CH_3}[b]	Ref.
t-Bu	14.40	171.5	11.4	
CN	12.53	176.1	0.06	43
CO_2Me	14.45	198.7	0.04	
CH_3	13.15	167.4	1	

[a] The major reaction channel is assumed for all aryl groups to give RCH=CHSiMe$_3$ + CH_3CO_2H with a minor contribution from RCH=CH_2 + $CH_3CO_2SiMe_3$ at temperatures above 750 K, analogous to 2-trimethyl silyl ethyl acetate[34]

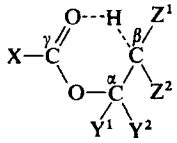
[b] k_{CH_3} is taken as $\frac{2}{3}$ the value of k for t-butyl acetate[45].

2. *Substituent effects at the C$^{\gamma}$ atom*

Whereas alkyl groups at the C$^{\alpha}$ carbon atom can have a major influence on the rate of thermolysis of these esters, the same groups substituted at the C$^{\gamma}$ carbon atom have relatively little effect. In the hope of promoting steric effects Chuchani and coworkers studied a series of isopropyl[46] and ethyl[47] esters substituted with relatively bulky alkyl groups at C$^{\gamma}$. Very little effect upon the rate of thermolysis was observed, as can be seen from the rate constants given in the first few entries in Table 2. Contrary to earlier suggestions it was also clear from this work that no correlation of rate with dissociation constants of the corresponding carboxylic acids is possible.

It is now well established that electron-withdrawing substituents at C$^{\gamma}$ increase the rate of thermolysis and that electron-donating substituents decrease it. Acceleration by the former is ascribed to increasing polarization of the C$^{\alpha}$—O bond and increasing tendency for the development of negative charge at C$^{\gamma}$ which is consistent with the preferential movement of electron pair (i) over electron pair (ii) in the formation of the transition state. Chuchani and coworkers[48] have confirmed this acceleration for a series of isopropyl esters with electron-withdrawing groups in the γ-position. Electronic effects on ester formation and hydrolysis of carboxylic esters in solution substituted by aliphatic groups are commonly evaluated in terms of the Taft σ^* parameter[49].

TABLE 2. Some kinetic results for esters with C^{γ} substituents



$\longrightarrow$ $XCO_2H + Y^1Y^2C{=}CZ^1Z^2$

X	Y^1	Y^2	Z^1	Z^2	$\log_{10}(A/s^{-1})$	E_∞/kJ mol^{-1}	$10^4k/s^{-1}$ (600 K)	Ref.
$C_2H_5CH_2$	H	Me	H	H	13.39	193.7	3.38	
$(CH_3)_2CHCH_2$	H	Me	H	H	13.01	189.5	3.27	
$(CH_3)_3CCH_2$	H	Me	H	H	13.65	197.1	3.11	46
CH_3OCH_2	H	Me	H	H	13.04	187.9	4.83	
$C_6H_5CH_2$	H	Me	H	H	13.63	194.1	5.43	
$(CH_3)_2CHCH_2$	H	H	H	H	12.70	202.5	0.118	47
$(CH_3)_3CCH_2$	H	H	H	H	13.04	207.1	0.103	
CCl_3	H	Me	H	H	13.55	178.3	107	
CCl_2H	H	Me	H	H	12.78	176.2	27.7	48
CH_2ClCH_2	H	Me	H	H	12.57	180.8	6.79	
CF_3	H	H	H	H	12.13	184.0	1.30	8
CF_3	H	Me	H	H	12.70	171.3	61.5	
CH_2F	H	H	H	H	12.57	194.0	0.482	52
CH_2OH	H	H	H	H	12.75	201.4	0.165	
CH_2CN	H	H	H	H	12.29	191.8	0.393	38
$CHCl_2$	H	H	H	H	12.62	193.9	0.552	
CCl_3	H	H	H	H	12.27	185.1	1.44	
$(CH_3)_3C$	$C(CH_3)_3$	H	H	H	13.44	169.1	525	
CCl_3	$C(CH_3)_3$	H	H	H	12.41	141.1	13420	53
$NCCH_2$	$C(CH_3)_3$	H	H	H	11.31	137.8	207	
F	H	H	H	H	12.73	180.6	10.2	
Cl	H	H	H	H	13.04	183.6	11.4	47
Br	H	H	H	H	12.87	181.2	12.5	
I	H	H	H	H	13.84	193.5	9.93	
CH_2Cl	H	H	H	H	12.70	197.0	0.356	
CH_2ClCH_2	H	H	H	H	12.54	196.8	0.256	54
$CH_2ClCH_2CH_2$	H	H	H	H	12.67	198.7	0.236	
C_6H_5	Me	Me	H	H	12.64	159.6	559	
3-Pyridyl	Me	Me	H	H	12.34	154.0	861	
4-Pyridyl	Me	Me	H	H	12.89	158.6	1215	
2-Furyl	Me	Me	H	H	12.12	152.0	775	55
3-Furyl	Me	Me	H	H	12.01	153.5	445	
2-Thienyl	Me	Me	H	H	12.34	153.8	896	
3-Thienyl	Me	Me	H	H	12.01	153.1	482	

For the gas-phase thermolysis of isopropyl esters of mono-, di- and trichloroacetic acids and some previously published results, Chuchani and coworkers[48] found a reasonable correlation of relative rate constants with σ^* parameters with a corresponding reaction constant ρ^* of 0.464 and correlation coefficient $r = 0.963$ at 330 °C.

These workers also re-investigated the thermolyses of isopropyl haloacetates (F, Cl, Br and I) for which previous work[50,51] was considered unreliable due to kinetic analysis based on pressure measurements rather than chromatographic product analysis. The Arrhenius parameters for these compounds re-determined by the latter method are also given in Table 2.

When the Arrhenius parameters for ethyl and isopropyl trifluoro acetates found by Blake and Shraydeh[8] (Table 2) are compared with the corresponding values for ethyl and isopropyl acetates ($\log_{10}A/s^{-1} = 12.5$, E_∞/kJ mol^{-1} = 200; $\log_{10}A/s^{-1} = 13.2$, E_∞/kJ mol^{-1} = 191.2 respectively, see Ref. 1 of the present Ref. 8) it is seen that the principal effect of replacing CH_3 by CF_3 at the C^γ carbon atom is to lower the activation energy by 16–18 kJ mol^{-1}. This is again confirmation of the enhanced rate due to enhanced electron-withdrawing power of CF_3 compared with CH_3.

When polar groups are insulated from the C^γ atom by one or more methylene groups, their effectiveness is diminished although the rates are still enhanced relative to ethyl acetate and an approximate linear relationship between log (k/k_0) and σ^* is found[52]. The rate constants k and k_0 (for ethyl acetate) were measured at 400 °C.

A consequence of increasing electron withdrawal at C^γ is increased polarity of the transition state. This was confirmed by Taylor[1], who showed that Hammett ρ-factors became more negative for 1-arylethyl esters in the order acetates < benzoates < methyl carbonates < phenyl carbonates; this is paralleled by increasing electron withdrawal in the corresponding substituents at C^γ, i.e. $CH_3 < C_6H_5 < CH_3O < C_6H_5O$.

Recent work by Al-Awadi and coworkers[55,58] has extended this type of study to include heteroaryl group substitution at the C^γ carbon atom. A series of *t*-butyl and isopropyl heteroaryl carboxylate esters were prepared and their gas-phase thermolysis rate constants determined. Good first-order rate constant data free from surface effects were recorded and log (k/k_0) values (600 K) where k_0 is the thermolysis rate constant for *t*-butyl benzoate were plotted against 'replacement' σ^0 values of the heterocyclic groups derived from solution-phase measurements[56]. The substituent constant σ^0 defined by Taft[57] is based on the ionization of phenylacetic acid and analogous systems where no conjugation is possible between the aromatic ring and the reaction centre. A good correlation with σ^0 values could therefore indicate that transmission of electronic effects through resonance between substituents and the reaction centre is minimal.

The results for both *t*-butyl and isopropyl esters were also used in an attempt to derive gas-phase σ^0 values. However, the wide variety of these 'replacement' σ^0 values which have been reported for a given heterocyclic substituent, and particularly the doubtful applicability of simple linear free-energy relationships to some of the groups concerned makes the derivation of such gas-phase substituent constants questionable. It has been pointed out previously by Charton[59] that the applicability of the Hammett equation to data sets which include heteroaryl groups by the use of replacement σ^0 constants is at best of limited utility.

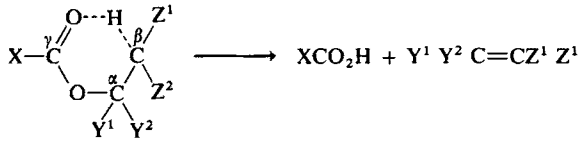
3. *Substituent effects at the C^β atom*

Since breaking the C^β—H bond is relatively unimportant compared with other changes involved in the transition state, substituent effects (with some notable exceptions) are relatively small at the C^β atom. Comparison of the Arrhenius parameters for C^β-substituted esters in Table 3 with those for C^α- and C^γ-substituted esters in Tables 1 and 2 shows that the differences are largely activation energy differences, as most reported A factors lie in the range $10^{12.5\pm0.5}$ s^{-1}.

Much of the recently reported work concerns substituted ethyl acetates and it is easier to compare these in terms of the rate constants relative to ethyl acetate at a common temperature of 623 K. This is shown in Table 4, together with brief comments on the explanation of rate changes suggested by the relevant authors.

In general, alkyl groups produce a small steric acceleration, which is deduced from a good correlation of log (k/k_{EtAc}) against the Taft steric constant E_s[60]. An explanation in terms of relief of strain due to the change in hybridization at C^β from sp^3 to sp^2 in the transition state was earlier put forward by Taylor[67]. The study of the thermolysis of

TABLE 3. Some kinetic results for esters with C^{β} substituents



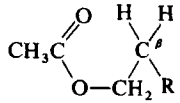
X	Y^1	Y^2	Z^1	Z^2	$\log_{10}(A/s^{-1})$	E_{∞}/kJ mol^{-1}	Ref.
CH_3	H	H	H	^{i}Pr	12.73	202.5	60
CH_3	H	H	H	^{t}Bu	12.34	194.1	
CH_3	H	H	H	^{s}Bu	13.6	211.9	61
CH_3	H	H	H	^{i}Bu	12.8	203.1	
CH_3	H	H	H	^{c}C$_6$H$_{11}$	13.2	207.4	
CH_3	H	H	H	^{c}C$_5$H$_9$	13.3	208.1	
CH_3	H	H	H	Me_2N	13.9	220.4	62
CH_3	H	H	H	MeO	12.0	203.7	
CH_3	H	H	H	MeS	11.3	179.0	
CH_3	H	H	H	Cl	12.1	202.0	
CH_3	H	H	H	F	12.7	211.2	
CH_3	H	H	H	CN	11.5	171.9	
CH_3	H	CH_3	H	^{t}Bu	12.9	181.2	37
CH_3	H	H	H	$CH{=}CH_2$	13.2	200.5	63
CH_3	H	H	H	$CH_2CH{=}CH_2$	13.0	203.6	
CH_3	H	H	H	$(CH_2)_2CH{=}CH_2$	12.4	197.5	
CH_3	H	CH_3	H	$CH{=}CH_2$	12.3	178.2	
CH_3	CH_3	CH_3	H	$CH{=}CH_2$	13.6	169.9	
CH_3	H	H	H	$Me_2C{=}CH$	13.2	200.0	64[a]
CH_3	H	H	H	*o*-MeC_6H_4-	12.5	192.5	65[b]
CH_3	H	H	H	*o*-$MeOC_6H_4$-	12.5	193.0	
CH_3	H	H	H	$SiMe_3$	12.2	175.4	34
CH_3	H	H	H	$SiEt_3$	12.2	173.6	
CH_3	H	H	H	$GeEt_3$	12.4	178.0	
CH_3	H	H	H	$SiMe_2Ph$	12.2	174.8	
CH_3	H	H	H	$CH_2CH_2SCH_3$	12.3	192.1	66

[a] Inhibited by C_3H_6.
[b] Inhibited by ^{c}C$_6$H$_{10}$.

esters with very bulky alkyl groups remote from C^{α} and C^{β} atoms enables steric effects to be studied under conditions when electronic effects are likely to be absent. Many such compounds possessing alternative C^{β}—H atoms for elimination lead to mixtures of alkenes and observed alkene ratios may be compared with statistical and thermodynamic predictions. It is generally concluded[37,68] that the formation of particular alkene products is governed by kinetic rather than thermodynamic considerations and that bulky alkyl– alkyl interactions may hinder the formation of an alkene if these are present in the eclipsed conformation necessary to form the transition state.

When vinyl groups are intoduced at a site remote from C^{β}, steric acceleration is found to occur[63] but the linear correlation of log (relative rate) against E_s breaks down if the vinyl group is directly attached[63,64]. This is attributed to allylic weakening of the C^{β}—H bond.

TABLE 4. Relative rates of thermolysis of some β-substituted ethyl acetates at 623 K



R	(k/k_{EtAc}) at 623 K	Comments	Ref.
H	1.00	Based on the preferred parameters[69] of Blades and Gilderson[70], $\log_{10}(A/s^{-1}) = 12.59$ $(E_\infty/kJ\ mol^{-1}) = 200.8$	67
^{i}Pr	1.00		
^{t}Bu	1.05		
^{s}Bu	1.21	Small steric acceleration	60,61
^{t}Bu	2.07		
^{c}C$_6$H$_{11}$	1.15		
^{c}C$_5$H$_9$	1.26		
$(CH_3)_2N$	0.468		
CH_3O	0.148	Polar groups, rate decrease due to	62
CH_3S	0.347	inductive withdrawal	
Cl	0.258		
F	0.174		
CN	21.6	Strong activation due to mesomeric electron withdrawal in multiply bonded groups	62
CH_2=CH—	4.106	Acceleration due to allylic	63
CMe_2=CH—	5.785	weakening of adjacent C$^\beta$—H bond	64
CH_2=CH—CH_2—	1.51	Steric acceleration	63
CH_2=CH—$(CH_2)_2$—	1.229		
CH_3S—CH_2—CH_2	2.77	Steric acceleration	66
$SiMe_3$	55.3		
$SiEt_3$	78.3	Strong activation by a combination	34
$GeEt_3$	52.9	of charge stabilization and steric	
$SiMe_2Ph$	62.1	acceleration	

Inductive electron withdrawal by a number of polar groups substituted at C$^\beta$ produces a decrease in the rate and an approximately linear correlation with the parameter σ^* has been found[62] in confirmation of earlier work and in agreement with the development of an electron-deficient reaction centre.

When electron withdrawal is due to a mesomeric effect associated with multiply-bonded or π-bonded substituents, however, a strong activation is observed and the CN group[62] has been found to resemble CH_3CO—, CH_2=CH— and CH≡C— in this respect.

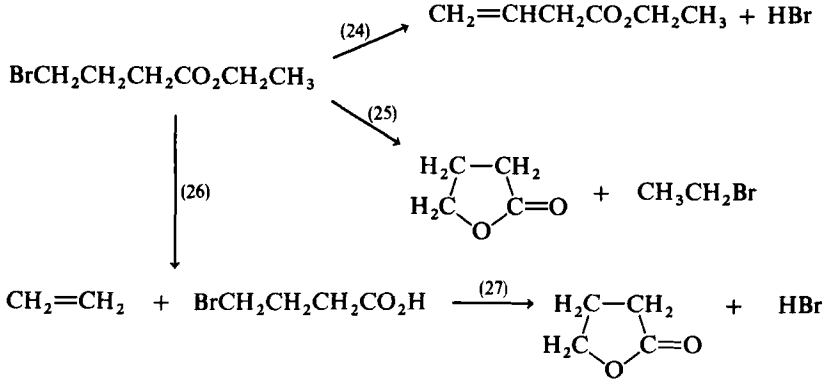
Eaborn, Mahmoud and Taylor[34] have shown that β-trialkyl metal groups can exert a very strong activating effect as is obvious from the relative rate data in Table 4. The effect may be attributed to a number of factors such as stabilization of the incipient β-carbanion thus increasing the C$^\beta$—H acidity, stabilization of the α-carbocation by C—X hyperconjugation and also by steric acceleration. This work highlights the difficulty of distinguishing these factors when they may operate concurrently.

B. Other Esters and Related Compounds

Most of the examples considered in the previous section have been alkyl, aryl or substituted alkyl or aryl esters for which the primary if not the sole mode of decomposition is that producing alkene (or arene) plus carboxylic acid via a six-centred transition state (reaction 22). Other esters such as those involving unsaturated groups like vinyl or allyl esters, some halogeno esters and esters without β—H atoms in alkyl groups show a variety of other types of decomposition. These will now be considered in the context of recently published work and previous studies of decomposition reactions for the various types of compound.

1. Halogeno esters

Complications arise when esters contain halogeno-alkyl groups from which hydrogen halide can be eliminated by the well-known four-centred mechanism exemplified by the thermolysis of ethyl chloride[71]. Chuchani and coworkers have investigated the thermolyses of a number of ethyl and methyl esters of ω-chloro- and ω-bromo-carboxylic acids. In the thermolysis of ethyl 4-bromobutyrate[72] a number of parallel and consecutive reactions were identified as outlined in Scheme 1.



SCHEME 1

Step 26 occurs by the six-centred unimolecular process typical of esters containing a β-hydrogen atom. Bromobutyric acid, however, is unstable in this temperature range and is known to decompose (see Section II.A) to butyrolactone and hydrogen bromide.

Step 24 is the 'normal' elimination for HBr from an alkyl bromide. Lactone formation (Step 25) is evidence for neighbouring-group participation in the elimination of the bromine atom, which is eliminated as ethyl bromide. This direct route to lactone formation, probably through an intimate ion-pair mechanism, was not considered likely for ethyl 4-chlorobutyrate since the chlorine atom is not as good a leaving group as bromine and elimination of ethene and 4-chlorobutyric acid followed by decomposition of the latter to the lactone and HCl (analogous to Steps 26 and 27) was considered to be the preferred route[11].

These ideas have been further developed for a series of methyl esters of ω-chloro carboxylic acids[73], where the elimination to form alkene is not possible structurally. For

methyl 3-chloropropionate the major reaction was found to be the production of methyl acrylate and HCl (reaction 28)

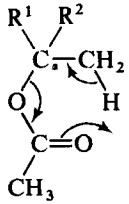
$$ClCH_2CH_2CO_2CH_3 \longrightarrow CH_2{=}CHCO_2CH_3 + HCl \qquad (28)$$

with a small amount (ca 0.6–0.7%) of viny chloride arising as a by-product of decomposition of the acrylate. No propiolactone was found in the temperature range used (410–490 °C). This is consistent with the results of a recent study of the thermolysis of propiolactone[74] which shows that propiolactone decomposes into ethene and carbon dioxide with a rate constant higher by a factor of 10^3 at temperatures over 100 °C lower than those employed in decomposition of methyl 3-chloropropionate.

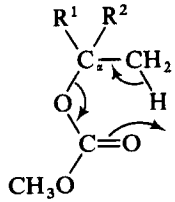
The Arrhenius parameters first reported[73] for the various modes of decomposition of these methyl esters have been shown to be in error. The reactions are influenced by surface effects and the occurrence of radical-chain processes. A re-investigation[75] using vessels seasoned with allyl bromide and excess of the radical inhibitor propene has provided more reliable data, which are given in Table 5.

The anchimeric assistance of the carboxymethyl group in the thermolysis of these halogeno methyl esters *via* an intimate ion-pair mechanism is further supported by results for the unsaturated ester methyl 4-bromocrotonate[76]. The high rate of thermolysis of this compound by parallel reactions leading to HBr elimination or lactone formation has been attributed to stabilization of polarization of the allylic C—Br bond in the transition state.

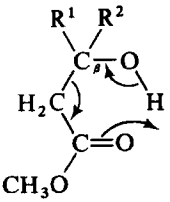
The thermolysis of β-hydroxyesters was first studied systematically by Yates and coworkers[77]. The thermolysis proceeds by a six-centred transition state to yield ultimately a ketone and an alkyl ester as indicated in Table 5. The data for some methyl 3-hydroxyalkanoates (31) obtained by Taylor and coworkers[78] show that the spread of rates on increasing methyl substitution at the β-carbon atom is much less than that in C^{α}-substituted alkyl acetates[1] (29) or alkyl methyl carbonates[79] (30). This can be attributed to a much lower polarity of the C—CH_2 bond in comparison with the C—O bond in the last two groups of compounds. The transition states are formally similar as shown below.



Alkyl acetates
(29)



Methyl carbonates
(30)

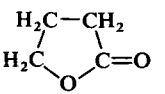
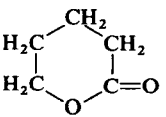
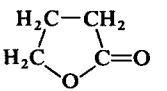


Methyl β-hydroxyalkanoates
(31)

The reduced polarity results in an increased importance in the transition state for nucleophilic attack of the carbonyl group on the O—H hydrogen atom in β-hydroxy esters. Comparisons of rates can also be made with other compounds of related structure, which are, however, outside the scope of this review. Taylor and coworkers have thus studied also β-hydroxyalkenes and β-hydroxyketones[78].

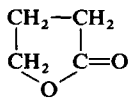
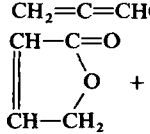
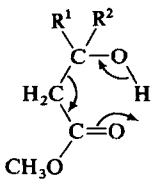
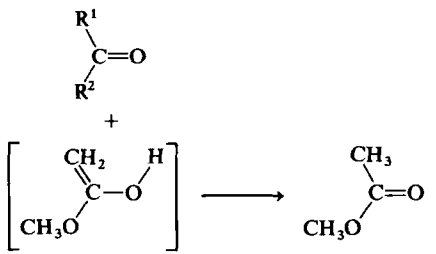
Similar considerations have arisen when the thermolysis of *vinyl acetate* is compared with that of acetic anhydride. An early report[80] that vinyl acetate is virtually stable at 420 °C was not confirmed by Taylor[81], who found the rate parameters given in Table 5 on heating this compound between 636.4 and 721.7 K. The expected mode of decomposition (reaction 32) to give ketene and acetaldehyde, however, plays only a

TABLE 5. Kinetic data for some other esters and related compounds

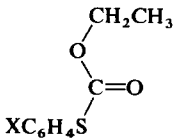
Reactant	Product(s)	$\log_{10}(A/s^{-1})$	E_a/kJ mol^{-1}	Ref.
Halogeno esters				
$ClCH_2CH_2CO_2CH_3$	$CH_2{=}CHCO_2CH_3 + HCl$	13.22	231.5	73
$ClCH_2CH_2CH_2CO_2CH_3$	$CH_2{=}CHCH_2CO_2CH_3 + HCl$ $CH_3CH{=}CHCO_2CH_3$	12.95	224.3	75[a]
		12.82	223.0	
$ClCH_2CH_2CH_2CH_2CO_2CH_3$	$CH_2{=}CHCH_2CH_2CO_2CH_3$ $CH_3CH{=}CHCH_2CO_2CH_3$ $CH_3CH_2CH{=}CHCO_2CH_3$ + HCl	12.98	229.3	
		12.83	226.2	
$BrCH_2CH_2CH_2CO_2CH_3$	$CH_2{=}CHCH_2CO_2CH_3$ $CH_3CH{=}CHCO_2CH_3$ + HBr	12.62	210.5	39
		12.59	210.8	
$Br(CH_2)_4CO_2CH_3$	$CH_2{=}CH(CH_2)_2CO_2CH_3$ $CH_3CH{=}CHCH_2CO_2CH_3$ $CH_3CH_2CH{=}CHCO_2CH_3$ + HBr	13.50	228.9	39
	δ-valerolactone + CH_3Br	13.51	228.3	

(*continued*)

TABLE 5. (*continued*)

Reactant	Product(s)	$\log_{10}(A/s^{-1})$	E_a/kJ mol^{-1}	Ref.
$Cl(CH_2)_3CO_2CH_2CH_3$	$[ClCH_2CH_2CH_2CO_2H] + CH_2{=}CH_2$ →  + HCl	12.21	197.6	11
$BrCH_2CH{=}CHCO_2CH_3$	$CH_2{=}C{=}CHCO_2CH_3$ + HBr  + CH_3Br	13.45 12.11 13.30[c]	190.6 175.3 185.2[c]	76[b]
β-Hydroxy esters				
				
R^1 / R^2: H / H; H / CH_3; CH_3 / CH_3		11.1[d] 10.9 11.18	178.01[d] 164.4 159.9	78
Vinyl acetate	$CH_2{=}C{=}O + CH_3CHO$ $(CH_3)_2CO + CO$	10.43	182.4	81

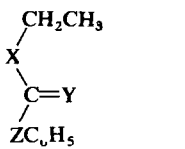
S-aryl O-ethyl thiocarbonates



$C_2H_4 + CO_2 + XC_6H_4SH$

X=H		12.7	195.4	89
X=4-MeO		12.6	193.9	
X=2-MeO		12.4	191.8	
X=4-Me		12.8	197.0	
X=4-Cl		12.5	191.2	
X=3-Cl		12.4	189.1	
X=4-NO_2		12.5	189.2	

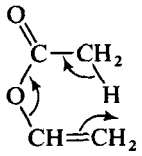
Mono, Di- and Trithiocarbonates



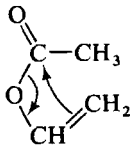
Z	Y	X				
O	O	S	$CH_2{=}CH_2 + PhOH + COS$	10.75	190.7	[e]
O	S	O	$CH_2{=}CH_2 + PhOH + CSO$	11.73	198.3	[f]
O	S	S	$CH_2{=}CH_2 + PhOH + CS_2$	13.02	201.3	[g] 90
S	S	S	$CH_2{=}CH_2 + PhSH + CS_2$ also $PhSEt + CS_2$	11.11	183.9	

[a] Inhibited by propene.
[b] Inhibited by toluene.
[c] Overall parameters.
[d] Some concurrent dehydration occurs.
[e] Low values of $\log_{10}(A/s^{-1})$, E_a and stoichiometry indicated some concurrent nucleophilic substitution (reaction 38).
[f] Evidence for some elimination from $PhOCOSC_2H_5$ produced by reaction 39.
[g] Some nucleophilic substitution occurs (reaction 38).

minor role and most of the reaction occurs via a four-centred transition state to give carbon monoxide and acetone (reaction 33). From the overall Arrhenius parameters (Table 5) it is estimated that the rate of reaction 32 is about 7500 times slower per β-hydrogen than that of acetic anhydride at 600 K. It was concluded that, as in the case



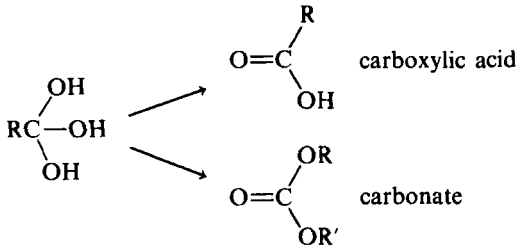
$$\longrightarrow \quad O{=}C{=}CH_2 + CH_3CHO \qquad (32)$$



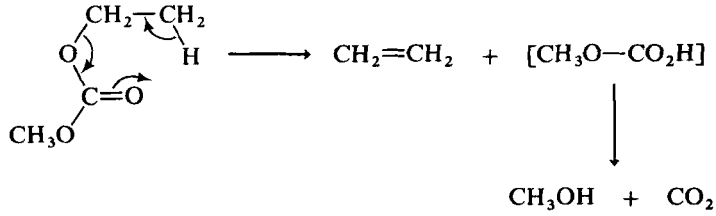
$$\longrightarrow \quad [CH_3COCH_2CHO] \longrightarrow (CH_3)_2CO + CO \qquad (33)$$

of β-hydroxyesters, the most important step in the transition state is breaking the β C—H bond. Acetic anhydride, on the other hand, which has a very polar C^{α}—O bond, shows a high rate of thermolysis[82] dominated by C^{α}—O breaking.

The thermolysis of *carbonates* is related to that of carboxylic esters, since both carbonates and carboxylic acids may be regarded as derivatives of the hypothetical trivalent *ortho* carboxylic acid $RC(OH)_3$, namely

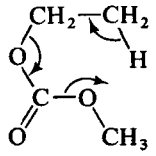


The thermolysis of carbonates was little studied until recently and early results for the simple alkyl carbonates[83,84] gave conflicting kinetic data. Taylor[1] has compared the thermolyses of carbonates, carbamates ($RNHCO_2R'$) and acetates and concluded that the rates decrease in the series carbonates > carbamates > acetates, due primarily to decreasing electron-withdrawal at the C^{γ}-atom in this sequence.



(34)

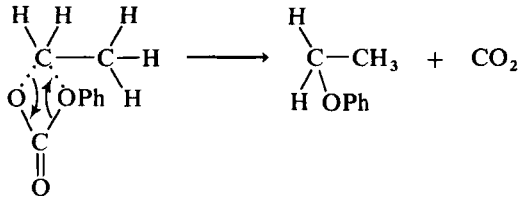
The reaction is described for alkyl methyl carbonates by reaction 34. In principle, an alternative mechanism (reaction 35) is possible but this is not supported by most of the experimental evidence available from substituent effects on aryl ethyl carbonates[85], and



$$\longrightarrow \quad CH_2{=}CH_2 \quad + \quad CH_3OH \quad + \quad CO_2 \qquad (35)$$

from comparison with data for carbamates[86]. In general, it is found that carbonates and carboxylic acid esters containing replaceable β-hydrogen atoms are thermolysed by similar mechanisms, although the instability of the acid produced in reaction 34 leads to rapid decomposition to alcohol and carbon dioxide. Accordingly, it would be expected from the effect of electron-withdrawing groups at the C^{α}-atom previously described that methyl alkyl carbonates would be less reactive than phenyl alkyl carbonates. Discrepancies in the data reported for the rate constant for ethyl methyl carbonate[83,87] led Taylor[79] to re-investigate the thermolysis of a series of alkyl and dialkyl carbonates over a 50 K range around 600 K. Relative rate constants at 600 K were found to be in the sequence ethyl:isopropyl:*t*-butyl, 1:29.6:2934. These values on comparison with similar ratios for a number of other esters showed the rates of the ethyl and isopropyl carbonates to be anomalously high. It was suggested that, since the transition states are less polar for these carbonates, β-carbon–hydrogen breaking may be relatively more important, and attack of the nucleophilic carbonyl group on the β-hydrogen atom the dominant factor.

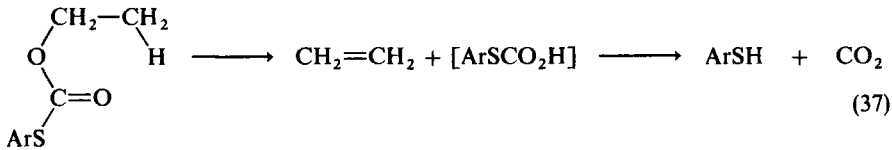
A complication which can arise in certain carbonate decompositions is the occurrence of a competing concurrent reaction involving a four-centred transition state (reaction 36). This reaction for ethyl phenyl carbonate was found[88] to occur slowly on a glass



(36)

surface at 175 °C to yield the product phenetole as well as the expected phenol in the ratio 2:1. Ethyl *p*-nitrophenyl carbonate was shown to be even more reactive, producing *p*-nitrophenetole as the major product at the same low temperature, although only *p*-nitrophenol at about 450 °C. It is therefore possible that some of the discrepancies found as a result of early studies on aryl ethyl carbonate decompositions could have been due to the occurrence of surface reactions.

A number of studies have been carried out in order to determine the effect of replacing oxygen in carbonates by sulphur. Al-Awadi and Taylor[89] have studied a series of *S*-aryl *O*-ethyl thiocarbonates which decompose according to reaction 37 between 671.4 and 722.6 K. The results were compared directly with the earlier results of Smith, Jones and Taylor[85] for aryl ethyl carbonates. These workers found a good correlation between



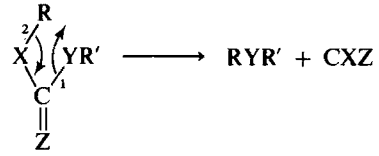
(37)

log (relative rate constant) and Taft's σ^0 values as was found for a number of other esters substituted by electron-withdrawing groups in the C^γ-position[1].

Use of the ethyl compounds in the two series of compounds meant that it could reasonably be assumed that the transition state polarities were similar. The Hammett ρ function is therefore a measure of the effectiveness of the system in transmitting electron effects. A ρ value of 0.30 (600 K) for the *S*-aryl compounds compared with 0.20 (600 K) for the O-aryl compounds indicates that sulphur appears to be a better transmitter of electronic effects than oxygen in this context. The rates for the sulphur-containing compounds were, however, found to be lower than for oxygen-containing compounds with the same substituent, since the inductive withdrawal of SAr is less than that of OAr.

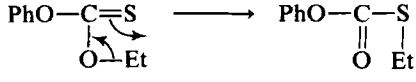
In a comprehensive study of a series of alkyl phenyl carbonates Al-Awadi and Taylor[90] have studied replacement of up to three atoms of oxygen by sulphur. The resulting rate parameters are given in Table 5 from which some general trends and conclusions may be derived. The results in general are explicable in terms of the relative polarities of the transition states under comparison. Comparison of carbonates with acetates can be explained in terms of increased polarity of the transition states for the former. Within a given class of compound the isopropyl derivatives have more polar (E1-like) transition states than the ethyl derivatives. In thermolyses involving polar transition states C^α—O bond breaking dominates, and replacement of this oxygen by sulphur is more influential on the rate (producing a decrease) than is replacement of C=O by C=S. In the case of reactions with less polar transition states, the high nucleophilicity of C=S compared with C=O can be the dominant factor.

Other secondary reactions were also found to occur. For *S*-ethyl *O*-phenyl thiocarbonate a nucleophilic substitution reaction to produce ethyl phenyl ether was observed. This is analogous to the surface-catalysed reaction for ethyl phenyl carbonate described earlier[88]. The four-centred reaction, which may be written generally as in reaction 38, was deduced to occur in a manner such that electron pair 1 moves before electron pair 2, i.e., C—Y bond breaking is more important than R—X breaking. Evidence for the occurrence of this mechanism in the case of *S*-ethyl *O*-phenyl thiocarbonate, apart from product formation, was the low stoichiometry and Arrhenius parameters compared with the normal mode of thermolysis of carbonates.

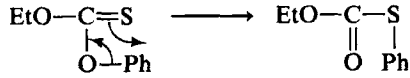


(38)

Evidence was also obtained for a different reaction path in the thermolysis of *O*-ethyl, *O′*-phenyl thiocarbonate. This showed a much slower rate than predicted by the normal mechanism and suggested that a thion to thiol rearrangement was occurring. In principle, two mechanisms could occur: reaction 39 or reaction 40. It was found that only reaction 39 occurred and rate measurements suggested that the overall rate was due to a slow elimination arising from the product of reaction 39 with a small contribution from the rapid decomposition of the starting material.



(39)



(40)

IV. LASER-INDUCED DECOMPOSITION OF ESTERS

The use of lasers to bring about chemical reactions, and in particular the use of infrared multiphoton absorption (IRMPA), has been the subject of many recent reviews. Of particular relevance to the unimolecular decomposition of esters are the reviews of Ashfold and Hancock[91], Danen and Jang[92] and Quack and Lupo[93].

Most of the work described in Section III concerned the elucidation of details of the mechanism of the thermolysis of esters and related compounds by interpretation of substituent effects. The 'well-behaved' nature of many of these thermolyses has also led to interest in them in connection with theories of gas-phase unimolecular reactions[6]. Most are found to be genuine unimolecular gas-phase processes free from competing free-radical pathways and surface effects. The use of multiphoton infrared laser excitation enables a detailed study of inter- and intramolecular energy exchange processes to be carried out at low pressures. When this is coupled with theoretical rate-constant calculations, the assumptions behind unimolecular rate theories can be tested. Laser excitation also initially appeared to offer the possibility of mode-selective chemistry in permitting excitation to very specific energy levels of reactant molecules by use of narrowly-defined incident radiation. Recent results, however, have shown that rapid intramolecular relaxation processes make such a possibility difficult to realize in practice.

One example of a detailed study of infrared laser-induced absorption and reaction of organic esters is that of Danen, Rio and Setser[94]. These workers studied the decomposition of ethyl acetate, ethyl fluoroacetate, ethyl acrylate, n-butyl acetate, *sec*-butyl acetate and ethyl-2-bromopropionate. All of these esters possess β-hydrogen atoms which are involved in the usual six-centred transition state to yield the corresponding carboxylic acid and alkene. Gaseous samples with pressures ranging from 0.05 to 1.0 torr were irradiated using the P20 (1046.85 cm^{-1}) and P38 (1029.44 cm^{-1}) lines from a pulsed TEA CO_2 laser. The pure reactants were mixed with 5% isopropyl bromide, which eliminates HBr with comparable Arrhenius parameters to those of ethyl acetate and functioned as a thermal monitor to distinguish laser-induced from purely thermal reaction[95]. The results were expressed in terms of absorption measurements and reaction probabilities. Absorption measurements showed that the absorption cross-section σ_L defined by the equation

$$\sigma_L = \frac{2.303}{lN} \log \frac{\phi}{\phi_0} \tag{41}$$

(where l is cell length and N the molecular concentration, ϕ and ϕ_0 the transmitted and incident fluence) was independent of pressure, and hence Beer's law was obeyed. Reaction probability $P(\phi)$ for a given laser fluence ϕ is defined as the number of molecules in the irradiated volume that react per pulse divided by the total number of molecules in the irradiated volume. Product analyses after a number of ca 130 ns pulses were done by gas liquid chromatography.

The results for ethyl acetate and ethyl fluoroacetate were considered to be more reliable than those of the other compounds studied and were used for detailed kinetic modelling. Experiments with the 'thermal monitor' present showed that thermal reaction was negligible at pressures below 0.1 torr. At higher pressures the reaction probability

was found to increase due to an increasing proportion of intermolecular collisional energy transfer. In the presence of added deactivating gases, decreases in the reaction probability occurred similar to those observed in chemical activation experiments. One interesting result was the dependence of reaction probability for a given amount of absorbed energy on the laser frequency. This was shown by comparison of the effects of the alternative *P*(38) and *P*(20) laser lines. A possible explanation for this would be slow intramolecular energy randomization, but this was rejected in favour of the more plausible explanation that different fractions of molecules actually absorb the laser energy when irradiated at either of the two wavelengths used. Further evidence for rapid intramolecular energy transfer was provided by the laser decomposition of *sec*-butyl acetate which occurs according to equation 42. Purely statistical considerations would produce 60% but-1-ene and 40% of a 1:1 mixture of *cis* and *trans* but-2-ene.

$$CH_3\overset{\overset{O}{\|}}{C}OCH(CH_3)CH_2CH_3 \longrightarrow CH_3CO_2H + \begin{cases} CH_2{=}CHCH_2CH_3\ (53 \pm 4\%) \\ \textit{trans}\ CH_3CH{=}CHCH_3\ (28 \pm 3\%) \\ \textit{cis}\ CH_3CH{=}CHCH_3\ (19 \pm 1\%) \end{cases} \quad (42)$$

The observed ratios shown above which are close to the statistical prediction were found to be unchanged when the laser-induced reaction was repeated at the same total pressure but in the presence of 90% SiF_4 sensitizer. Similar, but somewhat less reliable results, were obtained for the multi-channel decomposition of ethyl 2-bromopropionate according to reactions 43 and 44. In this case complications arose due to secondary decomposition of ethyl acrylate.

$$CH_3CH(Br)\overset{\overset{O}{\|}}{C}OCH_2CH_3 \rightarrow CH_3CH(Br)CO_2H + CH_2{=}CH_2 \quad (43)$$

$$CH_3CH(Br)\overset{\overset{O}{\|}}{C}OCH_2CH_3 \rightarrow HBr + CH_2{=}CHCO_2CH_2CH_3 \quad (44)$$

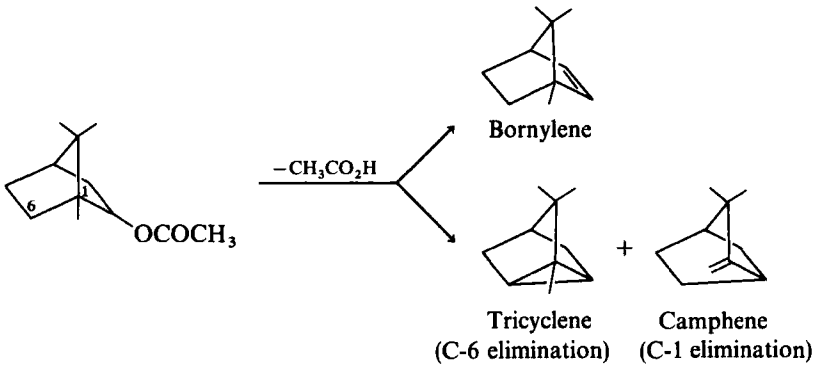
Theoretical modelling of the laser energy absorption, collisional energy transfer and unimolecular reaction steps can be done in terms of the so-called 'master equation' (see Reference 6, Chapter 10). Necessary energy-dependent rate constants for this purpose can be estimated by the standard methods of RRKM theory[6]. Agreements between calculated and observed reaction probabilities for ethyl acetate and ethyl fluoroacetate was obtained in this way[96] on the assumption that only a certain fluence-dependent fraction of the molecules absorbed the laser radiation. Laser-induced reactions of ester decompositions have thus provided much information about the fundamental processes of light absorption and inter- and intramolecular energy transfer of great importance to chemical reactions in the gas phase.

Experiments involving laser-induced decompositions of a rather different kind and for a different purpose have recently been carried out by Pola and coworkers[97,98]. These workers have employed the technique known as 'laser-powered homogeneous pyrolysis'[99] in which a continuous-wave infrared laser is used to heat an unreactive bath gas which then transfers energy by collision to the substrate. The advantage of this technique is that it enables reactions normally subject to surface catalysis to be studied under more nearly homogeneous conditions with fewer side products.

Whereas the transition state in the 'normal' *cis* 1, 2-elimination of esters is generally considered to be less polar than in solution, it is well known that a range of polarities exists, with reactions showing corresponding variation from E_i-like to *E*1-like beha-

viour[1]. When a high degree of polarity exists, as for example in some of the halogeno esters studied by Chuchani and coworkers[73,75,76], it has been suggested that ion-pair transition states occur, as in some alkyl halides, and anchimeric or neighbouring-group participation is found to occur.

Increased charge separation may be stabilized by reactor surface participation and some previous studies, where the possibility of active surfaces existed, could not be interpreted unambiguously in terms of purely homogeneous gas-phase reactions. Such considerations led Sedlácková and Pola[98] to re-investigate the thermolysis of isobornyl aceteate by cw-laser irradiation in the presence of SF_6 sensitizer in order to study the reaction under truly homogeneous conditions. Previous work on bornyl and isobornyl esters[100,101] showed the existence of bornylene (a product of the normal *cis* elimination) together with tricyclene and camphene which would be produced by elimination of neighbouring groups in the C-1 and C-6 positions (reaction 45).

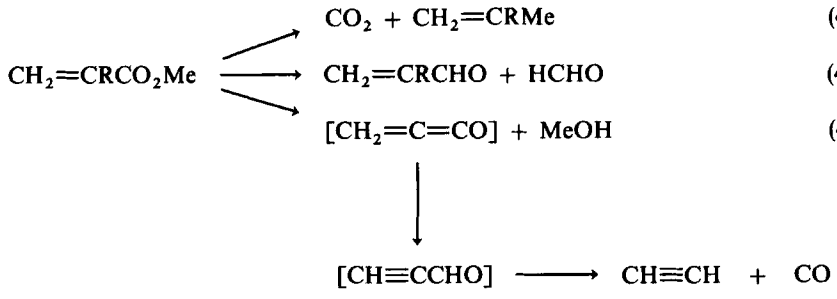


(45)

In the laser work, cyclohexyl acetate was co-decomposed into cyclohexene and acetic acid. Since the Arrhenius parameters for this decomposition are known, it can act as a thermal marker. Measurements of the total rate constant at various 'effective temperatures' gave Arrhenius parameters $A = (3 \pm 12)\ 10^{15}\ s^{-1}$ and $E_a = (220 \pm 20)$ kJ mol^{-1} compared with $A = 4.36 \times 10^{11}\ s^{-1}$ and $E_a = 176$ kJ mol^{-1} obtained previously by conventional thermolysis in a vessel coated with pyrolytic carbon[101]. It is known that carbon-coated vessels can in some circumstances be catalytically active and cannot be assumed to be inert[41]. The discrepancy found here could be attributed to the occurrence of some heterogeneous reaction occurring in a carbon-coated vessel. More detailed kinetic analysis showed that the rearranged products tricyclene and camphene are produced at a faster rate than bornylene at the higher temperatures used. A rapid retro-Diels–Alder reaction of bornylene producing initially ethene and 1,5,5-trimethylcyclopentadiene also occurs, although a number of other products result from further isomerization of the latter as well as from further reactions of camphene and tricyclene.

Similar work on the cw-laser-induced SF_6-sensitized decomposition of the unsaturated esters methyl acrylate and methyl methacrylate[97] also revealed differences from conventional thermolysis studies[102]. In the latter, the major decomposition channel is decarboxylation (reaction 46) with minor contributions from acyl-oxygen (reaction 47) and alkyl-oxygen (reaction 48) fissions.

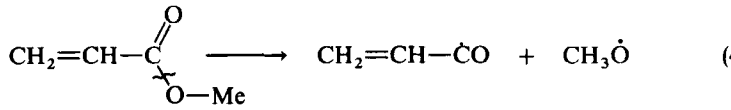
In the cw-laser study using the retro-Diels–Alder reaction of cyclohexene as a thermal marker, channel 47 producing acrolein or methacrolein and formaldehyde was found to



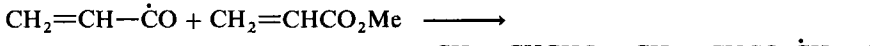
(46)
(47)
(48)

(Methyl acrylate R = H, methyl methacrylate R = Me)

predominate. This process can occur as a radical chain reaction, e.g. for methyl acrylate by the following steps 49–51:



(49)



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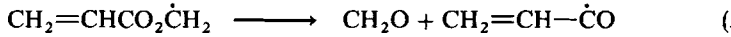
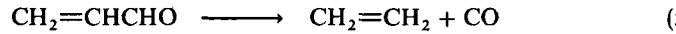


(51)

plus termination processes

Further decarbonylation of the acrolein by reaction 52 also occurred.



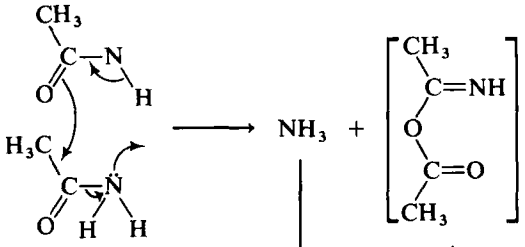
(52)

It was suggested that the cyclohexene used as a thermal marker functioned also as a radical chain inhibitor, so that the derived Arrhenius parameters for the total rate constant represent the initial fission into radicals (reaction 49). The values found, $\log_{10}(A/s^{-1}) = 16.8$ and $E_a = 316$ kJ mol^{-1}, are indeed close to those predicted for this type of process although the errors involved in the temperature estimation must lead to wider actual error limits than those derived from the reproducibility of the data.

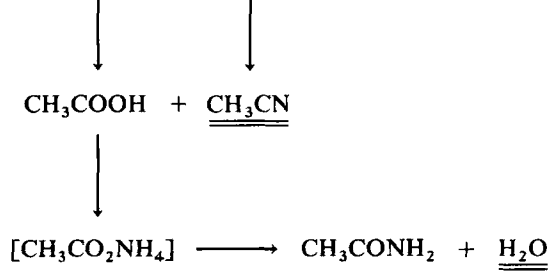
The use of infrared lasers in these studies is likely to increase both in order to probe the details of the chemical and physical processes occurring at the molecular level and also to re-examine the overall mechanisms of processes previously thought to have been studied under purely homogeneous conditions.

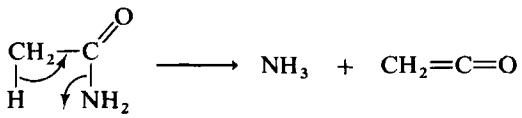
V. THE THERMOLYSIS OF ACID AMIDES AND ACID ANHYDRIDES

Taylor[1] has classified acid amides according to whether they possess or do not possess β-hydrogen atoms in the *N*-alkyl group. The latter group, which includes the primary amide acetamide, behaves on thermolysis in a manner similar to carboxylic acids with a bimolecular, six-centred mechanism at low temperatures leading (in the case of acetamide) ultimately to water and methyl cyanide (reaction 53). (Compare the process in equation 1 for thioacetic acid.) At higher temperatures a four-centred process is favoured yielding (from acetamide) ammonia and ketene (reaction 54, analogous to the process in equation 2 for thioacetic acid).



(53)

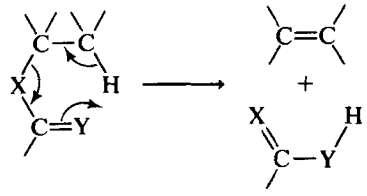




(54)

Amides which do possess β-hydrogen atoms in the *N*-alkyl group, however, were found to undergo the six-centred elimination reaction characteristic of esters with β-hydrogens (see Section III.A) and also of acid anhydrides and other related compounds.

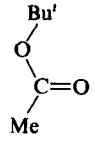
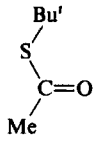
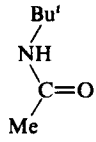
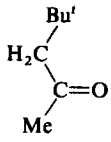
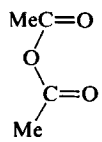
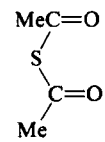
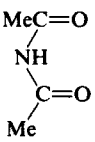
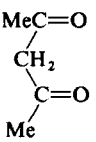
Considerable progress has been made in understanding the mechanisms of these six-centred processes by considering relative rates of thermolysis of analogous groups of compounds. It was noted that whereas the decompositions of acetic anhydride and ethyl acetate were formally similar, the former decomposes very much faster at 600 K, a fact difficult to reconcile with the activating effect of the adjacent carbonyl group in weakening the β-hydrogen bond, since this was not large enough to account quantitatively for the observation[1]. This led Taylor[103] to examine relative rates of elimination for the compounds acetic anhydride, diacetyl sulphide, diacetamide and pentane-2,4-dione. The relative rate constants at 600 K are shown in Table 6 (compiled from the data of Reference 103). The reaction common to all these carboxylic acid derivatives may be written as reaction 55.



(55)

where Y = O

TABLE 6. Relative rate constaants for some analogous carboxylic acid derivatives at 600 K

Compound	*t*-Butyl acetate	*t*-Butyl thioacetate	*N*-*t*-Butyl acetamide	4,4'-Dimethylpentan-2-one
				
Relative rate constant	1.00	0.0385	1.46×10^{-5}	$\sim 1.54 \times 10^{-7}$ [a]
Compound	Acetic anhydride	Diacetyl sulphide	Diacetamide	Pentan-2,4-dione
				
Relative rate constant	9.11	0.308	1.35	$\sim 2.46 \times 10^{-5}$

[a] Estimated (see Reference 103).

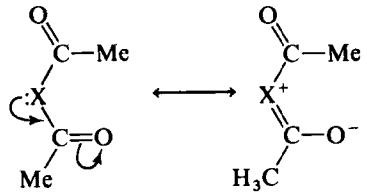
As discussed earlier for esters containing β-hydrogen bonds (see Section III.A), polarization of the C—X bond in an important factor in forming the transition state for these esters. The decreases in rate constant along the first row of Table 6 reflect the decreased polarity when X is successively O, S, NH and CH_2.

The activating effect of the acetyl group compared with the *t*-butyl group accounts for the fact that all the compounds in the second row of the table decompose with higher rate constants than those in the first row. Differences between the members of the second row, however, do not follow exactly the same order as they do in the first row. In particular, diacetamide decomposes more quickly than diacetyl sulphide in contrast to expectation. Despite some experimental uncertainties about the rate constant for diacetyl sulphide at 600 K due to its rapid disappearance giving thioacetic acid which decomposes further, and due also to surface complications, Taylor[103] concluded that the observed difference between these compounds is a real one.

The explanation is likely to be that anhydrides, amides and the others in this second series decompose by a transition state which differs from that of the esters. Whereas in the transition state for the esters, breaking the C^{α}—X bond is the most important factor, for the others nucleophilic attack of the carbonyl group upon the β-hydrogen atom is predominant.

The breaking of the C^{α}—X bond is considered less likely also in view of resonance between the lone pair on the X atom and the α-carbonyl group (reaction 56).

In an extension of this work Al-Awadi and coworkers[104] have examined some compounds whose thermolysis can also be represented by reaction 55 but in which Y = S. Their kinetic data are shown in Table 7; diacetamide was included in order to compare with the previously published data[103]. The Arrhenius parameters observed are consistent with the six-centred transition state and show that the sulphur-containing

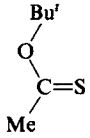
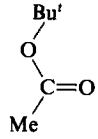
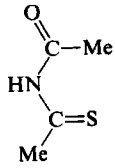
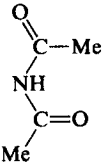
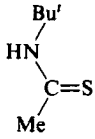
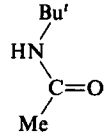


(56)

compounds are more reactive than their oxygen-containing analogues. The statistically-corrected rate-constant ratios shown in the final column of Table 7 indicate that the effect of replacing oxygen by sulphur as the Y group (in reaction 55) is larger in amides than in esters. This confirms the view of Taylor[103] that nucleophilic attack of Y upon the β-hydrogen is the predominant feature of the transition state for amides where it is enhanced by the lower polarity of the C^{α}—X bond (X = NH).

The effects of replacing C=O by C=S in amides and anhydrides are thus very similar to those for the comparable change in carbonates (see Section III.B) and a common

TABLE 7. Relative rate data and some Arrhenius parameters for some esters, amides and thione analogues (from Reference 104)

Compound	*t*-Butyl thioacetate	*t*-Butyl acetate	$k(C{=}S)/k(C{=}O)^c$
			83[a]
Compound	*N*-Acetylthioacetamide	Diacetamide	
			173[b]
$\log(A/s^{-1})$	10.64 ± 0.53	11.86 ± 0.41	
E_a/kJ mol^{-1}	117.15 ± 5.34	151.34 ± 2.68	
Compound	*N*-*t*-Butylthioacetamide	*N*-*t*-Butylacetamide	
			1404[a]
$\log(A/s^{-1})$	11.58 ± 0.31		
E_a/kJ mol^{-1}	169.45 ± 4.28		

[a] Calculated using data in Reference 103 and references cited therein.
[b] Statistically corrected for the number of β-hydrogen atoms.
[c] At 600 K.

interpretation related to the polarity of the transition states concerned is valid for all these classes of compounds.

The rapid thermal decomposition of acetic anhydride to acetic acid and ketene according to equation 55 was not followed analogously by trifluoroacetic anhydride to give difluoroketene as might have been expected. Corbett and Whittle[105] found that thermolysis below 260 °C produces almost entirely CO, CO_2 and CF_3COF. This can be explained by the initial step

$$(CF_3CO)_2O \longrightarrow CF_3COF + {}^{\cdot}CF_2CO^{\cdot}_2 \tag{57}$$

followed by polymerization of the ${}^{\cdot}CF_2CO^{\cdot}_2$ radical at the vessel walls. At higher temperatures C_2F_4 and $(CF_2)_n$ were found.

Pola[106] has investigated the cw–CO_2 laser-induced SF_6-sensitised decomposition of trifluoroacetic anhydride in order to reduce the importance of heterogeneous processes. Under these conditions it was found that the major reactions occurring are 58–61. The fate of the biradicals is to decompose by reactions 60 and 61 with the former leading to carbonyl fluoride being more important. This product was not observed in conventional thermolysis.

$$SF_6{}^* + (CF_3CO)_2O \longrightarrow (CF_3CO)_2O^* + SF_6 \tag{58}$$

$$(CF_3CO)_2O^* \longrightarrow CF_3COF + {}^{\cdot}CF_2CO^{\cdot}_2 \tag{59}$$

$${}^{\cdot}CF_2CO^{\cdot}_2 \longrightarrow COF_2 + CO \tag{60}$$

$$\searrow \quad CO_2 + \tfrac{1}{2}C_2F_4 \tag{61}$$

In a recent publication[107], Kubát and Pola have reported similar laser-induced decompositions of pentafluoropropanoic and heptafluorobutanoic anhydrides. These also show differences from conventional thermolysis studies. The thermal products form pentafluoropropanoic anhydride were found[108] to be decafluorobutane, CO and CO_2.

At low intensity (9 W) unfocussed radiation the products were found to be CF_3COF, C_2F_5COF, C_2F_4 and CO with minor amounts of CO_2.

These products could be explained on the basis of a mechanism similar to that proposed by Pola for trifluoroacetic anhydride[106]. Analogously to the reactions 60 and 61 the perfluoro biradical decomposes by reactions 62 and 63. Perfluoroalkanes were observed at higher intensity and with focussed radiation due to the formation of perfluoroalkyl radicals by C—C splitting.

$${}^{\cdot}CF_2CF_2CO^{\cdot} \longrightarrow CF_3COF + CO \tag{62}$$

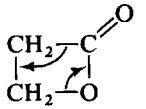
$$\searrow \quad C_2F_4 + CO_2 \tag{63}$$

Similar observations were made in the laser-induced decomposition of heptafluorobutanoic anhydride. Perfluoroacyl compounds formed by the homogeneous decomposition of the biradical were found in preference to the perfluorinated hydrocarbons produced by conventional thermolysis[109,110].

VI. THE THERMOLYSIS OF LACTONES

Although it has been known for some time[111,112] that β-lactones decompose readily into alkenes and CO_2, few gas-phase studies have been reported until recently.

Frey and Pidgeon[74] have reported the low-pressure (<6 torr) thermolysis of β-propiolactone (oxetan-2-one) which decomposes according to reaction 64. At tempera-



$$\longrightarrow \quad C_2H_4 \quad + \quad CO_2 \tag{64}$$

tures between 262 and 322 °C the reaction is homogeneous and unimolecular with a first-order rate constant given by the Arrhenius equation

$$\log_{10}(k_\infty/s^{-1}) = (14.86 \pm 0.30) - (180.46 \pm 3.20)\ \text{kJ mol}^{-1}/2.303\,RT \tag{65}$$

A similar reaction producing propene and CO_2 occurs with β-butyrolactone[113] (4-methyloxetan-2-one). Here the first-order rate constant (209–250 °C) is given by

$$\log_{10}(k_\infty/s^{-1}) = (14.39 \pm 0.10) - (163.4 \pm 1.0)\ \text{kJ mol}^{-1}/2.303\,RT \tag{66}$$

The relatively low pre-exponential factors and, in particular, the low activation energies for these reactions are difficult to reconcile with biradical mechanisms such as have been proposed for cyclobutane and oxetane decompositions (Reference 6, Chap. 7). The methyl substituent effect which enhances the rate of β-butyrolactone over β-propiolactone by about a factor of 20 in the middle of the temperature range is similar to that observed in cyclobutanone decompositions and supports the view[113] that the transition state for thermolysis of β-lactones may resemble the twisted concerted transition state with some zwitterionic character proposed by Egger[114] for cyclobutanone decomposition.

A major interest on these low-pressure lactone thermolyses has been comparison of the observed unimolecular fall-off curves with the RRKM theory. Good agreement has been obtained in both cases, indicating very efficient intermolecular energy transfer which may be related to the polarity of the molecules involved.

In comparison with β-lactones, those with larger rings are, as expected, thermally more stable. This has been noted recently by Chuchani and coworkers[39,75] (see Table 5) who found γ-butyrolactone and δ-valerolactone as stable products from the thermolysis of some ω-halogenoesters.

VII. RADICAL–MOLECULE REACTIONS

In comparison with unimolecular reactions, very little information on bimolecular reactions of carboxylic acids and their derivatives in the gas phase is available. One reason for this is that many bimolecular reactions which occur in solution, such as esterification and hydrolysis reactions, are those between ions or ions and molecules and as such can only be observed in the gas phase in high-energy sources such as the mass spectrometer (see Section VIII). An exception to this generalization is the case of atom– or radical–molecule reactions. A number of unrelated studies of such reactions have been made in the past, such as the reactions of methyl[115–117], ethyl[118] or methoxy[119] radicals with esters and methyl radicals with an acid or anhydride[120,121]. Of particular topical interest, however, in connection with atmospheric chemistry and the problems associated with environmental pollution, are the reactions of OH radicals and, to a lesser extent, O atoms with organic compounds at low pressures and frequently at low temperatures in the gas phase. The removal of organic compounds in the troposphere during daylight has been attributed[122,123] predominantly to reaction with the OH radical. A large accumulation of data exists and is proceeding rapidly[124] due to new initiatives in this area of research. Reviews[125,126] exist for OH–molecule reactions generally, although carboxylic acids and their derivatives are less well-studied than other species.

The reaction of hydroxyl radicals with formic acid has been studied incidentally as a part of work on the photolysis of formic acid[20]. (This was mentioned earlier in Section II.D.) Kinetic studies of the reaction have been carried out by Zetsch and Stuhl[127] at room temperature and by Wine and coworkers[128] over a range of temperatures (298–430 K). Both sets of workers used OH radicals generated by the flash photolysis of water and resonance fluorescence detection of OH radicals (or H atoms formed as products). Experimental difficulties are associated with adsorption of carboxylic acid on the vessel walls and with the complication of the presence of dimer molecules. The latter was minimized by using low pressures and assuming only monomer to be present.

The attack of OH on the formic acid molecules could remove either the 'aldehyde' hydrogen as in reaction 67 or the hydroxyl hydrogen as in reaction 68. The lack of an isotope effect for DCO_2H and the observed independence of the rate constant of temperature in the range 298–430 K[128] makes reaction 67 less likely than reaction 68 despite the higher bond energy of O—H compared with the C—H bond. Hydrogen

$$HCO_2H + OH \longrightarrow H_2O + CO_2H \quad (67)$$

$$HCO_2H + OH \longrightarrow H_2O + HCOO \quad (68)$$

atoms have also been found as products of the reaction. These could either arise from further decomposition of excited CO_2H or HCO_2 radicals produced in reactions 67 and 68 or by a direct process (reaction 69).

$$OH + HCO_2H \longrightarrow H_2O + CO_2 + H \quad (69)$$

Although production of H atoms *via* excited radicals should be subject to pressure quenching, no such effect has yet been demonstrated and the source of H atoms is unclear. Their presence, however, has been confirmed in more recent work by Singleton and coworkers[21] at 296 K, using a laser photolysis–resonance absorption technique. These workers used higher pressures where both formic acid monomers and dimers are present. The rate constants obtained for the monomer are in good agreement with those of Wine and coworkers[128] and the overall results indicate that the dimer is much less reactive.

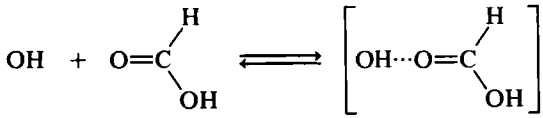
In a subsequent and more extensive study, Singleton and coworkers[23] compared the results of hydroxyl radical reactions with formic and deuteriated formic acids over the range of temperatures 297–445 K. Table 8 shows the relative rate constants for OH removal at 298 K and incicates clearly that substitution of hydrogen in the O—H group by deuterium has a marked effect upon the reactivity whereas, as found previously[128], little effect occurs in replacing C—H by C—D.

TABLE 8. Relative rate constants[23] for OH + formic acid reaction

Reaction	$OH + HCO_2H$	$OD + DCO_2D$	$OH + DCO_2H$
Relative rate constant (298 K)	1.0	0.14 ± 0.01	0.89 ± 0.06

The rate constants in Table 8 refer to reactions involving the acid monomers. Those for the dimers are much smaller, probably due to hydrogen removal from the C—H bond in this case since the O—H bonds are involved in association. For the monomers, hydrogen abstraction from the C—H bond is only thought to be important at higher temperatures. Most of the observations made at room temperature can be accounted for by a mechanism in which a hydrogen-bonded adduct is formed in equilibrium with

the reactants (reaction 70) and this then decomposes at a slower rate involving hydrogen transfer to HCO_2 radicals, which are themselves unstable yielding the observed H atoms as well as the product CO_2 (steps 71 and 72). The proposed two-channel mechanism, i.e. either via an adduct or by direct abstraction of alkyl hydrogen, has been confirmed in an extension of this work to the reactions of OH radicals with CH_3CO_2H, CD_3CO_2H, CD_3CO_2D and $C_2H_5CO_2H$[22]. In the case of propionic acid the monomer and dimer reacted with approximately equal rate constants.



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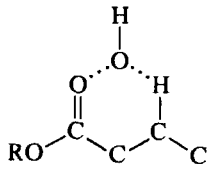
The reactions of OH radicals with esters have also been investigated recently in connection with atmospheric chemistry, since esters are known to be released into the atmosphere both naturally and from man-made sources. The absolute rate constants for OH reaction with methyl trifluoroacetate, methyl acetate and ethyl acetate have been measured over the temperature range 240–440 K at total pressures (in Argon diluent) of 25–50 torr by a flash photolysis–resonance fluorescence technique by Wallington and coworkers[129]. These measurements are the first to be made of the temperature dependence of OH/ester reactions. The low activation energies observed for the reactions involving these three molecules (ca 4 kJ mol^{-1}) are consistent with a hydrogen abstraction step, although subsequent reactions of the radicals produced have not been elucidated and further mechanistic work is required. In addition to the above-mentioned esters, rate constants at 296 K were obtained by these workers for a range of other esters with a view to establishing structure–reactivity relationships.

It was originally suggested[125], based on results of Campbell and Parkinson[130] which appeared to show that methyl acetate and methyl propionate rate constants are similar at 292 K, that OH reaction with an ester occurs mainly at the alcohol end rather than the acid end of the molecule. The more recent work of Wallington and coworkers[129] shows serious discrepancies with Campbell and Parkinson's results for methyl acetate and methyl propionate. It has been shown that abstraction of hydrogen by OH radicals occurs from both alkyl groups and that a linear increase in rate constant plotted against carbon number generally occurs, reflecting the increase in number of abstractable hydrogen atoms with chain length. For abstraction from the acid end, however, an anomalous increase in rate constant occurs between three and four carbon atoms. It is suggested that the additional CH_2 group, β to the carbonyl group present in C_4 and higher acids, permits enhanced reaction due to co-ordination of the OH radical to the carbonyl group in a six-membered ring before hydrogen atom abstraction occurs (73).



(73)

A change in activation energy for methyl and ethyl acetate which occurs at higher temperatures makes it likely that formation of an initial adduct may be replaced by a direct hydrogen abstraction mechanism under these conditions.

The data obtained by Wallington and coworkers for the OH radical reactions with n-propyl and *i*-propyl acetate is in good agreement with the independent measurements of Kerr and Stocker[131] who measured rate constants relative to that for OH reaction with C_2H_4. From their data, Kerr and Stocker concluded that the tropospheric lifetimes of isopropyl and n-propyl acetates are about four and five days respectively, using a mean tropospheric OH concentration of 1×10^6 molecules per cm^3.

The need to obtain similar information for a wide range of reactions of OH radicals with organic compounds has led to the development of methods for estimating rate constants from structure–reactivity relationships. One such method has been described by Atkinson[132]. As far as esters are concerned the calculation of the total rate constant is based upon a sum of the rate constants for abstraction from C—H bonds. These are expressed by equations 74, 75 and 76:

$$k(CH_3{-}X) = l^0_{prim} F(X) \tag{74}$$

$$k(X{-}CH_2{-}Y) = k^0_{sec} F(X)F(Y) \tag{75}$$

$$k\left(X{-}\underset{Z}{\overset{Y}{CH}}\right) = k^0_{tert} F(X)F(Y)F(Z) \tag{76}$$

where k^0_{prim}, k^0_{sec} and k^0_{tert} are defined for the 'standard' substituent group X = Y = Z = CH_3 and have the values

$$\left.\begin{aligned} k^0_{prim} &= 1.44 \times 10^{-13}\ cm^3\ molecule^{-1}\ s^{-1} \\ k^0_{sec} &= 8.38 \times 10^{-13}\ cm^3\ molecule^{-1}\ s^{-1} \\ k^0_{tert} &= 1.83 \times 10^{-12}\ cm^3\ molecule^{-1}\ s^{-1} \end{aligned}\right\} \text{at } 298\ K$$

Equations are also given to enable these rate constants to be evaluated at any temperature from 250–1000 K.

Application to esters then requires values for the substituent factors $F(X)$, $F(Y)$, $F(Z)$ for the groups to which the methyl, methylene or methine groups are attached.

Use of the given values for these substituent factors gave agreement within a factor of 2 of most of the existing data for oxygen-containing molecules. The method is clearly very valuable in view of the large number of organic molecules for which direct experimental measurement is difficult or precluded. The substituent factors, however, must be continuously revised as more experimental data are obtained.

A number of other attempts have been made in the past to correlate the rate constants for gas-phase reactions of OH with organic molecules (including carboxylic esters) with suitable physico-chemical parameters. These include correlations with ionization potential[133], the use of linear free-energy correlations[134] and correlations with the rate constants for reactions in solution[135].

It has been shown that a reasonable correlation can also be obtained between the rate constants for such OH reactions and chemical shifts in proton and ^{13}C NMR spectroscopy[136]. The assumption behind this method is that, for OH reaction with two different molecules of the same type, differences in structure are more important in the initial than in the transition states. It is therefore expected that rate constants would correlate with the chemical shift of the reacted hydrogen atoms or the reaction centres (carbon atoms) in the ground state molecules. The relative ease with which these measurements can be made compared with some of the measurements involved in previously attempted correlations make further investigation of this method worthwhile for predictive purposes. The results obtained so far appear encouraging but have only been applied, so far as esters are concerned, to a limited number of experimental data.

VIII. ION AND ION–MOLECULE REACTIONS

An important area of chemistry associated with carboxylic acids and acid derivatives in the gas phase is the study of ion and ion–molecule reactions by mass-spectrometric techniques. Among these studies are those associated with the determination of gas-phase basicities and proton affinities from proton transfer reactions. These studies lead to the determination of heats of formation of protonated species and hence the study of structural effects upon reactivity in the absence of solvent. Excellent reviews exist concerning both positive[137] and negative[138] ions and the subject is too extensive to be discussed fully here. Some recent examples, however, will illustrate how relevant information can be obtained from the measurement of equilibrium constants for proton transfer reactions.

For the proton transfer reaction 77 between the molecule, M, and a reference base, B, the equilibrium constant is given by equation 78.

$$M + BH^+ \rightleftharpoons MH^+ + B \tag{77}$$

$$K_{eq} = \frac{[MH^+][B]}{[M][BH^+]} \tag{78}$$

Bouchoux and coworkers[139] used this expression to derive gas-phase basicities of a series of acids, aldehydes and ketones having α,β-unsaturated C_4H_7 alkyl chains.

For the protonation of species M (reaction 79) the gas-phase basicity (GB) and proton affinity (PA), of M are defined as the negative standard free-energy change and standard enthalpy change, respectively.

$$M + H^+ \rightleftharpoons MH^+ \tag{79}$$

$$GB(M) = -\Delta G_3^\circ$$

$$PA(M) = -\Delta H_3^\circ$$

Since for

$$B + H^+ \rightleftharpoons BH^+ \tag{80}$$

$$GB(B) = -\Delta G_4^\circ \text{ and } PA(B) = -\Delta H_4^\circ$$

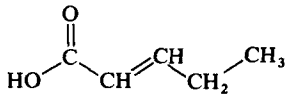
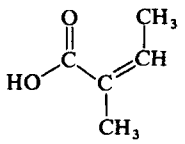
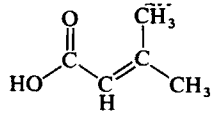
it follows that for the proton transfer reaction 77

$$\Delta G_1^\circ = \Delta G_3^\circ - \Delta G_4^\circ = GB(B) - GB(M) \tag{81}$$

and

$$\Delta H_1^\circ = \Delta H_3^\circ - \Delta H_4^\circ = PA(B) - PA(M) \tag{82}$$

TABLE 9. Derived ΔH°_{f298} values for some protonated species[139]

M			
	(*E*)	(*Z*)	
PA(M)/kJ mol^{-1}	834	836	838
ΔH°_f298(MH$^+$)/kJ mol^{-1}	313	299	294

Calculation of ΔG°_1 was from the equilibrium constant since $\Delta G^\circ_1 = RT \ln K_{eq}$. The ratio of concentrations of the ionic species [MH$^+$]/[BH$^+$] was obtained by the use of ion cyclotron resonance techniques[140], and the ratio [B]/[M] came from pressure measurements.

Equation 81 enables gas-phase basicity GB(M) to be obtained from ΔG°_1 relative to the known value for a reference base B.

The corresponding proton affinity PA(M) can then be obtained from

$$\Delta G^\circ_3 = \Delta H^\circ_3 - T\Delta S^\circ_3 \tag{83}$$

Therefore

$$-\mathrm{GB(M)} = -\mathrm{PA(M)} - T\Delta S^\circ_3 \tag{84}$$

or

$$\mathrm{PA(M)} = \mathrm{GB(M)} - T\Delta S^\circ_3 \tag{85}$$

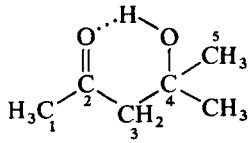
Since the major contribution to ΔS°_1 involves the translational entropy for the free proton, the value of $T\Delta S^\circ_3$ was taken to be approximately -34 kJ mol^{-1} in this work.

With the additional information ΔH°_f (H$^+$) = 1530 kJ mol^{-1} and estimated values of heats of formation of the neutral M species from Benson's rules[141], heats of formation of the protonated species MH$^+$ were obtained. The values given in Table 9 clearly illustrate the effect of structure upon the derived heats of formation of the cations. By examining a wide range of α,β-unsaturated carbonyl compounds it was found that the gas-phase basicity of acids is lower than that of corresponding aldehydes.

Similar measurements of proton affinities were made by Kamar, Young and March[142] for some gas-phase ketones and esters. These workers generated positive ions in a quadrupole ion store (QUISTOR) using a pulsed electron beam. Variation of the protonated ion intensities could be monitored up to 100 ms and the equilibrium values determined for mixtures of the substances investigated and reference substances of known proton affinity. This work was done in order specifically to elucidate some problems in the ion chemistry of 2-propanone and the infrared multiphoton dissociation of protonated dimers of 2-propanone.

The proton affinity of diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) was found to be 831.6 $\pm$ 0.8 kJ mol^{-1}. When compared with an estimated value for 4-methyl-2-pentanone of 848.5 kJ mol^{-1} it seems that substitution of an OH group for an H atom at the 4-position produces a stabilization of 16.9 kJ mol^{-1}.

This effect can be attributed to electron withdrawal by the hydroxy group with formation of an intramolecular H-bond (86).



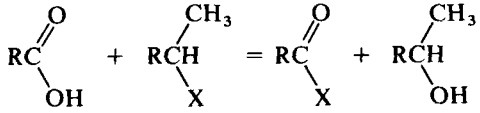
(86)

Gas-phase acidities have also received much attention in mass-spectrometric studies, and relative acidities may be obtained in a similar manner to relative basicities by measurements of proton transfer equilibria. The gas-phase acidity is related to the dissociation energy of the HA bond for acid HA, the electron affinity of the radical A° and the ionization potential of the atom I.P(H°) by equation 87:

$$\Delta H^{\circ}_{\text{acid}} = D^{\circ}(\text{H—A}) + \text{I.P(H}^{\circ}) - \text{EA(A}^{\circ}) \tag{87}$$

Many measurements of relative acidities in the gas phase have now been made by both high-pressure pulsed mass-spectrometric[143] and ion cyclotron resonance[144] techniques. The gas-phase acidities of substituted benzoic acids have been compared with solution reactions using free-energy relationships[145].

Thomas, Carroll and Siggel[146] have recently discussed the acidity of carboxylic acids relative to alcohols which has traditionally been explained as due to the extra resonance stability of the carboxylate anion. It has been argued that this is shown by the greater value of ΔH_{89} compared with ΔH_{88} for the pair of isodesmic* reactions 88 and 89, where



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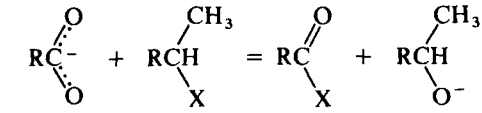


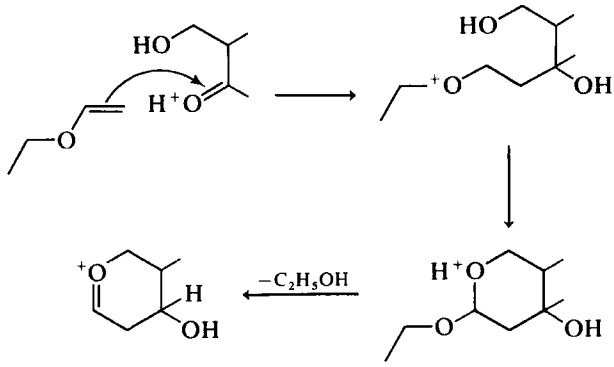
(89)

both R and X are CH_3. The difference may also be attributed to static Coulombic interaction between the polar bonds in the carboxylic acids or anions on the left-hand side of equations 88 and 89 which are not present in the species on the right-hand side. Siggel and coworkers have pointed out that other electronic effects may occur when X is an electronegative substituent of electronegativity comparable to that of OH. When a number of compounds with different X groups were compared, it was found that a wide variation in ΔH_{88} occurred depending on the reference compound chosen. The values of ΔH_{88} roughly correlated with the electronegativity of X, implying that static Coulombic effects play a major role in the energetics of these reactions and that these experiments do not unambiguously explain the differences in acidity between carboxylic acids and alcohols which are observed.

* Isodesmic reactions are those in which the same bonds are formed in the products as those broken in the reactants.

In addition to measurements of gas-phase basicity and acidity which are useful in complementing solution-phase studies and providing information on truly intrinsic structural effects in the absence of solvation, there are sometimes other reasons for the study of proton-transfer reactions. One recent example is where a proton transfer reaction has proved a convenient method of qualitative product identification. In the mass-spectrometric study of large organic ions from, for example, biomolecules, it is frequently found difficult to characterize the functional groups present. It has been found possible to characterize protonated carbonyl groups with a hydroxyl group in close proximity by their specific reaction with ethyl vinyl ether.

Kenttamaa and Cooks[147] found that protonated 4-Hydroxy-3-methyl-2-butanone obtained from the ion source of a triple quadrupole mass spectrometer by isobutane chemical ionization reacts with a low pressure of ethyl vinyl ether by the mechanism shown in reactions 90 and 91, leading ultimately to the loss of ethanol. The product was unambiguously determined by scanning the third quadrupole. The specific nature of this



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(91)

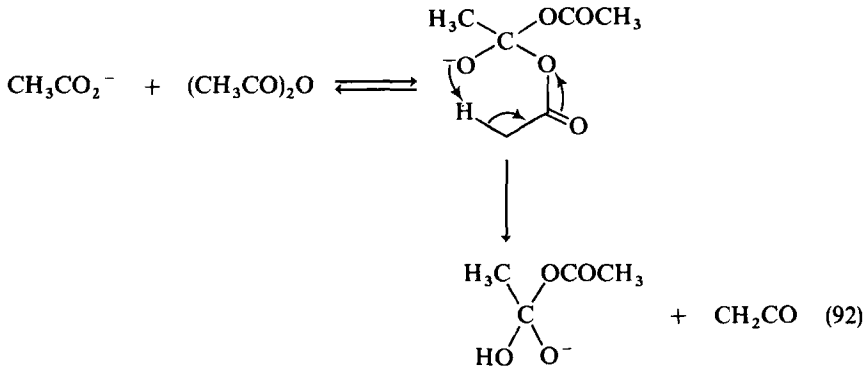
reaction was shown by the fact that it does not occur for protonated 3-hydroxy-2-butanone.

Among the ion–molecule reactions of importance in the chemistry of carboxylic acids and their derivatives are the nucleophilic substitution reactions of negative ions with carbonyl compounds. Examples of these are provided by the work of Bowie and coworkers[148,150,151] and of Bohme and coworkers[149]. When the acetate anion reacts with acetic anhydride, it was found[151] that a McLafferty rearrangement occurs producing ketene, and it was proposed to occur by nucleophilic attack at the carbonyl carbon producing a tetrahedral intermediate which subsequently decomposed (reaction 92).

There has been considerable discussion of whether reactions at the carbonyl group in the gas phase resemble acyl-transfer reactions in solution, which under both acid and base catalysis involve tetrahedral intermediates[152,153]. Fornarini[154] has recently studied the alcoholysis of esters in a radiolytic technique where the carboxylic ester is methylated by gaseous Me_2F^+ and the resulting intermediate produced by electrophilic attack at the carbonyl group is subsequently converted to a tetrahedral intermediate on reaction with an alcohol. Deprotonation of this intermediate produces an *ortho* ester which can be identified, providing proof for the intermediate existence of a tetrahedral species.

Under the conditions of ion cyclotron resonance experiments at low pressures it is difficult to decide from the available information whether a stable tetrahedral intermediate, a hydrogen-bonded association complex or a loose association complex resembling reactants or products is formed.

Han and Braumann[155] have reached this conclusion in general, although their study of the nucleophilic substitution reaction of chloride ions with acyl chlorides supports



the occurrence of a tetrahedral adduct $RCOCl_2^-$ as a transition state or possibly an unstable intermediate. In earlier work[156] on the reaction

$$X^- + RCOY \longrightarrow Y^- + RCOX \qquad (93)$$

$$X = F, Cl, CH_3O, CN, HS; Y = Cl, Br$$

it was concluded that loose ion-neutral clusters were involved.

Bowie and coworkers[157] have studied the gas-phase reactions of alkoxide negative ions with both anhydrides and esters by ion cyclotron resonance. In addition to the negative-ion McLafferty rearrangement (reaction 94) which is formally similar to that observed between carboxylate anions and acetic anhydride (reaction 92).

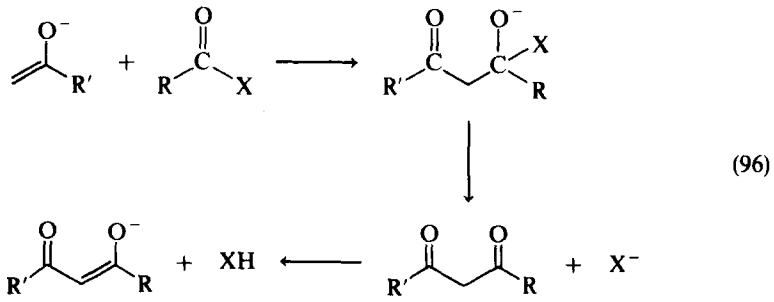
$$CD_3O^- + (MeCO)_2O \longrightarrow (CD_3O)(Me)(HO)C{-}O^- + CH_2CO \qquad (94)$$

deuteriated methoxide ions also undergo an elimination reaction:

$$CD_3O^- + (MeCO)_2O \longrightarrow {}^-CH_2CO_2CD_3 + CH_3COOH \qquad (95)$$

This elimination reaction was also observed to be the major pathway for methoxide and ethoxide ion–ester reactions, provided that the ester has at least one hydrogen atom on the carbon α to the carbonyl group. The use of deuteriated reactant enabled the kinetic isotope effect to be investigated and a four-centred transition state for reaction 95 was considered.

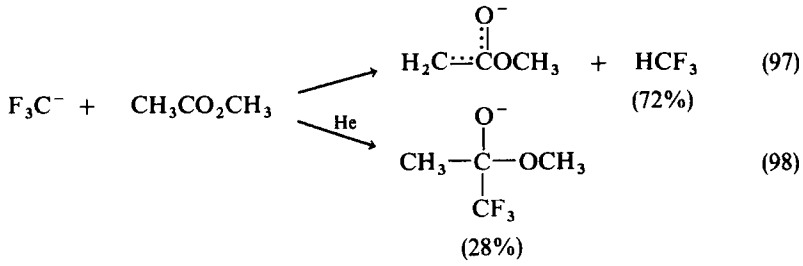
The reactions between carbanions and carbonyl compounds such as esters in the gas phase have been studied by Bartmess and coworkers[158]. Suitably substituted esters were found to undergo addition–elimination–deprotonation reactions similar to the Claisen condensation in solution (reaction 96).



(96)

Kinetic measurements for the ion–molecule reactions of trifluoromethyl anions with some carboxylic esters have been reported by McDonald and Chowdhury[159]. Ions were produced by the flowing afterglow technique[160] in a stainless steel flow tube and carried in a helium buffer gas stream to a mixing chamber for addition of the carbonyl substrate. A quadrupole mass spectrometer operating at ca 10^{-7} torr was used to monitor the ion concentration while the neutral reactant concentration was held in large excess. Under these pseudo-first-order conditions, first-order rate constants could be derived which, by varying the concentration of the neutral reactant, were converted to second-order rate constants.

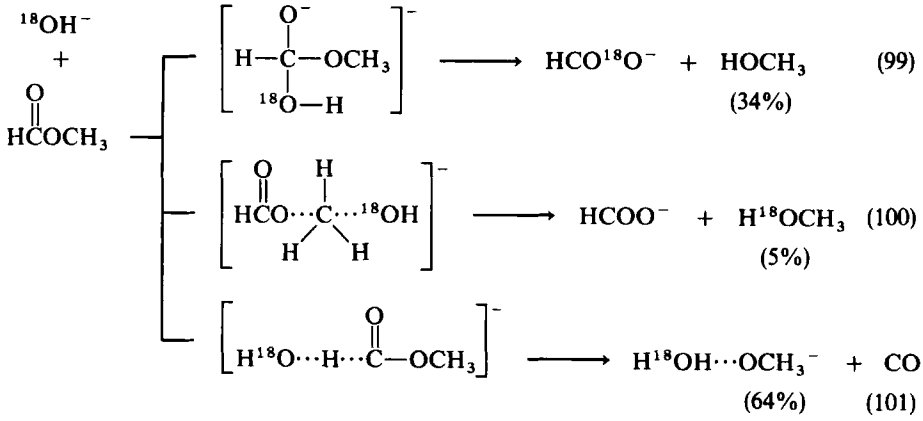
The reactions of the nucleophilic trifluoromethyl anion with a number of esters were shown to be occurring via an addition to the carbonyl group to give the tetrahedral intermediate. The large proton affinity of F_3D^- (PA = 1,572 kJ mol^{-1}) leads to a competing H^+ transfer reaction. The reaction with methyl acetate occurs with a modest rate constant by two competing channels, 97 (H^+ transfer) and 98 (adduct formation). When the same nucleophile reacts with $CF_3CO_2CH_3$, a much faster reaction occurs upon almost every collision and the S_N2 reaction is favoured over carbonyl addition by a ratio of 2:1.



(97)

(98)

Reaction of F_3C^- with methyl formate by contrast was found to produce a series of cluster ions and only a minor amount of carbonyl addition. The reactions of other nucleophiles such as NH_2^-, OH^- and O^- with methyl formate and with methyl pivalate have been more recently examined by Johlman and Wilkins[161] using Fourier transform mass spectrometry. The reaction of OH^- with methyl formate shows three different reaction pathways, 99, 100 and 101, which may be described as addition to carbonyl ($B_{AC}2$), nucleophilic substitution (S_N2) and proton abstraction processes. Reactions



(99)

(100)

(101)

similar to 101 producing clustered anionic species and ultimately stable solvated ions have been observed in alkyl formate reactions with other nucleophiles previously[162].

The reactions of some metal ions with both carboxylic esters[163,164] and carboxylic acids themselves[165] have been reported. For Co^+ ions, insertion is found to occur in bonds adjacent to the carbonyl group followed by other rearrangements such as alkyl- and hydrogen-atom shifts. Insertion into bonds remote from the carbonyl group can also occur in the case of esters or acids with larger alkyl groups.

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CHAPTER 13

Mechanistic aspects. Recent developments concerning mechanisms of acylation by carboxylic acid derivatives

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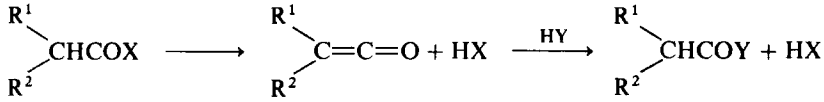
I. INTRODUCTION

This chapter seeks to update earlier chapters in this series[1–4] and elsewhere[5] by considering how our understanding of the mechanisms of acylation by carboxylic acid derivatives has advanced over the past twenty years. Although there has been no revolutionary change in viewpoint, with some parts of the field having received surprisingly little further attention, nevertheless many areas have been actively studied, and this has led to (i) a more detailed understanding and refinement of mechanisms current in the late 1960s, and (ii) some change in emphasis regarding mechanistic ambiguities that existed then. Some of these ambiguities are showing signs of resolution. The chapter will be limited to reactions, mostly with water, alcohols and amines, of amides, acids, esters, anhydrides and acyl halides. It will not include C-acylation on which relatively little progress has been made since the 1960s. One area of acylation which has, however, been mainly developed since then concerns reactions (especially of esters) via elimination mechanisms[6]. These acylations involve ketenes or isocyanates as intermediates[7]. Quite recently theoretical studies of acylation (primarily referring to the gas phase) have begun to appear, and promise to be most illuminating. Acylation mechanisms are normally heterolytic processes[8]; they can be spontaneous or catalysed. Of catalysed processes we shall exclude those involving enzymes, metal ions and heterogeneous systems; these special aspects could fill chapters by themselves.

The situation regarding mechanisms current in about 1970 can readily be summarized once the general framework of (direct) acylation by carboxylic acid derivatives is recalled[8,9]. Normally acylating agents (RCOX) act as electrophiles and their substrates (HY, e.g. H_2O, or N, e.g. Et_3N) as nucleophiles, and the overall acylation involves substitution, with the group R remaining intact throughout (equation 1). In principle

$$\begin{aligned} &\text{RCOX} + \text{HY} \longrightarrow \text{RCOY} + \text{HX} \quad \text{(a)} \\ &\text{RCOX} + \text{N} \longrightarrow \text{RCON}^+ + \text{X}^- \quad \text{(b)} \end{aligned} \tag{1}$$

the reactions are reversible but normally lie far to one side under chosen experimental conditions. For such acylations acid catalysts facilitate reaction by increasing the electrophilicity of the acylating agent, and base catalysts by increasing the nucleophilicity of the substrate[8]. In those acylations that involve the elimination of HX from RCOX, followed by attack of HY (or N), the group R must contain a sufficiently acidic hydrogen atom adjacent to the carbonyl group (e.g. equations 2 and 3). In these acylations, the overall result of which remains a substitution, catalysts can accelerate both steps. However, the main effect is of bases on the elimination process since the intermediate



(2)

$$\text{RNHCOX} \longrightarrow \text{RN=C=O} + \text{HX} \xrightarrow{\text{HY}} \text{RNHCOY} + \text{HX} \tag{3}$$

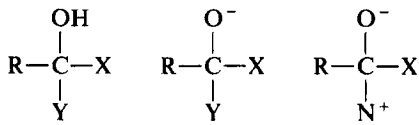
ketene or isocyanate then normally reacts relatively rapidly with HY. Acid catalysts favour route (1) rather than (2) or (3), and so far most cases of acylation via elimination have proved to be examples of the ElcB mechanism[9]. The subsequent addition of HY to the ketene or isocyanate can[7] be thought of as an example of equation 1 in which opening of the C=C or C=N double bond corresponds to loss of X in (1). For acylation via (2) and (3) much has been learned since the late 1960s when the study of their mechanisms was just beginning.

For acylations via equation 1 there exist two broad possibilities: either the substrate is not involved in the slow step (usually termed unimolecular mechanisms, equation 4) or it is involved (usually termed bi- or termolecular mechanisms, equation 5). A spontaneous or solvent-catalysed process (4) is similar to an S_N1 mechanism as defined

$$\text{RCOX} \xrightarrow{\text{slow}} \text{RC}^+{=}\text{O} + \text{X}^- \xrightarrow[\text{HY}]{\text{fast}} \text{RCOY} + \text{HX} \qquad (4)$$

$$\begin{aligned} \text{RCOX} + n\text{HY} &\xrightarrow{\text{slow}} \text{RCOY} + \text{HX} + (n-1)\text{HY} \quad \text{(a)} \\ \text{RCOX} + \text{N} &\xrightarrow{\text{slow}} \text{RCON}^+ + \text{X}^- \quad \text{(b)} \end{aligned} \qquad (5)$$

for alkyl halides[9]. The acid-catalysed counterpart of (4) is termed an A1 (or $A_{AC}1$) mechanism if it involves a pre-equilibrium protonation of RCOX, or an AS_E2 mechanism if slow proton transfer is involved[9]. There was much debate in the 1960s and 1970s as to whether reaction (5) always involved addition of HY to the carbonyl group (or the attachment of Y^- or N to the carbonyl group) to form a (transient) tetrahedral intermediate (e.g., **1**, **2**, or **3**) before the release of HX or X^-, or if reaction could sometimes approximate to a synchronous (or concerted*) S_N2-like process†. The facts



(1) **(2)** **(3)**

* Some authors distinguish between synchronous displacements in which bond-forming and bond-breaking occur synchronously, and concerted displacements in which these processes need not be synchronized so that formation can temporarily run ahead of breaking (or *vice versa*) provided that the energy surface is traversed without passing through a dip representing an intermediate. Concerted processes can be easier to treat theoretically[10].

† In this chapter symbols for mechanism are used in what we believe is the most usual current way[9]. S_N2, for example, implies only bimolecular nucleophilic substitution. The symbol does not convey anything about the synchronous or concerted nature of the substitution—a variety of extents of bond-forming and bond-breaking are covered by the S_N2 umbrella. It seems most idiosyncratic, and definitely confusing, to define[11] the S_N2 process as a 'coupled concerted displacement mechanism with a large amount of bond-breaking' and to state[11] that a 'bimolecular nucleophilic substitution is not ... an S_N2 displacement'. These aberrations are arising partly from an enthusiasm for, and an advocacy of, a new set of symbols mentioned below, and partly from the changes in attitude towards the involvement of S_N2 processes in acylation with which we shall deal. Another worrying feature of recent mechanistic discussions is the description[6] of equation 4 as an elimination-addition mechanism and of equation 5 via **2** and **3** as addition–elimination. The terms elimination and addition have agreed meanings[12] (*two* bonds have to be broken or made). It seems unwise to use these terms in a new sense; associative–dissociative seems preferable.

Another recently introduced[13a,b] way of describing the three possibilities for reactions (4) and (5), S_N1, S_N2, and substitution via carbonyl involvement, is ($D_N + A_N$), A_ND_N and $A_N{*}D_N$, respectively, where D and A refer to bond-breaking and bond-forming. The apparent discontinuities between the symbols remain, as for S_N1 and S_N2. Chemists realize that in practice a continuum between S_N1 and S_N2 must exist, and perhaps also between S_N2 and substitution via carbonyl involvement. S_N1–S_N2 borderline controversies hinge on particular definitions of 'involvement'. The A_ND_N symbolism is not used in this chapter; it is as yet insufficiently established. The more familiar system we use certainly has its limitations, but it is not easy to devise entirely satisfactory symbols for complex reactions[14]. The AC subscript system (e.g. $A_{AC}1$) was designed for ester hydrolysis to distinguish acyl from possible alkyl–oxygen fission. All (direct) acylations involve acyl fission by definition.

could in most cases be explained by either scheme. This debate continues and has recently flared into life again. Clearly S_N2 routes have most chance of competing if the substrate is a poor nucleophile and X is a good-leaving group. Acid-catalysed versions of (5) are usually termed A2 (or $A_{AC}2$) mechanisms and base-catalysed reactions are $B_{Ac}2$ routes[9], but there has been some refinement of this terminology. Uncatalysed reactions via an intermediate do not possess a symbol of their own. Those acylations that involve tetrahedral intermediates like **I** are (strictly speaking) the only acylations to involve addition–elimination mechanisms. It is important to realise that the addition–elimination mechanism involves addition to the carbonyl group whereas the elimination–addition mechanism, (2) and (3), may not: it depends upon the mechanism of addition of HY to the ketene or isocyanate.

With this outline in mind we can consider the mechanistic situation at about 1970 for each type of acylating agent RCOX. By then it had long been known that the reactivity of RCOX generally increases with the strength of HX as a Brönsted acid[8].

Acyl halides (*RCOHal*)[2,5a]. For these relatively reactive acylating agents both routes (4) and (5) were generally accepted, although it had (rather illogically) been suggested that 'S_N1' hydrolyses could take place via prior addition of water to the carbonyl group. In aqueous solution acid catalysis was limited to acyl fluorides, but had been found for other halides in non-hydroxylic solvents. No decision had been reached, even for strong nucleophiles, as to whether route (5) normally involved a tetrahedral intermediate. Factors that influence the relative importance of routes (4) and (5) were only hazily understood.

Anhydrides ($(RCO)_2O$)[5a]. For anhydrides both routes (4) and (5) were accepted, with acid or base catalysis being more necessary than for acyl halides. Base catalysis was often found to take the form of nucleophilic catalysis (equation 6), with the catalyst temporarily taking the place of the substrate to form a more powerful acylating agent. This type of catalysis is favoured by acylating agents with good-leaving groups; it is common for acyl halides and anhydrides but rare with, for example, amides. As for

$$\begin{aligned} (CH_3CO)_2O + HCO_2^- &\xrightarrow{\text{slow}} CH_3COOCOH + CH_3CO_2^- \\ CH_3COOCOH + H_2O &\xrightarrow{\text{fast}} CH_3CO_2H + HCO_2^- \end{aligned} \qquad (6)$$

RCOHal no decision had been reached about whether route (5) normally involved tetrahedral intermediates.

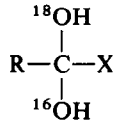
Esters (R^1COOR^2)[1,3,5b]. For esters very firm evidence was available both for the existence of tetrahedral carbonyl addition compounds and for their intermediacy during acylations (see Section II). In contrast there existed no firm evidence for synchronous (or concerted) acylations whether spontaneous or acid- or base-catalysed. $A_{AC}1$ routes were accepted, especially for strongly acidic media. Under other conditions $A_{AC}2$ mechanisms, and both nucleophilic and general base (rate-determining removal of a proton at some stage) catalysis were very commonly found, although the details of the mechanisms of general base- and of general acid-catalysed aminolysis were much debated.

Acids (RCO_2H)[1,2]. Rather little was known about mechanisms of acylation by acids. Generally poor acylating agents, their reactions were known to be subject to general base catalysis and perhaps to specific acid catalysis. Thiol acids (like thiol esters) were known to be more reactive in spontaneous acylations than their O-analogues but less susceptible to acid catalysis. Acid catalysis of hydrolysis in dilute acid was identified as an $A_{AC}2$ process.

Amides (R^1CONHR^2)[4]. For these poor acylating agents there was strong kinetic evidence for tetrahedral intermediates in base-catalysed hydrolysis. Examples of nucleophilic catalysis were known, especially intramolecular varieties. For acid-catalysed reactions both $A_{AC}1$ and $A_{AC}2$ paths were recognized. N-protonation seemed obvious for the A1 route but for the $A_{AC}2$ path there was much argument about the relative importance of reaction via the N- and the O-protonated amide. It is relevant that acyl derivatives of tertiary amines, $R^1CON^+R_2^2$, species which often occur during nucleophilic catalysis by tertiary amines of acylation by other acylating agents, are reagents of considerable strength with good-leaving groups.

II. TETRAHEDRAL INTERMEDIATES AND S_N2-LIKE DISPLACEMENTS

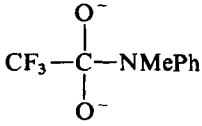
The idea that some bimolecular acylations (equation 5) take place as synchronous displacements rather than proceeding through transient tetrahedral intermediates has usually been a minority view, especially since the discovery[15,16] that during hydrolysis of species RCOX (equation 7) oxygen exchange between its carbonyl group and the water often occurs concurrently with hydrolysis. At first this oxygen exchange proved only the *existence* of an addition intermediate, e.g.



that could lose either oxygen atom, since the intermediate might not have been on the favoured reaction path for hydrolysis. Eventually, however, it was demonstrated kinetically that, for one system at least (ethyl trifluorothiolacetate), the intermediate served both exchange and hydrolysis[17,18]. There exists also apparently incontrovertible kinetic evidence for intermediates in the base-catalysed hydrolyses of amides, such as

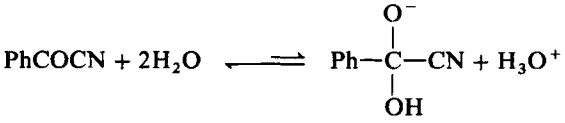
$$RCOX + H_2O \longrightarrow RCO_2H + HX \qquad (7)$$

trifluoro-*N*-methylacetanilide[19], where second-order terms in $[OH^-]$ are best explained by the involvement of

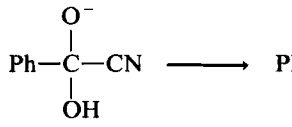


and in the acid-inhibited hydrolysis of both ethyltrifluorothiol acetate[17] and benzoyl cyanide[20] where added acid represses equilibrium (8), and its analogue for the thiol ester, and so inhibits hydrolysis (equation 9). Numerous other examples are known of discontinuities in kinetic behaviour that are readily explained by assuming changes in the partitioning of tetrahedral intermediates owing to a change in the rate-determining step as the conditions are altered. Cases were known in 1970, and others have been found since[9,21].

There now also exist many examples of relatively stable species corresponding to the

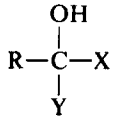


(8)

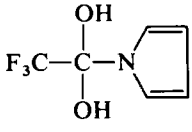


(9)

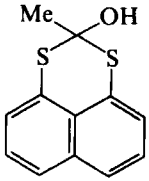
addition intermediates of notional acylations[22]. They involve mostly additions to esters or amides. Stable tetrahedral addition species



tend to be favoured over the corresponding free carbonyl forms, RCOX + HY, (i) if they involve a cyclic and especially a polycyclic structure, (ii) if a strongly electron-attracting group is attached to the pro-carbonyl carbon atom, (iii) if the group X is not strongly conjugated with the carbonyl group and (iv) if either X or Y, or both, are attached to the central carbon atom by sulphur atoms[22b]. Typical examples are **4**–**7**[23]. It is significant that the strong kinetic evidence for intermediates[17–20] mentioned above involves intermediates satisfying requirements (ii)–(iv).



(4)



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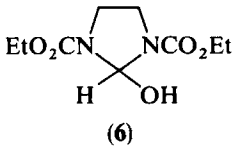

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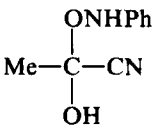
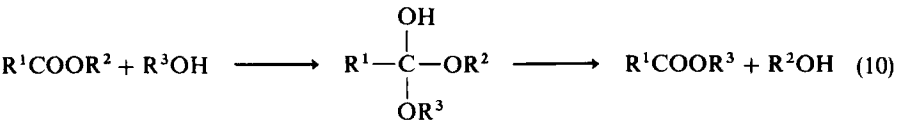


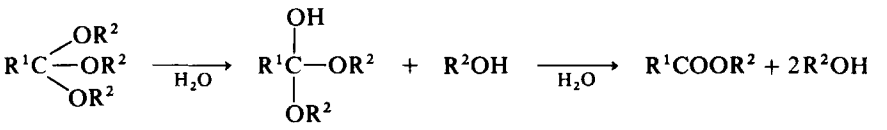
(7)

Even more significant for acylation mechanisms generally has been the development of methods for detecting much simpler and less special tetrahedral intermediates[22b,24]. So far these have mostly involved intermediates identical to those postulated for (aliphatic) ester alcoholyses (equation 10). Their preparation and detection has resulted



(10)

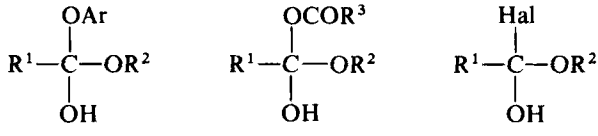
from developments in kinetic studies of the mechanisms of hydrolysis of orthoesters, ketene acetals and related compounds. These hydrolyses are now known to proceed via hemiorthoesters (e.g. equation 11) which are the type of species involved in equation 10.



(11)

Under appropriate conditions the hemiorthoester can be formed rapidly and its decomposition to the ester monitored. It has proved possible to study the spontaneous decomposition, and those catalysed by H_3O^+ and OH^- ions. pK_a values for the hydroxyl group have also been determined, and mechanisms of decomposition suggested[22b,24]. Since this decomposition, preceded by its reverse (equation 10), are the elements of ester alcoholysis, these elegant studies have implications for this latter reaction, and also for ester hydrolysis for which the stability of the intermediates are calculated to be similar[25].

These and other studies have led to more precise ideas of the lifetimes of tetrahedral intermediates of various structures, and it seems that certain types, e.g. **8–10**, may be so reactive, especially if OH is ionized, or if a potential leaving group is protonated, as to

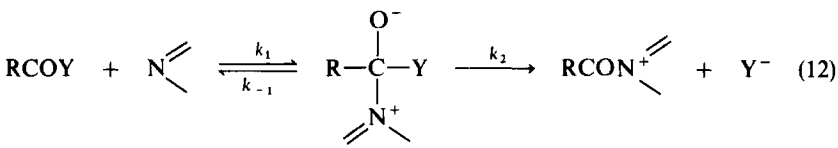


(8) **(9)** **(10)**

R^2 = H or alkyl

be hardly classifiable as intermediates. It is significant that the intermediates corresponding to alcoholysis or hydrolysis of anhydrides and acyl halides fall into this category: these are the reactions for which the existence of intermediates was most uncertain in the 1970s. This then is the background against which to view other recent work.

One approach to identifying the presence of an intermediate in an acylation that has continued to attract attention is that pioneered by Jencks[26], in which a particular acylation is studied with a series of nucleophiles (now usually pyridines, equation 12)

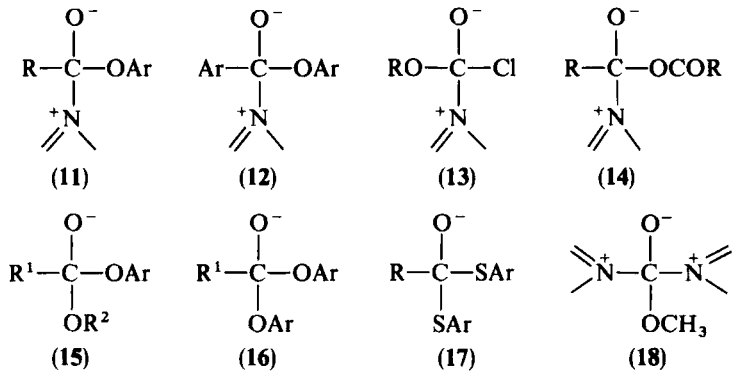


(12)

$$k_{obs} = k_1k_2\,[\text{pyridine}]/k_{-1} + k_2)$$

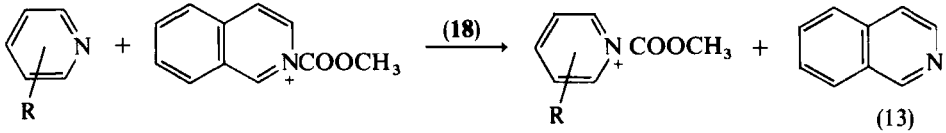
covering a wide range of basicity. Assuming equation 12, if the nucleophile is a relatively very strong base compared to Y^- then $k_2 \gg k_{-1}$, whereas for relatively weak bases $k_2 \ll k_{-1}$, so that k_{obs} will change from k_1 [pyridine] to (k_1k_2/k_{-1})[pyridine] at some intermediate basicity, and a plot of log k_{obs} against pK_a for the nucleophile would be expected to display curvature or a discontinuity, since different dependencies on basicity would be expected in the two regions. If the nucleophile and Y^- are species of the same type (e.g. both tertiary amines or both phenoxide ions) then it is possible to predict where on the pK_a axis the discontinuity should occur: it is where $(pK_a)_{nuc} = (pK_a)_{Y^-}$. If no discontinuity occurs, then this suggests that no addition intermediate of significant stability is formed, and that the mechanism of equation 12 is incorrect.

Studies of this type suggest that intermediates are formed in aminolyses of aryl esters[26,27] (**11** and **12**), chloroformates[28] (**13**) and anhydrides[29] (**14**), but not[21a,30] for reactions of ArO^- or RO^- with O-esters containing aryl leaving groups **15** and **16**, or of pyridines with acyl ammonium ions (**18**, equation 13). These results are compatible with conclusions from other sources (noted earlier), and the suggestion[21a] that zwitterionic ($T^\pm$) intermediates like **11–14** are stabilized electrostatically. That species **17** have



(11) (12) (13) (14)

(15) (16) (17) (18)



(13)

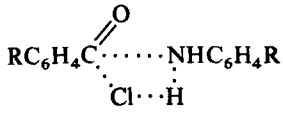
also been detected[31] is in line with expectations for S-based intermediates (see above). Reservations about the reliability of conclusions based on this approach are that the transition state for a concerted or a synchronous substitution might also vary with the strength of the attacking nucleophile, owing to greater or less bond formation or cleavage, and to different degrees of solvation[32], so that changes in the importance of substituent effects with changes in nucleophile basicity could occur even in concerted processes. Jencks admits as much but normally prefers the intermediate model[11,26]. For cases where discontinuities exist it is consistently found[26] that, with a given leaving group, the slope, β_{nuc}, of the plot of log k_{obs} against pK_a of the nucleophile decreases as pK_a rises, often falling from *ca* 1.0–0.8 to *ca* 0.3–0.2. Parallel behaviour is found for variations in the pK_a of the leaving group, using a fixed nucleophile: for weakly basic (good) leaving groups the slope of the plot of log k_{obs} against the pK_a of the leaving group, $\beta_{lg} \sim -0.3$, and for more basic groups $\beta_{lg} \sim -1.0$. It is not obvious that this pattern is compatible with the tetrahedral intermediate model which lacks the symmetry of the S_N2 mechanism; rationalization is not the simple matter sometimes suggested[21a]. The observed behaviour can, however, readily be explained using a synchronous or concerted model[10]. A somewhat similar point is made by DeTar[33]. Not all identifications of intermediates based on discontinuities in substituent effect need therefore be valid.

Other studies that have led to serious consideration of S_N2 acylations rather than the tetrahedral intermediate route fall mostly into three categories: (i) solvent effects on acyl halide hydrolysis and alcoholysis, (ii) isotope effects and (iii) theoretical calculations of reaction paths. Some experimental studies[34] of gas-phase acylations also suggest S_N2 mechanisms but at present this type of work, which is in its early stages, reveals rather complex behaviour and the frequent formation of a variety of products[35].

(i) The effects of changing the solvent composition, using various water–alcohol, water–acetone and similar mixtures, on the rates of solvolysis of substituted benzoyl halides in composition regions where the solvent ionizing power is high are sometimes similar to the effects found for the solvolysis of *t*-butyl chloride in the same solvents, but dissimilar to the effects found for the solvolysis adamantyl halides[36,37]. Since the adamantyl halides very probably display S_N1 mechanisms, it has been suggested that *t*-butyl chloride and the benzoyl halides[37] exhibit solvolyses with some (weak) solvent

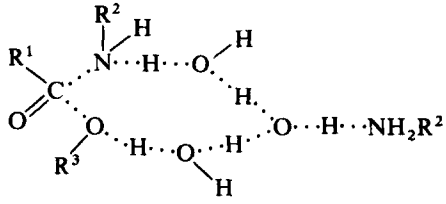
participation. A loose S_N2 transition state, with much acylium ion character, is postulated for benzoyl halides carrying electron-releasing substituents. Other work[38,39] on the alcoholysis of acyl halides in both pure alcohol as solvent and in acetonitrile has also been preferentially interpreted in terms of S_N2 transition states; the more electron withdrawal there is in the acyl portion, the tighter the transition state is suggested to be.

Much Russian work[40] on reactions of acyl halides involves use of aprotic solvents (hexane, benzene, etc.). Aminolysis and alcoholysis in these circumstances are frequently interpreted as involving synchronous cyclic processes incorporating proton transfer to the leaving halide (**19**). Assistance of leaving-group departure is at a premium in aprotic media and it has been suggested that mechanisms obtaining in hydroxylic solvents, where assistance of leaving-group departure is always available, will change to others in which the nucleophile itself assists with this departure[7].



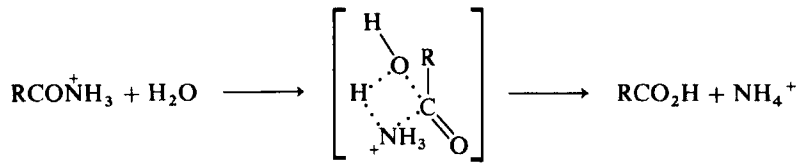
(19)

(ii) It has been argued[41] that secondary deuterium isotope effects can be used to characterize the geometry of transition states in acylation. Aminolysis of esters involves kinetic terms corresponding to base catalysis by a second molecule of amine, and to acid catalysis by a protonated amine molecule[1]. For paths of this sort secondary isotope effects suggest tetrahedral intermediates for the base-catalysed reaction of hydrazine with methyl formate and for the acid-catalysed reaction of $MeONH_2$ with phenyl acetate. However, for the base-catalysed reactions of hydrazine and semicarbazide with phenyl acetates the isotope effects are incompatible with effectively tetrahedral transition states and strongly suggest a trigonal planar structure (possibly **20**) with much concerted bond forming and breaking[41].



(20)

(iii) Theoretical chemists are making increasing contributions to mechanistic studies with recent advances in computational methods. It is possible to optimize reaction coordinates or to compare different paths. Most calculations refer to the gas phase, but comments on the differences expected for solution reactions are often made. Many of the calculations that concern acylation *assume* the formation of a tetrahedral intermediate, and perhaps calculate the energy barriers to its decomposition[25,42]. Calculations that seek to determine the most favourable reaction path have sometimes found that synchronous displacement routes are the best, and that intermediates are absent. The gas-phase hydrolysis of acetamide in the presence of acid is predicted[43] to involve a tetrahedral transition state (but no tetrahedral intermediate) with N- rather than O-protonation, and in which the exiting NH_3 picks up a proton from the entering water en route (equation 14). Similarly, for the ammonolysis of formic acid a theoretical study[44] suggests that stepwise and synchronous routes (equation 15) have similar energy barriers.



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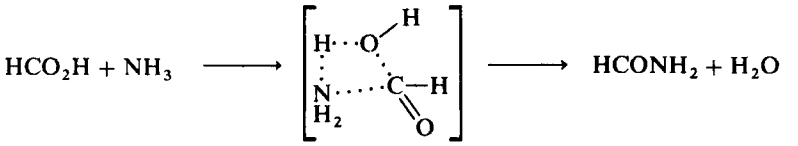


(15)

In general, theoretical calculations suggest that for charged nucleophiles the desolvation prior to attack on the acylating agent will be energetically very important[45,46], and that the actual path in any given case will not necessarily be some variety of the standard tetrahedral intermediate route, but will be individual to the molecules concerned[47]. That seems sensible. Just to divide acylation mechanisms up into acylium ion routes and paths with tetrahedral intermediates seems too simple to be realistic. For instance, it seems obvious[8b] that if slow unimolecular acylium ion formation is acceptable for some systems (as it is) there must be other systems in which much leaving-group departure and just a little nucleophilic participation are involved; there is surely not a sudden jump to a full carbonyl addition intermediate. The possibility of loose S_N2 acylations appears eminently reasonable and it is understandable that more authors are now interpreting results on this basis[11].

In summary, it can be said that bimolecular acylation involving tetrahedral intermediates was accepted for some systems before 1970. Such routes seem likely to be very common. Many transient intermediates of one type have now been prepared and studied. As a result, and because of other theoretical and experimental work noted above, it is becoming more recognized that the tetrahedral structure may not always represent a dip in the energy surface, and that a variety of concerted or synchronous paths may sometimes represent the favoured routes. Good leaving groups and poor nucleophiles, or situations (the gas phase and aprotic solvents) in which leaving-group departure requires assistance by the nucleophile, may be circumstances in which tetrahedral intermediates are absent. Intermediates have the advantage that they can be, and have been, detected; S_N2 routes only possess transition states, but it seems even less wise to ignore them than in 1970.

III. RECENT DEVELOPMENTS IN SUBSTITUTION IN SPECIES RCOX

A. Acyl Halides

1. Hydrolysis and alcoholysis

Previous conclusions[2,5a], that certain acyl halides in media of sufficient ionizing power react via equation 4, have been supported by recent experiments with substituted benzoyl fluorides[11]. The hydrolysis of *p*-dimethylamino benzoyl fluoride in water exhibits common ion inhibition by fluoride ions according to the expected equation 17. With

$$Me_2NC_6H_4COF \underset{k_{-1}}{\overset{k_1 \text{ slow}}{\rightleftharpoons}} Me_2NC_6H_4\overset{+}{C}O + F^- \xrightarrow[H_2O]{k_2} Me_2NC_6H_4CO_2H + HF \quad (16)$$

$$k_{obs} = k_1k_2/(k_{-1}[F^-] + k_2) \quad (17)$$

less electron-releasing substituents there is no common ion effect, but instead general base catalysis by F^-. The solvent deuterium isotope effect is $k_{H_2O}/k_{D_2O} = 1.1$ for equation 16, and *ca* 2.3 for the general base catalysis. Electron release reduces reactivity for most of the series studied, for which a reaction like (5) is involved and is dominated by bond-forming. This result supports earlier conclusions about acyl fluorides[48]. In a 60% ethanol–water solution even the dimethylamino derivative displays this route. Surprisingly[48] benzoyl fluoride shows no evidence of acid catalysis in 1.0 mol dm^{-3} acid, and for the *p*-nitro derivative the ratio of reactivities of the acyl chloride and fluoride is only *ca* 1.2, much less than usually found in other systems. These results suggest that the C—Hal bond-breaking process has very little influence on the rate of hydrolysis for most benzoyl fluorides, and also for *p*-nitrobenzoyl chloride. Whether a tetrahedral intermediate is formed in their hydrolyses is uncertain, but a concerted displacement is suggested[11].

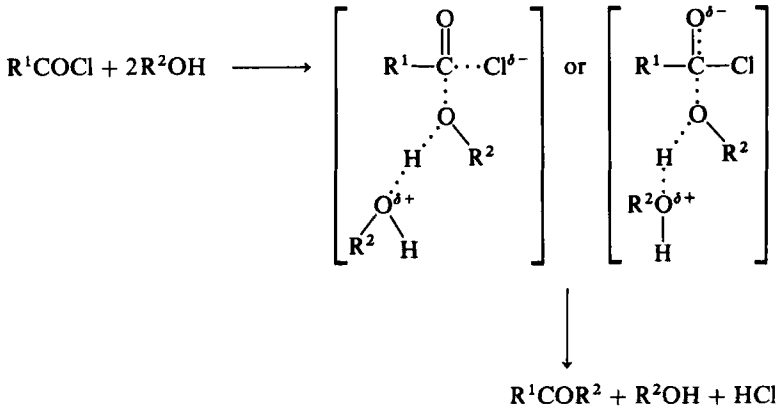
A series of substituted benzoyl chlorides was also examined using 90% trifluoroethanol–water as solvent[11]. For most of these compounds electron release accelerates reaction with $\rho^+ \sim -3.0$. There is no common ion effect, but no general base catalysis by fluoride except for the *p*-nitro derivative which behaves like the benzoyl fluorides just discussed. For the other derivatives much more bond-breaking is probable but since the ionization of cumyl chlorides shows an even greater dependence on electron release, for these other benzoyl chlorides a transition state with much acylium ion character but with some nucleophilic solvent involvement is proposed[11] (see Section II). These findings for benzoyl fluorides and chlorides are an example of how the same broad mechanism (equation 5) can lead to different substituent effects depending on the relative importance of bond breaking and making. The large rate ratios normally found[49] for acyl Cl/acyl F comparisons no doubt arise owing to the greater importance of bond-breaking in the chlorides.

It seems clear from the foregoing results, and from earlier work on the common ion effect with substituted benzoyl chlorides[50], that considerable electron release in the acyl group is needed for a clean S_N1 reaction, as well as a solvent of substantial ionizing power. This conclusion is entirely in line with recent results of studies using formic acid as solvent[51] and of those already mentioned, concerning various benzoyl chlorides in aqueous solvents of different ionizing power, which point only to loose S_N2 transition states even for the highly ionizing media.

Calculations of electrostriction parameters from measurements of rates of hydrolysis at various pressures suggest that, for benzoyl chloride itself in acetone–water mixtures, the S_N1 route is followed at high temperatures, pressures and water concentrations, and the S_N2 route under other conditions[52].

Of aliphatic acyl halides, chloroformates (ROCOCl) have been much studied since their reactions[53] are conveniently slower than those of the simple alkyl analogues such as CH_3COCl. Chloroformates with electron release by R equivalent to or better than that of the ^{i}Pr group are believed to undergo unimolecular hydrolysis in water. However, the position of the unimolecular–bimolecular mechanistic borderline for derivatives of acetic acid remains unclear. Most recent studies with both aromatic and aliphatic acyl halides have involved acyl halides possessing only moderate electron release, and/or media less ionizing than water. Very often for alcoholysis a low concentration of the

alcohol was used in a non-hydroxylic solvent. Under these conditions equation 5 is believed universally to be followed in the absence of acid catalysis. There is much agreement[38,39,54–56] via arguments involving the observed kinetic forms or isotope effects, from studies using pure water or alcohol as solvent and from those employing inert media, that in the spontaneous reactions more than one substrate molecule is often involved (usually two). The additional molecule(s) acts as a general base (equation 18) or as a bifunctional catalyst (equation 19). Appropriate solvent molecules can replace the extra substrate molecules, as can some deliberately added base catalysts (for F^- see the beginning of Section III.A.1). The loss of halide in equations 18 and 19 is thought to be concerted, or fast if a tetrahedral intermediate is involved, since HO^- or ^-OR are much poorer leaving groups than Cl^-.



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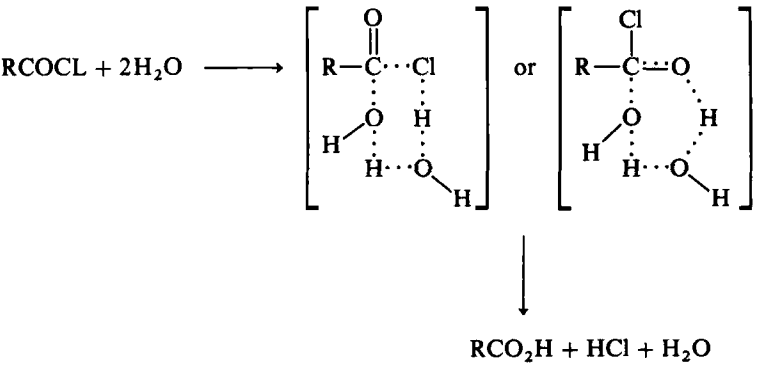


(19)

In non-hydrogen bonding solvents tetraalkyl ammonium chlorides can be useful catalysts for the alcoholysis of acyl chlorides[38]. They were originally thought[57] to act as electrophilic catalysts helping the chloride leaving groups to depart (equation 20), but their effect is now believed to arise from the enhanced basicity of Cl^- ions in such solvents (equation 21). Carboxylic acids catalyse the reaction of trichloroacetyl chloride

$$R^1COCl + R^2_4N^+Cl^- \rightleftharpoons R^1\overset{\delta+}{C}O\overset{\delta-}{C}lN^+R^2_4Cl^- \xrightarrow{R^3OH} R^1CO_2R^3 + HCl + R^2_4N^+Cl^- \quad (20)$$

$$R^2OH + Cl^- \rightleftharpoons R^2OH\cdots Cl^- \xrightarrow{R^1COCl} R^1COOR^2 + HCl + Cl^- \quad (21)$$

with butanol in aromatic solvents and their catalytic activity is inversely related to their acid strength[58]. They are thought to behave as bifunctional catalysts with their base role dominant, perhaps as in equation 22. Very similar results and conclusions have been reached for acylations by ketenes and isocyanates under similar conditions[7].

$$CCl_3COCl + BuOH + RCO_2H \longrightarrow \left[CCl_3{-}\overset{\overset{O}{\|}}{C}\cdots Cl \;\; O{-}Bu \;\; H \;\; O{-}H \;\; O\cdots CR \right] \longrightarrow CCl_3COOBu + RCO_2H + HCl \quad (22)$$

It is interesting that in the phenolysis of aliphatic acyl chlorides in acetonitrile[38,39] the spontaneous reactions (first order in phenol) can be inhibited, rather than catalysed, by added tetraalkylammonium chlorides. This effect was originally interpreted[59] as a repression of ionization induced by adventitious HCl (equation 23). Added Cl^- removes

$$\begin{array}{ccccc} CH_3COCl + HCl & \rightleftharpoons & CH_3\overset{+}{C}OHCl_2^- & \rightleftharpoons & CH_3\overset{+}{C}O + HCl_2^- \\ \downarrow ArOH & & \downarrow ArOH & & \downarrow ArOH \\ \text{Products} & & \text{Products} & & \text{Products} \end{array} \quad (23)$$

$$CH_3COCl + PhON \rightleftharpoons CH_3COCl\cdots HOPh \quad (24)$$

$$CH_3COOPh + HCl \longleftarrow \left[CH_3\overset{+}{C}O \;\; Cl^- \;\; PhO{-}H \right] \longleftarrow CH_3\overset{+}{C}O[Cl\cdots HOPh]^-$$

HCl as HCl_2^-. However, the inhibition has now been explained[38] via the mechanism in equation 24 (as in the reactions of certain alkyl halides with phenol[60]). When Cl^- is added the phenol is preferentially tied up as $PhOH\cdots Cl^-$, but why this interaction does not itself lead to catalysis, as postulated for aliphatic alcohols in equation 21, is not evident. The mechanism in equation 24 certainly involves the type of transition state one might expect in a non-hydrogen bonding solvent of moderate ionizing power.

A recent NMR study[61] confirmed that acetyl chloride reacts rapidly (equation 25) in acetic acid to give acetic anhydride[8a]. The fluoride ion is strongly hydrogen bonded in

$$CH_3COCl + CH_3CO_2H \overset{fast}{\rightleftharpoons} (CH_3CO)_2O + HCl \quad (25)$$

this solvent[61], $CH_3CO_2H\cdots F^-$, and its reactivity as a nucleophile is much lower than previously assumed.

In summary, recent work on reactions of acyl halides with O-nucleophiles is mostly supportive of previous experimental findings[2,5a,8a]. Interpretations are tending to change, and for some examples of route (5) involving acid chlorides, tetrahedral intermediates now seem quite unlikely. In other examples the choice between an intermediate and an S_N2 route remains largely a matter of taste. Clean S_N1 reactions are now believed to be less common than was thought in 1970. More work on oxygen exchange would be interesting and timely.

2. *Aminolysis*

Uncatalysed aminolysis via an intermediate (equation 26) will provide a dipolar structure (e.g. **21**). As noted in Section II, plots of log k_{obs} against pK_a for a series of

$$\mathrm{RCOCl + N{\equiv}} \rightleftharpoons \mathrm{R{-}\overset{\displaystyle O^-}{\overset{|}{C}}{-}Cl} \longrightarrow \mathrm{RCO\overset{+}{N}{\equiv} + Cl^-} \qquad (26)$$

(**21**)

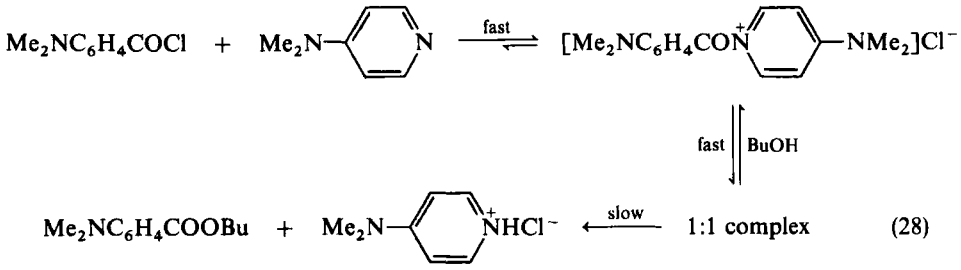
substituted pyridines attacking methyl chloroformate lead, for reaction in water, to a curved plot[28]. For reaction in alcohol–water mixtures the change in slope is more marked and shifted towards the most basic pyridines. This has been rationalized in terms of lower relative permittivity favouring expulsion of N rather than Cl^- from **21**. The result can also be explained by a shift in an S_N2 transition state towards the reactant (less polar) side, but obviously the intermediate mechanism is a possibility. Curved plots are also found[62] for 2,4-dinitrophenyl chloroformate. These reactions are, of course, the first stage of tertiary base nucleophilic catalysis of hydrolysis, alcoholysis or aminolysis by other amines (e.g. equation 27). Normally the second step is faster than the first[2].

$$\mathrm{R^1OCOCl + N} \longrightarrow \mathrm{R^1OCON^+ + Cl^-} \xrightarrow{H_2O} \mathrm{[R^1OCO_2H] + N + H^+ + Cl^-} \qquad (27)$$

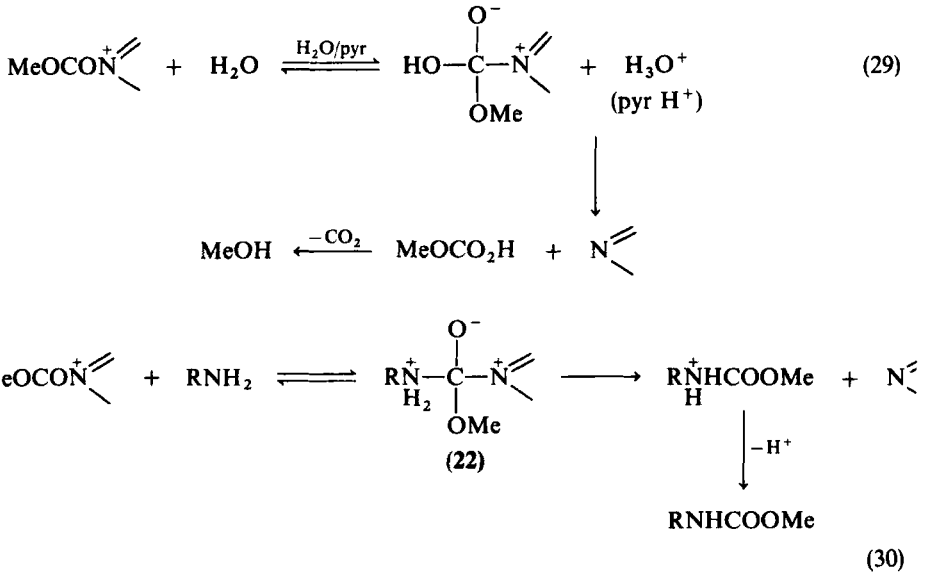
$$\mathrm{R^1OCON^+ + Cl^-} \xrightarrow{R^2NH_2} \mathrm{R^1OCONHR^2 + N + H^+ + Cl^-}$$

This shows that amines are much better leaving groups than Cl^- on a pK_a basis. Work[54] with phenyl chloroformate suggests that acetate ion behaves as a nucleophilic catalyst in aqueous solution and therefore that the mixed anhydride $PhOCOOCOCH_3$ is (surprisingly) a better acylating agent than PhOCOCl; perhaps $PhOCO_2^-$ becomes the leaving group. In methylene chloride the reaction of dimethylaminobenzoyl chloride with butanol[63] is catalysed by the powerful nucleophile 4-dimethylaminopyridine via equation 28 in which the final step is rate-determining.

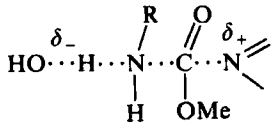
Dimethylaminopyridine, and other dialkylaminopyridines, have recently come to prominence as reagents[66], and have generally been used as the most basic pyridines in studies, such as those mentioned above, that seek to uncover the involvement of



tetrahedral intermediates by finding discontinuities in plots of log k_{obs} against pK_a. These pyridines are excellent nucleophilic catalysts and are routinely found[28,64,65] to be 10^2–10^5 more effective than simpler pyridines. They form relatively stable acylpyridinium salts which can be isolated[66]. By increasing sufficiently the concentration of the pyridine catalyst in equation 27 it is possible to form the pyridinium compound rapidly and completely, and then to study its subsequent reactions[67,68]. Methyl chloroformate has been used with a series of pyridines to generate the methoxycarbonyl pyridinium ions, and their reactions in aqueous pyridine buffers with water (equation 29), hydroxide ion and primary (equation 30) or secondary amines have been examined[68]. Reactions (equations 29 and 30) were formulated in terms of tetrahedral intermediates; equation



29 is general base catalysed, with formation of the intermediate rate-determining. Similar catalysis of the aminolysis (equation 30) by amine was not found, and it was suggested that for the least reactive pyridinium species (those from the most basic pyridines) the loss of pyridine was the slow step. The aminolyses are catalysed by OH^- ions. For this reaction an entirely synchronous route was preferred (equation 31). The charges on species **22** make it potentially unstable[21a] and it is difficult to see how it can be an intermediate if the OH^- catalysed route is S_N2-like when its corresponding intermediate **23** would be more stable than **22**.



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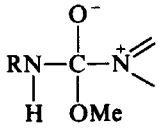


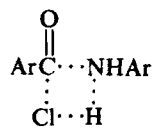
(23)

A recent study[69] of the aminolysis of substituted benzoyl fluorides in water (equation 32) shows that electron-withdrawing substituents R^1 facilitate reaction with primary amines. As for the acyl pyridinium ions, and in contrast to ester aminolysis (Section III.C.2.b) no kinetic terms representing general base catalysis by amine were observed. Nucleophilic-catalysis was not tested. It is evident that most acyl halides are easier for nucleophiles to attack than most esters, and it is reasonable that for nucleophiles as strong as amines, general base catalysis is relatively less important. Acyl pyridinium ions appear to behave rather similarly to acyl fluorides. As the pK_a of the amine is increased the slope of a plot of log k_{obs} against pK_a falls from *ca* 0.7 to *ca* 0.25,

$$R^1C_6H_4COF + R^2NH_2 \longrightarrow R^1C_6H_4CONHR^2 + HF \qquad (32)$$

and its centre of curvature is not affected by the substituent in the acyl group. The authors prefer a concerted displacement to a tetrahedral intermediate mechanism for this system. One would think there will be even less chance of an intermediate with the chlorides (see Section III.A.1).

Most other recent work on aminolysis involves substituted benzoyl chlorides reacting with substituted anilines in non-hydroxylic solvents. The effects of substituents, and of solvent polarity, on the uncatalysed reactions in a variety of solvents[40] (e.g. cyclohexane–chlorobenzene mixtures) suggests (cf Section II) that the transition state is a cyclic, hydrogen-bonded structure (**24**). The reaction of benzoyl chloride with aniline in the



(24)

presence of pyridine in benzene–nitrobenzene mixtures is believed to involve both nucleophilic and general base catalysis[70]. The same reaction, catalysed by tetrabutylammonium chloride[71], follows equation 33. This is reminiscent of the effect of

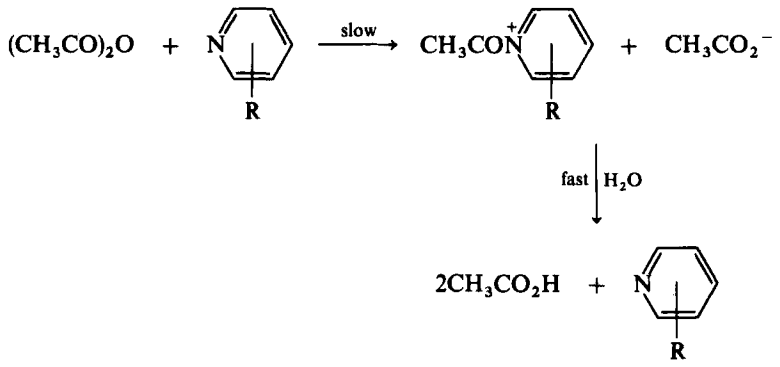
$$PhNH_2 + Bu_4N^+Cl^- \rightleftharpoons PhNH_2\cdots Cl^-N^+Bu_4 \xrightarrow{PhCOCl} PhCONHPh + HCl + Bu_4N^+Cl^- \qquad (33)$$

chloride salts on alcoholysis (Section III.A.1). All these conclusions are consistent with the expected greater difficulty of leaving-group departure in non-hydroxylic solvents. In summary, it can be said that recent work with acyl halides and N-nucleophiles has been

interpreted with less emphasis on tetrahedral intermediates than was common 20 years ago[5a].

B. Carboxylic Anhydrides

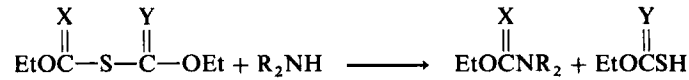
Rather few developments concerning mechanisms have involved anhydrides. For acetic anhydride the nucleophilically-catalysed hydrolysis (equation 34) has been studied[29] with a series of pyridines, and the plot of $\log k_{obs}$ against pK_a is curved, as for



(34)

various other reactions. The introduction of nucleophilic catalysts as powerful as dimethylaminopyridine has led to the use of anhydrides in combination with this or similar catalysts, for the acylation of resistant substrates[66]. Anhydrides are regarded as more satisfactory than acyl halides, since the carboxylate anion produced on forming the pyridinium species is able to catalyse the latter's decomposition (see III.A.2) better than a halide ion. Normally, an equivalent of triethylamine is also added to engage the carboxylic acid product and to prevent it deactivating the pyridine. It is convenient that triethylamine is a stronger base but a less powerful nucleophilic catalyst than the pyridine owing to the importance of steric hindrance in nucleophilic catalysis[5a,67].

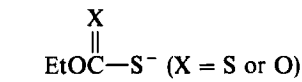
Acylation by some *O,S*-thioanhydrides provides an interesting pattern of results. In the reaction in equation 35 a C=S group is more easily attacked by amine than a C=O



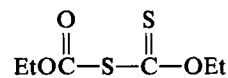
(35)

(X or Y = S or O)

group[72], but when[73] the nucleophile is



the symmetrical anhydride is always formed in reactions with



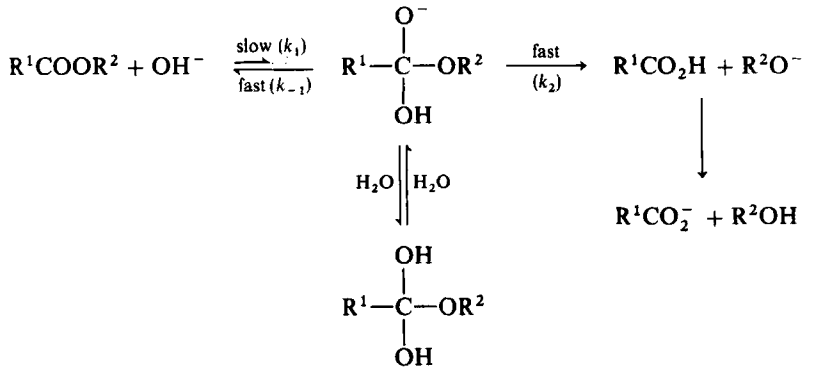
With more conventional *O,S*-thioanhydrides, RCOSCSR, the C=O group is the more easily attacked by nucleophiles[74].

There is still much to be learned about mechanisms of acylation by anhydrides. Although important intermediates in peptide synthesis[1], they have been strangely neglected so far as detailed studies of mechanism are concerned. Talbot[5a] could find relatively little to report in 1970.

C. Esters

1. Hydrolysis and alcoholysis

Ester hydrolysis has always been one of the most intensively studied areas of acylation. By 1970 the essence of what we know today was already available[3,5b], but work has continued unabated, and significant additions have been made. The picture is now more complete, although hazy areas are developing. In 1970, following Bender's work[15] on oxygen exchange, mechanisms of ester hydrolysis involving acyl–oxygen fission* were almost invariably written in terms of tetrahedral intermediates unless acylium ion routes were involved. For saponification the scheme ($B_{AC}2$) was (36), for the spontaneous and general base catalysed reaction it was (37) and for acid catalysis it was (38) in dilute aqueous acid ($A_{AC}2$) and (39) in concentrated acid ($A_{AC}1$). This pattern, which was built



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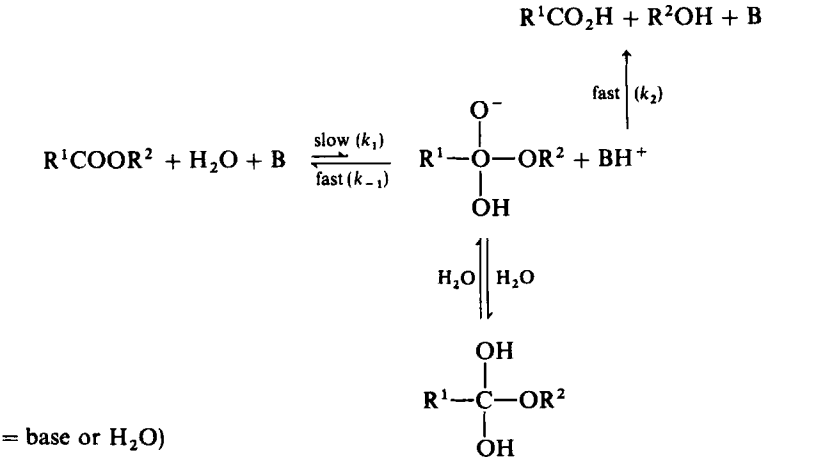
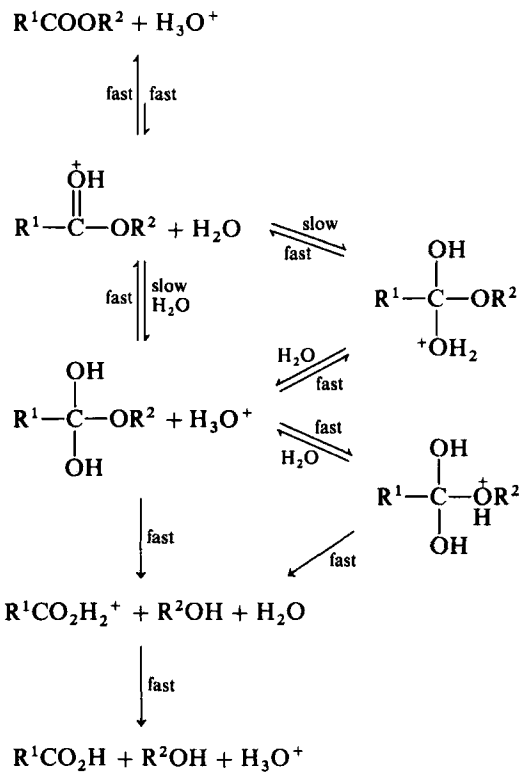


(37)

(B = base or H_2O)

* Esters of appropriate structure hydrolyse via alkyl–oxygen fission[3,5b], but this type of reaction is not acylation and is only briefly mentioned in this chapter.



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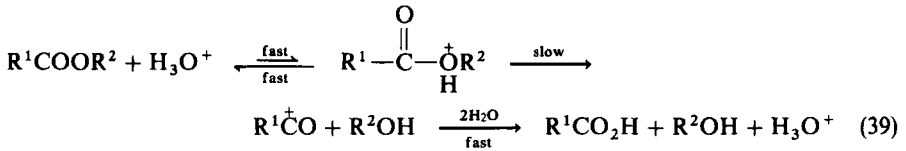


(39)

up from a wide variety of evidence, remains the framework of our understanding. An analogous pattern is thought to apply for alcoholysis. The relative importance of the different routes depends, of course, upon the substituents R^1 and R^2, the pH, the temperature and the solvent. For example, esters containing electron-withdrawing substituents are the most susceptible to routes (36) and (37). The main recent developments have concerned (1) further studies using concentrated acids, (2) the behaviour of esters containing electron-withdrawing substituents and (3) the details of the formation and decomposition of the tetrahedral intermediates. There has also been some suggestions of S_N2-like mechanisms for esters with good leaving groups (see Section II and below).

a. Acid catalysis. Leisten[75] was the first to show that if a simple ester such as ethyl acetate which hydrolyses via the $A_{AC}2$ mechanism in dilute aqueous acid is studied using more concentrated acid solutions, a change in mechanism is ultimately observed. In aqueous sulphuric acid solutions, for example, as the acid concentration is increased the concentration of free water falls (a_{H_2O} falls) but the protonating power of the medium greatly increases (h_0 rises faster than $C_{H_3O^+}$). These changes eventually disfavour the $A_{AC}2$

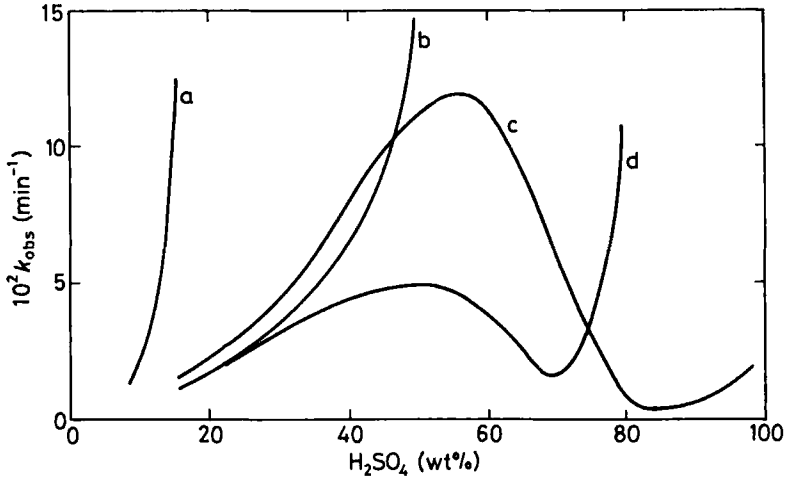


FIGURE 1. Ester hydrolysis in sulphuric acid: (a) *t*-butyl acetate; (b) phenyl acetate; (c) methyl acetate; (d) *sec*-butyl acetate[76]

route, whose slow step involves H_2O (and whose rate may therefore pass through a maximum if most of the ester is protonated) but favour an A1 path [$A_{AC}1$ or $A_{AL}1$ (depending[76] on the ester)]. This pattern of behaviour has now been observed for a relatively large number of esters (and also for other species RCOX) mainly owing to the subsequent work of Yates and colleagues[76–78], who have further developed methods for detecting the mechanistic change that is often, but not always, evident from plots of k_{obs} against acid concentration (Figure 1). Their two principal methods use plots of equations involving acidity functions.

In one method[76] (similar to that introduced by Lane[79] and Jacques[80]) they argue that, for any given mechanism (A2 or A1), a plot of $\log k_{obs} + H_S$ against $\log a_{H_2O}$ (equation 40), where H_S is the acidity function appropriate for the actual substrate S, will be rectilinear with slope r; r is identified with the increase in the number of water molecules on going from the protonated substrate ester to the transition state.

$$\log k_{obs} + H_S = r \log a_{H_2O} + \text{constant} \tag{40}$$

Since the $A_{AC}2$ mechanism and A1 mechanisms might sensibly be expected to involve different values of r for their slow steps, such plots should show discontinuities when changes in mechanism occur[80]. This is found to be so[76,80]. The second method, introduced more recently, uses the concept of the excess acidity (X) developed by Cox and Yates[81]. In this method it is argued[82] that an A2 mechanism should obey equation 41, and an A1 or an AS_E2 mechanism an equation of the form 42. In these equations

$$\log k_{obs} - \log C_{H_3O^+} - \log C_S/(C_S + C_{SH^+}) = r \log a_{H_2O} + m^* m^\ddagger X + \text{constant} \tag{41}$$

$$\log k_{obs} - \log C_{H_3O^+} - \log C_S/(C_S + C_{SH^+}) = m^* m^\ddagger X + \text{constant} \tag{42}$$

m^* is a parameter characteristic of the protonation of the substrate S, and $m^\ddagger$ a parameter characteristic of the transition state. For measurements of k_{obs} over a significant range of acidity (i.e. of X) a plot of $\log k_{obs} - \log C_{H_3O^+} - \log C_S/(C_S + C_{SH^+})$ against X should be a curve for an A2 mechanism (because the term in $\log a_{H_2O}$ is important for this mechanism) but rectilinear for an A1 or AS_E2 scheme. This too has

TABLE 1. Mechanisms of acid-catalysed ester hydrolysis in aqueous sulphuric acid solution at 25 °C[76–78,83]

Ester	Mechanism	Approximate region of change-over (%H_2SO_4)
$CH_3CO_2CH_3$	$A_{AC}2$–$A_{AC}1$	82
$CH_3CO_2C_3H_7$-n	$A_{AC}2$–$A_{AC}1$	82
$CH_3CO_2C_4H_9$-*sec*	$A_{AC}2$–$A_{A1}1$	72
$CH_3CO_2CH_2C_6H_5$	$A_{AC}2$–$A_{A1}1$	62
$CH_3CO_2C_6H_5$	$A_{AC}2$–$A_{AC}1$	>62
$CH_3CO_2C_6H_4NO_2$-*p*	$A_{AC}2$–$A_{AC}1$	65
$CH_3CO_2CH{=}CH_2$	$A_{AC}2$–AS_E2 (Ad_E2)	48
$CH_3CO_2C_4H_9$-*t*	$A_{A1}1$	—
$CH_3CO_2CH_2OMe$	$A_{A1}1$	—
$CH_3CO_2CH_2SMe$	$A_{A1}1$	—
$CH_3CO_2CH_2OC_6H_5$	$A_{AC}2$–$A_{AC}1$	40
$CH_3CO_2CH_2SC_6H_5$	$A_{AC}2$–$A_{AC}1$	20
$C_6H_5CO_2C_2H_5$	$A_{AC}2$–$A_{AC}1$	80
$C_6H_5COSC_2H_5$	$A_{AC}2$–AS_E2	60
$C_6H_5CSOC_2H_5$	AS_E2–$A_{Ac}2$	62

been found to be the case[82]. It is important to realize that procedures based on an acidity function approach are essentially empirical. They have to be validated by testing them with reactions of (supposedly) known mechanism. This is necessary because of the assumptions about the cancellation of activity coefficient ratios which is central to all acidity function approaches[82]. For the excess acidity method it is normally found that for A2 reactions $m^{\ddagger} \sim 1$, for A1 mechanisms $m^{\ddagger} > 1$ and for AS_E2 mechanisms $m^{\ddagger} < 1$. Values of r can also be obtained from the excess acidity method[82]. As just implied, the exact significance of the parameter r will depend upon the validity of the inbuilt assumptions. Normally for $A_{AC}2$ mechanisms $r \sim 2$; and for the $A_{AC}1$ mechanism $r \sim -0.2$, and for the $A_{A1}1$ scheme $r \sim -0.6$, but esters (e.g. *t*-butyl acetate) whose main acid-catalysed hydrolysis route is $A_{A1}1$ have much larger negative r values of uncertain interpretation[76].

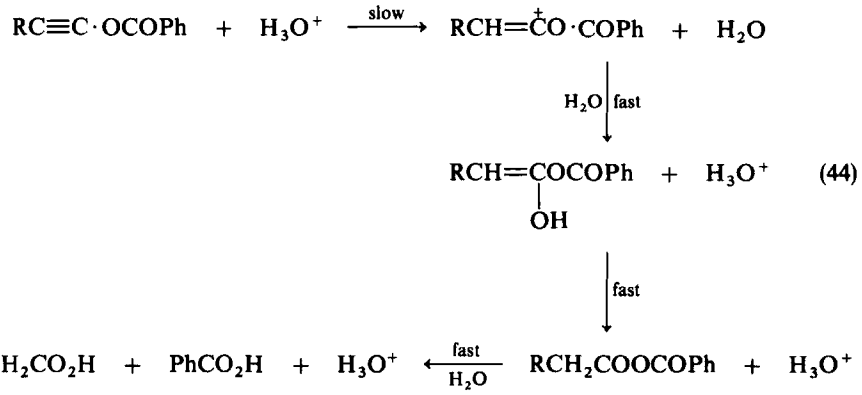
Although the acidity function methods must possess uncertainties, their use has produced self-consistent and sensible results which are also consistent[76] with other criteria of mechanism such as $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, kinetic isotope effects and the details of oxygen exchange during hydrolysis. Table 1 gives an idea of the pattern that has emerged for sulphuric acid solutions. Some of this pattern is expected on the basis of previous, more limited knowledge. The change to Ad_E2 for the vinyl esters arises from the onset of hydrolysis via slow proton transfer to carbon (equation 43), similar to that well-established for the hydration of vinyl ethers and related compounds[84]. Apart from this Ad_E2 route in strongly acidic solutions, vinyl esters behave similarly to ordinary

$$CH_3COOCH{=}CH_2 + H_3O^+ \xrightarrow{\text{slow}} CH_3COO\overset{+}{C}HCH_3 + H_2O$$

$$\xrightarrow[H_2O]{\text{fast}} CH_3C(=O)CH(OH)CH_3 + H_3O^+$$

$$\downarrow \text{fast} \qquad (43)$$

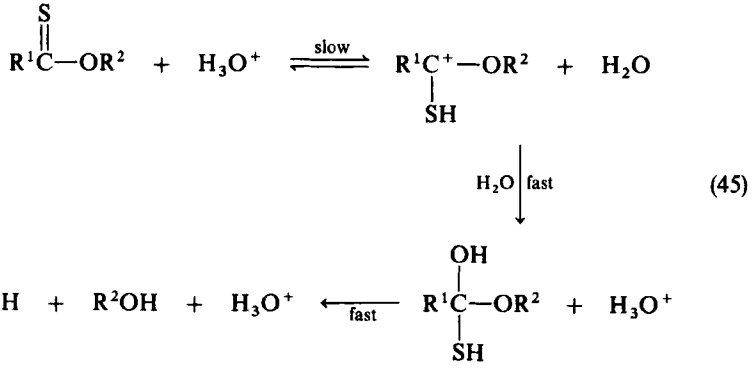
$$H_3O^+ + CH_3CO_2H + CH_3CHO$$



(44)

O-esters. Acetylenic esters have recently been found[85] to behave analogously (equation 44). Their Ad_E2 reactions have small negative values of $\Delta S^{\ddagger}$, and $k_{H_2O}/k_{D_2O} \sim 2.7$. As for vinyl esters, the spontaneous and base-catalysed hydrolyses of acetylenic esters probably involve the mechanisms used for simpler esters.

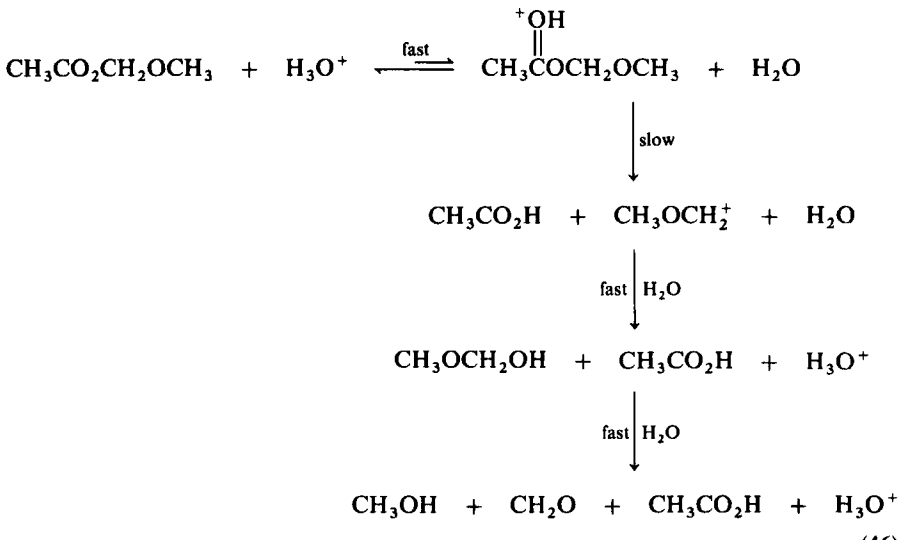
Thiol and thion esters show mixtures of $A_{AC}2$ and AS_E2 mechanisms[78]. Although difficult to protonate, thion esters ($R^1CS{\cdot}OR^2$) are very susceptible to the $A_{AC}2$ mechanism. The protonation on the C=S group leads to a larger positive charge on the carbonyl carbon atom than for C=O protonation, and in dilute acid the actual protonation itself is believed to be the slow step of hydrolysis (equation 45). Thion esters



(45)

do not exhibit the change-over to an A1 mechanism at very high acid concentrations shown by O-esters. This is believed to be due[86] to the instability of thioacylium ions $R\overset{+}{C}=S$. For thiol esters (R^1COSR^2), although easier to protonate on oxygen than even their *O,O*-analogues, the $A_{AC}2$ route is nevertheless disfavoured by comparison, because the leaving group SR^2 is reluctant to accept a proton. As a consequence an AS_E2 mechanism via the slow protonation of this group is thought to dominate at high acidities, with the transfer being mainly from the HSO_4^- ion.

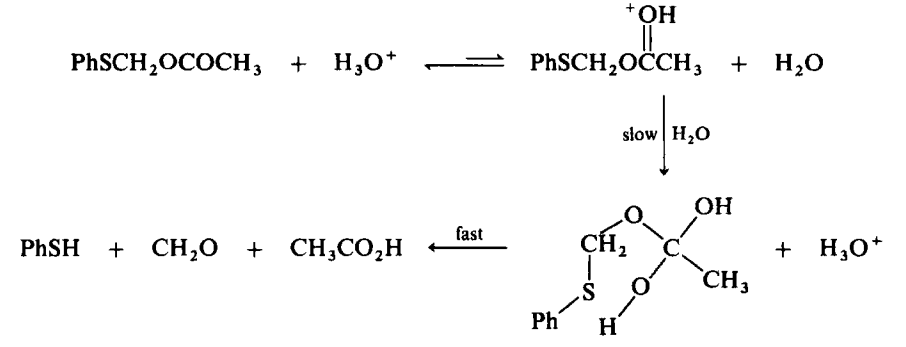
If the meaning of the *r* values mentioned above is accepted, the actual values (*ca* 2 for almost all the assigned $A_{AC}2$ routes[76], and mostly small and negative for A1 routes) have chemically sensible implications: two water molecules are indeed normally assumed to be involved in the slow step of equation 38, and it appears reasonable that the acylium or carbenium ions in A1 routes (e.g. equation 39) should be slightly less hydrated than the protonated ester species from which they are formed in the slow step[76].



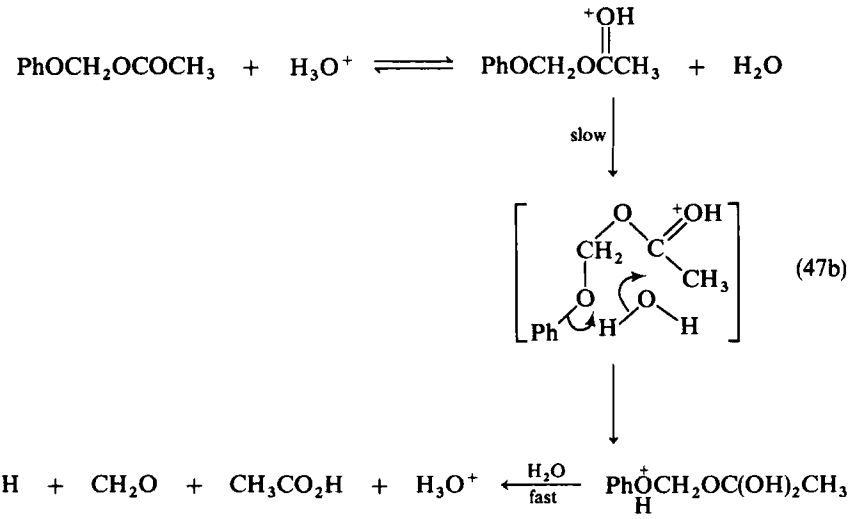
(46)

The behaviour[83] of the O- and S-acylals shown in Table 1 is nicely consistent with all the other results. The aliphatic acylals both exhibit rapid A1 routes via hemiacetals (equation 46). The aromatic compounds possess less electron release and therefore display some A2 behaviour also (at low acidities). They are suggested to decompose in cyclic $A_{AC}2$ routes (equations 47a and 47b). The formation of the tetrahedral intermediate is normal for the S-compound ($r = 2$), but requires only one H_2O molecule ($r = 1$) for the O-acylal, the ether oxygen being sufficiently basic in a cyclic route to replace the second water molecule as a general base catalyst.

Another approach used by Yates[87] to identify changes in the mechanism of acid-catalysed ester-hydrolysis (and other reactions) has been to use rate constants and acidity function data to calculate values of the activity coefficient $f_{\ddagger}$ of the transition state (relative to that of $Et_4N^+Cl^-$) over a range of acid concentrations to discover if $f_{\ddagger}$ varies. For the $A_{AC}2$ mechanism the transition state would be expected to be much more strongly stabilized by hydration than would $Et_4N^+Cl^-$, and therefore to be salted-out relative to that ion as the acid concentration rises (and a_{H_2O} falls); for an



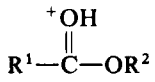
(47a)



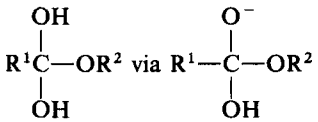
(47b)

A1 mechanism less salting-out relative to $Et_4N^+Cl^-$ is probable. If a change in mechanism occurs, this should therefore be reflected in a change in the slope of the plot of log f_t against $[H_2SO_4]$. Such changes are found[87], and support the conclusions detailed in the foregoing discussion.

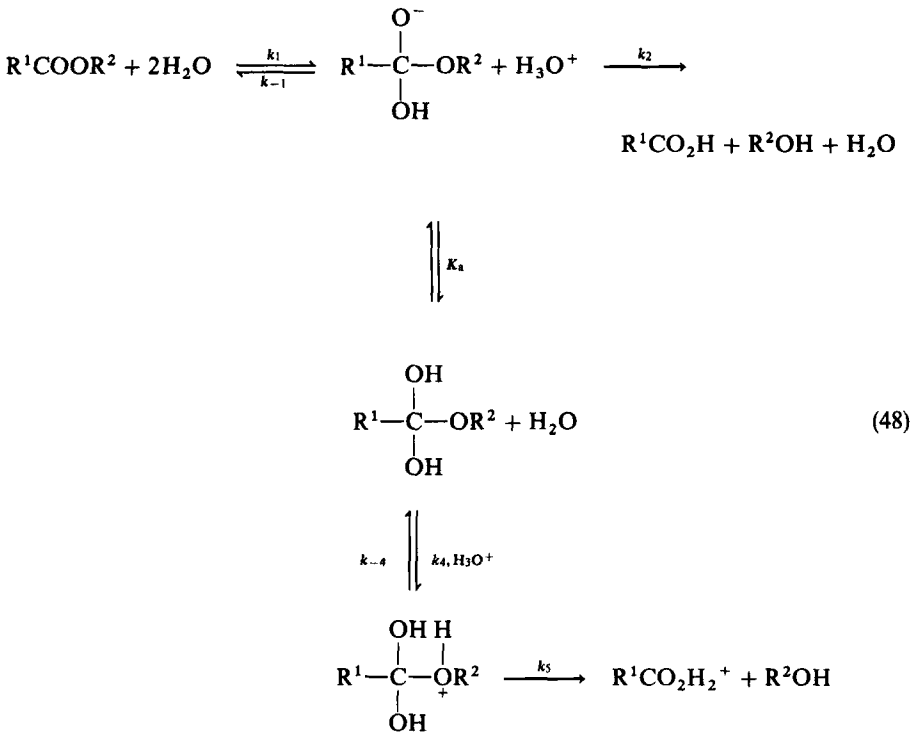
b. Esters containing electron-withdrawing substituents. Esters such as chloro-substituted alkyl acetates are activated towards base-catalysed and spontaneous hydrolysis (equations 36 and 37) and are found to display unusual dependencies upon acid concentration in their acid-catalysed hydrolyses[3,5b]: in dilute acid they do not show the behaviour expected for an $A_{AC}2$ scheme and sometimes display an early maximum rate not entirely attributable to salt effects[88,89]. Such esters also prove to be more susceptible to acid catalysis than substituent effects would predict. In 1970 satisfactory explanations were lacking. It has since been suggested[90–93] that these effects arise because the esters have another route for acid catalysis available to them, which can supervene before the $A_{AC}2$ mechanism appears, and which can sometimes replace it altogether. Thus, as well as the $A_{AC}2$ route via



(equation 38) it is proposed that they have an important path to



formed in reaction (37), a reaction which, as noted above, is more important for these esters than for those without electron-withdrawing substituents. This proposal (equation 48) gives scope for a variety of effects at modest values of $[H_3O^+]$. The corresponding rate equation[92] has the form of equation 49 in which $k_a = k_1k_2/(k_{-1} + k_2)$



(48)

is the rate constant for the mechanism of spontaneous hydrolysis (equation 37), and k_b and k_c involve also K_a, k_4, k_{-4} and k_5. If the $A_{AC}2$ route is also contributing, then equation 49 has an extra term $k_{A2}[H_3O^+]$, as in equation 50, corresponding to the mechanism of equation 38.

$$k_{obs} = (k_a + k_c[H_3O^+])/(1 + k_b[H_3O^+]) \quad (49)$$

$$k_{obs} = (k_a + k_c[H_3O^+])/(1 + k_b[H_3O^+]) + k_{A2}[H_3O^+] \quad (50)$$

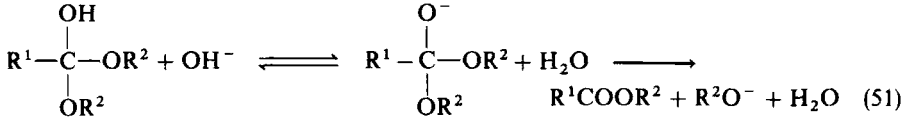
Euranto[91] has labelled this new acid-catalysed route an $AB_{AC}3$ mechanism, since he also calls the spontaneous or general base-catalysed route the $B_{AC}3$ mechanism as it involves three species in its slow step. That the $AB_{AC}3$ route takes the form shown is supported by solvent isotope effects: $k_{H_2O}/k_{D_2O} > 1$ as for the $B_{AC}3$ mechanism, whereas $k_{H_2O}/k_{D_2O} < 1$ for the $A_{AC}2$ mechanism.

The relative importance of the $AB_{AC}3$ and $A_{AC}2$ routes in particular cases can be assessed using equation 50. It is found to depend upon the amount of electron withdrawal, and to some extent upon the position of the electron-withdrawing substituents. Substituents in the leaving group have more effect than those in the acyl portion of the ester. The balance also depends upon the acid concentration, since the $A_{AC}2$ mechanism tends to take over at high acid concentrations. This pattern[94,95] found with chloro-substituted alkyl acetates is illustrated in Table 2. Similar but less pronounced effects are found for alcoholysis[95,96]. At very high acidities the hydrolysis of these esters goes over to an A1 mechanism as for other esters[90].

TABLE 2. Mechanisms of acid catalysis for esters with electron-withdrawing substituents in dilute acid solution.

Hydrolysis		Alcoholysis	
$CH_3CO_2CH_3$	$A_{AC}2$	$CHCl_2CO_2CH_2Cl$	$AB_{AC}3$–$A_{AC}2$
$CH_2ClCO_2CH_3$	$A_{AC}2$	$CCl_3CO_2C_2H_5$	$A_{AC}2$
$CH_2ClCO_2CH_2Cl$	$AB_{AC}3$–$A_{AC}2$	$CCl_3CO_2CH_2Cl$	$AB_{AC}3$
$CHCl_2CO_2CH_2Cl$	$AB_{AC}3$		
$CCl_3CO_2CH_3$	$AB_{AC}3$		

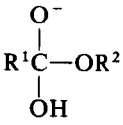
c. Formation and decomposition of tetrahedral intermediates. As mentioned in Section II, recent work on the mechanism of decomposition of hemiorthoesters[22b,24] has possible implications for ester hydrolysis because hemiorthoesters are identical with the intermediates that probably form in aliphatic ester alcoholysis, and are similar in structure to those probably involved in aliphatic ester hydrolysis. The mechanism of decomposition of hemiorthoesters proposed for alkaline solution (equation 51) is compatible with



(25)

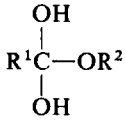
$$R^1COOR^2 + R^2O^- + H_2O \quad (51)$$

equation 36. For

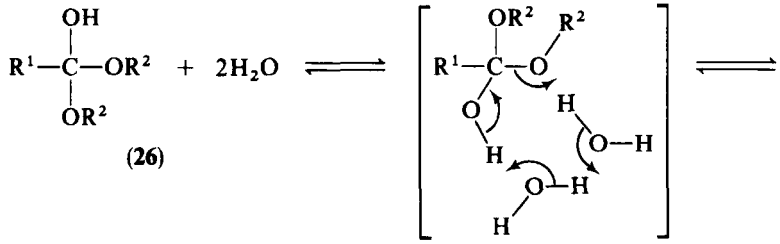


(equation 36) it has been calculated that loss of R^2O^- is faster than loss of H^+ from the —OH group[97].

The mechanism preferred for the spontaneous or water-catalysed decomposition (equation 52) implies that



in the $B_{AC}3$ mechanism (equation 37) could be formed directly from ester and three molecules of water, and decompose to acid via a similar cyclic transition state.

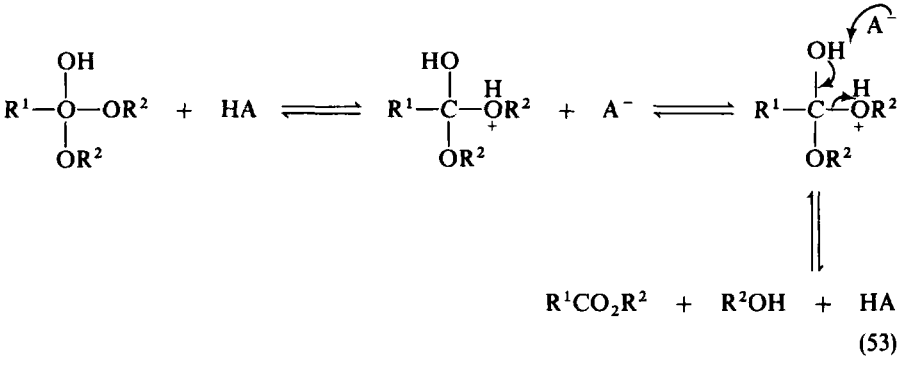


(26)

$$R^1COOR^2 + R^2OH + 2H_2O \quad (52)$$

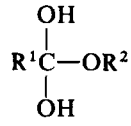
Decomposition of **26** via its anion **25** seems to be disfavoured in neutral solution[22b]. However, it is the anion that is thought to be formed directly in the $B_{AC}3$ mechanism. There is some evidence[98] that spontaneous ester hydrolyses are second (not third) order in $[H_2O]$, but third-order terms are possible in appropriate circumstances[99]. A cyclic scheme with more than two water molecules could better explain proton inventory studies[100] of the neutral hydrolysis of *p*-nitrophenyl dichloroacetate. It has also been suggested that the number of water molecules in the transition state for ester hydrolysis depends upon the hydrophobicity of the ester[100,101]. It may well be that the details of the spontaneous alcoholyses and hydrolyses of esters depend upon the structure of the esters. This is an area now in need of clarification.

A mechanism suggested[22b] for the acid-catalysed decomposition of hemiorthoesters is shown in equation 53. It is modelled on a route proposed[102] for the hydrolysis of

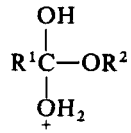


(53)

hemiacetals which, like that of hemiorthoesters, is general acid catalysed. For $HA \equiv H_3O^+$ this scheme is compatible with the finding that a proton and two water molecules are normally associated with the transition state in $A_{AC}2$ ester hydrolysis, but does not fit in with the pre-equilibrium protonation normally assumed. It seems possible that the mechanism of decomposition of

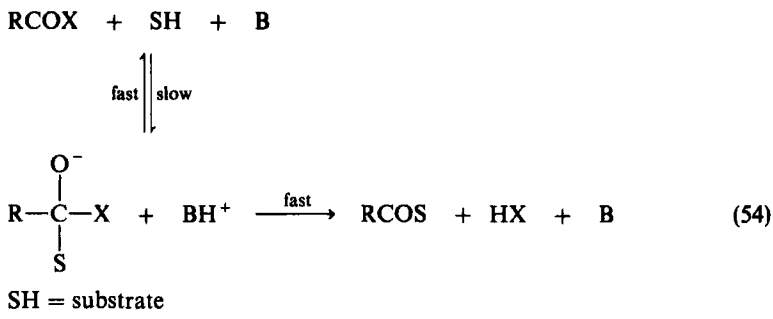


shown in the $A_{AC}2$ mechanism (equation 38) applies also to hemiacetal and hemiorthoester hydrolysis: it is compatible with general acid catalysis if

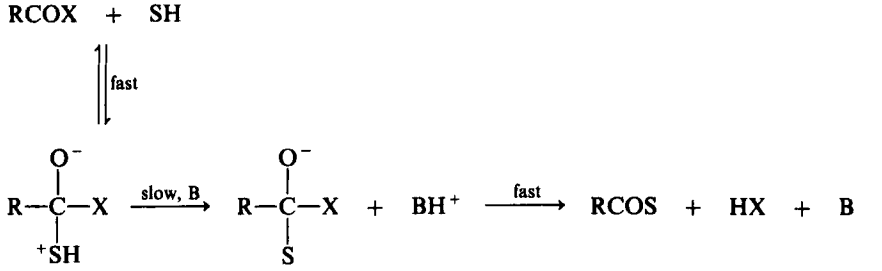


is omitted. But perhaps again alcoholysis differs from hydrolysis.

In considering general base-catalysed reactions of species RCOX occurring via tetrahedral intermediates, there are two principal ways in which the base can render the substrate (SH) more nucleophilic: by removing a proton during formation of the intermediate (e.g. equation 54), or after its formation (equation 55). For ester hydrolysis, mechanisms are almost invariably formulated along the lines of equation 54, it being



(54)



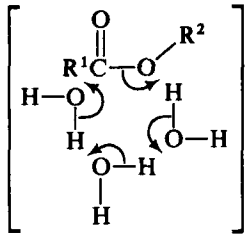
(55)

assumed that bond-forming is the rate-limiting step. The balance between general base and nucleophilic catalysis for any system depends upon the ease with which the leaving group can depart. For leaving groups that can depart easily, nucleophiles of only moderate strength can successfully attack the carbonyl carbon atom, and nucleophilic catalysis is prominent. For poor leaving-group ability powerful nucleophiles are needed, and can be provided by general base catalysis[103]. What this generalization amounts to is the obvious fact that substitution into RCOX without catalysis is easiest when the leaving group can easily depart. The sensitivity of general base-catalysed hydrolysis of esters to the basicity of the catalyst is less than is the sensitivity of nucleophilic catalysis ($\beta_{cat} \sim 0.5$ compared with $\beta_{nuc} \sim 0.9$) so that for sufficiently basic catalysts the nucleophilic path will eventually take over completely[104]. The effect of substituents in the acyl portion of an ester on leaving-group ability is well illustrated in a study using *p*-nitrophenyl acetate and trifluoroacetate. In hydrolysis by a low concentration of water in acetonitrile the former ester displays nucleophilic catalysis by pyridines, whereas the latter only displays general base catalysis[105,106].

The actual attack on an ester is doubtless more complicated than illustrated in conventional schemes such as equation 36, 37 or 52. For spontaneous hydrolysis, volumes of activation suggest[107] a preliminary volume decrease due to molecular association of the reagents prior to the bond formation which produces the tetrahedral intermediate. Theoretical models predict that in the attack of anionic nucleophiles most of $\Delta G^{\ddagger}$ is accounted for by desolvation of the anion, and by any deformation of the ester needed to permit the electron transfer necessary for bond formation. The addition of the bare anion to the carbonyl group may have a very low activation energy[46,108].

For esters with sufficiently good leaving groups it is tempting to speculate about the possibility of S_N2-like hydrolyses. It was concluded[99] from a study of the spontaneous hydrolysis of various nitrophenyl trifluoroacetates that intermediate formation was to

be preferred, but the leaving group did have an important influence on k_{obs}. Good leaving groups (relative to OH^-) can only exert this influence by affecting k_1 in schemes like (36) and (37) involving intermediates (since for such leaving groups $k_{obs} \sim k_1$). Other authors[109,110] favour S_N2-like routes for esters of this type and concerted cyclic schemes (**27**) are also compatible with proton inventory studies[100]. Experiments on the anionic



(**27**)

alcoholysis and phenolysis of aryl esters (equation 56), using a wide range of nucleophiles, lead to straight line plots of $\log k_{obs}$ against pK_a of the nucleophile, and have been interpreted[21,111] as indicating S_N2-like processes (see Section II). These recent developments, and the evidence from hemiorthoesters, cast doubt on the complete adequacy of

$$R^1CO_2Ar + R^2O^- \text{ (or } Ar^1O^-) \longrightarrow R^1CO_2R^2 \text{ (or } Ar^1) + ArO^- \quad (56)$$

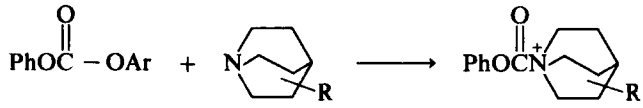
the 'standard' mechanisms given in Section III.C.1. This is an area in a state of rapid current development.

2. *Aminolysis*

a. Spontaneous aminolysis. Kinetic studies of ester aminolysis frequently involve unravelling rate equations containing several terms[1]: terms for spontaneous aminolysis by one amine molecule, for aminolysis catalysed by a second amine molecule, or by protonated amine, and for any concurrent amine-catalysed hydrolysis or solvolysis. Consequently, the kinetic form is often simpler in non-hydroxylic solvents[112–114]. One convenient type of system that has been much studied in recent years with hydroxylic solvents is that which represents the first stage of a nucleophilically-catalysed solvolysis using tertiary amines (equation 57). It leads to an acyl ammonium ion and is not

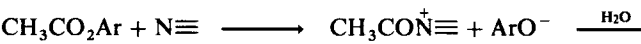
$$R^1CO_2R^2 + N\equiv \xrightarrow{k_{obs}} R^1CO\overset{+}{N}\equiv + R^2O^- \left(\xrightarrow{H_2O} R^1CO_2H + R^2OH + N\equiv\right) \quad (57)$$

complicated by proton transfer catalysis. This type of reaction has already been mentioned in Section II and in the discussions of acyl halides and anhydrides. As with these other acylating agents, the use of a given ester with a series of pyridines (or similar nucleophiles) of increasing basic strength provides data for a plot of $\log k_{obs}$ against pK_a. This plot proves to be curved for esters with sufficiently good leaving groups. Curvature generally begins when the pK_a of the amine has a value of *ca* 3–5 pK_a units greater than that of R^2OH and the slope (β_{nuc}) falls typically[26] from *ca* 1 to *ca* 0.2–0.3 at the highest pK_a values (see Section II). When the leaving group is so basic that amines of sufficient pK_a are unavailable to exceed its pK_a by 3–5 units, a straight line is obtained[115,116]. Esters with substituents in their acyl portion, that make leaving-group departure more difficult, shift the on-set of curvature to even higher pK_a values for the



(58)

attacking amine[117]. Since the curvature of these plots is evidently something to do with the change in the relative importance of the bond-breaking and bond-forming in the reaction, such substituents therefore have relatively more effect in hindering leaving-group departure than they have on assisting nucleophilic attachment. One of the most complete studies of these systems is that shown in equation 58 involving a series of substituted quinuclidines and different nitrophenyl phenylcarbonates[26]. Other systems that have yielded similar results[27,115–117] are substituted phenyl acetates (equation 59) and phenyl methylcarbonates (equation 60). Earlier work[26] on the hydrolysis of phenyl acetate catalysed by a variety of O- and N-nucleophiles shows a similar pattern. Aprotic

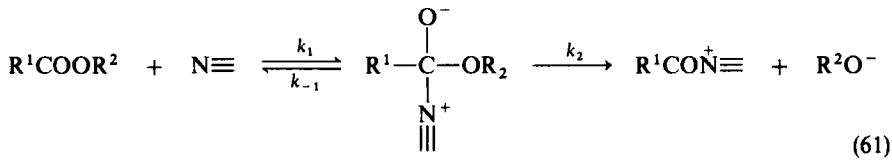


(59)

(60)

solvents tend to stabilise neutral amines more than ArO^- (or other) ions, and shift the balance of behaviour to more difficult loss of leaving group. Again the curvature of plots is shifted towards higher pK_a values for the attacking amine.

The general interpretation of these various findings as evidence for tetrahedral intermediates in uncatalysed aminolysis (equation 61) was mentioned in Section II. The

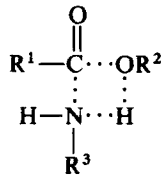


(61)

greater effect of substituents in R^1 on k_2 than on k_{-1} that it is necessary to postulate in the tetrahedral interpretation is difficult to understand, but one difficulty about the argument that the various effects can be explained on the basis of a concerted process with different amounts of bond breaking and forming is to account for rectilinear plots of $\log k_{obs}$ against pK_a when curvature might have been expected. It is frequently found that bulky amines react with esters more slowly than would be expected on a pK_a basis. This finding seems more compatible with the formation of a crowded intermediate than with a synchronous displacement. For strong amines and poor leaving groups, a rapid pre-equilibrium formation of the intermediate is often suggested.

In uncatalysed aminolysis the leaving group R^2O^- will have to depart as an anion (equation 57). This is reasonable in hydrogen-bonding solvents, or in media of high relative permittivity, but less reasonable in non-polar aprotic solvents in which ion pairs will be less stable and separate with difficulty. Aminolysis under such conditions often shows a greater sensitivity to catalysis by a second molecule of amine than do similar reactions in water, and there have been suggestions[113,118] that in non-polar solvents a proton from the incipient ammonium ion is transferred synchronously to the leaving group (e.g. **28**). This idea is supported by theoretical calculations concerning gas-phase reactions[44]. Because in aprotic solvents leaving-group departure will be more difficult, the effects of substituents in the leaving group would be expected to be large. This can be so[119]. When the effects are modest[112,113] this could point to the importance of

transition states like **28**. The fact that in diethyl ether solution aminolysis of *O*-hydroxylamino esters of type $ArCOONR_2$ with rather basic leaving groups does not involve catalysis by a second amine molecule, whereas that of most esters does, suggests that a transition state such as **29** is possible[112,113].



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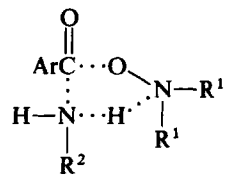
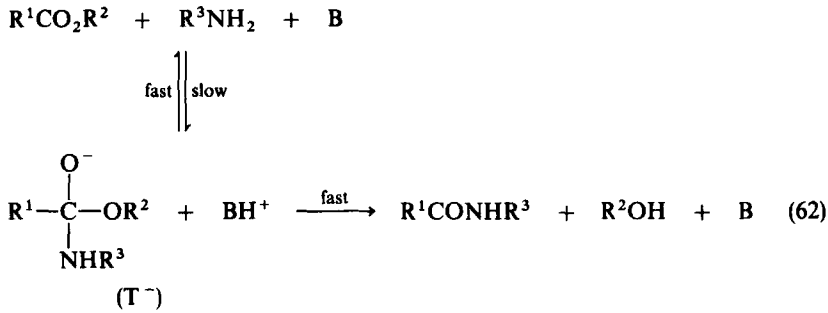
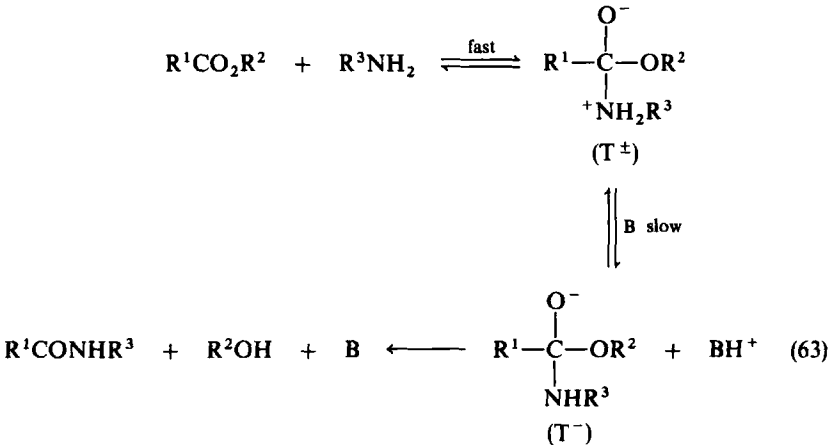
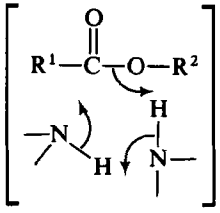


(29)

b. Base-catalysed aminolysis. Turning to catalysed reactions we find that, although for the hydrolysis of esters general base catalysis is almost invariably considered to follow mechanism (54) rather than (55), this is not true for aminolysis. Both the corresponding schemes in equations 62 and 63 have long been advocated, and cyclic transition states **30** involving simultaneous proton transfer to the leaving group have also had past





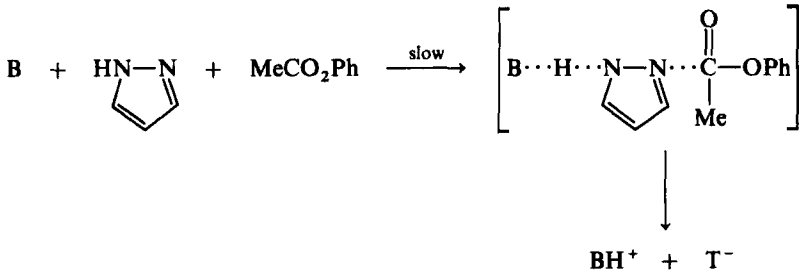


(30)

supporters[113,120], especially for media unable to stabilize the R^2O^- groups. However, general base catalysis by unhindered tertiary amines is now well established[114,121] in such media so that transfer of the proton to the anionic leaving group *after* the slow step is certainly possible even in chlorobenzene. The principal developments in recent years have concerned attempts to assess the relative importance of these three possible routes in different circumstances. Largely owing to Jencks' work, the schemes in equations 62 and 63 are now coming to be seen as complementary, rather than as the rival interpretations of twenty years ago. Support for cyclic transition states has dwindled since the discovery of general base catalysis by tertiary amines in both aqueous[26] and aprotic solvents.

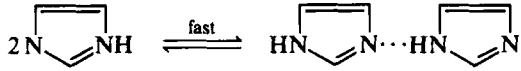
Current views on whether equation 62 or 63 is the path followed in any given general base catalysed aminolysis are in a rapidly developing state. Jencks[122,123] has argued that the stability of $T^{\pm}$ is the crucial feature. Its stability will depend upon the substituents R^1 and R^2 and on the basicity of the amine. For a particular ester a sufficiently basic amine will provide $T^{\pm}$ with a life-time sufficient for it to be trapped (as T^-) by proton transfer to the catalyst B (and then rapidly go on to products, since OR^2 will normally be a better leaving group than NHR^3). A rapid pre-equilibrium formation of $T^{\pm}$ is therefore assumed followed by slow proton transfer to the catalyst (equation 63). This slow proton transfer will be expected to show Eigen-like behaviour: insensitive to the pK_a of the catalyst when that pK_a is large, and sensitive when the pK_a is small, so that a plot of log k_{obs} against $(pK_a)_{cat}$ will be a curve with a slope ranging from *ca* 0 to *ca* 1. Different aspects of the transformation of $T^{\pm}$ to T^- will be the slow phase, depending upon the pK_a of the catalyst (because of the limitations of diffusion processes), and a maximum in the solvent deuterium isotope effect is expected at intermediate pK_a values. Effects of this type have been observed for the catalysed reaction of amines with methyl formate[122,123], and in other systems. When, for a particular ester, the amine is too weakly basic to give $T^{\pm}$ of sufficient stability to be trapped by the catalyst, then it is suggested the catalyst will be forced to operate via the mechanism in equation 62. Now T^- will be formed directly before the rapid loss of the leaving group. This type of behaviour is suggested for the base-catalysed reaction of pyrazole[124] with phenyl acetate (equation 64). With a given amine changes in the stability of $T^{\pm}$ can be produced by changes in R^1 or R^2. It is thought[26] that such changes have a parallel and predictable effect on the balance between the mechanisms in equations 62 and 63. In general, different authors favour one or other of the schemes in the latter two equations depending upon the pattern and extent of their results[125,126]. This account of course ignores the possibility of synchronous or concerted displacements. Trigonal transition states have been postulated[41] for the general base catalysed reactions of hydrazines with phenyl acetate on the basis of secondary isotope effects (see Section II).

For general base catalysed reactions in aprotic solvents, the mechanism in equation 63 has been usually advocated since Menger's discovery[127] of the very powerful effects produced by substituents in the leaving group on the reactions of piperidine with substituted phenyl acetates in toluene. It is considered that leaving-group departure



(64)

must be the dominant factor in this aminolysis. However, not all aminolyses in non-hydroxylic media show such powerful substituent effects[113]. Carboxylic anions (added as tetraalkyl ammonium salts) have been found to be especially powerful general base catalysts of aminolysis in aprotic solvents[127–129]. It is now recognized that amines undergo hydrogen-bonded self-association, and also associate strongly with anions, in such media, so that it is possible that aminolysis mechanisms under these conditions do involve an element of proton removal from the attacking amine *prior* to formation of the tetrahedral intermediate[128,129] (equations 65 and 66). The pre-association could account for some or all of the negative $\Delta H^{\ddagger}$ values sometimes obtained[114,121]. The substitution could even be synchronous or concerted.



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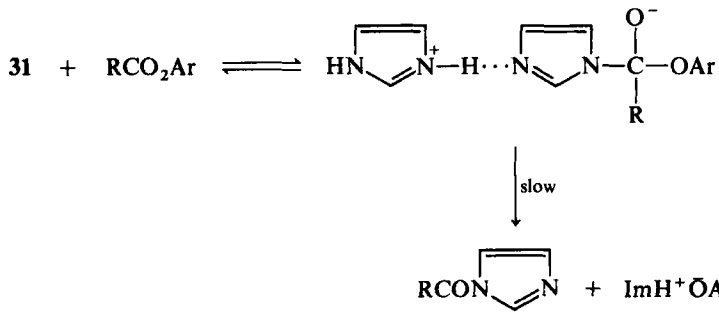
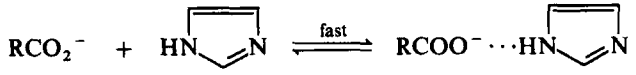


(65)

c. Acid-catalysed aminolysis. Acid catalysis of ester aminolysis has most often been studied using aqueous solutions containing the amine cation RNH_3^+, and other acids. Strongly acidic media are not useful since then too much of the amine is protonated, but general acid catalysis is frequently found using buffer solutions[1]. As for general base catalysis, the role of acid catalysis with a particular ester is now thought[124,130] to depend upon the strength of the attacking amine. For amines strong enough to rapidly form a



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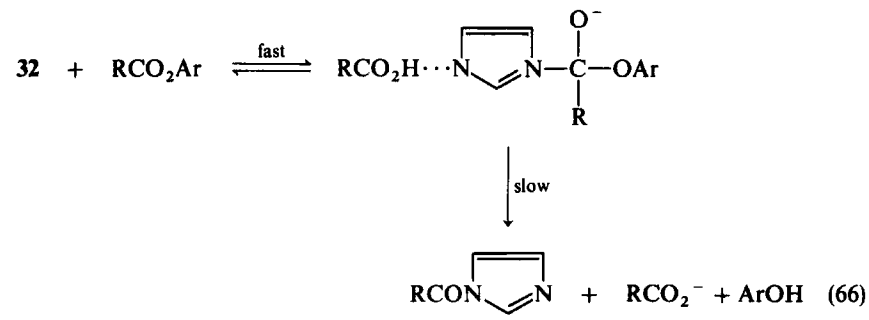
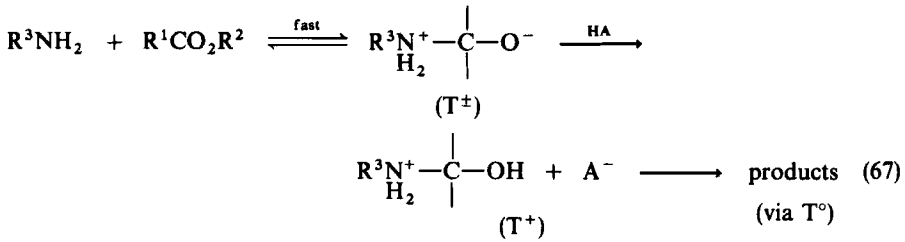
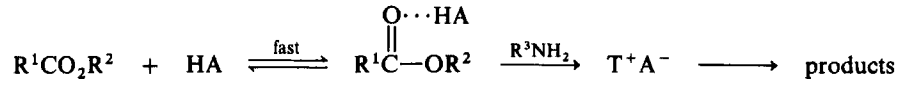


sufficiently stable tetrahedral intermediate $T^{\pm}$, the acid is able to assist the decomposition of $T^{\pm}$ to products by trapping it by proton transfer (equation 67). This type of



transfer is subject to diffusion control for strong acid catalysts. For such systems Eigen curves, and maxima in the solvent deuterium isotope effect, are found[129] if the pK_a of the catalyst is varied. With amines too weak[124,130] to give an intermediate of sufficient life-time for trapping, the acid assists the formation of the intermediate either by pre-equilibrium hydrogen bonding (equation 68), pre-equilibrium protonation or, with suitable acids, by a cyclic, bifunctional route, to give T^0 (equation 69). The effectiveness



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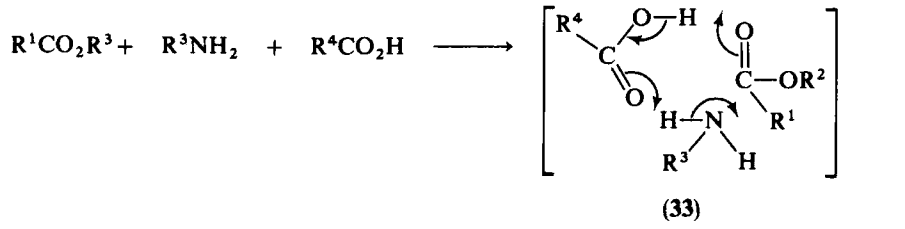

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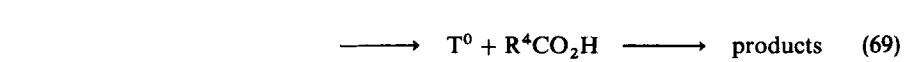


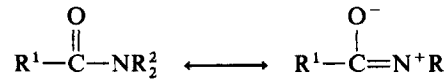
of this type of route can depend inversely on acid strength, showing it to be more like base than acid catalysis. Bifunctional catalysis is more efficient than catalysis by monofunctional acids, and can supervene even when $T^{\pm}$ has an adequate life-time for the route in equation 67.

In non-hydroxylic solvents, catalysis of ester and other aminolyses by bifunctional acids is frequently observed[7,112]. Again the catalytic effectiveness is often inversely related, or unrelated, to conventional acid strength. Cyclic transition states seem very likely; for esters they could involve the carbonyl group as in **33** or the leaving group.

D. Amides

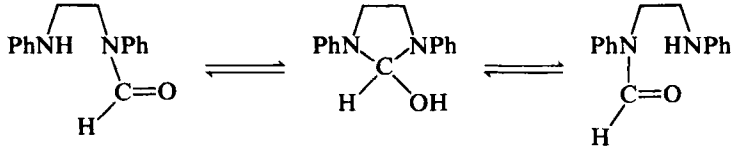
1. Hydrolysis

As a class of acylating agent, amides are less reactive than esters, usually having poor leaving groups which enjoy substantial resonance interaction[131] with the carbonyl group (equation 70). Amides are susceptible to acid and to base catalysis, but their spontaneous



(70)

hydrolyses usually contribute relatively little to the overall reaction rate[4,5a]. Typical amides are more basic ($pK_a \simeq -2$ for O-protonation) than are typical esters ($pK_a \simeq -6$), but protonation on nitrogen is difficult ($pK_a \simeq -7$). Amides, together with esters, have provided the bulk of the known examples of relatively stable tetrahedral intermediates (see Section II). Because of the possible resonance interaction (equation 70), which stabilizes the free amide, these stable addition species involve amides with electron-withdrawing substituents on the nitrogen atom, a feature that reduces the resonance. It may be that other amides form tetrahedral intermediates with some difficulty, but the first relatively simple intermediate to be detected[132] (spectroscopically) in any acylation was in an amide system (equation 71) and, as mentioned in Section II, some of the best kinetic evidence for tetrahedral intermediates involves the hydroxide ion-promoted hydrolysis of amides.



(71)

Concerning mechanisms of hydrolysis[4,5a], the chief advances since 1970 have involved acid catalysis, so we begin with this.

a. Acid-catalysed hydrolysis. For hydrolyses catalysed by strong mineral acids in aqueous solution, temperatures of between 50 and 100°C are required to produce convenient rates with the majority of amides. As for many esters (Section III.C.1.a), the rates of hydrolysis of many amides pass through a maximum value as the acid concentration is increased, and sometimes increase again at very high acid concentrations[5a,86,133,134]. The structurally related hydroxamic acids (RCONHOH) have been found to show similar behaviour[135]. In the 1970s and earlier, the interpretation of this behaviour was in terms of successive A2 and A1 hydrolyses* (equations 72–74) and

* A1 mechanisms can involve *N*-alkyl fission for appropriate *N*-alkyl amides[133,136].

$$R^1CONR_2^2 + H_3O^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} R^1\overset{\overset{+}{O}H}{\overset{\|}{C}}-NR_2^2 + H_2O \underset{\text{slow}}{\overset{H_2O}{\rightleftharpoons}}$$

$$R^1\overset{OH}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-NR_2^2 + H_3O^+ \xrightarrow{\text{fast}} R^1CO_2H + R_2^2NH + H_3O^+ \quad (72)$$

$$R^1CONR_2^2 + H_3O^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} R^1\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{+}{N}}R_2^2 + H_2O \xrightarrow[H_2O]{\text{slow}}$$

$$R^1CO_2H + R_2^2NH + H_3O^+ \quad (73)$$

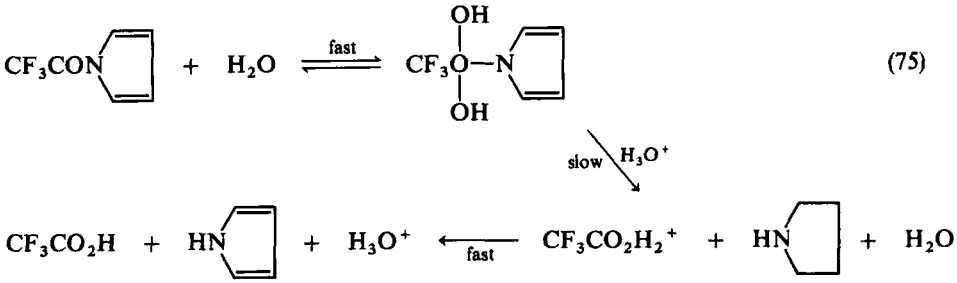
$$\downarrow \text{slow}$$

$$R^1CO^+ + R_2^2NH \xrightarrow[\text{fast}]{2H_2O} R^1CO_2H + R_2^2NH + H_3O^+ \quad (74)$$

was broadly along the lines of that used for acid catalysis of ester hydrolysis (Section III.C) except that direct initial protonation of the nitrogen atom of the leaving group was considered possible[137] for the A2 mechanism (equation 73). The maximum in the plot of k_{obs} against acid concentration normally occurs at lower acid concentration for amides than for esters owing to the greater basicity of the former: they become fully protonated on the carbonyl oxygen atom sooner, so that the effects* of the fall in a_{H_2O} with increase in acid concentration is reflected sooner in k_{obs}. Various early plots of k_{obs} against a_{H_2O} suggest that three water molecules are involved in the slow step of the A2 mechanism for a variety of amides, although Yates plots (see Section III.C.1.a) are not normally as rectilinear as for esters[133,137,139,140]. Another finding that suggests the A2 scheme for amides differs importantly from that for esters is that $k_{D_2O}/k_{H_2O} \simeq 1.0$ for the former[5a,141] whereas typical esters give $k_{D_2O}/k_{H_2O} \simeq 2$–3. As mentioned in the Introduction, there has been much debate as to the relative importance of routes (72) and (73): some workers have favoured one, some the other, and some a mixture of the two[133]. Over the past few years a clearer picture has begun to emerge, and three new mechanisms have been added to those above.

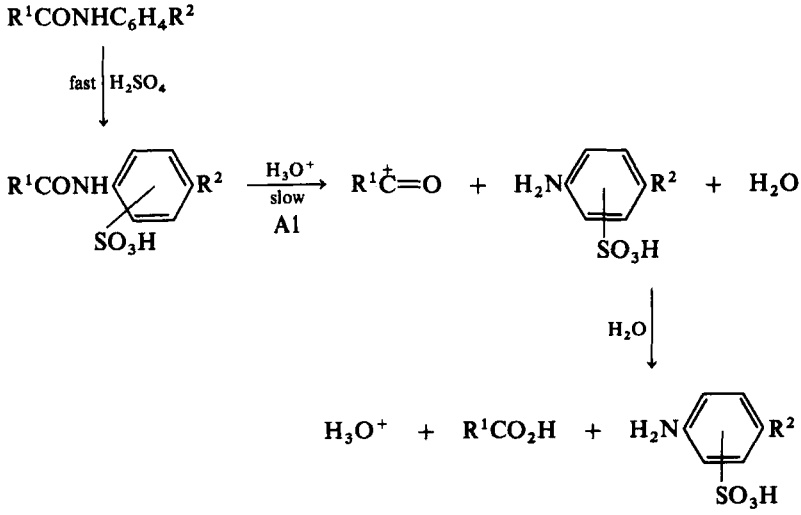
The first of the new mechanisms[142] concerns amides such as trifluoroacetyl pyrroles and indoles which exist in aqueous solution in rapid equilibrium with a substantial amount of their hydrated form. For these reactive compounds hydrolysis to the carboxylic acid is thought to involve slow proton transfer to nitrogen, an AS_E2 mechanism (equation 75). General acid catalysis has been detected in buffer solutions. These hydrolyses display a rate maximum at quite low (1–3 mol dm^{-3}) acid concentrations which may reflect the strong dependence of the hydration equilibrium on a_{H_2O}.

* An alternative formulation[138] of the rate maximum in terms of two different acidity functions, one for protonation and the other for formation of the transition state, the latter being more dependent on a_{H_2O}, amounts in practice to the more usual and simpler explanation.

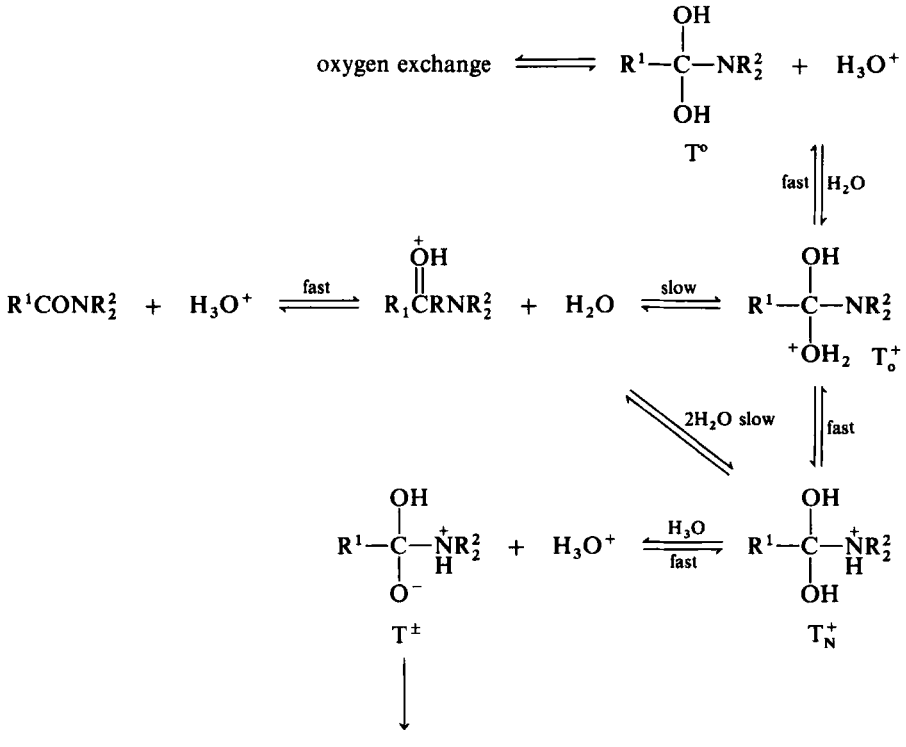


There is much evidence[139] that amide hydrolyses in dilute aqueous acid involve substantial dependence on a_{H_2O}.

The other new mechanisms[133,143] are variations on equations 72–74. If the amide contains an aromatic ring, as do anilides, then if the ring contains substituents that activate it towards electrophilic substitution the amide is rapidly sulphonated in sufficiently concentrated sulphuric acid solutions. Thereafter for anilides, the amide possesses a leaving group containing a powerful electron-withdrawing group and is liable to undergo *N*-acyl cleavage, perhaps via an A1 scheme (equation 76). This type of scheme is, of course, restricted to hydrolysis in sulphuric acid.

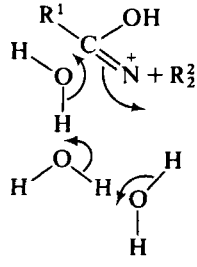


As already mentioned, plots to determine r, the number of extra water molecules in the transition state compared to the protonated amide, are frequently curved. This may be[139] because the a_{H_2O} data usually used refer to 25°C whereas the hydrolyses are normally conducted a higher temperatures. However, recent work by Yates[133,143], using the excess acidity approach, has shown that the A2 region—often the only region since amides undergo A1 hydrolyses less readily than do esters—can be treated as a composite of two different A2 mechanisms, the first at the lower acidities with $r = 3$, and the second at the higher acidities with $r = 1$. The value of $\Delta S^{\ddagger}$ is *ca* $-180\ J\ K^{-1}\ mol^{-1}$ for the $r = 3$ route, but only *ca* $-45\ J\ K^{-1}\ mol^{-1}$ for the $r = 1$ route for which $\Delta H^{\ddagger}$ is *ca* 8 kJ mol^{-1} larger. Yates suggests a scheme (equation 77) for these two 'A2' routes. The $r = 1$ route via T_0^+ can lead to some opportunity for oxygen exchange via T^0. The



(77)

$r = 3$ route leads directly to T_N^+ which will rapidly form the products, and provide less opportunity for oxygen exchange. It is interesting and significant that oxygen exchange was long thought to be absent in acid-catalysed amide hydrolysis, but has recently been detected[131,141,144]. Yates suggests that the route involving three water molecules employs a cyclic, eight-membered hydrogen-bonded transition state (**34**) to give T_N^+. The behaviour[143,145] of methyl benzimidium ions (**35**) towards hydrolysis in sulphuric acid is compatible with this scheme and such ions behave analogously to the corresponding benzamide, in showing both $r = 1$ and $r = 3$ routes. A cyclic transition state (**36**) similar to (**34**) but involving four water molecules, and leading directly to products, has been suggested on the basis of a proton inventory study[146] of the relatively



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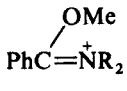

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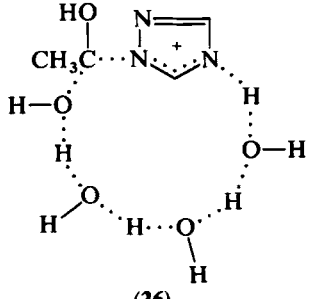


(36)

rapid hydrolysis of 1 acetyl-1,2,4-triazole at acid pH. Synchronous, cyclic transition states involving nitrogen are also supported by theoretical calculations for gas-phase hydrolyses[43].

Apart from the A1 route, and the special routes (equations 75 and 76), which probably all involve direct N-protonation (although not everyone would agree[137]) it is the A2 mechanism over which the N- versus O-protonation controversy has lingered. The scheme in equation 77 is expressed in terms of O-protonation. It could be recast in terms of primary N-protonation which theoretical calculations suggest leads to a lower activation energy[43]. Current reasons for preferring O-protonation are (i) the usual great predominance of the O-protonated form[147], (ii) the conclusion[148] that although *N*-acetyl trialkylamine salts, e.g. $CH_3CON^+R_3BF_4^-$ (which are models for N-protonation), hydrolyse rapidly, they are probably not sufficiently reactive to account for the observed rates of hydrolysis of comparable acetamides when the very small fraction that is N-protonated in solution is taken into account, (iii) the finding that variation with acidity of the transition state activity coefficient[87] for amide hydrolyses, when compared to the variation of other activity coefficients, suggests O-protonation, (iv) the fact that the hydrolysis of thiobenzamide[149] leads initially to substantial amounts of the corresponding O-amide (equation 78); this can only occur via a thiocarbonyl addition route, and such addition is unlikely to follow N-protonation (equation 73), and (v) the parallelism noted already between benzamide and benzimidate behaviour[143,145].

$$PhCSNH_2 + H_3O^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} PhC(=\overset{+}{S}H)NH_2 + H_2O \underset{\text{slow}}{\overset{H_2O}{\rightleftharpoons}}$$

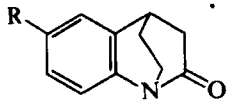
$(pK_a = -2.4)$

$$Ph{-}C(SH)(OH){-}NH_2 + H_3O^+ \xrightarrow[\text{fast}]{H_2O} PhCONH_2 + SH^- + 2H_3O^+ \quad (78)$$

$$\downarrow \text{fast}$$

$$PhC(=S)OH + H_3O^+ + NH_3$$

Circumstances that favour N-protonation are distortions[131] of the amide group that reduce its resonance stabilization (the same circumstances that favour carbonyl addition, Section III.D.1). Such distortion will be expected[131] materially to increase the basicity of the nitrogen atom (and to decrease that of the oxygen atom to provide an inversion of their usual relative basicities). β-Lactams (four-membered ring) display[143] only the A1 mechanism (equation 74) and the resonance-free benzoquinuclidones (**37**) are some



(37)

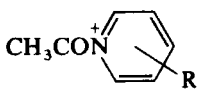
of the most reactive amides studied, and exhibit acid catalysis in the pH region[131]. They have $pK_a \simeq 3$–5, and are believed to protonate principally on nitrogen. They therefore probably hydrolyse via route (73). A substantial amount of oxygen exchange is reported for these compounds at pH < 7. This is a surprising finding in view of the predominant

TABLE 3. Reactivity of amides in alkaline hydrolysis[a]

Amide	k_{OH^-} (dm^3 mol^{-1} s^{-1})
3-Methyl-1-acetylbenzimidazolium ion	2×10^5
3-Methyl-1-acetylimidazolium ion	1.5×10^5
1-acetylimidazole	3.2×10^2
37, R = Cl	3.7×10^2
37, R = MeO	1.7×10^2
N-Acetylpyrrole	8.5
α,α,α-Trichloro-*N*-methylacetanilide	0.49
p-Nitroacetanilide	2.2×10^{-3}
p-Methylacetanilide	6.8×10^{-6}

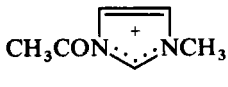
[a] k_{HO^-} = second-order rate constant for hydroxide ion-catalysed hydrolsis (equation 79) at 25 °C. Data from Reference 131.

N-protonation, and of other results for oxygen exchange[141,144]. It presumably occurs via a tetrahedral intermediate formed after O-protonation. The most reactive of all amides (Table 3) involves an amine of low basicity and a pre-formed cationic leaving group. Examples are the acetylimidazolium ion (**39**), 1-acetyl-3-methylimidazole (**40**) and acetylpyridinium ions (**38**). They probably[5a] hydrolyse via attack by water in a concerted or synchronous mechanism, in keeping with our assumption in equation 73 that initial N-protonation (where it occurs) does not lead to a tetrahedral intermediate. (See, however, Section III.A.2.)

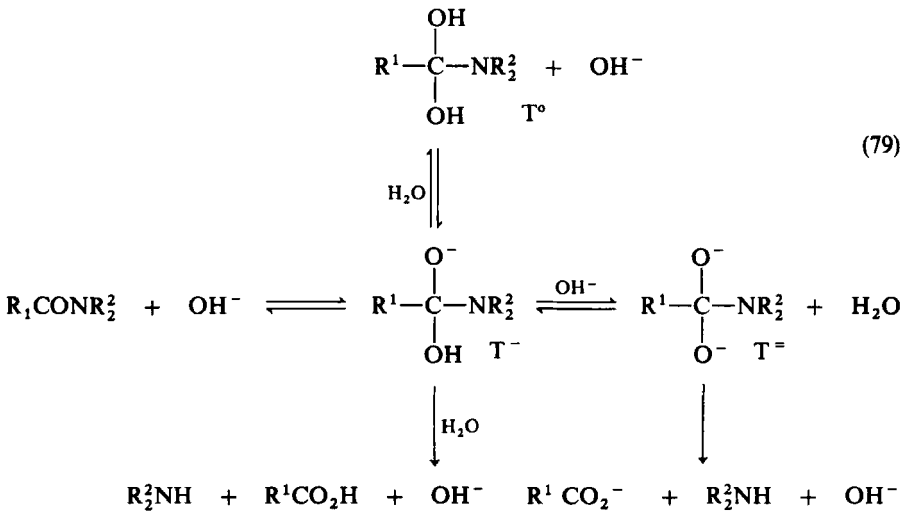


(**38**)

(**39**)



(**40**)



(79)

b. Neutral and alkaline hydrolysis. The mechanism of hydrolysis of amides in water in the presence of hydroxide ions (equation 79) has long been agreed[4,5a] in outline. Recent work has done little except to confirm its versatility as an explanation appropriate to widely different amides, including imides[150,151]. The rate equation for equation 79 can be written in the general form given in equation 80, where *a*, *b*, *c* and *d* involve rate and/or equilibrium constants[152]. In some systems, especially those containing general bases, the conversion of T^- to $T^=$ may be concerted with the loss of R_2^2N. For any

$$k_{obs} = (a[OH^-] + b[OH^-]^2)/(c + d[OH^-]) \quad (80)$$

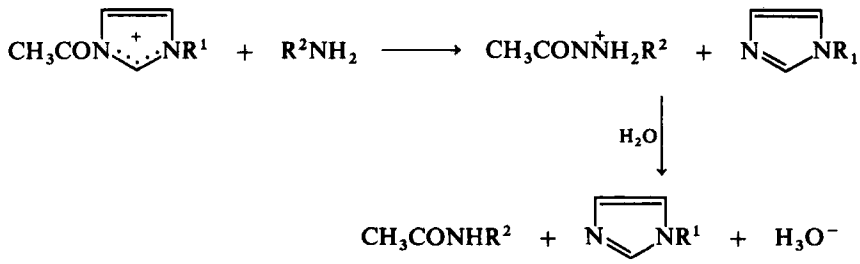
given amide the observed rate equation will depend upon the magnitudes of *a–d*, and on $[OH^-]$. For some amides the whole equation 80 is detected, for others only part of it[5a,152]. Clearly when R_2^2N leaves with difficulty, the term in $[OH^-]^2$ is likely to be important, whereas when R_2^2N is easily lost, or when $[OH^-]$ is large, the initial addition of OH^- should become rate-limiting. It is the inherently poor leaving group of most amides that leads to the frequent importance of $T^=$ and to kinetic terms in $[OH^-]^2$ in their hydrolyses. The same situation does not normally arise for ester hydrolysis in alkaline solution[153]. The actual dependence of the observed rate equation on amide structure is, in practice, complex[5a,152], and it seems likely that when R^1 is strongly electron-withdrawing T^- forms some $T^=$ without help from an OH^- ion. As would be expected from the scheme in equation 79, oxygen exchange takes place during the alkaline hydrolysis of amides[131,154]. Theoretical calculations[45] suggest that if the OH^- ion was not solvated in solution its attack on the carbonyl group would have $\Delta H^{\ddagger} \sim 0$. These calculations also support the assistance of the departure of R_2^2N from T^- by proton transfer from water molecules. The relative reactivities of a variety of amides towards OH^- ions are given in Table 3.

Strained amides[131] and those[5a] possessing strongly electron-withdrawing substituents in either R^1 or R^2, display significant spontaneous hydrolyses. When the leaving group is positively charged, as in 1-acetyl-3 methyl imidazole (**40**), reaction with water is relatively fast. The spontaneous hydrolysis exhibits general base catalysis by buffer components, and by other molecules of water. It probably proceeds via $T^{\pm}$ unless the leaving group is very good, when a concerted mechanism is likely (Sections III.A.2 and III.D.1.a). In acetonitrile solution results for some amides suggest[155] the intermediates are stabilized by several water molecules. Reactive amides are susceptible to nucleophilic catalysis and carboxylate buffer components lead[148] initially to the anhydride (equation 81). Intramolecular routes permit the acylation of carboxylate groups even by unreactive amides[156].

$$CH_3CON^+R_3 + CH_3CO_2^- \longrightarrow (CH_3CO)_2O + R_3N \xrightarrow{H_2O} 2CH_3CO_2H + R_3N \quad (81)$$

2. Aminolysis

The acylation of amines by most types of amide is not generally useful in synthesis[9], and still rather little is known about the mechanisms involved. In 1970 information was sparse indeed[4]. Recent studies have mainly concentrated on reactive amides. This work is particularly important in that it has provided some of the best examples of systems for which plots of log k_{obs} against the pK_a of the attacking amine are straight lines over a wide pK_a range and can therefore (Section II) be interpreted as pointing to a concerted or synchronous mechanism for acylation. The first study of this type with amides employed the acetylimidazolium ion (**39**) and 1-acetyl-3-methylimidazole (**40**) with a variety of amines[157,158]. The reactions (82) are first order in the attacking amine as for other similar aminolyses of powerful acylating agents, no catalysis being required. A



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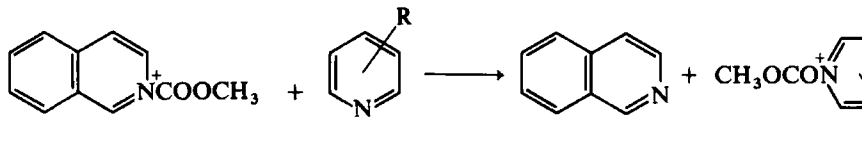
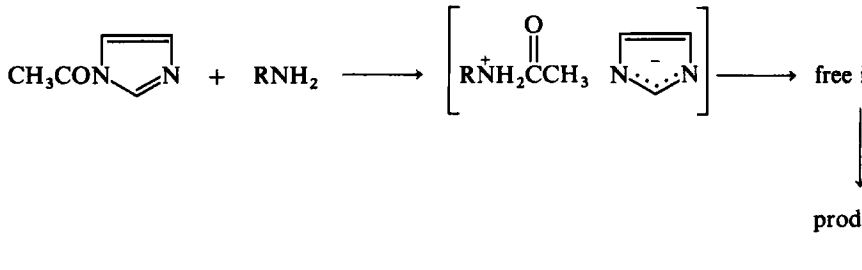


(83)

more recent study[30] involved a series of pyridines attacking *N*-methoxycarbonyl isoquinolinium ions (equation 83). Williams concluded that the transition state for equation 83 is symmetrical and square planar. With these reactive amides $\beta_{nuc} \sim 0.6$ but for less reactive (although still quite reactive, Table 3) amides such as (neutral) acetylimidazole[159] $\beta_{nuc} \sim 1.6$, k_{obs} now being found to change much more as the basicity of the attacking amine is changed. For acetylimidazole weak amines lead mainly to general base catalysis of hydrolysis of the amide; strongly basic amines are required to displace imidazole to give a new amide. Because of the large value of β_{nuc} Page and Jencks[159] assume that the attacking amine is experiencing a large charge on the carbonyl carbon atom, and therefore that bond-breaking is essentially complete in the transition state (and the new N—C bond essentially formed) so that the slow process may even be diffusional separation of the ion pair (equation 84).

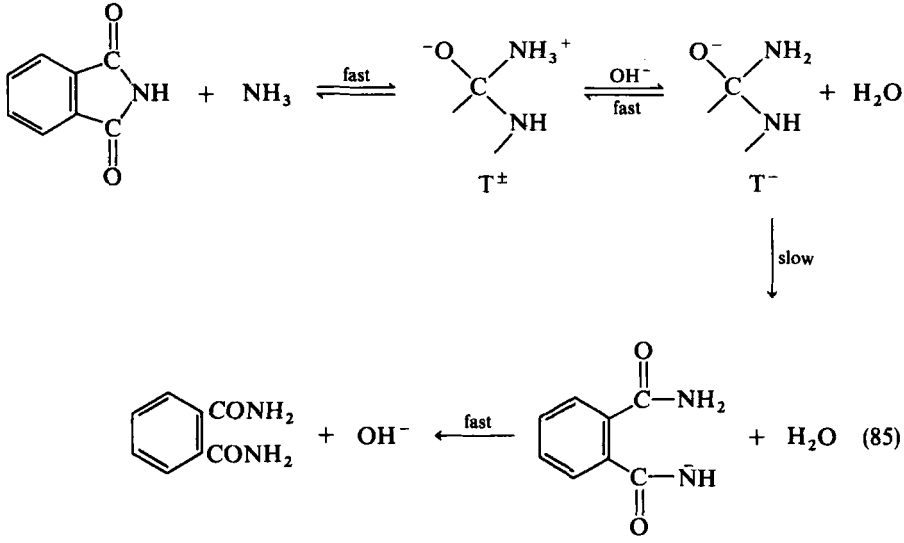


(84)

Conversely for the reaction in equation 82, which involves a better leaving group, much less bond-breaking is postulated. The idea that there exists more bond-breaking in the transition state with poor leaving groups than with good leaving groups seems perverse, and to attribute the value of β_{nuc} directly to charge development seems unnecessary: with only a small amount of bond-breaking, the bond-forming capacity of the lone pair of electrons on the nucleophile will be at a premium, and therefore k_{obs} will depend more strongly on the pK_a than for good leaving groups which will be able to depart further. With little empty orbital available, a lot of overlap is needed. The lack of charge development with poor leaving groups is the reason why general base catalysis

is much more important with these groups: the catalysis provides locally a nucleophile better able to attack the carbonyl carbon atom. This interpretation, which is consistent with recent theoretical treatments[10], suggests that in concerted reactions there exists a tight transition state for poor leaving groups and a loose transition state for good leaving groups. The general base catalysed aminolysis of acetylimidazole has been characterized as concerted[159].

As in hydrolysis, concerted reactions are unlikely for the aminolysis of the less reactive amides. In line with this the ammonolysis of phthalimides[150] is thought to follow the mechanism in equation 85. The reaction is reversible, and since the imide also undergoes



(85)

concurrent hydrolysis in alkaline solution, the reverse represents intramolecule nucleophilic catalysis of amide hydrolysis by another amide group[160]. Many examples of intramolecular catalysis of amide hydrolysis were known in 1970[4,5a]. The variety of general base catalysed mechanisms currently believed to exist for aminolysis of esters (Section III.C.2.b) has recently been invoked for aminolysis of amides[161].

E. Carboxylic Acids

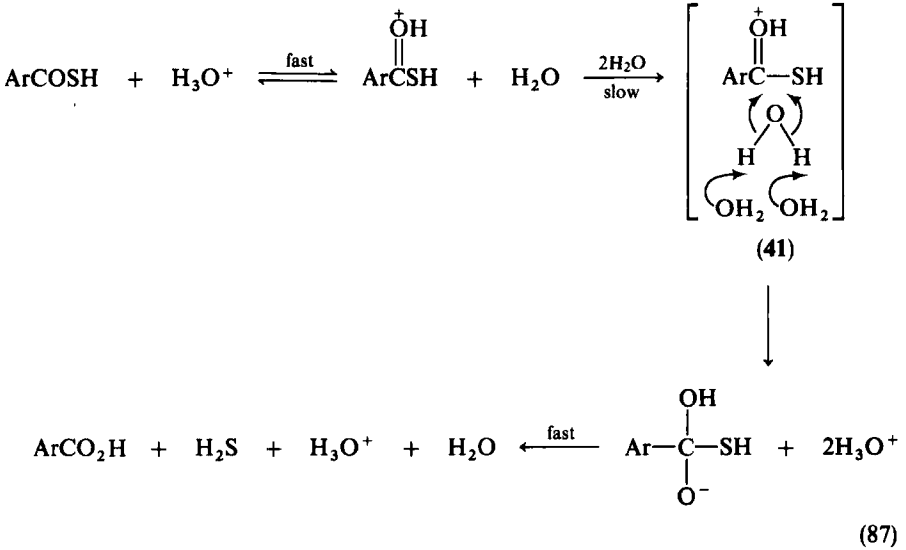
Acids, of course, acylate alcohols in esterification. The mechanisms must reflect those already discussed for ester hydrolysis. Reactions of acids with water can be monitored by oxygen exchange, but there seems to be little new of significance to report[1]. An analogous reaction, and one easier to study, is the hydrolysis of thioacids, RCOSH (equation 86). Some early work[162] showed that, in dilute aqueous mineral acid,

$$RCOSH + H_2O \longrightarrow RCO_2H + H_2S \qquad (86)$$

thiocarboxylic acids are hydrolysed by the A2 mechanism. More recent studies[76,163] have revealed that, as for esters and amides, the A2 mechanism is replaced by another mechanism at high mineral acid concentrations. The change-over tends to occur at lower mineral acid concentrations for thioacids than for esters. Application of the excess acidity approach suggests[78] that the A2 scheme for thioacetic acid and for substituted thiobenzoic acids involves three water molecules in the rate-determining attack on the

protonated acid (as for amides at low acid concentration, Section III.D.1.a) and that the mechanism obtaining at high mineral acid concentrations is probably an AS_E2 scheme. The excess acidity treatment leads to the conclusion that S-substrates are particularly susceptible to the AS_E2 mechanism: it turns up also for thion esters (Section III.C.1.a).

Finding roles for all three water molecules in the A2 scheme is a problem for thioacids if it is assumed that the cyclic transition state **34** proposed for amides is unlikely for thioacids owing to the low basicity of the leaving group, and to the fact that for hydrolysis of substituted thiobenzoic acids $\rho \sim 1.6$. Cox and Yates[78] suggest a transition state (**41**, equation 87) similar to that proposed[139] for amides in the 1960s.



(87)

Acylation of amines by carboxylic acids presents obvious mechanistic problems[1], still largely untackled.

IV. ACYLATION VIA ELIMINATION

If the group R in an acylating agent RCOX contains an ionizable hydrogen atom on an atom adjacent to the carbonyl carbon atom, then in principle acylation is possible via routes such as those in equations 88 and 89 where B is a suitable base[6]. Examples of this type of reaction have been known for some time: in the absence of HY, ketenes and isocyanates can be prepared this way starting, for example, with the corresponding acyl halide or its precursors[5]. When HY (e.g. H_2O) is present then, in any particular case, there will be a competition between route (88) or (89) and the routes discussed in Section III, none of which involve an initial elimination*.

Acylation via routes (88) and (89) began[164–167] to attract detailed mechanistic attention in the 1960s; most of the work has concerned the hydrolysis of esters. Since

* It is unsatisfactory, even if convenient, to classify[6] an $A_{AC}1$ or S_N1 mechanism as an elimination–addition route; two entities are lost in elimination, not one. Dissociative–associative is more acceptable (see Section I).

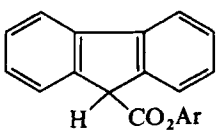
$$\begin{array}{l} RCH_2COX \\ \downarrow B \\ R\bar{C}HCOX + BH^+ \longrightarrow RCH{=}C{=}O + BH^+ + X^- \\ \qquad\qquad\qquad\qquad\qquad\qquad \downarrow HY \\ \qquad\qquad\qquad\qquad\qquad\qquad RCH_2COY \end{array} \qquad (88)$$

$$\begin{array}{l} RNHCOX \\ \downarrow B \\ R\bar{N}COX + HB^+ \longrightarrow RN{=}C{=}O + BH^+ + X^- \\ \qquad\qquad\qquad\qquad\qquad\qquad \downarrow HY \\ \qquad\qquad\qquad\qquad\qquad\qquad RNHCOY \end{array} \qquad (89)$$

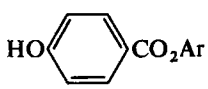
the first step is proton removal, the reactions are usually confined to basic or near-neutral conditions, and have mostly been studied using aqueous solution at pH $\lesssim$ 4. For route (88) or (89) to compete successfully with other mechanisms of hydrolysis it is found that X must be a sufficiently good leaving group (i.e. the pK_a of HX must be sufficiently small). How good a leaving group X needs to be depends upon the actual acylating agent concerned, because the ease of loss of X^- depends also upon the detailed structure of the anion RCHCOX or RNCOX. Normally (but not invariably) HX should be at least as acidic as a phenol, and the rate of formation of the ketene or isocyanate intermediate depends much more strongly on the pK_a of HX than does the rate of the accompanying $B_{AC}2$ or $B_{AC}3$ routes. A plot of $\log k_{obs}$ against pK_a of HX therefore displays a discontinuity[168–170] where X is no longer a sufficiently good leaving group to support a significant contribution to acylation from equation 88 to 89.

The general scheme (equation 90), written with X = OAr and referring to pH > 3, is suggested by a variety of studies of esters such as substituted carbamates[164,171,172] (**42**), thiocarbamates[173,174], acetoacetates[167,170] (**43**), cyanoacetates[167] (**44**), malonates[167] (**45**) fluorene-9-carboxylates[175] (**46**) and *p*-hydroxybenzoates[169] (**47**).

$RNHCO_2Ar$ (**42**) $R^1COCHR^2CO_2Ar$ (**43**) $RCH(CN)CO_2Ar$ (**44**) $R^1OCOCHR^2CO_2Ar$ (**45**)



(**46**)



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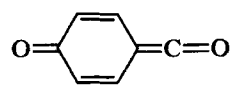
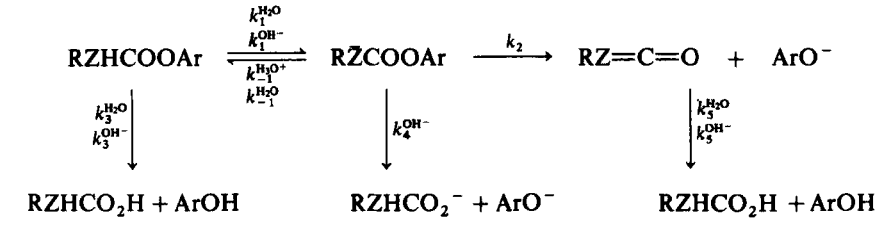


(**48**)

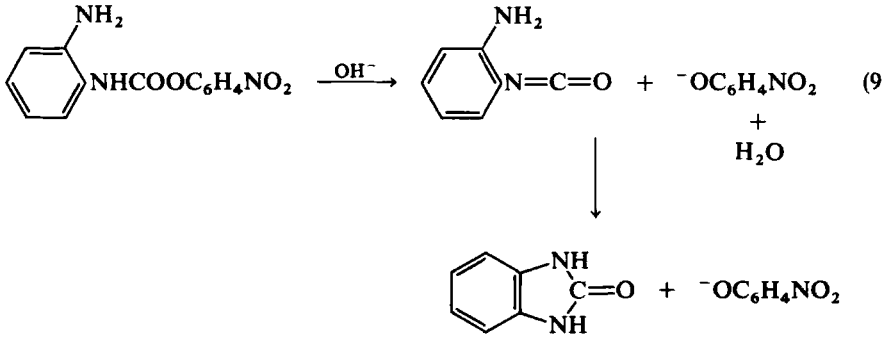
In the last type of ester the H atom lost is not α to the carbonyl group, and a *p*-oxoketene (**48**) is formed. In the Scheme shown in equation 90 R can be H, alkyl or



(90)

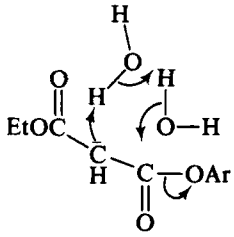
aryl, and Z can be N or CR. The state of ionization of the products depends upon the actual pH, and on the product species involved. When Z = N the carbamic acid product undergoes further decomposition (fast or slow depending on the pH) to the amine and carbon dioxide[9,176]. Since ketenes and isocyanates normally[7] have greater reactivities towards water (or towards other compounds HY, such as alcohols or amines) than do the parent esters, the ketene or isocyanate is not usually detected in these elimination reactions. However, the use of thioncarbamates[173,174] (RNHCSOAr) leads to isothiocyanates (RNCS) which are surprisingly unreactive towards water, and can readily be isolated from aqueous solutions[176]. For such systems a relatively stable equilibrium can be set up[177] between RN̄CSOAr, RNCS and ArO⁻. Analogous equilibria are normally impossible with the O-compounds. The study of other thionesters (e.g. fluorene thionesters) would be interesting: little is yet known about the behaviour of thioketenes[7].

Apart from the easy identification of isothiocyanate intermediates, the intermediacy of isocyanates or ketenes in the reactions of the O-analogues is inferred principally from the yields of trapping products[6] (sometimes effected intramolecularly[171], equation 91),



(91)

and the fact that esters in which the ionizable hydrogen atom is replaced by a methyl or similar group hydrolyse very much (usually 10^3–10^6 fold) more slowly[6,164,170]. This dramatic difference clearly justifies the assumption of a different route to hydrolysis. Cyclic routes in which the free ketene is not involved (such as equation 92) have also been suggested[159] as alternatives to steps 2 and 5 in the scheme in equation 90. This possibility, a concerted $B_{AC}3$ route of the anion, is not attractive in general since the pH dependencies of some of the relatively very rapid hydrolyses (see below) imply that it would need to be faster than the reprotonation of the anion by water ($k_{-1}^{H_2O}$) which is a similar process without the extra constraints of the attack on the carbonyl group.



$$\longrightarrow \quad EtOCOCH_2CO_2H + ArO^- + H_2O \qquad (92)$$

The general pH profile corresponding to the scheme in equation 90 is shown in Figure 2a. Region A is thought[170,178,179] to correspond to $B_{AC}3$ hydrolysis ($k_3^{H_2O}$); region B marks the onset of a significant contribution from rapid equilibrium formation of $R\bar{Z}CO_2Ar$ (proportional to $[OH^-]$) followed by slow (k_2) loss of ArO^-, region C is where $k_{-1}^{H_3O^+}[H_3O^+]$ becomes negligible and, if $k_{-1}^{H_2O} < k_2$, then $k_1^{H_2O}$ becomes the slow step (the size of this plateau depends upon the magnitude of $k_1^{OH^-}$, etc.); region D corresponds to $k_1^{OH^-}[OH^-]$ as the slow step, and region E to complete, rapid formation of $R\bar{Z}CO_2Ar$ with k_2 as the slow step; region F represents the $B_{AC}2$ reaction of $R\bar{Z}CO_2Ar$ with OH^-. The profile actually exhibited by particular reactants is usually simpler; typical examples are b, c and d in Figure 2. Region F appears mainly important for carbamates, and region C is absent for esters for which $k_2 < k_{-1}^{H_2O}$ where the anion equilibrium is always established rapidly. The most common behaviour is a single plateau (c); at the plateau $R\bar{Z}CO_2Ar$ is completely and rapidly formed, and k_2 controls the rate. Esters that contain no ionizable hydrogen atom exhibit simple curves like d; these correspond to routes $k_3^{H_2O}$ and $k_3^{OH^-}[OH^-]$ in equation 90. The situation is complicated by the circumstance that esters with ionizable hydrogen atoms can, in principle, display the other more complex behaviours whether they employ the route via the ketene (or isocyanate) or only suitable B_{AC} routes[178,179]. For example, the scheme in equation 93 leads to a pH profile such as b or c in which the plateau at high pH corresponds to the attack of HO^- on residual, neutral ester[179]. Entertaining the

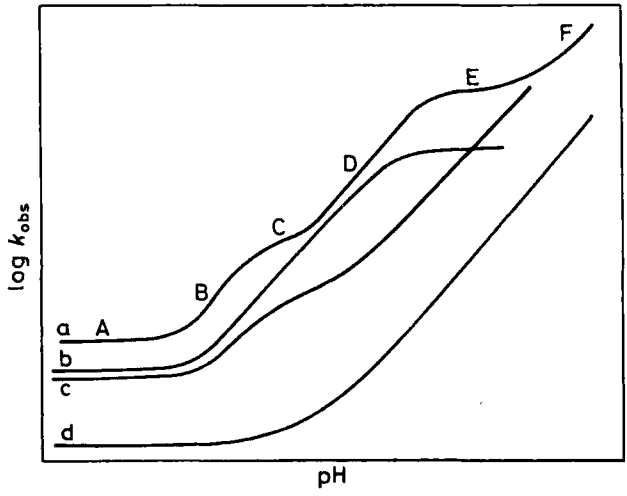


FIGURE 2. Typical pH profiles for acylation via elimination

$$\begin{array}{ccccccc} RZHCO_2Ar & + & H_2O & \overset{\text{fast}}{\rightleftharpoons} & R\bar{Z}CO_2Ar & + & H_3O^+ \\ \Big\downarrow {\scriptstyle B_{AC}2/3}\ {\scriptstyle k_3^{HO}},\ {\scriptstyle k_3^{OH^-}} & & & & \Big\downarrow {\scriptstyle B_{AC}2}\ {\scriptstyle k_3^{OH^-}} & & \\ \text{Products} & & & & \text{Products} & & \end{array} \qquad (93)$$

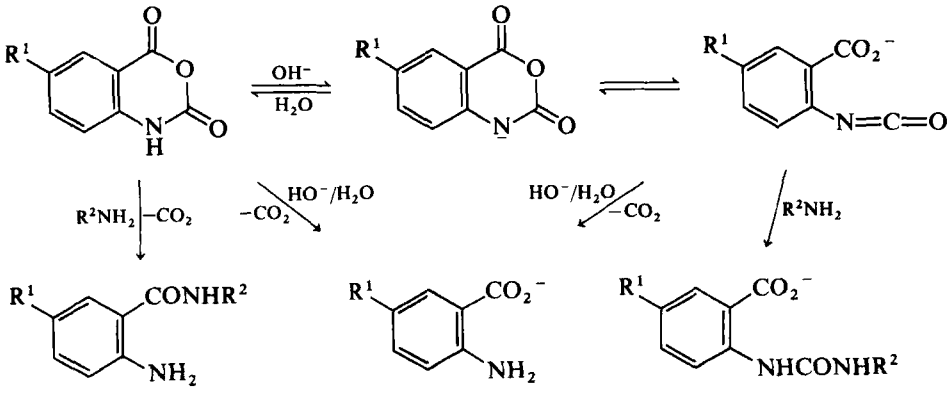
possibility of a dianionic tetrahedral intermediate at high pH can account (rather less satisfactorily[179]) for two plateaus (compare Figure 2a). Because of these various ways of interpreting the pH profiles, it is necessary to rely on other ways of deciding if a ketene (or isocyanate) plus B_{AC} route is involved, or whether it is just a B_{AC} system of some complexity. One powerful tool already mentioned is the quantitative comparison with the hydrolysis of an analogue which contains no ionizable hydrogen α to the carbonyl group; the profile will be lower by three or four orders of magnitude for the latter. Suspected ketene and isocyanate routes have also been found usually to have $\Delta S^{\ddagger} \simeq 40 \pm 20$ J K^{-1} mol^{-1}; and $\Delta V^{\ddagger} \simeq 10 \pm 4$ cm^3 mol^{-1}, for the k_2 step[180]. For B_{AC} 2/3 routes values of $\Delta S^{\ddagger}$ and $\Delta V^{\ddagger}$ are normally $\gtrsim -20$. The positive values of these parameters for suspected examples of the ketene and isocyanate mechanism are compatible with the slow loss of anion in step 2 of this mechanism. Various lines of evidence can therefore be called upon.

In spite of some interpretative complications noted above, it is generally believed that appropriately substituted esters undergo hydrolysis via the elimination route of the scheme in equation 90. As written, it represents an ElcB process, and Bruice[178] has subdivided the mechanism into $(ElcB)_R$, $(ElcB)_i$ and $(ElcB)_{anion}$ depending upon whether the conditions of regions B, C and D, or E, respectively, are involved. For $(ElcB)_i$, slow formation of the anion $R\bar{Z}CO_2Ar$ is kinetically dominant, whereas for $(ElcB)_R$ and $(ElcB)_{anion}$ the loss of the leaving group ^-OAr is the slow step. Most systems do not involve an $(ElcB)_i$ region. Added acids and bases (e.g. buffer components) can take the roles of the solvent species in establishing step 1, the deprotonation equilibrium[167]. Increasing the buffer concentration at fixed pH should not affect k_{obs} for pre-equilibrium deprotonation $(ElcB)_R$, but can increase k_{obs} to the k_2 plateau region in the $(ElcB)_i$ region.

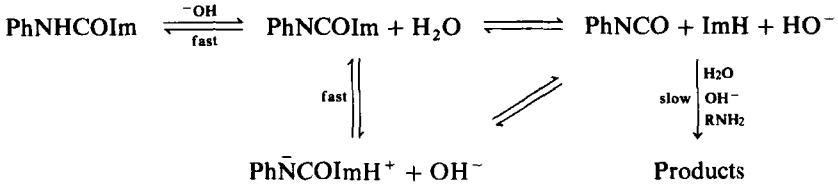
There are other aspects of this type of acylation that are worth attention. First, it would be expected that other appropriate acylating agents RCOX might, under alkaline conditions, show behaviour essentially similarly to that of esters, and secondly, that elimination mechanisms might be found under less alkaline conditions. A little work exists in these areas, and general support for the expectations is provided by the known preparative routes to ketenes and isocyanates from acyl halides and anhydrides. In one interesting example concerning anhydrides the hydrolysis and aminolysis of isatoic anhydrides (equation 94) are suggested[181] to involve some contribution from a (presumably ElcB) elimination route; for the aminolysis a different product results from this path (equation 94).

Another interesting case is equation 95, which involves base-catalysed elimination from a urea (ImH ≡ imidazole). Deliberate additions of imidazole led to a low equilibrium concentration of PhNCO and the first measurements of its reactions with nucleophiles in aqueous solution[182]. (Quantitative studies of ketenes in aqueous solutions have also begun to appear recently[183–185].)

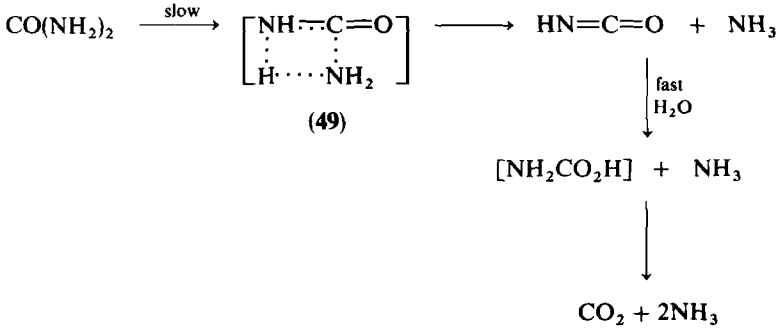
Studies using less basic conditions, and/or less polar environments, have led to several suggestions of E2 rather than ElcB mechanisms (i.e. concerted rather than stepwise eliminations[9]). Not all the examples involve overall acylation, but the hydrolysis of urea (equation 96) in neutral aqueous solution is believed[139c] to proceed via the cyclic transition state **49**. The rate of the uncatalysed formation of isocyanates from



(94)

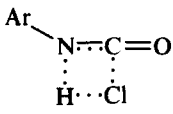


(95)

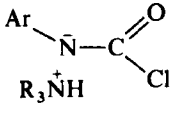


(96)

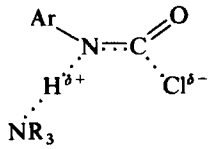
N-phenylcarbamyl chlorides in weakly basic, non-hydroxylic solvents has a rather low sensitivity to substituents in the phenyl ring ($\rho \simeq 0.5$). When a tertiary amine is present, the Hammett plot has a change of slope from $\rho \simeq 0.9$ for electron-withdrawing substituents to $\rho \simeq 0$ for electron-releasing groups. These results, and the effects of substituting H by D on the nitrogen atom, led to suggestions of transition states **50**, **51** and **52**, respectively[186]. **50** is similar to **49**, and these and **52** all represent E2 eliminations. The gas-phase eliminations from acetic and thioacetic anhydrides[187] also lead to the ketene via a cyclic transition state, such as **53** in equation 97. Owing to the principle of microscopic reversibility, concerted eliminations imply concerted additions for the reverse reactions. We shall return to this point below.



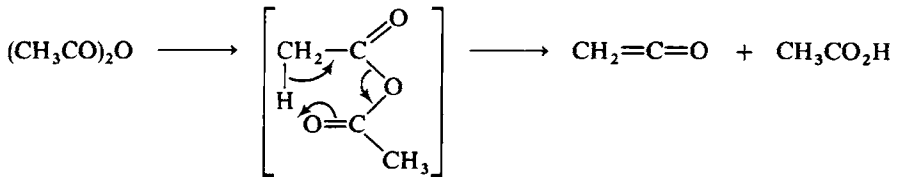
(50)



(51)

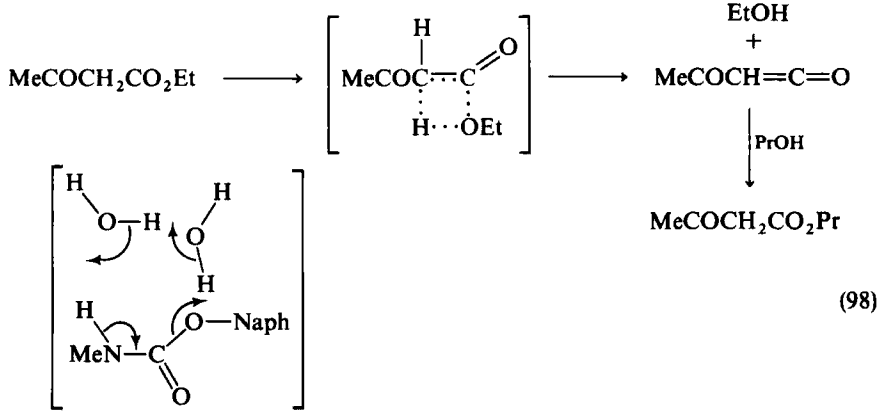


(52)



(53) (97)

In another example, the rate of spontaneous propanolysis of acetoacetates and malonates in different non-aqueous solvents was found to be insensitive to the propanol concentration and to the polarity of the solvent (heptane, acetone, propanol); $\Delta S^{\ddagger} \simeq -30$ to -60 J K^{-1} mol^{-1}. These facts also led to the suggestion[188] of an E2 reaction (equation 98). This scheme implies that alcohol monomers are involved in the reverse



(56) (98)

reaction, which is unlikely in heptane solution[189,190], but concerted elimination is certainly suggested by findings for the alcoholysis of ketenes and isocyanates in non-hydroxylic solvents[7,189].

Another circumstance that has led to the postulation of an E2 elimination is the fact, noted already, that the entire pH profile for an ester able to eliminate lies well above that of the analogous ester carrying a methyl group in place of hydrogen α to the carbonyl group. In the horizontal portion at low pH (region A, Figure 2) earlier attributed entirely to the $B_{AC}3$ mechanism, the magnitude of this effect seems unlikely to be always completely explicable as steric hinderance of the $B_{AC}3$ mechanism by the extra methyl substituent. For example, with the esters $MeNHCO_2Naph$ (**54**) and Me_2NCO_2Naph (**55**) (Naph = naphthyl) the difference in k_{obs} in this region is *ca* 5×10^4. This suggests that there is some special effect operating for **54** even in this pH region. The E2-like transition state **56** has been proposed[191]. Other work[192] dealing with the effects on k_{obs} in this region of the pK_a of the leaving group also indicates that, for the best leaving groups, a mechanism different from the $B_{AC}3$ route operates. It cannot be a residual ElcB mechanism since that would not be independent of the pH. Transition state **56** is compatible with suggestions for the addition of alcohols or water to isocyanates in non-hydroxylic solvents[189]. Little is yet known about the corresponding mechanism of addition in aqueous solution.

As noted, the mechanisms proposed for the foregoing elimination reactions have implications for the reverse reactions under the same conditions. The mechanisms imply that, in basic aqueous solution, phenols, alcohols and probably water add to the ketenes and isocyanates by initial attack of the phenoxide ion, etc. at the carbonyl carbon atom, followed by protonation of the α-C or α-N atom. Addition via enol formation is not suggested. The orbitals available[193] for a specifically nucleophilic attack at the carbonyl carbon atom point to an in-plane reaction to give the anion

$$R_2\ddot{C}-\underset{\displaystyle OR}{\underset{|}{C}}-\ddot{O} \quad \text{or} \quad R\ddot{N}-\underset{\displaystyle OR}{\underset{|}{C}}-\ddot{O}$$

The reaction of ketenes with hydroxide ions have been interpreted this way[184].

The proposals, under a variety of less basic conditions, of E2 mechanisms which involve cyclic transition states and kinetically important proton transfers from the α-N or α-C atoms are mostly concordant with ideas[7,183,189] for the reverse reactions under similar conditions. These have often been suggested to be examples of concerted addition perpendicular to the molecular plane*. For this geometry the details of the HOMO for aliphatic ketenes make protonation at carbon relatively easy, whilst the concurrent attack at the carbonyl carbon atom will be more sensitive to the nucleophilic properties of the attacking species. This is found experimentally for concerted additions to ketenes[7,196]. Overall, the mechanisms proposed for acylation via elimination can be said to be rather strongly supported by conclusions reached independently concerning additions to isocyanates and ketenes, but more work is required to integrate properly these two aspects. It is an area where theoretical studies are likely to be particularly informative.

The final step of acylation via elimination has normally been the acylation, by the intermediate ketene or isocyanate, of water in a predominantly aqueous medium. Under sufficiently alkaline conditions the mechanism of this reaction very probably involves

* In-plane concerted addition to the carbon–carbon double bond is impossible[193].

initial attack by OH^- at the carbonyl carbon atom. Over an (often wide) pH range in less alkaline conditions the attacking species is neutral water[184,185(b),195]. For such conditions mechanistic information about isocynates is sparse, but isothiocyanates[196] undergo a general base-catalysed attack by water, other solvent molecules acting as the general base. A similar mechanism has been suggested for ketenes[184], but alternatives exist[183]. Kinetic work on the hydrolyses of ketenes and isocyanates by low concentrations of water in solvents of low dielectric constant is most easily interpeted in terms of additions via cyclic transition states involving trimeric water[7,183,197]. These reactions have usually been formulated as direct additions across the C=C or N=C double bond with transition states analogous to (**56**) (with nap = H), rather than as carbonyl additions. Whether cyclic transition states can be supported in largely aqueous media is still uncertain[183], but recent work[185b] with some (rather special) ketenes has shown that the initial additon of water under such conditions is across the carbonyl double-bond, and is followed by prototropic rearrrangement.

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CHAPTER 14

Thio derivatives

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I. INTRODUCTION

During the last three decades, the chemistry of the thio and dithio carboxylic acids and their derivatives has been vigorously developed. The work in this area performed before the early 1979s had been exhaustively reviewed[1,2], including review articles on practical synthetic methods[3,4]. Thiono esters[5], acyclic dithio esters[6,7] and 1,2-dithiol-3-thiones[8] have been reviewed.

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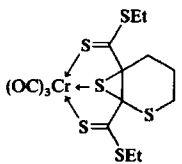
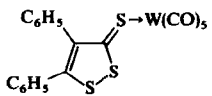
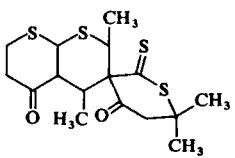
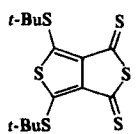
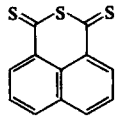
TABLE 1. Bond lengths and angles of dithiocarboxylic acid derivatives

Compounds	Bond lengths (pm)				Angles (deg)		Ref.
	C=S	(S)C—S	M—S	M—M	SCS	SMS	
	173.0						9
	168	170	2.528				10
	164	171			113		11
	164.0 164.1	173.1 173.3			113.2		13

	161.7 163.0	176.9 175.4					14
$C_5Me_5CSSCuPPh_3$	168	168	238 −242		118		21
$(CH_3CSS)_4Au_4$			230	298.9		94 193	16
$C_5Me_5CSSAuP(Pr\text{-}i)_3$	165	172	231.7 −327.3		120.7		21
$[(CH_3CSS)_2V]_2S_2$	167.0	167	247.3 −250.1	280.0	114.8		18
$C_5Me_5CSSAuPPh_3$	165	172	231.7		120.7		21
$(CH_3CSS)_4Mo_2 \cdot 2THF$	167	167	246.9 −247.2	213.3	118.3	68.6	15
$(CH_3CSS)_4Ni_2$	167	168	219.7	256.4	126.2	90.4	20
$(CH_3CSS)_4Ni_2I$	167	169	225 −242.4		115.6 −116.4	72.1 −72.7	20
$[(C_6H_5CSS)_3Ni]^-K^+(Crypt)^a$	168	169	240.2 −241.8		115.6 −116.4	72.1 −72.7	21
$(n\text{-}C_6H_{13}CSS)_4Pt_2$	168	169	231 −232.8	276.7	129.0		17
$(i\text{-}C_3H_7)_4Pt_2$	168	168 170	233	279.5			17

[a] Crypt = 4,7,13,16,21,24-hexa-1,10-diazabicyclo[8,8,8]hexacosane

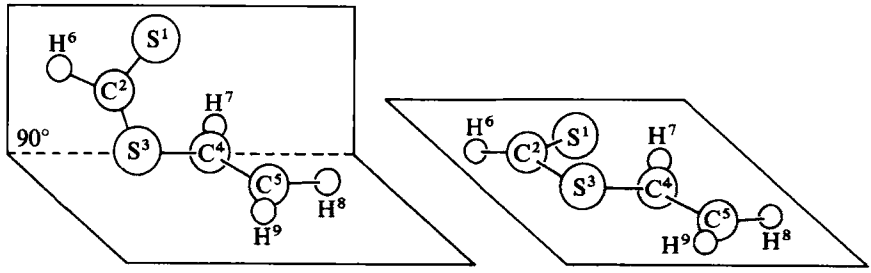
The aim of this chapter is to provide coverage of the sulfur isologues of carbocyclic acid derivatives which have been described in the literature after 1979. No attempt was made to provide coverage of 1,2-dithiol-3-thiones[7] reviewed recently and of cyclic thio and dithio esters. The literature survey covers papers published up to the early 1991s.

II. STRUCTURE AND PHYSICAL PROPERTIES

A. X-Ray Analysis and MO calculations

Since 1979, the X-ray structural analysis of two dithio esters coordinated to metal[9,10], two cyclic dithio esters[11,12], two cyclic bis(thioacyl) sulfides[13,14] and several dithiocarboxylato–metal complexes[7–20] have been reported. Their most important bond lengths and angles are collected in Table 1. The C=S bond lengths of dithio esters and bis(thioacyl) sulfides are almost equal. The coordination of the thiocarbonyl sulfur atom in a dithioester to a metal lengthens the C=S bond[9,10]. The —C(S)S(S)C— moiety of cyclic bis(thioacyl) sulfides is planar[13]. In contrast, the most stable conformer of bis(thioacetyl) sulfide predicted by MINDO/3 calculation shows that the angle between the S=C—S plane and the plane containing the other C=S group is perpendicular[28]. The C—S bond lengths of dithiocarboxylato metal complexes are 165–170 pm, which is the average between the C—S single bond and C=S double bond of dithio esters. It is noted that cyclopentadiene–dithiocarboxylato gold complexes have the —CSS— moiety showing C=S double-bond character. Tetrakisdithiocarboxylato dimolibdenium[15], nickel[22], palladium[27] and platinium[24] complexes contain a metal–metal bond in the molecules.

Molecular orbital calculations for dithio formic acid[29,30] and dithioacetic acid[31] show that the *Z* conformation is more stable than the *E* one. Two of the conformers (I and II) of vinyl dithioformate have been optimized by *ab initio* MO calculation (STO-3G)[32] (Figure 1). The calculation of the total energy showed that II is more stable than I by 0.154 eV (1.49 kj mol^{-1}). The HOMO of the conformer I is the nonbonding orbital of the thiocarbonyl sulfur, whereas the HOMO of the conformer II is a π-allyl type orbital at the carbodithioate moiety (Figure 2). The most stable conformations of acyl thioacyl sulfides[28] and bis(thioacyl) sulfides[33,34] were also calculated. The results of the calculations of the charge distributions and the frontier electron densities predict that nucleophiles or electron-donating reagents attack the sulfide sulfur in a charge-controlled reaction (in case of a 'hard' base) and the thiocarbonyl sulfur in a frontier-orbital



(I) Total energy = −24492.86 eV

(II) Total energy = −24493.02 eV

FIGURE 1. The stable conformers of dithioformic acid vinyl esters

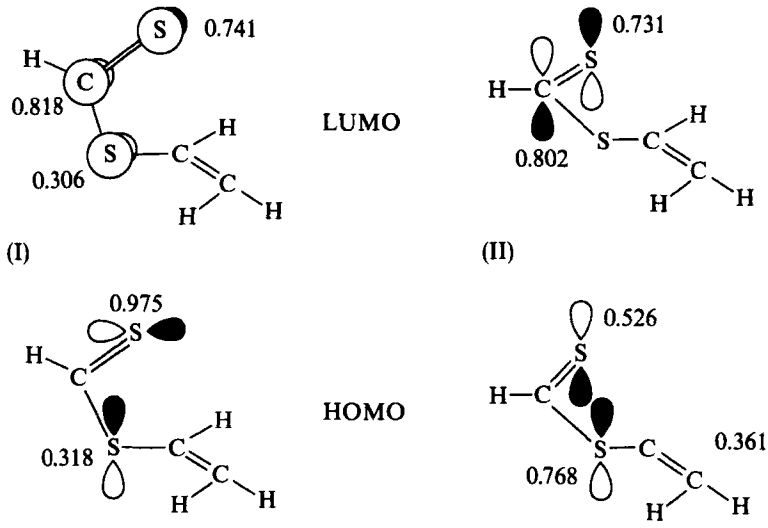


FIGURE 2. Frontier orbitals and frontier orbital coefficients of vinyl dithioformate (I and II) (Coefficients of 3d-atomic orbitals of sulfurs and 2p-atomic orbitals of carbons)

controlled reaction (in case of a 'soft' base). The HOMO is localized on the thiocarbonyl sulfur. 'Soft' and 'hard' electrophiles are predicted to react at the thiocarbonyl sulfur and carbon, respectively (Figure 3).

B. IR Spectra

It is well known that the S—H stretching frequencies of thio- and dithio-carboxylic acids are observed in the region of 2450–2550 cm^{-1}. The ν_{SH} bands of RCOSH appear at a region lower by *ca* 5–10 cm^{-1} than those of the corresponding dithio acid. The S—D stretching frequencies of *S*-deuterothio- and dithiocarboxylic acids are observed in the region 1820–1950 cm^{-1} [35]. The bands of RCOSD appear at a region lower by *ca* 50–60 cm^{-1} than those of the corresponding *S*-deutero dithio acids. The ν_{SD} bands of the aromatic derivatives appear at a higher region by *ca* 50–80 cm^{-1} than those of the aliphatic ones (Table 2).

The thiocarbonyl stretching frequencies predicted by a simplified force constant are in the vicinity of 1200 cm^{-1} [36]. A number of $\nu_{C=S}$ bands of thiono and dithio esters have been tentatively assigned in the region of 1000–1270 cm^{-1} [2]. However, there is no exact assignment as yet of these thiocarbonyl stretching frequencies. In Table 3, $\nu_{C=O}$ and $\nu_{C=S}$ bands of diacyl, acyl thioacyl and bis(thioacyl) sulfides which have been synthesized in the last decade are collected.

The $\omega_{C=O}$, ω_{S-X} (X = Cl, Br, I) and δ_{S-X} bands of benzenesulfenyl halides have been assigned (Table 4)[41]. The $\nu_{C=O}$ bands of acylsulfenyl halides shift to lower frequency regions in going to Cl, Br and I.

C. Proton and Carbon-13 NMR Spectra

The proton NMR spectrum of a dilute solution of dithioacetic acid at $-106°C$ shows separate methyl and SH signals for the *E* and *Z* conformation, with the *Z* isomer favored

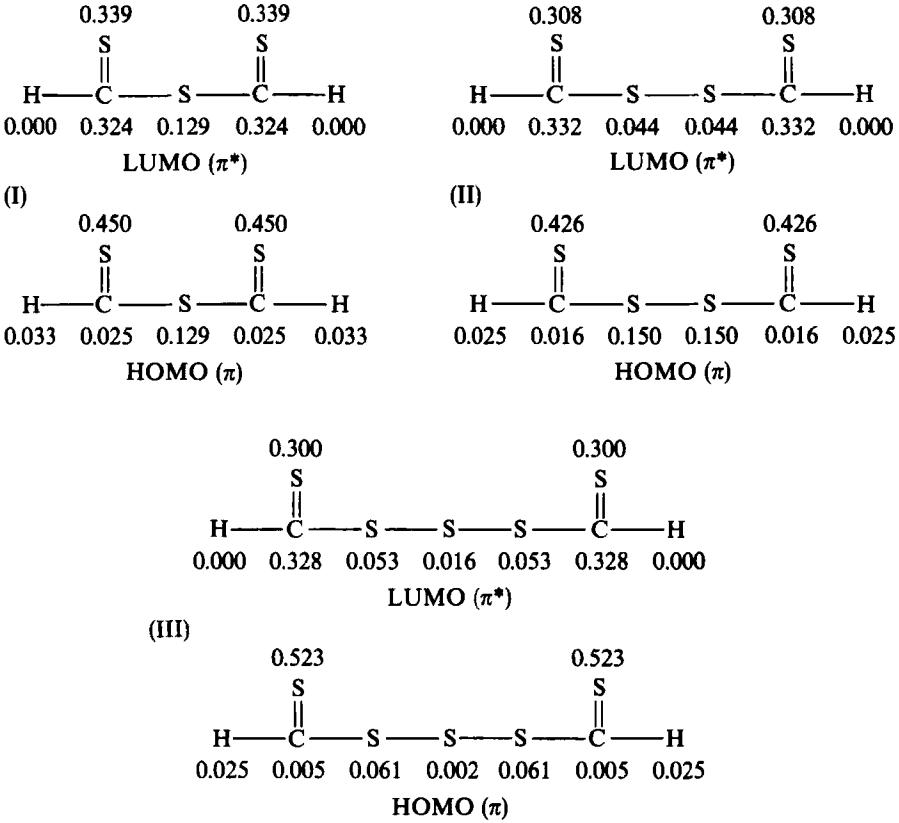


FIGURE 3. Frontier-orbital electron densities of bis(thioformyl) sulfides I–III

TABLE 2. IR bands of *S*-deutero thio- and dithiocarboxylic acids

Compounds	IR (neat) (cm^{-1}) ν_{S-H}	IR (neat) (cm^{-1}) ν_{S-D}	Ref.
CH_3COSH	2550		37
CH_3COSD		1865	38
CH_3CSSH	2470		37
CH_3CSSD		1811	35
C_2H_5CSSD		1809	35
i-C_3H_7CSSD		1815	35
Cyclo-$C_6H_{11}CSSD$		1810	35
4-$CH_3C_6H_4CSSD$		1915[a]	35
4-ClC_6H_4CSSD		1900	35
CF_3CSSH	2577[a]		39
CF_3CSSD		1870[a]	44

[a] Solvent = CCl_4.

TABLE 3. Infrared bands of diacyl, acyl thioacyl and bis(thioacyl) sulfides

E E′ ‖ ‖ RC—Sx—CR	E	E′	x	IR(KBr) (cm^{-1}) $\nu_{C=O}$	IR(KBr) (cm^{-1}) $\nu_{C=S}$	Ref.
$R = C_6H_5$	O	O	1	1740 1670		42
	O	O	2	1700		43
	O	S	1	1690	1235	28
	O	S	2	1690	1242	44
	S	S	1		1240	33
	S	S	2		1240	45
	S	S	3		1221	34
	S	S	4		1240	34

by 0.12 kcal mol^{-1}. In concentrated solution, the acid exists as a mixture of monomer (*ca* 61%), dimer (38%) and cyclic trimer (0.1%)[49].

The thiocarbonyl carbon chemical shifts appear at δ 209–220 for thiono esters and δ 220–260 for dithio esters (Table 5).

In general, the $^{13}C{=}S$ chemical shifts of aliphatic dithio esters (RCSSR′, R = alkyl) appear at higher field than those of the aromatic ones (RCSSR′, R = aryl). In the order $R = CH_3$, CH_3CH_2, $(CH_3)_2CH$ and $(CH_3)_3C$, the $^{13}C{=}S$ chemical shifts show downfield shifts. The thiocarbonyl carbon chemical shifts of trimethyl Group 14 metal dithio esters give a linear correlation against the Allred–Rochow electronegativities of the metals except for the Si-dithio ester in which the effect of the C—Si δ^* is large (Figure 4)[55]. The empirical equation [$\delta_{(C=S)}$ 1.45, $\delta_{(C=O)}$ 46.5] predicting the ^{13}C chemical shifts of the C=O and the C=S group, which has been presented by Kolinowski and Kessler[56], cannot be applied to these triorgano Group 14 metal esters[55].

D. Electron Spectra

In general, the bands due to the n–π^* transitions of aromatic dithiocarboxylic acid esters ($ArCS_2R$) appear in the region of 500–515 nm, i.e. at longer wavelengths than those (460–490 nm) of aliphatic ones (RCSSR′, R = alkyl)[2]. Then n–π^* transitions of the C=S group of acyl thioacyl[28] and bis(thioacyl) sulfides[33] can be observed in the region of 510–590 nm (Table 6). The bands of acyl thioacyl sulfides appear at longer wavelength regions than those of the corresponding bis(thioacyl) sulfides, while the bands of acylthioacyl disulfides appear at shorter wavelength regions than the corresponding bis(thioacyl) disulfides (Figure 5)[28].

TABLE 4. IR and Raman spectra of benzoylsulfenyl halides

RCOSX R	X	$\nu_{C=O}$	Raman (Et_2O) (cm^{-1}) ν_{S-X}	Raman (Et_2O) (cm^{-1}) δ_{C-S-X}
C_6H_5	Cl	1688[39]	522[41]	190[41,46]
	Br	1685[40]	446[41]	153[41]
	I	1667[41]	397[41]	138[41]

[a] KBr.

TABLE 5. The $^{13}C{=}S$ chemical shifts of thiono and dithiocarboxylic acid derivatives

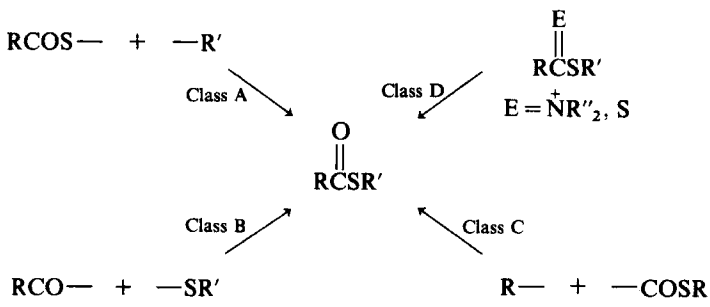
Compounds	Solvent	^{13}C NMR $\delta_{C=S}$	Ref.
i-$C_3H_7CSOSi(CH_3)_3$	$CDCl_3$	226	55
4-$CH_3C_6H_4CSOC_6H_5$	$CDCl_3$	228.3	50
$C_6H_5CSOCH_3$	$CDCl_3$	210.9	51
3-$NO_2C_6H_4CSOC_6H_5$	$CDCl_3$	209.4	50
4-$NO_2C_6H_4CSOC_6H_5$	$CDCl_3$	209.8	52
$FcCSOCH_3$	$CDCl_3$	217.3	53
$FcCSOC_6H_5$	$CDCl_3$	216.1	53
CH_3CSSCH_3	—[a]	231.7	50
$C_2H_5CSSCH_3$	—[a]	239.6	50
i-$C_3H_7CSSCH_3$	—[a]	247.0	50
C_6H_5CSSH	—[a]	228.5	50
$C_6H_5CSSCH_3$	—[a]	228.5	55
$C_6H_5CSSC_2H_5$	—[a]	225.5	50
$C_6H_5CSSC_3H_7$-i	—[a]	226.8	50
$C_6H_5CSSC_4H_9$-t	$CDCl_3$	228.9	55
4-$CH_3C_6H_4CSSC_6H_5$	$CDCl_3$	227.6	51
$FcCSSCH_3$	$CDCl_3$	229.3	50
$FcCSSC_6H_5$	$CDCl_3$	227.9	53
4-$CH_3C_6H_4CSSeC_6H_5$	$CDCl_3$	231.8	51
$FcCSSeC_6H_5$	$CDCl_3$	229.2	53
$(4\text{-}CH_3C_6H_4CS)_2S$	$CDCl_3$	223.2	54
$(CH_3)_2CHCSSC(CH_3)_3$	$CDCl_3$	247.1	55
$(CH_3)_2CHCSSSi(CH_3)_3$	$CDCl_3$	252.0	55
$(CH_3)_2CHCSSGe(CH_3)_3$	$CDCl_3$	252.9	55
$(CH_3)_2CHCSSn(CH_3)_3$	$CDCl_3$	257.1	55
$(CH_3)_2CHCSSPb(CH_3)_3$	$CDCl_3$	259.2	55

[a] Without solvent.

III. SYNTHESIS

A. Thio Esters

A number of the improved and new preparation methods of thio esters have been reported in the last decade. They are roughly divided into four types (Class A to D) on the basis of the final step of bond formation (see Scheme 1).



SCHEME 1

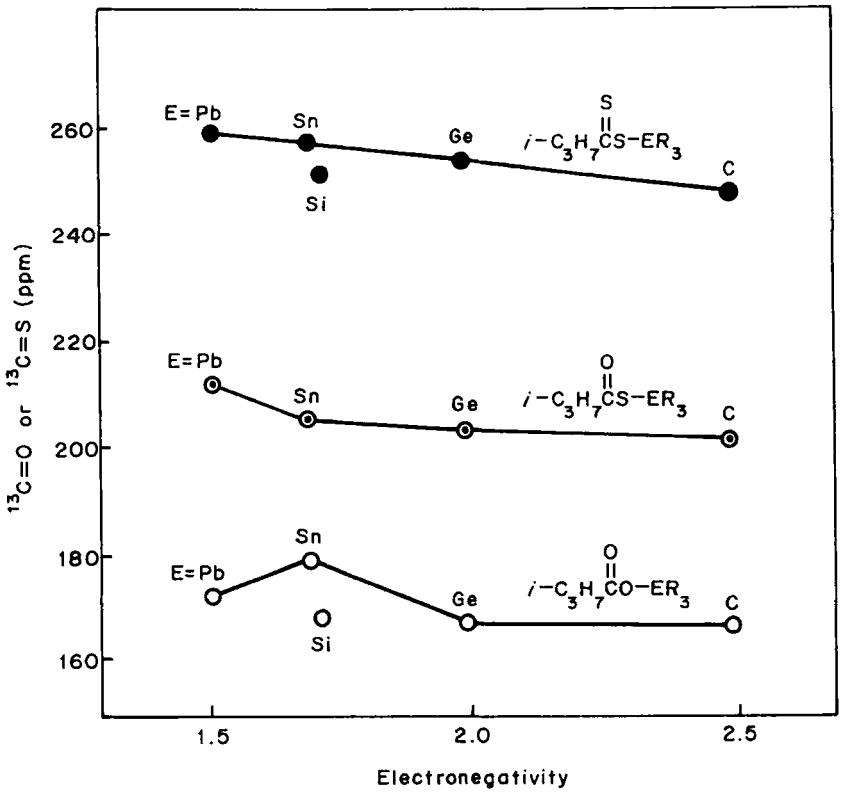


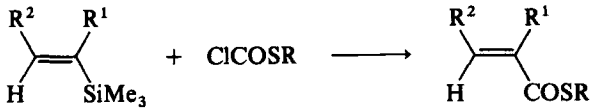
FIGURE 4. Plot of the thiocarbonyl carbon chemical shifts against Allred–Rochow electronegativities of triorgano Group 14 metal isobutyrates, thioisobutyrates and dithioisobutyrates

Class A. This class contains alkylation of thiocarboxylic acid salts[57–60], reaction of thiocarboxylic acids with alcohols[61–67], addition of thiocarboxylic acids to alkenes[64–71] and addition of acylsulfenyl bromide to alkenes[47].

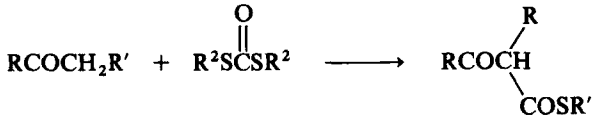
Class B. A variety of acylating reagents, carboxylic acids[71–74], acyl fluorides[75,76], acyl chlorides[77–84], acid anhydrides[75,86,87], mixed acid anhydrides[88–90], acylimidazoles[91], esters[92,93] lactones[64,95], ketenes[96,97] and amides[98] with thiols[73–76, 82, 89, 90, 92, 93, 96, 97], metal thiolates[75, 77, 81, 88, 94, 95], thiiranes[83], thioamides[98], 1,3-thiazoles[86], 1,3-thiazolizines[86] and enaminothiones[85] have been reported.

Class C. Thioalkoxycarbonyl halides[99–102], *S,S'*-dialkyldithiocarbonates[87] and *S*-alkylthiocarboxonium hexafluorantimonates[103] have been used as thioalkoxycarbonylating agents (equations 1–3).

Class D. Acid hydrolysis of imidoylthioethers and oxidation of dithio esters belongs to this class. The former has been employed widely, but in the last decade no significant improvement has been reported.



(1)



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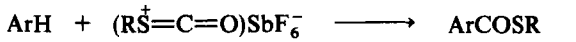
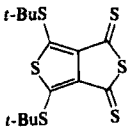
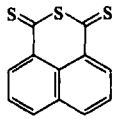
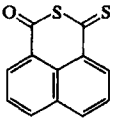
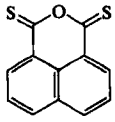
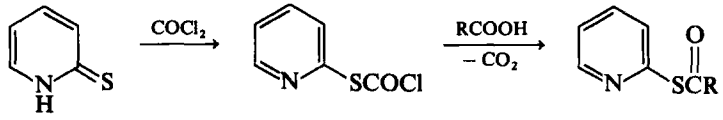


(3)

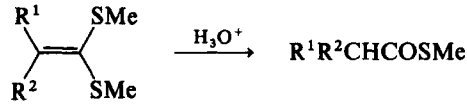
TABLE 6. Ultraviolet-visible spectra of acyl thioacyl and bis(thioacyl) sulfides

Compounds	π–π^* λ_{max}(log ε)	n–π^* λ_{max}(log ε)	Solvent	Ref.
$CH_3C(O)SC(S)C_6H_5$	310, 340	577	Hexane	28
$C_6H_5C(O)SC(S)C_6H_5$	313	583	Hexane	28
4-$CH_3C_6H_4C(O)SC(S)C_6H_4CH_3$-4	325	584	Hexane	28
$(CH_3CS)_2S$	348	512, 566sh	Hexane	33
$(i\text{-}C_3H_7CS)_2S$	351	517sh	c-Hexane	33
$(4\text{-}CH_3C_6H_4CS)_2S$	334	568, 585sh 620sh	c-Hexane	33
$(4\text{-}CH_3OC_6H_4CS)_2S$				
$[2,4,6\text{-}(CH_3)_3C_6H_2CS)_2S$	312	517, 620sh 537, 585	c-Hexane CH_2Cl_2	25
$(FcCS)_2S$	324	590	CH_2Cl_2	52
	493	578	Hexane	14
		562, 633 681	$C_3H_4Cl_2$	13
	375 410	566, 600 640	CS_2	13
	330sh 414	556	$C_2H_4Cl_2$	13

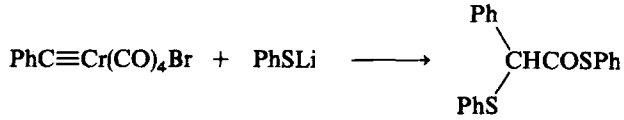
Miscellaneous. A number of new preparative routes have been reported (equations 4–16)[71, 104–117]. A convenient preparation of *S*-2-pyridyl thiolesters, which are excellent acylation reagents in the synthesis of peptides, ketones, macrolides, etc., was developed by Corey and Clark (equation 4)[71].



(4)[71]



(5)[104]



(6)[105]

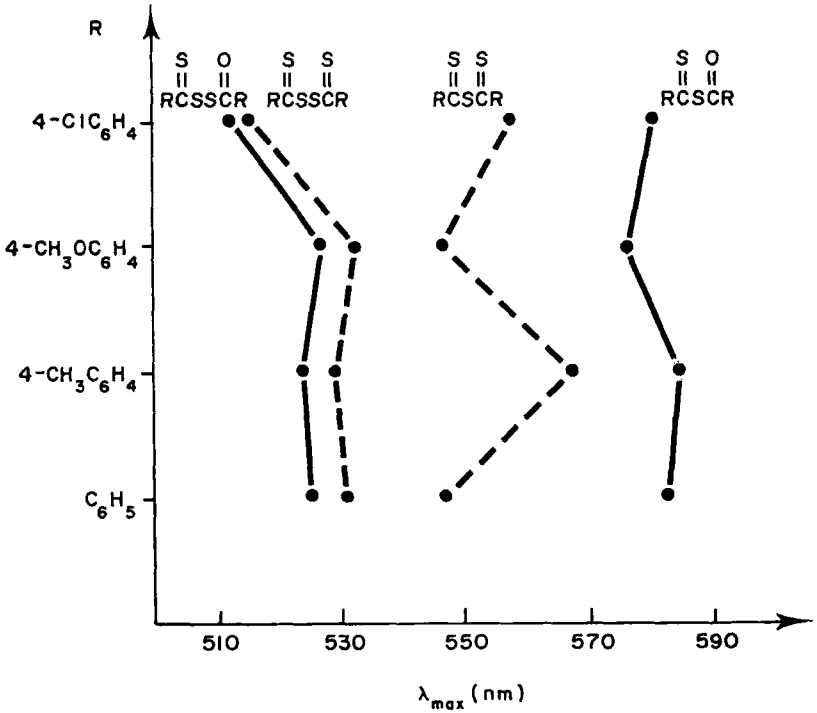
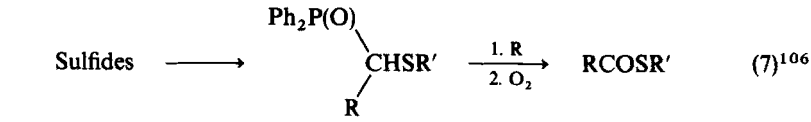
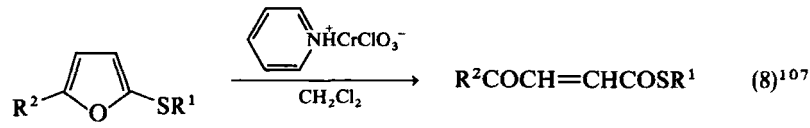


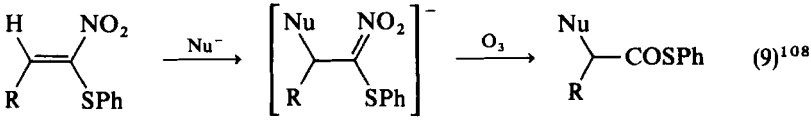
FIGURE 5. The n–π^* transitions of the thiocarbonyl group in acyl thioacyl sulfides and disulfides, and bis(thioacyl) sulfides and disulfides



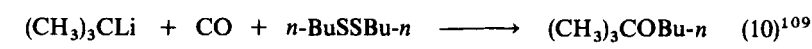
(7)[106]



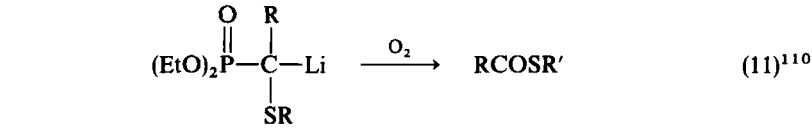
(8)[107]



(9)[108]



(10)[109]



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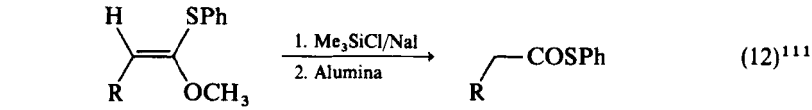
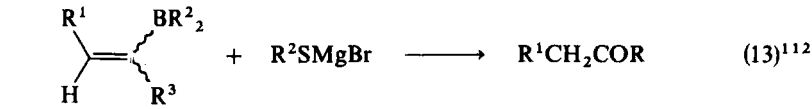
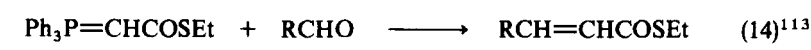


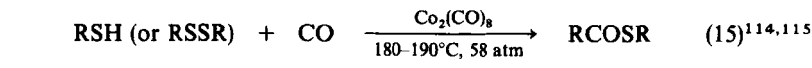
(12)[111]



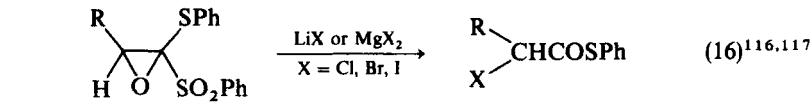
(13)[112]



(14)[113]



(15)[114,115]

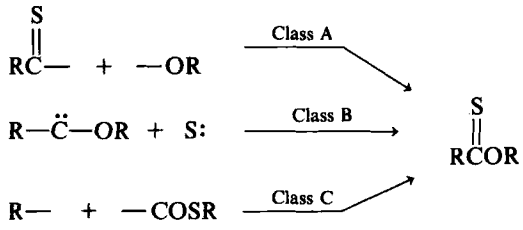


(16)[116,117]

A considerable number of thio esters have been prepared by reactions on other portions of the molecules while leaving the thiocarboxylic *S*-ester group intact. The stereochemical controlled synthesis of thio esters has been developed[118–120].

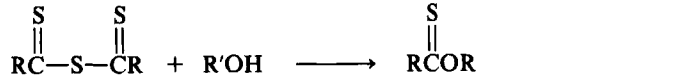
B. Thiono Esters

The preparation of thiocarboxylic acid *O*-esters (thiono esters) are roughly divided into three classes (Scheme 2) on the basis of the final step of bond formation.



SCHEME 2

Class A. Thioacylation reaction of alcohols is included in this class. As thioacylating reagents, thioacyl halides[121] bis(thioacyl) sulfides[33,53], phenylmercurydithiocarboxylates[122], thio ketenes[123,124] (generated by photolysis or thermolysis of precursors such as 1,2,3-thiazoles) and α-triphenylphosphine stabilized ketenes have been reported (equations 17 and 18). Ketones such as acetophenones react with thionyl chloride to give thioacyl chloride precursors (**1** and **2** equation 19)[125].



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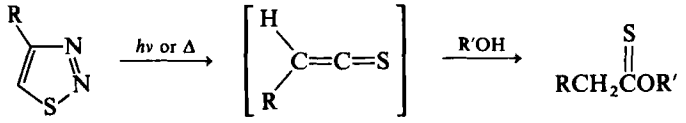

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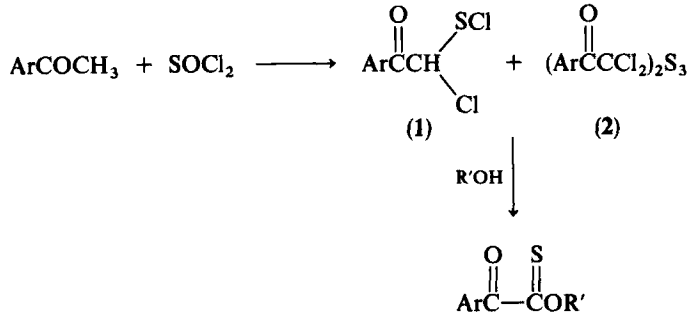


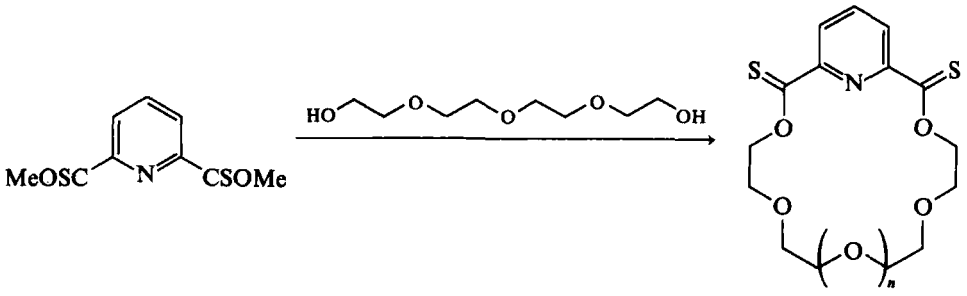
(19)

Treatment of dithio esters with a Mannich base affords a thio ester (equation 20)[126]. Ester exchange reaction of a thiono ester leading to a macrocyclic ether is also relevant (equation 21)[127].

Class B. Reaction of imino esters with hydrogen sulfide[128–133], and thionation of esters with Lawesson's reagent (L.R.)[134–136] or with phosphorus pentasulfide[137] belongs to this class (equation 22).

The former has been widely employed due to the availability of the starting nitriles. The latter two have also been proved to be effective for the synthesis of cyclic thiono esters, through requiring relatively high temperature. Bis(tricyclohexyl)tin sulfide acts as thionating agents in the presence of trichloroborane (equation 23)[138]. Treatment of

$$i\text{-}C_3H_7CSSR + (CH_3)_2NCH_2OR \longrightarrow (CH_3)_2NCH_2CMe_2CSOCH_3 \quad (20)$$



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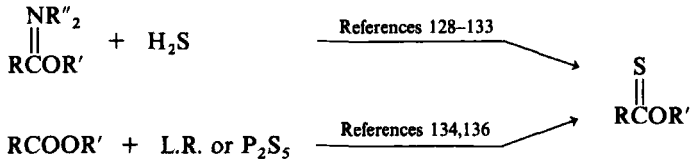

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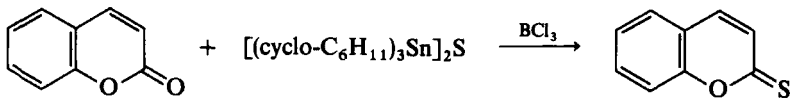


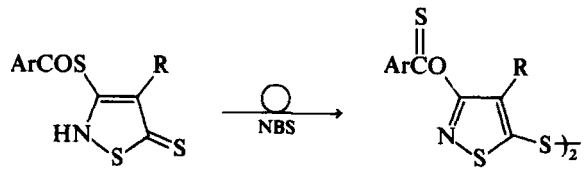
(23)

dialkoxycarbonium tetrafluoroborate with sodium sulfide or hydrosulfide leads to moderate to good yields of thiono esters (equation 24)[139–142].

Miscellaneous. A considerable number of thiono esters have been prepared by *S*-thio ester → *O*-thio ester rearrangement (equation 25)[143–145].

This type of rearrangement occurs in the presence of CH_2N_2, RI, RCOX, Et_3OBF_4, ROTl(I), RCOOOH and NBS. The *S*-alkyl group of certain conjugated thio esters is dealkylated to give 2*H*-pyran-2-thiones (equation 26)[146,147]. Treatment of acetophenones with CS_2 in a base (equation 27) leads to pyran-2-thione(3)[148]. Photochemical decarbonylation of cyclic dithiocarbonates generates 1,4-dioxane-2,3-dithiones (equation 28)[149].

$$R\overset{+}{C}(OR)_2BF_4^- + Na_2S \longrightarrow \underset{\displaystyle RCOR}{\overset{\displaystyle S}{\overset{\|}{}}} \quad (24)$$



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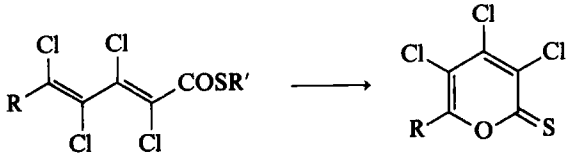

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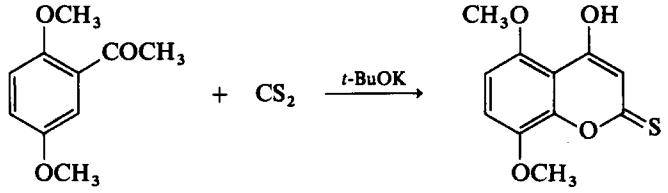

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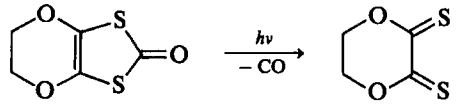
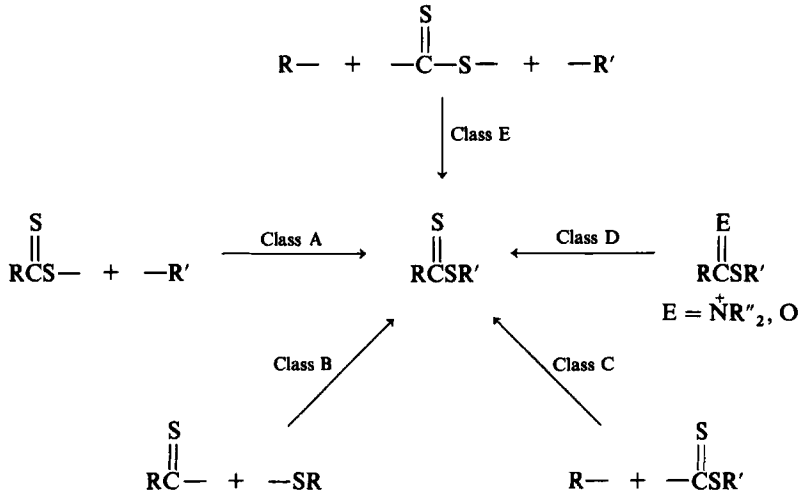


(28)

C. Dithio Esters

Similarly to thiolo esters, preparation of acyclic dithio esters can be roughly divided into five types (Classes A to E) on the basis of the final step of bond formation (Scheme 3).



SCHEME 3

Class A. In this category, alkylation[150,151] and arylation[152] of dithiocarboxylic acid sodium salts, and addition of dithio acids to imines[153] have been reported.

Class B. Thioacylation of thiols or thiolates belongs to this class. Bis(thioacyl) sulfides[33,53], dithiocarboxylic acid boron esters[154], phenylmercury dithiocarboxy-

lates[122] and thioketenes[10] and bis(2,4-dicarboethoxymethylene)-1,3-dithiethane[155] have been employed as new thioacylating agents.

Class C. In general, alkyllithium undergoes thiophilic attack at the thiocarbonyl group. α-Sulfoxymethyllithium and α-sulfonylmethylsodium attack the thiocarbonyl carbon of dimethyltrithiocarbonate to give the corresponding dithio esters (equation 29)[156,157]. Alkylcuprate reacts with thioethoxythiocarbonyl chloride to lead to the dithio ester[160].

$$CH_3—A—CH_2M + CH_3S\overset{\overset{S}{\|}}{C}SCH_3 \longrightarrow CH_3CH_2CSSCH_3 \qquad (29)$$

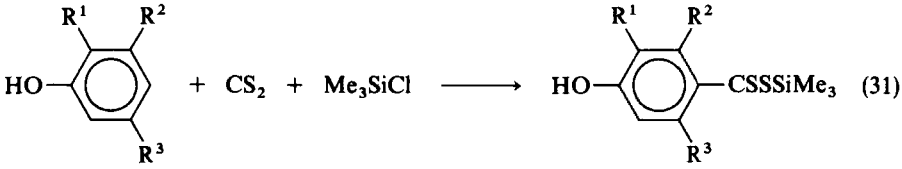
$A = \diagdown\!\!\diagup SO,\ \diagdown\!\!\diagup SO_2$

M = Li, Na

Class D. The synthesis of ethane-1,2-bis(dithioic acid) esters has been reported by treatment of the corresponding imino thio esters with hydrogen sulfide[133], Thionation of nitro-, halogen- and hydroxy-substituted aliphatic thio esters has been achieved by the use of Davy's reagent (D.R.)[158,159] instead of P_4S_{10} or Lawesson's reagent (equation 30). Aromatic thio esters having a nitro group are readily thionated by heating with P_4S_{10}[160].

$$X\text{-}(CH_2)_nCOSR \xrightarrow{MeS—P(S)(S)P(S)—SMe\ (D.R.)} X(CH_2)_nCSSR \qquad (30)$$

Class E. The reaction of phenols with carbon disulfide in the presence of aluminum trichloride (equation 31) is useful for the synthesis of hydroxy-substituted aromatic dithio esters[161].

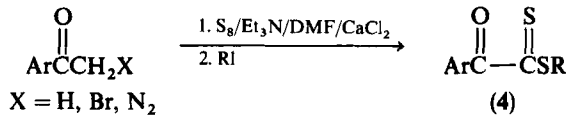


(31)

Miscellaneous. Several synthetic methods to yield stereospecific dithio esters using enolizable dithio esters have been developed (equation 32)[160–166]. Treatment of ketene

$$RCH_2CS_2R' \xrightarrow{\text{Base}} RCH{=}C(S^-)(SR') \xrightarrow[2.\ H_2O]{1.\ E} CH(R)(E)CSSR' \qquad (32)$$

dithioacetals with acid leads to dithio esters[167–169]. Various 2-oxodithiocarboxylic acid alkyl esters **4** have been prepared by the reaction of acetophenone, phenacyl bromides or acyldiazomethane with elemental sulfur/Et_3N/DMF. This reaction proceeds in the presence of $CuCl_2$ (equation 33)[152,170]. Conversion of β-hydroxy dithio esters into α-olefinic dithio esters was accomplished (equation 34)[171]. Other new formation routes (equations 35–38) of dithio esters have been described in the literature[172–177].



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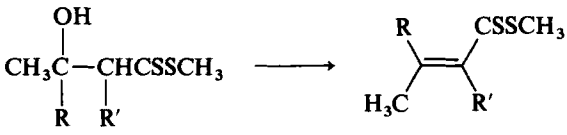

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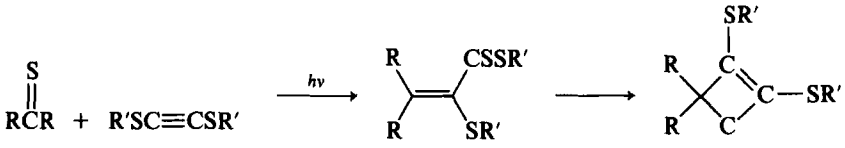
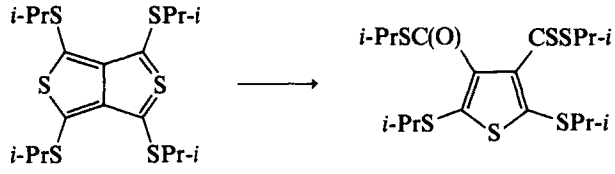
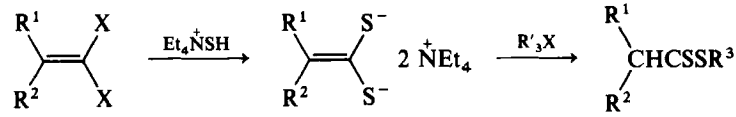


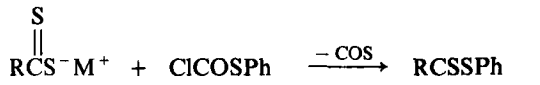
(35)[172,173]



(36)[175]



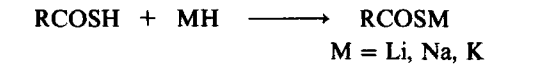
(37)[176]



(38)[177]

D. Thio Acid Salts

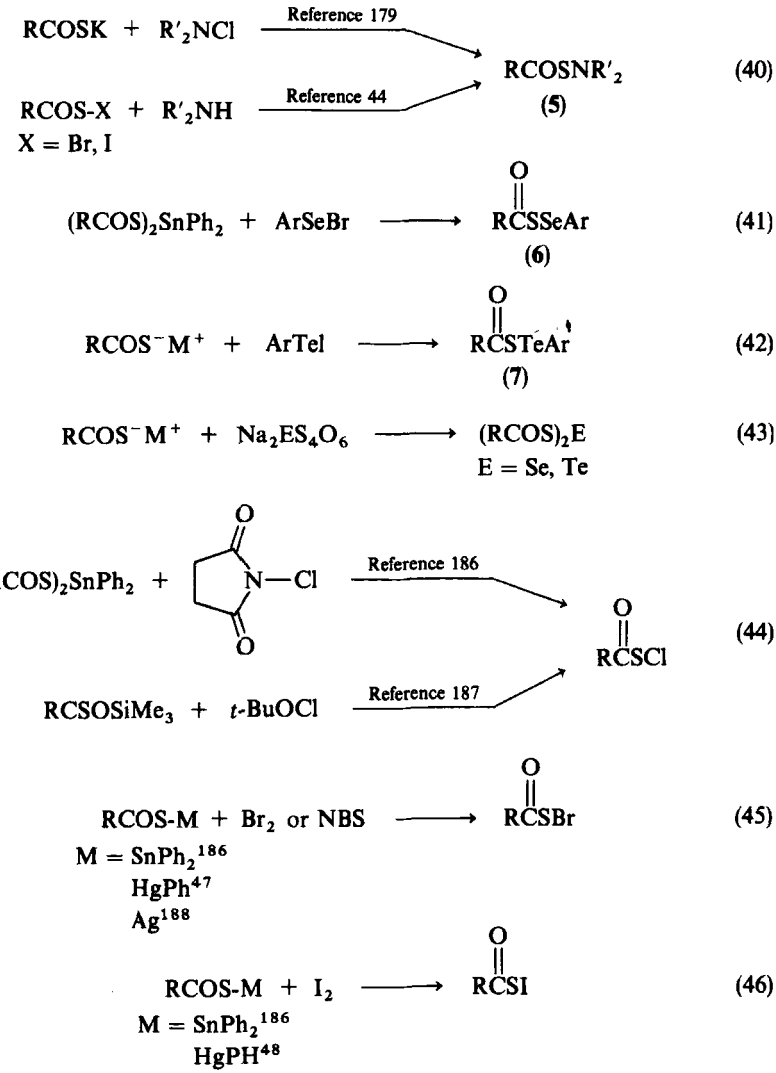
In general it is difficult to obtain sodium and potassium thiocarboxylates in the anhydrous state. A convenient preparation of these anhydrous salts has been carried out from thiocarboxylic acid with the corresponding alkali metal hydrides (equation



(39)

39)[178]. Rubidium and cesium thiocarboxylates can be obtained by using the corresponding metal acetates[178]. The preparation of *N*-(acylthio)-sulfenamides (**5**) has been reported by two routes (equation 40)[44,179].

Acylsulfenyl aryl selenides (**6**)[180–182] and tellurides (**7**)[183] have been prepared (equations 41 and 42). The most practical methods leading to these compounds are the reactions of diphenyltin bis(thiocarboxylates) with areneselenenyl bromides[180] and of



potassium thiocarboxylates with aryltellurenyl iodides[181]. Selenium and tellurium bis(-thiocarboxylates) are obtainable from the reaction of thio acid potassium salts with sodium seleno- and telluro-pentathionates, respectively (equation 43)[183]. The synthesis of acylsulfenyl halides had been limited to only acetylsulfenyl chloride because of their instability[184,185]. The isolation of aromatic acylsulfenyl chlorides[186,187], bromides[47,186,188] and iodides[48,186,188] has been achieved by the reactions in equations 44–46.

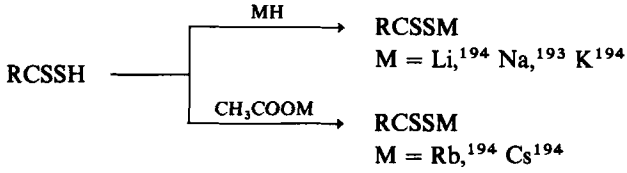
The following coin metal and transition metal complexes of thiocarboxylic acids have been described in literature in the last fifteen years: $RCOSAg$[188], $RCOSHgPh$[122], $RCOSFe(CO)_2Cp$[189], $(RCO)_2RuL_2$ ($L = R'_3P$, etc.)[190], $[(PhCOS)_2Pd]_n$[191], $(PhCOS)_2PdL_2$ ($L = R_3P$)[191] and $(PhCOS)_2PtL_2$ ($L = R_3P$ etc.)[191].

E. Dithio Acids and their Salts

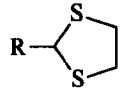
Dithio acids. A facile synthesis of *S*-deuteriodithio acids by deuteriolysis of trimethylsilyl dithio esters is feasible (equation 47)[35]. β-Alkylimino-α-cyano dithiocarboxylic acids can be synthesized from the reaction of β-alkylimino nitriles with carbon disulfide in the presence of base, followed by acidolysis[192].

$$RCSSSiMe_3 + D_2O \longrightarrow RCSSD \qquad (47)$$

Similarly to thiocarboxylic acid salts, alkali metal dithiocarboxylates can be prepared as anhydrous salts from the reaction of dithio acids with the corresponding alkali metal hydrides[193,194] or acetates[194] (Scheme 4). The formation of lithium dithioates has been described from 2-substituted 1,3-dithiolanes and LDA (equation 48)[195]. Alkali metal 5-imidazolecarbodithioates[196] and ammonium 2-iminocyclohexyl-1-enecarbodithioate[197] have been prepared. Sulfhydrolysis of dithio esters leads to sodium dithioates (equation 49)[177].



SCHEME 4

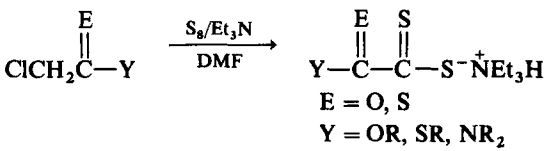


$$+ \text{ LDA} \longrightarrow RCSSLi \qquad (48)$$

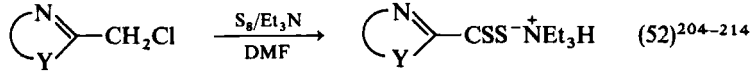
$$RCSSCH_3 + NaHS \xrightarrow[MeOH]{r.t.} RCSS^-Na^+ \qquad (49)$$

The reaction of aromatic dithiocarboxylic acid ammonium salts with trimethylsilyl chloride gives often unsatisfactory yields of the silyl dithioesters. An improved method utilizing cesium dithioates and trimethylsilyl iodide has been reported (equation 50)[35]. In 1969, Becke and Hagen[198] reported a practical preparation of aromatic dithiocarboxylic acid sodium salts from halomethylarenes with elemental sulfur in the presence of sodium methanolate. The reaction in DMF in the presence of triethylamine has been proved to be effective for the preparation of di, tri- and tetrathiooxalic acid salts[199–203] and 1,3-oxazole- and 1,3-thiazole-2-carbodithio acid triethylammonium salts (equations 51 and 52)[204–214].

$$ArCSSCs + Me_3SiI \longrightarrow ArCSSSiMe_3 \qquad (50)$$

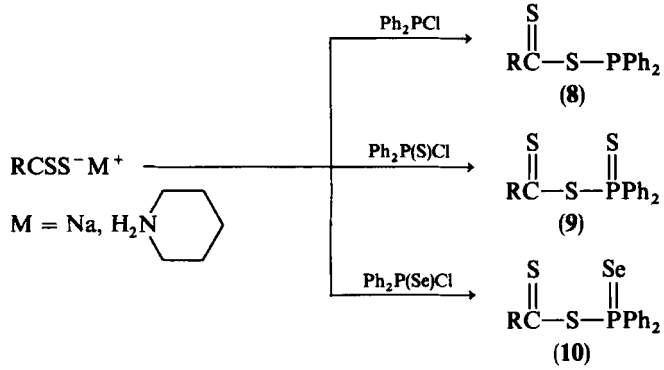


(51)[199–204]

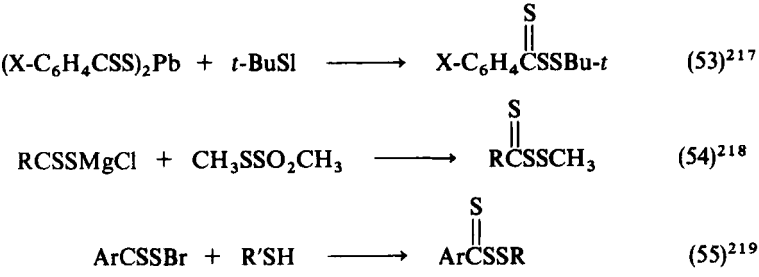


Y = NR, O, S

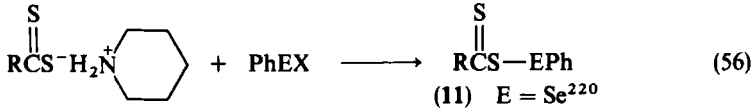
Diphenylphosphino- (**8**), diphenylthiophosphinoyl (**9**) and diphenylselenophosphinoyl dithiocarboxylates (**10**), which act as thioacylating agents in both protic and aprotic solvents, have been prepared (Scheme 5)[215]. It has been known that the reaction of piperidinium dithiocarboxylates with arylsulfenyl chloride leads to good yields of thioacyl aryl disulfides[216]. Other preparative methods have also been employed[217–219] though they are less satisfactory (equations 53–55).



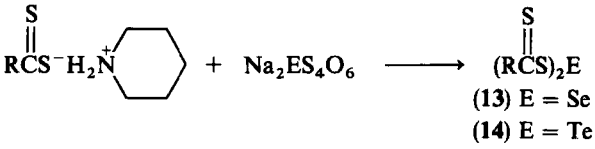
SCHEME 5



Phenylselenenyl thioacyl (**11**)[220] and phenyltellurenyl thioacyl sulfides (**12**)[221] can be obtained in moderate yields from the reaction of piperidinium dithioates with phenylselenenyl bromide and phenyltellurenyl iodide, respectively (equation 56). Selenium (**13**) and tellurium bis(dithiocarboxylates) (**14**) have been prepared by the treatment of piperidinium dithiocarboxylates with sodium seleno- and telluro-pentasulfides (equation 57)[222]. The formations of thermally labile thioacylsulfenyl bromides (**15**)[211] and iodides



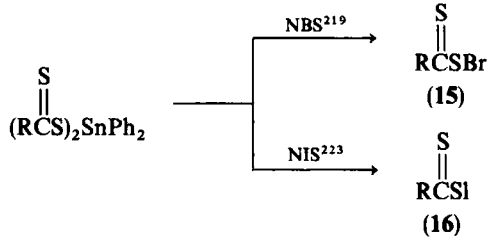
(**11**) E = Se[220]
(**12**) E = Te[221]



(57)

(13) E = Se
(14) E = Te

(16)[223] have been proven in the reaction of diphenyltin bis(dithiocarboxylates) with NBS and with *N*-iodosuccinimide (NIS), respectively (Scheme 6).



SCHEME 6

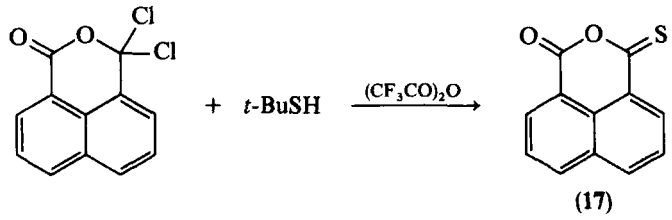
Since 1978, *ca* 60 dithiocarboxylato-coin and -transition metal complexes have been described in the literature. They are of the types $(RCSS)_2M$[16,122,224,228], $(RCSSM)_4$[17], $(RCSS)_4M$[225,229], $(RCSS)_4M_2$[10,15,16,229], $RCSSML_n$ (L = ligand, n = 1–4)[23,26,227,230], $(RCSS)_4M_2X$ (X = halogen, n = 1,2)[22,26,231], $(RCS_3)(RCS_2)M$[25,26], $[(RCSS)_2M]_2S$[10,18] and $[(RCSS)_2M]^-K^+$(2,2,2-crypt)[232]. The metals (M) are Cu[23], Ag[23], Au[17], Hg[122], V[18,228], Nb[229], Cr[227], Mo[224,226,227,229], W[227], Mn[227,230], Re[227,230], Fe[227], Ni[22,24,225,232], Pd[16,225] and Pt[24,225,231]. The preparative methods of these complexes are roughly divided into three types involving (a) the insertion of carbon disulfide into the metal–carbon bond, (b) the reaction of dithio acids or their alkali metal salts with metals halides or bis(benzene) metal and (c) addition of halogen to dithiocarboxylato complexes such as $(RCSS)_4M_2$.

F. Thio Anhydrides

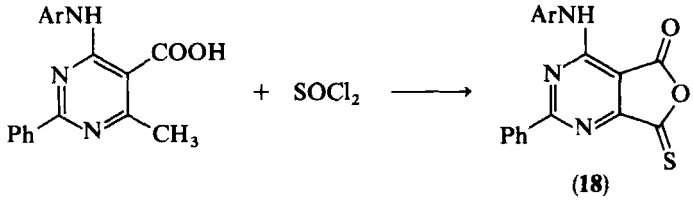
The first synthesis of diacetyl sulfide was carried out in 1891[233]. In the last decade, four new methods have been described in the literature: (a) reaction of acyl chloride with lithium sulfide and triphenylphosphine in the presence of a phase transfer catalyst[235], (b) desulfurization of a diacyl disulfide by Ph_3P in the presence of a phase-transfer catalyst[234], (c) reaction of acyl chloride with sodium sulfide in the presence of a phase transfer catalyst[236] and (d) treatment of piperidinium thiocarboxylates with 2-chloro-1-methyl pyridinium salts[42].

Acyl thioacyl oxides. Although acyl thioacyl oxides [RCOOC(S)R], an isomer of diacyl sulfides, have been considered to be difficult to isolate due to extreme, instability, two cyclic derivatives (**17** and **18**; equations 58 and 59) have been isolated recently[13,237].

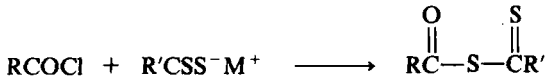
Acyl thioacyl sulfides. Acyclic acyl thioacyl sulfides (**19**) have been prepared and characterized from the reaction of acyl chlorides with sodium or potassium dithiocarboxylates (equation 60)[28] and by addition of dithio acids to ketene (equation 61)[238]. The isolation of **19** from desulfurization reaction of acyl thioacyl disulfides with phosphines appears to be difficult. Only one cyclic derivatives (**22**) has been prepared by thermal rearrangement of bis(thioacyl) oxide (**21**)[13].



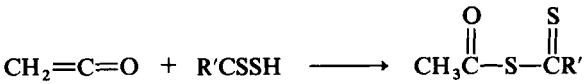
(58)



(59)

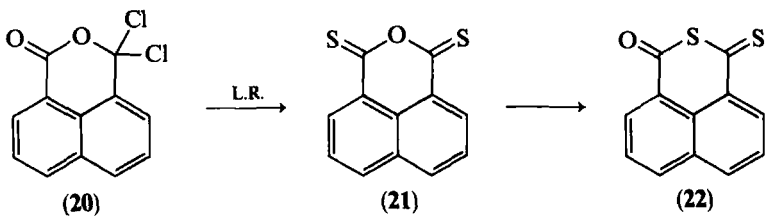


(60)



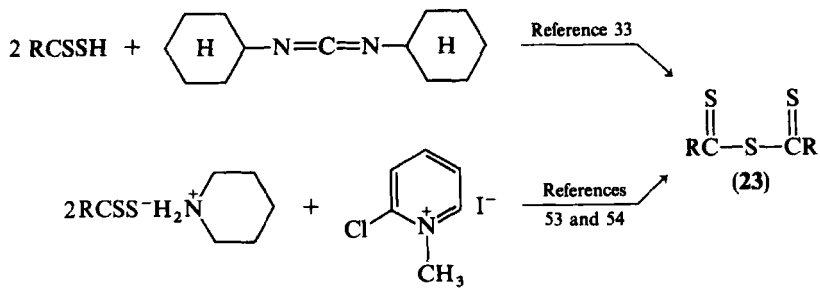
(61)

Bis(thioacyl) oxides. This type of compound was prepared by thionation of lacton esters (**20**) with Lawesson's reagent (L.R.) (equation 62)[13].

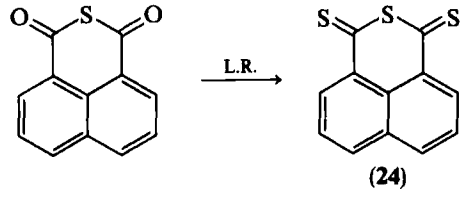


(62)[13]

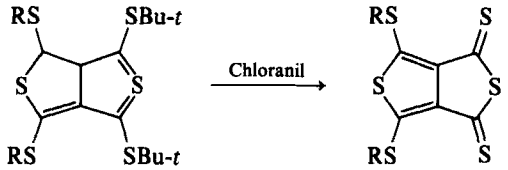
Bis(thioacyl) sulfides (trithioanhydrides). A series of aliphatic and aromatic bis(thioacyl) sulfides (**23**) have been prepared and characterized by the following two routes[33,53,54]. The method utilizing piperidinium dithioates and *N*-methylpyri-



(63)



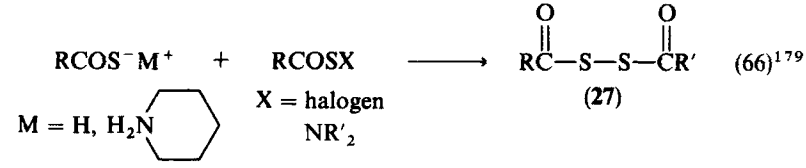
(24) (64)[13,14]



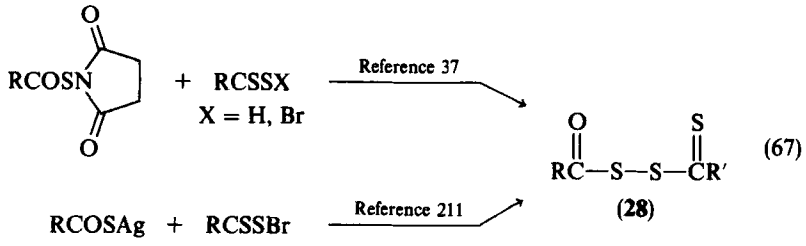
(25) (26) (65)[239,240]

dinium iodide is very convenient[53,54] (equation 63). Two cyclic derivatives (**25, 26**) have been isolated (equations 64 and 65)[13,14,239,240].

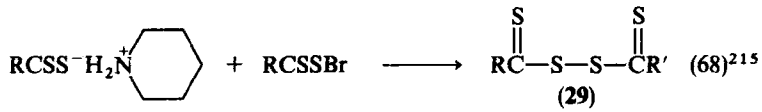
Diacyl disulfides. Diacyl disulfides acyl thioacyl disulfides, bis(thioacyl) disulfides: The isolation of symmetrical diacyl $[RCO)_2S_2]$[241] and bis(thioacyl) disulfides $[(RCS)_2S_2]$[242] were reported in 1903 and 1906, respectively. In contrast, unsymmetrical diacyl disulfides (**27**)[179], acyl thioacyl disulfides (**28**)[37,211] and unsymmetrical bis(thioacyl) disulfides[215] have been prepared in the last decade (equations 66–68). Acyl thiophosphoroyl (**30**)[44], thioacyl thiocarbamoyl (**31**)[219] and thioacyl thiophosphoryl disulfides (**32**)[219] have been also synthesized.



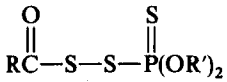
(27) (66)[179]



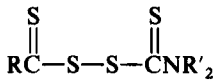
(28) (67)



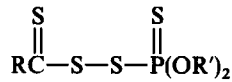
(29) (68)[215]



(30)

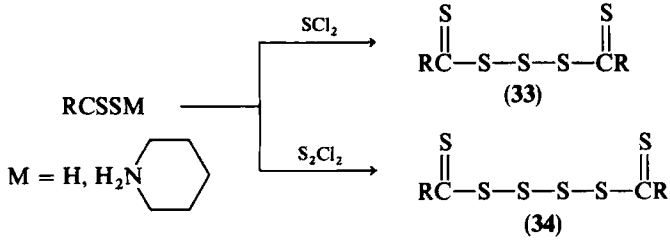


(31)[219]



(32)[219]

Bis(thioacyl) tri- and tetrasulfides. These tri- (**33**) and tetrasulfides (**34**) can be isolated by the reaction of dithiocarboxylic acids or their piperidinium salts with dichloromonosulfane and disulfane, respectively (Scheme 7)[215].



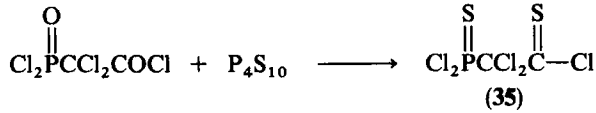
(33)

(34)

SCHEME 7

G. Thioacyl Halides

The synthesis of aromatic thioacyl chlorides has been well known for some time. The synthesis of alipathic ones is, however, more recent. The treatment of α-dichloroacetyl chloride with P_4S_{10} was found to give the corresponding thioacyl chloride (**35** equation 69)[243]. An equilibrium exists between trichlorothioacetyl chloride and 1,2,2-trichloroethenesulfenyl chloride[244].



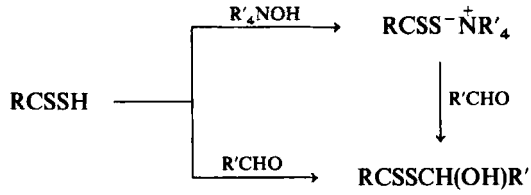
(35) (69)

N-Methyl-2-thioacylthiopyridinium salts[245,246], thioacyl thiophosphoroyl sulfides[215] and phenylmercury[122], triphenyllead[247] and catecholboranyl dithioates[154] have been shown to act as thioacylating agents.

IV. CHEMICAL PROPERTIES

A. Thio and Dithio Acids

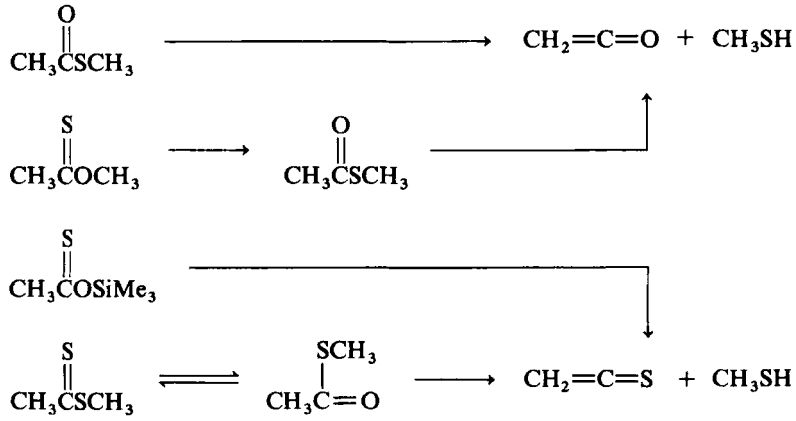
Treatment of dithio acids with tetraalkylammonium hydroxide gives the corresponding ammonium dithioates[150]. The reaction with aliphatic aldehydes affords 1-hydroxyalkyl dithioates (Scheme 8)[150]. Reduction with hydroborane in the presence of dimethyl sulfide affords thiols[154]. Dithio acids have been employed as the starting compounds for the synthesis of dithiocarboxylato transition metal complexes such as vanadium[18], molybdenum[326], platinum[22] and gold[23].



SCHEME 8

B. Thio Esters

Thermolysis of *S*-methyl[248] and *O*-methyl thioacetates[249,250] produces ketene, while *O*-trimethylsilyl thio ester having α-hydrogen[251] and methyl dithioacetate generates thioketenes[252]. (Scheme 9). Reduction of thio esters with sodium borohydride gives



SCHEME 9[248–251]

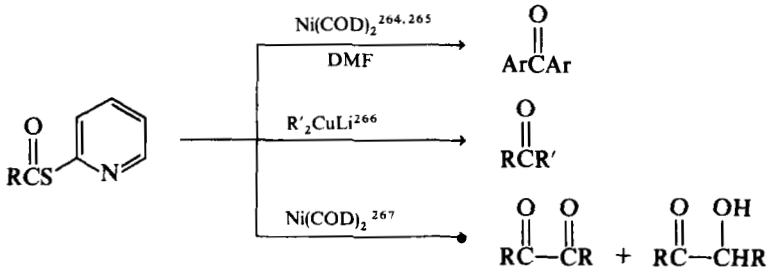
alcohols[253–255]. The treatment with Et_3SiH in the presence of palladium leads to aldehydes (equation 70)[256]. The coenzyme B_{12} mediated rearrangement of a thio ester group has been investigated[257–260]. β- and γ-thiolactones[259–261] and sulfides[262] have

$$RCOSR' \xrightarrow{Et_3SiH/Pd/C} RCHO \qquad (70)^{256}$$

been synthesized by photolysis of the thio esters having β-organo cobaloximine. Thio esters are versatile and relatively stable functional groups which transfer acyl or thio groups under mild conditions[263]. A facile synthesis of olefins[264], ketones[263,265,266], diketones[268], (Scheme 10), esters[94,263,266,268–272], lactones[263], unsymmetrical sulfides (Equation 72)[273], diacyl sulfides[42] and oranotin sulfides[266] has been developed.

The ring closure reaction of α,ω-bis(thio ester)[274–276], β-hydroxy thio esters[277], ω-hydroxy-2-pyridylthio esters[278,279], vinylogous thio esters[280] and *S*-acyl thioeneiminium salts[281] afford Dieckmann condensation products, β- and γ-lactones, α-pyrones and thiopyrane-2-one, respectively.

Conversion of thio esters to alkenes[282,283] and ketene thioacetals[284], and synthesis of α-vinylthio esters[285], *S*-vinyl thio esters[286] by Wittig reaction, and optically active dithioacetals[287,288] have also been reported (equation 73–78). An asymmetric aldol



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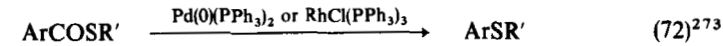
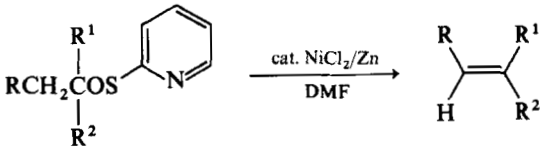
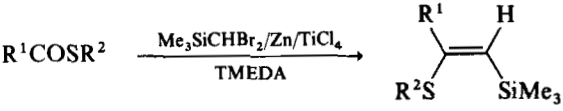
SCHEME 10



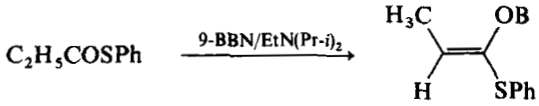
(72)[273]



(73)[282]



(74)[283]



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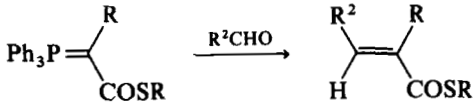

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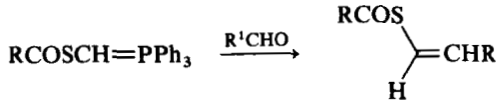
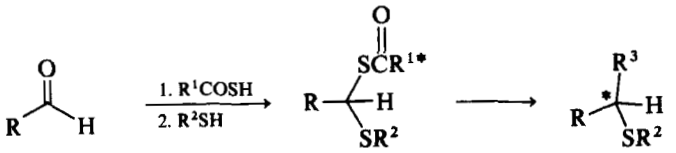
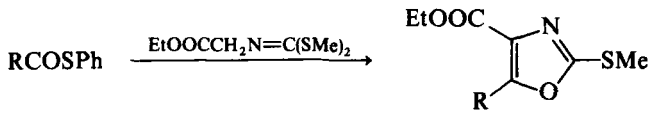


(77)[286]



(78)[287,288]

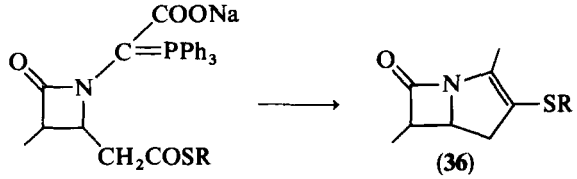
reaction using thio esters has been developed[289–291]. *S*-Phenyl thio esters react with *N*-(ethoxycarbonylmethyl)iminodithiocarbonate to give cyclocondensation products, 1,3-oxazoles (equation 79)[292]. 5-Thioxo-3-isothiazolin-3-yl *S*-thiobenzoates readily re-



(79)

arrange into the corresponding thiono esters by treatment with acylating reagents, peracids, NBS and aluminum chloride[144,145].

Application. The ring system construction of penem derivatives (**36**) has been achieved by intramolecular Wittig reaction of the thioesters having a phosphorous ylide group in the molecule (equation 80)[293–298].

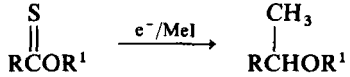


(36) (80)

S-(2-Pyridyl) thio esters have been used as active acylating agents in the synthesis of β-lactams[299] and of ketones during the total synthesis of crobarbatine acetate[300], erythronolide A[301] and monesin[302]. *t*-Butyl acetothioacetate is a useful starting compound for the synthesis of bis-β-ketomacrolides[303] and the plasmodial pigment fuligorubin A[304]. Cyclic thio esters have also been used for the synthesis of biologically active compounds[305–307].

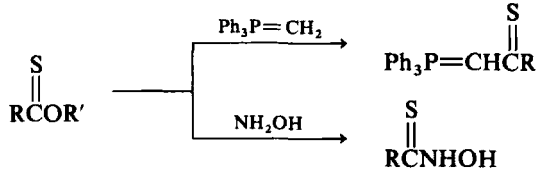
C. Thiono Esters

Oxidation and Reduction. A facile oxidation of thiono esters to the corresponding esters by benzeneselenenic acid anhydride[308,309], bis(4-methoxyphenyl)telluroxide[310,311] and aminoxide[312] and by photoirradiation[313] under oxygen has been carried out. *O*-Methyl benzenecarbothioate has been reduced with $LiAlH_4$, LiH/BF_3 and $NaBH_4$ to give complex mixtures of products including toluene, $PhCH_2SH$, $PhCH{=}CH_2$ and $PhCH_2H_2Ph$[136]. Reduction of thiono esters with organotin hydride leads to an alkane[314], while the treatment with borane/dimethyl sulfides leads to thiols[315]. Electrolysis

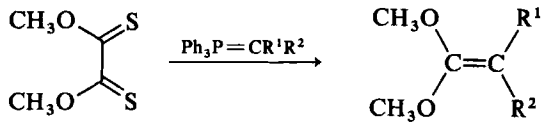


(81)

the presence of methyl iodide gives α-methylated ethers (equation 81)[316]. Alkylidenetriphenylphosphoranes[317,318] and hydroxylamine[319] are readily thioacylated by thiono esters (Scheme 11). *O,O'*-Dimethyl dithiooxalate is transformed into α,β-unsaturated thiono esters by alkylidenephosphoranes (equation 82)[320].

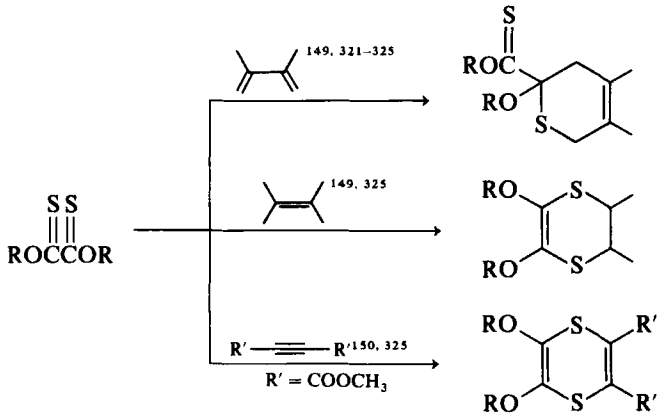


SCHEME 11

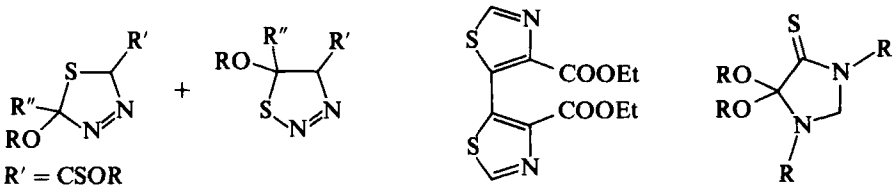


(82)

[4 + 2] *and* [3 + 2] *Cycloaddition.* *O,O'*-Dialkyl 1,2-dithiooxalates act either as dienophiles or dienes to give [4 + 2] cycloadditions[149,321–325] (Scheme 12), while the reaction with diazomethane,[324] isonitrile,[326] phenyl azide,[327] and carbodiimides[328] affords the corresponding [3 + 2] cycloadducts (**37–40**).

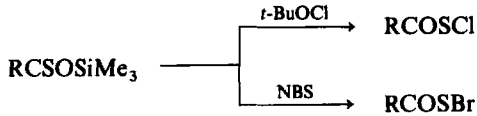


SCHEME 12



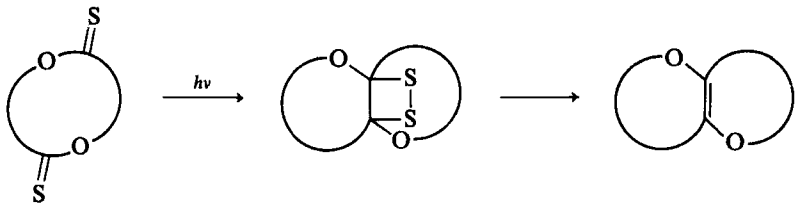
(**37**)[324] (**38**)[324] (**39**)[326] (**40**)[328]

Like organotin thioates ($RCOSSnR'_3$), *O*-trimethylsilyl thiono esters react with *t*-butyl hypochlorite and NBS to give acylsulfenyl chlorides and bromides, respectively (Scheme 13)[329].



SCHEME 13

Application. A series of oxapolycyclic systems has been synthesized by photoirradiation of macrodithionolactones (equation 83)[330,331].

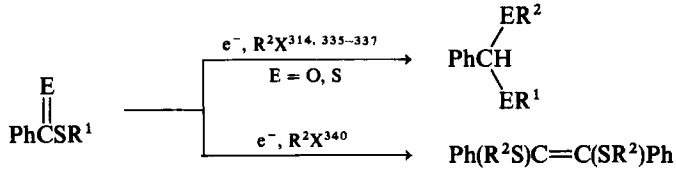


(83)

D. Dithio Esters

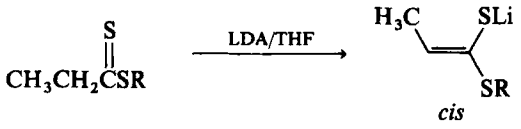
Thermolysis. In general, dithio esters are thermally stable. However, simple α-vinyldithio esters such as methyl ethenecarbodithioate[332,333] and 1-propenecarbodithioate[129] are too labile to isolate at room temperature. Upon gas-phase pyrolysis of methyl dithioacetate, no 1,3-sulfur methyl group migration takes place[250].

Oxidation and Reduction. Dithio esters are readily oxidized to thio esters by selenenic acid anhydride[308,309] and diaryl telluroxide[311,334]. Voss and coworkers have demonstrated a new thio- and dithioacetal[314,335–337] and ketene dithioacetal synthesis[340] by electrochemical reduction of dithio esters in the presence of alkylating agents (Scheme 14). The absence of alkylating agent affords alkynes[338]. The synthesis of thiiranes[336], 1,3-[151,339] and 1,4-dithianes[336] and *S*-alkyl *S'*-aryl dithioacetals[340] was also described. 1,2-Dithiol-3-thiones are electrochemically reduced[341–343]. Radical anion intermediates have been observed by polarographic reduction of dithio esters[344,345] and also in the electrochemical reduction of sterically hindered dithio esters[346,347] and 1,2-dithio-3-thiones[348,349]. Photochemical stannylation[350] and borane reduction[154] of dithio esters lead to stannyl sulfides and thiols, respectively.

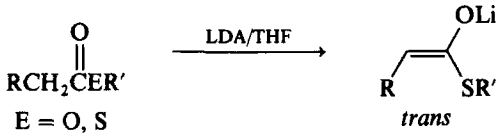


SCHEME 14

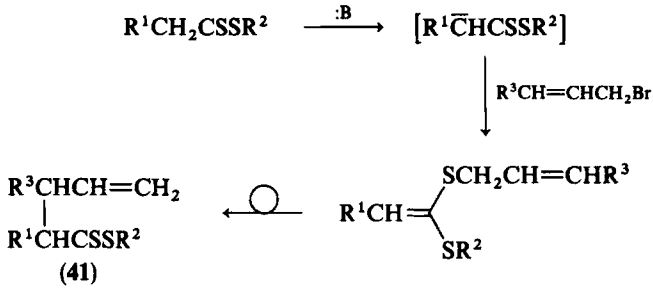
Abstraction of α-Hydrogen. α-Hydrogen of dithio esters is more easily abstracted by base than that of the corresponding thiol esters[275]. Deprotonation of dithiopropanoate with LDA in THF solution at −78°C leads to the *cis* lithium thioenolate[351,352], while esters[353,354] and thio esters[355] yield the *trans* enolates (equations 84 and 85). Stereochemically pure dienethiolates are formed by deprotonation of β-unsaturated dithio esters[356]. Trapping of the dithio ester anions with aldehydes[164,352,357,358], ketones[359,360], enones[165,166,361–365], 4-vinylbutyrolactone[162], allyl alcohols[366], bromides[367], trimethylsilyl chloride[368,369], alkanethiosulfonate[368,369] and carbon disulfide[133], and ethylchlorodithioformate[133] has been described in the literature. The reaction with enones proceeds in 1,4-fashion[165,166,361–365] while lithium enolates add to enones in 1,2-fashion[166,362,363]. The diastereoselectivity of the adducts is in favor of the *syn*-isomer[364]. In addition, the tin thioenolates in the presence of chiral diamines react with enones to give the enantioselective Michael adducts[165]. The *S*-allyl ketene-dithioacetals obtained by allylation of dithio ester anions rearrange into α-allyl substituted dithio esters (41)[367] (Scheme 15). Treatment of tetrathiosuccinic acid dimethyl ester with base leads to thiophenes[370].



(84)



(85)

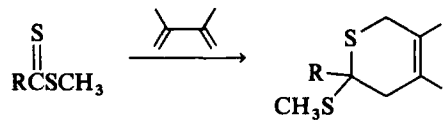


SCHEME 15

Abstraction of α′-Hydrogen. The α′-hydrogen of alkyl arenecarbodithioates can be deprotonated by base[371]. Treatment of α-triphenylphosphoniomethyl dithio esters with potassium *tert*-butanolate, followed by aldehydes, produces vinyl dithioates in good yields (equation 86)[372].

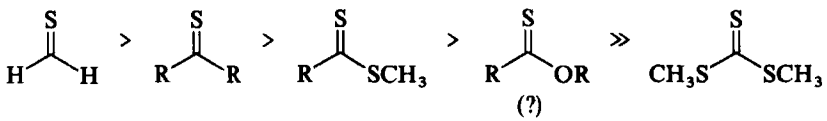
$$RCSSCH_2\overset{+}{P}Ph_3Br^- \xrightarrow{t\text{-BuOK}} \xrightarrow{R'CHO} RCSSCH{=}CHR' \qquad (86)$$

Cycloaddition. Dithio esters having an electron-withdrawing group such as CF_3CSSEt[373], $R_2NC(S)CSSMe$[374] or $EtOC(O)CSSR'$[375] have been known to react with dienes to give [4 + 2] adducts (equation 87). Common alkanedithio esters undergo

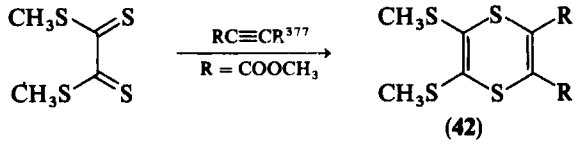


(87)

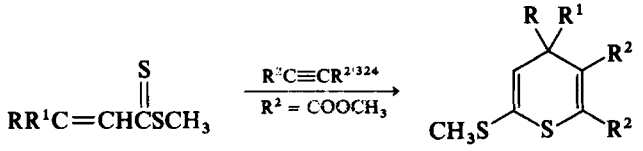
the hetero Diels–Alder reaction at 160°C[376] while no cycloaddition of aromatic dithio esters occurs. The following reactivity order of various thiocarbonyl compounds has been suggested[376]:



Dimethyl tetrathiooxalate[377] and α,β-unsaturated dithio esters[378] act as dienes to give [4 + 2] adducts (**42** and **43**, equations 88 and 89). The reactions of common dithio esters

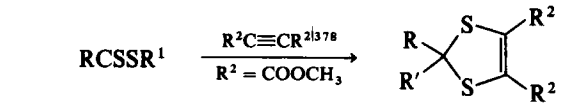


(42) (88)



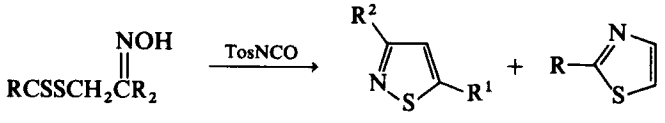
(43) (89)

with dimethoxycarbonylacetylene leads to 1,3-thiolanes (**44**, equation 90)[378]. The reactions with benzyne[379], isonitriles[379] and ylides[320] have been reported.

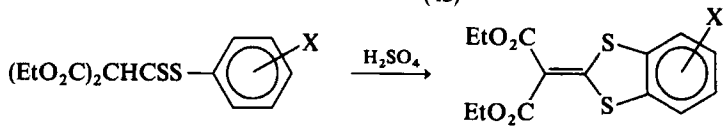


(44) (90)

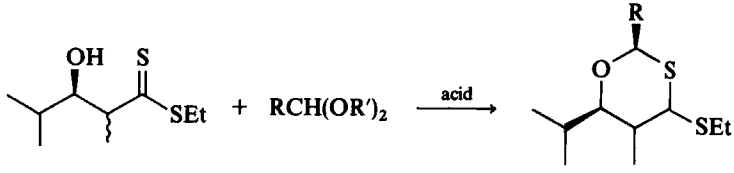
In general, carbanions such as Grignard reagent and alkyllithium attack the thiocarbonyl sulfur atom (thiophilic attack) of dithio esters. However, lithium organocuprates attack selectively at the thiocarbonyl carbon atom[380]. The α-hydrogen of dithio esters is chlorinated by *t*-BuOCl[381]. Treatment of oximes of dithio esters with tosyl isocyanate[382] and of β-aminoalkanecarbodithioic esters with iodine[383] leads to isothiazoles (**45**) together with 1,3-thiazoles (equation 91). Aryl bis(ethoxycarbonyl)methanecarbodithioates are cyclized in sulfuric acid to produce 2-ylidene-1,3-benzothiazoles (**46**) in good yields (equation 92)[155]. β-Hydroxydithio esters react with dimethyl or diethyl acetals in the presence of an acid catalyst to form the six-membered endocyclic ketene dithioacetals **47** via transacetalization (equation 93)[384,385]).



(45) (91)



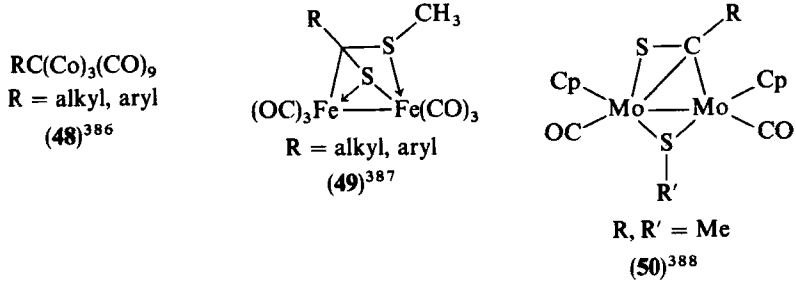
(46) (92)



(47) (93)

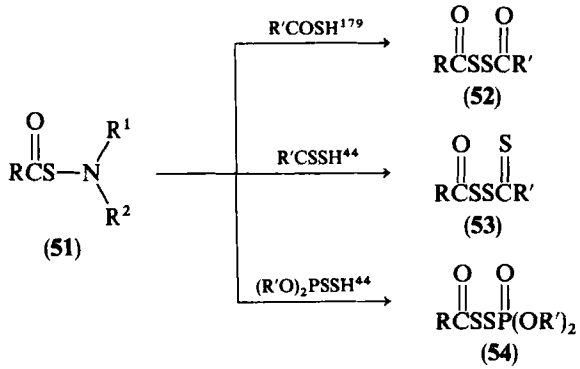
Miscellaneous. Dithio esters react with $Co_2(CO)_8$[386], $Fe_2(CO)_9$[387] and $Cp_2Mo_2(CO)_4$[388] affording the corresponding metal clusters (**48, 49** and **50**), respectively). The pyridinium ylides possessing dithio ester groups on the ylide carbon were used for the synthesis of pyrazolo[1,5-*a*]pyridines[389], thiazines[390] and pyridinothiophenes[391].

Application. *N*-methylmysenine[393], maytansine[394,395] and maytansinoides[384–386] have been synthesized by using dithio esters.

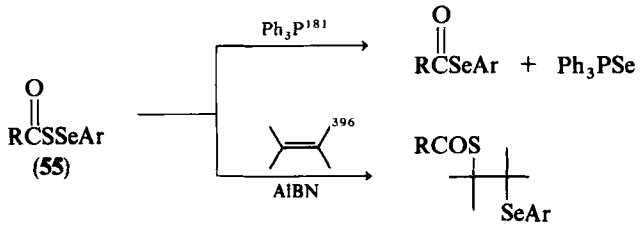


E. Thio Acid Salts

Acylsulfenamides **51** react with thio- and dithiocarboxylic acids to give the corresponding unsymmetrical disulfides (**52–54**) (Scheme 16)[44,179]. Acylsulfenyl aryl selenides (**55**) are readily desulfurized by triphenylphosphine to afford seleno esters[181] and undergo radical addition to alkenes in the presence of azobisisobutyronitrile (AIBN) (Scheme 17)[396].

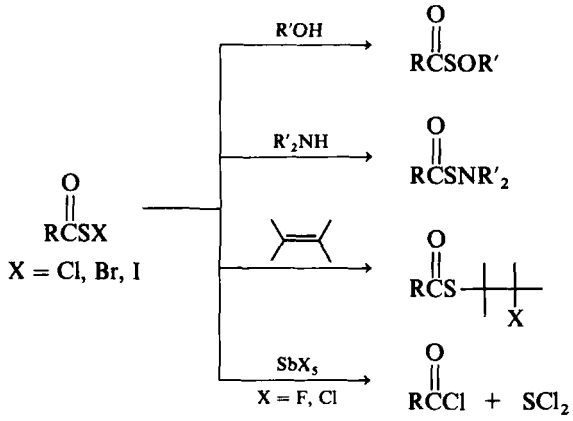


SCHEME 16



SCHEME 17

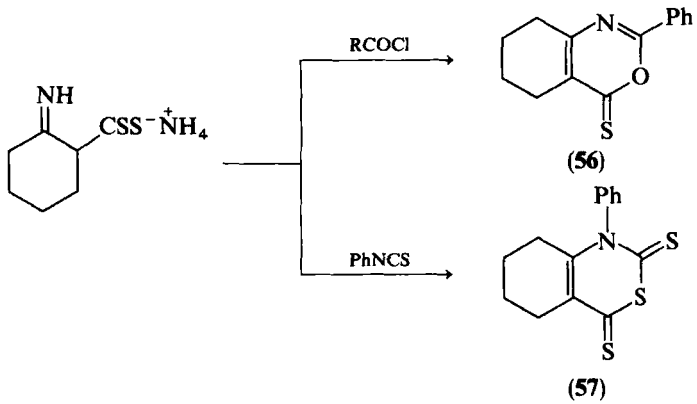
The reaction mechanism of selenium and tellurium bis(thiocarboxylates) with halogen has been discussed[183]. Acylsulfenyl bromides and iodides readily react with thio- and dithiocarboxylic acids and their piperidinium salts to produce unsymmetrical diacyl and acyl thioacyl disulfides[47]. The reactions with alcohols[397,398], amines [397–400], alkenes[47,397–401] and antimony pentahalides[400] have been reported (Scheme 18) Thiocarboxylic acid diphenyltin esters and silver, zinc and phenylmercury salts can be used as the starting compounds for the preparation of acylsulfenyl halides[40,48,186,188,397].



SCHEME 18

F. Dithio Acid Salts

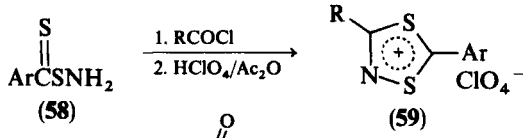
Ammonium dithiocarboxylates react with aldehydes and epoxides to give α- and β-hydroxyalkyl dithio esters, respectively[150]. Treatment of 2-iminocyclohex-1-enecarbodithioic acid ammonium salt with acyl chlorides and phenylisocyanate is a direct route to benzoxazine-4-thione (**56**) and benzothiazine-2,4-dithione (**57**) (Scheme 19)[197]. Muraoka and coworkers have also found that ammonium 2-cyano-3-iminodithioisobutyrate is an excellent reagent for the determination of silver[402].



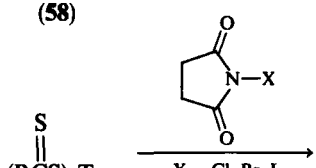
SCHEME 19

The reaction of *S*-(thioacyl)sulfenamides (**58**) with an acyl chloride, followed by perchlorate (equation 94), affords 1,4,2-dithiazolium salts (**59**)[403]. The tellurium atom of tellurium bis(dithiocarboxylates) is readily halogenated with NBS or analogues to give halotellurium dithiocarboxylates (**60**)[222]. Diphenylthiophosphinoyl dithiocarboxylates are effective thioacylation agents in both protic and aprotic solvents[215]. Diphenyltin dithiocarboxylates react with NBS to yield thioacylsulfenyl bromides (equation 96)[219].

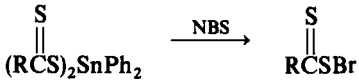
Lead bis(dithiocarboxylates) also react with *t*-butylsulfenyl iodide under mild conditions to afford thioacyl *t*-butyl disulfides (equation 97)[217]. Thioacylsulfenyl bromides add to alkenes to give *trans*-β-bromoalkyl dithio esters and in addition react with a variety of nucleophiles such as silver thioates, piperidinium dithioates, ammonium dithiocarbamates and aliphatic alcohols to give the corresponding unsymmetrical disulfides (**61–63**) and *O*-alkyl thioacylsulfenates (**64**) (Scheme 20)[219].



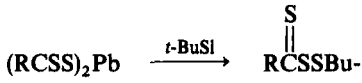
(94)



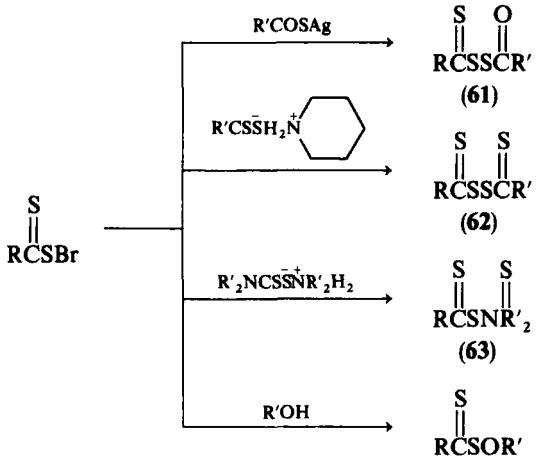
(95)



(96)



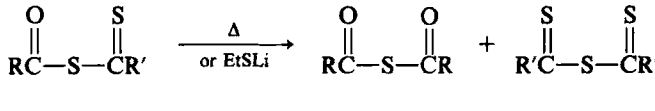
(97)



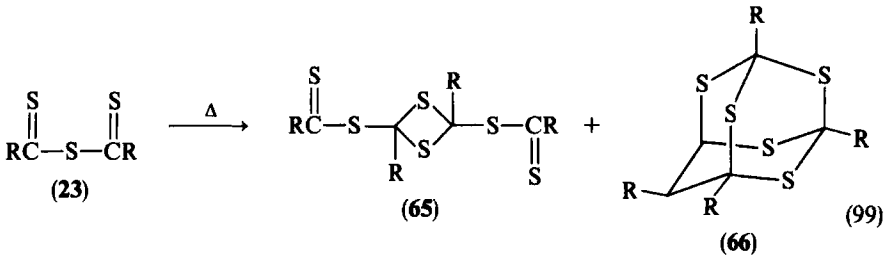
SCHEME 20

G. Thio Anhydrides

By heating[238] or treatment with lithium ethanethiolate[28], acyl thioacyl sulfides (**19**) disproportionate to give symmetrical diacyl sulfides and bis(thioacyl) sulfides (equation 98). Heating of bis(thioacyl) sulfides (**23**) above their melting points produces both 1,3-dithianes (**65**)[55] and thioadamantanes (**66**) (equation 99)[33]. The reaction of **19** with amines such as piperidine produces exclusively ammonium dithioates together with amides[28], whereas the reaction with tributyltin hydride affords both thio- and dithiocarboxylic acid tributyltin esters[28].

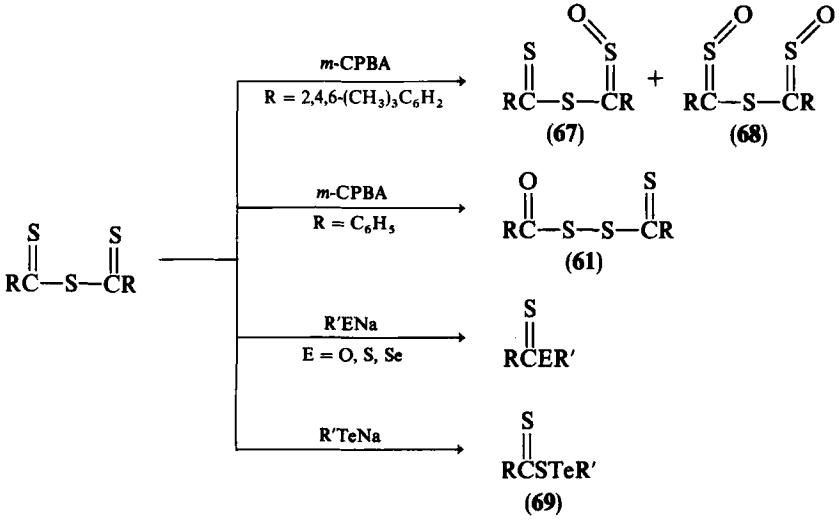


(98)



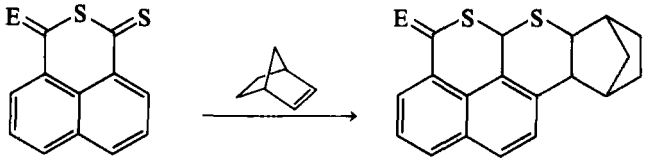
(99)

The trithioanhydrides (**23**) are reduced by lithium aluminum hydride into lithium thiolates via lithium dithioates[36]. Oxidation of **23** with *m*-CPBA gave thioacyl sulfine sulfides (**67**), bis(sulfine) sulfide (**68**) and acyl thioacyl disulfides (**61**) in moderate yields[404], Bis(thioacyl) sulfides **23** act as effective thioacylating agents for amines, alkali metal alcoholates, thiolates and selenolates[33]. The reaction with sodium benzenetellurolate gives phenyl thioacylsulfenyl tellurides (**69**, (Scheme 21)[33,53].



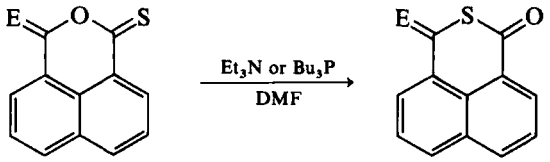
SCHEME 21

Cava and collaborators have demonstrated that di- and tri-thioanhydrides undergo thio Diels–Alder reaction (equation 100)[13] and cyclic thiono esters (**21**) readily isomerized in the presence of bases (equation 101)[239]. Treatment of bis(thioacyl) trisulfides with amines leads to dithio acid ammonium salts (equation 102)[34].



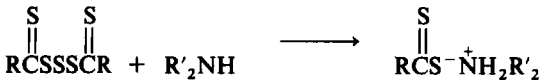
(70)
E = O, S

(100)



(7)

(101)



R′ = H, alkyl

(102)

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CHAPTER 15

Hydroxamic acids

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I. INTRODUCTION

Hydroxamic acids are weak acids formed usually by the action of hydroxylamine on carboxylic acid derivatives (Equation 1):

$$RCOX + NH_2OH \rightleftharpoons RCONHOH + HX \quad (1)$$

where X is OH, *O*-alkyl, *O*-aryl, acyl, amine or halide. The most common reaction product is the *N*-acyl derivative of the hydroxylamine but the reaction to form the *O*-acyl derivative is not unknown. Hydroxamic acids can exist in the tautomeric forms shown below.

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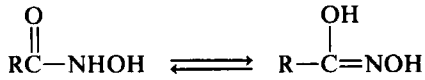


The direct formation of hydroxamic acids from the reaction of a carboxylic acid and hydroxylamine is unfavorable from an equilibrium standpoint[1] and the reverse reaction, i.e. solvolysis of the hydroxamic acid, is significant.

As will be discussed later, the use of coupling reagents is required to get a reasonable yield of hydroxamic acids from the reaction of carboxylic acids and hydroxylamine. The formation of hydroxamic acids from carboxylic acids is also facilitated by nickel-ion catalysis, although this has been investigated primarily on an analytical scale only. The reaction of other carboxylic acid derivatives with hydroxylamine has also been shown to be facilitated by nickel-ion catalysis[2]. More examples of the formation of hydroxamic acids from activated carboxylic acid derivatives will be given in the section on synthesis.

Hydroxamic acids are weak acids, $pK_a = 9$–10, and can function as weak nucleophiles. The interest in these compounds has been largely centered around their ability to chelate with transition metal ions to form complexes that absorb light in the visible spectrum (λ_{max} 500–650 nm). These complexes have been used in the analysis of transition metal ions in colorimetric determinations. Literally hundreds of such applications have been developed which are beyond the scope of this work. Similarly, carboxylic acids and their derivatives have been analyzed colorimetrically by conversion to the hydroxamic acid and complexation with a metal ion, usually ferric iron. The molar absorptivities typically range from 1000 to 1500 liter mol^{-1} cm^{-1} with absorption maxima in the region of 480–550 nm. A complete review of the analytical applications of this type is also beyond the scope of this chapter. Finally, the metal ion/hydroxamate complexes can be extracted from aqueous solutions into organic solvents as a method of purifying or recovering the metal ions.

Molecules containing the hydroxamic acid moiety have been shown to have important biological activities. The simple hydroxamic acid, acetohydroxamic acid, is an approved drug in the US for the treatment of urinary calculi[3]. *p*-Butoxyphenylacetohydroxamic acid (bufexamac) possesses antiinflammatory and analgesic effects and has been shown to be comparable in activity to betamethasone valerate[4].

Desferrioxamine, in the form of the mesylate salt (desferoxamine mesylate USP), contains the hydroxamic acid moiety and is marketed in the US for the treatment of acute iron intoxication and chronic iron overload. Desferrioxamine belongs to a class of naturally occurring compounds called siderophores, which are very specific low-molecular-weight iron chelators. There are several naturally occurring hydroxamate-containing siderophores: ferrichrome, mycobactins, rhodorulic acid and pseudobactin as well as desferrioxamine. Because of the strong ability of these molecules to complex iron, considerable interest has been generated in the synthesis and evaluation of hydroxamic acid analogs. A comprehensive review article has been published recently on the synthesis and therapeutic potential of hydroxamic acid-based siderophores and analogs[5].

Many of the examples contained in this review pertain to synthesis of hydroxamic acids possessing a variety of biological activities.

II. SYNTHESIS

A. Direct Reaction to Carboxylic Acids and Hydroxylamine

As discussed earlier, synthesis via this route is not very useful due to the unfavorable equilibrium. Further investigations into the acid-catalyzed formation of hydroxamic

acids from carboxylic acids showed that the rate of hydroxamic acid formation decreases as the chain length of the alkyl portion of the carboxylic acid increases[6].

In a study of the acid-catalyzed formation of the boron analog of acetohydroxamic acid, yields were obtained as high as 85%[7]. This suggests that the reverse reaction, hydrolysis of the boron–hydroxamic acid, is not significant contrary to what was observed for the formation of acetohydroxamic acid.

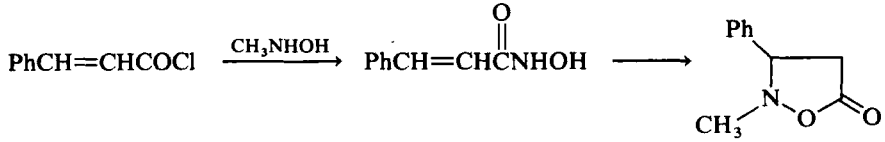
$$(CH_3)_3N \cdot BH_2COOH(aq) + NH_2OH \cdot HCl \rightleftharpoons (CH_3)_3N \cdot BH_2CONHOH + HCl(aq) \quad (2)$$

B. Formation from Acid Chlorides

One of the most widely used methods for the direct formation of hydroxamic acids is the reaction of hydroxylamine with highly reactive acid chlorides (equation 3).

$$RCOCl + NH_2OH \longrightarrow RCONHOH + HCl \quad (3)$$

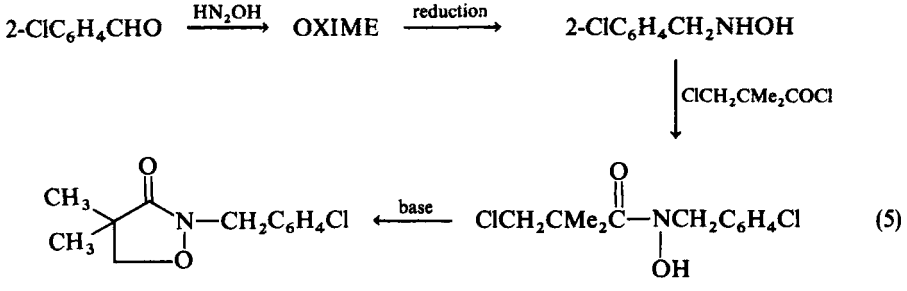
This method is quite attractive because of the commercial availability of acid chlorides and the ease of acid chloride formation through reagents such as thionyl chloride, ethyl chloroformate and oxalyl chloride. In many cases the acid chloride need not be isolated before reaction with a hydroxylamine. The high reactivity of the acid chloride, however, favors side products if appreciable levels of contaminating nucleophiles are present. This route is widely used and only a few examples are given here. Reaction of cinnamoyl chloride with *N*-methylhydroxylamine leads to a hydroxamic acid which undergoes cyclization to form the corresponding isoxazolidinone in a 'one-pot' procedure (equation 4)[8]. Choudhary and Tandon[9] used the same approach to synthesize a series of aryl and long-chain alkyl hydroxamic acids via the reaction of the acid chloride and *N*-(*p*-chloro)-phenylhydroxylamine.



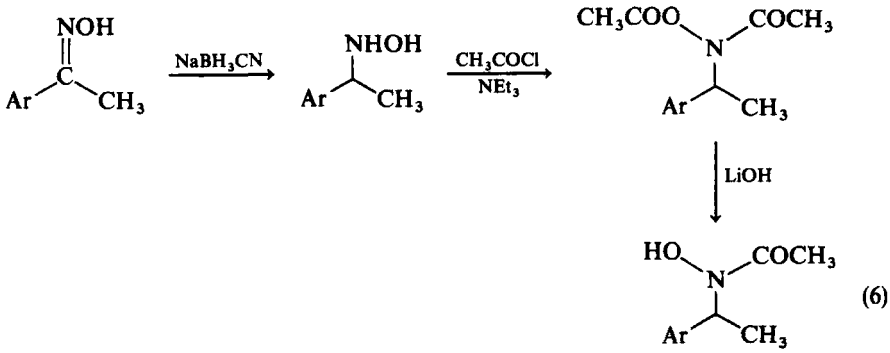
Isoxazolidinone

(4)

Chang[10] used a similar approach in synthesizing some herbicidal hydroxamic acids and the corresponding isoxazolidine. The substituted hydroxylamine was produced by reaction of hydroxylamine with an aldehyde to form an oxime which was subsequently reduced to form a hydroxylamine. This was reacted to form the hydroxamic acid which, upon treatment with base, cyclized to form the isoxazolidine (equation 5). A similar approach to forming the hydroxylamine was used in the synthesis of some orally active inhibitors of leukotriene synthesis[11]. In this work, oximes were reduced to the hydroxylamine which was reacted with acetyl chloride to form the *N*,*O*-dihydroxamic acid, which in turn was converted to the *N*-acetyl derivative (equation 6). In a similar vein, N-substituted hydroxylamines were prepared by reduction of the corresponding nitro compound with zinc dust and ammonium chloride[12]. Reaction of the N-substituted hydroxylamine with aryl and alkyl acid chlorides at low temperatures produced N-substituted hydroxamic acids.



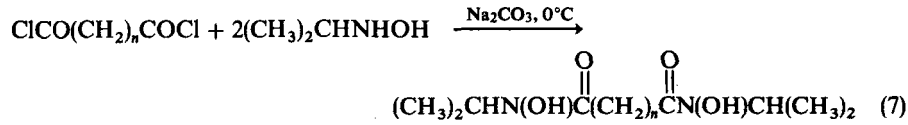
(5)



(6)

Al-Jallo and coworkers prepared a series of cyclohydroxamic acids and N-substituted hydroxamic acids through the acid chloride route, but purified some of the resulting hydroxamic acids by forming and extracting the copper salt[13].

Bifunctional bis-*N*-isopropylhydroxamic acids were prepared by the reaction of isopropylhydroxylamine and compounds with two acyl chloride moieties of the general structure shown in equation 7, where $n = 4$, 6, 8 or 10[14].

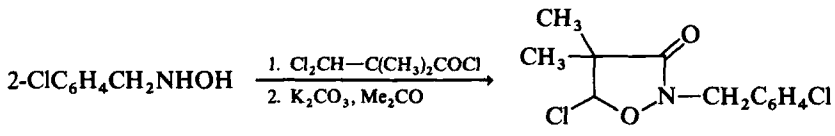


(7)

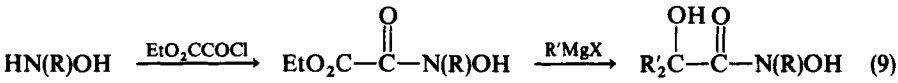
A commonly used approach is to form the acid chloride from the carboxylic acid by the action of thionyl chloride. Usually the resulting acid chloride can be purified by distillation. Several hydroxamic acids of potential use in analytical chemistry have been prepared in this fashion[15–17]. A hydroxamic acid was produced in the same manner from 8-phenyloctanoic acid that had *in vivo* anti-inflammatory activity comparable to indomethacin[18]. This activity is attributed to its action as an inhibitor of 5-lipoxygenase.

Seki and coworkers[19] utilized a similar reaction in the formation of a highly substituted hydroxamic acid which, when treated with base, cyclizes to the corresponding isoxazolidinone (equation 8).

Ethyl oxalyl chloride reacts with hydroxylamines to form a monohydroxamic acid (the ester group does not react) which, when treated with a Grignard reagent, yields *N*-alkyl (aralkyl) glycolohydroxamic acids (equation 9)[20]. In this reaction the intermediate hydroxamic acid is not isolated.

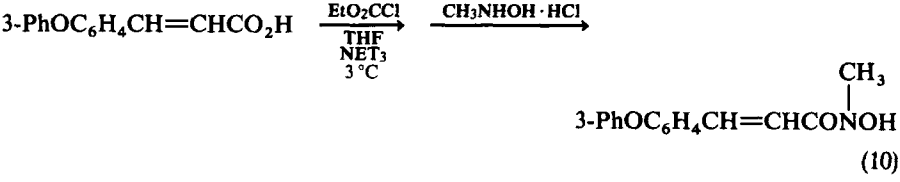


(8)

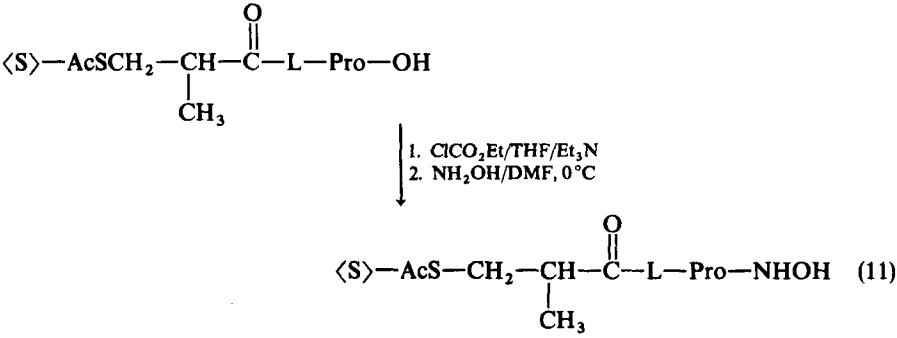


(9)

Activation of the carboxylic acid group for nucleophilic attack by hydroxylamines is a convenient synthesis route, since the activated form is not isolated prior to the addition of the hydroxylamine. The acid is reacted with ethyl chloroformate in the presence of a tertiary amine and subsequently reacted with the hydroxylamine. Kneen and coworkers[21] used this approach to synthesize 3-phenoxy-*N*-methylcinnamohydroxamic acid which was evaluated as an inhibitor of cyclooxygenase and lipoxygenase (equation 10). Hydroxamic acid derivatives of acyl thio amino acids have been produced in the same way[22] (equation 11).

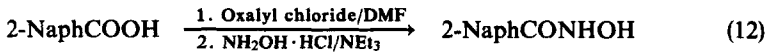


(10)



(11)

Carboxylic acids react with oxalyl chloride in DMF to form an acid chloride, which converts to the hydroxamic acid upon the addition of a hydroxylamine. Summers and colleagues[23] synthesized a series of aryl hydroxamic acids by this method. 2-Naphthalenecarbohydroxamic acid was produced in this manner (equation 12) and was evaluated



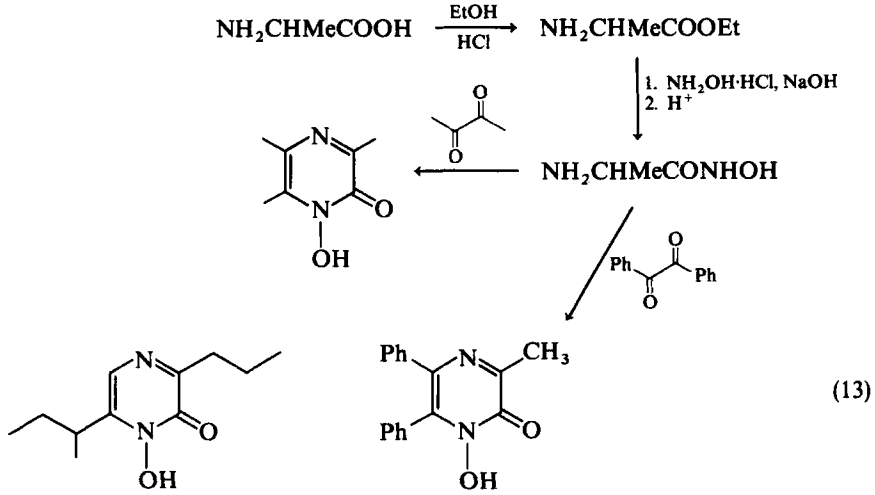
(12)

with similar compounds as inhibitors of 5-lipoxygenase. Hashimoto and coworkers used this approach to synthesize hydroxamic acids from carboxylic acids containing a long

hydrocarbon chain such as 7-(4-fluorophenyl)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-heptanoic acid[24]. These compounds were evaluated as inhibitors of cell-proliferation.

C. Formation from Esters and Amides

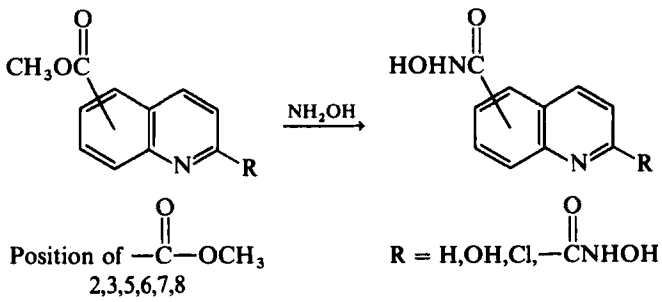
Hydroxamic acid formation from esters, amides, acid anhydrides and imides by reaction with hydroxylamine base is well established and forms the basis for many analytical applications. Consequently, only a few synthetic applications will be presented here. An attraction of this method is the commercial availability of many esters as well as the ease of forming simple methyl or ethyl esters by acid-catalyzed solvolysis in methanol and ethanol, respectively. Synthesis of cyclic hydroxamic acids derived from glycine begins with this reaction followed by reaction with hydroxylamine to form the glycine hydroxamic acid (equation 13)[25]. Reaction of this hydroxamic acid with diacetyl forms the cyclic hydroxamic acid, 5,6-dimethyl-1-hydroxy-2-oxo-1,2-dihydropyrazine, which is structurally related to the natural occurring hydroxamic acid, aspergillic acid.



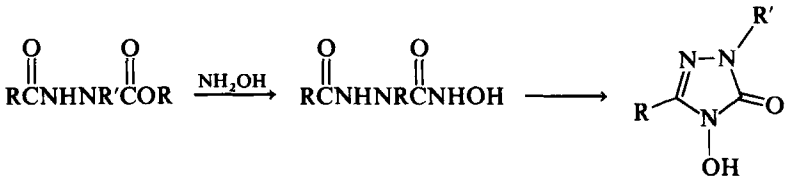
(13)

Aspergillic acid

A series of quinolinecarbohydroxamic acids was synthesized from the corresponding ester and hydroxylamine[26]. In this study the hydroxamic acids were isolated both as the free acids and as the hydrochloride salts on the quinoline nitrogen (equation 14).



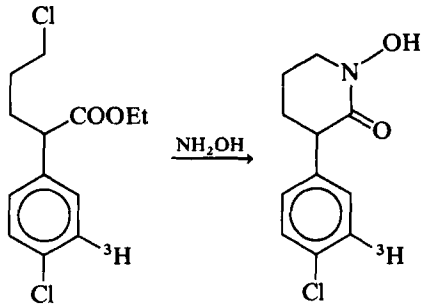
(14)



(15)

Reaction of an acyl derivative of an acid hydrazide with hydroxylamine gave a hydroxamic acid which undergoes an intramolecular cyclization[27] (equation 15). Acid hydrazides, though carboxylic acid derivatives, do not react under the same conditions as employed for the reaction of esters. Much more severe conditions or nickel-ion catalysis are required to get an appreciable reaction.

In a study designed to label an anti-inflammatory hydroxamic acid in a metabolically stable position, reaction of ethyl 5-chloro-[2-(3-tritio-4-chlorophenyl)] pentanoate with hydroxylamine led to the desired cyclic hydroxamic acid[28] (equation 16). Substituted acetohydroxamic acids containing sulfur have been synthesized via the same route[29].



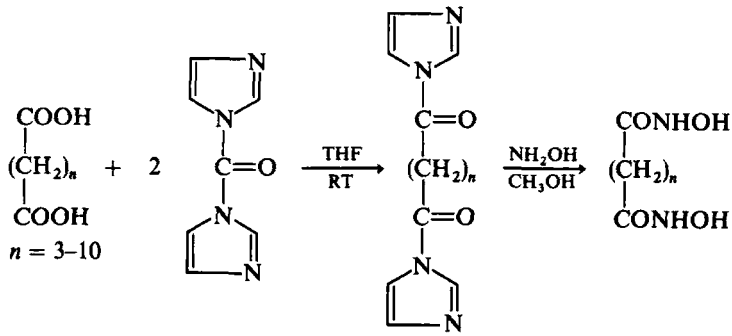
(16)

For example, a mercaptobenzyl compound was treated with methyl chloroacetate to form the methyl ester, which in turn was converted to the hydroxamic acid by the action of hydroxylamine (equation 17). Hydroxamic acids with anti-inflammatory/analgesic properties[30] and with urease inhibiting activities[31] have been synthesized using this chemistry.

$$4\text{-}ClC_6H_4CH_2SH + ClCH_2COOMe \xrightarrow[K_2CO_3, KI]{Me_2CO} 4\text{-}ClC_6H_4CH_2SCH_2CO_2Me \xrightarrow[MeOH,\ MeONa]{NH_2OH\cdot HCl} 4\text{-}ClC_6H_4CH_2SCH_2CONHOH \xrightarrow{H_2O_2} 4\text{-}ClC_6H_4CH_2SOCH_2CONHOH \quad (17)$$

D. Formation via Carbodiimide Reagents

Coupling reagents such as dicyclohexylcarbodiimide (DCC) have been shown to be useful in coupling carboxylic acids and hydroxylamine to form hydroxamic acids from substituted benzoic acids[32]. Dihydroxamic acids are readily formed from dicarboxylic acids by the action of *N,N'*-carbodiimidazole to form an activated intermediate which

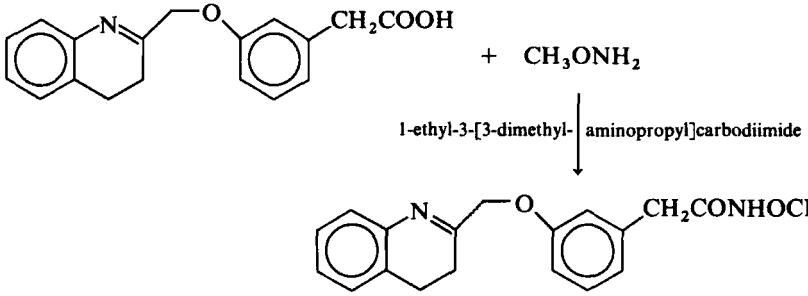


(18)

is subsequently reacted with hydroxylamine, *N*-methylhydroxylamine or *O*-methylhydroxylamine[33] (equation 18). In this reaction the intermediate can be isolated.

Thienylglycolic acids react with N-substituted hydroxylamines in the presence of DCC at room temperature to form the appropriate hydroxamic acids[34].

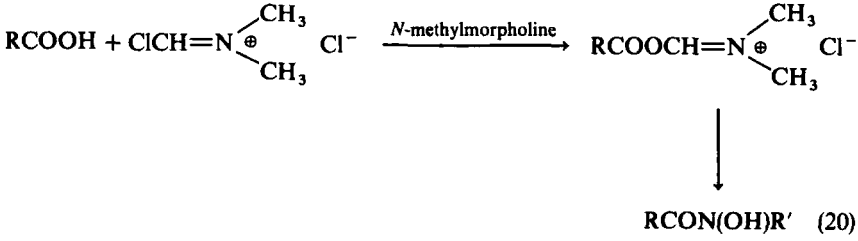
Musser and coworkers used 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide to form hydroxamic acids of *N*-[(arylmethoxy)phenyl] carboxylic acids and *O*-methylhydroxylamine[35]. These hydroxamic acids (14 were synthesized and studied) were evaluated as leukotrien D_4 antagonists. The hydroxamic acid shown in equation 19 was the most effective inhibitor in the series. In this study, the authors varied the hydroxylamine (*O*-methyl-, *O*-benzyl- and *N,O*-dimethyl-) and also used DCC as a coupling reagent.



(19)

E. Miscellaneous Syntheses from Carboxylic Acids and Derivatives

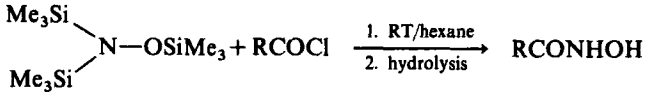
N,N-Dimethylchloro-methaneiminium chloride reacts with carboxylic acids in the presence of *N*-methylmorpholine to form an activated intermediate that, when treated with a hydroxylamine, forms the corresponding hydroxamic acid[36] (equation 20). This method is useful for forming hydroxamic acids from amino acids as long as the



(20)

N-terminal amine is protected. In the reaction scheme in equation 20, R can be phenyl, benzyl or cinnamyl and R′ is ethyl or phenethyl.

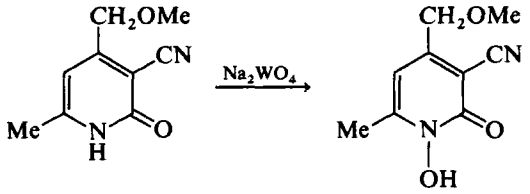
N,N,O-Tris(trimethylsilyl)hydroxylamine reacts with carboxylic acid chlorides at room temperature in dry hexane to form a silylated hydroxamic acid which hydrolyzes to the desired hydroxamic acid[37] (equation 21). This method is presented as a simple and clean method for the synthesis of aliphatic hydroxamic acids.



(21)

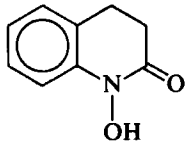
F. Formation by Oxidation or Reduction

Trimethylsilylamides are oxidized by a molybdenum pentaoxide complex to form hydroxamic acids, which are recovered from the reaction mixture as a molybdenum/bis-hydroxamate[38]. To recover the hydroxamic acid, the molybdenum/hydroxamate complex is dissolved in tetrasodium EDTA. This mixture is adjusted to pH 7.5 and extracted with dichloromethane. The free hydroxamic acid is recovered on evaporation of the solvent.

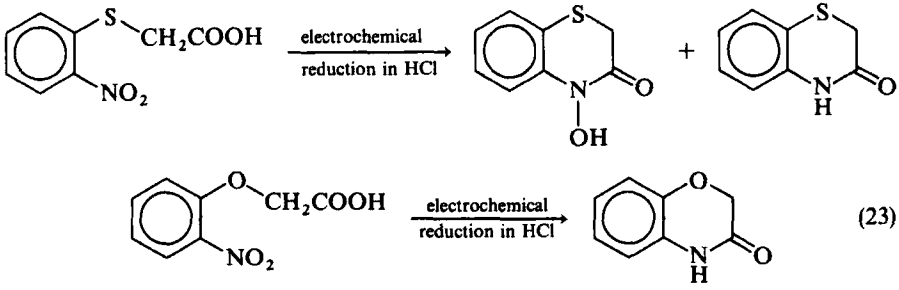


(22)

Oxidation of pyridones with sodium tungstate leads directly to the corresponding cyclic hydroxamic acid[39] (equation 22). Sodium tungstate catalyzed oxidation of 1,2,3,4-tetrahydroquinolines with 30% aqueous hydrogen peroxide in methanol gives the cyclic hydroxamic acid, 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one[40] shown below:



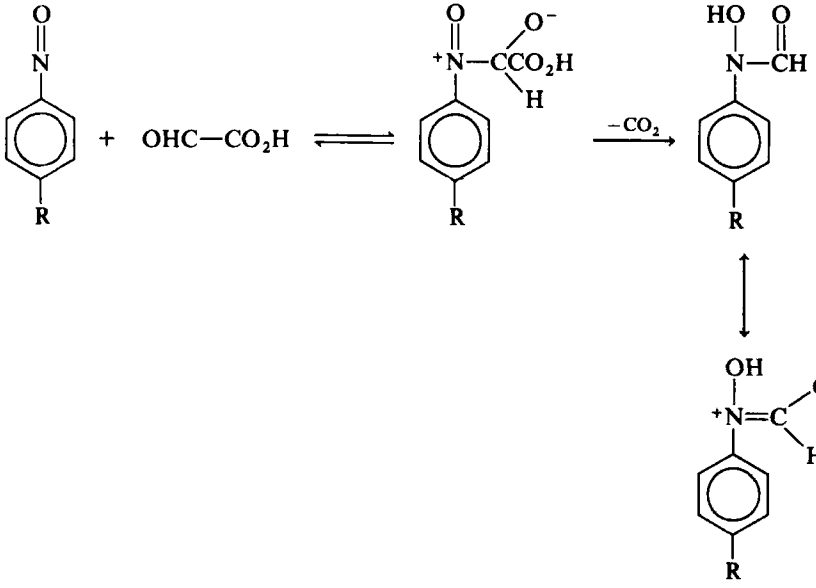
Electrochemical reduction of 2-nitrothiophenoxyacetic acid in hydrochloric acid yields a cyclic hydroxamic acid and a cyclic amide. Reduction of 2-nitrophenoxyacetic acid yields only the amide under these conditions[41] (equation 23).



(23)

G. Synthesis from α-Ketocarboxylic Acids and Nitrosoaromatics

Corbett and Corbett[42] demonstrated that nitrosoaromatics react with glycolic acid to form *N*-hydroxyformanilides (equation 24). Under the conditions employed, pyruvic acid did not react nor did other aldehydes and carboxylic acids. The mechanism proposed for this reaction is consistent with that proposed for pyruvate decarboxylase catalyzed conversion of nitrosoaromatics to *N*-acetyl hydroxamic acids. In a later paper, these authors described the generality of the nitrosoglyoxylate reaction in converting *p*-nitro-nitrosobenzene to the hydroxamic acid[43]. Hassner and colleagues demonstrated that *o*-nitrophenylpyruvic acid reacts with *p*-nitrosodimethylaniline to form the corresponding hydroxamic acid, which undergoes concentration-dependent self-condensation and disproportionation leading to amides and carboxylic acids[44]. The existence of the transient hydroxamic acid was detected by differences in the infrared spectrum during the reaction and the positive deep-red ferric chloride test.

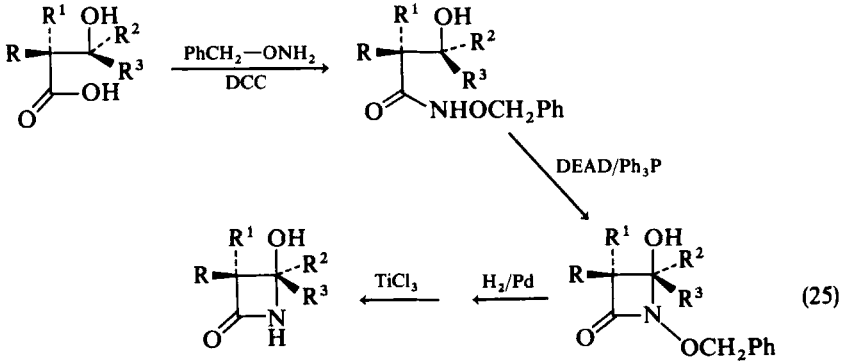


(24)

Sakamoto and coworkers have recently demonstrated a general method for the synthesis of *N*-arylhydroxamic acids from nitrosoaromatics and α-oxo acids including pyruvic and glyoxylic acids[45]. The formation of hydroxamic acids was found to be favored by low pH. Consequently, reactions were carried out in aqueous acetic acid. Finally, the synthesis of *N*-phenylhydroxamic acid by the acid-catalyzed reaction of formaldehyde and nitrosobenzene has been reported[46,47].

H. Hydroxamic Acid Mediated Synthesis of β-Lactams

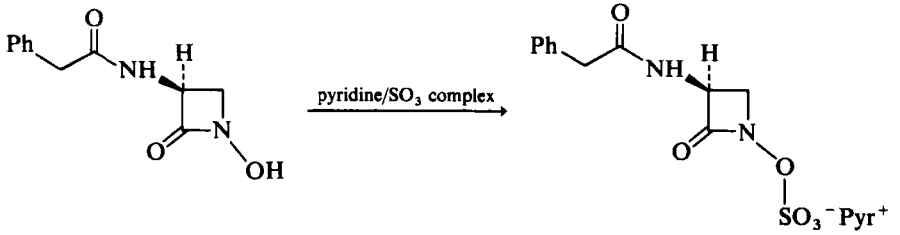
The β-lactam moiety is an important structural feature of penicillin and cephalosporin antibiotics. Consequently there is considerable interest in synthetic methods for β-lactams. In an early report, Miller and coworkers formed a hydroxamic acid through the DCC coupled reaction of *O*-benzylhydroxylamine and a substituted carboxylic acid[48]. The hydroxamic acid is treated with diethylazodicarboxylate/triphenyl phosphine (DEAD/Ph_3P) to induce an N—C4 bond closure to form the *N*-alkoxy-2-azetinone.



(25)

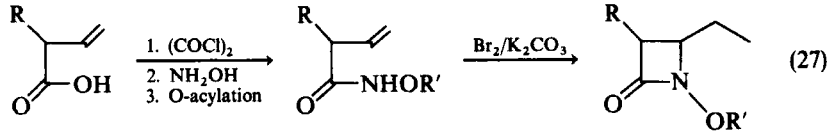
The O-substituted hydroxamic acid is reduced with hydrogen (Pd catalyst) and the N—O bond is then cleaved with titanium(III) chloride (equation 25).

Gordon and colleagues employed similar chemistry to form a hydroxamic acid from carbobenzyloxy-D-cycloserine[49]. Treatment of the hydroxamic acid with a pyridine/SO_3 complex produced an O-sulfated β-lactam hydroxamate (equation 26). In a later study, Miller[50] treated 2-benzylvinylacetic acid with oxalyl chloride to form an acid chloride,



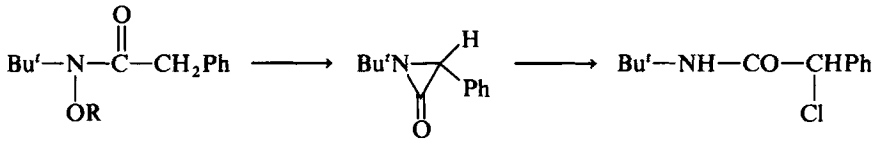
(26)

which yielded a hydroxamic acid upon treatment with hydroxylamine. After protecting the hydroxylamine group by adding an *O*-carbobenzyloxy group, oxidative cyclization was accomplished by the action of Br_2/K_2CO_3 in aqueous acetonitrile to produce a cyclic hydroxamic acid, which could be further treated to form the β-lactam. A general reaction scheme for this is shown in equation 27.



(27)

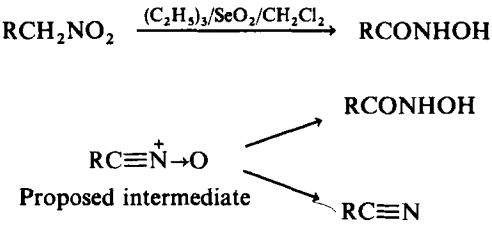
Bladon and Kirby[51] have recently demonstrated a pathway involving cyclization of hydroxamic acids to form α-lactams. In this work, *N*,O-disubstituted derivatives of chloroaceto- and phenylacetohydroxamic acids cyclized with base to give aziridinones with cleavage of the N—O bond (equation 28). These authors used this chemistry to introduce an α-lactam into *N*-*t*-butoxycarbonylnorthebaine.



(28)

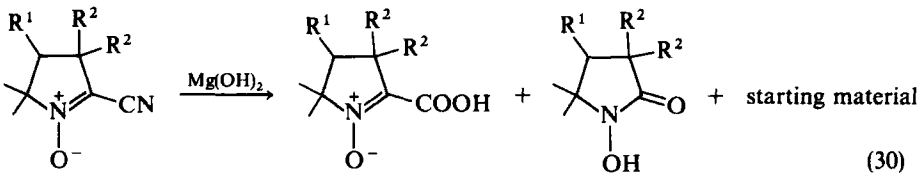
I. Miscellaneous Syntheses

Primary nitroalkanes have been converted directly to hydroxamic acids by the action of selenium dioxide and triethylamine in dichloromethane[52]. If the nitroalkane/selenium dioxide/triethylamine ratio is maintained at 1:1:2, the product is the hydroxamic acid. If the ratio is held at 1:2:2, a mixture of the hydroxamic acid and the corresponding nitrile is produced. If triethylamine is left out the reaction does not proceed. These reaction products are explained by a proposed intermediate (equation 29).



(29)

Cyclic hydroxamic acids can be synthesized by the action of magnesium hydroxide on cyanonitrones[53]. In this reaction a mixture of the cyanonitrone/hydroxamic acid/carboxylic acid in the ratio of 6:5:2 was produced (equation 30). Similar compounds were produced by the reaction of cyanonitrones with sodium ethoxide or hydrochloric acid.

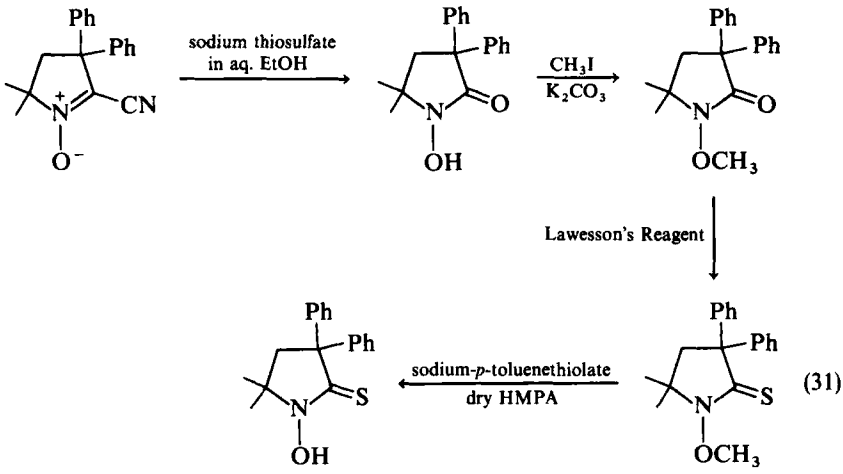


(30)

In an extension of this work, cyanonitrones were treated with potassium ethyl xanthate to form the corresponding imino ester[54]. When the cyanonitrone is treated with sodium thiosulfate in aqueous ethanol, a mixture of the imino ester and the cyclic hydroxamic acid is formed. Treatment of the hydroxamic acids (1-hydroxypyrrolidin-2-ones) with excess methyl iodide and anhydrous potassium carbonate forms the *O*-methyl hydroxamic acid. When these compounds are reacted with Lawesson's Reagent (*p*-methoxyphenylthionophosphine sulfide), the corresponding alkylated thiohydroxamic acid is formed (equation 31). After dealkylation, a 1-hydroxypyrrolidin-2-thione is produced.

Cyclic hydroxamic acids (3-isoxazolones) have been synthesized directly from α,β-unsaturated linear hydroxamic acids using palladium-induced intramolecular cyclization[55]. Cyclic hydroxamic acids have also been prepared by the reaction of aldehydes with 2-aminobenzohydroxamic acid[56]. In this reaction an intermediate oxime formation is postulated (equation 32).

Prabhakar and coworkers reported a convenient method for the synthesis of *C*-



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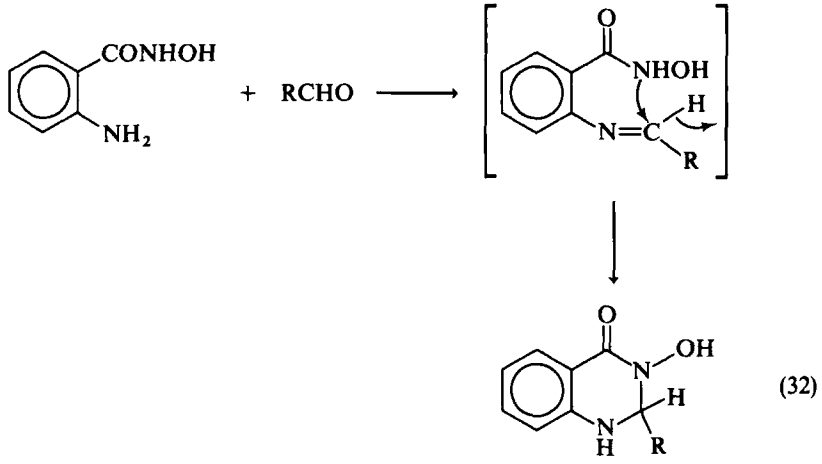
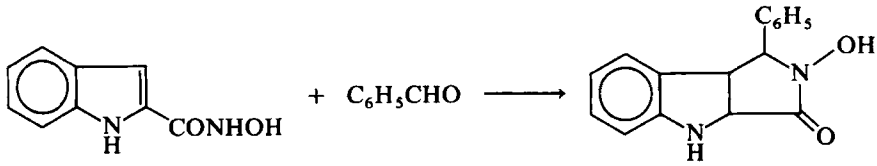


(32)

arylthiohydroxamic acids (*N*-hydroxythiobenzamides)[57]. Treatment of an N-substituted benzohydroxamic acid with an acid chloride forms the *O*-acyl derivative of the hydroxamic acid which, when treated with Lawesson's Reagent, yields the corresponding *O*-acyl thiohydroxamic acid. Hydrolysis of the latter produces the thiohydroxamic acid.

N-Substituted hydroxamic acids can be formed by the reaction of hydroxamic acids and aldehydes. Indomethacin hydroxamic acid reacts with formaldehyde in the presence of morpholine to form *N*-morpholinomethyl indomethacin hydroxamic acid[58]. In a similar reaction, indole-2-hydroxamic acid reacts with benzaldehyde to form a cyclic hydroxamic acid[59] (equation 33).

Aminoacetohydroxamic acids have been shown to react with diketones to form a hydroxypyrazone[60] (equation 34). Some of the compounds showed antibacterial activity and some formed copper chelates.



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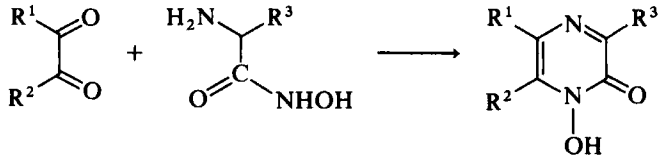
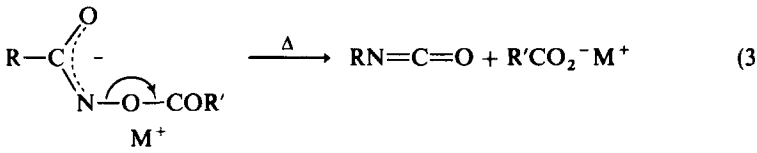


(34)

III. REACTIONS

A. The Lossen Rearrangement (Amide Modification)

In the traditional Lossen rearrangement, acylated hydroxamic acids react when heated to form an isocyanate and the carboxylate (equation 35). Using the 'amide modification' of the Lossen rearrangement, the hydroxamic acid need not be acylated. In this reaction the hydroxamic acid is heated in the presence of formamide to yield an isocyanate, which can undergo further reactions. Eckstein and coworkers have studied this reaction using both mono and dihydroxamic acids. When substituted 2-aminobenzohydroxamic acids react, a cyclic amide (urea) is formed[61] (equation 36). When dihydroxamic acids (or monohydroxamic acids with an adjacent carboxyl group) are subjected to the same conditions, a cyclic hydroxamic acid (Leuchs anhydride-type intermediate) is formed[62]. Upon hydrolysis, this compound produces the 2-aminonicotinic acid (equation 37). When nicotinic hydroxamic acid was subjected to the same conditions it reacted only sluggishly.



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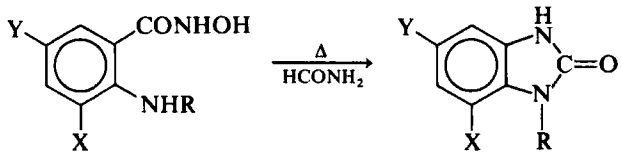
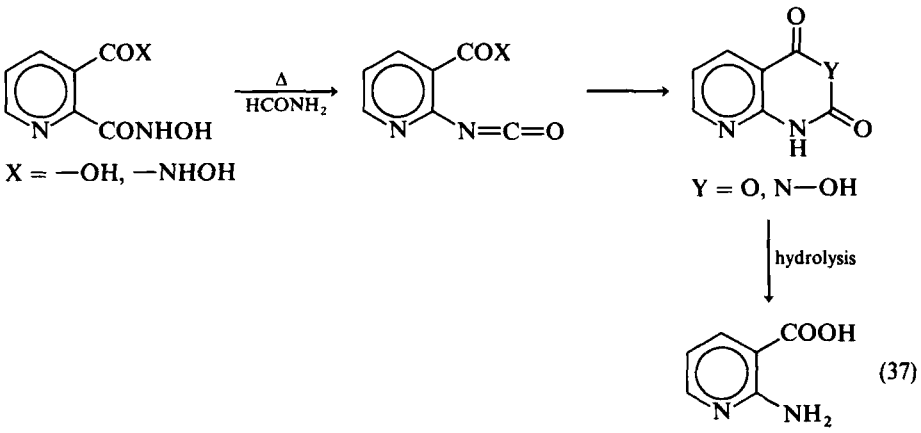
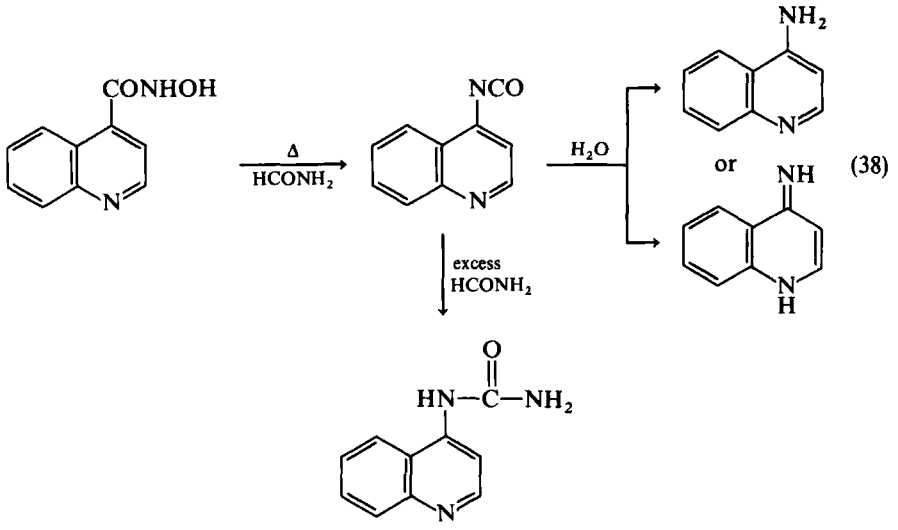


(36)

X,Y,R = H,CH_3, C_2H_5, Br, Cl

These workers also studied the rearrangement of 4-quinolinecarbohydroxamic under the same conditions[63]. When the intermediate isocyanate is treated with water, 4-aminoquinoline is formed. When the intermediate is treated with excess formamide, *N*-(4-quinolyl) urea is formed (equation 38).



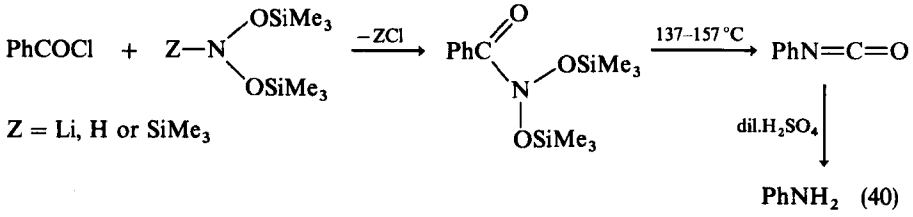


The Lossen rearrangement of hydroxamic acids has been postulated as a metabolic mechanism by which hydroxamic acids can have an effect on DNA[64] as outlined in equation 39. This mechanism could account for the mutagenic activity of some hydroxamic acids.

$$\text{ArCONHOH} \xrightarrow[\text{acylation}]{\text{enzymatic}} \text{ArCONHOAc} \xrightarrow{\text{Lossen rearrangement}}$$

$$\text{ArN=C=O} \xrightarrow{\text{DNA}} \text{Modified DNA} \qquad (39)$$

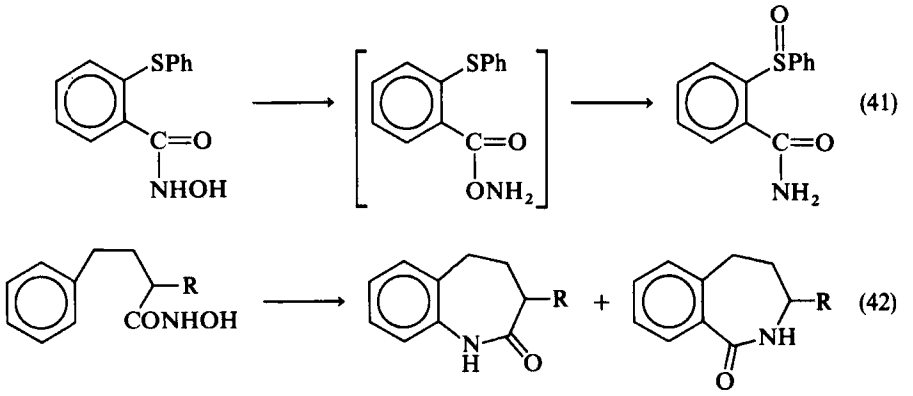
In a similar reaction, acid chlorides are reacted with hexamethyldisilazane hydroxylamines to form silylated hydroxamic acids which, upon heating, form the isocyanate[65]. Treatment of this with aqueous sulfuric acid leads to the amine (equation 40). Orlov and Mironov reported that when acetohydroxamic acid was treated with



phenylsilylchloride, methyl isocyanate was formed[66]. Phenyl isocyanate and isobutyl isocyanate were also synthesized from the corresponding hydroxamic acids.

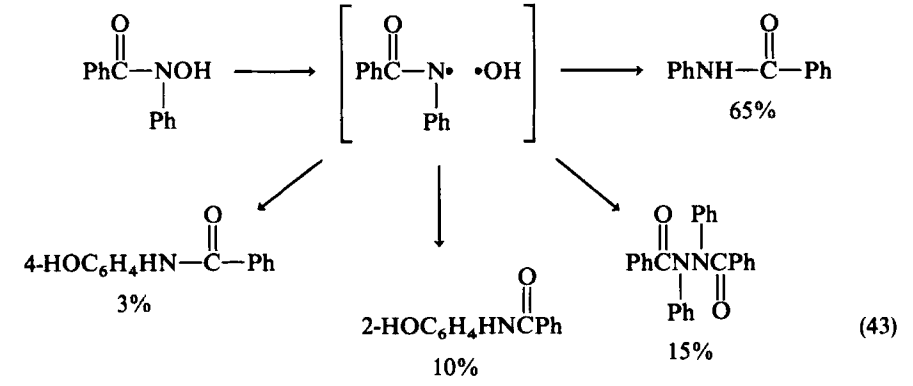
B. Reactions with Phosphoric Acids

The reaction of 2-arylthiobenzohydroxamic acids in polyphosphoric acid gives the corresponding 2-(arylsulfinyl) benzamide[67] (equation 41). This reaction was investigated with several hydroxamic acids and was found to be general. Cyclization reactions have also been observed in polyphosphoric acid leading to the formation of isomeric lactams[68] (equation 42).



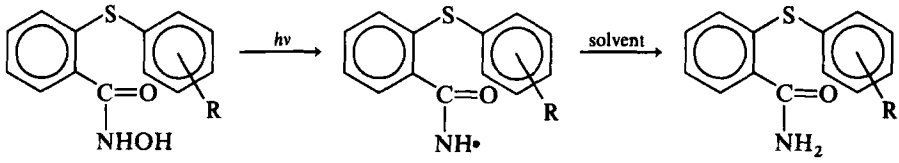
C. Photochemical Reactions

Lipczynska-Kochany and coworkers studied the photochemical reactions of *N*-phenylbenzenecarbohydroxamic acid in cyclohexane and methanol[69]. Benzanilide was



the predominant product (65%) but several other products were also present. All products can be rationalized by the formation of a radical intermediate and then various recombinations (equation 43).

Hosangadi and colleagues found that 2-arylthiobenzohydroxamic acids undergo a photochemical reduction to the amide in benzene and methanol[70]. They had expected either lactam formation via ring closure or 2-arylsulfinylbenzamide formation via oxygen transfer as they had previously observed. The authors postulated the formation of a free radical which interacts with the solvent to form the amide (equation 44).



(44)

D. Acylation Reactions

Hydroxamic acids react with acyl chlorides to form the O-acylated form of the hydroxamic acid. Sharma and coworkers synthesized *N*-(*p*-bromobenzyl)-*O*-benzoylhydroxylamine by the reaction of *p*-bromobenzohydroxamic acid and benzoyl chloride[71]. In the same study these authors reacted *N*-benzoyl-*O*-cyclohexylhydroxylamine with α-naphthyl isocyanate to form *N*-benzoyl-*N*-(α-naphthylcarbamoyl)-*O*-cyclohexylhydroxylamine, thus also demonstrating a method for forming the N-substituted derivative of an O-substituted hydroxylamine (equation 45).

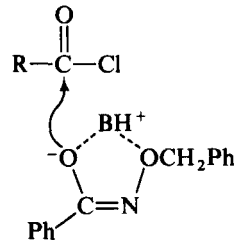
$$4\text{-BrC}_6\text{H}_4\text{CONHOH} + \text{PhCOCl} \longrightarrow 4\text{-BrC}_6\text{H}_4\text{CO—NH—OOCPh} \quad (45)$$

In later work, these authors studied the reaction of *O*-benzylbenzohydroxamic acids with a variety of acylating agents (acid chlorides and sulfonyl chlorides)[72] in the presence of either trimethylamine or pyridine. In every case the (*Z*)-isomer was formed exclusively. To account for this observation a mechanism involving an ion-pair intermediate was postulated (equation 46).

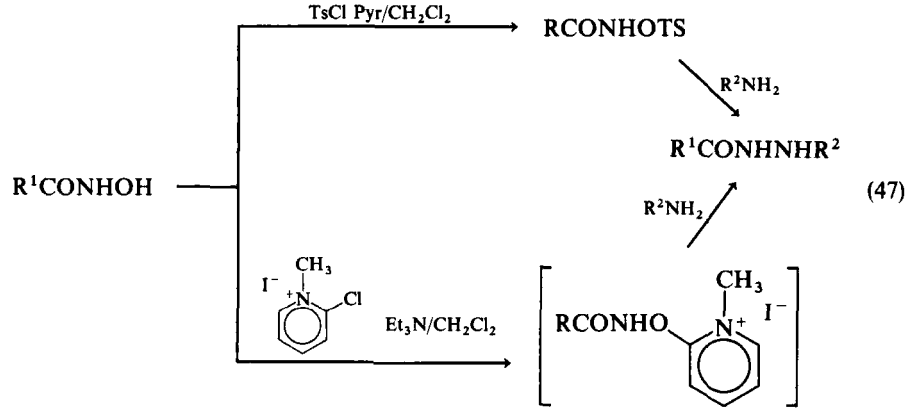
O-Acyl hydroxamic acids have been formed from a carboxylic acid by using a DCC coupling reaction. Fukuoka[73] reacted *p*-maleimidobenzoic acid with *p*-chlorobenzohydroxamic acid in the presence of DCC in an acetonitrile/DMF mixture to form the *O*-acyl hydroxamic acid *O*-(*p*-maleimidobenzoyl)-*p*-chlorobenzohydroxamic acid.

Okawara and colleagues reported the synthesis of 1-acyl-2-alkylhydrazines by the reaction of alkylhydroxamic acids with *p*-toluenesulfonyl chloride or 2-chloro-1-methylpyridinium iodine and an amine[74] (equation 47). The proposed mechanism was based on the reported isolation of the acylated methyl pyridinium compound. These results imply that the traditional Lossen rearrangement is suppressed. In a subsequent study, Hartmann[75] was unable to confirm these results. In his study, he observed that the reaction of benzohydroxamic acid with methylpyridinium iodide and alkyl amines gave good yields of the corresponding benzylureas. He was unable to detect any 1-acyl-2-alkylhydrazines under the same conditions. His results argue for the formation of the isocyanate by the Lossen rearrangement before reaction with the amine.

Acylation of amines and alcohols has been reported to occur during the electrolysis of hydroxamic acids in acetonitrile[76]. The proposed reaction mechanism involves the formation of a free radical which loses a C-nitroso moiety to form an acyl cation, which in turn reacts with a nucleophile (amine or alcohol) to yield an amide or an ester (equation 48).



(46)



(47)

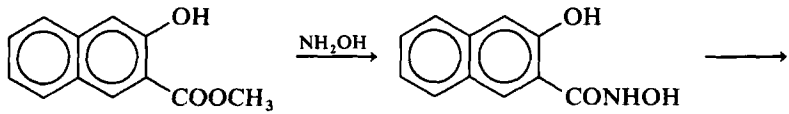
$$R^1CON(R^2)OH + B \rightleftharpoons \left[R^1CO{-}\underset{\displaystyle R^2}{N}{-}O\cdots H\cdots B^+\right] \xrightarrow{-e}$$

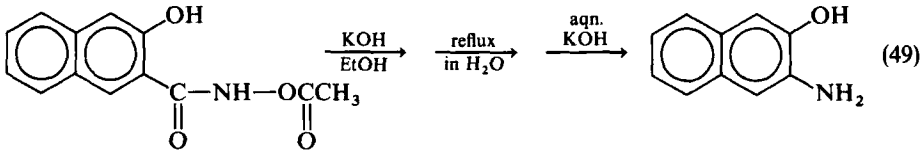
$$[R^1CONR^2O\cdot] + BH^+ \xrightarrow{-e} \left[R^1{-}\overset{\displaystyle O}{\overset{\|}{C}}{}^+\right] + R^2{-}N{=}O \quad (48)$$

Acylation of methyl-2-hydroxy-3-naphthoylhydroxamic acid with acetic anhydride leads to the *O*-acetyl form of the hydroxamic acid which undergoes the Lossen rearrangement to form the 2-naphtho-[2,3-*d*]-oxazolone[77]. This compound yields 3-amino-2-naphthol when refluxed with aqueous potassium hydroxide (equation 49).

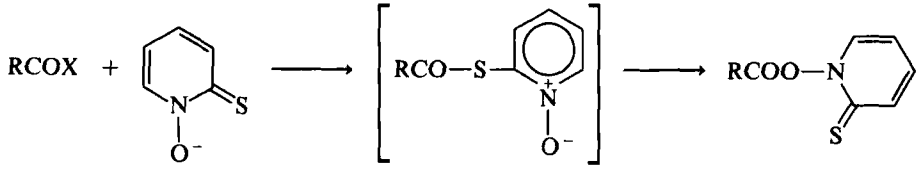
E. Reactions of *O*-Acylthiohydroxamates

O-Acylthiohydroxamates provide a convenient source of carbon radicals ideally suited for synthesis. The versatility of their use is only limited by the availability of carboxylic acid precursors. Synthetic applications of these compounds have been extensively reviewed by Crich[78]. A few of the applications are presented here as examples. One of the more useful reagents, 2-mercaptopyridine-*N*-oxide (*N*-hydroxypyridine-2-thione), reacts with suitably activated carboxylic acids to form the *O*-acyl thiohydroxamate





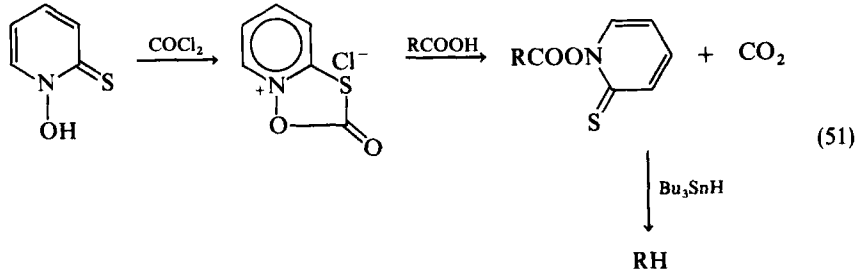
(49)



(50)

(equation 50). This reaction occurs best with the acid chloride which can easily be achieved with oxalyl chloride.

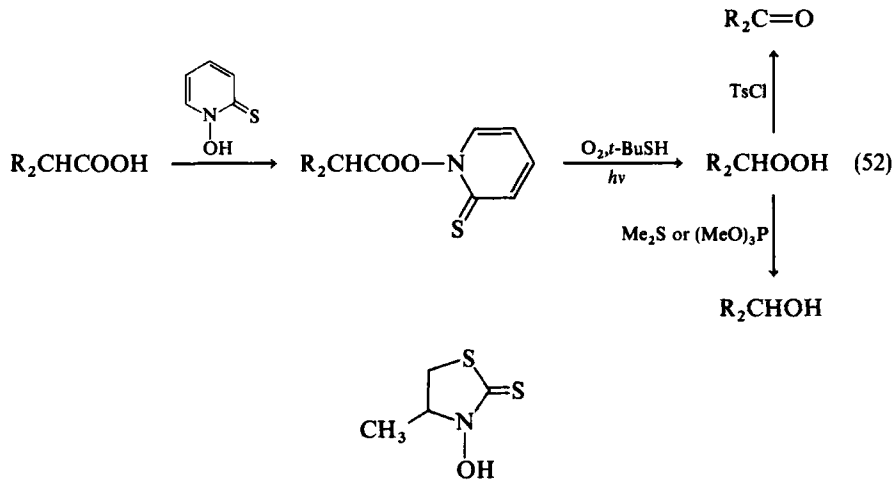
Treatment of 2-mercaptopyridine-*N*-oxide with phosgene forms a cyclic carbonate salt which reacts with carboxylic acids in refluxing benzene to form the *O*-acylthiohydroxamate. Reaction of this ester, *in situ*, with tri-n-butyl tin forms the alkyl compound derived from the carboxylic acid (equation 51).



(51)

Alkyl carboxylic acids react to form the *O*-acylthiohydroxamate, which is transformed to the alkyl peroxide by the action of triplet oxygen or photolysis. Addition of *t*-butyl mercaptan helps to eliminate side reactions to give a good yield of the alkyl hydroperoxide. Alcohols are formed by the *in situ* treatment of the alkyl hydroperoxide with dimethyl sulfide or trimethyl phosphite. Treatment with *p*-toluenesulfonyl chloride in pyridine leads to the corresponding carbonyl compound (equation 52).

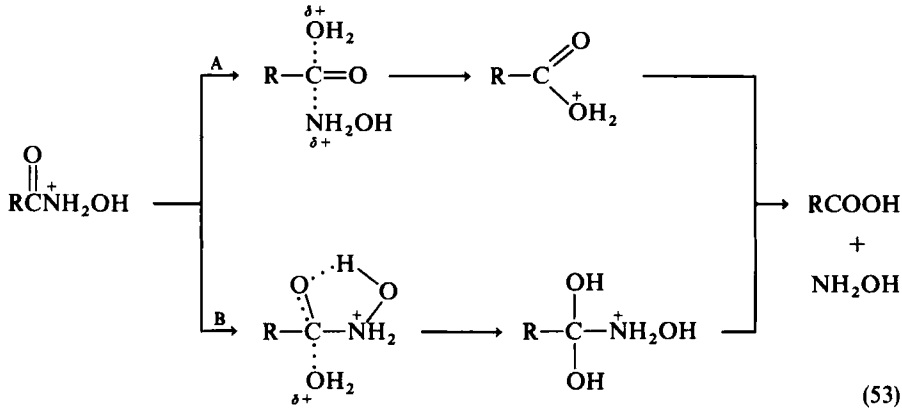
Another useful reagent of this type is 4-methyl-3-hydroxythiazoline-2-thione, which reacts with activated carboxylic acids to form an *O*-acylthiohydroxamate.



4-methyl-3-hydroxythiazoline-2-thione

F. Hydrolysis Reactions

The hydrolysis of hydroxamic acids under acidic conditions has been studied extensively. DiFuria and coworkers[79] studied the acid-catalyzed hydrolysis of hydroxamic acids using an oxygen-18 label in the carbonyl oxygen of the hydroxamic acid. Their results showed negligible exchange with the solvent. The authors postulated two possible mechanisms shown in equation 53. The first mechanism, pathway A, is an 'S_N2-like' displacement of hydroxylamine by water. This mechanism is unlikely in that it requires a large carbonium ion character with extended bond breaking in the transition state. Furthermore, hydroxylamine, being a strong base, would be a rather poor leaving group. The other pathway, B, requires a rate-determining attack of water on the carbonyl carbon giving rise to a highly energetic zwitterionic species. The internal hydrogen bonding between the hydroxylamine hydrogen and the carbonyl oxygen facilitates the formation of this heavily charged structure which easily leads to the N-protonated tetrahedral intermediate.

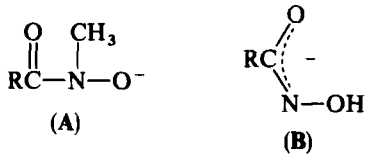


Micellar catalysis of the hydrolysis of hydroxamic acids has also been studied. Berndt and colleagues[80] studied the hydrolysis of octanohydroxamic acid and *N*-methyloctanohydroxamic acid in the presence and absence of sodium-1-dodecanesulfonate in dilute acid and in the presence of cetyltrimethylammonium bromide (CTAB) in dilute base. In this study, pseudo-zero-order kinetics were observed for the hydrolysis of octanohydroxamic acid in the presence of CTAB while the usual pseudo-first-order kinetics were observed in all other cases. This suggested that the alkaline hydrolysis of some hydroxamic acids conforms to the rate law given in equation 54,

$$-dS/dt = kS/(K + S) \tag{54}$$

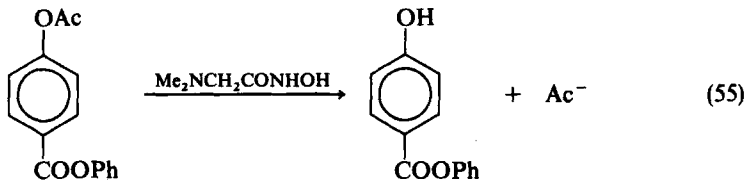
where S is the substrate concentration, k is the zero-order rate constant and K is the reciprocal of the association constant for the substrate with the micelle.

In subsequent studies, Berndt and coworkers[81] studied the hydrolysis of several hydroxamic acids under alkaline conditions in the presence of CTAB. While many displayed the usual pseudo-first-order behavior, some displayed pseudo-zero-order and pseudo-one-half-order. *N*-Methyl hydroxamic acids displayed pseudo-first-order behavior only. The observed differences in the order of the hydrolysis reaction can be rationalized by the ionic form of the hydroxamate anion. For the *N*-methylhydroxamates, only the localized anion can be formed (**A**), while for the other hydroxamates, a delocalized anion (**B**) can also be formed. The delocalized anion can be expected to form stronger associations with the micelles thus changing the order of the reaction.



(**A**) (**B**)

Hydroxamic acids have also been studied as catalysts for the hydrolysis of activated esters. Ueoka and Matsumoto[82] studied the catalytic effect of several hydroxamic acids on the hydrolysis of *p*-nitrophenyl esters in the presence of cationic surfactants above their critical micelle concentration. In this study, the surfactants with the bulky substituents gave the greatest enhancement of the catalytic effect of the hydroxamic acid. Other workers have extended these studies in an investigation of the catalytic effect of long-chain aliphatic hydroxamic acids[83]. Hydroxamic acids containing a dodecyl or a tetradecyl group as the hydrophobic portion showed excellent micellar catalytic effect for long-chain (C 8–12) aliphatic *p*-nitrophenyl esters. This work shows that the hydrophobic alkylhydroxamic acids can be used as micellar catalysts without the addition of other organic surfactants as in earlier studies. *N*-Methyl-2-dimethylaminoacetohydroxamic acid has been shown to be an effective catalyst for the selective cleavage of esters under neutral conditions[84]. When reacted with 4-acetoxy-phenylbenzoate, the acetate ester is cleaved selectively (equation 55).



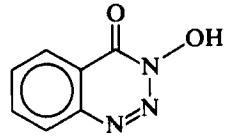
(55)

G. Miscellaneous Reactions

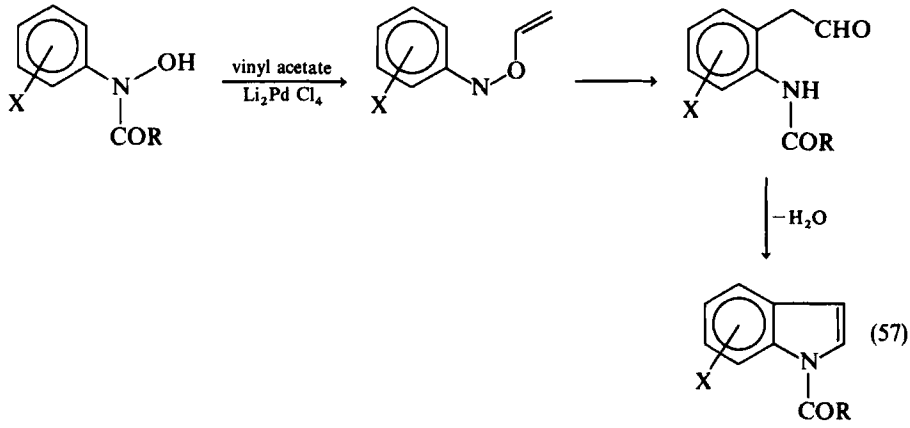
Several reactions of hydroxamic acids have been reported that do not conveniently fit into one category and hence are included in this section. 4-Formylaminobenzohydroxamic acid reacts with allyl bromide to form the *O*-allyl derivative of the hydroxamic acid[85]. Acyl derivatives of hydroxamic acids have also been used as a source of carbonyl radicals. Dihydrocinnamohydroxamic (*O*-acyl) acid, formed by the DCC coupling of dihydrocinnamic acid and *N*-hydroxybenzotriazin-4-one, reacts with tri-n-butyl tin hydride in the presence of azo-isobutyronitrile (AIBN) to form ethylbenzene[86] (equation 56). These reactions form products similar to those from radical reactions of acyl derivatives of thiohydroxamic acids, particularly using *N*-hydroxy-2-thiopyridone[87,88].

$$PhCH_2CH_2CO_2H + HONRR' \xrightarrow[THF]{DCC} PhCH_2CH_2CO_2NRR' \xrightarrow[AIBN]{BU_3SnH} PhCH_2CH_3 \qquad (56)$$

HONRR′ =



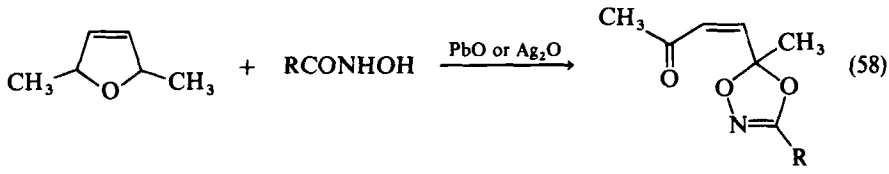
N-Phenylhydroxamic acids react with vinyl acetate in the presence of palladium salts to form an *N*-phenyl-*O*-vinylhydroxamic acid, which undergoes a hetero-Cope rearrangement and eventually cyclizes to an *N*-acylindole[89] (equation 57).



(57)

Hydroxamic acids react oxidatively with 2,5-dimethylfuran in the presence of lead oxide or silver oxide to form *cis*-1,4,2-dioxazolyl butenones[90]. The reaction is thought to proceed through a very unstable 1,4,2-dioazine intermediate (equation 58).

Refluxing hydroxamic acids for five hours in benzene with a two-fold excess of phosphorus tribromide gave good yields of the corresponding nitrile directly[91]. This reaction was applied to a number of aromatic hydroxamates. Hussain and Perkins studied the thermal rearrangement of *N*-*t*-butylbenzohydroxamic acids[92]. Prolonged



(58)

heating of benzene solutions of hydroxamic acids caused them to rearrange to the corresponding *O*-benzoylhydroxylamine.

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CHAPTER **16**

The chemistry of amidoximes

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I. INTRODUCTION

Amidoximes are compounds bearing both a hydroxyimino and an amino function at the same carbon atom, and thus closely associated with amides, amidines and hydroxamic acids. Although they are sometimes referred to as *oxamidines*, the name *amidoxime*, proposed by Tiemann, has been largely established in the form of a suffix, either to the respective trivalent radical (in early German literature), or to the hydrocarbon itself, as recommended by Rule 32 of IUPAC. French publications, however, treat them as oximes of the corresponding amides, a nomenclature used in *Chemical Abstracts* for polyderivatives, the monoderivatives being considered as hydroxamic acid amides.

Although the honor of definitely elucidating the structure of amidoximes should be attributed to Tiemann (1884)[1], their chemistry begins with the synthesis of formamidoxime by Lossen and Schifferdecker eleven years earlier[2]. A large number of contributions concerning substitution reactions appeared in the 1890s, but interest diminished gradually, except for structural studies, accomplished mainly by Ponzio after 1920. In recent years, however, amidoximes again became a promising field of research. Though the obvious cause for this lies in their biological activity, the many technological applications of amidoxime polymers and coordination compounds certainly contributed to the renewed interest in their chemistry. Furthermore, their importance as synthones never ceased, due to their versatility that allows them to undergo ready cyclization to 1,2,4-oxadiazoles and other heterocycles.

The following reviews on amidoximes cover various selected aspects: 'Amino–imino tautomerism in amidoximes' (in Dutch) by L. Brandt in *Meded. Vlaam. Chem. Ver.*, **29**, 56 (1967); 'Amidoximes as analytical reagents' (in Russian) by A. I. Busev, T. N. Zholondovskaya, L. S. Krysina and L. I. Korobkina in *Sovrem. Metody Anal. Mater.*, 153 (1969); and 'Adsorption of uranium in seawater' (in Japanese) by Y. Kobuke in *Hyomen*, **26**, 461 (1988). Three other reviews deal in detail with preparative methods, structural questions and the chemical properties of amidoximes: 'The amidoximes' (in French) by Ng. Buu Hoï and P. Gagnant in *Traité de Chimie Organique* (Ed. V. Grignard), Vol. XV, Paris, 1948, pp. 697–714; 'The chemistry of amidoximes and related compounds' by F. Eloy and R. Lenaers in *Chem. Rev.*, **62**, 155 (1962); and *The Chemistry of Amidoximes* (in Russian) by I. A. Poplavskaya and R. G. Kurmangaliyeva, Alma Ata, USSR, 1988.

In the present chapter the synthesis and chemical reactions of amidoximes are thoroughly discussed, whereas biological activity and technological applications are

indicated briefly, and the long controversy concerning their structure is only summarized, in order to expose the latest results on the subject. The literature has been fully covered up to the end of 1990.

II. SYNTHESIS OF AMIDOXIMES

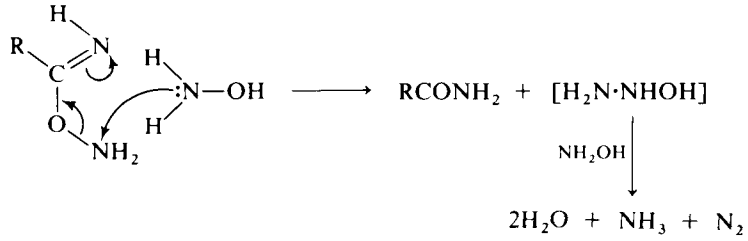
A. Action of Hydroxylamine on Nitriles

As early as 1884 Tiemann and Krüger[1] observed that condensation of nitriles with hydroxylamine hydrochloride affords amidoximes. Since then, this method has been used more than any other, although it yields solely fully unsubstituted amidoximes, according to the general scheme:

$$RCN + NH_2OH \longrightarrow RC(=NOH)NH_2$$

The experimental procedure recommended[1,3] consists in liberating the hydroxylamine from its hydrochloride by means of sodium carbonate, adding an equivalent amount of the appropriate nitrile and enough alcohol to obtain a clear solution, and finally keeping the mixture at 60–80 °C for several hours. More recent studies[4–8] brought about yields reaching even 98%[9]. The presence of potassium or sodium hydroxide, sodium methoxide or ethoxide leads to considerable yield lowering[10–13]. Use of pyridine in methanol[14] and of aqueous-methanolic solutions of sodium acetate[15] has also been reported. In order to avoid the laborious final separation of amidoxime from the alkali chloride, free hydroxylamine in absolute ethanol or methanol may be used[13,16–30]. In the absence of base, heating of the nitrile with hydroxylamine hydrochloride in aqueous-methanolic solution gives the hydrochloride of the amidoxime[30,31].

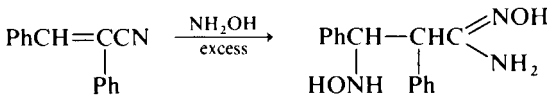
Warburton and coworkers reported in 1969[25] that treatment of 4-cyanopyridine or substituted benzonitriles, bearing 4-nitro, 4-cyano, 4-chloro or 4-perfluoromethyl functions, with an excess of hydroxylamine in anhydrous methanol, results in amidoximes contaminated by up to 55% of the corresponding amide. Detailed investigation of the reaction led to the suggestion that these amides are probably obtained via an initial attack on the nitrile carbon by the hydroxylamine oxygen and subsequent interaction of the intermediate with a further molecule of hydroxylamine:



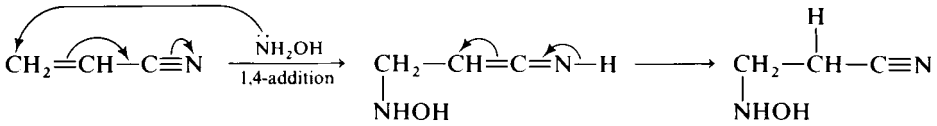
The synthesis of amidoximes from nitriles found wide application, since the latter may bear double[19,32–35] and triple[36] bonds, or contain various functional groups, such as hydroxyl (phenolic and alcoholic)[1,37–42], carboxyl[43], ester[35,43–46] primary[8,14,17,23,28,30,47–53], secondary[50,53,54] and tertiary[55] amino, free carbamyl[26,56,57], N-substituted carbamyl[5,6,30,58–60], phthalimido[52,61], isonitroso or hy-

droxyimino[11], arylsulfonyl[6,53,62–65], sulfonamido[63,66], azo[67,68] and hydrazono[46] groups. The importance of the method is augmented by the fact that most of the aforementioned substituents do not remain inert towards reactants employed in other synthetic approaches of amidoximes, and thus a series of interesting compounds can be obtained solely in that way. Furthermore, the use of appropriate nitriles leads to heterocyclic amidoximes, including 2-furyl[65], 2-benzofuryl[65], 3-benzofuryl[4,65], 2-pyridyl[65], 3-pyridyl[68b], 4-pyridyl[65,68b], 2-quinolyl[65], 3-quinolyl[65], 4-quinolyl[65], 6-quinolyl[69], 2-thienyl[65,70], 3-thienyl[70], 5-imidazolyl[71,72], 2-benzimidazolyl[15], 2-quinoxalinyl[14], 5-thiazolyl[58], 3-(1,2,4-oxadiazolyl)[12], 2-(4-pyridyl-thiazolyl)[9], 4-imidazolyl[26], 2-imidazolyl[73], 3-(pyrazolo[1,5*a*]pyridinyl)[28], 3-(2-oxo-1,2-dihydropyrazinyl)[74] and 3-pyrazinyl[74] derivatives.

Action of an excess of hydroxylamine on 2,3-diphenylacrylonitrile yields 3-hydroxylamino-2,3-diphenyl propionamidoxime (**1**) by double addition of the hydroxylamine both to the cyano and to the olefinic bond[75]. However, unsubstituted acrylonitrile undergoes a 1,4-addition of hydroxylamine leading to 3-hydroxylaminoproprionitrile (**2**)[34,76].



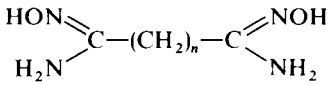
(**1**)



(**2**)

Aromatic amidoximes are obtained in better yields than aliphatic ones, while an excess of hydroxylamine may also ameliorate the percentage. Perfluoroalkyl nitriles react rapidly at room temperature with hydroxylamine to afford the corresponding perfluorated amidoximes, a fact probably due to the increased positive character of the cyano group carbon, caused by the inductive effect of the perfluoroalkyl moiety[77a]. Similarly, (difluoroamino)difluoro acetonitrile is readily transformed to (difluoroamino)difluoro acetamidoxime[77b]. Furthermore, *trans*-3-(2- or 3-thienyl)-acrylonitriles react faster with hydroxylamine than their *cis* isomers[27].

Action of hydroxylamine on dinitriles yields diamidoximes (**3**), with $n = 1$[78], $n = 2$[79–81,84], $n = 3$[82,83], $n = 4$[84,85] and $n = 8$[85].

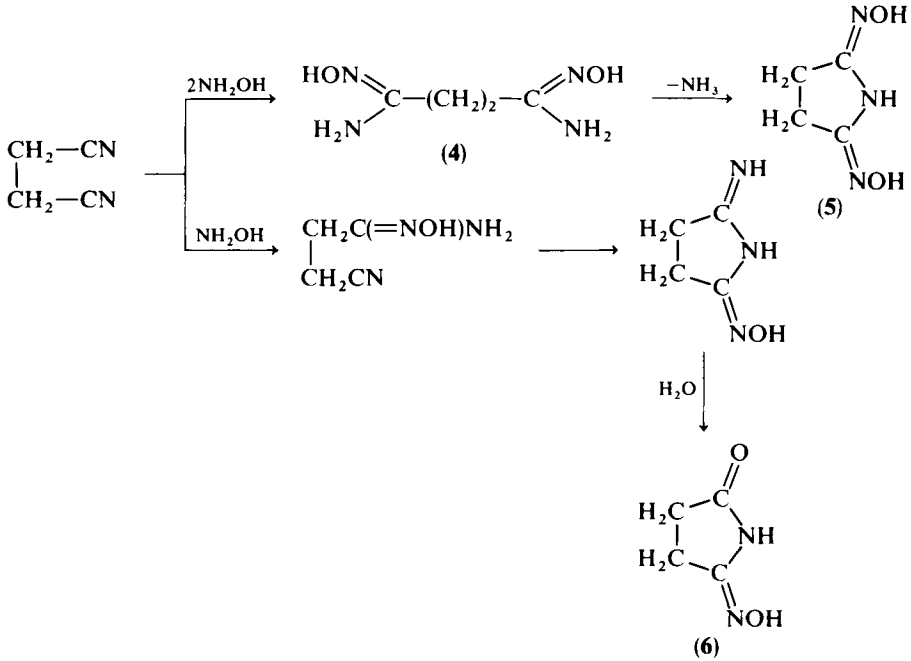


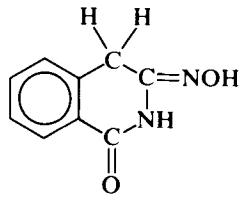
(**3**)

The general procedure given for $n = 5,7,9,10,11,13$[56] is to mix a cold ethanolic solution of the dinitrile with a quadruple amount of hydroxylamine hydrochloride, to add sodium slowly with shaking, and then heat the reaction mixture in a pressure bottle at 60 °C for 20–30 hours. The lowest yields were reported for the homologues with $n = 7$ or 9, while in some cases 1-amidoxime-ω-amides, 1-amidoxime-ω-nitriles or 1-amide-ω-nitriles have been isolated as by-products. Heating hexanedioic acid dinitrile in butanol at 50 °C for

16–18 hours with a slight excess of hydroxylamine afforded 76% of δ-cyanovaleric acid amidoxime. ω-Cyanopelargonic acid amidoxime was also prepared in a similar way[85]. In the case of oxamide dioxime (**3**, $n = 0$), there is evidence for higher yields and fewer by-products, if gaseous cyanogen is led directly into an aqueous hydroxylamine solution at 0 °C[61]. Generally, the best yields in diamidoxime are obtained when free hydroxylamine in butanol is used, but high-molecular-weight dinitriles require an excess of hydroxylamine[61].

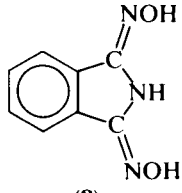
Should intramolecular cyclization occur, mono- and dioximes of the corresponding imides are formed. These reactions take place, for instance, with the dinitriles of succinic, glutaric or *o*-phthalic acids and with *o*-cyanomethylbenzonitrile. Thus, 1 mole of succinonitrile and 2 moles of hydroxylamine in aqueous ethanol at room temperature yields a small amount of succinimidedioxime (**5**) accompanying the major product, succinamidedioxime (**4**), while at 60–70 °C the yield of **5** increases[79]. Using the reactants in molar ratio, the main product is the open-chain diamidoxime (**4**), if the reaction takes place in absolute ethanol at room temperature, or the cyclic imidoxime (**6**), if water is present at 60–70 °C[83]. From 2-cyanomethylbenzonitrile an imidoxime of the type **7** was also prepared[86,87].





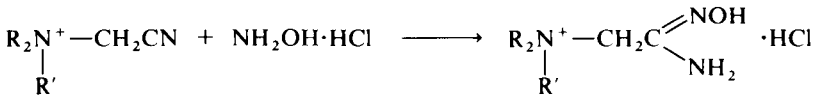
(7)

The reaction of phthalonitrile is of particular interest, in that it affords 85% of the phthalimide 'dioxime' (1,3-dihydroxyiminoisoindoline) (**8**) instead of the diamidoxime[88].



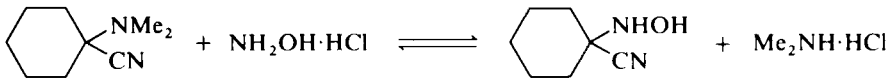
(**8**)

Unusually rapid reactions have been reported for succinonitrile[79], cyanogen[89] and tribromoacetonitrile[90]. Perfluoroglutaronitrile is so exceptionally reactive, that even adding hydroxylamine rapidly at 0 °C yields almost quantitatively the corresponding diamidoxime[77]. Generally, an adjacent highly electron-withdrawing group (e.g. a substituted ammonium group) favors the addition of hydroxylamine to the nitrile function by activating the latter. When substituted aminoacetonitriles react with hydroxylamine, the liberation of the latter from the hydrochloride by means of a base may be avoided, because the exothermic reaction rapidly affords the hydrochloride of the corresponding amino acetamidoxime. The aminonitrile is believed to participate in the reaction in its ammonium form, and the reaction is formulated as follows[55]:

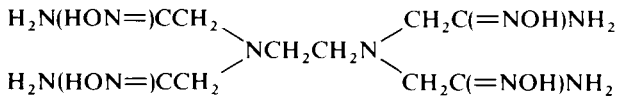


$R' = H$, alkyl

N-Benzyl-*N*-cyanomethyl-*N*,*N*-dimethylammonium chloride also yields a quaternary ammonium substituted acetamidoxime when treated with free hydroxylamine. α-Aminonitriles derived from isobutyraldehyde or cyclohexanone do not give the usual reaction, and instead, an amine displacement occurs[55]:



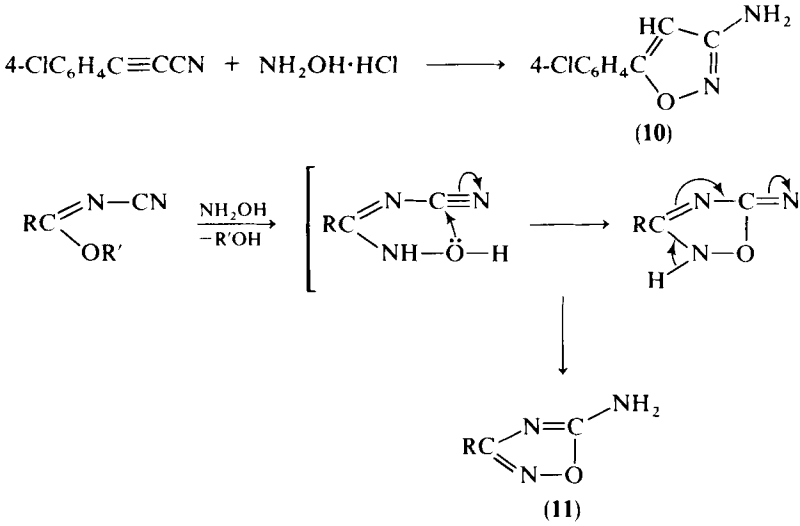
On the other hand, *N*,*N*,*N'*,*N'*-tetrakis(cyanomethyl)ethylenediamine is converted in good yields to the tetrakis-amidoxime (**9**) upon action of hydroxylamine[55].



(**9**)

4-Chlorophenylpropiolonitrile treated with hydroxylamine at − 20 °C in the presence of EtOH/EtONa does not afford an amidoxime, but only 3-amino-5-(4-chlorophenyl)-isoxazole (**10**)[27].

Furthermore, action of hydroxylamine on *N*-cyanoimidates leads to 5-amino-1,2,4-oxadiazoles (**11**)[91].



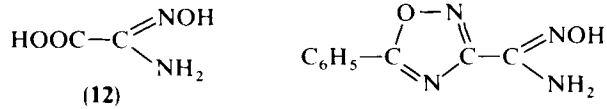
(10)

(11)

Polyamidoximes and polymeric amidoximes[92] can be prepared from polynitriles[93], polyacrylonitriles[94–100], cyanoethylcellulose[94], poly(vinylidene cyanide)[94] and acrylonitrile-vinyl acetate copolymer[101], by action of hydroxylamine (usually in DMF), converting at least part of the nitrile functions into amidoxime moieties.

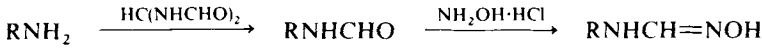
B. Action of Hydroxylamine on Amides or Thioamides

Normally hydroxylamine does not react with amides, as it can be deduced from the synthesis of carbamyl-substituted amidoximes, when carbamyl nitriles are treated with hydroxylamine[5,6,26,30,56–60]. Therefore, this method had only been reported in the past for the preparation of the two amidoximes **12** and **13**[41,102], and recently for the synthesis of several N-substituted heteroaryl-formamidoximes (**14**), where R = pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, in 34–95% yields[103].



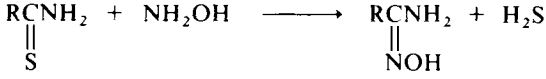
(12)

(13)



(14)

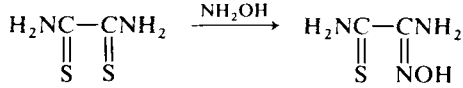
Tiemann observed in 1886[104] that thioamides react with hydroxylamine to afford amidoximes, some aromatic ones being indeed prepared in that way[32,105,106]:



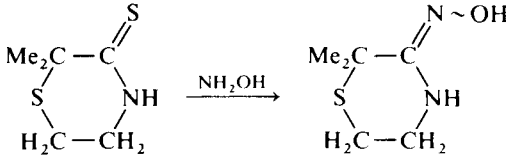
This method did not find wide application, since the general precursors of the thioamides are nitriles which yield directly the amidoximes themselves. However, in 1969

Warburton and coworkers reported that pure, amide-free amidoximes containing electron-withdrawing groups, such as 4-nitrophenyl, 4-pyridyl, 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-carboxyphenyl, as well as 2,4-, 3,4- and 3,5-dichlorophenyl, can often be obtained in high overall yields, exceeding 90% in the case of 4-chlorobenzamidoxime[25], by converting the nitriles into thioamides and treating these with hydroxylamine. Similarly, ethoxycarbonyl formamidoxime was prepared from ethylcyanoformate upon action of hydrogen sulfide followed by treatment of the thioamide thus obtained with hydroxylamine, while direct interaction of ethylcyanoformate gave inferior results[107]. This procedure found a limited application for the synthesis of N-substituted amidoximes[108–111].

According to Ün and Sümengen, interaction of *N*-methyl thioacetamide with hydroxylamine hydrochloride and anhydrous sodium carbonate in absolute ethanol affords[112] methylamine hydrochloride and a very poor yield of the hydrochloride of *N*-methylacetamide oxime. Using sodium ethoxide instead of the carbonate, the sole detectable product is methylamine hydrochloride, since complete decomposition takes place, probably due to the greater basicity of the latter agent[112]. Treatment of dithio oxamide with one equivalent of hydroxylamine gave thiocarbamoyl formamidoxime[12]:

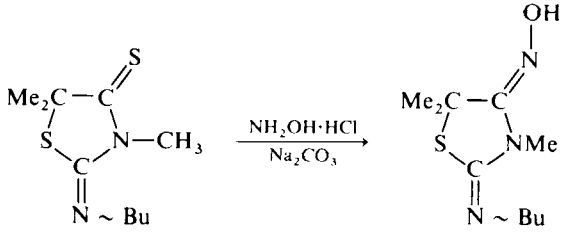


Treatment of 2,2-dimethyl-3-thioxothiomorpholine with hydroxylamine affords 55% of the corresponding cyclic amidoxime (**15**), while a similar action on the respective *N*-methylmorpholine derivative does not lead to any results[113].



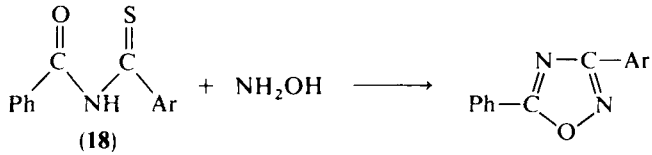
(**15**)

On the contrary, by treating *N*-methyl-thiazolidine-4-thione (**16**) with hydroxylamine, the (*E*) isomer of the thiazolidine-4-oxime (**17**) was obtained[113].



(**16**) (**17**)

In a similar way, *N*-benzoylthioamides (**18**) (Ar = phenyl, 4-Tol, 4-isopropylphenyl) react with hydroxylamine to form 3,5-diaryl-1,2,4-oxadiazoles (**19**) in high yields[114], in



(**18**) (**19**)

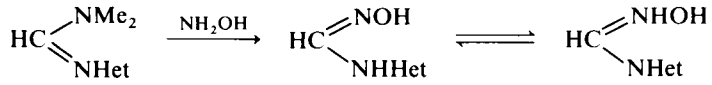
agreement with the general assumption that the acyl derivatives of amidoximes may easily be dehydrated to the corresponding 1,2,4-oxadiazoles.

C. Action of Hydroxylamine on Amidine Hydrochlorides and on Hydrazide Imides

As early as 1884, Pinner prepared benzamidoxime by treating benzamidine hydrochloride with hydroxylamine[115]:

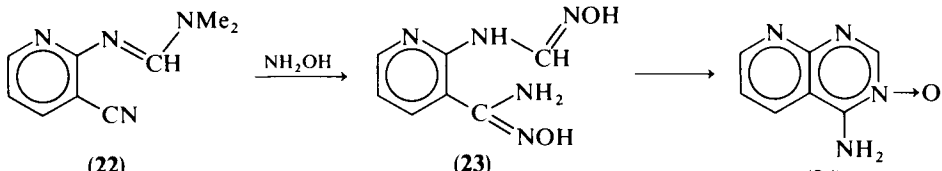
$$PhC(=NH)NH_2 \cdot HCl + NH_2OH \longrightarrow PhC(=NOH)NH_2 + NH_4Cl$$

This method has only limited practical interest, since amidines are obtained from nitriles, thioamides and iminoethers, compounds used as such in the synthesis of amidoximes. Kanazawa and collaborators reported that 3,4-dimethylbenzamidoxime was prepared in almost quantitative yield by treating 3,4-dimethylbenzamidine hydrochloride with hydroxylamine, while a similar treatment of the corresponding 3,4-dimethyl benzonitrile gave 86% of the amidoxime[116]. Several *N*-hetaryl-substituted formamidoximes (**21**) were prepared from hydroxylamine and the appropriate *N,N*-dimethylamino-methyleneamino derivatives (**20**)[117].



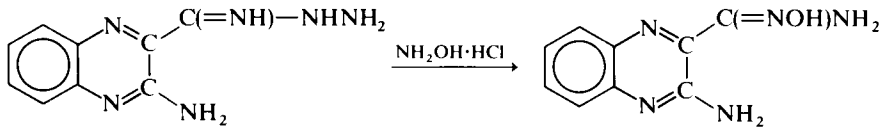
(**20**) (**21**)

In the case of compounds **22** both the nitrile and the amidine functions react with hydroxylamine, resulting in 2-[(hydroxyimino) methylene amino]-pyridine-3-carboxamide oximes (**23**). The latter undergo, in the presence of polyphosphoric acid, an intramolecular condensation to 4-aminopyrido[2,3-*d*]pyrimidine-3-oxide (**24**)[118].



(**22**) (**23**) (**24**)

The formation of 3-amino-2-quinoxalinecarboxamide oxime (**25**) in 56% yield starting from the corresponding 3-amino-2-quinoxalinecarbohydrazide imide and hydroxylamine hydrochloride has recently been reported[14], while the 4-oxide of the carbohydrazide imide leads to the 4-oxide of **25** in 42% yield.



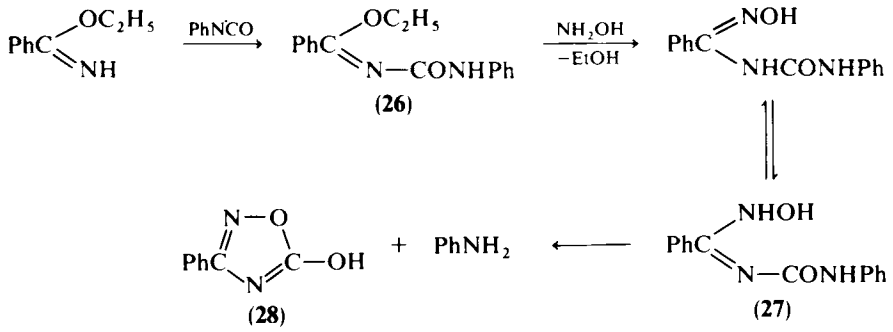
(**25**)

D. Action of Hydroxylamine on Iminoethers and on Imidoyl Chlorides

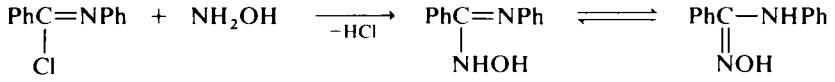
The synthesis of benzamidoxime by treatment of ethyliminobenzoate with hydroxylamine was reported by Pinner[115] and Lossen[119]:

$$PhC(=NH)—OC_2H_5 + NH_2OH \longrightarrow PhC(=NOH)NH_2 + C_2H_5OH$$

Since benzonitrile is the starting material for the synthesis of iminoethers, this reaction has not found practical application. In an analogous way, the action of hydroxylamine on ethyl *N*-carbanilino-iminobenzoate (**26**), a product of the treatment of ethyl imino-benzoate with phenylisocyanate, affords *N*-carbanilino-benzamidoxime (**27**) in 60% yield. When kept for some minutes at the melting point, the amidoxime (**27**) underwent cyclization to 3-phenyl-5-hydroxy-1,2,4-oxadiazole (**28**)[120].



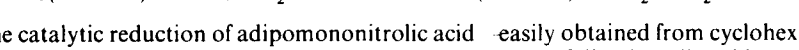
While *N*-carbanilino-4-nitro-benzamidoxime demonstrated the same behavior as well[120], action of hydroxylamine on the *N*-benzoyl and *N*-acetyl derivatives of ethyl iminobenzoate at 0 °C yielded the corresponding 3-phenyl-5-phenyl (or methyl) -1,2,4-oxadiazole[121]. Furthermore, already in 1898 benzanilide oxime was obtained from benzanilide imide chloride and hydroxylamine[122]:



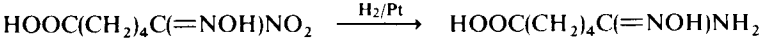
Bacchetti and Alemagna[123] made use of this method to synthesize a series of amidoximes Ar'C(=NOH)NHAr (Ar' = phenyl, 4-nitrophenyl, 4-An and Ar = phenyl, 2-Tol, 4-An, 2-, 3-, 4-nitrophenyl, β-naphthyl) while several N-substituted benzanilide-oximes were later prepared by analogous procedures[124].

E. Reduction of Nitrosolic and Nitrolic Acids, of Hydroxyamidoximes and of other Related Compounds

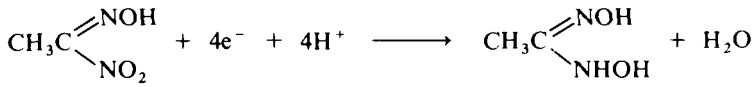
Reduction of the title compounds has also been used to a small extent for the synthesis of amidoximes. Thus, Wieland and Bauer prepared benzamidoxime by reducing benzoni-trosolic acid with hydrogen sulfide[125]:



The catalytic reduction of adipomononitrolic acid -easily obtained from cyclohexanol and cold nitric acid- and of other mononitrolic derivatives of dicarboxylic acids, proved to be a quite general method to yield the corresponding amidoximes[126]:

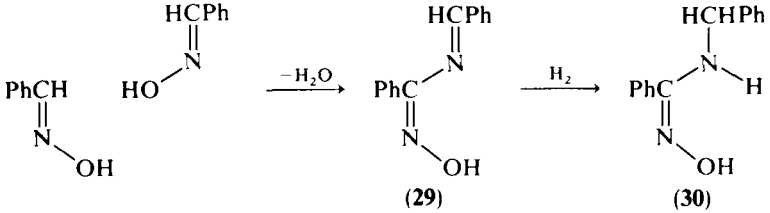


Heterocyclic nitrolic acids may also be reduced to amidoximes by means of $SnCl_2$/HCl[127]. In contrast, polarographic reduction of ethylnitrolic acid leads to the hydroxy-amidoxime[128]:



N-Hydroxyamidoximes, easily prepared from the corresponding hydroximic acid chlorides and hydroxylamine, were reduced with sulfur dioxide to the corresponding amidoximes[129]:

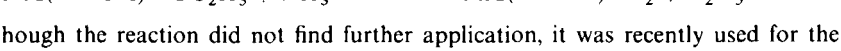
The thermolysis of (*E*)-benzaldoxime at 140 °C gives a 10% yield in *N*-benzylidenebenzamidoxime (**29**), which is further almost quantitatively reduced to (*Z*)-*N*-benzylbenzamidoxime (**30**) by means of sodium-dihydro-bis(2-methoxy-ethoxy)aluminate (Red-Al)[130].



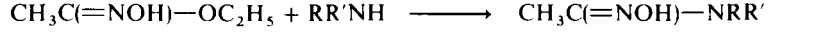
(**29**) (**30**)

F. Action of Ammonia and Amines on Oximinoethers

Lossen[17a] prepared benzamidoxime by heating in a pressure bottle an alcoholic solution of ammonia and ethyl benzhydroximic acid for 8 hours at 175 °C:



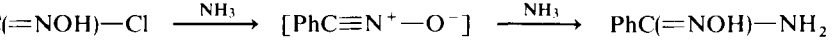
Although the reaction did not find further application, it was recently used for the synthesis of some *N*-alkyl and *N*,*N*-bis-alkylacetamidoximes (**31**) by heating at 80–90 °C a solution of ethyl *N*-hydroxyacetamidate with a large excess of a primary or secondary amine[113].



(**31**)

G. Action of Ammonia and Amines on Hydroximic Acid Chlorides and on Nitrile Oxides

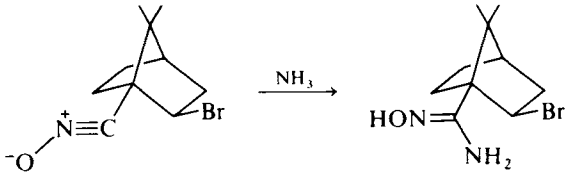
The reaction of benzhydroximic acid chloride with ammonia[131] to afford benzamidoxime belongs to the very beginnings of the chemistry of the hydroximic acid derivatives. Owing to the remarkably fast dehydrohalogenation of hydroximic acid halides in the presence of bases it is highly probable that the first step yields the corresponding nitrile oxide, which subsequently adds the nucleophile:



The reaction of hydroximic acid chlorides with two moles of an amine to yield *N*-substituted amidoximes was first reported already in 1894 by Nef[132], who treated the simplest homologue, formhydroximic acid chloride, with aniline and obtained the

so-called *phenyl-iso-uretin*. Soon afterwards the method was extended to aromatic hydroximic acid chlorides and secondary amines[133], and it is still the best way for preparing N-mono- or disubstituted amidoximes. (*E*)-Benzhydroximoyl chlorides have recently been examined in these type of reactions and proved to react about 10^{-7} times slower than the (*Z*)-benzhydroximoyl chlorides. This large rate difference should be attributed to the favorable antiperiplanar lone pair on the adjacent nitrogen, which facilitates a Cl^- loss from the (*Z*) substrate[134].

The nucleophilic 1,3-addition of a nitrile oxide to amines was first reported by Ponzio in the cases of oximinophenylacetonitrile[135] and oximinomalonomononitrile oxides[136]. The addition is quite a general one, taking place with both aliphatic and aromatic nitrile oxides, as well as with primary or secondary aliphatic or aromatic amines[137]. Even the singularly stable nitriloxide (**32a**) is converted almost quantitatively to **32b** on overnight treatment with NH_3 in ether[138].



(**32a**) (**32b**)

The reaction of nitrile oxides with n-butylamine is so fast and complete that it was chosen as the basis for their volumetric analysis in kinetic experiments[126,139,140].

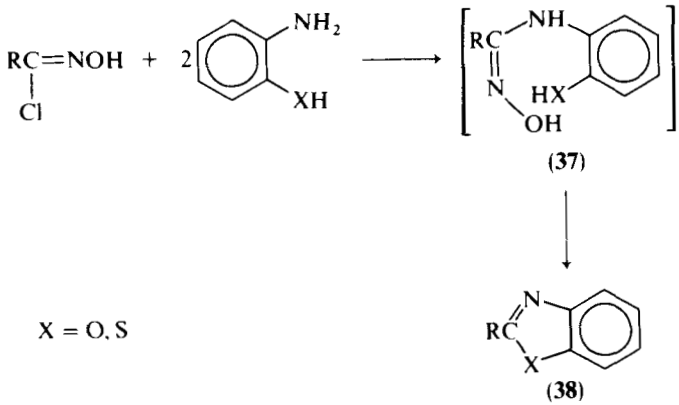
Primary and secondary amines react in aqueous solution stereospecifically with nitrile oxides to give (*Z*) amidoximes. With primary amines or ammonia this structure is thermodynamically favored, but with the bulkier secondary amines subsequent isomerization to the more stable (*E*) configuration occurs[141–143]. Gozlan and coworkers isolated both isomers of *N*,*N*-dimethyl benzamidoxime[144] by treating benzhydroximoyl chloride with dimethylamine, whereas Exner and Motekov obtained only the (*E*) form when using methanol as solvent[145]. A detailed discussion of the isomerization of amidoximes shall be given later on.

Several arylhydroximoyl chloride esters (**33** and **34**) react vigorously with secondary amines, such as pyrrolidine, piperidine or morpholine, to yield[36] ureas of the type **35**. A notable exception is offered[36] by *O*-methanesulfonyl-3-nitrobenzhydroximoyl chloride, which yields the amidoxime mesylate **36**, with an excess of pyrrolidine. Compounds **33** are easily prepared in alkaline *milieu* from the corresponding arylhydroximoyl chlorides or nitrile oxides with an alkanesulfonyl chloride or an aryl chloride, respectively[36].

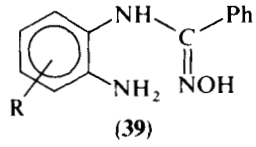
$$\underset{\textbf{(33)}}{ArC(Cl)=N-OSO_2R} \text{ or } \underset{\textbf{(34)}}{ArC(Cl)=N-OCOR} \xrightarrow[2.\ H_2O]{1.\ R'NHR''} \underset{\textbf{(35)}}{ArNH-CO-NR'R''}$$

$$3\text{-}NO_2C_6H_4C(Cl)=N-OSO_2CH_3 \xrightarrow[2.\ H_2O]{1.\ \text{pyrrolidine}} 3\text{-}NO_2C_6H_4C(=N-OSO_2CH_3)(N\text{-pyrrolidino}) \quad \textbf{(36)}$$

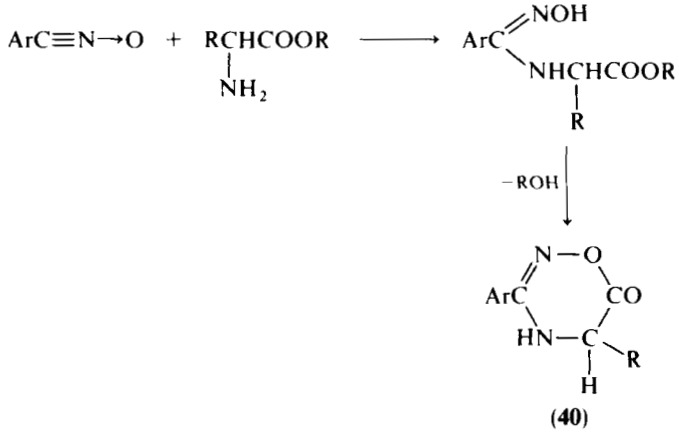
Sometimes amidoxime formation is followed by ring closure, as in the reaction with *o*-amino-phenol or -thiophenol, leading respectively to benzoxazoles or benzothiazoles (**38**), obviously via the intermediate **37**[146].



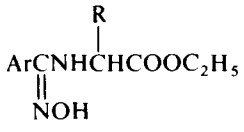
In contrast, the *N*-(2-aminoaryl)-benzamidoximes (**39**) resulting from the action of benzonitrile oxide on *o*-phenylene diamines are stable compounds, though leading to benzimidazoles or benzotriazoles when treated with HCl or with $NaNO_2/HCl$[147].



Furthermore, the condensation of arylnitrile oxides with α-amino acid esters other than those of glycine and alanine constitutes a facile synthetic route to the hitherto unknown 1,2,4-oxadiazin-6-ones (**40**)[148].



The reaction takes place between the appropriate hydroximoyl chloride and the L-amino acid ester under mild conditions in absolute ethanol and in the presence of triethylamine. The amino esters probably behave towards nitrile oxides in the same way as primary and secondary amines do, and the resulting (*Z*)-amidoximes most likely undergo intramolecular cyclization to the corresponding oxadiazinones through oxygen in an allowed '*6-Exo-Trig*' process[149]. Glycine and alanine ethyl esters yield the acyclic addition products **41** and **42**, while β-alanine likewise affords the corresponding acyclic derivative **43**[148].



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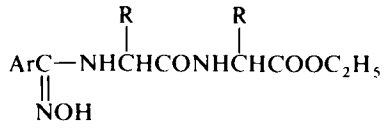

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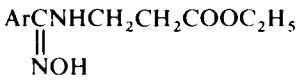
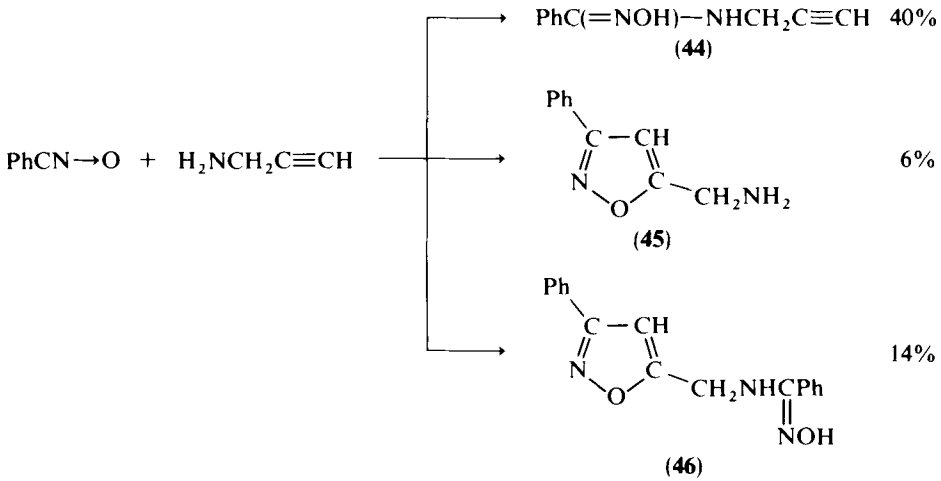


(43)

It is known[150] that nitrile oxides are active towards various nucleophiles as well as towards different multiple bonds. In case the amine bears further functional groups, they may possibly react along with the amine function, or even instead of it. Thus, propargyl amine on treatment with benzonitrile oxide yields a mixture of the three possible adducts **44**, **45** and **46**, which are formed by 1,3-addition prevailing over the cycloaddition to isoxazole derivatives[151].



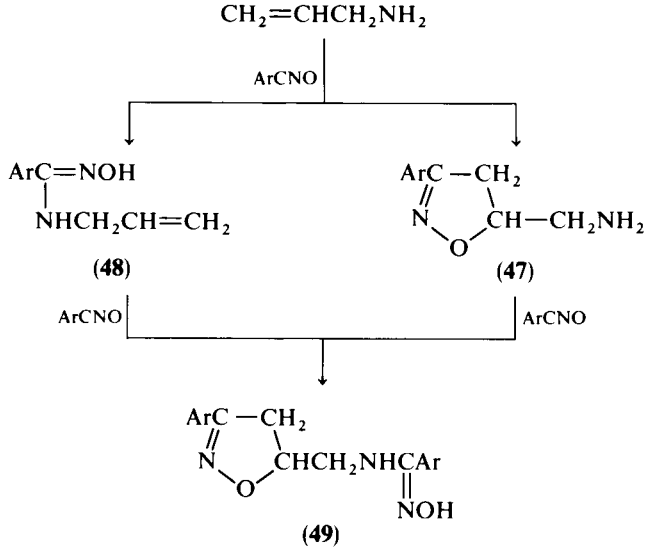
(44) 40%

(45) 6%

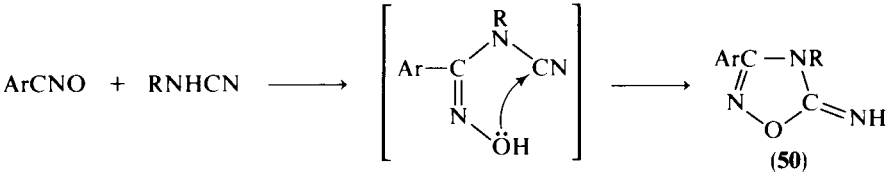
(46) 14%

Benzo- and mesitonitrile oxides with allylamine afford 5-aminomethyl-2-isoxazolines and open-chain N-substituted amidoximes. An excess of the nitrile oxide produces from both monoadducts **47** and **48** the same bis-adduct (**49**); in case the dipolarophile is in a tenfold amount, only the monoadducts are obtained in fair yields and in 1:2 or 1:1 molar ratios for benzo- and for mesitonitrile, respectively. These data indicate that the

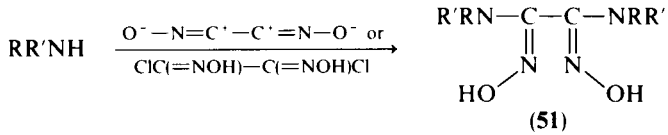
nucleophilic additive activity of the primary amino group is almost equal to the dipolarophilic activity of the unsaturated bond[152].



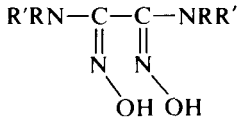
Cyanamide and phenylcyanamide have been reported to add aromatic nitrile oxides through an initial nucleophilic attack of the amino moiety, followed by cyclization to 1,2,4-oxadiazolin-5-one imines (**50**)[153],



Bifunctional nitrile oxides and their precursors bis-hydroximoyl chlorides behave in close analogy to amines and ammonia. Thus, primary and secondary amines on action upon the simplest homologue, oxalonitrile-bis-*N*-oxide (i.e. cyanogen-di-*N*-oxide), afford *N*,*N*'-bis- and *N*,*N*,*N*',*N*'-tetra-alkyl substituted oxalyl-diamide-dioximes (**51**) for which the *anti*-configuration was suggested on the basis of the NMR spectra[154,155].

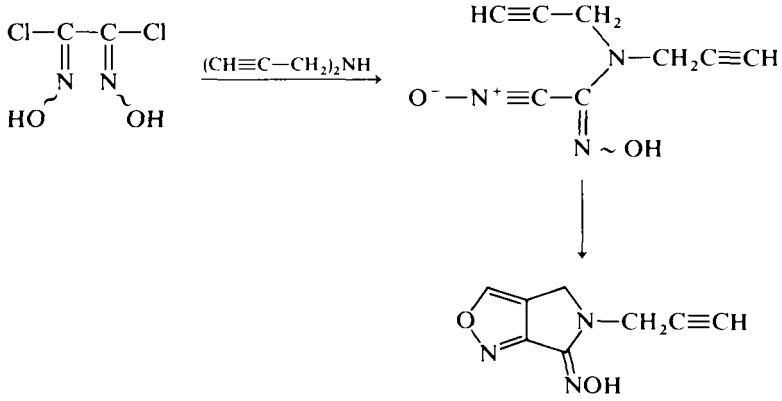


The synthesis of similar diamidoximes bearing an *amphi* configuration (**52**) was reported to take place when primary and secondary amines are treated with *anti* dichlorodioxime diacetate[156]. The observations made on the structure of diamidoximes in general shall be summarized further on.



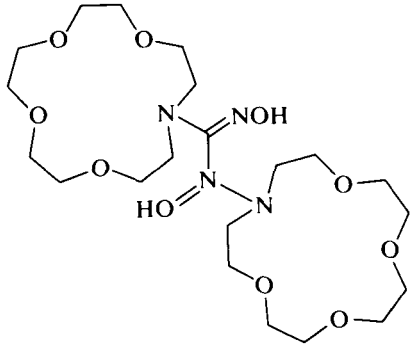
(52)

From the reaction between dipropargylamine and dichloroglyoxime the substituted pyrrolo[3,4-*c*]isoxazole (**53**) is isolated, as product of a further intramolecular 1,3-dipolar cycloaddition of the second nitrile oxide function on the triple bond of one of the *N*-propinyl groups of the intermediate amidoximes[157].



(53)

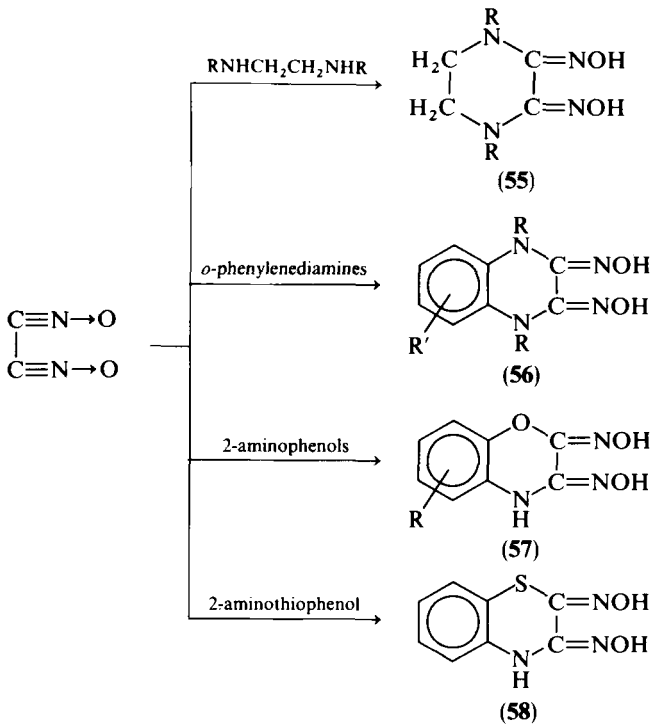
Quite recently 1,2-bis{(monoaza[15]crown-5)-*N*-yl}glyoxime (**54**) was prepared from cyanogen-di-*N*-oxide and monoaza[15]crown-5, and was used to form complexes with Ni(II), Pd(II) and Pt(IV)[158].



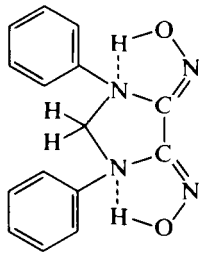
(54)

The same bis-nitrile oxide undergoes ring closure with diamines to yield 1,4-diazines of the types **55** or **56**; e.g. with *o*-phenylenediamine the 2,3-dioximino-1,2,3,4-tetrahydro quinoxaline **56** has been obtained[154,159–161]. In an analogous way, 2-aminophenols give benzoxazines **57** by intramolecular attack of the hydroxyl on the second nitrile oxide

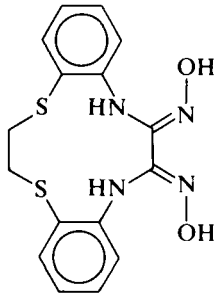
function[162], while recently 2,3-bis(hydroxyimino)-2,3-dihydro-4*H*-1,4-benzothiazine (**58**) has been synthesized from 2-aminothiophenol and cyanogen-di-*N*-oxide, the *amphi* isomer being obtained by crystallization of the crude product in pyridine/water 1:5[163].



1,3-Diphenyl-4,5-bis(hydroxyimino)imidazolidine (**59**)[164] and dibenzo[*e*, *k*]-2,3-bis-(hydroxyimino)-1,4-diaza-7,10-dithia-2,3,8,9-tetrahydrocyclododecine (**60**)[165], both possessing marked chelating affinity towards various metals, have also been prepared by action of cyanogen di-*N*-oxide on *N*,*N*′-diphenyl-methylenediamine and 1,2-bis(2-aminophenylthio)ethane, respectively.

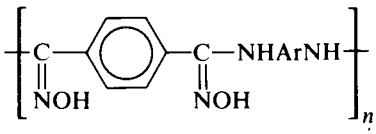


(**59**)



(**60**)

Bifunctional nitrile oxides may also react with several bifunctional amines to yield polyamidoximes of various degrees of polymerization[166]. Thus the polyamidoximes **61** (Ar = 2-phenyl, 4-phenyl and 4,4′-diphenyl) and **62** were obtained by treating terephthalohydroximoyl chloride (or the corresponding bis-nitrile-oxide) with aromatic diamines or benzidine[167].



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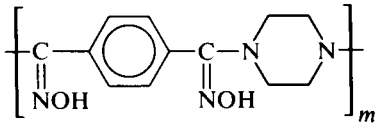
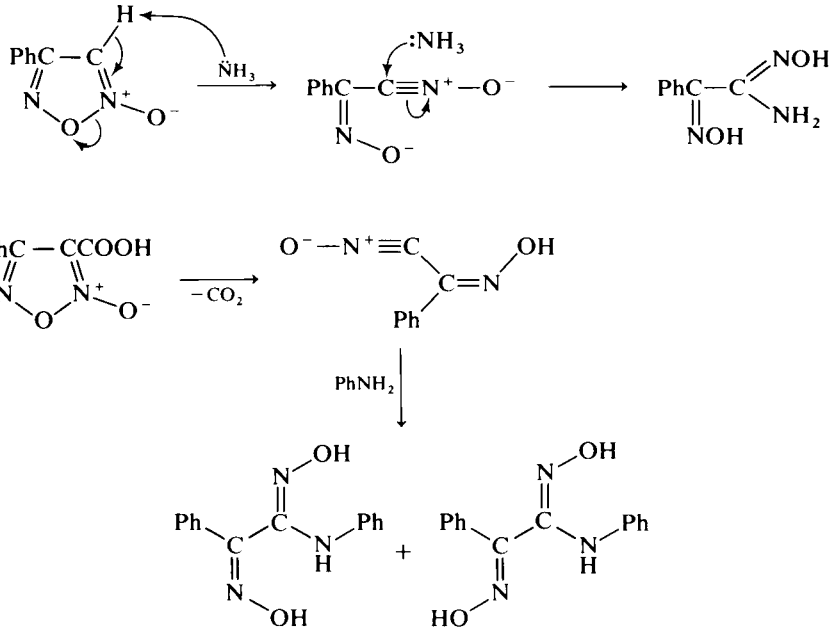


(62)

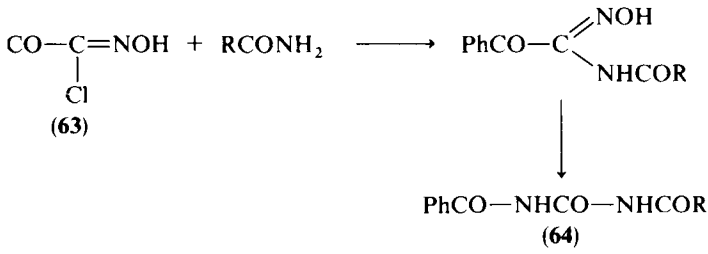
In the same reaction type may be included the heating of furoxans with ammonia and amines, resulting in ring opening to a nitrile oxide, as illustrated by the following examples[11,168]:



Certain strained furoxans were found to undergo this transformation under much milder conditions[169].

The action of $RCONH_2$ (where R = methyl, ethyl and phenyl) on the hydroximoyl chloride **63** bears a certain interest due to the fact that the intermediate *N*-acylated amidoxime did not afford the 3-benzoyl-5(R-substituted)-1,2,4-oxadiazole expected, but instead the urea derivative **64**, formed by Beckman rearrangement[170].

Furthermore, the one-step procedure outlined below gives a 1:1 mixture of **65** and **66** in 47% overall yield[113]:



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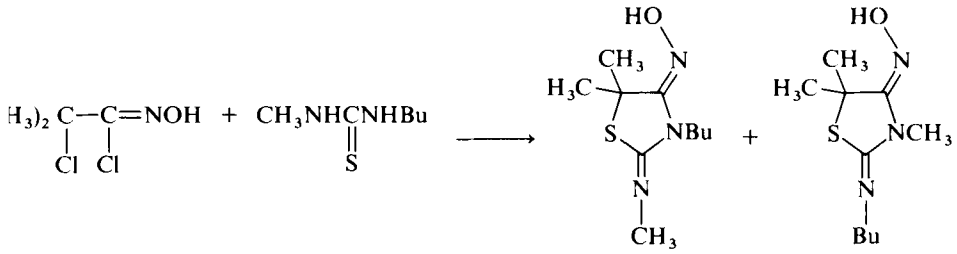
(64)



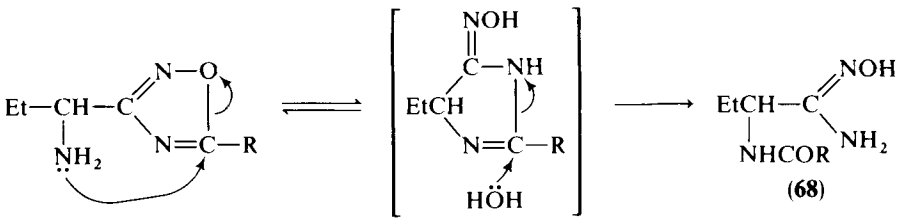
(65) (66)

H. Ring Opening of Nitrogen-containing Heterocycles

1. 1,2,4-Oxadiazoles

Lithium aluminum hydride (LAH) always breaks the C—O bond of the 1,2,4-oxadiazole ring yielding N-substituted amidoximes[171]:

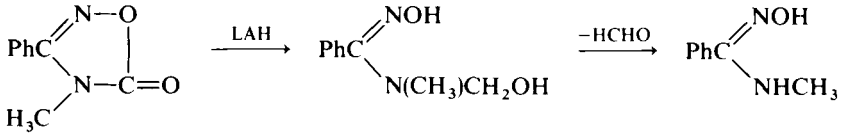
A mixture of 3-(1-aminopropyl)-5-methyl-1,2,4-oxadiazole hydrochloride (**67**) in 1N NaOH allowed to stand for four weeks at ambient temperature yields 78% of 2-(acetylamino)butyramidoxime (**68**). Analogous preparation of the (benzoylamino) and the [(3-piperidinopropionyl)amino] amidoximes gave similar yields. The reaction consists of at least two steps, in which the alkaline medium obviously plays an important role[30].



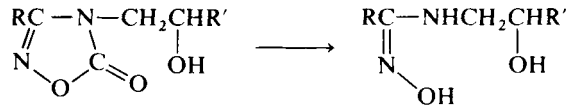
(67) (68)

2. Δ^2-1,2,4-Oxadiazolin-5-ones or Δ^2-1,2,4-oxadiazolines

LAH may open Δ^2-1,2,4-oxadiazolin-5-ones to N-substituted amidoximes[171,172a]:

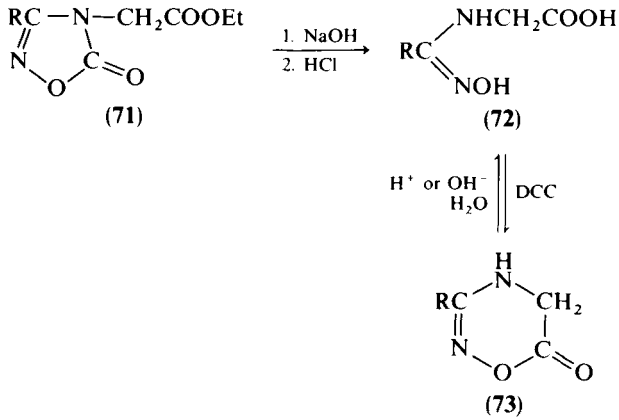


N-Monosubstituted amidoximes of the type RC(=NOH)NHR′—where R = methyl, phenyl, 4-tolyl, benzyl or 3,4-dimethoxybenzyl and R′ = methyl, benzyl, carboxymethyl, 2-diethylaminoethyl, allyl—were prepared in 58–90% yield[172b] by alkaline hydrolysis of 3-(R-substituted)-4-(R′-substituted)-Δ^2-1,2,4-oxadiazolin-5-ones with alkyl halides R′X (X = Cl, Br, I). Similarly, compounds **69**, with R = phenyl, 1,1-diphenylethyl, R′ = H, methyl, CH_2R'' (R″ = cyano, piperidino), gave by alkaline hydrolysis the amidoximes **70**[173].



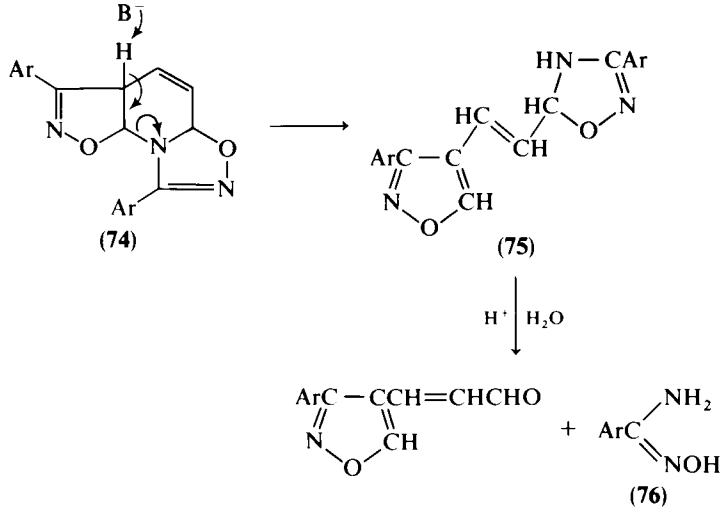
(69) **(70)**

Furthermore, 4*H*-1,2,4-oxadiazin-6(5*H*)-ones (**73**), were prepared from 4-(ethoxycarbonylmethyl)-Δ^2-1,2,4-oxadiazolin-5-ones (**71**: R = phenyl, benzyl and 2,2-diphenylethyl) by hydrolysis in basic media and subsequent cyclization of the amidoxime derivatives (**72**)[174].



(71) **(72)** **(73)**

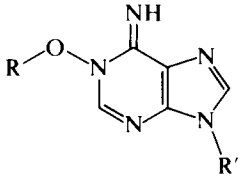
The Δ^2-1,2,4-oxazolines **75**, obtained by alkaline cleavage of the bis-adducts **74** (prepared from aromatic nitrile oxides and pyridine), were further hydrolyzed to the corresponding amidoximes (**76**) in 43–49% yields[175].



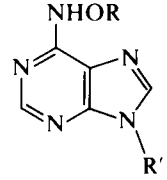
(74) (75) (76)

3. 1-Alkoxyadenines

The Dimroth rearrangement of 1-alkoxy-9-alkyladenines (**77a–d**) to 6-alkoxyamino-9-alkyl purines (**78a–d**) was readily effected by treating the free bases **77** with boiling water, while at lower temperatures the intermediate *N'*-alkoxy-1-alkyl-5-formamido-imidazole-4-carboxamidines (**80a–c**) were obtained. Heating of the latter in water led to recyclization to the rearranged products (**78a–c**). The adenines (**77**) on treatment with hot aqueous alkali yielded *N'*-alkoxy-1-alkyl-5-amino-imidazol-4-carboxamidines (**79**), the deformylated products of **80**.[176]. The rates of these transformations have been measured as well[177].

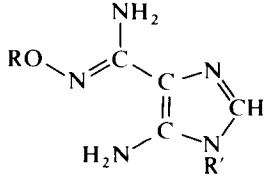


(77a–d)

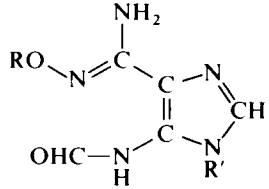


(78a–d)

(**a**) R = R' = Me
(**b**) R = Et, R' = Me
(**c**) R = R' = Et
(**d**) R = R' = $PhCH_2$

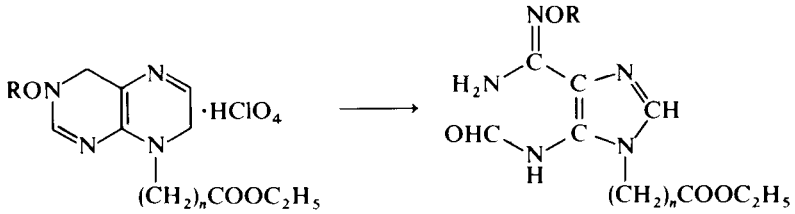


(79)



(80a–c)

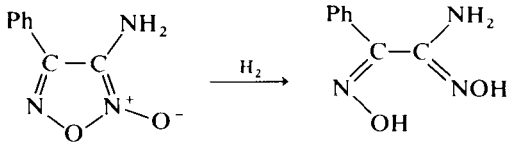
Very recently, the transformation of the heterocycle **81** to **82**, a derivative of **80**, was also reported. The reaction consists in heating **81** with Amberlite IRA-402 in water at 40 °C for seven hours and yields were 35% for $n = 1$ and 63% for $n = 3$[178].



(81) **(82)**

4. 1,2,5-Oxadiazoles

The reductive ring opening of 3-amino-4-phenylfuroxan on a Pd/C catalyst at room temperature affords 83% of 1-phenyl-2-aminoglyoxime, confirming the constitution of the furoxan used[11]:



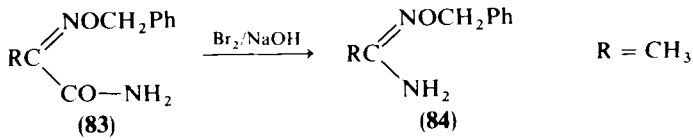
I. Miscellaneous Synthetic Reactions

According to Conduché formamidoxime with aromatic aldehydes affords α-hydroxylated amidoximes through an 'aldol condensation'[179]:

$$ArCHO + HC(=NOH)NH_2 \longrightarrow ArCH(OH)—C(=NOH)NH_2$$

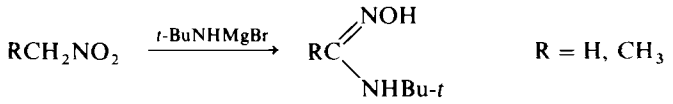
Recently, α-hydroxy amidoximes derived from a variety of sugars have also been reported[180].

Several *O*-benzylamidoximes were prepared from α-benzyloxyiminocarboxamides (with R = Me, Et, amyl, Ph or $PhCH_2$), by the Hofmann hypobromite reaction. By adding to an aqueous sodium hydroxide solution at 0 °C first bromine and then α-benzyloxyiminopropionamide (**83**) and slowly raising the temperature to 75 °C, there resulted *O*-benzylacetamidoximes (**84**), in rather low yields (5–46%)[181].



(83) **(84)**

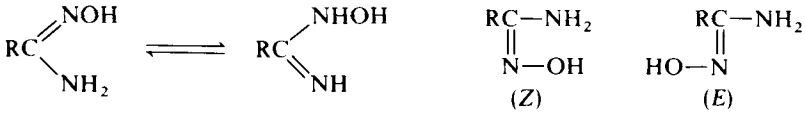
Recently, it has been reported that refluxing primary aliphatic nitro compounds with a magnesium amide in THF gives about 45% of N-alkylated amidoximes[182]:



III. PHYSICAL PROPERTIES OF AMIDOXIMES

Amidoximes are crystalline, colorless compounds that usually decompose if heated over their melting point, while those bearing an aromatic substituent are more stable than the aliphatic ones[3]. The solubility decreases with increasing molecular weight and strongly depends on the hydrocarbon moiety of the molecule. The structure of the functional group allows amidoximes to exhibit amphoteric properties. Thus, studies on the question as to which nitrogen atom is protonated[10,23,183–188], as well as measurements of the ionization constants, were carried out several decades ago. Indeed, potentiometric titration of a series of N-substituted amidoximes resulted in pK_a values of about 5 to 6[10,23,186], while a general study of amino amidoximes suggested a primary ionization of the amino function with pK_a values reaching 9.60, followed by that of the hydroxyimino group (pK_a usually about 3.6–3.8)[10,186]. Detailed studies on the potentiometric and thermochemical behavior of succinic acid diamidoxime[189] and certain ring substituted isoxazolyl acetamidoximes[190,191] were carried out, while polarographic investigations on *N*-hydroxy amidoximes proved them to be less basic than the corresponding unsubstituted ones[183,184].

The spectral data of amidoximes bear great interest, since they contribute decisively to their structural elucidation, concerning both their amino–imino tautomerism and geometrical isomerization.



Ultraviolet spectra of numerous amidoximes have been recorded, exhibiting average absorption maxima of 210–280 mμ, that shift to longer wavelengths under simultaneous decrease in absorbance as the solution becomes more basic[192,193]. More important information can, however, be taken from the infrared spectra. Barrans and coworkers attributed the data of several simple amidoximes to their hydroxyimino–amino tautomer[194], while Eloy and Lenaers[195] similarly assigned to the two NH_2 stretching modes the doublet in 2.87–2.93 and 2.96–3.03 μ, to the hydroxyl a very broad band having its maximum at 3.2 μ, and to the C=N stretching an absorption at 5.95–6.08 μ. The frequencies for oxamidoximes[196], amino acetamidoximes[55], 3-amino amidoximes[10], *O*-acyl amidoximes and 2-amino amidoximes[25], as well as their intensities[197], and also the quite modified absorptions of perfluoro acylamidoximes[77], hydroxyguanidines[198], arylamidoximes[199], α-(acylamino)butyramidoximes[30] and of the macrocycle **60**[165] also fit this pattern. N- and O-acylated amidoximes have been discerned by measurement of their spectral data[200], and the relation between N-substituents and C=N frequency was studied[201]. Furthermore, the amino group values are compatible with sp^2 hybridization of the nitrogen[202]. Even so, Ungnade and Kissinger[203] assigned the C=N stretching to an imino and not to a hydroxyimino function, though the strong dependence of that band on other substituents rather weakened the argument[201]. Spectra recorded after partial deuteration of several amidoximes[204] confirmed the presence of the amino group,

and the similarity in the data led to the same assumption for *N*-alkyl amidoximes as well[205], and further proof was offered by dipole moment measurements[206]. In addition, amidoximes may undergo intramolecular hydrogen bonding[202,204], to be detected in certain cases by ^{15}N-NMR measurements[207].

The proton magnetic resonance spectra also elucidate the tautomerism question. Indeed, the numerous data recorded in the last decades[30,172,208] verified the hypothesis of the hydroxyimino–amino structure[192,204,209], that was also strengthened by means of ^{15}N-NMR measurements[168]. Thus, the amidoxime function is represented by two single peaks, the hydroxyl absorbing at approximately $\delta = 10$ ppm and the amino group at about 4–5.5 ppm, in accordance with the signals of other analogous classes. In conclusion, both infrared and nuclear magnetic resonance spectra lead to the assumption that amidoximes favor the hydroxyimino–amino structure, a fact confirmed also by crystallographic X-ray analysis[210].

Information about the geometrical isomerism of amidoximes mainly relies on NMR and X-ray observations. The extinction coefficient in ultraviolet spectral measurements is smaller in the (*Z*) isomer, as shown in the example of morpholino-4-nitrobenzamideoxime[171]; the ^{13}C-NMR value[144] is larger for the same configuration. The electron spin resonance spectra of amidoxime radical-anions should also be attributed to the (*Z*) form[109]. X-ray studies allowed the assignment of a (*Z*) structure to formamidoxime[210,211] and pyridine-2-amidoxime[212] and also for their N-monosubstituted derivatives[213–219], and when an amidoxime moiety is inserted in an oligopeptide structure[220].

The tendency to undergo hydrogen bonding defines the configuration of un- and N-monosubstituted amidoximes in solution, and is complemented by sophisticated[221] electric dipole moment calculations, all pointing[142,222] to the (*Z*) form, as well as the PMR shifts, indicating the presence of only one isomer for simple amidoximes[223–225]. Nevertheless, heterocycles of the piperazine, thiomorpholine, imidazolidine, 2-iminothiazolidine series[113] apparently exist in an equilibrium of both structures, due to marked stereochemical interactions. The behavior of (2-alkyl-aryl) amidoximes is complicated[142] by nonequivalence of the *ortho*-alkyl protons, that could, however, depend on rotation about the C—N bond[226]. The aforementioned data as well as steric considerations[227] allow one to assign to unsubstituted or *N*-aryl benzamidoximes a conformation of the *s-trans* type about the C—N and N—O bonds, while taking into account the partial double-bond character of the former[142,212,223].

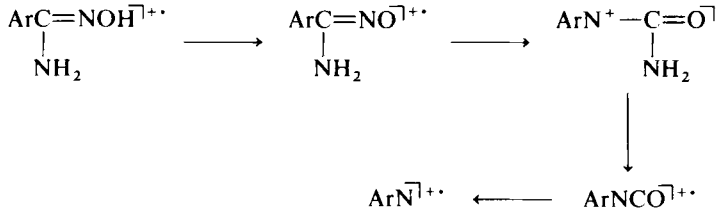
A stereospecific addition of primary amines to benzonitrile oxide in aqueous solutions, leading to the thermodynamically favored (*Z*) isomer, has also been reported[141]. Should, however, secondary amines act upon 1,3-dipoles, the initially obtained (*Z*) structure isomerizes into the more stable (*E*) form[141–143], in both inert or acidic solutions, the latter reaction proceeding via the N-protonated forms and being affected by pH changes[228]. In an analogous manner, dimorpholino (or dipyrrolidino) 4-nitrobenzamidoxime finally yields the (*E*) configuration, the kinetic (*Z*) isomer maintained solely at low temperatures[229]. In the NMR spectra of *N*,*N*-dialkyl arylamidoximes taken at -90 °C similar observations are made[230]. In *N*,*N*-disubstituted amidoximes both isomers can exist, the configuration depending upon the synthetic pathway and on kinetic control[221]. X-ray diffraction intensities of *N*,*N*-dimethyl acetamidoxime point to intermolecular hydrogen bonding and to the (*E*) form[231], while sterically hindered *N*,*N'*-disubstituted 1,4-diazines of the type **55** exist in both conformations, since ^{13}C-NMR spectra show unambiguous evidence for their existence[160]. The isolation of the isomers of *N*,*N*-dimethyl benzamidoxime and the assignment of the respective configurations allowed a more profound study of the (*Z*) to (*E*) rotation, assumed to proceed even in basic media through a catalyzed mechanism involving nitronium ions[144]. Thus, the isomerization of *N*,*N*-disubstituted amidoximes in aqueous *milieu*, easily followed by ultraviolet spectroscopy[232], is strongly acid catalyzed, but takes place at measurable

rates in alkaline solutions as well. Reduction of the double-bond character of the C=N linkage, induced by electron-donating substituents, may increase the reaction rate[232]. Dipole moment measurements[145] attributed to *N,N*-disubstituted amidoximes the (*E*) structure, which is apparently the preferred one both in the crystalline and in the dissolved state, because of steric actions of the two substituents.

Irradiation of several fully substituted amidoximes with ultraviolet light resulted in a photochemically induced isomerization about the C=N bond[233]. Solvent shifts of benzene in the NMR spectra of amidoximes compared to those of benzal anilines Ar—N=CH—Ar' also favor the existence of the hydroxyimino–amino tautomer, while the geometry of the solvent–solute 'collision complex' is in good agreement with the above results[234].

The hydroxyls of N-substituted simple bis-amidoximes (**51**), prepared from cyanogen-di-*N*-oxide and amines, apparently have the *anti* configuration, as may be concluded from their NMR data[154,155]. Treatment of *anti* dichlorodioxime diacetate with an amine yielded compounds **52**, that appeared, however, as *amphi* isomers[156]. Furthermore, synthesis of 2,3-bis-(hydroxyimino)-2,3-dihydro-4*H*-1,4-benzothiazine (**58**) from 2-aminothiophenol and cyanogen-di-*N*-oxide affords[163] also the *amphi* derivative.

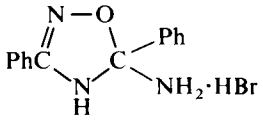
The mass spectra of amidoximes show rather expected patterns. One interesting feature observed in arylamidoximes is the abundant M-17 ion, formed by ejection of a hydroxyl radical, and its daughter ion M-32, deriving by loss of (NH)[199]. An extended degree of randomization of hydrogen in the molecular ion, before fragmentation occurs, cannot be excluded[199]. Furthermore, *O*- and *N*-aroyl arylamidoximes are clearly distinguishable on the basis of their mass spectra, since the *O*-derivatives afford the ion corresponding to the acid $[ArCOOH]^{+\cdot}$, while *N*-substituted compounds yield the amidic fragment $[ArCONH]^{+}$[235]. In addition, the ion $[ArN]^{+\cdot}$, found in all analogous spectra, obviously arises through a Beckmann-type rearrangement, sustained by metastable peaks[236]:



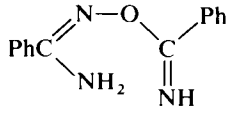
IV. CHEMICAL PROPERTIES AND REACTIONS OF AMIDOXIMES

A. Oxidation

In 1980 Ooi and Wilson reported[237] that treatment of benzamidoxime with *N*-chlorosuccinimide affords the hydrochloride of a base of the formula $C_{14}H_{13}N_3O$, while use of NBS or bromine leads to the corresponding hydrobromide. This base proved to be identical to the one obtained by Stieglitz in 1889[238] from the reaction between benzamidoxime and an alkaline solution of potassium ferricyanide or a solution of benzenediazonium salts. Krümmel also prepared the aforementioned salts by treating benzamidoxime with the respective halogen[239] and proposed structure **85**, while Ooi and Wilson suggested the open-chain tautomer **86**, in good agreement with the spectroscopic characteristics and chemical properties of the compound.

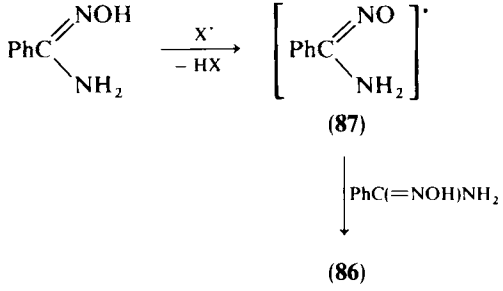


(85)



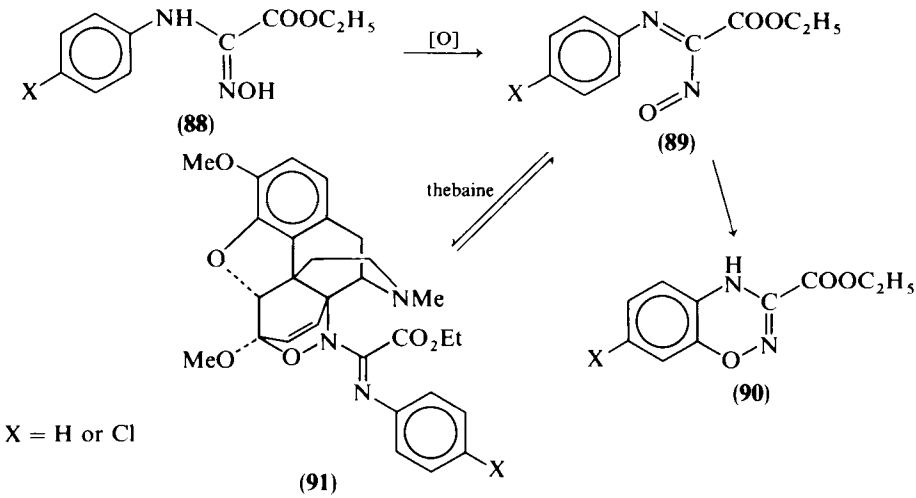
(86)

Although the reaction mechanism is not known, it is likely that an intermediate radical (**87**) is formed[109], which then adds to a second molecule of benzamidoxime; subsequent hydrogen abstraction and loss of hydroxylamine would give **86**.



Nevertheless, it has been reported that direct action of bromine, ferricyanide[239,240] and other mild oxidizing agents[241,242] on benzamidoxime affords the corresponding 3,5-diphenyl-1,2,4-oxadiazole. While it is clear that one nitrogen has been oxidized, no intermediate could be isolated.

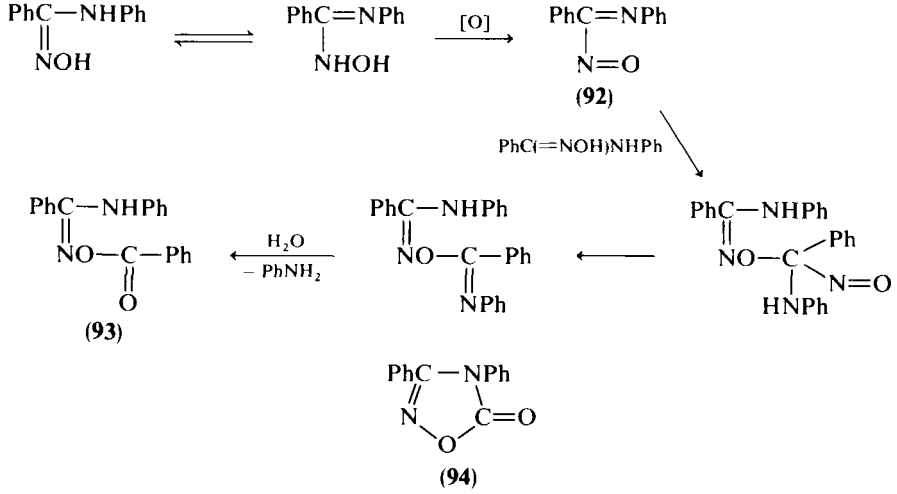
Oxidation of the amidoximes (**88**) with lead tetraacetate yields the nitroso imine **89**, which undergoes spontaneous cyclization to the 1,2,4-benzoxadiazine **90**, but can also be reversibly intercepted in a Diels–Alder reaction with thebaine, giving **91**[242,243].



X = H or Cl

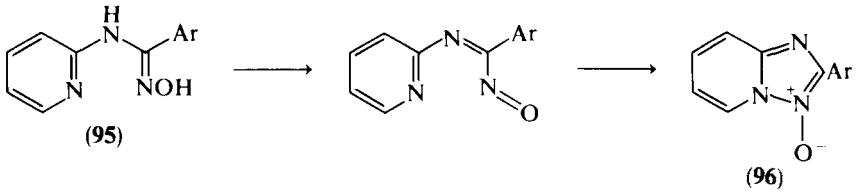
Boyer and Frints[110] invoked the nitroso imine **92** as an intermediate in the oxidation of *N*-phenyl benzamidoxime with lead tetraacetate, NBS or diethyl azodicarboxylate.

Finally, the *O*-benzoylated derivative **93** was obtained with the three oxidants in 15, 13 and 58% yields, respectively, in the last case together with a small amount of 3,4-diphenyl-1,2,4-oxadiazolone-5 (**94**). These data led to the hypothesis that both oxidation and dehydrogenation proceed from the imino–hydroxylamino tautomer of the amidoxime. It should be noted that ethyl hydrazocarboxylate does not interact under comparable conditions with *N*-phenyl benzamidoxime.



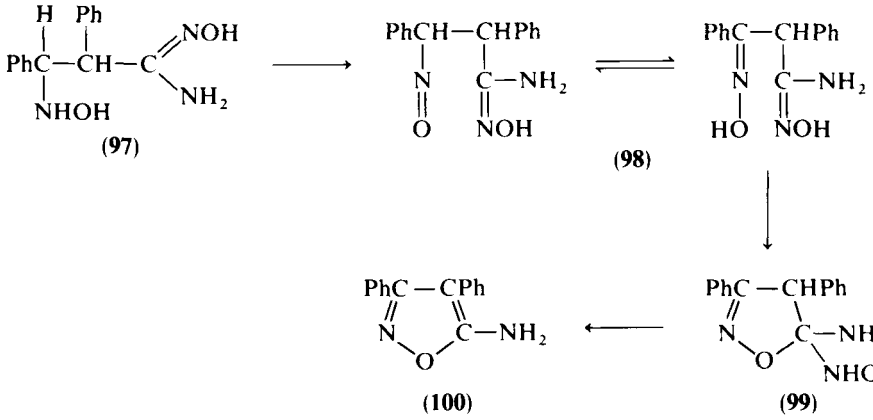
The difference in the behavior of *N*-phenyl benzamidoxime and that of **88** apparently lies in the susceptibility of nitroso imines to nucleophilic attack. Indeed, the *C*-phenyl substituted compounds **92** readily undergo a nucleophilic addition of unchanged benzanilide oxime, whereas the *C*-ethoxycarbonyl derivatives **89** preferentially cyclize[243].

Similarly, the heterocyclic amidoxime (**95**) upon treatment with diethyl azodicarboxylate affords the *N*-oxide **96**[244,245].

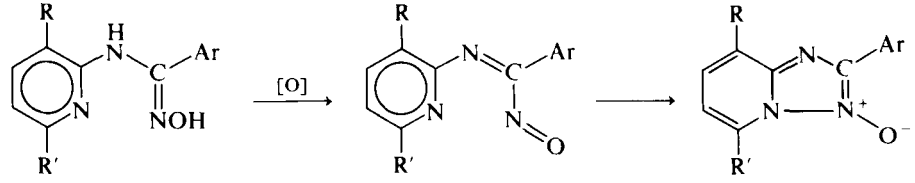


Reaction of 3-hydroxylamino-2,3-diphenyl-propionamidoxime (**97**) with the same reagent produced the heterocycle **100**, via selective cyclization of the intermediate β-nitroso amidoxime **98** to **99** and subsequent elimination of hydroxylamine[75].

Oxidation of the *N*-pyrido amidoximes (**101**) with lead tetraacetate in presence of thebaine at −78 °C results in the oxidation product (**102**), which can afford a Diels–Alder adduct of type (**91**), while by heating in benzene it yields the corresponding 2-aryl-1,2,4-triazolo[1,5-a]pyridine 3-oxide (**103a–d**); the latter is also synthesized in absence of thebaine at −20°C[111,242]. *N*-Aryl-*C*-nitroso imines (**104a–d**), obtained by oxidation of the corresponding amidoximes by lead tetraacetate, may undergo rapid but reversible ring closure to the 1,2,4-oxadiazines (**105a–d**), even if they bear methyl groups at the position to be attacked. While the imines **104** can be intercepted in a Diels–Alder reaction with thebaine, their tautomers (**105**) slowly dimerize[245].

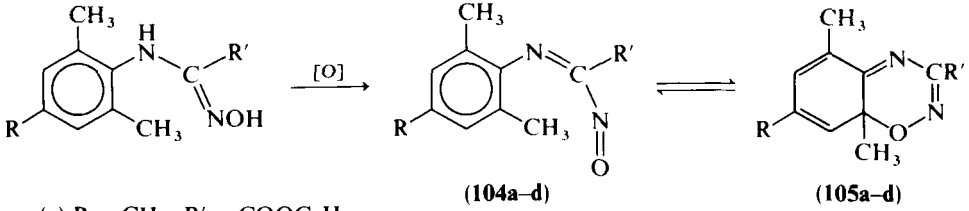


(97) (98) (99) (100)



(101) (102) (103a–d)

(a) R = H, R′ = CH_3, Ar = Ph
(b) R = H, R′ = H, Ar = 4-Tol
(c) R = CH_3, R′ = H, Ar = 4-Tol
(d) R = H, R′ = CH_3, Ar = 4-Tol



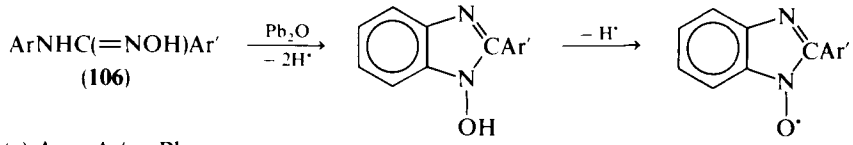
(104a–d) (105a–d)

(a) R = CH_3, R′ = $COOC_2H_5$
(b) R = CH_3, R′ = 4-Tol
(c) R = CH_3, R′ = COPh
(d) R = H, R′ = $COOC_2H_5$

Oxidation of the *N*-arylamidoximes (**106a–c**) yields the benzimidazolyl-N^1-oxides (**107**)[246]. Nevertheless, only the amidoxime *N*-oxyl radicals of type **108** were found to possess marked stability[247a].

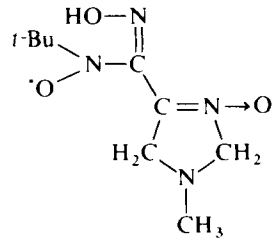
Furthermore, several fully substituted aminoglyoximes were oxidized by potassium ferricyanide[156] or bis(trifluoroacetoxy)iodobenzene[155] to afford the corresponding furoxans (**109**), that were not detected in the case of incomplete N-substitution.

Oxidation of 2,3-bis(hydroxyimino)-1,2,3,4-tetrahydroquinoxaline with bis(trifluoroacetoxy)iodobenzene results in good yields of the furoxano[3,4-*b*]quinoxalines (**110**)[247b]:

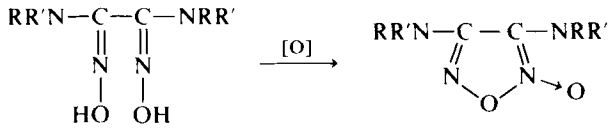


(106) (107)

(a) Ar = Ar′ = Ph
(b) Ar = 3,5-(*t*-Bu$_2$ C$_6$H$_3$, Ar′ = Ph
(c) Ar′ = 2,5-(*t*-Bu)$_2$ C$_6$H$_3$, Ar′ = 2,4,6-(MeO)$_3$C$_6$H$_2$



(108)



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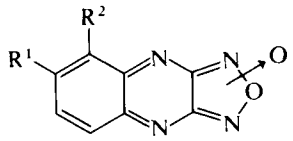


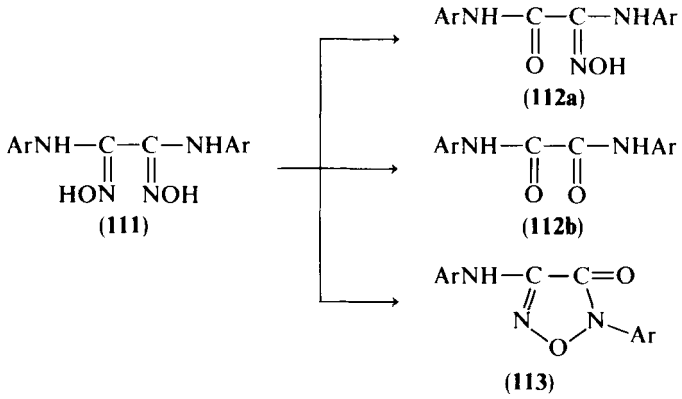
(110a–c)

(a) $R^1 = R^2 = H$
(b) $R^1 = H$, $R^2 = CH_3$
(c) $R^1 R^2 = -(CH{=}CH)_2-$

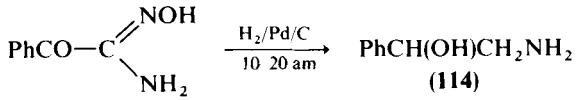
When diamidoximes of the type **111**, with Ar-phenyl or 4-Tol, undergo oxidation by bis(trifluoroacetoxy)iodobenzene, lead tetraacetate, potassium ferricyanide or sodium hypochlorite, the reaction always results in a mixture of the mono amidoxime **112a**, the diamide **112b** and the oxadiazolone **113**, while lead tetraacetate affords in addition also the acetylated derivative of **113**. Since the partially unchanged amidoxime **112a** is easily and almost quantitatively oxidized to the heterocycle **113** by potassium ferricyanide, it may be assumed that the latter is obtained by dehydrogenation of the —NH— and —NOH functions of two adjacent amidoxime moieties[248].

B. Reduction

The reduction products of amidoximes closely depend on the reactants used. Thus reduction of benzamidoxime with sodium amalgam yields about 10% each of ammonia and benzaldoxime, with most of the amidoxime remaining unchanged[3,249]. Phenylglyoxal amidoxime has been reduced to phenyl ethanolamine (**114**)[250] by absorbing four moles of hydrogen.



(111) → (112a), (112b), (113)



(114)

In contrast, N-substituted amidoximes took up only three moles of hydrogen, to yield compounds of as yet unestablished structures[250]. Hydrogenation of the *O*-acetylated amidoxime **115** with $LiAlH_4$ gave only a deacetylated derivative[251].

$$PhCO{-}C(=NOCOMe){-}NHCHMe_2$$

(115)

Aliphatic and aromatic amidines bearing an aryl or alkylaminoalkyl N-substituent can be synthesized by reducing the corresponding amidoximes in the presence of Raney-nickel[198,252,253] or of 5% Rd/alumina[159], as well as with phenyldichlorophosphine[254]. The reaction in the case of some diamidoximes yields diamidines[252], and the polarographic and electrochemical reduction of amidoximes may follow similar pathways[255,256]. The acetylation of benzamidoxime with thioacetic acid led to benzamidine probably by action of the hydrogen sulfide produced during the reaction[257].

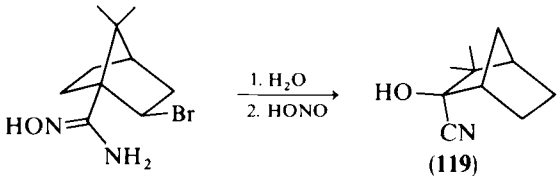
2-Oximino-1,2,3,4-tetrahydroquinoxaline gives by treatment with palladium/charcoal in absolute ethanol 2-aminoquinoxaline in 82% yield[255]. Zinc in hydrochloric acid does not reduce the amidoxime function, affording the *p*-amino derivative when acting upon *p*-nitrobenzamidoxime[17b].

C. Action of Nitrous Acid

Tiemann and Krüger already observed[3] that benzamidoxime yields benzamide and nitrogen oxide when treated with nitrous acid. This analogy to hydroxylamine allowed the identification of the oximino function present in the then unknown compound. In a similar manner, acetamidoxime[258] as well as other *N*,*N*-disubstituted amidoximes (**116**; R′ = alkyl, carboxymethyl, aryl) give with nitrous acid the corresponding amides **117**[174,259].

$$\underset{\textbf{(116)}}{R'C(=NOH)NR_2\cdot HCl} + NaNO_2 \longrightarrow \underset{\textbf{(117)}}{R'CONR_2} + N_2O + H_2O + NaCl$$

Strangely, the amidoxime (**118**), if treated at first with hot water and afterwards with nitrous acid at 0 °C, undergoes a transformation to compound **119**[138].

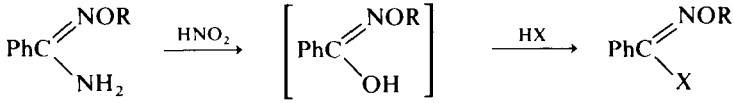


(118) (119)

Action of nitrous acid on α-hydroxyimino-amidoximes (**120**)[260] affords α-hydroxyimino-amides (**121**) in yields reaching 75%.

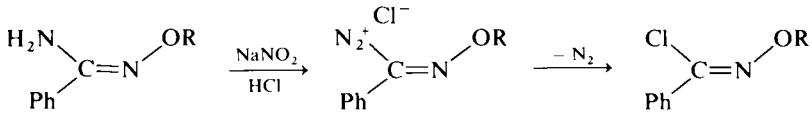
(120) (121)

The reaction of *O*-alkylated amidoximes (**122**) with nitrous acid proceeds under nitrogen evolution, showing the presence of the amino group in these compounds[258]. Though the intermediate hydroximic acid (**123**) could not be isolated, an excess of hydrohalic acid yielded almost quantitatively the corresponding halide (**124**)[3,105,261–269].



(122) (123) (124)

Interestingly, the formation of **125** is stereospecific and leads to the (*Z*) isomer, possibly owing to attack by the nucleophile on a nonlinear nitrilium ion before the latter reaches the normal equilibrium state[270].



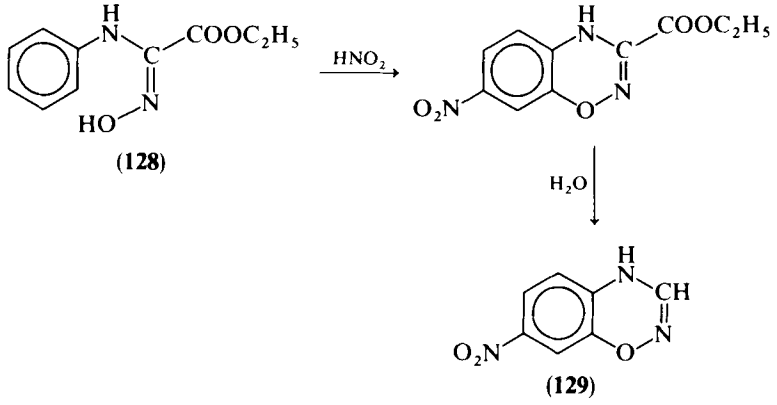
(122) (125)

In case the reaction of nitrous acid with *O*-alkylated amidoximes is carried out in the presence of sulfuric or acetic acid, compounds of the types **126**[176,267–270] and **127**[269–271] are formed.

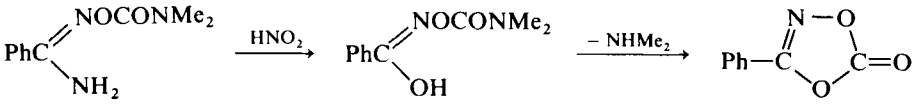
(126) (127)

Treatment of *N*-phenylhydroximic acid ethyl ester (**128**) with nitrous acid yielded 6-nitro-1,3,4-benzoxadiazine (**129**)[272,273].

Furthermore, nitrous acid reacts with *O*-dimethylcarbamyl benzamidoxime (**130**) to afford small amounts of 5-phenyl-1,3,4-dioxazol-2-one (**132**), probably by intramolecular attack by the hydroxyl of the intermediate hydroximic acid (**131**) on the amidic carbonyl function and elimination of dimethylamine[120].

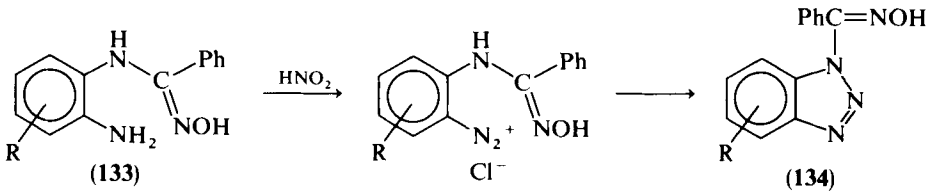


(128) (129)



(130) (131) (132)

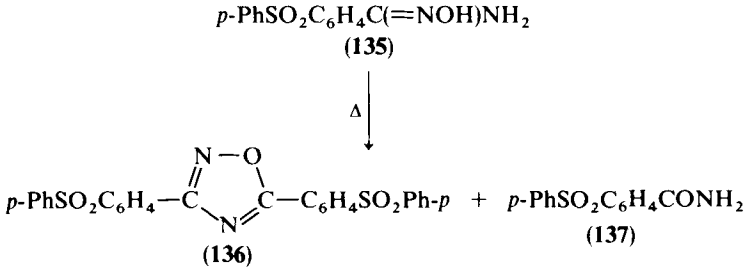
Finally, action of nitrous acid on *N*-(2-aminoaryl)benzamidoximes of the type **133** results in the 1-benzo-hydroximoyl-benzotriazoles (**134**) through diazotisation of the *o*-amino group[147].



(133) (134)

D. Thermal Decomposition

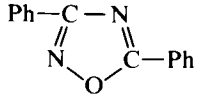
Although amidoximes usually decompose when heated to temperatures approaching their melting point, benzamidoxime (mp 80 °C) proved to be stable up to 170 °C, yielding then various primary and secondary products, such as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, 3,5-diphenyl-1,2,4-oxadiazole, 3,5-diphenyl-1,2,4-triazole and 2,4,6-triphenyl-1,3,5-triazine[274]. Thermal decomposition of *p*-phenylsulfonyl-benza-



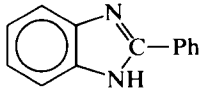
(135) (136) (137)

midoxime (**135**) affords 3,5-bis(*p*-benzenesulfonylphenyl)-1,2,4-oxadiazole (**136**) along with 4-phenylsulfonylbenzamide (**137**)[274].

Heating benzamidoxime in low-molecular-weight fatty acids produces 3,5-diphenyl-1,2,4-oxadiazole (**138**)[275], whereas pyrolysis of benzanilide oxime at 165–200 °C yields a small amount of 2-phenylbenzimidazole (**139**)[123].



(**138**)



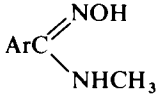
(**139**)

Several amidoxime esters are thermally cyclized to 3,5-disubstituted 1,2,4-oxadiazoles.

In contrast to their nonhalogenated analogs, perfluoroalkyl amidoximes appear to be quite stable towards heating; indeed, perfluoropropionamidoxime decomposes only slowly in air at 170 °C, requiring 24 hours for a 60% disappearance of the sample, yielding only about 40% of an identified product, i.e. 3,5-bis(perfluoroethyl)-1,2,4-oxadiazole. Nevertheless, pyrolysis at 250 °C resulted in etching of the apparatus, indicating rupture of the C—F bond in the fluoroalkyl group[77].

E. Hydrolysis

Although most amidoximes form soluble salts with dilute mineral acids and alkalies[276], they are completely hydrolyzed if heated in the same media[277,278], giving hydroxylamine and amides, which are further hydrolyzed to the corresponding acids under more drastic conditions. Thus, heating ammonium hydroxide and benzamidoxime in a pressure bottle at 200 °C for 9 hours affords benzamide and ammonium benzoate[17a,278], while perfluorobutyramide is obtained by heating the corresponding amidoxime in dilute alkaline solution[77]. Oxamide dioxime[80,279] gives oxalic acid, ammonia and hydroxylamine by treatment with concentrated hydrochloric acid. Furthermore, polyacrylamidoximes of low molecular weight have been hydrolyzed in aqueous solutions at various pH values[98,280]. In general, suitable selection of the experimental conditions permits limitation of the reaction to the amino group or its extension to both the amino and the hydroxyimino moieties. In the first case, partial formation of hydroxamic acid functions occurs, which are further hydrolyzed by strong acids, yielding a polymer containing side by side amide, carboxylic acid and hydroxamic acid substituents[98]. Similarly, heating of *N*-3,4-trimethylbenzamidoxime (**140**) with 10% aqueous hydrochloric acid at 80 °C gave the benzoic acid **141**, while keeping the amidoxime at 40 °C in a 5% hydrochloric acid solution resulted in the benzamide **142**. Alkaline hydrolysis of **140** affords both **141** and **142**[116].



(**140**)

ArCOOH (**141**)

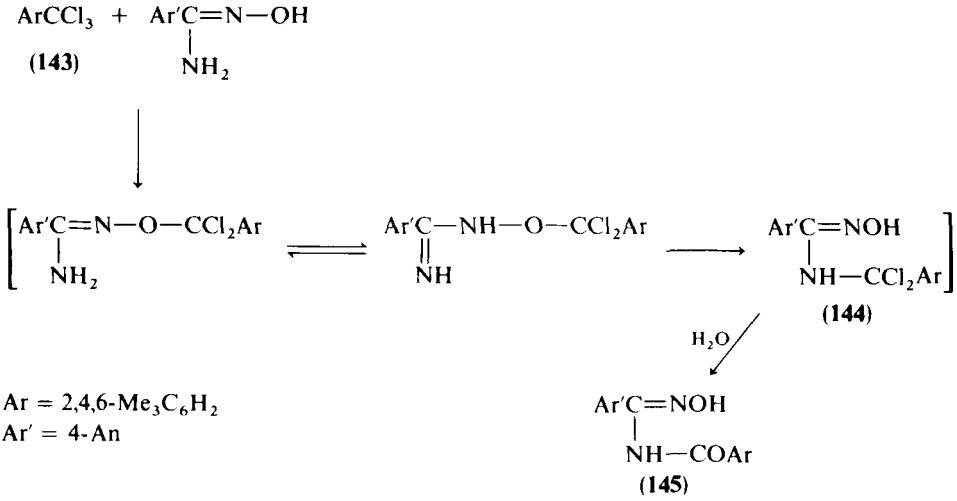
$ArCONH_2$ (**142**)

Ar = 3,4-$Me_2C_6H_3$

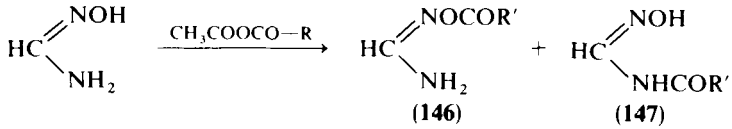
F. N-Substitution

N-alkylation, arylation or acylation of the amino function of amidoximes constitutes an important synthetic pathway, although several methods of N-substitution[35,103,113,120,122,123,149,151–156,182] result simultaneously also in O-substitution[116].

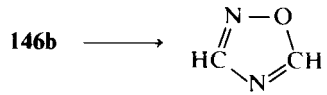
Heating the hydrochlorides of acetamidoxime or of formamidoxime at 80–90 °C in the presence of aniline affords the corresponding *N*-phenyl derivatives[258,281], whereas interaction of the trichloromethylarene (**143**) with an arylamidoxime in boiling benzene and further hydrolysis leads to the *N*-acylated amidoxime (**145**), failing to undergo cyclization into the 1,2,4-oxadiazole[208].



Acylation of formamidoxime with acetic, acetic-propionic[200] or acetic-formic anhydride[282] yielded mainly the *O*-acyl-formamidoxime (**146**), undergoing in the last case cyclization into the unsubstituted 1,2,4-oxadiazole (**148b**), along with a small amount of the *N*-acylated derivative **147**. It should be pointed out that while **143** causes *N*-acylation of the arylamidoxime, the common acylating agents attack the hydroxyimino oxygen, as will be discussed further on.

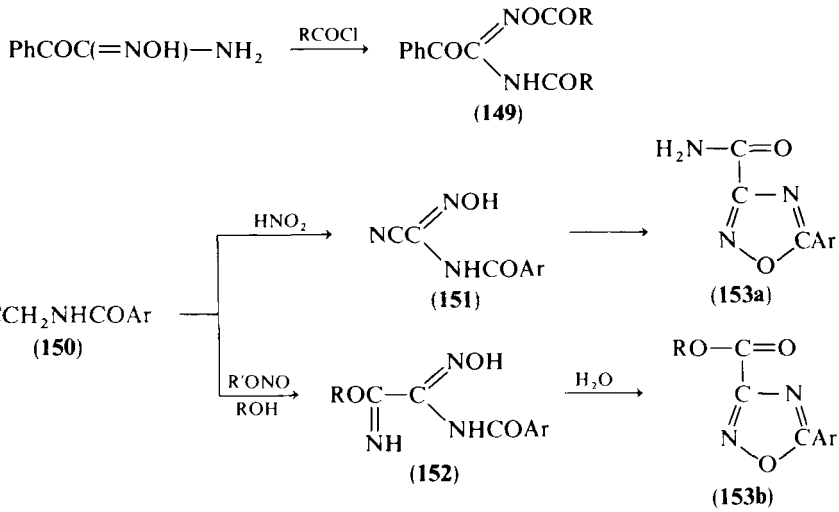


(**a**) R = Me, Et; R′ = Me
(**b**) R = H; R′ = H



Treatment of phenyl glyoxalamidoxime with aliphatic acid chlorides results in the *N*,*O*-diacylated derivative **149**[283].

N-Acyl substituted amidoximes of the types **151** and **152** are intermediates in the nitrosation of (acylamino)acetonitriles (**150**) to yield 1,2,4-oxadiazoles (**153a,b**), with nitrous acid or alkyl nitrites[284,285].

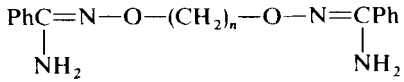


G. O-Alkylation

O-Alkylation of amidoximes proceeds mainly[3,116,233,263,286,287] by action of aliphatic halogen compounds on their sodium salts[266]. A suspension of sodium hydride in DMF was also used for preparing the sodium salt of 2,6-dichlorophenyl acetamidoxime, further O-methylated with methyl iodide[7].

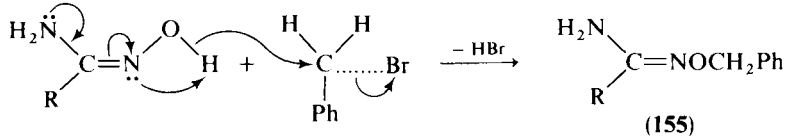
Treatment of 4-methylbenzamidoxime with EtOH/EtONa and then with 1-chloro-2,4-dinitro-benzene yields the *O*-(2,4-dinitrophenyl)-4-methylbenzamidoxime[243].

Reaction of benzamidoximes with α,ω-dihalides leads to the *O,O'*-derivatives **154**[288,289].



(154)

While (*Z*) *O*-(*p*-nitrobenzyl)morpholino-*p*-nitrobenzamidoxime was synthesized from the corresponding oxime and *p*-nitrobenzyl bromide in the presence of sodium ethoxide[290], it was reported that benzyl bromide reacts rapidly with amidoximes resulting in *O*-alkylated products of the type **155**, the high reactivity being attributed to a stabilization of the transition state by intramolecular base catalysis[232].

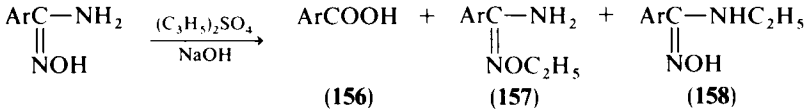


(155)

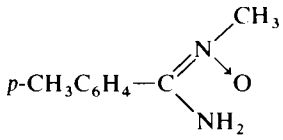
O-Methyl derivatives may be prepared by action of methyl iodide on amidoxime sodium salts[7], though treatment of amidoximes in the neutral form by methyl sulfate[230,261,270,291,292] has found wider application. Furthermore, adding ethyl sulfate to a

boiling methanol solution of 3,4-dimethylbenzamidoxime and 20% aqueous sodium hydroxide yields 16% of the acid **156**, 64% of the *O*-ethyl derivative **157** and 7% of the N-substituted one **158**, the relation becoming 60% of **156** and 16% of **157** at pH 6.6–7[116].

N-Alkylated compounds such as **158** do not constitute the sole by-products of the method, since the corresponding nitrones **159** have been identified as well in a different case[230].

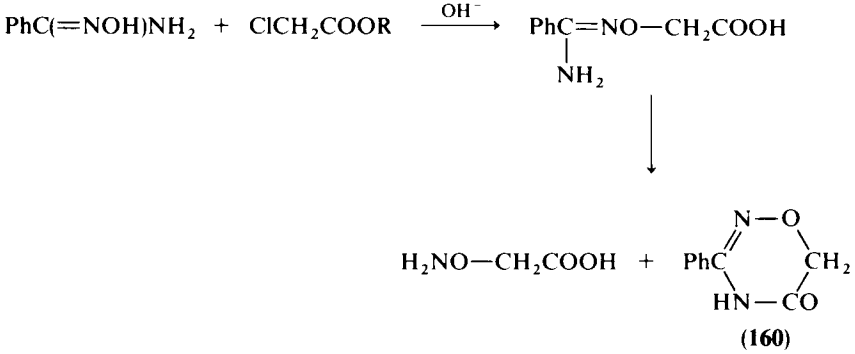


Ar = 3,4-$Me_2C_6H_3$

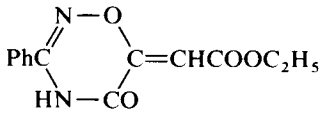


(159)

α-Halogenated carboxylic esters proved useful for the synthesis of α-hydroxylamino derivatives of carboxylic acids, e.g. acetic, propionic, butyric and isobutyric, the corresponding 6-substituted-3-phenyl-5,6-dihydro-1,2,4-oxadiazine-5-ones (**160**) being always present as well[293–295], and even constituting the sole product (**161**) when ethyl chlorofumarate reacts with benzo- or α-phenylacetamidoxime[296].

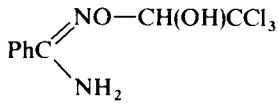


(160)



(161)

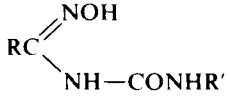
Finally, *O*-alkylation of amidoximes also occurs as the first step of their reaction with aldehydes or with dimethyl acetylene dicarboxylate (see Sections IV.M and IV.R). In some cases the products of the primary reaction were stable enough to be isolated, such as *O*-(2,2,2-trichloro-1-hydroxyethyl)benzamidoxime (**162**), prepared from benzamidoxime and chloral[297].



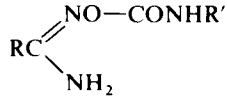
(162)

H. Action of Isocyanates, Isothiocyanates and Carbonyl Chlorides

Tiemann assumed that the reaction of benzamidoxime with cyanic acid and phenyl isocyanate gave products with an ureide or phenylureide oxime structure (**163**) respectively, rejecting without any argumentation the isomeric carbamates (**164**)[277,298].

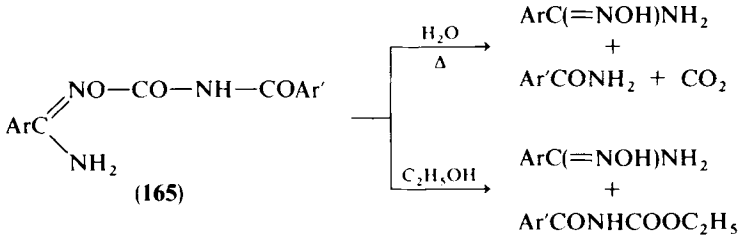


(163)



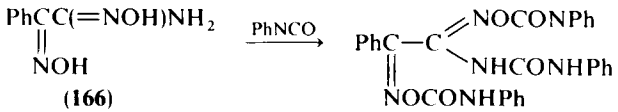
(164)

This latter structure proved nevertheless to be the correct one, and the same *O*-carbamoyl derivatives (**164**) were also obtained[120] by a treatment of the parent amidoximes with N-substituted carbamyl chlorides. The behavior of 2-hydroxyiminopiperidine- and 3,5,5-trimethyl-2-(n-butylimino)-thiazolidine-4-oxime towards phenyl[299] or methyl isocyanate[113], respectively, is similar, while action of acyl isocyanates on amidoximes at 0–20°C in inert solvents yields the corresponding *O*-acyl-carbamoyl-substituted compounds (**165**), undergoing easily hydrolysis when heated in the presence of ethanol or water[300].



(165)

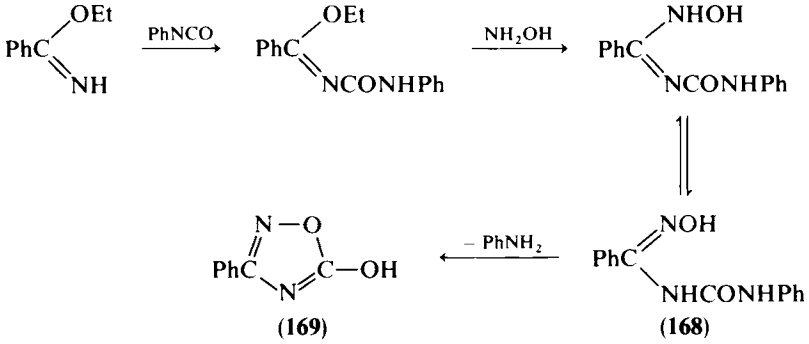
N-Substituted carbamates are obtained from *O*-alkyl-amidoximes with isocyanates[120,267,291], whereas an excess in phenylisocyanate results in a triple substitution, e.g. phenylaminoglyoxime (**166**) yielding compound **167**[120].



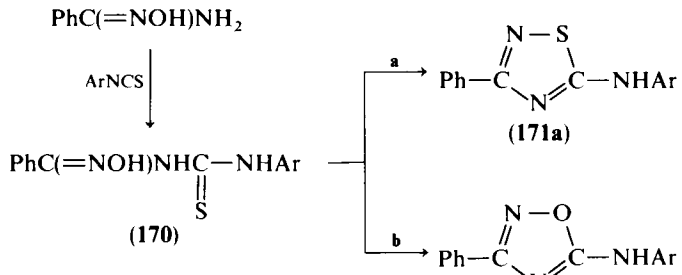
(166)

(167)

In the following case, an ureide oxime (**168**) is indirectly produced and further cyclized to the corresponding oxadiazole (**169**)[120]:



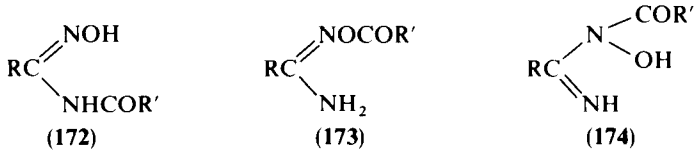
Equimolar amounts of isothiocyanates and amidoximes yield, at room temperature and under evolution of hydrogen sulfide, thiourea oximes, such as those obtained from benzamidoxime and allylisothiocyanate[301] or from 2-hydroxyiminopiperidine and phenyl isothiocyanate[299]. The action of the latter on benzamidoxime has been thoroughly studied[28,263,301] and it was found that a twofold excess of the isothiocyanate results in cyclization of the thiocarbamate (**170a**) into the 3-phenyl-5-anilino-1,2,4-thiadiazole (**171a**)[301], autoxidative phenomena probably taking place as well, since free sulfur is also produced[302]. It is interesting to note that, under similar conditions, *p*-tolyl isothiocyanate forms the oxadiazole **171b**[301].



(**a**) Ar = Ph
(**b**) Ar = 4-Tol

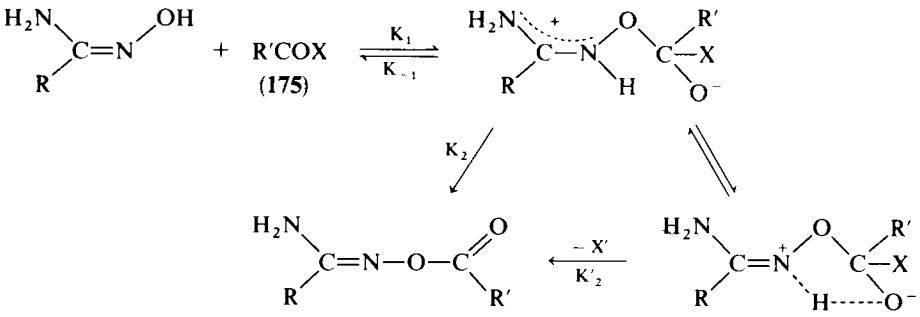
I. O-Acylation

Theoretically, amidoximes can undergo three types of acylation, affording the N- (**172**) or O- (**173**) derivatives of the amino–hydroxyimino tautomer, or bearing the imino–hydroxyamino structure (**174**). In fact acylation almost invariably occurs on the oxygen,



unless the hydroxyimino function is substituted, with the exception of formamidoxime, yielding both isomers **146** and **147**[200]. Treatment of amidoximes with trichloromethyl arenes (**143**)[208] and nitrosation of (acylamino)acetonitriles (**150**)[284,285] also constitute two special cases leading to *N*-acyl derivatives. N-acylation claimed in an early work[303] for halogenated acetamidoximes proved erroneous on reinvestigation[121]. Furthermore, the acidic behavior of the compounds disappears in the presence of acylating agents[1], while in their spectra only the amino function absorption remains[200].

Amidoximes are highly reactive towards 4-nitrophenyl acetate, benzoyl fluoride or ethyl chloroformate (**175a–c**) in the pH range 6–9, the reactivity depending on the lability of the leaving group[304]. Two alternative reaction mechanisms can be envisaged, since the hydroxyimino nitrogen is probably more basic than the amino function, and since intramolecular catalysis leading to high reactivity in neutral solution may involve a proton migration.

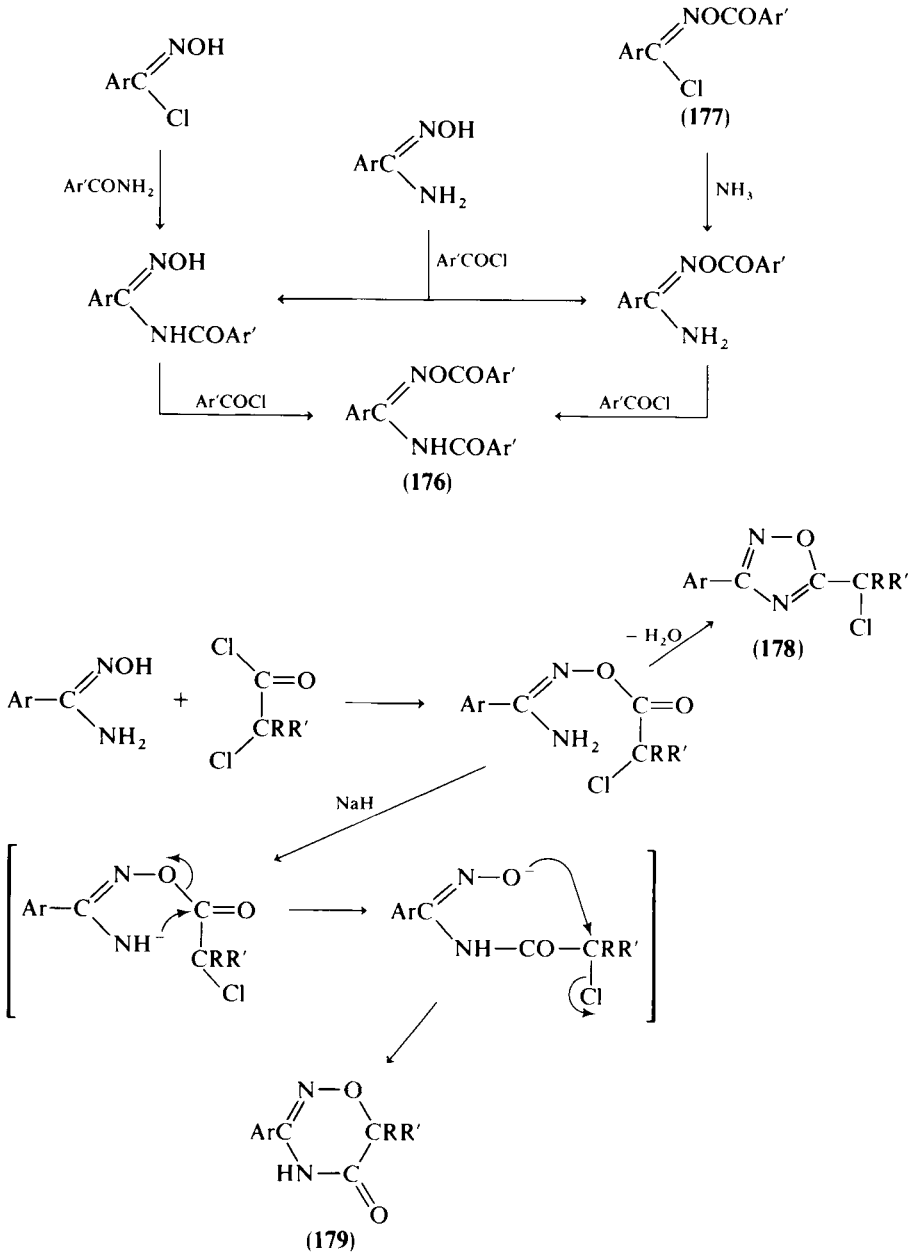


(**a**) R′ = CH_3, X = 4-$O_2NC_6H_4O$—
(**b**) R′ = Ph, X = F
(**c**) R′ = C_2H_5O, X = Cl

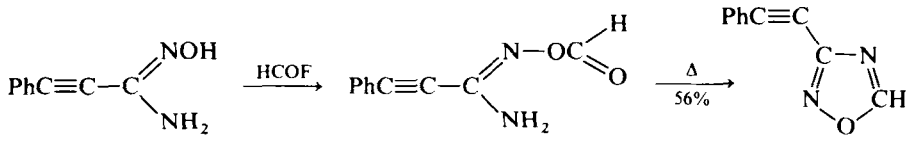
Although *O*-benzoyl amidoximes are formed by benzoyl chloride and most amidoximes[88], formamidoxime yields only dibenzhydroxamic acid[2], the *O*-benzoyl derivatives being only obtained with benzoic anhydride[200]. Furthermore, 2- or 4-methoxybenzamidoximes undergo aroylation with benzoyl and 4-nitrobenzoyl chloride affording mixtures of O- and N-substituted products. These are easily distinguishable by their IR spectra, since the former display a carbonyl absorption at 1720–1740 cm^{-1}, whereas the latter absorb at 1660–1670 cm^{-1}. Both derivatives yield the bis(aroyl)arylamidoximes (**176**) with an excess of aroyl chloride[235]. *O*-Benzoyl benzamidoxime has been synthesized unequivocally by action of ammonia on the hydroximoyl chloride (**177**), while treatment of benzamide with benzhydroximoyl chloride in the presence of sodium ethoxide results in pure *N*-aroyl benzamidoximes[235,306].

These results suggest that the O-acylated compound is the predominant initial product, and no evidence has been found for an oxygen-to-nitrogen aroyl migration[305]. Furthermore, chloroacetyl or β-chloropropionyl chlorides also give the O-derivatives of type **173**[24,307], and α-chloroacid chlorides yield under thermal conditions 5-(1-chloroalkyl)-1,2,4-oxadiazoles (**178**). Nevertheless, in the presence of a strong base an oxygen-to-nitrogen acyl migration takes place, leading to a convenient synthesis of the 4*H*-1,2,4-oxadiazin-5-(6*H*)-ones (**179**)[308].

Acyl chlorides with amidoximes in pyridine give a vividly exothermic reaction, sometimes resulting in immediate ring closure to the 1,2,4-oxadiazole[309]. Similarly,

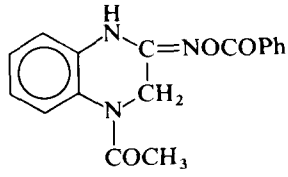


formyl fluoride with phenylpropiolamide oxime at −78°C in dry ether and in the presence of triethylamine gives almost quantitatively the O-formylated amidoxime (**180**), which may be cyclized to the 1,2,4-oxadiazole (**181**) by reflux in anhydrous ethanol[27].



(180) (181)

If 2-hydroxyimino-1,2,3,4-tetrahydroquinoxaline is treated with benzoyl chloride and acetic anhydride[310] both the hydroxyimino function and the heterocyclic nitrogen undergo acylation to compound **182**. Furthermore, the *O*-(5-nitro-2-furoyl)amidoximes (**183**), bearing a sulfonamide moiety and known as active antibacterial and antifungal agents, were prepared from equimolar amounts of 5-nitro-2-furoyl chloride and the corresponding amidoxime[311].



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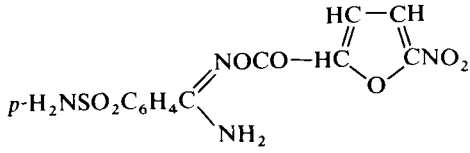
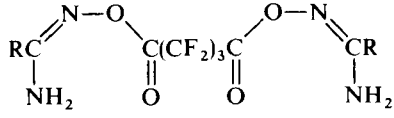


(183)

O,O'-hexafluoroglutaryl di(pentadecafluoro-n-octanamidoxime) (R = C_7F_{15}) and *O,O'*-hexafluoroglutaryl di(arylamidoximes) (R = Aryl) (**184**) are prepared from hexafluoroglutaryl chloride and the corresponding amidoximes[312]. Oxalyl chloride has also been successfully used as an acylating agent for perfluorobutyramidoxime in ether at 0 °C, resulting in 75% of the high-melting product **185**; the same amidoxime upon reaction with phosgene gave the *O*-chloroformyl derivative **186**[77].



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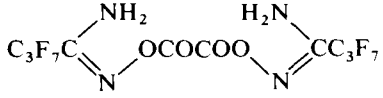

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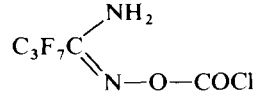
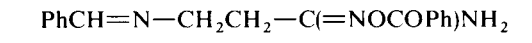


(186)

Perfluorinated alkyl or alkyl ether 1,2,4-oxadiazoles are obtained by heating up to 100 °C the corresponding alkyl or alkyl ether imidoyl amidoximes *in vacuo* in the

presence of an acid compound able to accept ammonia, the procedure being used for either polymeric or nonpolymeric amidoximes[313].

O-acylamidoximes have been synthesized on treatment of the parent compounds either with acyl chlorides or with carboxylic acid anhydrides[23,200]. Thus, 3-benzylideneaminopropanamidoxime undergoes O-substitution to **187** by an equimolar amount of benzoic acid anhydride, whereas the same reagent results in the *N,O*-dibenzoylated derivative **188** of the analogous 3-cinnamylideneaminopropanamidoxime[209].



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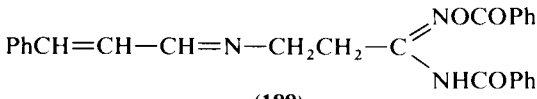
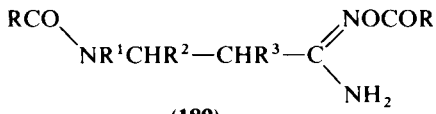


(188)

Similarly, 3-aminopropanamidoximes with a threefold amount of benzoic or acetic anhydride yielded the N^3-,*O*-bis-acylated derivatives **189**[10].

2-Aminobenzamidoxime with two moles of benzoic anhydride yields the *O*-benzoyl derivative **190**, while three equivalents of acetic anhydride lead to the *o*-acetylamino-*O*-acetyl benzamidoxime (**191**)[314].

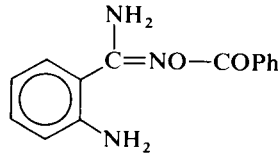
Similarly, the acetylation product of 2-styryl-4-hydroxyimino-1,2,3,4-tetrahydroquinazoline depends on the ratio of the reactants, being the *O*-acetyl derivative **192** if 1.5 equivalents of acetic anhydride are used, or the diacetylated compound **193** when the ratio used is 1:3[315].



(189)

$R = CH_3$, Ph $\quad R^2$ = H, CH_3, Ph

R^1 = H, CH_3, C_4H_9 $\quad R^3$ = H, CH_3



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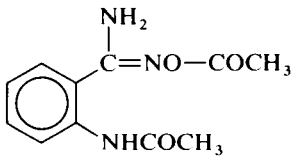

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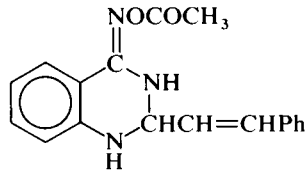

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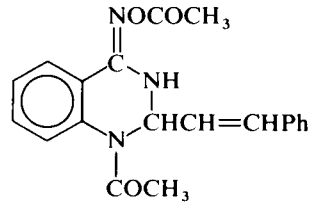
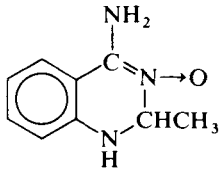


(193)

The analogous 2-methyl-4-acetoxyimino-3,4-dihydroquinazoline (**195**) results from the action of acetic anhydride on 2-methyl-4-amino-1,2-dihydroquinazoline-*N*-oxide (**194**) via initial N^3-acetylation, ring opening and recyclization[315].

Acylation or benzoylation of D,L-α-amino-β-phenylpropionamidoxime also gave the *O,N*-diacyl derivatives **196**[52].

2-Hydroxyiminopiperidine reacts exothermically with acetic anhydride to 2-acetoxyiminopiperidine[299]. Furthermore, 2-hydroxyimino-1,2,3,4-tetrahydroquinoxaline (**197**) in boiling acetic anhydride yields the 2-acetaminoquinoxaline (**199**). This unusual



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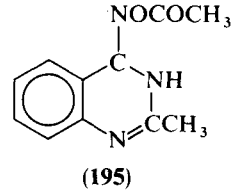

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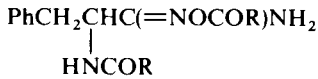
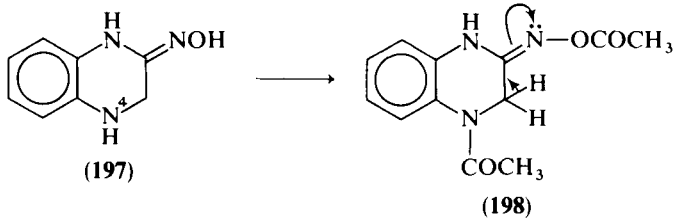


(196)

R = CH_3, Ph

aromatization proceeds via the N^4-, *O*-diacetyl derivative **198** by a synchronous elimination of the N^4-acetyl and acetoxy groups as acetic anhydride[255]:



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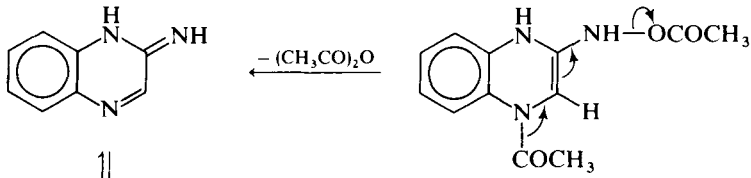
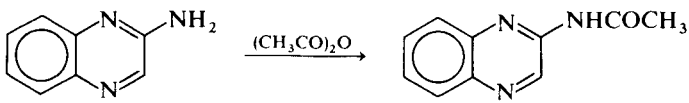
(198)





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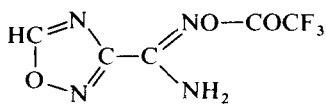
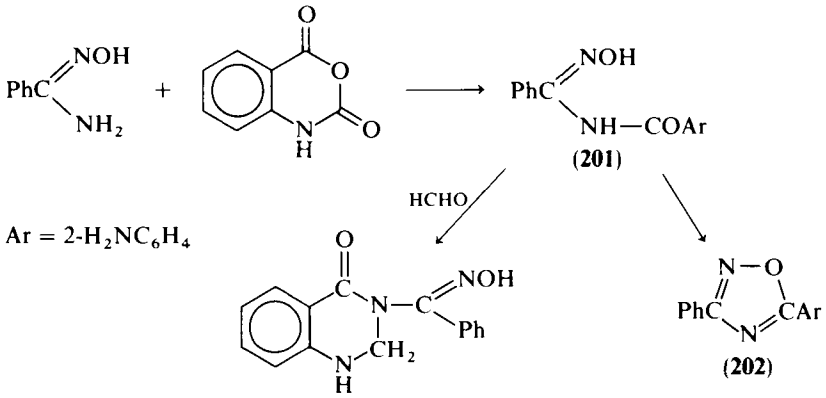


(200)

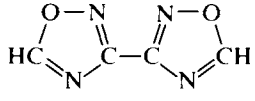
Treatment of 1,2,4-oxadiazole-3-carboxamidoxime with trifluoroacetic anhydride at 0 °C in trifluoroacetic acid yields 65% of the expected *O*-acylamide oxime (**200**)[12].

Nevertheless, benzamidoxime failed to undergo O-acylation when treated with isatoic anhydride, yielding instead the open-chain amide (**201**), that affords by ring closure 5-(2-aminophenyl)-3-phenyl-1,2,4-oxadiazole (**202**). Condensation of the amide **201** with formaldehyde in methanol resulted in 2,3-dihydro-3-(hydroxyimino-benzyl)-4(1*H*)quinazolinone (**203**)[310]. Reaction of 2,4-dichlorobenzamidoxime with an equimolar amount of the same anhydride in boiling ethanol led directly to the corresponding oxadiazole[317].



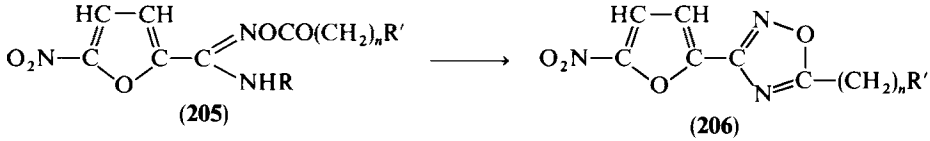
Mixed carboxylic and carboxylic–carbonic anhydrides have also been used as acylating agents. Thus, treatment of benzamidoxime and acetamidoxime with acetic-ethylcarbonic anhydride leads quantitatively to O-acetylation[318], whereas formamidoxime yields, as already mentioned, both acyl derivatives **146** and **147**[200], the former undergoing cyclization into the oxadiazole **148** if acetic-formic anhydride is used as a formylating agent[282,319]. With oxamide dioxime the same agent yields the diformyl ester[320].

O-Acyl derivatives of amidoximes may also be synthesized in fair yields with carboxylic acids in the presence of a highly efficient dehydrating reagent, such as *N,N'*-dicyclohexylcarbodiimide[321,322] or phosphorous pentoxide[77], but there are not many examples for this reaction without a dehydrating agent. Nevertheless, 4-nitrobenzamidoxime undergoes acylation with boiling glacial acetic acid, and 4-sulfamidobenzamidoxime with chloroacetic acid[66]. Unsubstituted benzamidoxime affords by treatment with benzoic acid 3,5-diphenyl-1,2,4-oxadiazole, claimed to be the dehydration product of its benzoylated derivative. It is, however, rather doubtful that a normal acylation occurs, since the same 5-phenylated product is obtained whether acetic, propionic or butyric acid are the acylating agents[264,275]; therefore this cyclization has been interpreted[239] as an autoxidation of the amidoxime. Thioacetic acid can acylate benzamidoxime at room temperature with evolution of hydrogen sulfide, the reaction taking place also in water[323]. In most cases O-acylation takes place and the nonisolated derivatives are immediately converted into the corresponding heterocycles. Thus, 3,3'-bi-(1,2,4-)-oxadiazole (**204**) has been prepared from oxamide dioxime and formic acid in the presence of boron trifluoride[320].



(**204**)

Acylation occurs also by dropping into an acetone solution of 5-nitro-2-furylamidoxime the filtrate resulting from dissolving an *N*-acyl-amino acid and triethylamine in dry acetone, adding one equivalent of ethyl chloroformate and removing the amine salt. The O-acylated derivative (**205**) is then thermally cyclized to the respective oxadiazole (**206**)[324].

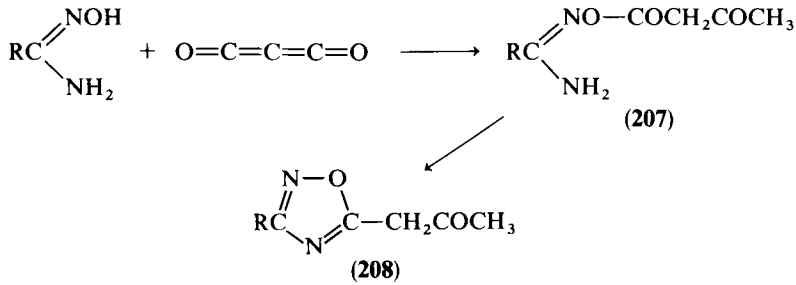


(**205**) (**206**)

R = H, CH_3
R′ = CH_3, CH_2Cl, Ph

n = 1,2,3,5

Carboxylic acid esters with amidoximes afford directly the corresponding 1,2,4-oxadiazoles and shall be discussed later. Carboxylic acid azides readily react at room temperature with amidoximes, benzoyl azide constituting the sole O-benzoylating agent for formamidoxime[200]. Ketene also instantaneously attacks benzamidoxime in inert solvents[195,200] to yield quantitatively the respective O-acetylated product, while diketene affords the *O*-acylacetyl derivatives (**207**), which are further transformed into 5-acetonyl-3-alkyl (or aryl)-1,2,4-oxadiazoles (**208**)[325,326].

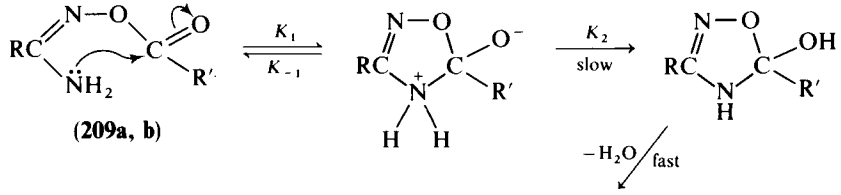


(**207**)

(**208**)

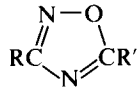
The most important chemical properties of O-acylated amidoximes are their readiness to hydrolyze into the parent compounds, as well as their ability to cyclize into the corresponding 3,5-disubstituted 1,2,4-oxadiazoles[327]. It has already been pointed out[284–286] that several *O*-acyl derivatives immediately undergo ring closure. Nevertheless, the dehydration is usually accomplished under drastic conditions, i.e. by heating the compounds either in the solid state or dissolved in glacial acetic acid, acetic anhydride, water, dilute sodium hydroxide or sulfuric acid[27,120,287,301,324]. However, if the acylation is carried out above 100 °C, spontaneous formation of the heterocycle occurs[309]. A systematic study, to make clear whether this reaction constitutes a general and versatile synthetic approach would be most worthwhile.

Ooi and Wilson[237] studied the thermal cyclization of O-acylated amidoximes (**209a,b**) into oxadiazoles (**210a,b**) at 100–145°C, and proposed the mechanism below. In accordance with it, a small kinetic isotope effect (K_H/K_D) has been found for the cyclization of *N*,*N*-dideutero-*O*-acetyl benzamidoxime, while the rate-determining step is the proton transfer occurring after the heterocycle was formed. The reaction can also take place at ambient temperature by treating **209** in deuterochloroform with sodium hydride, through an attack of the amide ion on the carbonyl carbon of the acyl group[237].



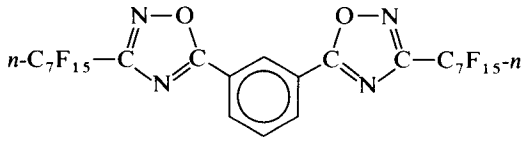
(209a, b)

(a) R = Ph, R′ = CH_3
(b) R = CH_3, R′ = Ph



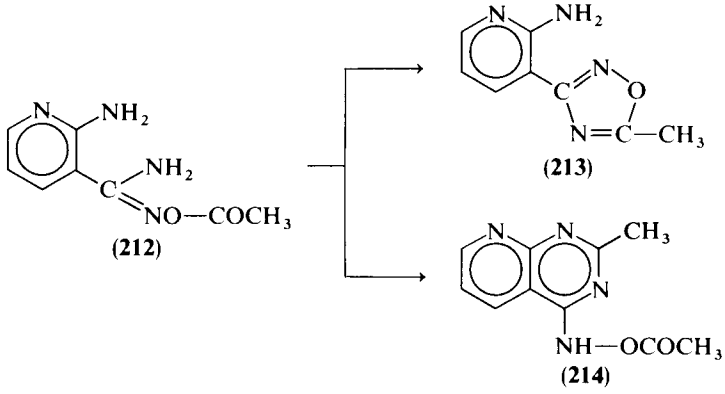
(210a,b)

The antitussive 3-(2,2-diphenylethyl)-5-(β-piperidinoethyl)-1,2,4-oxadiazole was prepared[328] from 3,3-diphenylpropionylamidoxime with ethyl 3-piperidinopropionate in the presence of sodium ethoxide or with 3-piperidinopropionyl chloride in pyridine. Prolonged action of diphenyl-isophthalate on pentadecafluoro-*n*-octanamidoxime in DMF at 130°C affords low yields of 1,3-bis-(3-perfluoro-n-heptyl-1,2,4-oxadiazol-5-yl) benzene (**211**)[312].



(211)

5-Substituted 3-(2-aminophenyl or 2-aminoheteroaryl)-1,2,4-oxadiazoles were obtained by refluxing the appropriate amidoxime and an ethyl carboxylate in EtOH/EtONa[8]. Similarly, heating in water the O-acetylated amidoxime (**212**) yields 2-amino-3-(5′-methyl-1′,2′,4′-oxadiazolyl-3′)pyridine (**213**), while interaction of the same derivative (**212**) or its parent amidoxime with acetic anhydride results in 26% of 4-(acetoxyamino)-2-methylpyrido[2,3-*d*]pyrimidine (**214**)[118].



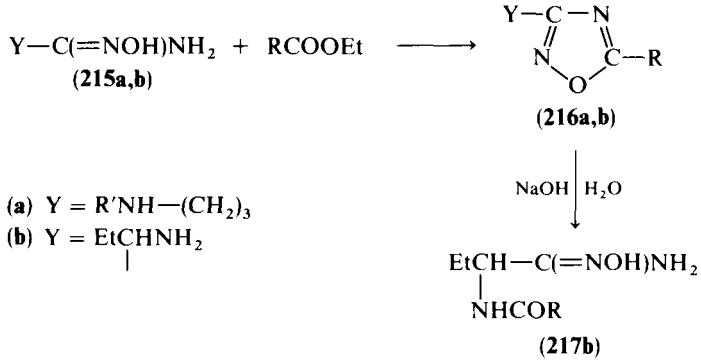
(212)

(213)

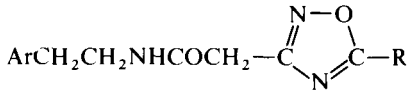
(214)

Cyclization of 4-aminobutanoic amidoxime derivatives (**215a**) with various esters gave the oxadiazoles (**216a**) in 69–97% yields[54], while some β-amino-propanamidoximes[329],

as well as the α-aminobutyramide oxime (**215b**) react in an analogous manner[30] affording compound **216b**, that undergoes ring opening to the corresponding α-acylaminobutyramide oximes (**217b**) in dilute aqueous sodium hydroxide. This reaction presumably proceeds by nucleophilic ring fission[30].

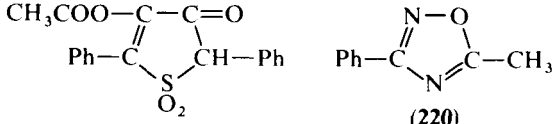


A series of 23 5-substituted 3-{[2-(3,4-dialkoxyphenyl)ethyl]carbamoylmethyl}-1,2,4-oxadiazoles (**218**) was obtained by treatment of the respective amidoximes with carboxylic acid esters[330].



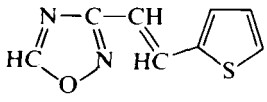
(**218**)

Furthermore, a mixture of benzamidoxime, 4-acetoxy-2,3-dihydro-2,5-diphenyl-3-oxothiophene 1,1-dioxide (**219**), 4-(dimethylamino) pyridine and triethylamine in toluene affords, by heating at 90°C, the oxadiazole **220**[331].



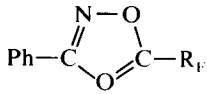
(**219**) (**220**)

Cyclization of 2-chloro-, 4-chloro- and 2,4-dichlorophenyl, as well as of *trans*-2,4-dichlorostyryl and 2,4-dichlorophenylethyl amidoximes has been effected with acid chlorides, methyl acetoacetate or isatoic anhydride, yielding the corresponding 3,5-disubstituted 1,2,4-oxadiazoles[317]. 36% of 3-phenylethynyl-1,2,4-oxadiazole (**181**) were obtained by heating phenylpropiolamide oxime with ethylorthoformate in the presence of boron trifluoride, whereas action of the latter and triethyl orthoformate upon *cis*-3-(2-thienyl)acrylamidoxime afforded only the *trans* heterocycle **221**[27].



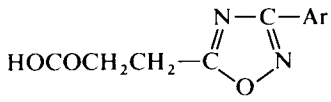
(**221**)

Several 3-*R*-5-*R'*-1,2,4-oxadiazoles are prepared in fair to good yields by a short, one-pot reaction of amidoximes $RC(=NOH)NH_2$ (where R = Me, Ph, 4-Tol, 4-An or 4-dimethylaminophenyl) and acyl chlorides R'COCl (R' = Me, Et, vinyl, Ph, 4-Tol, 4-An, $4\text{-}ClC_6H_4$, 1-Naph) in pyridine[309]. As already mentioned[308], amidoximes with α-chloroacid chlorides yield 5-(1-chloroalkyl)-1,2,4-oxadiazoles (**178**), or, in the presence of NaH, the 4*H*-1,2,4-oxadiazin-5-ones (**179**). Although a series of 5-perfluoroalkyl-3-phenyl-1,2,4-oxadiazoles (**222**, where R_F perfluoro-propionyl, -*n*-butyryl or -*n*-octanoyl) was smoothly synthesized from benzamidoxime and perfluoromonoacyl chlorides, a more complex pattern of products was observed upon varying the conditions of the reaction between arylamidoximes and perfluorodiacyl chlorides[312].



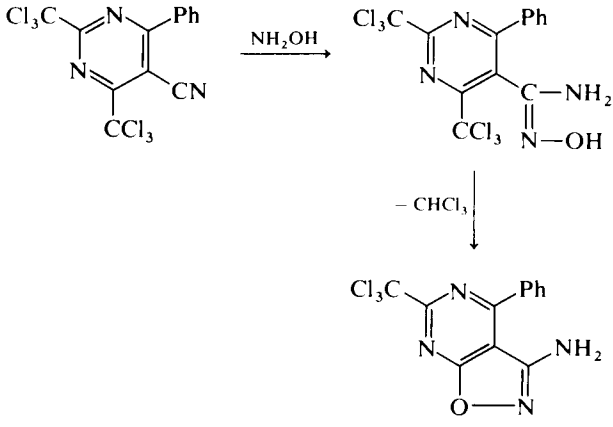
(**222**)

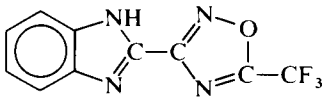
Heating a mixture of arylamidoximes and succinic anhydride at 120 °C yielded 25–58% of the corresponding 3[3'(aryl)-1,2,4-oxadiazol-5-yl]propionic acids (**223**)[332]; this acylating agent has found many analogous applications[38,43,65,89,264,333–336a].



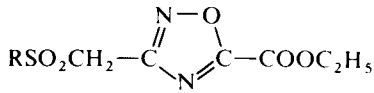
(**223**)

Similarly, treatment of 5-cyano-2,4-ditrichloromethyl-6-phenylpyrimidine with hydroxylamine hydrochloride and sodium acetate in boiling ethanol yields 3-amino-6-tri-





(**224**)

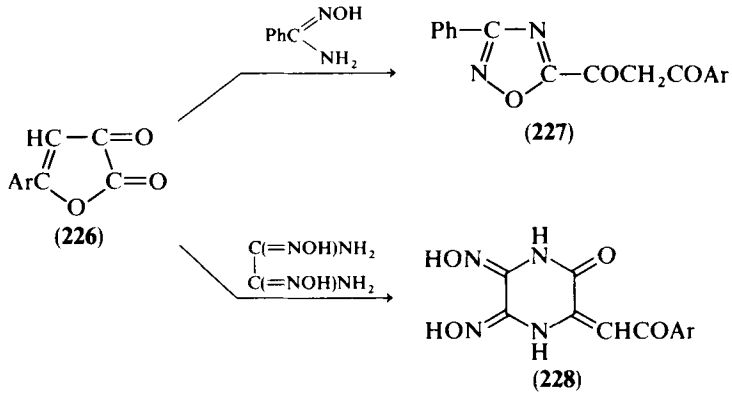


(**225**)

chloromethyl-4-phenyl-isoxazolo[5,4-*d*]pyrimidine[336b], obviously via an intermediate monocyclic amidoxime.

Condensation of 2,6-dichlorophenylacetamidoxime with trichloroacetic anhydride in trichloroacetic acid at 115 °C affords 77% of 5-trichloromethyl-3-(2,6-dichlorobenzyl)-1,2,4-oxadiazole[7]. In a similar manner reaction of 2-benzimidazole carboxamidoxime with trifloroacetic anhydride in refluxing toluene[15] gave 69% of the corresponding 2-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)benzimidazole (**224**), whereas 3-arylsulfonyl-methyl-1,2,4-oxadiazole-5-carboxylic acid esters (**225**) were obtained from arylsulfonyl-acetamidoximes with oxalic acid monochloride monoethyl ester[6].

Treatment of benzamidoxime with 5-aryl-2,3-dihydrofuran-2,3-diones **226** in refluxing dioxane results in the oxadiazole **227**, while **226** with oxamidoxime under the same conditions yields pyrazinones of the type **228**, obviously via an *N*-acylated amidoxime intermediate[337].



1,2,4-Oxadiazoles may be synthesized by heating amidoxime hydrochlorides or formates with amides in the absence of a solvent[72,338,339]. This process is quite general and allows the preparation of oxadiazoles containing acylable groups in the substituent, as, for example, 3-phenyl-5-hydroxymethyl oxadiazole, a product of the interaction of benzamidoxime formate and glycolamide.

Certain bis-oxadiazoles were already mentioned, such as **204**[320] or **211**[312]. Benzamidoxime on acylation with malonic or succinic acid yields 1,1-bis(3-phenyl-5-oxadiazolyl) methane (or respectively ethane)[321]. Finally, polymers bearing recurring 1,2,4-oxadiazole rings were prepared[340] by heating polymeric *O,O*-diacylated diamidoximes containing units of the type **229**, where R and R′ are alkylene or arylene radicals.

$$—ON=C(NH_2)—R—C(NH_2)=NO—CO—R'—CO—$$

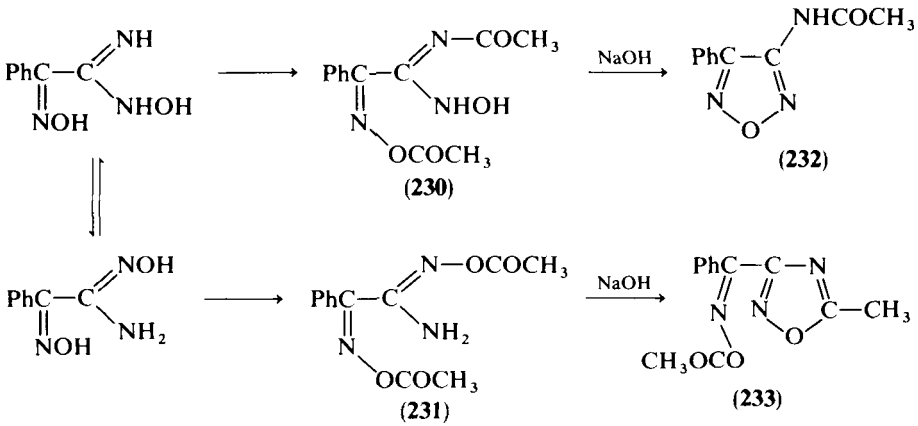
(229)

Before discussing the rare cases of *N,O*-diacylation of amidoximes, their tendency to yield preferably O-monosubstituted derivatives should be examined closer. Indeed, and with the sole exception of formamidoxime[200,282], they bear an unusually inert amino group. Recently, MO-SCF-FORCE calculations on benzamidoxime confirmed the greater stability of the amino–hydroxyimino tautomer compared to the imino–hydroxy-amino one, and explained the anomalous chemical behavior of the amino function[341].

It has thus been suggested[341] that formamidoxime is both O- and N-acylated via the corresponding tautomeric forms, the more stable amino–hydroxyimino structure being

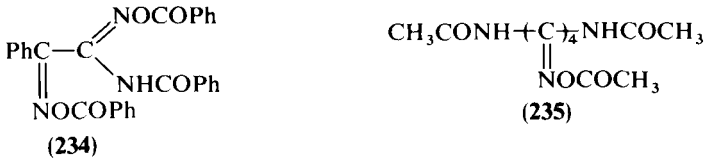
less subject to N-acylation and constituting the energetically preferred form of benzamidoxime.

Ponzio claimed[342] that α-hydroxyimino amidoximes were acetylated via both their tautomers, yielding respectively the α-hydroxyimino, β-imino (**230**) and the α,β-bishydroxyimino (**231**) derivatives. The cyclization products of the latter, furazan (**232**) and oxadiazole (**233**)[343,344], confirm this approach unequivocally, in addition to the fact that deacetylated **233** is transformed into deacetylated **232** in basic media[345].

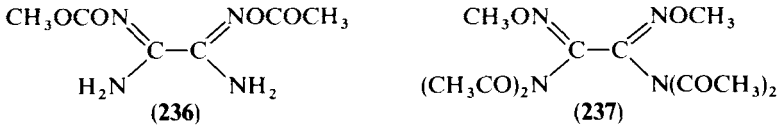


J. N,O-Diacylation

Several diacyl-derivatives of amidoximes have already been mentioned, e.g. **196**[52], **149**[283], **176**[235] and **188**[207]. The tribenzoylated product **234**[342] was obtained from phenylaminoglyoxime with aroyl chlorides. In a similar manner, diaminotetraoxime yields the hexaacetyl derivative **235** with boiling acetic anhydride[49].

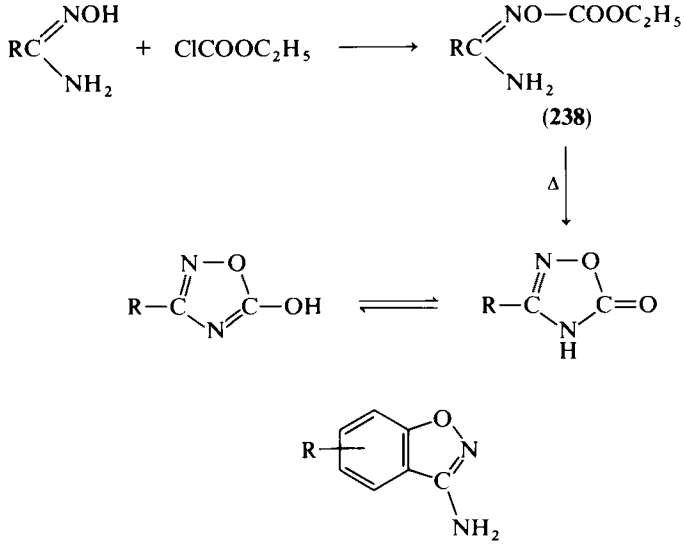


Longo and Randoni reported in 1936 *N,O*-diacetyl compounds, in which both acetyl radicals were supposed to be linked to the oxygen and the nitrogen of the hydroxyimino group of the imino tautomer of amidoximes; but this structure was not definitely elucidated[346]. Acetic anhydride in excess interacts exothermically with oxamidoxime to afford 99% of the diacetate **236**[196], whereas the *O,O'*-dimethylated dioxime is forced to undergo N-acylation to the tetra acetyl derivative **237**.



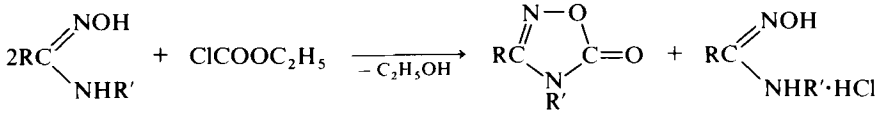
K. Carbonic Acid Derivatives of Amidoximes

Ethyl chloroformate reacts with the hydroxyimino group of amidoximes to yield the carbonic acid derivatives **238**[298,347], which in turn are cyclized under elimination of EtOH into 5-hydroxy-1,2,4-oxadiazoles[289,347–349]. However, *O*-carbethoxy-salicylamidoxime provides 3-amino-indoxazene on heating[350].



(238)

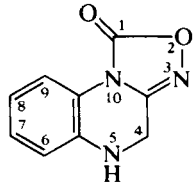
It appears that compounds **238** are formed solely in the case of low-boiling-point solvents (e.g. benzene or chloroform)[349]. Even so, *N*-alkyl-amidoximes afford under the same conditions 3,4-dialkyl-Δ^2-1,2,4-oxadiazolin-5-ones (**239**) and the corresponding amidoxime hydrochloride[112]. No acylation products corresponding to **238** were ever isolated, in spite of the many applications the reaction has found[108,123,351–353].



(239)

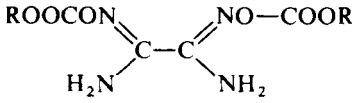
It has been pointed out[304] that amidoximes are highly reactive towards ethyl chloroformate in the pH range 6–9, yielding **238**; *N,N*-disubstituted amidoximes behave in a similar manner, as proved by the products of the treatment of *N,N*-dimethyl-3-nitrobenzamidoxime with the same acylating agent[261]. In contrast, action of ethyl chloroformate on 2-hydroxyimino-1,2,3,4-tetrahydroquinoxaline does not afford the diacyl compound **176**, but instead directly the 1-oxo-4,5-dihydro-[1,2,4]oxadiazolo[4,3-*a*]quinoxaline (**240**), without isolation of the intermediate *O*-carbethoxy-amidoxime[310].

Under analogous conditions, oxamidedioxime forms a disubstituted derivative (**241**, R = Et)[354], whereas oxanilide dioximes in boiling dioxane yield 3,3′-bis(4-aryl-

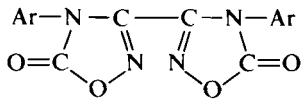


(240)

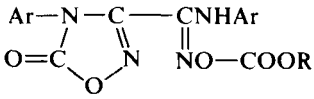
1,2,4-oxadiazole-5-ones) (**242**)[123], but in boiling toluene give 4-aryl-5-oxo-Δ^2-1,2,4-oxadiazolin-3-(*N*-aryl)carboxamide *O*-ethoxycarbonyloximes (**243**)[355].



(241)

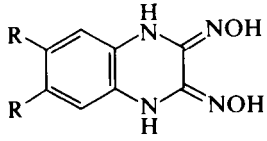


(242)

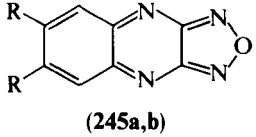


R = C_2H_5. (243)

Refluxing of 2,3-bis-hydroxyimino-1,2,3,4-tetrahydro quinoxalines (**244a,b**) with an excess of ethyl chloroformate in dry benzene resulted solely in furazano-[3,4-*b*]quinoxalines (**245**) and an unidentified high-melting compound[355].



(244a,b)

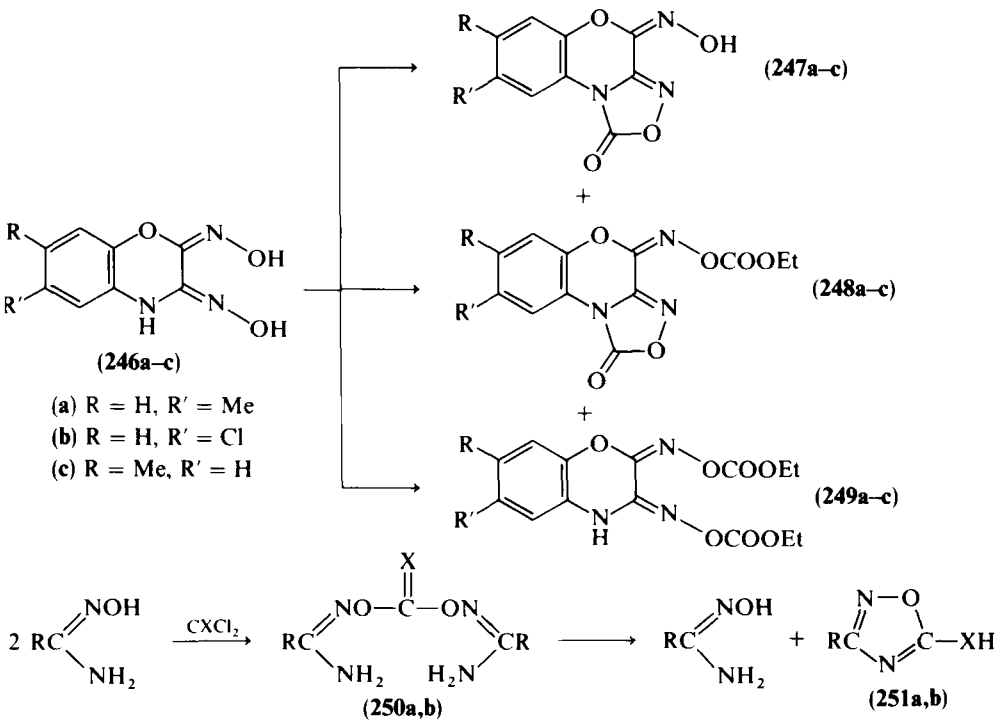


(245a,b)

(**a**) R = R′ = H
(**b**) R = R′ = Me

Furthermore, bis-hydroxyimino-benzoxazines (**246a–c**) are converted under comparable conditions, but in toluene, into fused oxadiazolones of types **247** and **248**, as well as into the bis-ethoxycarbonyl derivatives **249**[355].

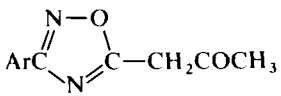
Phosgene with amidoximes gives carbonic acid derivatives (**250a**), usually undergoing direct cyclization to 5-hydroxy-1,2,4-oxadiazoles (**251a**) under regeneration of one molecule of the initial amidoxime[108,265,356]. Thiophosgene brings about analogous results, leading to **251b** via the nonisolated structure **250b**[239]. Furthermore, *N*-methylacetamidoxime affords 26% of 3,4-dimethyl-Δ^2-1,2,4-oxadiazoline-5-thione on treatment with thiophosgene in chloroform at room temperature[357]. An attempt to prepare 5-mercapto-3-phenyl-1,2,4-oxadiazole (**251b**, R = Ph) from benzamidoxime and ethyl chlorothioformate led to evolution of hydrogen sulfide, the required compound not being detected[358]. It should finally be mentioned that perfluoro butyramidoxime resulted in the respective *O*-chloroformyl derivative on action of phosgene[77].



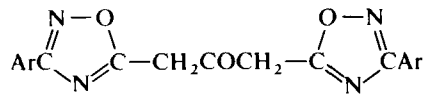
(a) X = O
(b) X = S

L. Reaction with β-Ketocarboxylic Esters

Although amidoximes are indifferent towards nonactivated esters, they react thermally with an excess of ethyl acetoacetate affording 3-aryl-5-acetonyl-1,2,4-oxadiazoles (**252**) under elimination of water and ethanol[17b,264,359,360], yields being best in boiling toluene[317,361]. Ethyl benzoylacetate and *p*-methoxybenzoylacetate show an analogous behavior, whereas aromatic amidoximes on action of diethyl acetonedicarboxylate yield 1,3-bis(3-aryl-1,2,4-oxadiazol-5-yl)2-propanone (**253**)[361].



(252)



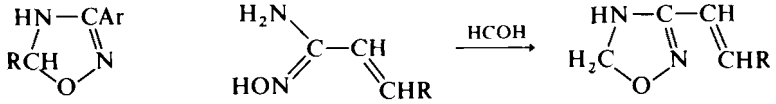
(253)

M. Reaction with Aldehydes and Ketones

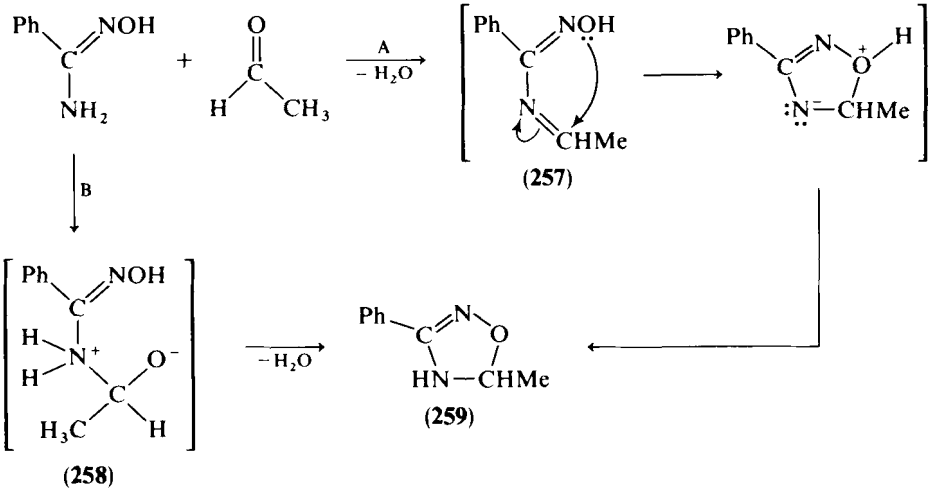
Aromatic amidoximes with aldehydes in cold alcoholic or aqueous solutions afford good yields in 1,2,4-oxadiazolines (**254**)[23,360], that usually oxidize rapidly to the corresponding oxadiazoles[362]. This condensation has been carried out with formalde-

hyde[363], acetaldehyde[17,263,335,359,360,362–367], as well as propionaldehyde, isobutyraldehyde, phenylacetaldehyde and salicylaldehyde[368], benzaldehyde only reacting in glacial acetic acid[297]. However, chloroacetaldehyde with 4-chlorophenyl-, 2,4-dichlorophenyl- or 2,4-dichlorobenzyl-amidoximes gives only very poor yields of **254**. The same amidoximes do not react at all with 4-chlorobenzaldehyde[317].

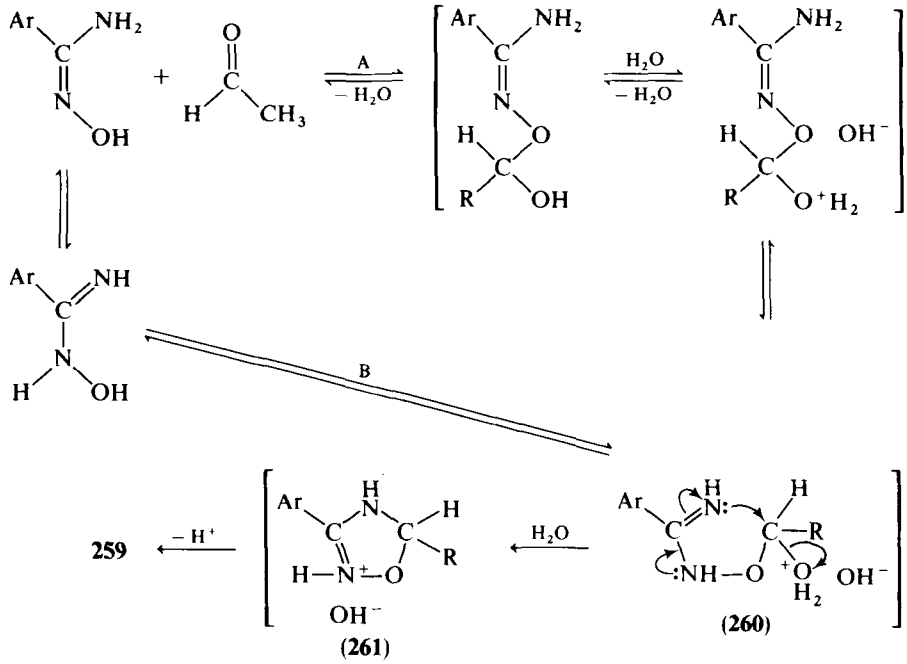
Unsaturated amidoximes of the structure **255** give, with formaldehyde, oxadiazolines (**256**, where R = 4-Tol, 4-methylthiophenyl, 4-halophenyl) which are further oxidized to oxadiazoles by nitrous acid or manganese dioxide[27].



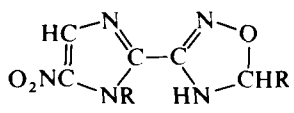
Although the first oxadiazoline was prepared in 1884[1], only very much later did Malavaud and coworkers[369] propose two different mechanisms. According to route A, the intermediate aldimine (**257**) is cyclized to an aldimine affording the heterocycle **259**, while route B presumes formation of compound **258**, that undergoes S_N2 attack of the acetal carbon by the hydroxyimino group oxygen and water displacement to yield **259**. In both cases, a C—N bond formation between the amino group and the carbonyl carbon was assumed. Though the same investigators[369] immediately rejected pathway A, since *O*-methyl benzamidoxime proved to be insensitive towards acetaldehyde, they insisted on the validity of route B and attributed this lack of reactivity to a conjugation between the π-electrons of the benzene ring and the lone electron pair of the amine nitrogen[369].



However, the aforementioned behavior of O-substituted amidoximes, shown in the case of propionaldehyde as well[297], led Srivastava and collaborators to a re-examination of the mechanism and to the assumption that a non-isolated protonated hemiacetal intermediate (**260**) is obtained via two possible pathways A and B, undergoing further ring closure and proton elimination to **259**, as shown below[297]. Strong evidence in support of this mechanism is the reaction of benzamidoxime with chloral, giving a crystalline derivative, proved by X-ray studies to be the corresponding hemiacetal $Cl_3CCH(OH)—O—N{=}C(Ph)NH_2$[297].



Treatment of 1-methyl (or propyl)-5-nitroimidazole-2-carboxamide oxime with the appropriate aldehyde resulted in compounds of type **262**[73], while cyclization of benzamidoxime with 2,3-*O*-isopropylidene-D-glyceraldehyde produced predominantly the 4,5-dihydro-1,2,4-oxadiazole **263a**, and a small amount of **263b**[370].



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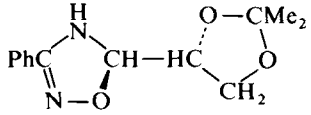
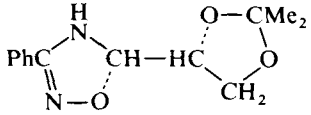


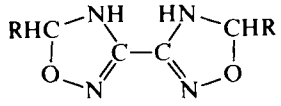
(263a)



(263b)

Acetone and acetone dimethyl acetal are also reported to give 5-dimethyl-4,5-dihydro oxadiazoles[51], oxamide dioxime affording with aliphatic aldehydes the bis-oxadiazoline **264**[371]. Action of hydrochloric acid in ethanol on the acetal amidoxime $CH_3C(OR)_2CH_2C(=NOH)NH_2$ yields through intramolecular cyclization the 3-amino-5-methylisoxazole **265**[372].

Equimolar amounts of 3-aminopropanamidoxime and aromatic aldehydes result in 3-(arylidene)amino-propanamidoximes (**266**), while a twofold excess of the aldehydes leads to the 3-[2(arylidene)amino-2-ethyl], 5-aryl-4,5*H*, 1,2,4-oxadiazole (**267**)[209,373].



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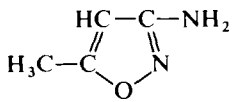

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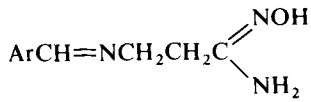

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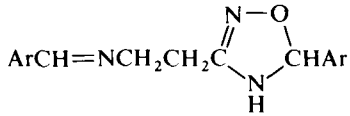
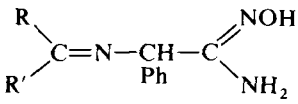


(267)

3-Benzoylaminopropanamidoxime with n-pentanal in acetic acid yields 3-[(2-benzoylamino)ethyl]-5-n-butyl-4,5-dihydro-1,2,4-oxadiazole[10].

Furthermore, treatment of 2-amino-2-phenylacetamidoxime with equimolar amounts of benzaldehyde, cinnamic aldehyde, propanal or acetylacetone at 80 °C yielded the imino derivatives **268**[23], while action of a 2:1 excess of aromatic aldehydes bearing electronegative substituents[23,374] produces 4- (or 5-) (arylmethylideneamino)-2,4- (or 2,5-) arylimidazoles (**269**), a path followed by propanal as well under the same conditions[374].



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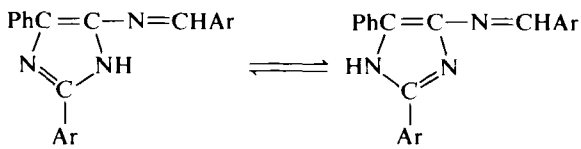
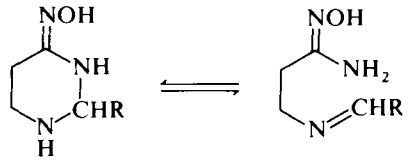


(269)

R = $COCH_3$, R′ = Me R = Ph, R′ = H

R = Et, R′H R = $C_6H_4CH{=}CH_2$, R′ = H

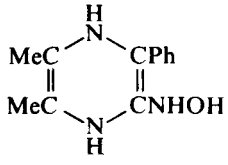
Reaction of 3-aminopropionamidoxime with benzaldehydes bearing electron-attracting substituents affords products existing in an equilibrium mixture of the tautomers **270a** and **270b**, whereas benzaldehydes with electron-releasing groups result solely in the open-chain imine **270b**[375]. Diacetyl with 2-amino-2-phenyl acetamidoxime yields



(270a) (270b)

5,6-dimethyl-3-phenyl-2-hydroxylaminopyrazine (**271**)[23], and with benzamidoxime affords compound **272**, which gives on melting 3-phenyl-5-methyl-1,2,4-oxadiazole[23]. In case simple or N-monoalkylated amidoximes are refluxed in toluene with diphenylcyclopropenone, they yield the 2-aryl-5,6-diphenylpyrimidin-4-ones or the 3-substituted derivatives (**273**, R = H or alkyl, aryl)[376,377]. Finally, the amidoxime hydrazides of malonic acid on treatment with benzaldehyde, salicyl aldehyde, cinnamoyl aldehyde,

4-dimethylaminobenzaldehyde or acetone afford the hydrazones of the respective carbonyl compounds[187].



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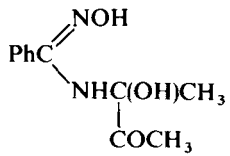

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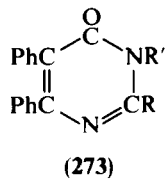
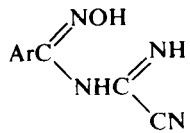


(273)

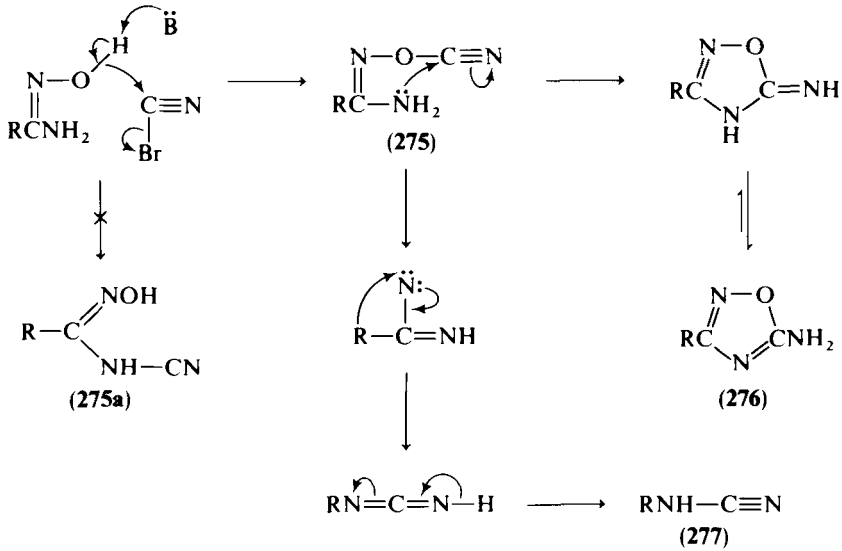
N. Action of Cyanogen and Cyano Derivatives

Benzamidoxime and β-naphthamidoxime add cyanogen, affording the unstable products **274**. These are readily hydrolyzed to the initial amidoximes, or yield the O-acetylated derivatives in the presence of acetic anhydride[378].



(274)

Treatment of methanol solutions of amidoximes with cyanogen bromide and potassium bicarbonate results in 3-substituted-5-amino-1,2,4-oxadiazoles (**276**)[7,35]. The fact that O-substituted amidoximes do not interact with the same reagent suggests that the initial nucleophilic attack is due to the hydroxyl group or its conjugate anion and not to the amino function. Indeed, the existence of the intermediate **275**, and not of its isomer



(275)

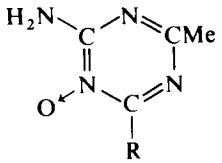
(275a)

(276)

(277)

275a, may be reasonably assumed from the isolation of the cyanamide **277**[7], that can only arise by loss of cyanic acid from **275** via an aza-Curtius reaction.

Action of methyl *N*-cyanoacetimidate upon benzamidoxime and lactamidoxime[379] yields 2-amino-*s*-triazine 1-oxides (**278**, R = phenyl, 1-hydroxyethyl), whereas treatment of amidoximes with disubstituted cyanamides $R_2N—CN$ gives the corresponding 5-amino-1,2,4-oxadiazoles along with 5-diaminomethyleneamino derivatives of the type **279**, which are the main products if the reaction is carried out under high pressure[380].



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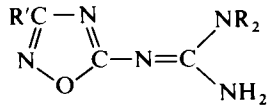
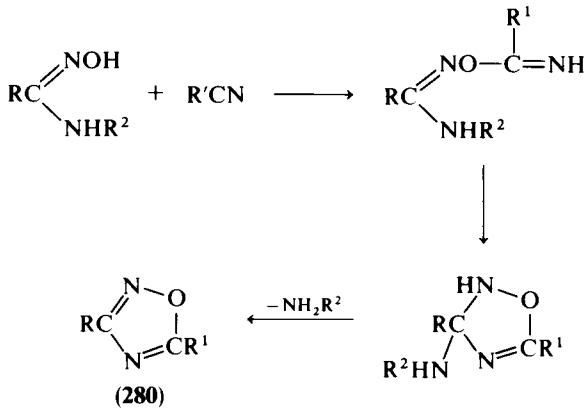


(279)

Condensation of benzamidoxime with acetonitrile or benzonitrile to 3-phenyl, 5-methyl- (or phenyl-) 1,2,4-oxadiazoles (**280**) requires high pressures[380] or the presence of catalysts, e.g. $ZnCl_2/HCl$[381], in a suitable solvent. The oxadiazole formation involves elimination of the amidoxime amino group, proved by use of amidoximes enriched with ^{15}N at that group[381].

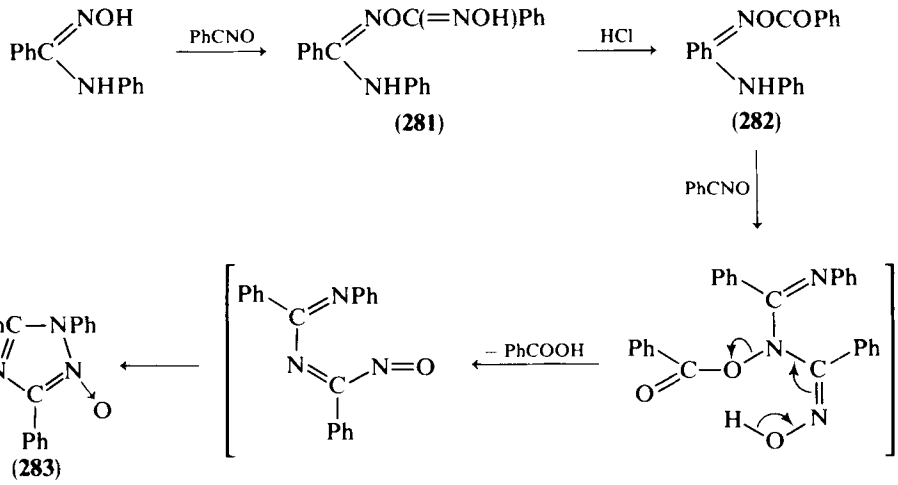


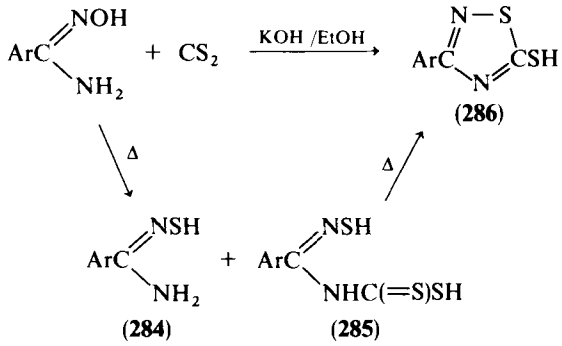
(280)

Benzanilide oxime with benzonitrile oxide at ambient temperature yields 75% of the *O*-benzoyl derivative **282**, through the intermediate **281**[110]. A large excess of the nitrile oxide in refluxing ether yields the 1*H*-1,2,4-triazole-2-oxide **283**[382,383].

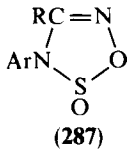
O. Action of Sulfur Dioxide, Carbon Disulfide and Thionyl Chloride

Amidoximes derived from long-chain fatty acids afford unstable addition compounds of not fully elucidated structure upon action of sulfur dioxide[384]. Carbon disulfide with amidoximes yields 5-mercapto-1,2,4-thiadiazoles (**286**)[385]. Analogous heterocycles are obtained from benzamidoxime and methylbenzamidoxime even in the absence of alkali, if cyclization occurs on heating with an excess of the sulfide. In this case the initial product is thought to be a mixture of arylamidesulfime (**284**) and its *N*-dithiocarbonic acid derivative (**285**), thermally condensing into the thiazole **286**[386].





N-Substituted amidoximes with thionyl chloride in boiling benzene yield the corresponding 3,4-disubstituted-3*H*-1,2,3,5-oxathiadiazol-2-oxides (**287**) in good yields[254]. This cyclization requires the (*Z*) configuration of the amidoximes[142], as is also the case with phosgene[352].

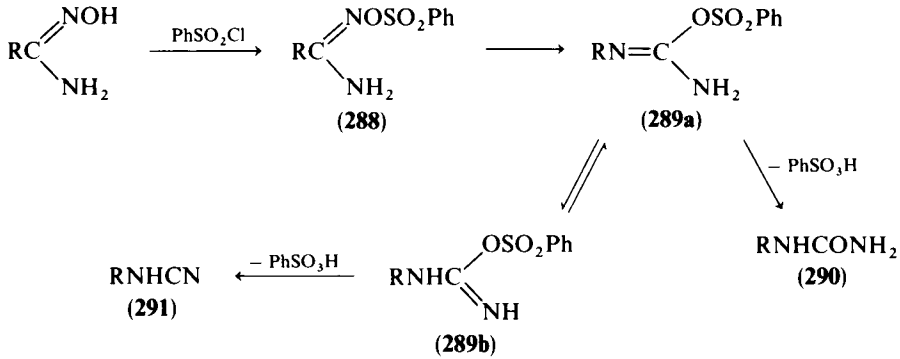


(287)

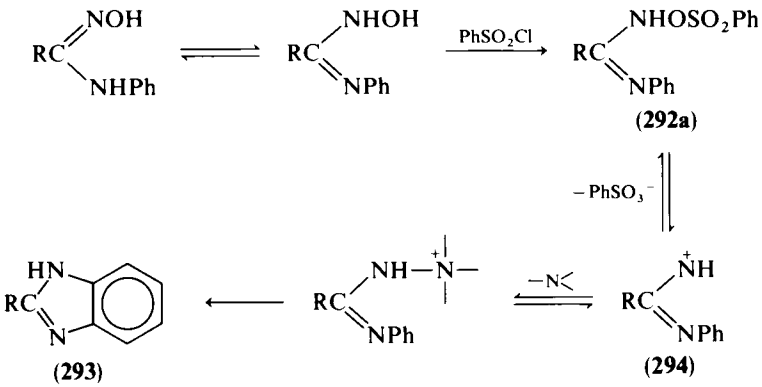
P. Action of Arylsulfonyl Chlorides

Tiemann[387] already obtained unsymmetrical ureas (**290**) by action of benzenesulfonyl chloride on amidoximes, and assumed that the mechanism involves formation of an *O*-benzenesulfonyl derivative (**288**) undergoing Beckman rearrangement to the *O*-benzenesulfinylisourea (**289a**), which is further hydrolyzed to **290**. Early work[388,389]

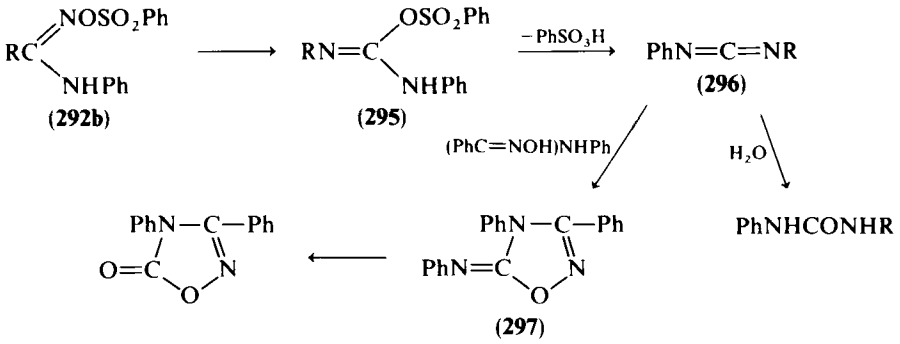
supported this hypothesis, but later it was found[390] that at least *O*-benzenesulfonyl-phenylacetamidoxime (**288**, R = phenylacetyl) followed, in a refluxing inert solvent, a different pathway, leading to **289b**, which in turn affords spontaneously benzenesulfonic acid and the cyanamide **291**. Thus, urea (**290**) is a secondary reaction product and the mechanism obviously involves an intramolecular process, in which the hydrogen bond controls any subsequent electronic displacements.



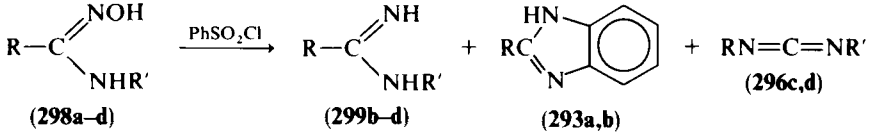
However, from *N*-phenyl amidoximes with benzenesulfonyl chloride under anhydrous conditions and in the presence of pyridine or triethylamine, 2-substituted benzimidazoles (**293**) are readily produced, possibly through the imino derivative (**292a**), that tends to ionize and thus results in the strongly electro-philic imidinium cation (**294**), being further partially stabilized by the organic base. No rearrangement was observed even on heating[391].



In the presence of aqueous alkali, a Beckmann transformation of the amino form **292b** apparently occurs, and leads to **295**, an N-phenylated derivative of **289a**, yielding by elimination of benzenesulfonic acid the carbodiimide intermediate **296**, which in turn is readily hydrolyzed to an *N*,*N*′-disubstituted urea. Evidence for the formation of **296** is provided by adding benzanilide oxime in an analogous anhydrous reaction mixture. This yields 3,4-diphenyl-5-phenylimino-1,2,4-oxadiazoline (**297**), which is further transformed into the corresponding 5-oxo-oxadiazoline[391], as is also the case on treatment of the same amidoxime with diphenyl carbodiimide in dry benzene[391].

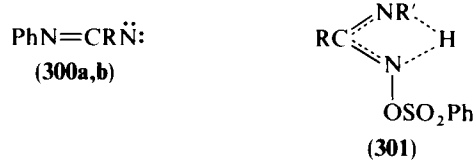


Reaction of several N-substituted amidoximes with benzenesulfonyl chloride was carried out[392] in pyridine, anhydrous benzene or dioxane, the products depending on the substituents. Thus, benzanilide oxime (**298a**) and *N*-phenyl-benzylamidoxime (**298b**) afford 70–75% of the 2-substituted benzimidazole (**293**, R = phenyl or benzyl) and 10% of the amidine (**299**), while *N*-cyclohexyl- (**298c**) and *N*-benzylbenzamidoxime (**298d**) yield up to 88% of the corresponding carbodiimide (**296**, R = phenyl, R′ = cyclohexyl or benzyl) and traces of the amidine **299**.



(**a**) R = R′ = Ph (**c**) R = Ph, R′ = cyclohexyl
(**b**) R = $PhCH_2$, R′ = Ph (**d**) R = Ph, R′ = $PhCH_2$

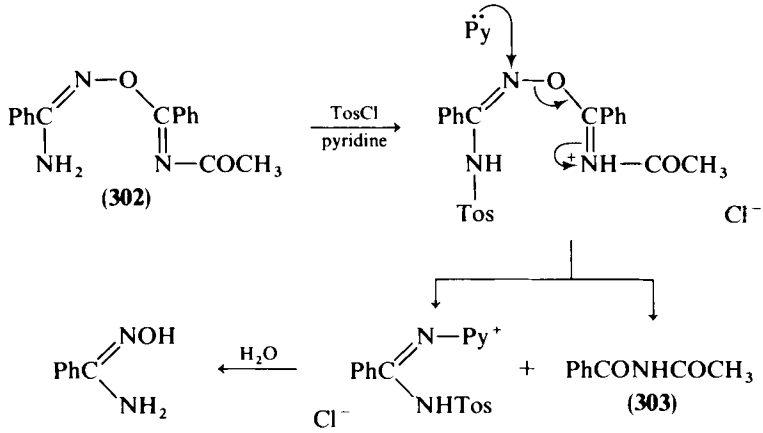
It has been proposed that the products **293a,b** and **299** result from a dehydration of the amidoxime to an azomethine nitrene (**300**) without rearrangement.[392]



Presumably, the nitrene, as a triplet, abstracts a hydrogen from the solvent to bring about the formation of amidine **299**. Ring closure by intramolecular insertion into an appropriate aromatic C—H bond might also proceed from a nitrene of the above type[392]. However, the cyclization into benzimidazoles of the structure **293** does not necessarily depend on a nitrene intermediate, but may result from a nitrenium cation as well. It has also been suggested that the carbodiimide (**296c,d**) derives from *O*-benzenesulfonyl esters (**301**) simultaneously with a 1,3- or α-elimination.[392]

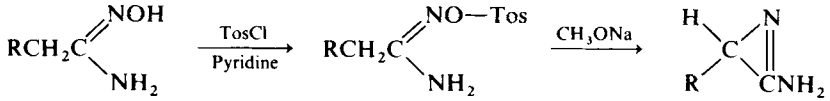
Heating unsubstituted amidoximes with benzenesulfonyl chloride at 100°C in pyridine, subsequently passing hydrogen sulfide at room temperature, affords unsymmetrical thioureas RNH—C(=S)—NH_2, with R-benzyl, Me, 4-Tol, 4-An, 4-ClC_6H_4[393].

Tosyl chloride in pyridine at ambient temperature converted *O*-(*N*-acetylbenzimidoyl)benzamidoxime (**302**) into *N*-acetyl benzamide (**303**) and benzamidoxime[237].



(**302**) (**303**)

Tosylation of amidoximes (**304**) in pyridine yields 69–82% of the stable *O*-tosylates, yielding upon treatment with sodium methoxide in methanol the 2-amino-1-azirines **305**[59], a transformation that can be viewed as a new variant of the Neber rearrangement of ketoxime-*O*-sulfonates to aminoketones, proceeding via 1-azirine intermediates.

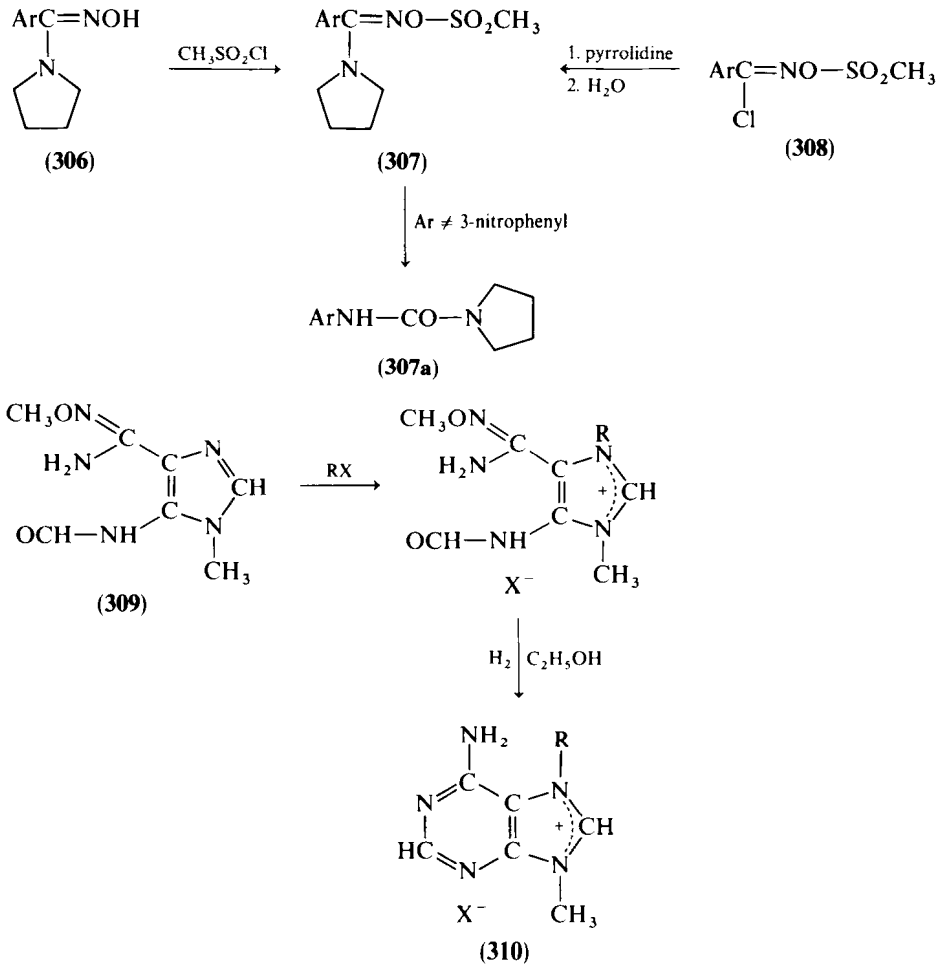


(**304a,b**) (**305a,b**)

(**a**) R = 2,4,6-$Cl_3C_6H_2NHCO$
(**b**) R = $C_6H_5SO_2$—

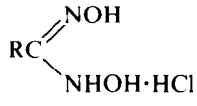
Action of methanesulfonyl chloride upon the amidoxime **306**, where Ar = 3-nitrophenyl, in the presence of anhydrous pyridine results[392] in the *O*-methanesulfonyl derivative (**307**), easily obtained also from benzhydroximoyl chloride (**308**) by treatment with pyrrolidine in excess. This behavior constitutes a notable exception, since most compounds of the type **308** react vigorously with secondary bases, e.g., piperidine, pyrrolidine or morpholine, yielding finally in the presence of water ureas of structure **307a**[401]. The formation of the latter is probably due to a Tiemann-type rearrangement of the intermediate **307**[387], which is stabilized solely in the case of Ar = 3-nitrophenyl.

Treatment of 5-carbamoyl-4-imidazolecarboxamidoximes with organic sulfonyl chlorides in alkaline media leads to guanine or isoguanine, depending on the reaction conditions[26], whereas alkylation of *N'*-methoxy-1-methyl-5-formamido-imidazole-4-carboxamidine (**309**) with alkyl halides in DMF, hydrogenolysis of the *N'*- alkoxy group with Raney-Ni and cyclization (or *vice versa*) produced in acceptable yields the 7,9-dialkyladeninium salts **310**[403].

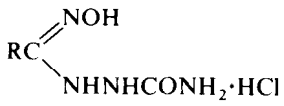


Q. Action of Nitrogen-containing Nucleophiles and Azamethines

Upon treatment of simple aliphatic amidoximes with hydroxylamine hydrochloride, high yields of the corresponding *N*-hydroxy amidoxime hydrochlorides (**311**) have been obtained, the analogous reaction of benzamidoxime being slower and less effective[394]. Similarly, simple amidoximes afford at 40–90 °C with semicarbazide the hydrochlorides of the respective *N*-ureido-amidoximes (**312**).[394]

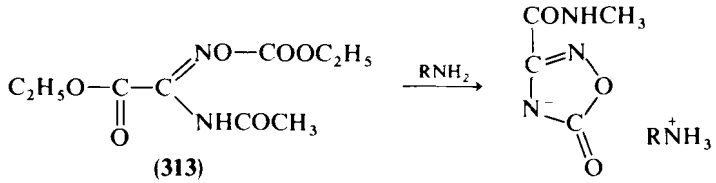


(311)



(312)

Unsubstituted amidoximes are obtained from their *O*-carbethoxy derivatives $RC(=NO—COOC_2H_5)NH_2$ with ammonium hydroxide at 0 °C[349], while under the same conditions *O*-carbethoxy-*N*-acetyl-ethyl-oxamate oxime (**313**) is cyclized to the ammonium salt of 5-keto-Δ^2-1,2,4-oxadiazoline-3-methylcarboxamide (**314**), the reaction resulting in the methylammonium salt if 30% aqueous methylamine is used[349].



(**313**)

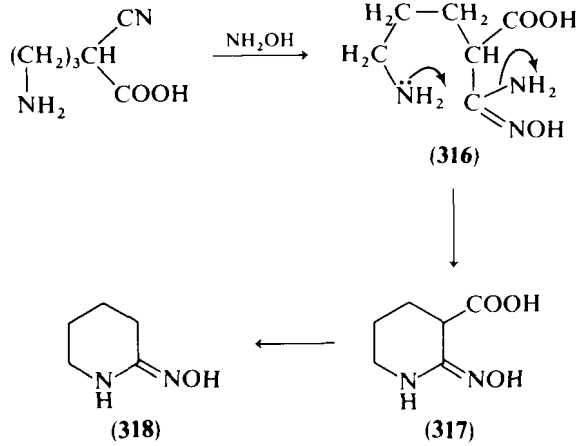
(**314**) R = H, CH_3

With benzylamine, O-acylated amidoximes yield the parent compound and amide (**315**)[395], thus behaving as acylating agents.

(**315**)

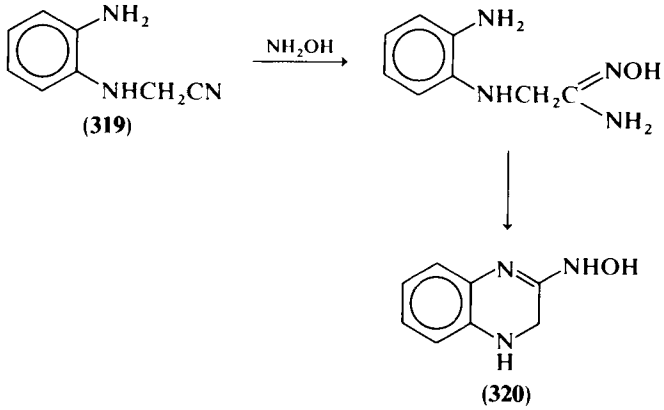
Heating 5-amino-2-cyanopentanoic acid and free hydroxylamine in ethanol yields 2-hydroxyiminopiperidine (**318**), assumed to arise by decarboxylation of the heterocycle (**317**), that is formed from the intermediate **316** as shown in the nearby scheme[299]. Similarly, addition of hydroxylamine to *N*-(cyanomethyl)-*o*-phenylene diamine (**319**) gave 2-oximino-1,2,3,4-tetrahydroquinoxaline (**320**) in the imino–hydroxyamino tautomeric structure[310].

While interaction of phenylhydrazine hydrochloride at 40 °C with acet- or propionamidoxime, as well as with the derivative **312**, results in the expected *N*-anilino compound **321**, treatment with basic phenylhydrazine at 90 °C yields the 1,5-diphenylformazane (**322**)[394]. Action of phenylhydrazine upon benzamidoxime in dilute acetic acid affords the corresponding hydrazone, undergoing oxidation in the 1,5-diphenylformazane (**322**) as well[289].

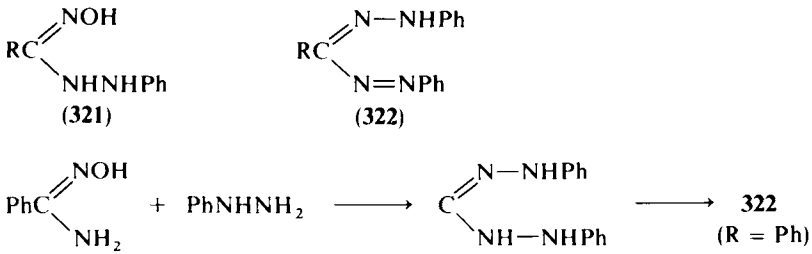


(**316**)

(**318**) (**317**)

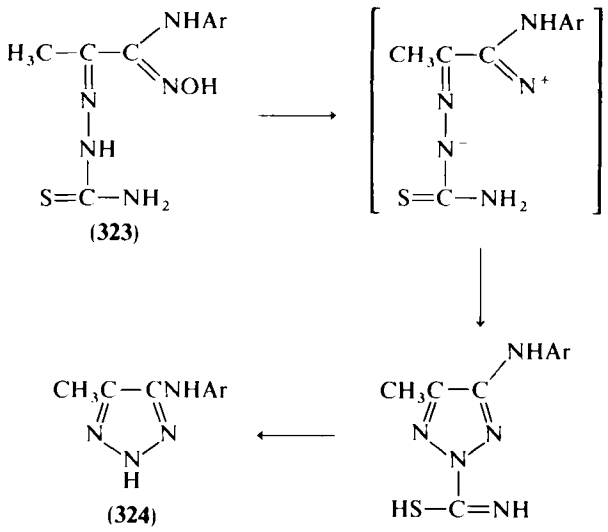


(319) (320)



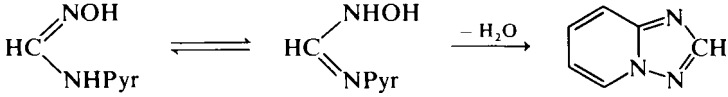
(321) (322)

Intramolecular thermal reaction of *amphi* α-thiosemicarbazone-*N*-aryl propionamidoxime (**323**) leads to 4-arylamino-5-methyl-1,2,3-triazoles (**324**), probably according to the following scheme[396]:



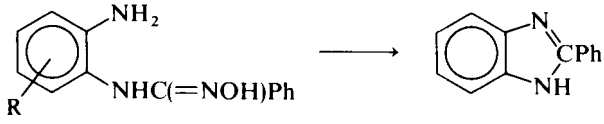
(323) (324)

Dehydration of *N*-pyridylformamidoxime by polyphosphoric acid or through heating over the melting point leads to the *s*-triazolo(1,5*a*)pyridine (**325**), where the triazole ring is fused at its N^2—C^3 bond to the pyridine moiety[117]. A similar cyclization pattern was observed in *N*-pyridazine- and *N*-pyrazine-formamidoxime as well and resulted in *s*-triazolo(2,3-*b*)pyridazine and *s*-triazolo(1,5-*a*)pyrazine, respectively.

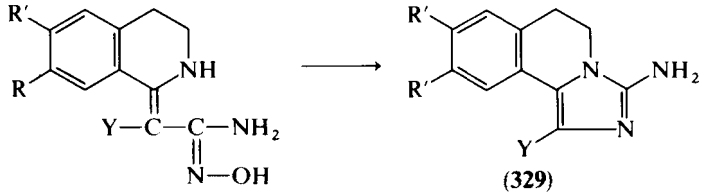


(**325**)

Upon treatment with hydrochloric acid, *N*-(2-aminoaryl)-bezamidoximes (**326**) afford almost quantitatively 2-phenylbenzimidazoles (**327**)[148], while the heterocyclic amidoximes (**328**) are cyclized to amino-imidazoles of type **329** upon action of halogenated sulfonic acids in the presence of pyridine[397].



(**326**) (**327**)



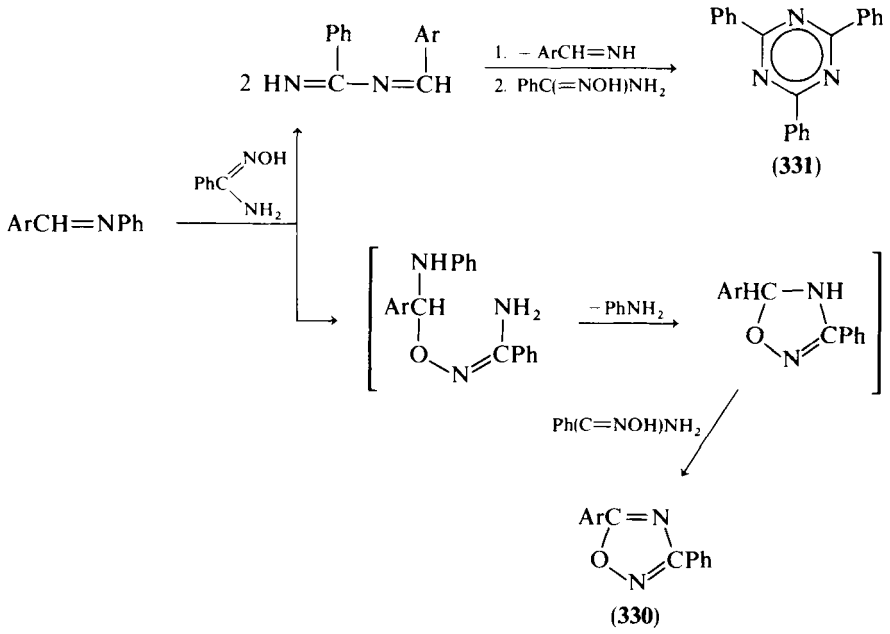
(**328**) (**329**)

The nitrogen atom of azomethines undergoes electrophilic attack by the hydroxyimino group proton of benzamidoxime and is further cyclized into a 4,5-dihydrooxadiazole. The latter is subsequently dehydrogenated to the 1,2,4-oxadiazole (**330**) by an excess of benzamidoxime. The parallel formation of triphenyl-*s*-triazines (**331**) apparently proceeds via an initial Schiff's base formation[398].

R. Action of Dimethyl Acetylenedicarboxylate

Various amidoximes condense with dimethyl acetylenedicarboxylate (**332**) to yield the 1:1 adducts **333**; this addition was predominantly *cis*-oid in methanol or acetonitrile and mainly *trans*-oid in benzene[399a], although it had formerly been claimed that treatment in refluxing methanol affords a 1:3 mixture of the two geometrical isomers[400a]. Further cyclization was not uniform and led to a variety of products[399,400], as shown.

Thus, prolonged heating of **333** in methanol (route A) results by internal cycloaddition in the 1,2,4-oxadiazole **334**[400a], while thermal action of diphenyl ether (route B) gives the 5,6-dihydroxy-2-aryl-4-pyrimidine carboxylic acid methyl ester **335** rather[400a] than the previously proposed[399,400] 4,5-dihydro-α-4-dioxo-2-aryl-1*H*-imidazol-5-acetic acid methyl ester (**336**). The heterocycle **335** may be formed either by displacement of an ester function of the initial adduct **333** by the amidoxime amino group, or through tauto-

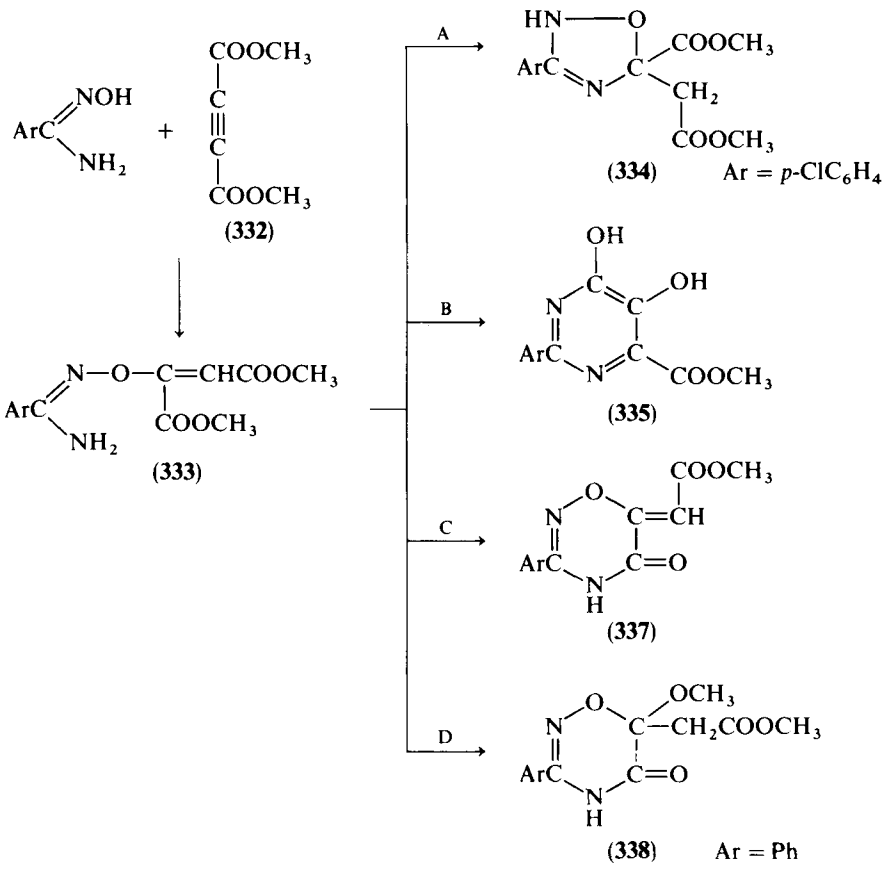


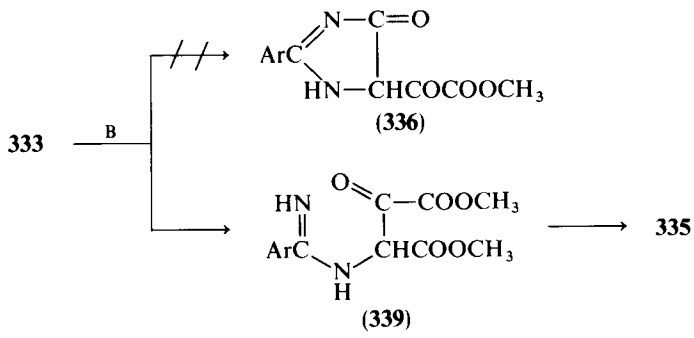
merization of the same and subsequent Claisen rearrangement to the amidine **339**[400a]. Compound **333** yields, with sodium hydroxide (route C), methyl(3-aryl-4,5-dihydro-5-oxo-6*H*-1,2,4-oxadiazin-6-yliden)acetate (**337**)[400a]. Effecting the cyclization of solely the (*E*) or (*Z*) isomer of **333** by means of 1,4-diazabicyclo[4.3.0]non-4-ene in refluxing acetonitrile yields the corresponding (*E*) or (*Z*) structure of the derivative **337**[399a]. It should be noticed that action of diethyl chlorofumarate on the sodium salt of benzamidoxime also affords the *trans*-oid ethyl ester of the oxadiazinone **337**[399a]. However, when ring closure of the *cis*-oid form of the adduct (**333**) was attempted with sodium methoxide in boiling methanol (route D), the reaction produced compound **338**[399a].

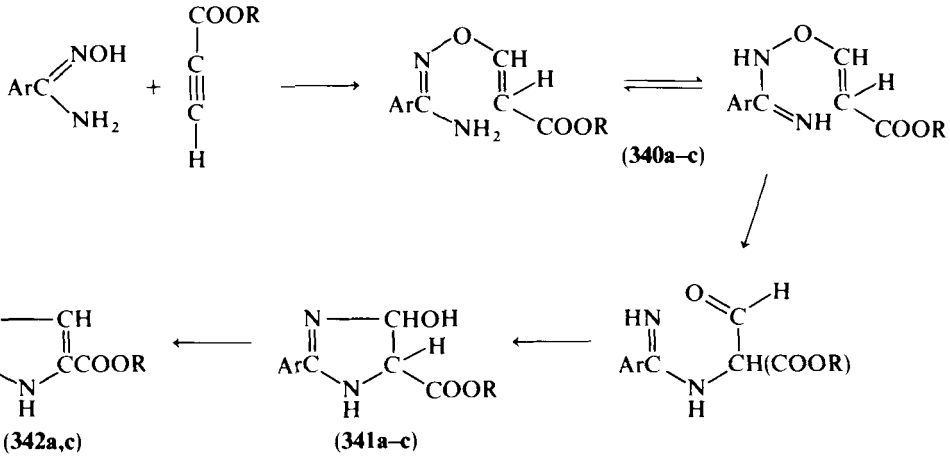
In an analogous manner, on heating in methanol, aromatic amidoximes are condensed in 50–60% yields at the alkyne linkage of propiolate esters. The *trans*-oid adducts (**340**) afford, on pyrolysis in diphenyl ether, the imidazole carboxylates **342**, obviously through a 'no mechanism' rearrangement of the imino–hydroxyamino tautomer of **340**, representing a Claisen-type shift with three hetero atoms in the rearranging cycle, and leading to amidines of the structure **341**[402]. A similar mechanism could possibly account for the formation of **337** as well.

S. Action of *N,N'*-Dicyclohexylcarbodiimide

N,N'-Dicyclohexylcarbodiimide, DCC (**343**), a useful dehydrating agent in the field of peptides, nucleosides or heterocyclic compounds, gives with benzamidoxime in boiling chloroform up to 52% of 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**344**), 40% *N,N',N''*-tricyclohexyl guanidine (**345**) and traces of *N,N'*-dicyclohexyl urea (**346**), apparently via an O-substituted amidoxime intermediate[322]. Addition of acetylacetone or diacetyl resulted in lower yields of **344**, whereas a twofold excess of **343** or a trap such as acetone and ethyl acetoacetate slightly improved the percentage, affording in the last case a small amount of 3,5-diphenyl-1,2,4-oxadiazole as well. The presence of a


A
B
C
D
(332)
(333)
(334) Ar = p-ClC6H4
(335)
(337)
(338) Ar = Ph

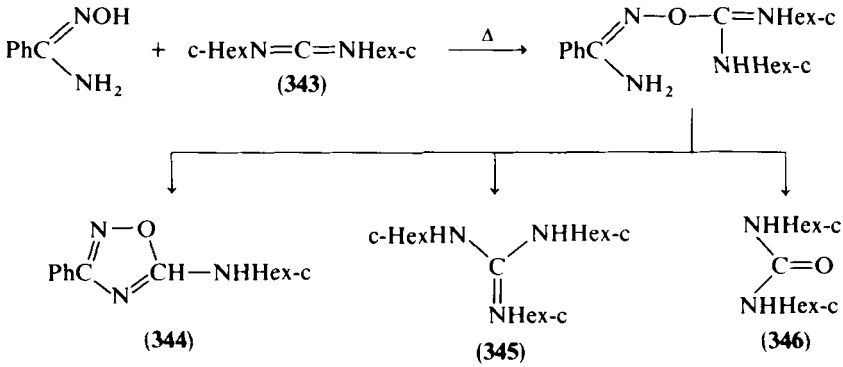

333
B
(336)
(339)
335



(340a–c)

(342a,c) (341a–c)

(a) Ar = Ph, R = CH_3
(b) Ar = Ph, R = C_2H_5
(c) Ar = 3-ClC_6H_4, R = CH_3

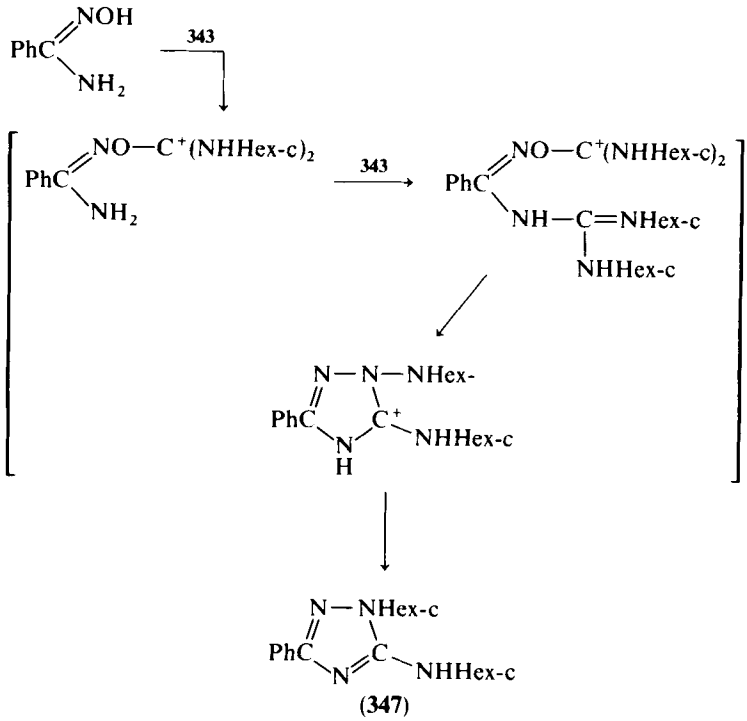


(343)

(344) (345) (346)

carboxylic acid in the reaction mixture, however, resulted in *O*-acyl benzamidoxime derivatives[322]. 4-Toluenesulfonic acid catalyzed the formation of 1-cyclohexyl-5-cyclohexylamino-3-phenyl-1*H*-1,2,4-triazole (**347**)[322].

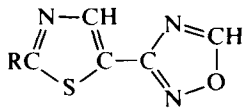
The action of diphenylcarbodiimide upon benzanilide oxime, yielding the substituted 1,2,4-oxadiazoline (**297**)[391], as well as the cyclization of *N*-carboxymethyl amidoximes (**72**) to 4*H*-1,2,4-oxadiazin-6(5*H*)-ones (**73**) by means of **343**[174], have already been mentioned. In addition, it should be noted that treatment of amidoximes with the imide ester hydrochloride RC(=NH)OC_2H_5·HCl produces 3,5-disubstituted 1,2,4-oxadiazoles by elimination of ethanol and ammonium chloride[102].



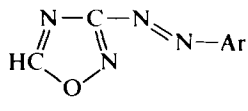
(347)

T. Action of Trialkyl Orthoformates

Treatment of arylamidoximes with triethyl orthoformate in the presence of boron trifluoride yields 3-aryl-1,2,4-oxadiazoles[404]. Thus phenylpropiolamidoxime affords 3-phenylethynyl-1,2,4-oxadiazole (**181**)[27] and ethyl 1,2,4-oxadiazole-3-carboxylate is obtained[12] from ethoxycarbonylformamidoxime. The same method is also used for the synthesis of 3-(thiazol-5-yl)-1,2,4-oxadiazole (**348**)[58], of the *trans* heterocycle **221**[27] and of *trans* 3-arylazo-1,2,4-oxadiazole (**349**)[68a]. An analogous transformation of 2-amino-



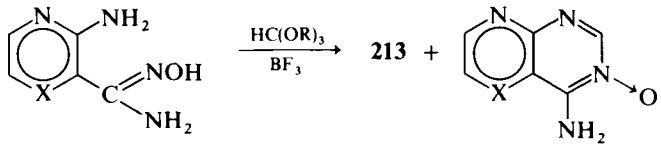
(348)



(349)

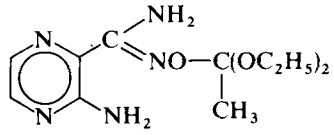
pyridine-3-carboxamidoxime (**350**) and 2-amino-pyrazine-3-carboxamidoxime (**352**) leads to high yields of the respective N-oxides **24** and **351**[74,118]. **352** with diethoxymethyl acetate in boiling toluene gave **24** as well, but treatment with triethyl orthoacetate in the absence of boron trifluoride yielded **353**, which reacted further with hot glacial acetic acid to yield the parent amidoxime **352**, 2-methyl-4-aminopyrazino[2,3-*d*]pyrimidine-3-oxide (**354**) and the oxadiazolyl-pyrazine **355**[74].

Finally, O-substituted 2-aminopyrazine-3-carboxamide oximes give with triethyl orthoformate the corresponding O-substituted 4-hydroxyaminopteridines (**356**)[405], whereas 2-oxo-1,2-dihydropyrazine-3-carboxamide oxime leads to 3-(1′,2′,4′-oxadiazolyl-3′)-2(1*H*)-pyrazinones (**357**)[74].



(350) X = CH
(352) X = N

(24) X = CH
(351) X = N



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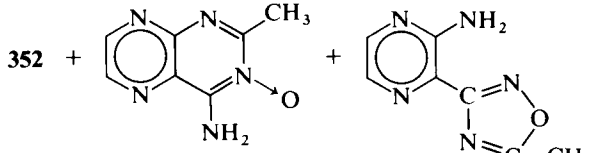

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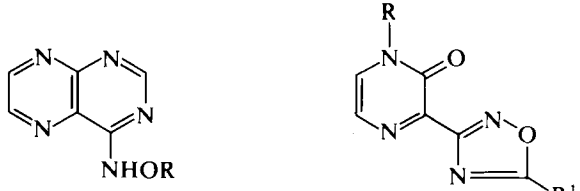
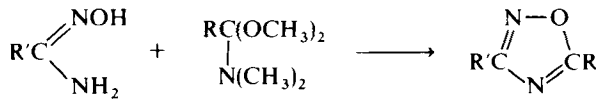


(356)

(357)

U. Action of Dimethylformamide Dimethyl Acetal

Treatment of substituted *trans* styrylamidoximes with dimethylformamide dimethyl acetal (**358**, R = H) in refluxing anhydrous benzene affords the corresponding *trans* 3-styryl-1,2,4-oxadiazoles (**221**) in better yields than by means of triethyl orthoformate[27]. In an analogous manner, the acetal **358**, R-methyl or ethyl, result in the 3,5-disubstituted 1,2,4-oxadiazoles (**359**)[68,74,331].

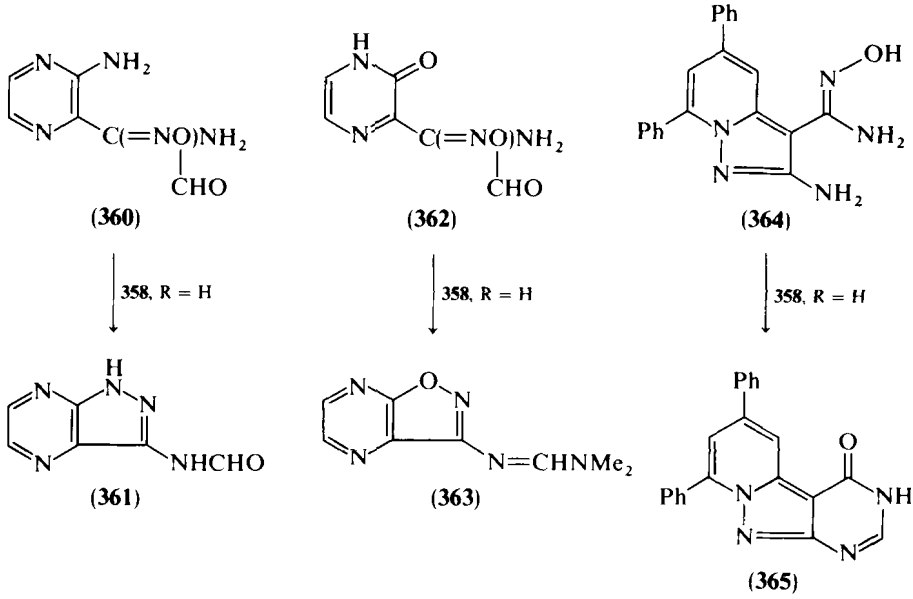


(358)

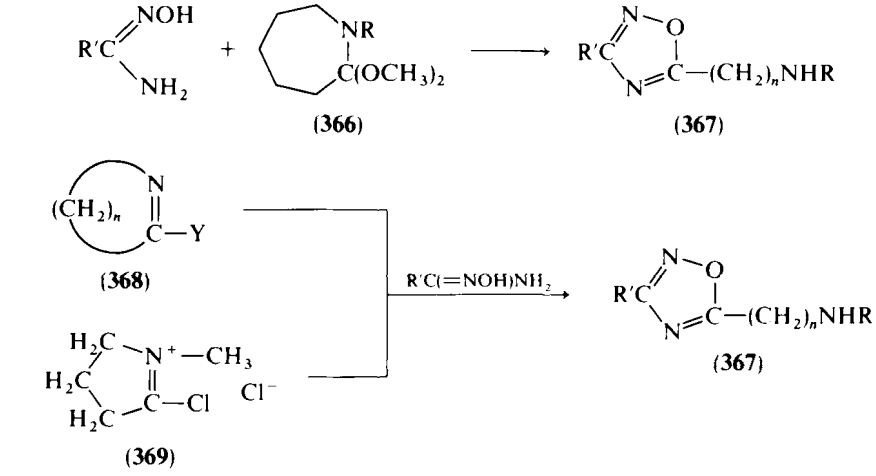
(359)

By heating *N*-methyl benzamidoxime with **358**, R = H, benzonitrile and *N,N,N'*-trimethylurea are obtained[27].

The same acetal and the 2-amino or 2-hydroxy substituted hetaryl amidoximes **360**, **362** and **364** produced the condensed heterocycles **361**, **363**, and **365**, respectively[28,68b,406].

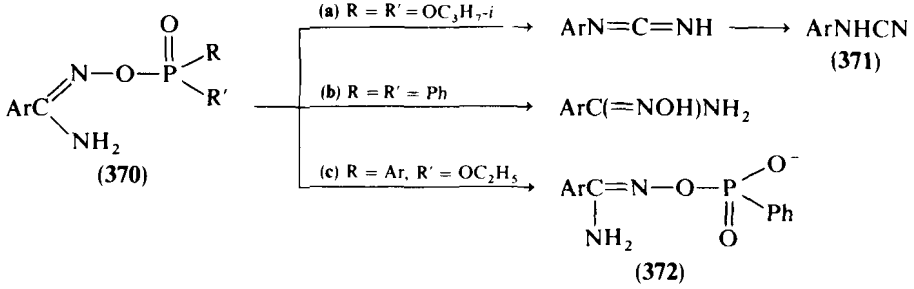


Benzamidoxime reacts with the lactam acetal **366** to give 5-(ω-aminoalkyl)-1,2,4-oxadiazole (**367**), with $n = 5$, R = methyl, R' = phenyl, when both the N- and O-substituted derivatives of the amidoxime may act as intermediates[407]. Analogous disubstituted oxadiazoles (**367**) were also obtained by heating simple amidoximes with the lactim ether or lactim chloride (**368**)—where Y = OCH_3, R = H, n = 3,5,11 and Y = Cl, R = H, $n = 5$, respectively—as well as with the lactam chloride **369**, the latter yielding **367** with $n = 3$, R = methyl[407a,407b].

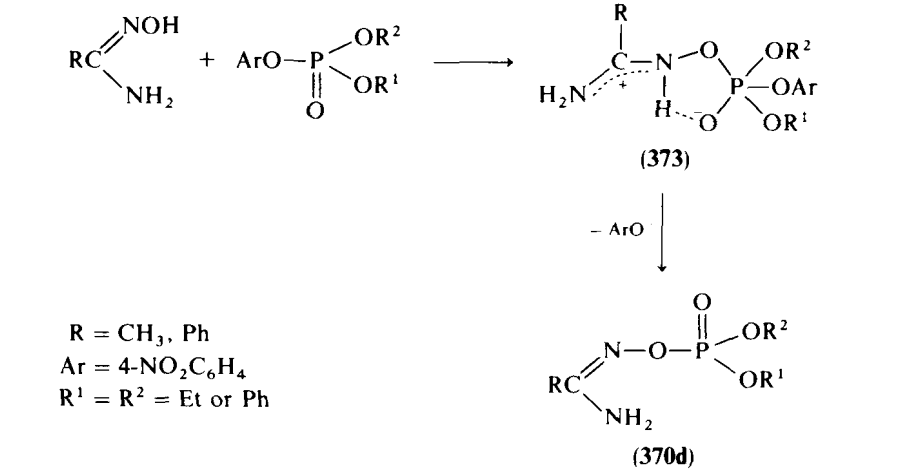


V. Derivatives of Amidoximes Containing P, Si, B and Sn

Treatment of simple arylamidoximes with isopropyl-methyl-phosphonofluoridate (*Sarin*) or diisopropyl-phosphonofluoridate in buffered aqueous solutions, as well as with the corresponding chloridates in nonaqueous media, results in O-substituted derivatives **370**. These undergo in alkaline solutions a Tiemann-type rearrangement with aryl migration to the aromatic cyanamide **371**[408]. Phosphinylated amidoximes (**370b**), however, hydrolyze rapidly to the parent compounds, whereas phosphonylated ones (**370c**) are intramolecularly rearranged under simultaneous dealkylation, affording **372**[409],

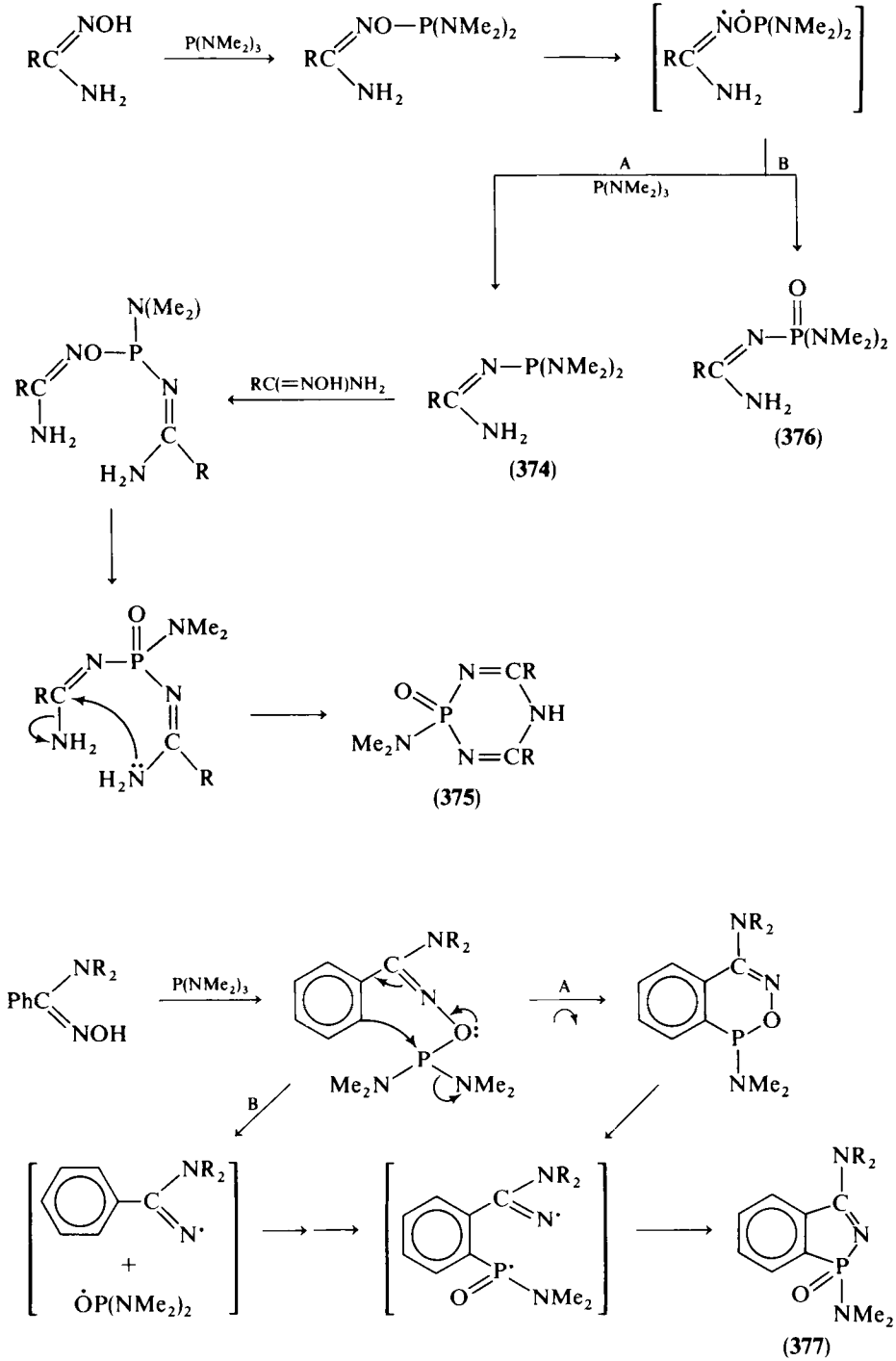


Acetamidoxime is a good nucleophile towards 4-nitrophenyl-diethyl (or diphenyl) phosphate, yielding compound **370d** along with the 4-nitrophenolate anion through the intermediate **373**; thus, it constitutes a potential dephosphorylating agent. Benzamidoxime is less reactive by a factor of 10^{410}.



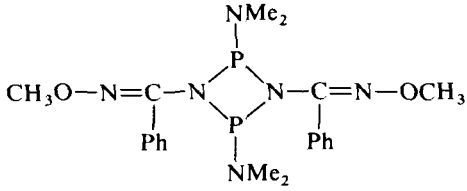
Interaction of unsubstituted amidoximes with tris(dimethylamino)phosphine leads to both 2,5-dihydro-1,3,5,2-triazaphosphorine 2-oxides (**375**)—path A— and N^2-[bis(dimethylamino)phosphinoyl]amidines (**376**)—path B—the relative ratio depending mainly on the temperature[411].

Under the same conditions *N*,*N*-disubstituted amidoximes usually give compounds analogous to **374**, but in the case of *N*-alkyl aromatic amidoximes 3-dialkylamino-1-


P(NMe2)3
A
B
RC(=NOH)NH2
(374)
(376)
(375)
PhC
NOH
(377)

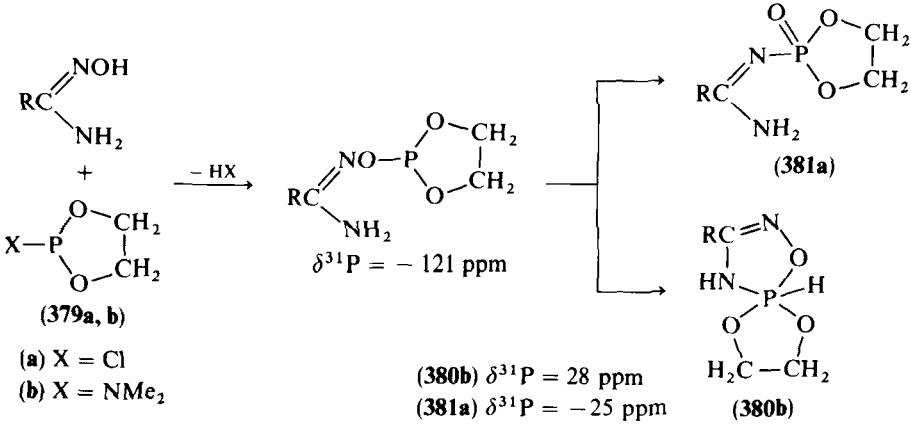
dimethylamino-1*H*-2,1-benzazaphosphole-1-oxides (**377**) are usually the main products probably through the mechanism shown nearby[411,412].

However, *O*-methyl benzamidoxime treated with $P(NMe_2)_3$[413] yields 1,3-diaza-2,4-diphosphetidine (**378**).



(**378**)

In the reaction between amidoximes and 2-chloro- or 2-dimethylamino-1,3,2-dioxaphospholane (**379**) at ambient temperature[411,414], the ^{31}P NMR signal pointed to a P^{III} intermediate, which could lead either to a tetra- (**380**) or to a penta-coordinate (**381**) phosphorous compound. A similar treatment of benzamidoxime affords **382**, whereas interaction with phosphorous trichloride and triethylamine results in the heterocycle **383**, dimerizing into **382** with an additional amount of the initial amidoxime[414].



(**379a, b**)

(**a**) X = Cl

(**b**) X = NMe_2

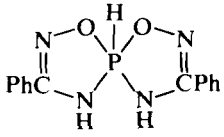
$\delta^{31}P = -121$ ppm

(**380b**) $\delta^{31}P = 28$ ppm

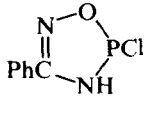
(**381a**) $\delta^{31}P = -25$ ppm

(**381a**)

(**380b**)



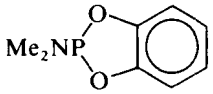
(**382**)



(**383**)

Furthermore, action of 2-dimethylamino-benzo[4,5]-1,3,2-dioxaphospholane (**384**) on simple amidoximes $RC(=NOH)NH_2$[415] gave spirophosphoranes **385** and spirobenzo-dioxaphospholanes of the types **386a** and **386b**.

Hexa-coordinated phosphorous compounds containing a P—OCH_3 bond could arise by oxidation of penta-coordinated ones with iodine in basic media, via perhaps a monocyclic phosphorane of the structure **387**, and they proved electrophilic enough to yield adducts in nonpolar solvents[416].



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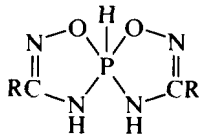

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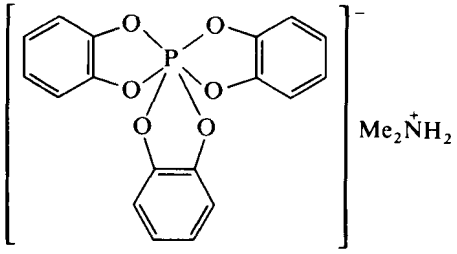
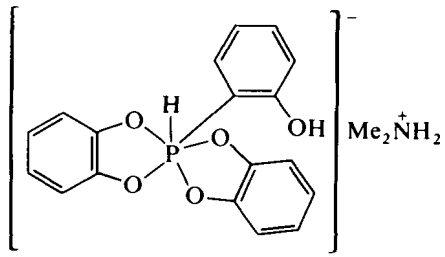
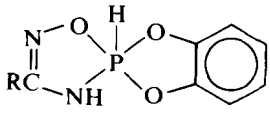


(386a)



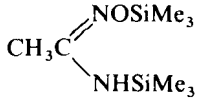
(386b)



(387)

Finally, *N*-phenylbenzamidoxime is reduced by phenyldichlorophosphine to the corresponding amidine hydrochloride, while its interaction with phosphorous trichloride yields the *N,N'*-disubstituted urea as a result of a Beckman rearrangement[254].

Treatment of simple amidoximes with an equimolar amount of Me_3SiCl in solvents such as benzene, hexane or ether and in the presence of triethylamine leads to O-substitution (**389**). A second $-SiMe_3$ function is only introduced in the case of acetamidoxime, probably due to the absence of steric hindrance, giving the *N,O*-bis(trimethylsilyl) derivative **388**, while synthesis of the respective monoproduct requires use of hexamethyldisilazane $(Me_3Si)_2NH$ and a catalytic trace of trimethylchlorosilane. Action of butyllithium upon the O-silylated amidoximes (**389**) can result in further N-silylation to *N,O*-disubstituted amidoximes[417] and even to *N,N,O*-tris-substituted amidoximes under the same conditions[417].



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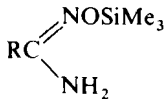
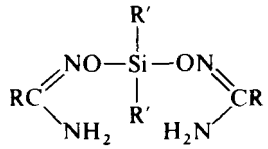


(389)

R = Et, Pr, Ph

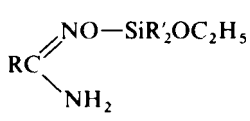
Hexamethyldisilazane also yields the O-derivatives of aryl amidoximes as well, while hexamethylcyclotrisilazane $(Me_2SiNH)_3$ or octamethylcyclotetrasilazane $(Me_2SiNH)_4$ afford diamidoximes of the type **390a**[418]. Reaction of simple amidoximes with dimethyl- (or diphenyl) diethoxy-silanes $R'_2Si(OC_2H_5)_2$ and a small amount of sodium leads to the analogous dimers (**390b**)[419], while tetra(acetoxy)silane $Si(OCOCH_3)_4$ produces **390c** under the same conditions[420].



(390)

(a) R′ = Me
(b) R′ = Me, Ph
(c) R′ = $COCH_3$

Nevertheless, the mono products (**391**) could be obtained on treatment of alkyl amidoximes with dimethyl (or diethyl) (ethoxy) chlorosilanes $R_2Si(OC_2H_5)Cl$ in the presence of triethylamine[419], whereas triethoxy and alkyltriethoxysilanes $R'Si(OC_2H_5)_3$, with R′ = H, Me, Et and allyl, result in dimers of general structure **392**, with the exception of benzamidoxime, yielding **393a**, R = Ph, R′ = H, Me, Et, allyl[420].



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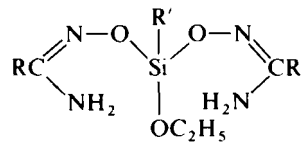

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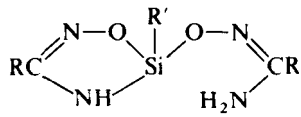
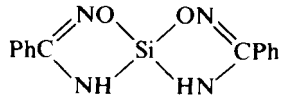


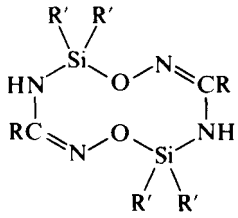
(393a,b)

Finally, upon reaction with tetraethoxysilane, acetamidoxime is converted in **393b** (R = Me; R′ = ethoxy), and benzamidoxime yields the spiro compound **394**[420].



(394)

Treatment of simple amidoximes with dialkyldichlorosilanes gave dioxadisila-tetraazacyclodecanes (**395**)[421], as well as the oxasiladiaza compounds **396**[419].



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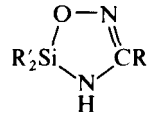
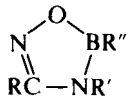


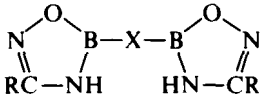
(396)

Cyclodehydration between unsubstituted amidoximes and an arene- or arylethaneboronic acid affords the corresponding 2,3-dihydro-1,3,5,2-oxadiazaboroles (**397a**)[4,422,423], while N-substituted ones give **397b** with phenylboronic anhydride[254]. Furthermore, simple amidoximes yield upon action of boric acid in boiling benzene the 2-alkoxy derivatives **397c**, as well as the dimers **398a,b** and compound **399**[422,423].

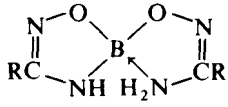


(397)

(a) R′ = H, R″ = aryl
(b) R′ = Ph, $CH_2COOC_2H_5$, R″ = Ph
(c) R′ = H, R″ = alkoxy



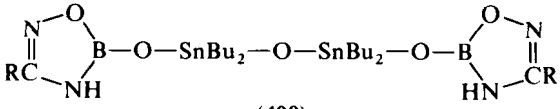
(398a, b)



(399)

(a) X = O
(b) X = [—ON=CRNH—]

Reaction of amidoximes with boric acid and bis(tributylstannyl)- or bis(triphenylstannyl)-oxide in a 2:2:1 ratio and simultaneous azeotropic removal of water with benzene leads to 2-[tributyl (or triphenyl) stannoxy]-3-hydro-4-alkyl-1,3,5,2-oxadiazaboroles (**397d**, with R′ = H, R″ = $OSnBu_3$, or $OSnPh_3$)[424], whereas dibutylstannyl oxide (Bu_2SnO) affords with the same reagents a dimeric species, assumed to be bis-(1,3,5,2-oxadiazaborol-2-yloxy)tetrabutyl-distannoxane (**400**)[425].



(400)

Treatment of amidoxime salts with tributylstannyl chloride, however, results in O-substituted derivatives, while the presence of diethyl(tributylstannyl)amine is required in order to obtain bis-(tributylstannyl)amidoximes[426].

W. Salt Formation and Complexes of Amidoximes

Thorough investigations on the analytical reactions of amidoximes with Cu, Hg, Pb and Group VIIIA metals have been carried out[427]. Numerous studies have reported on the properties of a long series of salts concerning both aliphatic[42,81,428–430] and aromatic amidoximes[196,394,431–441], as well as amino-[57,394,431–445] and bis-amidoximes[446]. Polarographic and X-ray measurements were also performed[447,448].

Several complex-forming amidoximes have already been mentioned, such as the crown glyoxime (**54**)[158], the bis(hydroxyimino)-imidazolidine (**59**)[164] or the bis(hydroxyimino)cyclododecine (**60**)[185]. Among the coordination compounds, those with Mo and W central atoms are the most important[449–454]. Amidoximes are versatile ligands, able to stabilize various stereochemistries. In addition, both the *anti* and *amphi* isomers of certain cyclic *vic* diamidoximes[165,184,451] led to interesting transition metal complexes, some of them bearing crown ether groups[452]. Possible technological applications of the aforementioned derivatives will be discussed in Section V.

V. TECHNOLOGICAL APPLICATIONS OF AMIDOXIMES

Amidoximes have found numerous technological applications. Thus, several aromatic ones inhibit corrosion effects in oil circulating systems[453], whereas Ag salts of benzamidoxime and of succinic diamidoxime bear pronounced photothermographic properties[458]. Derivatives obtained by treating isophthalic diamidoxime and benzamidoxime with Sn oxides are stabilizers for chlorinated polymers[95,455,456]. Some azo-diamidoximes have been proposed as suitable blowing agents for potential expanded thermoplastic materials[457], while cationic starches containing an amidoxime group act as paper-strengthening agents[458]. In addition, amidoximate anions may exert controlling effects upon dephosphorylation and spontaneous hydrolysis of mustard simulants[459].

Nevertheless, amidoximes are mainly used in polymer chemistry. While polyamidoximes as such do not possess notable qualities[281,460], when complexed with a radioactive metal they provide an efficient and safe radioactive source[461]. Perfluorinated imidoylamidoxime polymers possess high stability, impermeability and good plasticity[462]. Foams with alkylamidoxime functions exhibit ameliorated uniformity in their rise and prevent excess heat generation[463], while amidoxime-derived oxadiazole elastomers proved to be heat resistant[464]. Compounds bearing an amidoxime terminal group often show surface active properties of cationic or nonionic type[29,30,465,466]. The interfacial condensation of Ti or Zr salts with diamidoximes was thoroughly studied as well[467,468].

Amidoxime functionalized polymeric coatings with highly sensitive and specific absorption for particular vapors have promising qualities regarding the development of chemical electronic microsensors for surface acoustic wave detection[469], whereas partial amidoximation of polyacrylonitrile fibers improved dyeing capacity[470–473], gave them a pH-selective dye affinity[479] and made them more water swellable[475]. Further acrylonitrile-based amidoxime polymers act as semipermeable membranes[476,477] or facilitate solute separation[478], and several cellulose derivatives thereof have marked ion-exchange qualities[479,480]. Amidoxime moieties bonded on silica gel increase its separation efficiency for $V^{(V)}$[481], $Cu^{(II)}$[482], Group VIA[483] and transition metals[29,484], the latter exhibiting strong chelating affinity for polyamidoximes in general[164]. Similarly, $V^{(V)}$[481,485,486], $Fe^{(III)}$[487] and some rare earth metals[488,489] have affinity towards macroreticular resins containing amidoxime functions, even protonated ones[490]. An exhaustive series of heavy metals[491–499] is also strongly absorbed by related media, and the recovery of Ga has recently been studied as well[500–503]. It should be noted that creation of small mattresses by means of plastic nets ameliorates the handling characteristics of those fibrous adsorbents[156,504], that can furthermore be synthesized by radiation-induced grafting[505]. Chelating resins with amidoxime groups were tested towards many metal ions[506,507], and the effects of alkaline and acidic treatment or of temperature changes[508,509] have been published.

The importance of a possible uranium recovery from seawater has led to serious investigations in that field, and polyacrylamidoxime derivatives were classified among the best adsorbents. Thus, in 1963 it was shown that the amidoxime moiety of cyanoethylated cotton flannel fabrics regains about 70% of uranium from seawater-like solutions[491], and by 1977 a resin of that type was commercially available[510]. Further research was aimed at a rapid and high-yield elution, at selectivity in complexing solely uranium and at the long-term recyclability of the adsorbents. Resins containing at least two types of functional groups, e.g. open-chain amidoxime and cyclic imidoxime moieties, seem most effective[511]. In the last decade numerous optimization studies were published in this area[512–540], including some testing the parallel behavior of hydrous TiO_2[541], the effects of dissolved ions[542] and the recovery from phosphoric acid solutions[543]. Several recent reports on this field elucidate the present state of research[544–548].

VI. BIOLOGICAL ACTIVITY OF AMIDOXIMES

The possibility of varying the substituents at the α-carbon and at the two N-containing groups enabled the synthesis of a large number of amidoximes with pronounced biological activity. Among antibacterial agents can be considered amidoximes containing an arylsulfonyl[4,549,550], a sulfamide[62,63,253,551] or a sulfone[65] moiety at the α-carbon. Further general bacteriostatics are to be found among compounds possessing a 5-nitro-substituted five-membered heterocycle, such as 5-nitro-2-furyl-[552], *O*-(5-nitrofuroyl)-[311] and 5-nitro-2-thiazolyl-carboxy amidoximes[553]. Trypanocidic properties were ascribed to long-chain alkylene diamidoximes[56,554], while 4-sulfamyl-benzamide dioxime exhibits antiricketsial activity[63]. Several hydroxy-halo benzamidoximes[253,433], as well as some pyridyl-, furyl- or thionyl-substituted ones[65] show tuberculostatic action.

Interesting hypoglycaemic agents have been detected among 2-alkoxy-2-arylacetamidoximes and among those bearing a pyridyl moiety[555 557]. Furthermore, compounds combining a quinoxaline oxide, a hydroxyimino and an amino function proved to inhibit platelet aggregation[13], whereas the presence of a guanidine group bound to thiazolyl may stop gland secretion[558]. Amidoximes of (2-oxopyrrolidino)-alkanoic acids show marked antiamnesia features[559], those with triazolyl rings can be considered as analgesics[560] and some fully substituted aliphatic ones prolong antihistaminic activity[561]. Various α-heterocyclic amidoximes are antihypertensics[288,562–565], while several arylamidoximes might be used as haemostatics[254,566].

The presence of substituents connected to the functional group by a thioether linkage results in pronounced antiarrhythmic properties[567,568]. α-Aryloxy (or arylthio) acetamidoximes and α-alkyloxy propanamidoximes[12,569–578], as well as numerous benzoxazoles bearing an amidoxime moiety[579–583] are potential antidepressants, whereas *N*-arylacetyl formamidoximes intensity the biosynthesis of α-amylase[584].

Cytostatic properties of various amidoximes have also been reported. Thus, *N*,*N*-chlorethylated α-acetyl or α-aroyl formamidoximes act against sarcomas[584–589], α-bipyridyl formamidoximes exhibiting analogous behavior[590,591], and a series of simple aliphatic ones proved to possess antileukaemic properties[592–594]. Some heterocyclic amidoximes of the aza-thia type[595,596], and also several *N*-aryl formamidoximes are both acaricides and fungicides[597], and moderate antifungal activity was detected in 4,5-dihydro-1,2,4-oxadiazoles of the structure **259**[297] and in *N*-allyl benzamidoxime[154].

Finally, amidoximes have been tested as potential pesticides and *O*-alkyl, aryl, thienyl or arylcarbamoyl, *N*-alkyl formamidoximes were evaluated as interesting herbicides[598–605], while 2-(benzothiazolyl-3) acetamidoximes may regulate the growth of bean cultures[606].

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CHAPTER 17

Preparation and chemistry of ortho acids, ortho esters and ortho amides

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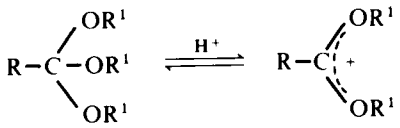
I. INTRODUCTION TO THE CHEMISTRY OF ORTHO ACIDS AND ORTHO ESTERS

The extensive synthetic potential of ortho esters (1,1,1-triorganyloxyalkanes or 1,1,1,1-tetraorganyloxymethanes ≡ tetraorganyl orthocarbonates)[1,2], and thus of the di- and trialkoxycarbenium ions[2–5] generated *in situ* from ortho esters, is reflected in their widespread use as versatile electrophiles in synthetic chemistry. Examples of these applications include the construction of selectively protected diketones and esters, acylated aromatic and heteroaromatic systems, heterocyclic compounds and cyanine dyes. Some of the cyclic ortho esters are useful reagents for the protection of hydroxy and carboxy groups during multi-stage syntheses[2]. Since numerous reactions of ortho esters take place in the presence of proton or Lewis acids by way of the *in situ* generated carboxonium ions, a knowledge of the reactivities and structural features of this class of compounds is also considerable importance for the prediction and interpretation of their modes of activity. Numerous reports on the chemistry of ortho esters have been published in the past 10–15 years, hence the treatment in the present chapter will be selective with emphasis being placed on recent developments of general interest. Readers of this chapter will, of course, be familiar with the first review in this series[6].

II. GENERAL STRUCTURAL AND REACTIVITY ASPECTS OF ORTHO ESTERS AND DI- OR TRIALKOXYCARBENIUM IONS

Molecular mechanics calculations[7] were first performed for some simple acyclic and cyclic ortho esters 1–3 (Figure 1). Of the acyclic representatives, the ortho esters **1a** and **1b** adopt almost C_3 conformations; the trimethoxymethane (**1d**) has a propeller conformation with C_1 symmetry. The dioxolane rings in compounds **2** possess throughout the envelope conformation whereas the 1,3-dioxane rings in compounds **3** take up the optimal chair geometry. Of this series, the 2,2-dimethoxy-1,3-dioxane (**3d**) exhibits the highest thermodynamic stability.

In most cases, heterolyses of acyclic (conformationally not constrained) ortho esters proceed spontaneously to furnish the highly stabilized alkoxycarbenium ions (equation 1) and this process is now well understood in terms of the 'antiperiplanar lone pair'[4,8,9]. In conformer **I** (Figure 2), the overlap of the free electron pairs with the antibonding σ^*



(1)

R = Alkyl, aryl, OR
R^1 = Alkyl

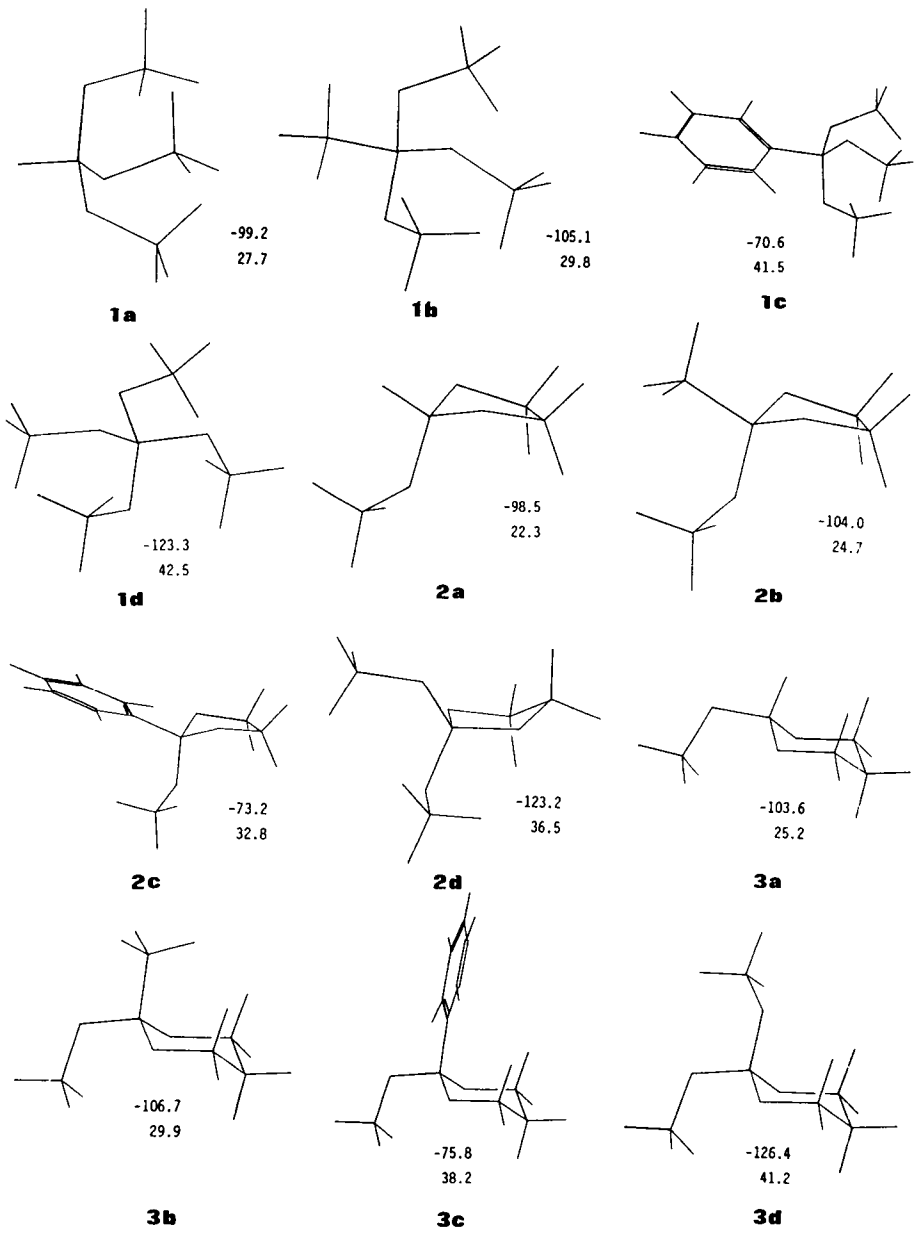
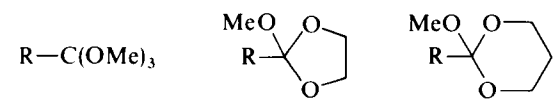


FIGURE 1. Minimum conformations of some *ortho* esters **1–3** from MM2 molecular mechanics calculations: first energy value: ΔH_f (kcal mol^{-1}), second energy values: E_{steric} (kcal mol^{-1})



R = H, Me, Ph, OMe **(1a–1d)** **(2a–2d)** **(3a–3d)**

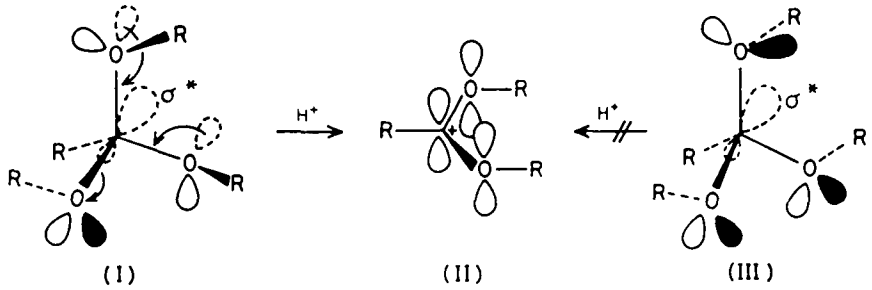


FIGURE 2. Stereoelectronic control of the ortho ester cleavage

orbital of the leaving group 'OR' reaches a maximum so that the starting orbitals can undergo transformation into the product orbitals in **II** with a minimal structural change. In a (hypothetically) fixed conformation **III**, however, a stereoelectronic barrier to heterolysis affording **II** exists.

Thus, in general, when the conformational equilibrium in the direction leading to conformer **I** is blocked in any way, the typical ortho ester cleavage (and also hydrolysis, see Section IV) becomes more difficult.

Acyclic and cyclic di- or trialkoxycarbenium salts (with the counter ions $[BF_4]^-$ or $[SbCl_6]^-$) possess sufficient thermal stability for structural characterization and for further synthetic utilizations[4,5,10] as a consequence of their ambident nucleophilic reactivity[4,5]. The ^{13}C-NMR spectra of the dialkoxycarbenium ions provide information on the relative π-electron densities at the carbenium centres. Thus, as expected, the following order can be derived from the ^{13}C-NMR resonance positions of the central carbon atoms in some acyclic representatives (CD_3NO_2, δ scale, ppm)[4]:

199.0	185.1	178.5	167.3	
$[HC(OEt)_2]^+$	$[MeC(OEt)_2]^+$	$[PhC(OMe)_2]^+$	$[(MeO)_3C]^+$	$[BF_4]^-$.

In the cyclic series, for example, the highly strained, five-membered ring analogue of trimethoxycarbenium tetrafluoroborate, 2-methoxy-1,3-dioxolan-2-ylium tetrafluoroborate, exhibits the same ^{13}C-NMR chemical shift (167.2 ppm) in liquid SO_2 at $-20^\circ C$ as the acyclic trimethoxycarbenium salt. For further ^{13}C-NMR chemical shifts of alkoxycarbenium ions, the reader should consult Reference 11.

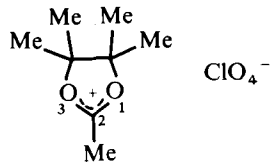
A series of oxonium and carboxonium ions was prepared from ^{17}O-enriched precursors and studied by ^{17}O-NMR spectroscopy[12]. As model compounds for acyclic dialkoxycarbenium ions, the spectra of some O-protonated carboxylic acids were recorded and compared with those of other oxonium ions (Table 1)[12]. A ^{17}O-NMR spectrum of the protonated acetic acid, obtained by addition of ^{17}O-enriched acetic acid to an SO_2 solution of $HF–SbF_5$ at $-25^\circ C$, showed a broad ($\Delta\nu_{1/2} = 300$ Hz) resonance at 204 ppm. A similar spectrum was obtained upon protonation of propanoic acid ($\delta^{17}O = 199.1$ ppm, $\Delta\nu_{1/2} = 280$ Hz). The chemical shifts observed for these ions are in good agreement with the preservation of substantial π-bond character in the carbon–oxygen bonds. The ^{17}O chemical shifts of ethanoic (acetic) and propanoic acid are 250.5 and 244 ppm, respectively. A shielding of about 50 ppm is observed for each oxygen atom upon protonation. This implies a loss of about 20% of π-bond order for each carbon–oxygen bond or a total loss of 40% for both bonds.

An X-ray crystallographic analysis of 2,4,4,5,5-pentamethyl-1,3-dioxolan-2-ylium perchlorate (**4**) has been reported[13]. The bond lengths between $C_{(2)}$ and $O_{(1)}$ and $O_{(3)}$

TABLE 1. ^{17}O-NMR chemical shifts of oxonium ions, referred to liquid SO_2 (δ = 505 ppm) according to Reference 12

Ion	^{17}O-NMR chemical shift δ (ppm)	$\nu_{1/2}$ (Hz)
$[H_3O]^+$	10.2 ($J_{O,H}$ = 103.5 Hz)	59
$[(H_3C)_3O]^+$	40.6	>400
$[H_3C(C{=}OH)CH_3]^+$	310.3 ($J_{O,H}$ = 74 Hz)	110
$[H_3C(C{=}OCH_3)CH_3]^+$	306.6	280
$[H_3CC(OH)_2]^+$	203.7 ($J_{O,H} \approx$ 50 Hz)	300
$[H_3CCH_2C(OH)_2]^+$	199.1 ($J_{O,H} \approx$ 49.9 Hz)	280

are 1.28 Å and 1.24 Å. A comparison with the C=O bond length (1.24 Å) thus reveals significant double-bond character in both the $C_{(2)}/O_{(1)}$ and $C_{(2)}/O_{(3)}$ bonds of **4**. Pittman and coworkers obtained similar but not completely concordant results from SCF-MO calculations using the INDO approximation for the 1,3-dioxolenium system[14]. The calculated bond lengths, π-bond orders and barriers to rotation about the exocyclic σ-bonds at the 2-positions of some 2-substituted 1,3-dioxolan-2-ylium ions are summarized in Table 2. The relevant π-bond orders ($O \dashuline{\cdots} C^+ \dashuline{\cdots} O$) range from about 0.5 to 0.65 Hevesi and coworkers[15] discussed a π-bond order of about 0.7 to 0.8 for acyclic carboxonium ions on the basis of a graphical extrapolation of the relationship bond length/π-bond order.



(**4**)

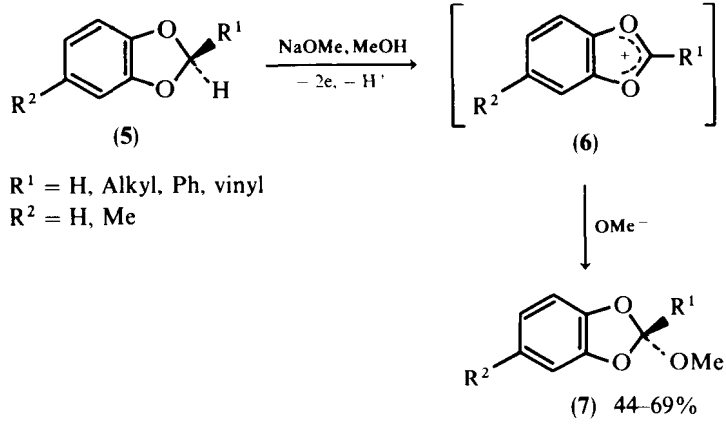
TABLE 2. Calculated bond lengths. π-bond orders and barriers to rotation for some 2-substituted 1,3-dioxolenium ions[14]

R	$C_{(2)}/O$ bond length (Å)	π-Bond order	Barrier to rotation about $C_{(2)}/R$ bond kJ mol^{-1} (kcal mol^{-1})	
H	1.313	0.650	—	—
Me	1.328	0.587	0.54	(0.013)
OH	1.328	0.540	35.6	(8.5)
NH_2	1.336	0.485	128.1	(30.6)

III. PREPARATION OF ORTHO ESTERS

A. Oxidation of Aldehyde Acetals

The electrochemical methoxylation of aldehyde acetals is, in general, a convenient procedure for the preparation of ortho esters bearing a wide range of groups[16] which are not so readily accessible by the more conventional transesterification methods (see Section III. C). Thus, the 2-methoxy-1,3-benzodioxoles 7, compounds of interest for protecting group strategies in peptide, nucleoside and nucleotide chemistry, were synthesized by anodic methoxylation of 1,3-benzodioxoles **5** (equation 2)[17]. It was shown by cyclic voltametry that the reaction proceeds via a two-electron oxidation (ECEC mechanism). Heterolyses of compounds **5** via 1,3-benzodioxolium ions **6** as stable intermediates are plausible on account of the high stabilization of such cations[5].

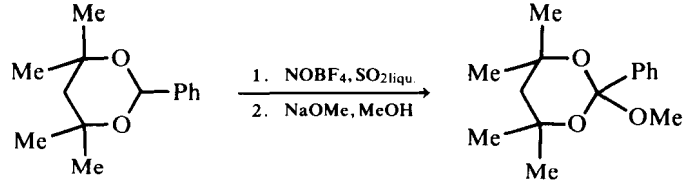


(5) (6)

R^1 = H, Alkyl, Ph, vinyl
R^2 = H, Me

(7) 44–69% (2)

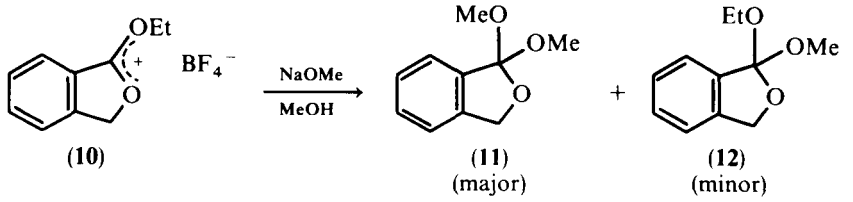
The oxidation step can also be realized chemically. For example, 2-methoxy-2-phenyl-4,4,6,6-tetramethyl-1,3-dioxane (**9**), also heterocyclic ortho ester, was prepared from the corresponding acetal **8** by oxidation with nitronium tetrafluoroborate and subsequent reaction with sodium methoxide (equation 3)[18].



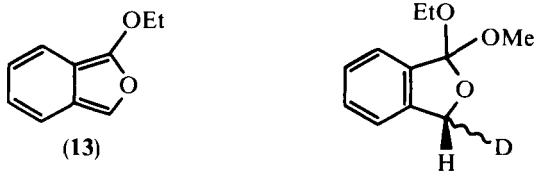
(8) (9) 25% (3)

B. From Dialkoxycarbenium Ions

One of the standard methods of ortho ester synthesis, first introduced by Meerwein and coworkers[19], consists of the addition of a dialkoxycarbenium tetrafluoroborate to an excess of a sodium alkoxide in the corresponding alcohol. Mechanistic aspects of this process, called the Meerwein ortho ester reaction, have been discussed[20]. In this way, the reaction of *O*-ethylphthalidium tetrafluoroborate (**10**) with an excess of sodium



(10) (11) (major) (12) (minor) (4)



(13) (12-d)

methoxide in methanol gives rise to the ortho ester **11** as the major product (equation 4). A plausible intermediate, the 1-ethoxyisobenzofuran **13**, has been prepared in solution and isolated. This compound reacts readily with, for example, CH_3OD to give a mixture of the ortho esters **12**/**12-d** containing approximately one atom of deuterium per molecule of product. This indicates that **13** reacts by way of a rate-determining proton transfer step followed by collapse of the ion pair to furnish **12**. Thus, **13** can be excluded as an intermediate in the reaction of **10** to produce **11**. The main product **11** probably results by way of further selective hydrolysis of **12** and subsequent solvolysis of the intermediarily formed cation.

C. From Orthocarboxylic Acid Derivatives

The classical chloroform to ortho ester transformation[21] has been extended and found to be amenable to phase-transfer catalysed conditions. Trialkyl orthoformic esters have thus been obtained in 33–36% yields[22]. Trimethoxyacetonitrile (**15**), conveniently accessible in 58.5% yield from trichloroacetonitrile (**14**) and sodium methoxide (equation 5)[23], is a synthetically attractive and versatile building block. For further transformations of **15** to orthocarbonic esters, see Section III.G. Compound **15** is also an interesting reagent for the syntheses of trimethoxyacetamides and other derivatives[24].

$$\underset{\textbf{(14)}}{NC{-}CCl_3} \xrightarrow[Et_2O]{NaOMe} \underset{\textbf{(15)}}{NC{-}C(OMe)_3} \qquad (5)$$

Alkyl esters of trialkoxyacetic acid have been obtained in high purities from alkyl dichloro(methoxy)acetates in the presence of an alcohol and pyridine[24]. The dialkyl oxalate formed as a by-product was removed by reaction with pyrrolidine prior to distillation of the desired product. 1,1,1-Trimethoxyacetates can be transformed into a variety of amides[24]. Pentaalkoxyethanes **18** are formed from α-alkoxycarboxylates **16** by chlorination with PCl_5 (to give **17**) and subsequent nucleophilic displacement reactions with sodium methoxide (equation 6)[25].

Alkoxymethyleneiminium salts can be converted directly by alcoholysis into ortho esters[26], whereas the presence of carboxylic acids is necessary in the case of 1,1-dialkoxy-1-dialkylaminoalkanes[18,27,28]. Dialkoxycarbenium ions have been discussed as inter-

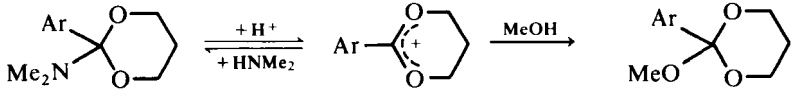
$$R^1OCH_2COOR^1 \xrightarrow{PCl_5} R^1OCHClCCl_2OR^1$$

(16) (17)

$$\xrightarrow[MeOH]{NaOMe} R^1OCH(OMe)CCOMe)_2OR^1 \quad (6)$$

(18) ~60%

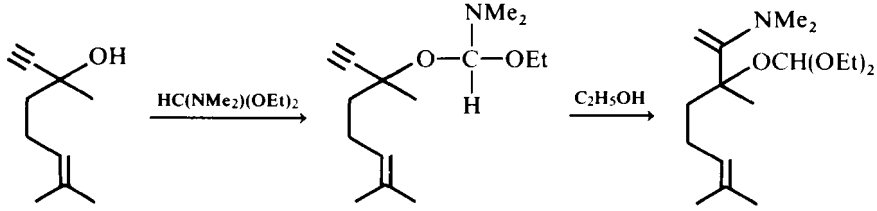
mediates in both cases. This procedure is attractive for the syntheses of aryl(organyloxy)methanes which cannot be obtained easily and/or in high purities by other routes. For example, the preparation of 2-methoxy-2-(4-methoxyphenyl)-1,3-dioxane (**21**) commences with the readily available dimethoxy(dimethylamino)(4-methoxyphenyl)methane and 1,3-propanediol to furnish the dioxane **19** (equation 7). Acetic acid-catalysed methanolysis of **19** then proceeds through the 1,3-dioxanium ion **20** to give the cyclic ortho ester **21**[18].



(19) (20) (21) (7)

Ar = *p*-Anisyl 65%

In an analogous procedure, the (2-amino-2-alkenyloxy)diethoxymethane **24** and related compounds can be synthesized in reasonable yields via the sequence **22** → **23** → **24** (equation 8)[29].



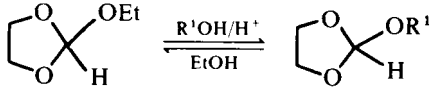
(22) (23) (24) 40% (8)

The most important method for the preparation of ortho esters bearing higher molecular or functionally substituted primary alkoxy groups consists of the simple transesterification of 1,1,1-trimethoxy- or 1,1,1-triethoxyalkanes[2]. On the other hand, the Pinner reaction[2] or the reactions of 1,1,1-trihalomethanes with higher alkanols sometimes result in poor yields[2] while reactions of secondary and tertiary alcohols or phenols do not proceed to completion. Transesterification is also a useful method for the synthesis of mixed ortho esters[30,31]. Thus, trialkoxymethanes **26** were easily converted to the mixed ortho esters **25** or **27** in the presence of a phenol and, in most cases, under catalysis by 4-toluenesulphonic acid (equation 9)[30–32].

Transesterification reactions of 2-alkoxy-1,3-dioxolanes (**28** → **29**) can be realized in

$$\underset{\textbf{(25)}}{HC(OAr)_2(OR^1)} \underset{+2ArOH/H^+}{\overset{+R^2OH}{\rightleftharpoons}} \underset{\textbf{(26)}}{HC(OR^2)_2(OR^1)} \underset{+R^1OH}{\overset{+ArOH/H^+}{\rightleftharpoons}} \underset{\textbf{(27)}}{HC(OR^2)_2(OAr)} \quad (9)$$

a similar manner (equation 10)[33]. The related transesterification of 2-alkoxy-1,3-dioxolanes with deoxyribonucleosides in the presence of pyridinium 3-nitrobenzenesulphonate represents an important procedure for protection of the 5′-hydroxy function[34].



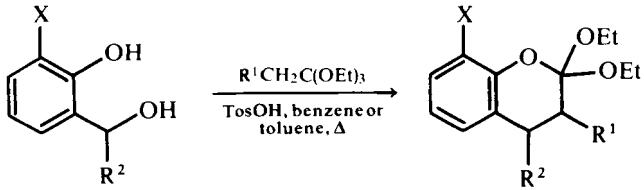
(10)

(28) **(29)** 41–58%

$R^1 = [CH_2CH_2]_nOMe$

$n = 1$–4

2-Hydroxybenzyl alcohols **30** react with 1,1,1-triethoxyalkanes to produce 2,2-diethoxychromanes **31** (equation 11). The reaction mechanism involves a 1,4-polar cycloaddition betweeen the 5-methylene-6-oxo-1,3-cyclohexadiene and the ketene acetals[35].



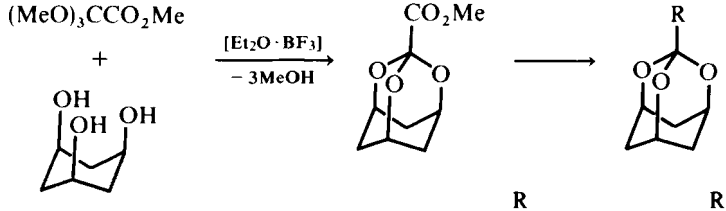
(11)

(30) **(31)** up to 67%

X = H,OMe

R^1 = H,Me

R^2 = H,Ph



(12)

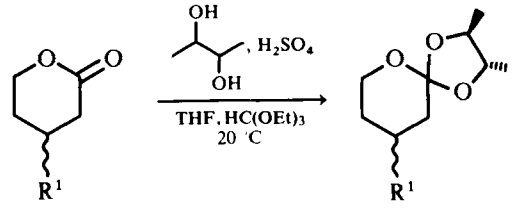
	R		R
a	CH_2OH	g	
b	Ph_2COH	h	
c	$CO_2H \cdot H_2O$	i	n—BuCO
d	$CONH_2$	j	i—PrCO
e	$NHNH_2$	k	PhCO
f			

Further synthetically attractive transesterification reactions of 1,1,1-trialkoxyalkanes with diols and triols are described elsewhere[18,36–39].

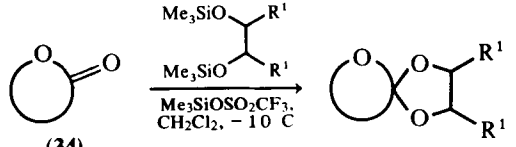
Methyl trimethoxyacetate and *cis*-1,3,5-cyclohexanetriol react readily to give methyl 2,4,10-trioxoadamantane-3-carboxylate which can be transformed into further derivatives (**a–k**) of 2,4,10-trioxoadamantane (equation 12)[40].

D. From Carboxylic Acid Derivatives

The lactones **32** and **34** react with 1,2-diols or bis(trimethylsilyl) ethers via intermediarily generated lactonium ions to furnish the spirocyclic ortho esters **33** or **35** (equations 13 and 14)[41–43]. The reaction **32** → **33** (equation 13) has been employed for the resolution of chiral 1,2-diols[43].

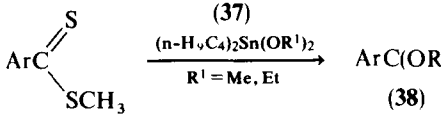


(32) ((±) **33**) 43–73% (13)



(34) (35) (14)

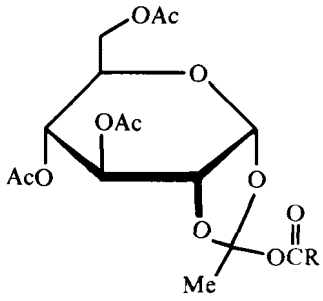
Aromatic ortho esters **38** are also obtained from the reactions of methyl dithiocarboxylates **36** with dialkoxy-di-n-butylstannanes **37**; the reaction mechanism involves an addition/elimination process at the thiocarbonyl group of **36** (equation 15)[44].



(36) (38) (15)

The reactions of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver carboxylates in tetrahydrofuran furnish cyclic acyl *ortho* esters **39**[45]. These reactions are of interest in glycoside synthesis and in the study of neighbouring group effects in general.

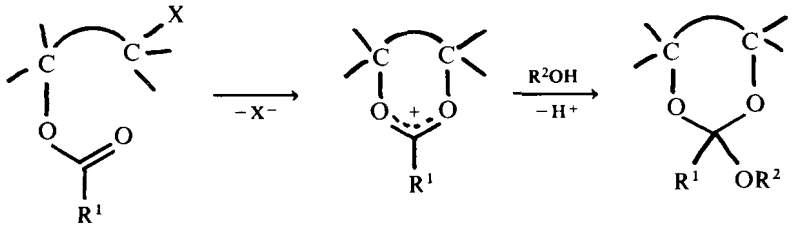
When an acyloxy group is located in an appropriate conformation and orientation with respect to a neighbouring leaving group such as tosylate or bromide, solvolytic replacement of the leaving group in buffered alcoholic solution gives rise to the cyclic *ortho* ester through the intermediacy of dioxolenium or dioxenium ions (equation 16)[2,5]. This method is also valuable for the preparation of 1,2-*ortho* esters of sugars starting from acylglycosyl halides[2]. Since *ortho* esters of sugars serve as starting materials for



39	R
a	Me
b	Et
c	t-Butyl
d	MeO_2C
e	$-(CH_2)_3-$

(50–80%)

the syntheses of di- and oligosaccharides, such reaction sequences are also of importance for synthetic carbohydrate chemistry[2].

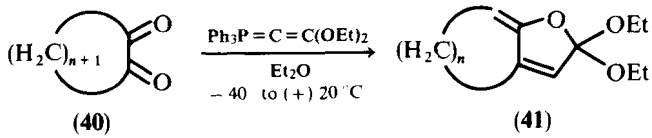


(16)

X = Tos, Br

E. From Activated Alkenes

Ketene acetals undergo addition reactions which are, in most cases, reversible with alcohols and phenols to form simple and mixed ortho esters[2]. Phosphaketene acetals are particularly interesting building blocks for the synthesis of annellated 2,2-dialkoxy-2,5-dihydrofuranes **41** (equation 17) starting from the readily available and enolisable 1,2-diketones **40**[46]. 1,1-Dihalo-2-nitroalkenes react with alkoxides or phenoxides to furnish functionalized ortho esters through an addition/elimination mechanism[47].

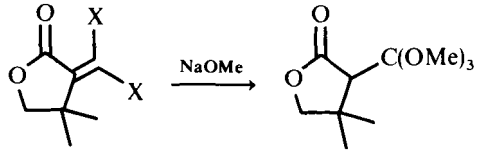


(17)

(40) **(41)**

$n = 3$ (81%)
$n = 4$ (54%)
$n = 9$ (65%)

In the same way, the geminal dihalomethylenelactones **42** react with sodium methoxide to form the ortho esters **43** (equation 18)[48]. The starting materials **42** are readily accessible from 4,4-dimethyloxolane-2,3-dione and triphenylphosphine/carbon tetrahalide.



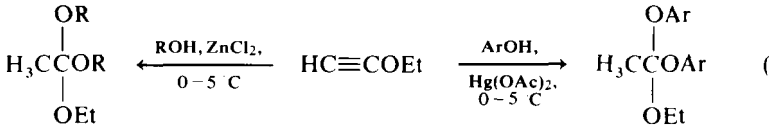
(18)

(42)
(a) X = Cl
(b) X = Br

(43)

F. From Alkoxy-1-alkynes

Drastic reaction conditions are generally necessary for the addition of hydroxy compounds to 1-alkoxy-1-alkynes **44** to furnish 1,1,1-trialkoxyalkanes[2]. A development of this methodology is the $Hg(OAc)_2$- or $ZnCl_2$-catalysed addition of alcohols or phenols to **44** which proceeds under mild conditions to give mixed 1,1,1-trialkoxyethanes **45** or 1,1-diaryloxy-1-ethoxythanes **46** in reasonable yields (equation 19)[49].

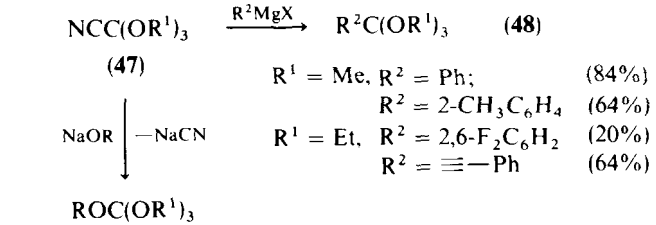


(19)

(46) 35–64% (44) (45) 58–75%

G. From Orthocarbonic Acid Derivatives

Trialkoxyacetonitriles **47** undergo substitution reactions with Grignard reagents to produce a variety of ortho esters **48** in reasonable to good yields (equation 20)[23,50]. This sequence is a valuable supplement to the relatively few known methods for the preparation of aryl(triorganyloxy)methanes. Reactions of **47** with alkoxides give rise to a variety of orthocarbonic esters **49** (equation 20)[51].

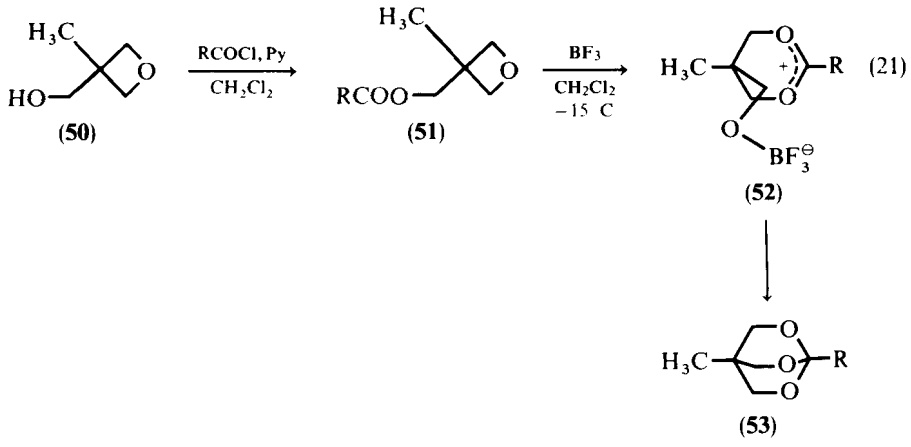


(20)

49	$R^1 = R$
a	Me
b	Et
c	n-Bu
d	$CH_2CH{=}CH_2$

H. Ortho Esters from Rearrangement Reactions

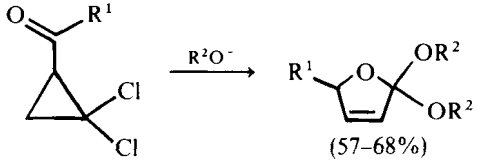
A novel and general route to bridged carboxylic ortho esters starts from the readily available 2-hydroxymethyl-2-methyloxetane, **50** (equation 21)[52]. Acylation of **50** gives rise to the corresponding oxetane esters **51**, which undergo smooth rearrangement in the presence of boron trifluoride etherate in dichloromethane at −15°C to yield ortho esters of the 2,6,7-trioxabicyclo[2.2.2]octane series **53**. The reaction is assumed to proceed through the intermediate zwitterion **52**.



(21)

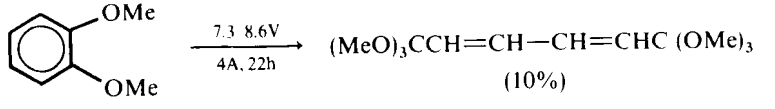
R = $PhCH_2CH_2CH_2$— (75%)
R = n-C_5H_{11}— (90%)
R = $HC{\equiv}CCH_2CH_2CH_2$— (90%)

The rearrangement reactions of 2-acyl-1,1-dichlorocyclopropanes in the presence of alkoxides proceed via oxidative C/C bond cleavage and are useful for the synthesis of 2,2-dialkoxy-2,5-dihydrofuranes (equation 22)[53].



(22)

The electrochemical methoxylation of 1,2-dimethoxybenzene gives rise to 1,1,1,6,6,6-hexamethoxy-2,4-hexadiene by way of a ring-opening reaction (equation 23)[16].



(23)

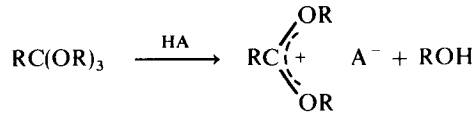
IV. REACTIONS AND SYNTHETIC APPLICATIONS

A. Hydrolysis

The kinetics and mechanisms of the hydrolysis of ortho esters have already been reviewed comprehensively in this series by Cordes[6]. Since then, further investigations on this subject have been reported and some of the results are summarized in this section.

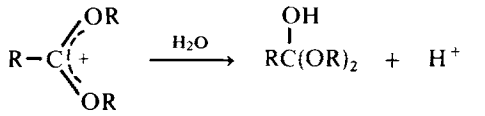
The three-step mechanism established by Cordes[54] and Fife[55] has been further substantiated through more recent experiments by Kresge[56] and McClelland[57] (equations 24–26).

Step I. Formation of a carboxonium ion



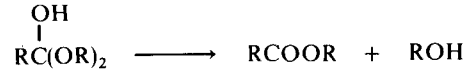
(24)

Step II. Addition of the nucleophile (H_2O)



(25)

Step III. Decomposition of the hemi-ortho ester



(26)

The rate-limiting step of the hydrolysis (step I, II or III) is determined by the pH value of the medium. Kinetic investigations have shown that, at low pH values, step III is rate-limiting whereas, at high pH values of the medium, step I is the rate-limiting process[57–60]. The presence of donor substituents at the proacyl carbon atom of the ortho esters should enhance step I as a result of the stabilizing effect in the generated carboxonium ion (product development control). The transition state of the decomposition of the hemi-ortho ester in step III should not be significantly influenced by the presence of a donor group at the tetrahedral carbon atom[18].

Acyclic and cyclic (e.g. dioxolane-type) ortho esters exhibit different kinetics in steps I/III[56]. A comparison of the rates of hydroxonium ion catalysed hydrolysis determined at low and high pH values reveals that the cyclic ortho ester, 2-methoxy-2-methyl-1,3-dioxolane, undergoes a change in the reaction mechanism from rate-determining generation of a dialkoxycarbenium ion (step I) to rate-determining decomposition of the hemi-ortho ester intermediate (step III) whereas the acylic analogue, trimethyl orthoacetate, does not. This difference is not caused by the dimethylenedioxy structure of the cyclic ortho ester since an acyclic ortho ester with a similar structure, tris(2-methoxyethyl) ortho acetate, does not undergo an analogous change in the rate-determining step.

The difference in behaviour is not consistent with a previously advanced hypothesis involving differing effects of the substituents on steps I and III; in fact, a retrospective analysis of the previously published data shows that the effects of the substituents on these two steps are quite similar.

Two other effects, namely (1) the entropic disadvantage of the ring-opening processes and (2) solvational stabilization of the hemi-ortho ester intermediates, are suggested as possible factors which may control the rate-determining step in these reactions.

In the cases of trimethyl orthomesitoate[61] and conformationally fixed ortho esters[62], step II may also become the rate-limiting process. Here, steric and stereoelectronic effects are suggested as playing a significant role.

In an investigation of the hydrolysis of 3-aryl-2,4,10-trioxaadamantane ortho esters as bridged systems, it was found that these compounds undergo rapid equilibration with the corresponding ring-opened dioxan-2-ylium ions prior to the hydrolysis to the 1,3,5-cyclohexanetriol monobenzoates[57]. The ratio 'dialkoxycarbenium ion/ortho ester' at the equilibrium has been measured as a function of the acidity.

B. Synthetic Transformations of Ortho Esters

1. Introduction

Ortho esters have been found to possess highly versatile applications in the preparation of reagents and building blocks for a variety of compounds in the fields of technical, natural product and medicinal chemistry[1–4,6,63]. Of the numerous known reactions, some of the synthetically highly important transformations of ortho esters can be summarized as follows:

Selective hydrolysis to carboxylic esters or carboxylic acids (e.g. protecting group methodologies).

Heterolysis to alkoxycarbenium ions for further preparative uses (such as, for example, acylation or alkylation of a variety of nucleophiles).

Acetalization of aldehydes and ketones as well as the synthesis of enol ethers.

Electrophilic addition (mostly Lewis acid-catalysed) of ortho esters to alkenes, alkynes, enol ethers and trialkylsilyloxyalkenes to provide selectively functionalized synthons for a range of preparative uses.

Addition reactions with ketenes to form 3,3-dialkoxypropanoic acid alkyl esters.

Synthesis of ketene O,O-acetals via β-elimination of alkanols.

Aminolysis with primary amines or acylamines to give carboxylic ester imides or amidines and with secondary amines to furnish ketene aminals or carboxylic dialkylamides.

Alkoxyalkenylations or dialkoxyalkylations of CH_2- and CH-acidic compounds.

Synthesis of cyanine dyes.

Synthesis of heterocyclic ring systems.

Synthesis of aldehyde acetals from Grignard reagents.

Synthesis of aromatic and heteroaromatic aldehydes or ketones as well as triaryl- or triheteroarylmethanes under acid catalysis.

Halogenation to provide α-halogenated ortho esters.

Reactions with complex metal hydrides to form aldehyde acetals.

Three component reactions of the ortho ester/primary amine/carbon acid type.

Rearrangement reactions of ortho esters with 3-alkenols (Claisen ortho ester rearrangement).

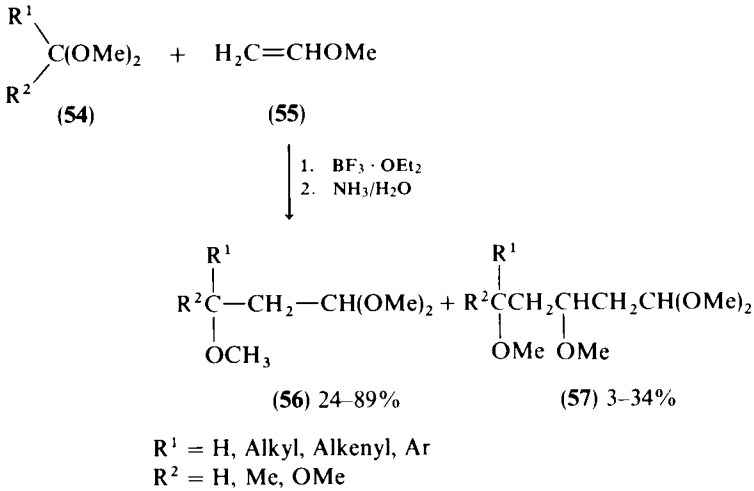
A selection of some of the more generally interesting, synthetically attractive and recent applications from the manifold reports in this field will be discussed in the following sections.

2. Reactions with C-nucleophiles

The Lewis acid-catalysed reactions of acetals or ortho esters with enol ethers give rise to alkoxyalkanes and are of general synthetic interest as C—C bond-forming processes[1,64]. The relative reactivities of acetals and ortho esters in boron trifluoride diethyl etherate-catalysed reactions with methyl vinyl ether were studied and a systematic investigation of the synthetic potential of this type of reaction in electrophilic alkoxyalkylations of enol ethers was reported[65]. The relative reactivities of acetals and ortho esters **54** in the BF_3–OEt_2-catalysed reactions with methyl vinyl ether (**55**) (– 78°C, CH_2Cl_2) have been determined by means of competition experiments (equation 27). A reactivity increase of 5 orders of magnitude was found in the series:

saturated acetals < methyl orthoformate < benzaldehyde
acetals < α,β-unsaturated acetals

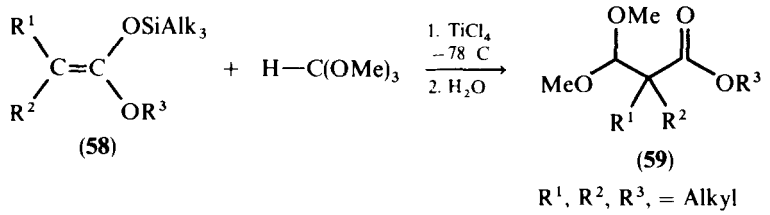
Formaldehyde acetals as well as orthoacetates and orthobenzoates did not react under these conditions. The experimentally determined k_{rel} values can be used to predict the results of Lewis acid-catalysed additions of acetals and ortho esters to vinyl ethers and are thus of importance for synthesis planning.



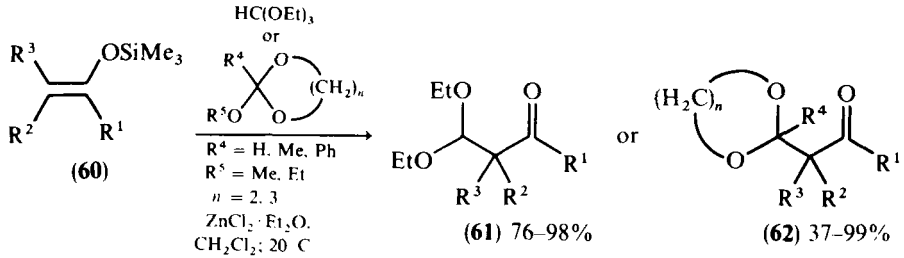
R^1 = H, Alkyl, Alkenyl, Ar
R^2 = H, Me, OMe (27)

In the last decade, silyloxyalkenes[42,66] have been developed as highly versatile and interesting d^2 or d^4 synthons[205] for regiospecific functionalizations with ortho esters in an alkoxyalkylation process which, in most cases, proceeds under kinetically controlled conditions. Mukaiyama and coworkers[67] performed the first reactions of trialkylsilyl enol ethers with orthoformates. In most cases it was found that the presence of $TiCl_4$ as a lewis acid catalyst is necessary for activation of the reaction. The ketene acetals **58** also react with acetals and orthoformates at –78°C in the presence of $TiCl_4$ to afford the corresponding β-alkoxy esters or β,β-dialkoxy esters **59** in good yields (equation 28)[67].

This methodology for the highly selective functionalization of trialkylsilyloxyalkenes was further developed by Pindur and coworkers[68–71] and zinc chloride diethyl etherate was found to be a very effective and mild Lewis acid catalyst. Thus, trimethylsilyloxyalkenes **60** were smoothly converted to selectively protected 1,3-diketones **61**, **62** by reaction with a variety of acyclic and cyclic ortho esters (equation 29)[68–71]. However,



(28)

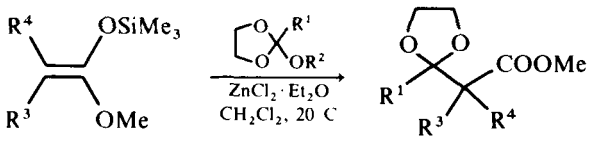


R^1	R^2	R^3
Ph	H	H
$PhCH_2$	Ph	H
Me	Me	Ph

(29)

orthoacetoacetates and trimethoxybenzoates did not react under these conditions in spite of the high reactivity of the dialkoxycarbenium ion formed *in situ* towards the (nucleophilic) chloride ion always present in the reaction medium. On the other hand, the more reactive 2-alkoxy-1,3-dioxolanes and 2-alkoxy-1,3-dioxanes possess a greater electrophilic reactivity towards the trimethylsilyloxyalkenes **60**.

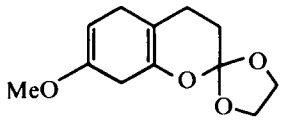
In the same way, *O*-methyl-*O*-trimethylsilylketene acetals **63** react with a 2-alkoxy-1,3-dioxolanes to yield selectively α-protected β-ketocarboxylic esters (equation 30)[70]. Furthermore, the reactions of the enolic ester **65** with silylketene acetals **66** in dichloromethane in the presence of $TiCl_4$ at low temperature gave the corresponding ketoacetal esters **68** via the titanium enolates **67** (equation 31)[72].



(30)

R^3	R^4
H	Me
H	Ph

R^1	R^2
H	Me
Me	Et
Ph	Me



(65)

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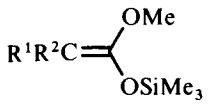
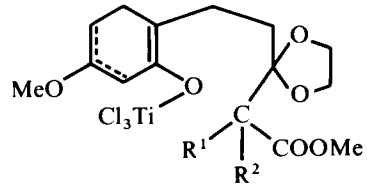


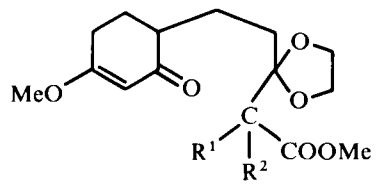
(66)

R^1	R^2
H	H
H	Me
Me	Me



(67)

R^1	R^2
H	H
H	Me
Me	Me



(68)

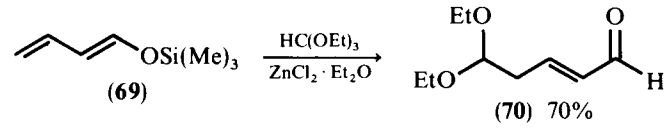
R^1	R^2
H	H
H	Me
Me	Me

(31)

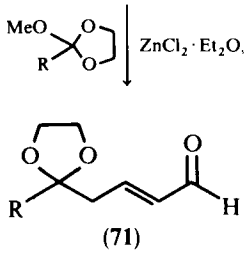
Triethyl orthoformate or 2-methoxy-1,3-dioxolanes are able to functionalize 1-trimethylsilyloxybutadiene (**69**) in a highly regioselective manner (equation 32)[73]. The resultant γ-protected 1,5-dicarbonyl compounds **70** or **71** are the result of frontier molecular orbital controlled reactions (d^4 reactivity of **69**).

Further acetalizations of trimethylsilyl enol ethers are described elsewhere[42,66] (e.g. reactions of *E*/*Z*-1-*t*-butyl-1-trimethylsilyloxypropene with trialkyl orthobenzoates) and in Reference 74 (reactions of ortho esters with 2-trimethylsilyloxyfurans).

Allylsilanes, acting as allyl anion equivalents, are smoothly functionalized upon reaction with orthoformates. For example, triethyl orthoformate reacts with allyl-(trimethyl)-silane (**72**) to furnish the bis-allylated compound **74** via **73** (equation 33)[75]. It was concluded that the reaction of the allylsilane with the resulting acetal **73** is apparently faster than the monoallylation of the orthoformate. The scope of the reaction

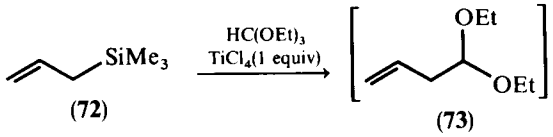


(69) (70) 70% (32)

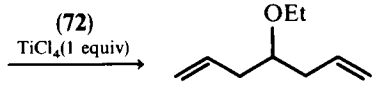


(71)

R = H (100%)
R = Me (62%)
R = Et (50%)
R = Ph (47%)



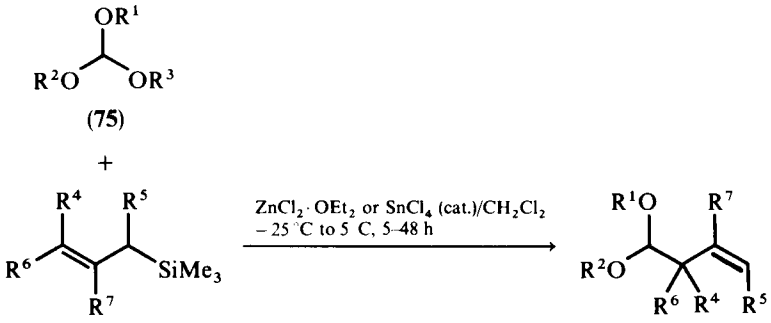
(72) (73)



(74) (33)

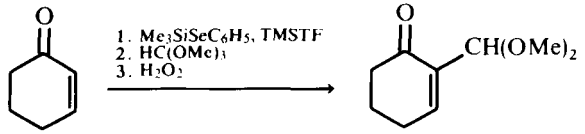
was extended in a more recent investigation[76]. In the presence of $ZnCl_2$-OEt_2 or $SnCl_4$ as Lewis acid catalysts, a variety of β,γ-unsaturated aldehyde acetals **77** were synthesized from the ortho esters **75** and allylsilanes **76** in moderate to good yields (equation 34).

In particular cases, α,β-unsaturated ketones are α-alkoxylated by a combined reaction with trimethylsilyl phenyl selenide and ortho esters or acetals in the presence of trimethylsilyl triflate (TMSTF)[77] (see, for example, the reaction **78** → **79** in equation 35).



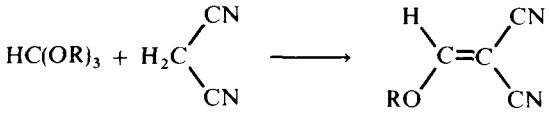
(75) (76a–g) (77a–g) 45–83% (34)

75,	76,	77	R^1	R^2	R^3	R^4	R^5	R^6	R^7
a	a	a	Et	Et	Et	H	H	H	H
b	b	b	Me	Me	Me	H	H	H	Me
	c	c	Me	Me	Me	$-(CH_2)_3-$		H	H
	d	d	Me	Me	Me	H	H	$-(CH_2)_2-$	
	e	e	Me	Me	Me	H	H	$-(CH_2)_4-$	
c	f	f	$-(CH_2)_2-$		Me	Me	H	Me	H
	g	g	$-(CH_2)_2-$		Me	Me	H	Me	Me



(78) (79) (35)

Alkoxymethylenemalonodinitriles **82** are readily obtained from the reactions of malononitrile (**81**) and ortho esters **80** in the presence or absence of acetic anhydride (equation 36)[78]. Orthobenzoates, orthoacetates or orthoformates may be used and the products **82** are interesting starting materials for the synthesis of a variety of heterocyclic systems[78].



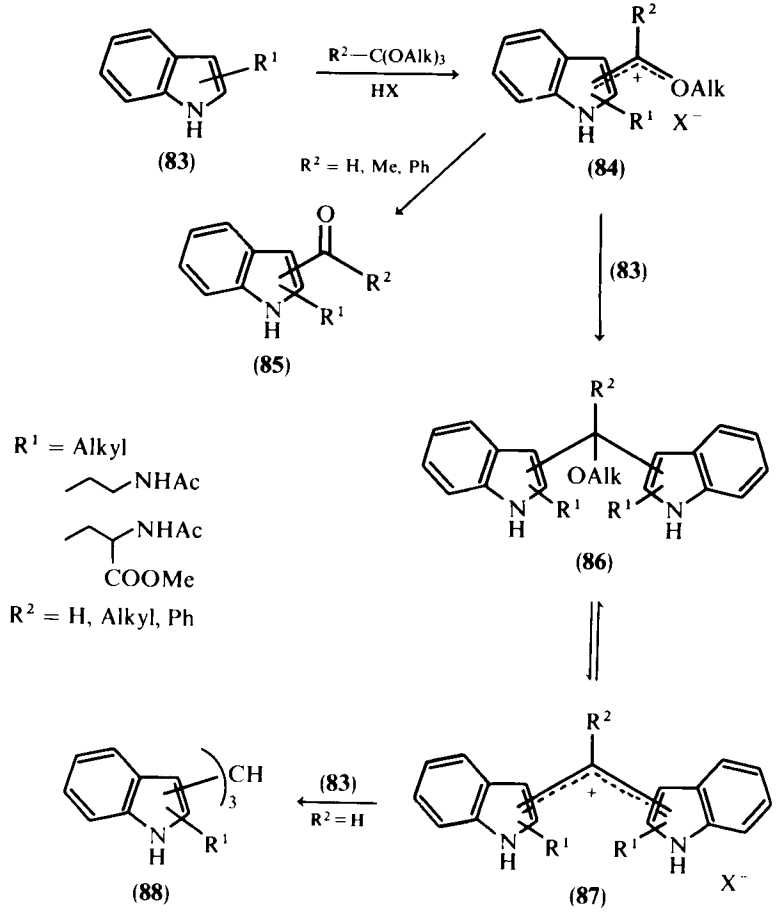
(80) (81) (82) (36)

R = Et, Me, Bu

Ortho esters, and in particular the most reactive orthoformates, are widely employed for the functionalization of electron-rich arenes and of some heterocyclic compounds in cyanine dye synthesis[1]. In the last few years, the reactions of a variety of electron-rich heteroarenes with ortho esters were investigated thoroughly. For example, the indoles **83** react as heterocyclic enamines with various acyclic and cyclic ortho esters under proton-catalysed conditions to furnish the preparatively useful, functionalized indole derivatives **84–88** as dependent on the reaction conditions (equation 37)[79–84]. The acylindoles **85** thus formed are of particular interest as building blocks for alkaloid syntheses[85]. Cyclic ortho esters such as, for example, 2-alkoxy-1,3-dioxolanes also react to form products of the type **85**[86]. Triethyl orthoacetate reacts as an a^1-C_2-synthon[205] with 3-unsubstituted indoles to give products of the 3-vinylindole type[87].

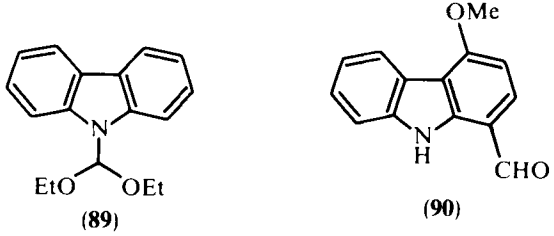
4-Methoxyindole is regiospecifically functionalized at the 3 position on reaction with triethyl orthoformate to furnish a C_3-symmetrical 3,3′,3″-tris(indolyl)methane of the type **88**[88].

The parent carbazole is preferentially dialkoxyalkylated at N-9 on reaction with an excess of triethyl orthoformate to give **89**[89]. The analogous reaction with 4-methoxycarbazole proceeds with regiospecific formylation at $C_{(1)}$ to produce compound **90**.



(37)

Depending on the reaction conditions prevailing in the latter reaction, carbazole derivatives analogous to compounds **85**, **86**, **87** and **88** (equation 37) can be formed as subsequent products[89].



Compounds of the type **88** represent a new class of heteroaromatic molecular propellers and are thus of interest for theoretical and/or stereochemical studies[90]. The

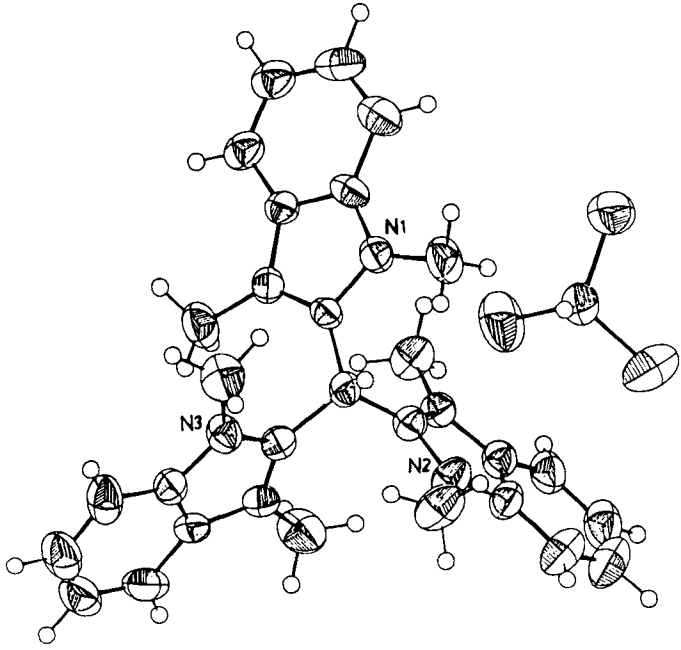
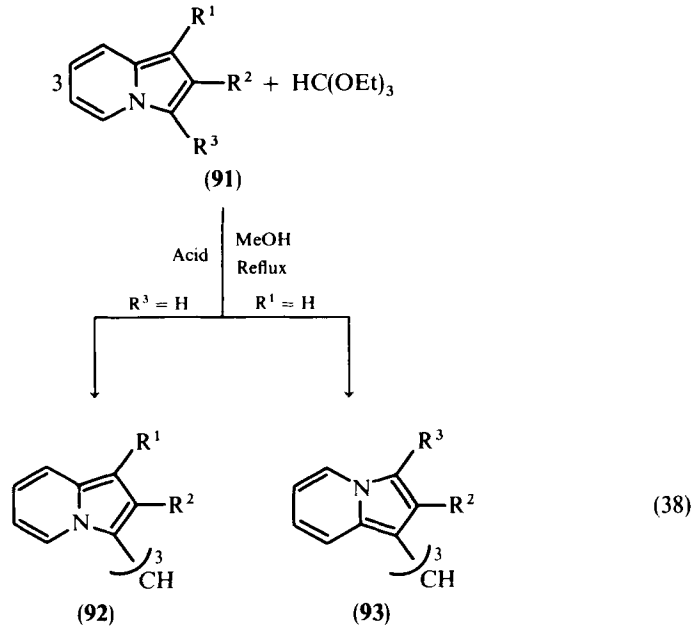


FIGURE 3. C_3-Conformation of 2,2′,2″-tris(1,3-dimethylindolyl)methane in the crystal state (ORTEP plot)[90]. Projection in the direction of the propeller axis. One molecule of chloroform is associated with the crystal



(38)

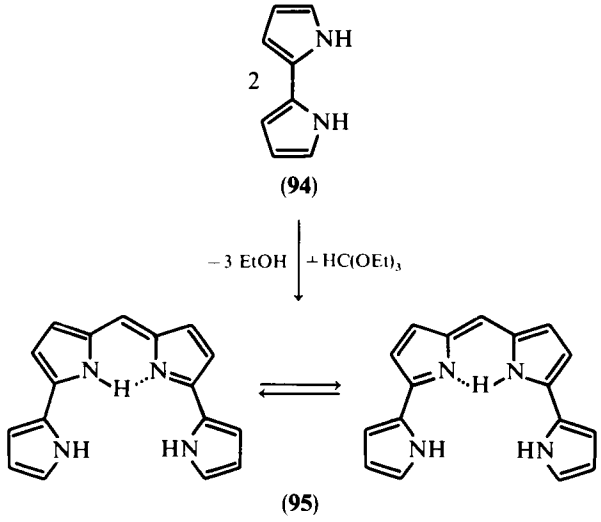
92	R^1	R^2
a	H	Me
b	Me	Me
c	Me	Ph
d	CO_2Et	Me
e	CN	Me

93	R^2	R^3
a	Ph	Me
b	Me	CO_2Me
c	Me	COC_6H_6Me—2

reaction of 1,3-dimethylindole with triethyl orthoformate gave rise to a highly C_3-symmetrical 2,2′,2″-tris(indolyl)methane and the propeller conformation of this product was established by X-ray crystallographic analysis (Figure 3)[90]. Temperature-dependent ^{1}H-NMR spectroscopic investigations additionally revealed that C_3-symmetrical conformations are also favoured in solution.

A series of tris(indolizinyl)methanes **92**, **93** has been prepared from triethyl or orthoformate and the indolizines **91** bearing substituents on the five-membered ring (equation 38)[91]. These products constitute a further new class of three-bladed molecular propellers for which eight stereoisomeric conformations are possible.

2,2′-Bipyrrole (**94**) and triethyl orthoformate, as a C_1-synthon[205], react in the presence of phosphoryl chloride to furnish 1,9-bis(2-pyrrolyl)pyrromethane (**95**) (equation 39)[92]. Compound **95** is a formal precursor of a porphyrine which is ring-contracted by two carbon atoms. ^{1}H-NMR spectroscopic analysis has revealed that **95** exists in a tautomeric equilibrium.



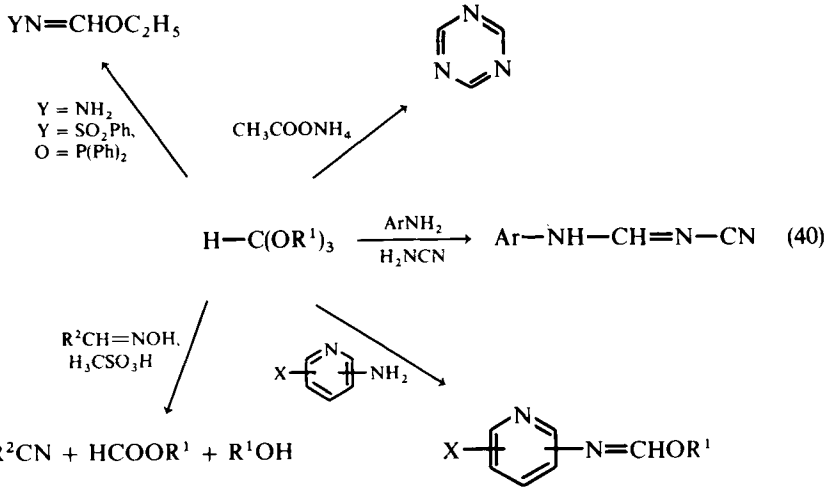
(39)

Triethyl orthoformate has also attracted attention as an a^1-synthon[205] for the derivatization of some electron-rich drugs possessing aromatic and heteroaromatic frameworks[93]. The products are formylated drugs or drug derivatives of the tris(aryl)- and tris(heteroaryl)methane types.

3. *Reactions with N-nucleophiles*

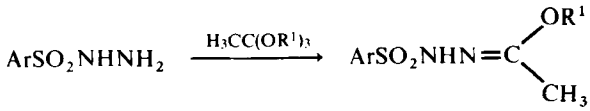
The reaction of orthoformates with ammonium acetate (equation 40) constitutes a simple preparation of 1,3,5-triazines[94]. Aminopyridines are easily transformed to hetero-

cyclic iminoesters by reaction with orthoformates[95], oximes to synthetically interesting nitriles under methanesulphonic acid catalysis[96] and anilines to *N*-cyanoformamidines in the presence of cyanamide[97] (equation 40).



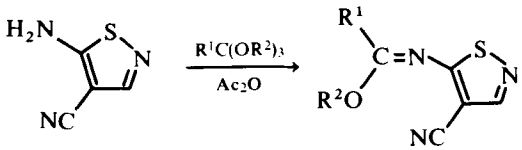
(40)

Triethyl orthoformate reacts with benzenesulphonamide or diphenylphosphono-*N*-phenylamide to form *N*-functionalized ethyl formimidates (equation 40)[98]. In an analogous manner, orthoacetates react with arylsulphonylhydrazines **96** to furnish (*E*)-*N*-arylsulphonylhydrazimidates **97** (equation 41)[99]. 5-Amino-4-cyanoisothiazole (**98**) reacts readily with ortho esters to give the imidates **99** (equation 42)[100]. Compounds **99** are synthetically useful as precursors of pyrimidine derivatives.



(41)

(**96**) (**97**)



(42)

(**98**) (**99**)

Aminoacetonitrile hydrochloride (**100**) reacts with trimethyl orthoformate to give *N*-formylaminoacetonitrile (**102**) (equation 43)[101]; the reaction proceeds through methyl *N*-cyanomethylformimidate (**101**).

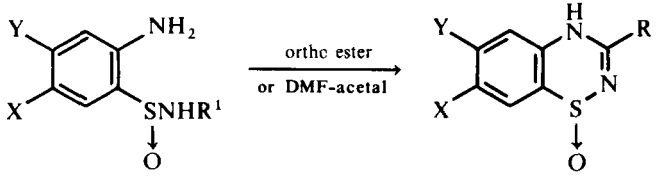
Secondary amines of the aniline series **103** react with ortho esters under *p*-toluenesulphonic acid catalysis to furnish *N*-alkylformanilides **104** (equation 44)[102]. Aliphatic cyclic amines such as morpholine and piperidine react with orthoformates to give the corresponding ortho amides; the above two reaction sequences thus constitute new and convenient syntheses of these useful reagents.

$$\underset{(100)}{NCCH_2NH_2 \cdot HCl} \xrightarrow[\text{excess}]{HC(OCH_3)_3} \underset{(101)}{[NCCH_2N{=}CHOCH_3]} \xrightarrow[-MeCl]{HCl} \underset{(102)\ 93\%}{NCCH_2NHCHO} \qquad (43)$$

$$\underset{(103)}{ArNHR^1} \xrightarrow[Tos{-}OH]{R^2{-}C(OR^3)_3} \underset{(104)}{ArN(COR^2)(R^1)} \qquad (44)$$

The reactions of ortho esters with specific amide derivatives, acting as *N*-nucleophiles, constitute a useful access to a variety of amide acetals (for references, see Section VII).

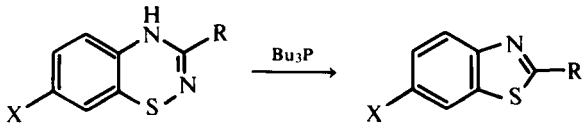
Bifunctional nucleophiles are versatile and interesting synthons for a range of heterocyclic systems; thus, for example, reactions of some acyclic ortho esters or dimethylformamide acetals with *o*-aminobenzenesulphinamides **105a–c** gave 1,2,4-benzothiadiazine 1-oxides **106a–d** (equation 45)[103], while reactions of the benzothiazine derivatives **107** with one equivalent of tributylphosphine proceeded with rearrangement to furnish the benzothiazoles **108a–c** (equation 46). A mechanism for this rearrangement has been proposed[103].



(45)

(105a)	Y = X = Cl; R′ = H
b	R′ = Y = H; X = Cl
c	X = Y = Cl; R′ = Me

(106a)	Y = X = Cl; R = H
b	Y = R = H; X = Cl
c	Y = X = Cl; R = Ph
d	Y = X = Cl; R = Me

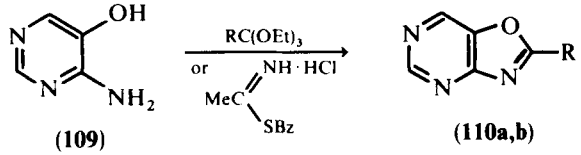


(46)

(107a)	X = H; R = Ph
b	X = Cl; R = SMe
c	X = Cl; R = Ph

(108a)	X = H; R = Ph
b	X = Cl; R = N=PB$_3$
c	X = Cl; R = H

Novem purine isosters **110a** possessing oxazolo[4,5-*d*]pyrimidine structures have been prepared by the condensation of appropriate *o*-hydroxyaminopyrimidines **109** with some ortho esters (equation 47)[104]. Benzyl thioacetimidate reacts in the same manner to furnish **110b**. These products have found use in the synthesis of *C*-nucleosides having isosteric structures.

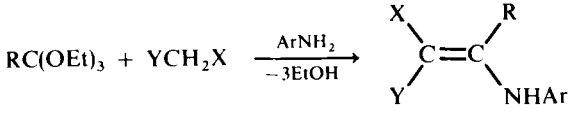


(109) (110a,b)

R = H, Me (45%, 40%) (47)

4. Three-component reactions of the type ortho ester/primary amine/carbon acid

The combination of ortho esters with, above all, primary aromatic amines and carbon acids represents a preparatively efficient procedure for a variety of amino-functionalized alkenes **111** (equation 48)[105]. The products **111** are of general interest as synthetic building blocks and some of them exhibit bacteriocidic, fungicidic and psychomimetic activities[106,107]. This three-component system was further developed by Wolfbeis and coworkers[106,107].

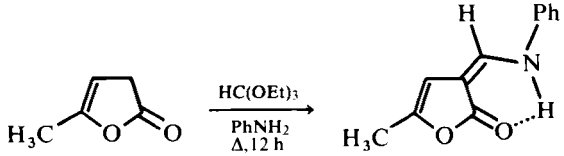


(111) (48)

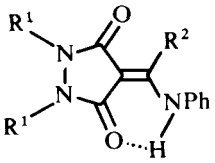
Dimedone and other cyclic, active methylene compounds possessing six-membered rings react readily with triethyl orthoformate and anilines but not with trimethyl orthoacetate, orthopropanoate or orthobenzoate. However, the latter ortho esters do undergo condensation with anilines and five-membered-ring carbon acids[106]; these reactions also take place with primary aliphatic amines. For example, γ-angelica lactone (**112**) reacts with triethyl orthoformate and aniline to furnish 3-anilinomethylene-5-methyl-2,3-dihydro-2-furanone (**113**) (equation 49). Pyrazolidine-3,5-diones also react with orthoformates, orthoacetates or orthopropanoates in the presence of aniline to yield aminomethylenepyrazolidine-3,5-diones **114**. Hence, this methodology also provides a convenient and general approach to β,β-diacylenamines.

The mechanism of the three-component reaction aniline/triethoxymethane/dimedone has been investigated by ^{1}H-NMR spectrometry and the rate-determining steps have been established in several solvent systems[107]. The initial step involves the condensation of aniline with the ortho ester to form diphenylformamidine via ethyl phenylformimidate; the second step comprises the reaction of the intermediate diphenylformamidine with dimedone. The rates are highly dependent on the nature of the solvent and the concentration of the acid catalyst.

Three-component reactions of anilines/triethyl orthoformate/acyclic methylene compounds have also been realized under $ZnCl_2$ catalysis[108]. The resultant ethyl α-ethoxycarbonyl-β-(arylamino)acrylates were obtained in 80–96% yields under reflux conditions.



(112) (113) 38% (49)

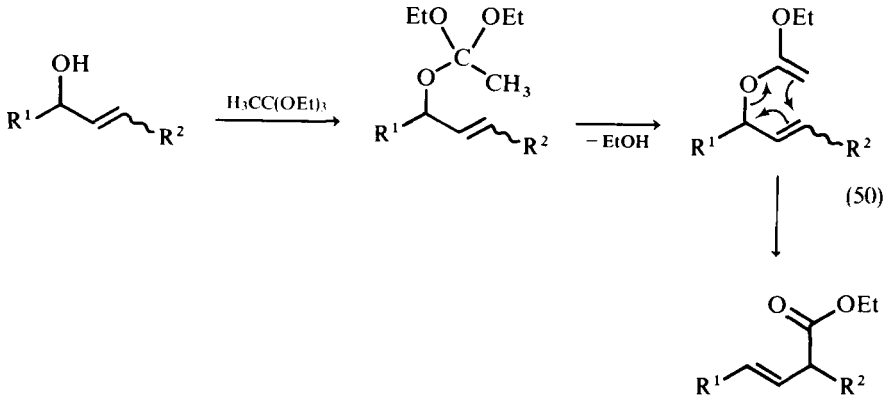


(55–72%)

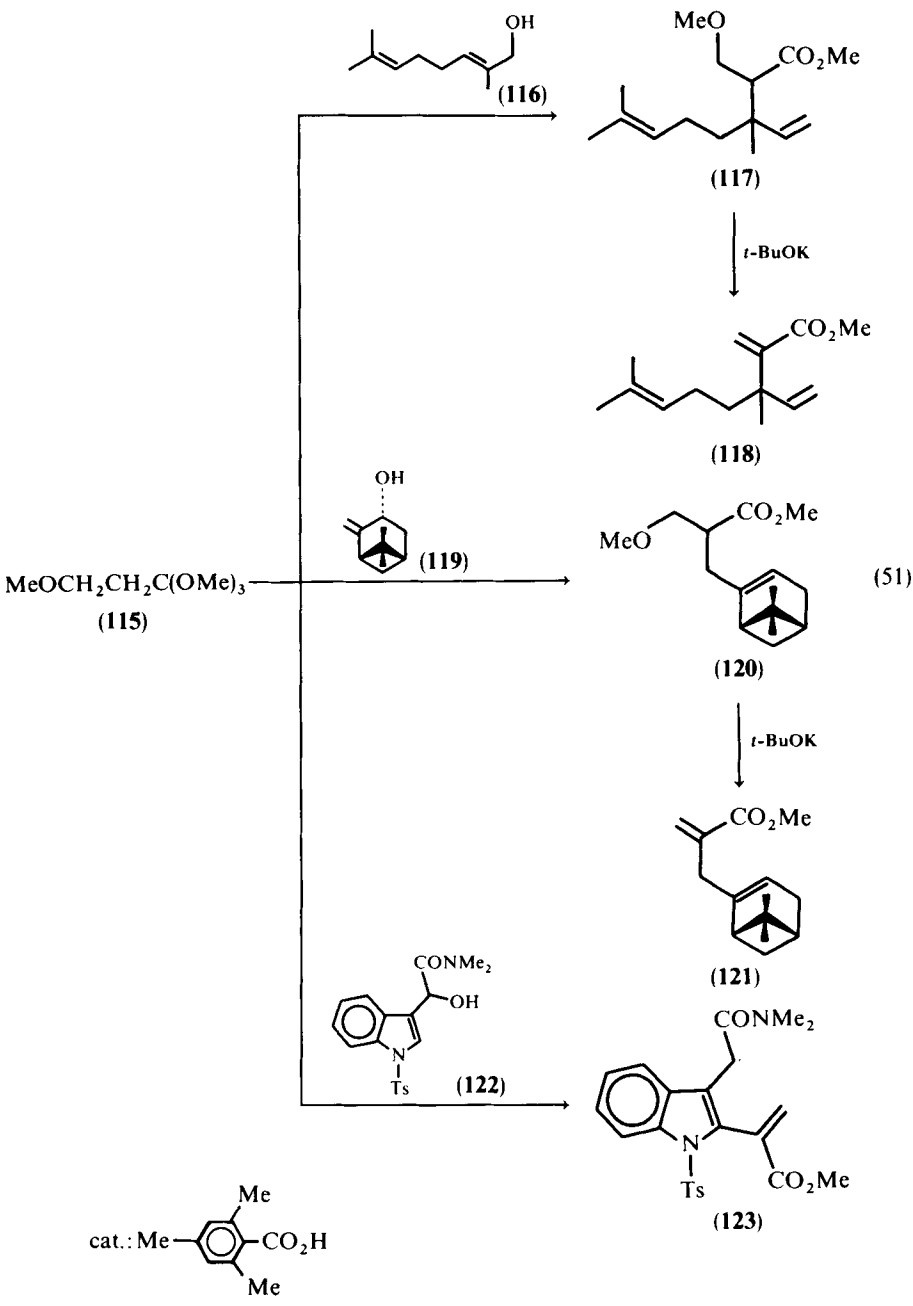
(114)	R^1	R^2
a	Me	H
b	Ph	H
c	Ph	Me
d	Ph	Et

5. Rearrangement reactions and special cleavage processes with ortho esters and carboxonium ions

In the field of rearrangement reactions of ortho esters, the [3,3]-sigmatropic reaction with allyl alcohols (Claisen ortho ester rearrangement of the oxa-Cope type) plays an important role in the highly regio- and stereo-selective syntheses of a variety of unsaturated carboxylic esters (equation 50)[109]. The reactions proceed through ketene *O,O*-acetals as the key intermediates.



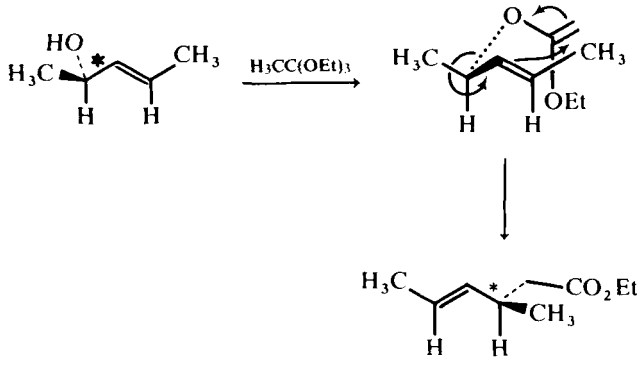
(50)



The formation of ketene *O,O*-acetals from mixed ortho esters is accelerated in the presence of catalytic quantities of propanoic acid. Hence, trimethyl 3-methoxyorthopropanoate (**115**), a compound that is thermally stable at 190°C for prolonged times, can

be utilized as the starting material for the preparations of the β-substituted methyl acrylates **118**, **121** and **123** by way of 2,4,6-trimethylbenzoic acid-catalysed Claisen ortho ester rearrangements with allylic alcohols and subsequent β-eliminations of methanol under the influence of a base (equation 51)[110]. The products are interesting and versatile building blocks for natural product syntheses.

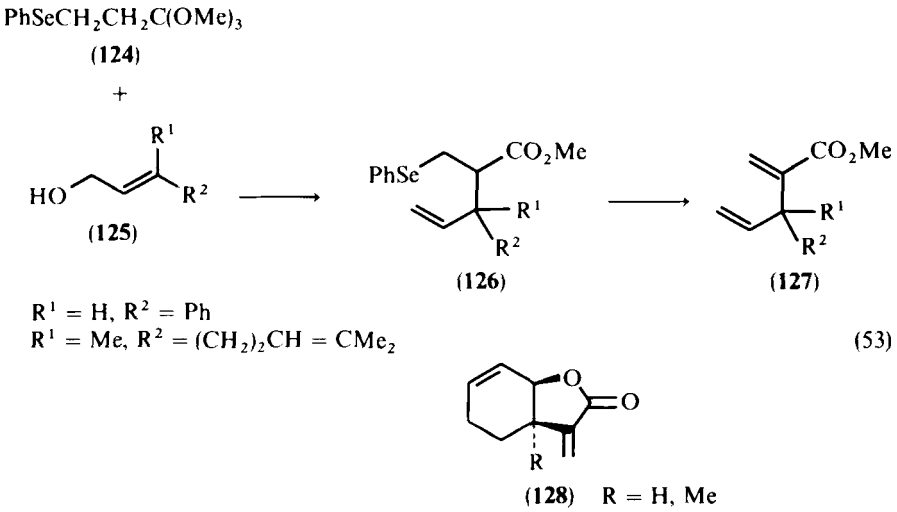
In some cases, the use of chiral alkenols can induce chirality transfer via a six-membered ring, chair-like transition state of the [3,3]-sigmatropic process (equation 52)[109].



(52)

chemical yield: 68%
optical yield: >90%
(*E*)-configuration: >98%

Trimethyl 3-(phenylseleno)orthopropanoate (**124**) may also be utilized as the starting material for the preparation of either 2-substituted acrylates **127** (equation 53) or α-methylene-γ-butyrolactones **128** via Claisen ortho ester rearrangements with allylic alcohols and subsequent oxidative elimination of phenylselenol[111].

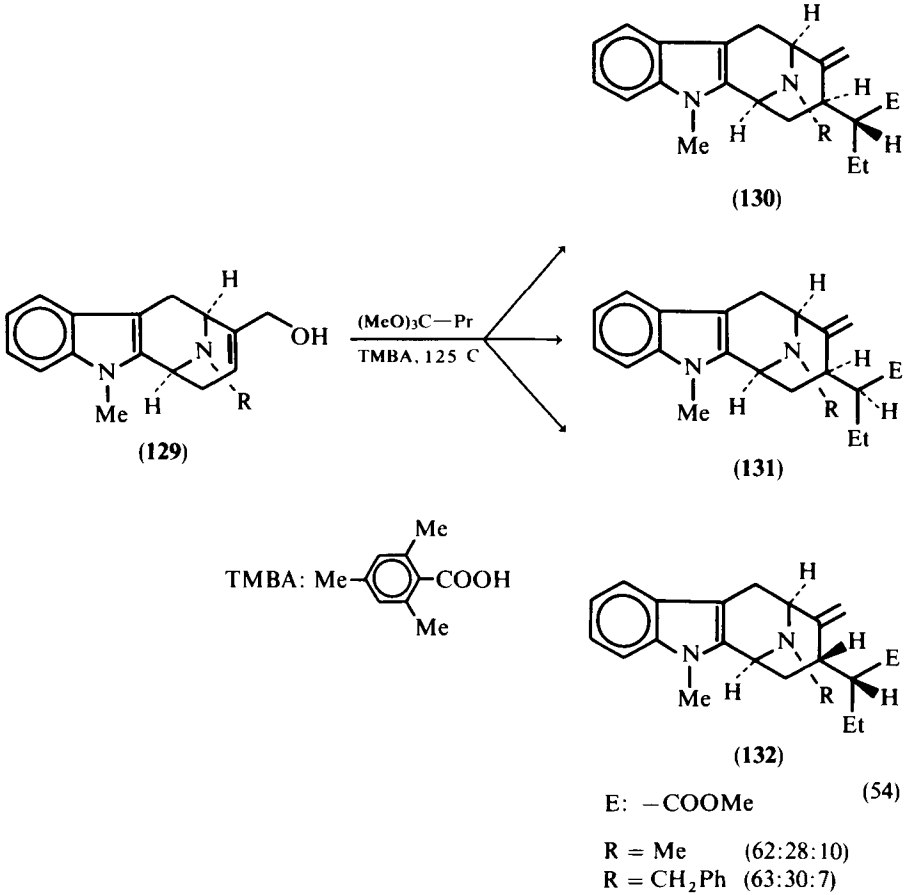


$R^1 = H, R^2 = Ph$
$R^1 = Me, R^2 = (CH_2)_2CH = CMe_2$

(53)

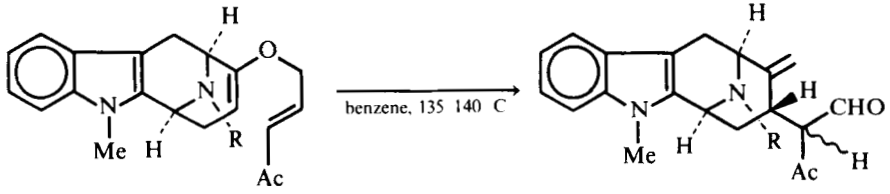
(**128**) R = H, Me

[3,3]-Sigmatropic rearrangements of indoloazabicyclo[3.3.1]nonene systems have been investigated and reversed stereofacial selectivity in the Claisen versus ortho ester Claisen rearrangements established[112]. Irrespective of the spatial requirements of the substituent R, both allyl alcohols **129** undergo acid-catalysed ortho ester Claisen rearrangement preferentially from the β-face of the molecule to give the diastereomers **130** and **131** as the main products (equation 54). In contrast, the enol ethers **133** possessing similar stereochemical constraints undergo the Claisen rearrangement stereospecifically from the α-side of the azabicyclo[3.3.1]nonene system to furnish the aldehydes **134** as the sole products (equation 55). The differing stereochemical courses of the two reactions can be explained in terms of a boat transition state in the ortho ester rearrangement and a chair transition state in the Claisen rearrangement. The products of both reactions are of interest for alkaloid synthesis.



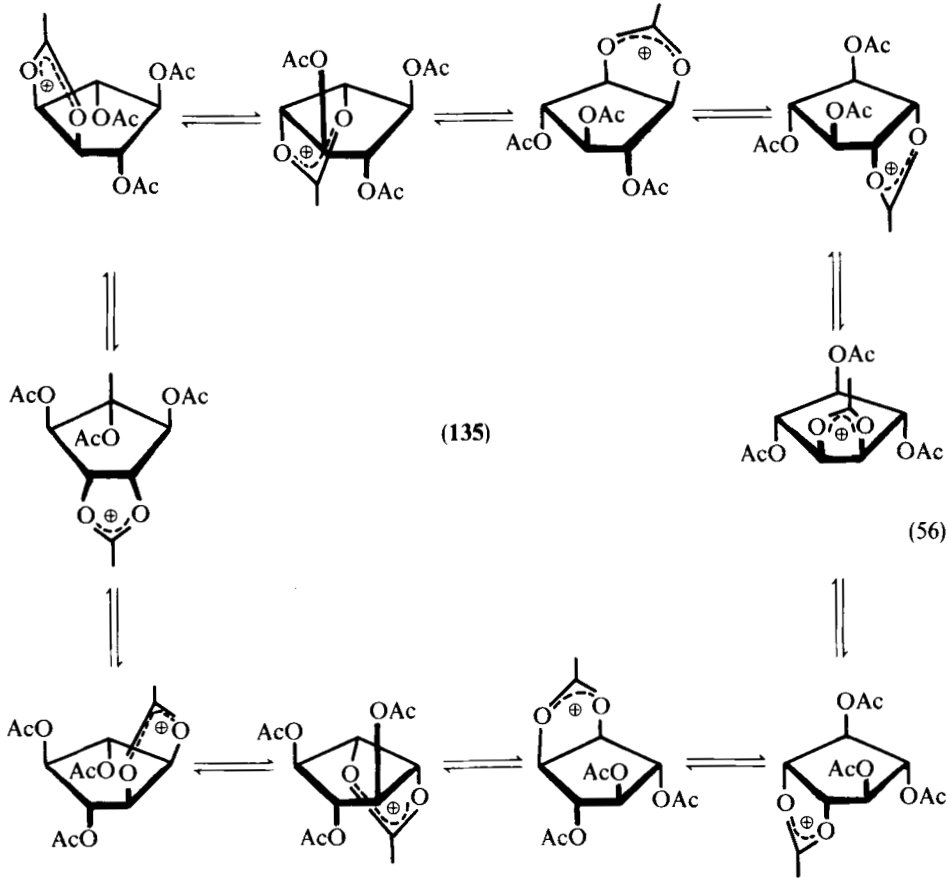
(54)

Numerous rearrangement reactions involving carboxonium ions and in which, above all, neighbouring group participation plays a central role have been described in the chemistry of carbohydrates and polyols[5,113]. A specific example which has been examined in detail is the cation **135** (equation 56) which should exhibit tenfold degeneration as a consequence of successive acyloxonium rearrangements[114–116]. And



(133) (134) (55)

R:—Me 65%
R:—CH_2Ph 55%


OAc
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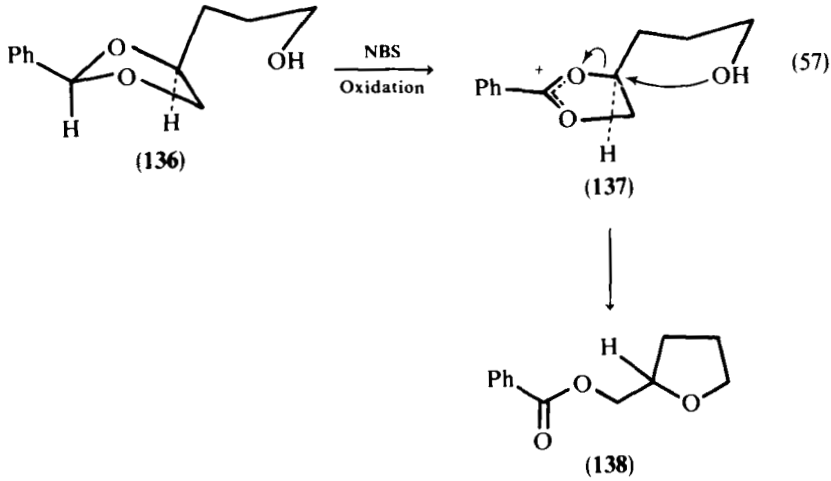
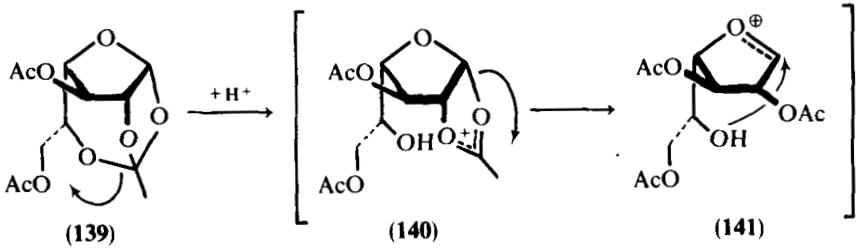
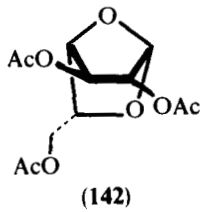
Investigations of the oxidations of 1,3-dioxolane and 1,3-dioxane precursors bearing a neighbouring hydroxy group by *N*-bromosuccinimide (NBS) have demonstrated the intramolecular formation of selectively substituted tetrahydrofurans[117]. Hence, for example, the stereochemical development is impaired by initial formation of ortho ester intermediates followed by cleavage to dioxolenium cations **137** and subsequent five-membered ring closure by intramolecular nucleophilic attack through a colinear, backside displacement to produce **138** (equation 57).



(136) (137) (138) (57)



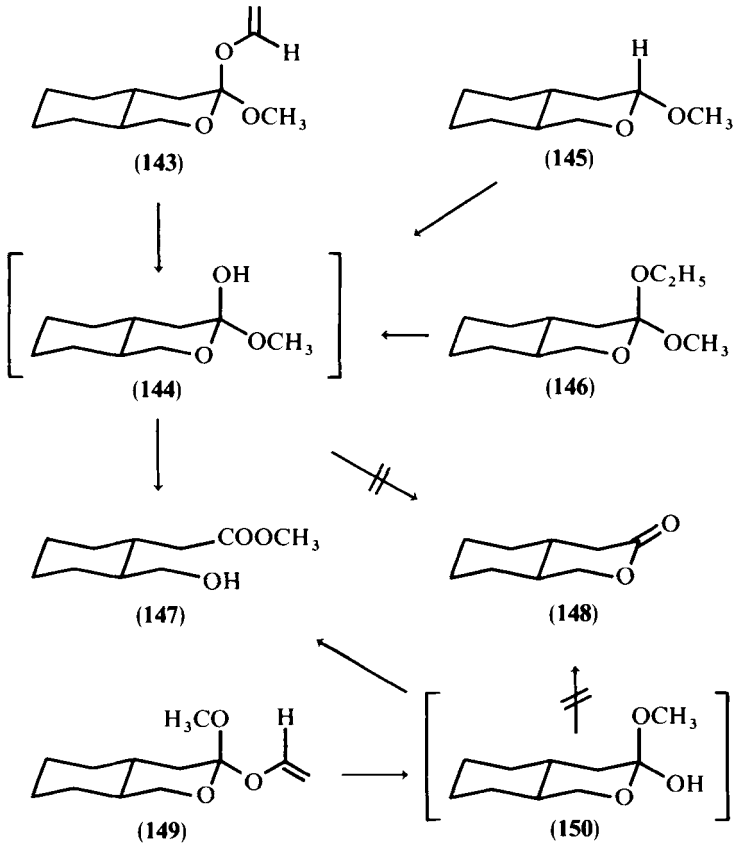
(139) (140) (141)



(142) (58)

Internal (tricyclic) ortho esters of sugars undergo acid-catalysed rearrangements in polar solvents to furnish acylated anhydro-sugars[118]. This is valid above all for compounds bearing ortho-acylated *cis*-hydroxy groups in the 1,2-positions. Thus, the galactofuranose derivative **139** can be converted to 2,3,5-tri-*O*-acetyl-1,5-anhydro-α-D-galactofuranose (**142**) (equation 58); this rearrangement is assumed to proceed by way of the carboxonium ions **140** and **141**.

In the field of stereoelectronically controlled reactions, Deslongchamps and coworkers have studied the oxidative cleavage of conformationally rigid vinyl ortho esters[9]. Hence, potassium permanganate oxidation of either the axial vinyl ortho ester **143** or the equatorial vinyl ortho ester **149** yields essentially only the hydroxy ester **147**. These results can be interpreted in terms of stereoelectronic effects which control the cleavage of the tetrahedral intermediates **144** or **150**, respectively (equation 59).



(59)

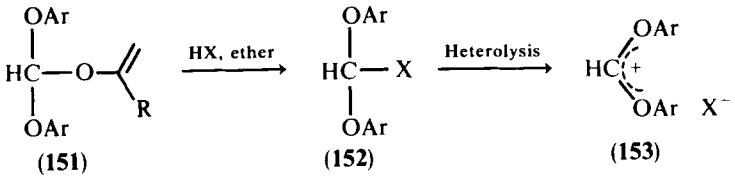
6. *Syntheses of di- and trialkoxycarbenium ions*

The syntheses of acyclic and cyclic di- and triorganyloxycarbenium ions have been described in detail and reviewed previously[5,119-121]. Thus, only some selected developments of synthetic interest will be discussed in this section.

The preparations of 1,3-dioxolanium salts by the oxidation of 1,3-dioxolanes with

tritylium salts[121,122] or acetyl perchlorate[123] have been reported. Cyclic acetals can also be transformed into 1,3-dioxolenium ions via disproportionation in the presence of a Lewis acid[124].

Solvolyses of ortho esters in pure (100%) sulphuric acid give rise to dialkoxycarbenium ions[125,126]. Dialkoxycarbenium ions can also be generated *in situ* from ortho esters in the presence of elemental halogens[127,128] or hydrohalic acids[128,129]. A broadly applicable method consists of the hydrohalogenolysis of the diaryloxy(vinyloxy)methanes **151** to give the acetals **152**, which readily undergo subsequent heterolysis to furnish the oxocarbenium ions **153** (equation 60)[129].

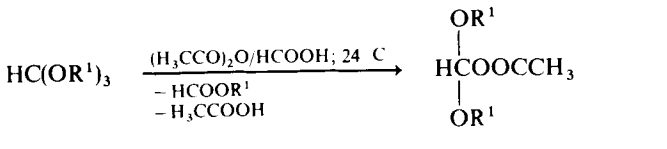


(151) (152) (153) (60)

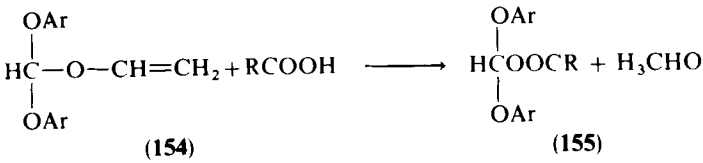
Ar = Ph, R = H, X = Cl (60%)
X = Br (50%)

The heterolytic cleavage of ortho esters by Lewis acids such as, for example, boron trifluoride diethyl etherate of antimony(V) chloride constitutes one of the simplest methods for the preparation of 1,1-di or 1,1,1-triorganyloxycarbenium salts[5,10,130]. Alternatively, the tetrafluoroboric acid diethyl ether complex may be employed[10,130]. However, the synthetic availability of the ortho esters does represent a limitation of this methodology.

Acyloxy(dialkoxy)alkanes can also serve as interesting precursors for the generation of dialkoxycarbenium ions via heterolysis. Hence, for example, the general reaction sequence illustrated in equation 61 for orthoformates is typical for the synthesis of acetoxy(dialkoxy)methanes possessing high S_N 1-reactivities[131]. On heating to above 50 °C, disproportionation to furnish the corresponding formate and acetate takes place. Acyloxy(diaryloxy)methanes **155** may also be obtained from the orthoformates **154** in the presence of the pure carboxylic acid by way of an exchange reaction (equation 62)[129].

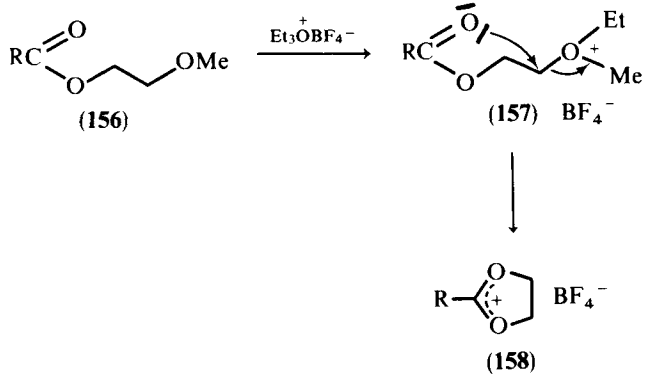


(61)



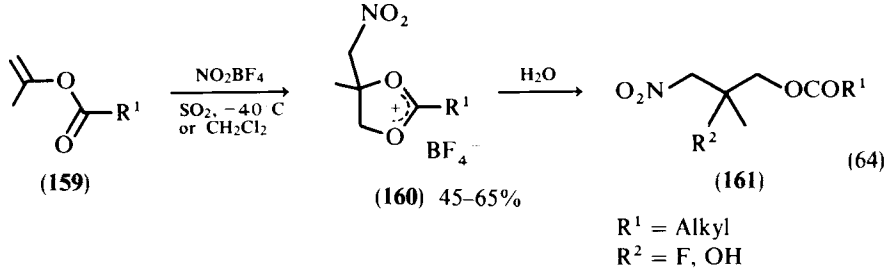
(154) (155) (62)

The *O*-alkylation of carboxylates or lactones with Meerwein salts provides another convenient procedure for the generation of dialkoxycarbenium ions[5,119] as do the cycloalkylation of 2-haloalkyl carboxylates in the presence of silver tetrafluoroborate[5,132] and the cyclization of 2-methoxyethyl carboxylates **156** with triethyloxonium tetrafluoroborate (equation 63)[133]. The latter reaction proceeds through the intermediate cation **157** to furnish the 1,3-dioxolenium tetrafluoroborate **158**.



(63)

The neighbouring-group induced formation of 1,3-dioxolenium salts was also achieved by nitration reactions of allyl esters with NO_2BF_4 via an Ad_E mechanism[34]. Thus, for example, compounds **159** reacted with NO_2BF_4 to furnish the isolable nitro-substituted oxonium salts **160**, which can easily be transformed to the fluoronitro derivates or to the solvo-adducts **161** by quenching with water (equation 64).



(64)

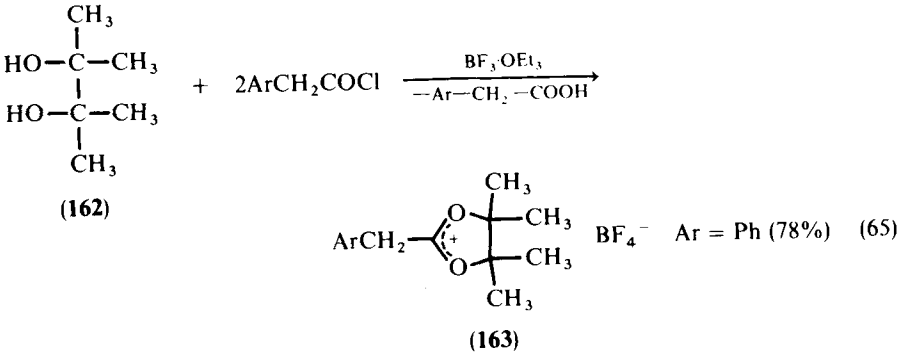
R^1 = Alkyl
R^2 = F, OH

In the presence of carboxylic acid anhydride/perchloric acid[135–137] (or boron trifluoride diethyl etherate[138]) or acyl halide/silver perchlorate[139], 2- or 3-hydroxyalkyl carboxylates undergo cyclization to yield 1,3-dioxolan-2-enium[139] or 1,3-dioxan-2-enium[140] salts.

In general, the reactions of 1,2-diols such as, for example, **162** with arylacetyl chlorides represent an efficient route to the 1,3-dioxolan-2-enium tetrafluoroborates **163** (equation 65)[138].

In some cases, dialkoxycarbenium salts are not so easily accessible by the simple alkylation of alkyl carboxylates with Meerwein salts. However, the alkylation is generally realizable when the more reactive diethoxycarbenium hexachloroantimonate $[HC(OEt)_2{}^+SbCl_6{}^-]$ is employed[141].

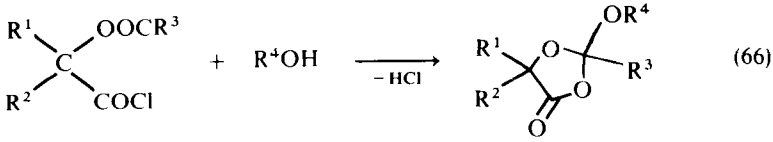
As a result of neighbouring group effects, 2-alkoxy-4-oxo-1,3-dioxolanes **165** were



(162)

(163)

obtained from the reactions of 2-substituted 2-acyloxycarboxylic acid chlorides **164** with alcohols (equation 66)[142,143].



(164) (165)

7. *Reactivity and synthetic applications of dialkoxycarbenium salts*

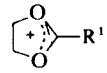
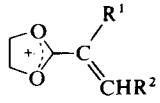
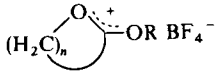
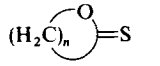
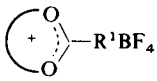
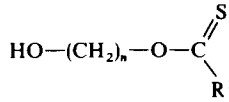
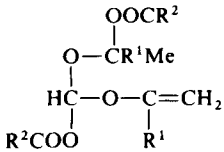
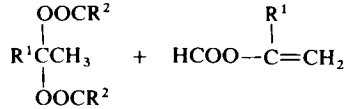
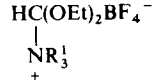
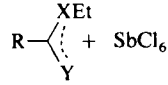
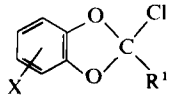
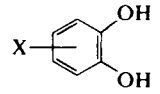
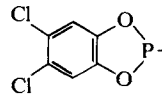
Since the first synthesis of dialkoxycarbenium ions[5], this class of highly stabilized cations with potential ambident nucleophilic reactivity has been widely utilized in various synthetic processes. In some cases the 1,1-dialkoxy-1-halo- or 1-acyloxy-1,1-dialkoxyalkanes were used as precursors with S_N 1-reactivity. Dialkoxycarbenium ions have also been used for the preparation of ortho esters by reaction with a wide range of alkoxides (Meerwein ortho ester reaction; see Section III.B)[19]. Some specific applications of general interest in dialkoxycarbenium ion (or their precursor) chemistry are summarized in Table 3.

A further novel variant for the preparation of functionalized ketones from dialkoxycarbenium salts should be mentioned. The reactions of 2-alkyl-1,3-dioxolan-2-ylium fluorosulphonates **166** with alkynyl(trialkyl)borates occur at the β-position of the alkynylborate by a rearrangement reaction (equation 67)[157]. On hydrolytic work-up, (*Z*)-α,β-unsaturated ketones **168** are obtained whereas, on oxidative work-up, the mono-protected 1,3-diketones **169** are formed specifically

Several reactions of electron-rich heteroarenes (e.g. indoles, pyrroles, carbazoles) with some acyclic dialkoxycarbenium tetrafluoroborates were described recently[158–163]. The acylation and alkylation reactivities of these ambident cations are now well established in heterocyclic chemistry; for typical reaction sequences, see equation 68. Compounds **172** represent a new class of highly stabilized oxycarbenium ions. The conformational behaviour of cations of the type **172** was recently examined by temperature-dependent NMR spectroscopy and X-ray crystallography[163].

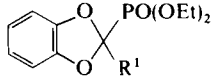
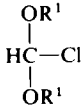
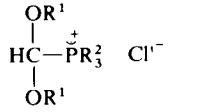
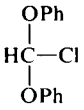
The decay of 2-phenyl-1,3-dioxolane-2-ylium salts in dichloromethane solution has been investigated recently by means of ^{1}H-NMR and UV spectroscopy as well as by conductometry[164]. The influence of the nature of the anion ($SbCl_6^-$, $SbCl_5Br^-$, AsF_6^-) and the presence of methyl substituents on the rate constants of the decay were discussed.

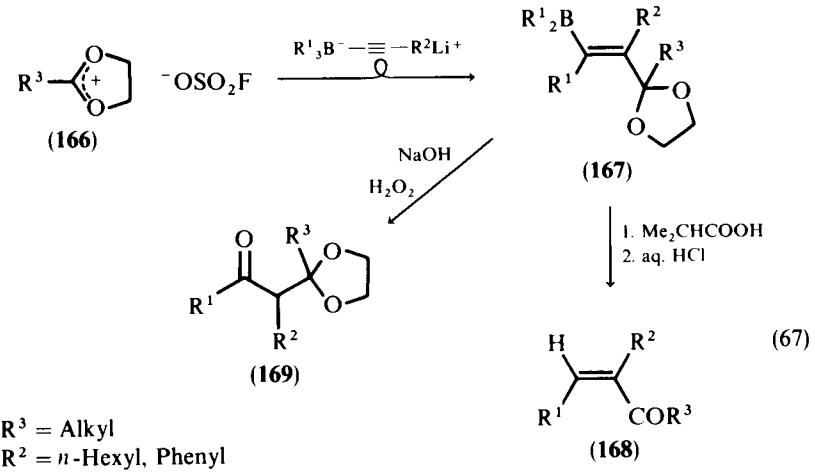
TABLE 3. Synthetic transformations of 1-acyloxyl-1,1-dialkyloxyalkanes, 1,1-dialkoxy-1-haloalkanes and dialkoxycarbenium salts

Substrate	Reaction partner	Product	Reference
			144, 145
$R^1 = H; ClO_4^-$	ArH	ArCHO	
R^1 = Alkyl; ClO^-	R^2—MgX 2. H_3O^+	R^1COR^2	146
BF_4^-	$^1[(HgC_4)_4N]^+BH_4^-$	R^1CHO	133
	Y = Hal^-, R—OH	$YCH_2CH_2OOCR^1$	144
	ArO^-, R—COO^-,		147
	R_3N, Ar—NH_2		147
R^1 = Me,	$R^2CH(OR^3)_2$ or	 ClO_4^- or BF_4^-	138
CH_2—Ph	R^2CHO		
	NaSH		148
	H_2O		144
	Na_2S or NaSH		148
	20–80 °C		
$[HC(OEt)_2]^+X^-$	R_3^1N		150
		 $SbCl_6^-$ or BF_4^-	151
 R^1 = H	H_2O	 + HCOOH	152
	$[Me_2N]_3P$		153

(continued)

TABLE 3 (*continued*)

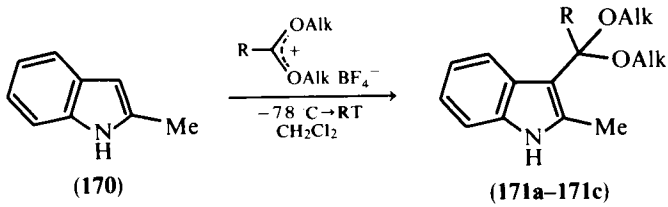
Substrate	Reaction partner	Product	Reference
R^1 = Alkyl	$P(OEt)_3$		154
	PR^2_3		155
	$LiAlH_4$	$(PhO)_2CH_2$	156



(166) (167) (169) (168)

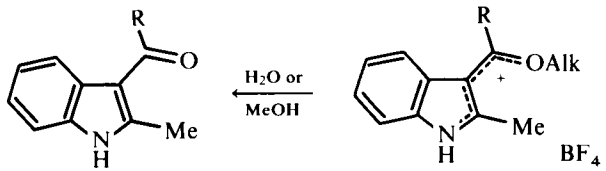
(67)

R^1, R^3 = Alkyl
R^2 = *n*-Hexyl, Phenyl



(170) (171a–171c)

(68)



(173a–173c) (172)

	R
a	H
b	Me
c	Ph

Kinetic measurements via first-order rate constants demonstrated that the salt with the $SbCl_5Br^-$ anion has, compared to the other anions, the lowest stability in this series.

V. INTRODUCTION TO THE CHEMISTRY OF ORTHO AMIDES

The chemistry of ortho amides of carboxylic acids and carbonic acids was first reviewed comprehensively by Kantlehner in this series[165] and additionally by Simchen[173]. These reviews give information on the various types of ortho amides and their nomenclature. As can be seen in the numerous references cited, it is usually practice to include a discussion of the chemistry of the corresponding cationic species such as, for example, amidinium, guanidinium, alkoxymethyleneiminium ions and other related species in reviews on ortho amides. Even so, ortho amides themselves continue to be a very important class of compounds in synthetic organic chemistry, especially for functionalization, cyclization and many other processes. In the following sections, the first review of the previous series[165] is continued and more recent structural, synthetic and reactivity aspects are discussed. References published between 1979 and 1990 have been taken into consideration.

VI. STRUCTURAL ASPECTS AND MECHANISM OF HYDROLYSIS OF ORTHO AMIDES

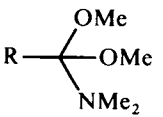
Physical characteristics and some structural aspects of ortho amides have been discussed comprehensively[165]. In the meantime, molecular mechanics calculations have been performed for some amide acetals, aminal esters and amide aminals (**174–176**) using the Monte Carlo–Metropolis approach for the global conformational minimum search[166] (Figure 4).

Considering thermodynamic and steric aspects in vacuum, the amide acetal **174a** and the aminal ester **175a** are the most stable compounds of these series. In each group, the steric energy increases from H < Me < Ph in accordance with the spatial requirements of these substituents at the central carbon atom. With the exception of **176a** which adopts an almost C_3-symmetrical conformation, all conformers exhibit C_1 symmetry. The calculated C(central)—O bond lengths in all compounds are in the range 1.43 to 1.44 Å, whereas the C(central)—N bond lengths are predictably longer (in the range 1.48 to 1.50 Å). However, these values are not significantly different from normal C—O (1.43 Å) and C—N (1.47 Å) bond lengths.

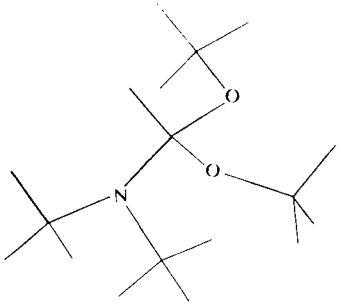
In heterolysis reactions of compounds of the type **174** and **175**, the methoxy group is eliminated first since the resultant *N,O*- or *N,N*-stabilized cations possess the greater stability.

CNDO/2 and MINDO/3 calculations were carried out for $CH(OH)_2NH_2$ a hemi-ortho amide model compound, the imidate salt $[CH(OH)NH_2]^+$ and $[CH(OH)_2]^+$ the dihydroxycarbenium ion[167]. The $CH(OH)_2NH_2$ hypersurface shows that the most stable conformations do not correspond to the Deslongchamps antiperiplanar conformations[4,8,9] which lie 2 to 5 kcal mol^{-1} higher.

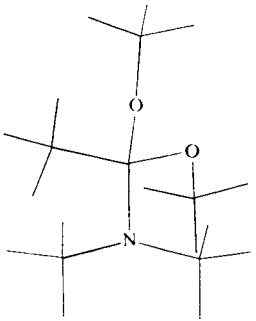
Low-temperature X-ray analyses of a crystalline tricyclic ortho amide and its trihydrate **177b** were reported[168]. Two crystalline modifications were found: (i) a cubic trihydrate of space group Pa3($Z = 8$) in which the molecule has crystallographic threefold rotation symmetry and (ii) an anhydrous monoclinic form of space group P2, Ic ($Z = 8$) in which two symmetry-independent molecules have different configurations, one being all-*trans*, the other *cis,cis,trans*. In the cubic trihydrate, each ortho amide molecule is attached to a triade of H_2O molecules by OH···NH bonds. A remarkable feature of this structure is the nearly eclipsed conformation about the central C—CH_3 bond in the anhydrous crystal; both types of molecule have the normal staggered



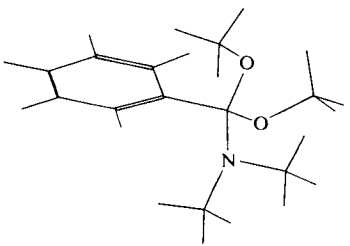
174	R
a	H
b	Me
c	Ph



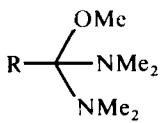
−73.7
19.8
(174a)



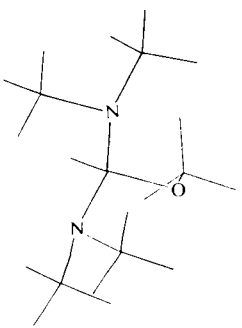
−86.0
21.3
(174b)



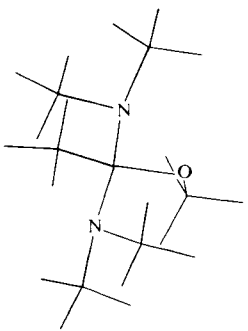
−50.0
34.45
(174c)



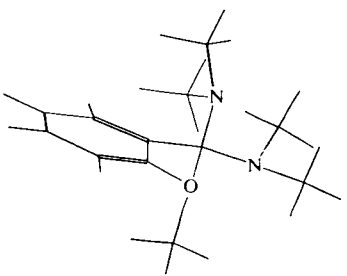
175	R
a	H
b	Me
c	Ph



−42.14
19.8
(175a)



−39.9
29.9
(175b)



−0.8
45.9
(175c)

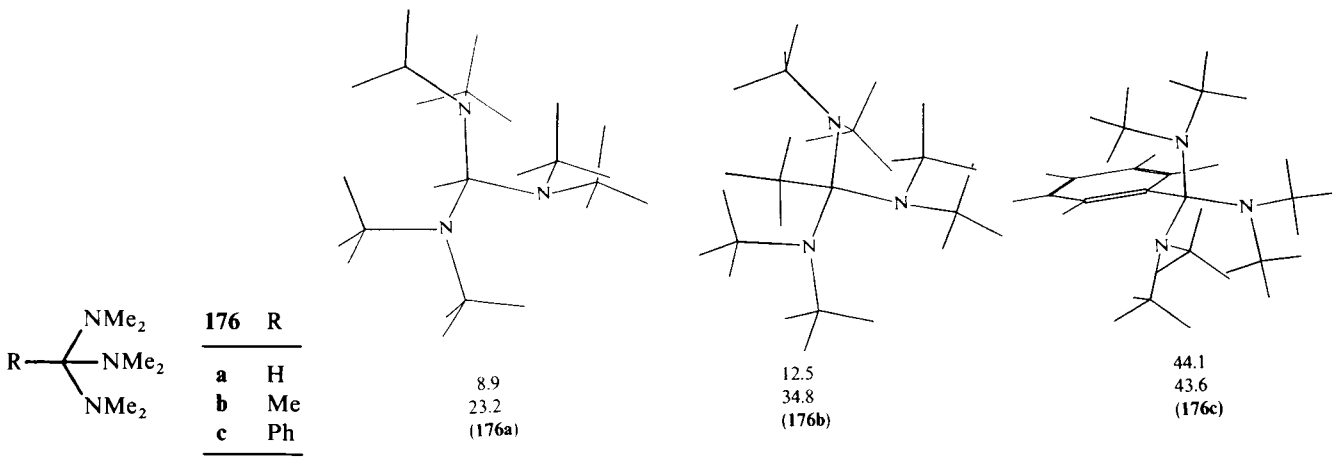
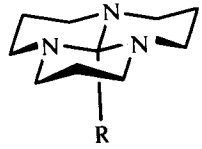


FIGURE 4. Global minimum conformations of *ortho* amides **174a–c, 175a–c** and **176a–c** according to MMX molecular mechanics calculations using the Monte Carlo–Metropolis approach[166]. First energy value: ΔH_f (kcal mol^{-1}); second energy value: E_{steric} (kcal mol^{-1})

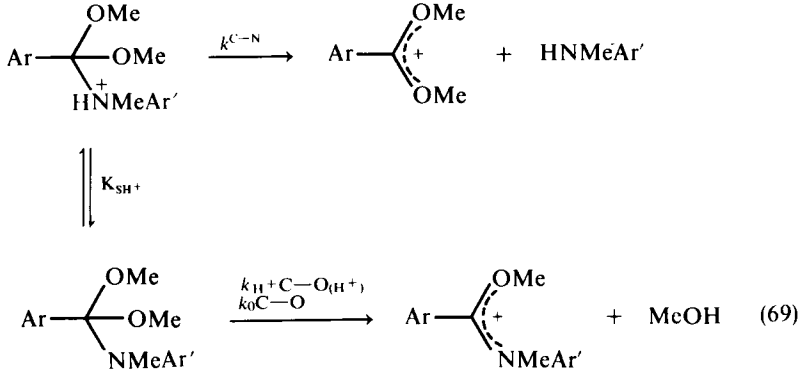
orientation of their CH_3 groups. The reversal of the CH_3 orientation in the trihydrate is attributed to C—H···OH bonding; this must be much stronger and much more directionally specific than had been assumed previously.



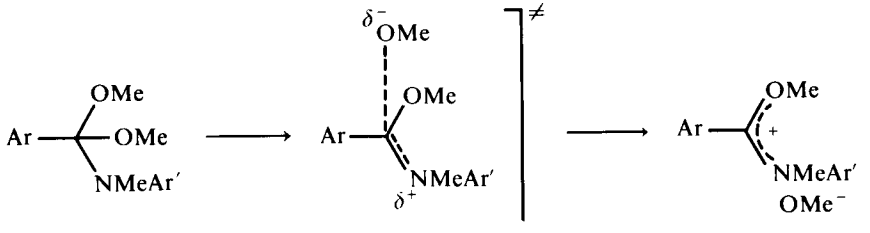
(**177a**) R = H
(**177b**) R = Me

The NMR spectroscopic properties of the demethylated compound **177a** and an analysis of its conformation and configuration (all-chair, all-*trans*) have been reported[169].

The kinetics and mechanism of the hydrolysis of amide acetals have been investigated[170,171]. For example, benzamide acetals [$ArC(OMe)_2NMe_2$] provide a model for the tetrahedral intermediate of an amide hydrolysis or an ester aminolysis and also provide an interesting comparison with simple acetals and ortho esters[56,57]. Investigations on anilide acetals [$ArC(OMe)_2NMeAr'$] reveal that, at high pH values (> 10), a pH-independent C—O cleavage reaction to produce methanol and the benzimidatonium ion is observed. The latter ion is further hydrolysed to amide and ester products (equation 69). The nature of the substituents and solvent effects support a simple ionization mechanism with a transition state near the ion (equation 70). At pH < 10, the anilide acetals hydrolyse to the benzoate ester, aniline and methanol in a reaction involving initial protonation at nitrogen and C—N bond cleavage to furnish a dial-



(69)



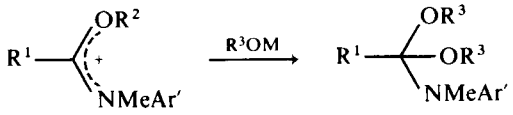
(70)

koxycarbenium ion and aniline (equation 69). At pH 7 to 10, this reaction shows specific H^+ catalysis attributable to a pre-equilibrium protonation followed by the rate-determining cleavage. Estimation of the pK_a value of the protonated anilide acetal (−1) provides an approximation of the rate of its C—N cleavage ($\approx 10^8\ s^{-1}$), which is near the diffusion limit. At pH < 7, there is a change of the rate-determining step of the product formation in this C—N cleavage reaction and the result of kinetic decomposition is the hemi-ortho ester $ArC(OMe)_2OH$, the product of hydration of the dialkoxycarbenium ions.

VII. PREPARATION AND SYNTHETIC APPLICATIONS OF ORTHO AMIDES

Almost all of the known syntheses of ortho amides start with precursors already possessing the mostly complete carbon skeleton. Synthetic applications and transformations of numerous ortho amides and derivatives have been described previously[1–3,165,173–175].

Alkoxymethyleneiminium salts react readily with alkoxides to furnish a variety of amide acetals[165]. In particular cases, the alkoxymethyleneiminium trifluoromethane sulphonates **178a** are interesting substrates for the preparation of the diorganoyloxy-(*N*-methylanilino)-phenylmethanes **178b** via treatment with alkoxides (equation 71)[171].



(71)

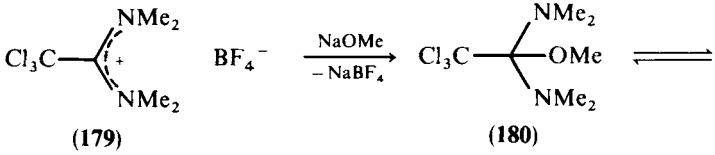
$CF_3SO_3^-$ (**178a**) $R^1 = Ar$, $R^2, R^3 = Alk$ (**178b**)

In general, sterically more bulky substituents at the α-position to the amino group and at the alkoxide as well as higher reaction temperatures are more in favour of nucleophilic substitution than nucleophilic addition as a consequence of the enhanced ambident reactivity[144]. Moreover, in reactions with the highly resonance-stabilized alkoxymethyleneiminium salts (and similarly highly stabilized alkoxycarbenium salts), the alkylation reactivity of the ambident cations is significantly increased.

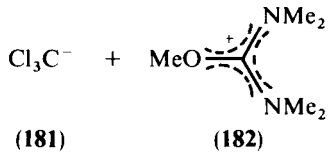
Trichloroacetamidinium tetrafluoroborate (**179**) reacts with sodium methoxide to furnish the aminal ester **180**[175] which, in turn, undergoes fast heterolysis to yield the trichloromethide anion (**181**) and the bis(methylamino)methoxycarbenium cation (**182**). Either excess methoxide or the carbanion **181** then acts as a demethylating reagent and the products **183** and **184** are formed immediately (equation 72)[175].

A very useful method for the synthesis of amide acetals is the nucleophilic substitution of the readily accessible dialkylaminoacetonitriles[165,175]. Thus, for example, ethoxy(1-pyrrolidinyl)(triethoxymethyl)carbenium tetrafluoroborate (**185**) reacts with sodium cyanide to furnish 2,3,3,3-tetraethoxy-2-(1-pyrrolidinyl)propanenitrile (**186**) which, in turn, is converted by pyrrolidine into a mixture of the nitriles **187a** and **187b**; these products can be separated by distillation (equations 73 and 74)[175]. On reaction with an alkoxide, the nitrile group of **187** is substituted to provide the bis(orthooxalic acid) derivatives **188** (equation 75)[175].

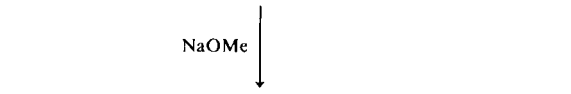
The synthetic utility of bis(amino)acetonitriles to furnish a variety of formamidinium salts has been extended[176]. Thus, the bis(dialkylamino)acetonitriles **189a–d** react with acetyl chloride and antimony pentachloride to give the *N,N,N′,N′*-tetraalkylformamidinium hexachloroantimonates **190a–d** (equation 76). Reactions of *p*-nitrophenol with



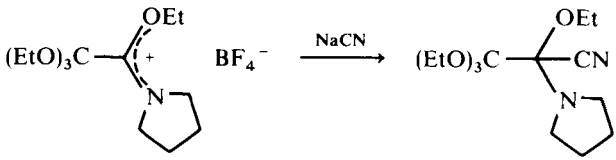
(179) (180)



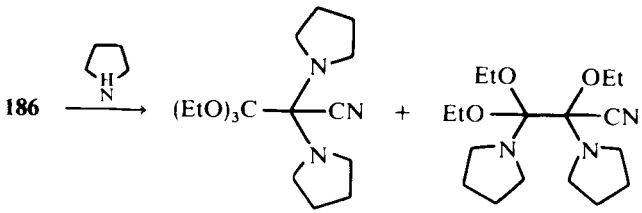
(181) (182)



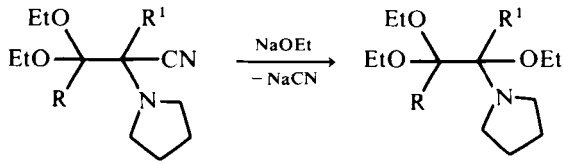
(183) (184) (72)



(185) (186) (73)

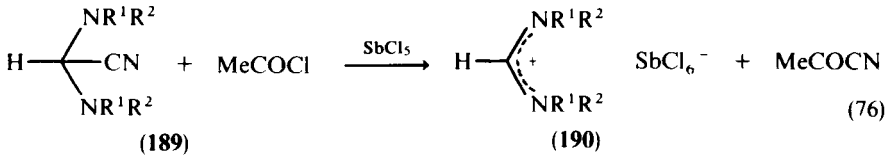


(187a) (187b) (74)



(187) (188) (75)

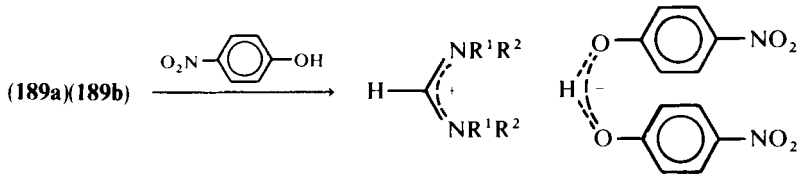
(187, 188)	a	b	c
R	OEt	OEt	—N
R^1	OEt	—N	OEt



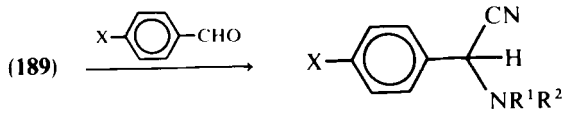
(189) (190) (76)

(189, 190)	a	b	c	d
R^1	Me			
		$-(CH_2)_4-$	$-(CH_2)_5-$	$-(CH_2)_2-O-(CH_2)_2-$
R^2	Me			

189a and **b** afford the *N,N,N'*,N'-tetraalkylformamidinium *p*-nitrophenolates **191a** and **b** (equation 77). Aromatic aldehydes react with **189** to produce the aryl(dialkylamino)acetonitriles **192a–g** (equation 78). The nitrile **189a** reacts with *CH*-acidic compounds to give the enamines **195a–c** (equation 79). The mechanism for this behaviour probably involves an initial dissociation of **189a**; the thus generated CN^- base then deprotonates the carbon acid to furnish the salt **193**. The final step of the process is stabilization via the adduct **194** and elimination of dimethylamine to provide the enamines **195** (equation 79)[176].



(191a) (191b) (77)

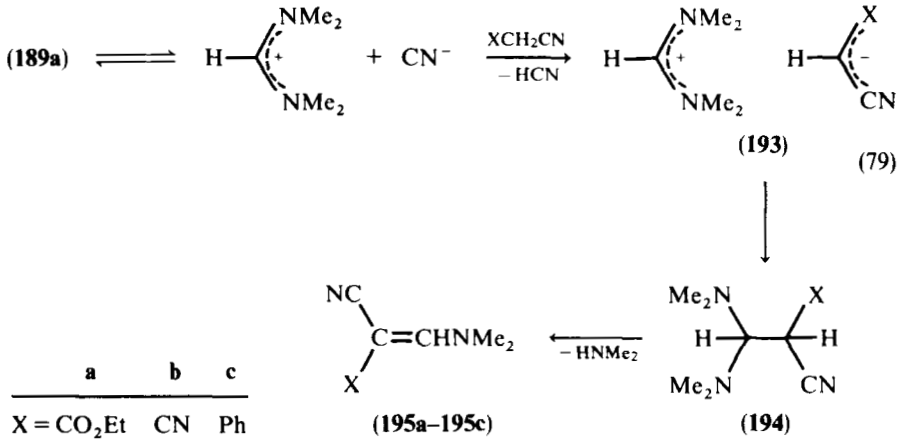


(78)

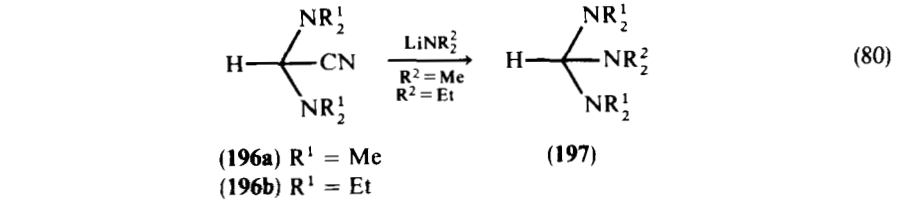
(192)	a	b	c	d	e	f	g
R^1	Me	Me	Me	Me	$-(CH_2)_4-$	$-(CH_2)_5-$	$-(CH_2)_5-$
R^2	Me	Me	Me	Me			
X	H	Cl	Me	OMe	OMe	H	OMe

The bis(dialkylamino)acetonitriles **196** react with lithium dialkylamides to furnish the tris(dialkylamino)methanes **197** (equation 80)[177]. Compound **196b** is easily accessible through nucleophilic substitution of **198** by diethylamine (equation 81)[177].

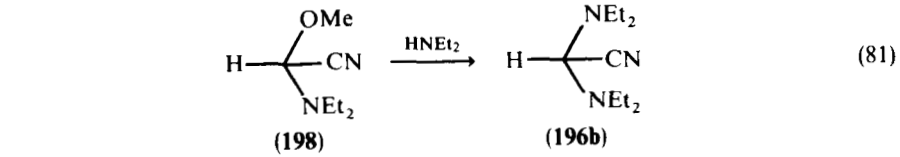
In both cases, the nucleophilic substitutions probably proceed through formamidinium or methoxy(amino)carbenium ions.



(79)

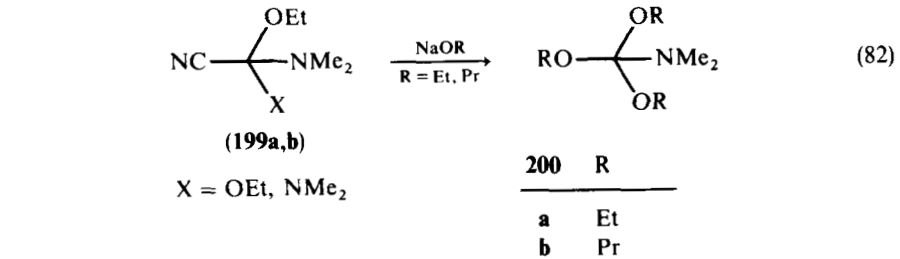


(80)



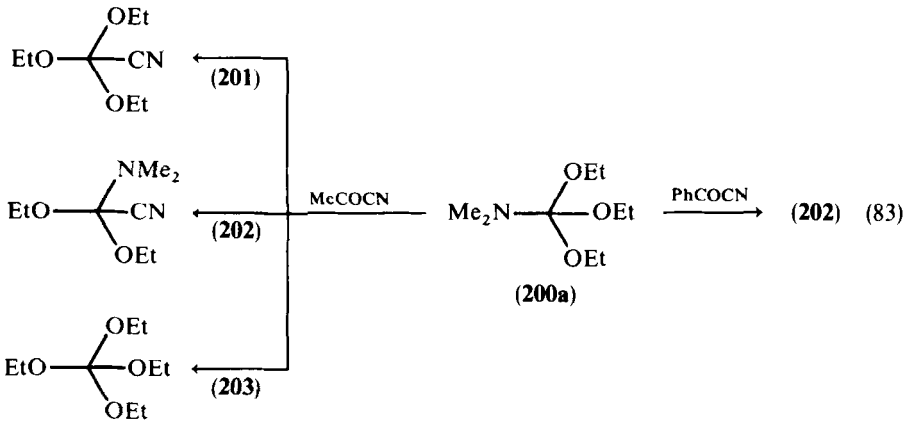
(81)

The nitriles **199a** and **b** react with alkoxides by a sequential nucleophilic substitution process to furnish the orthocarbamic acid esters **200a** and **b**, respectively (equation 82)[51].



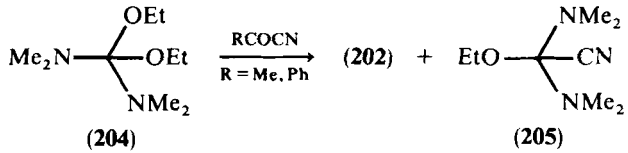
(82)

An interesting approach to *O,N*-functionalized, trisubstituted acetonitriles is possible starting from either orthocarbamic esters or from urea acetals[178]. Accordingly, **200a** reacts with acetyl cyanide to yield compounds **201–203** in an exothermic reaction

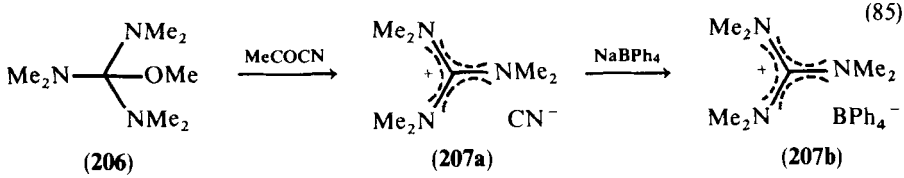


(83)

(equation 83), whereas cleavage of **200a** with benzoyl cyanide furnishes product **202** exclusively (equation 83)[178]. The ortho amide acetal **204** is converted by acyl cyanides into products **202** and **205** (equation 84)[178].*N*,*N*,*N*',*N*',*N*'',*N*''-Hexamethyl(methoxy)-methanetriamine (**206**) reacts with acetyl cyanide to give the guanidinium cyanide **207a**, which can be transformed readily into the corresponding tetraphenylborate **207b** (equation 85)[178].

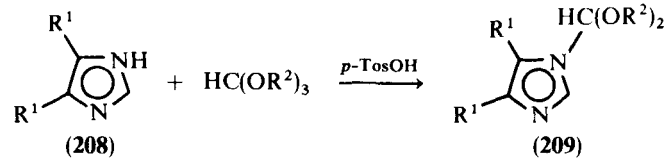


(84)



(85)

A variety of ortho amides are conveniently accessible from the reactions of orthoformates with secondary aliphatic amines under acid catalysis[102]. By way of an analogous reaction mechanism, heterocyclic systems containing an integrated amide acetal unit are easily available from orthoformates and hetereoarenes. Thus, compounds **209** can be obtained from the imidazoles **208** and an orthoformate under *p*-toluenesulphonic acid

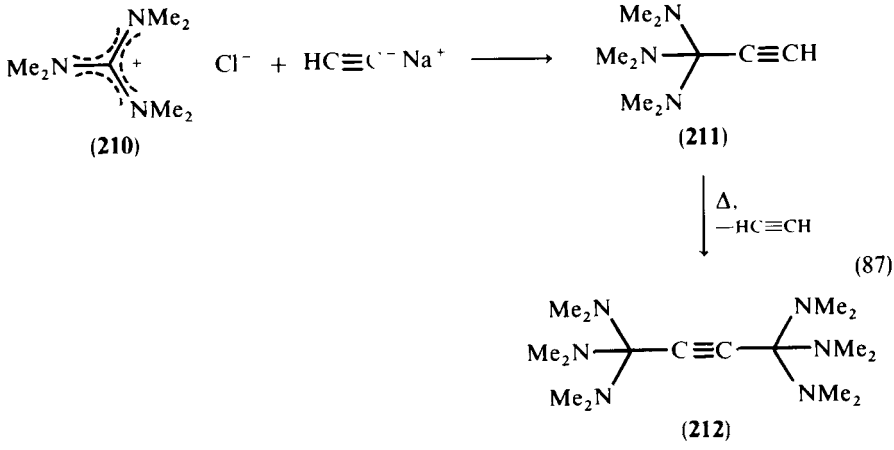


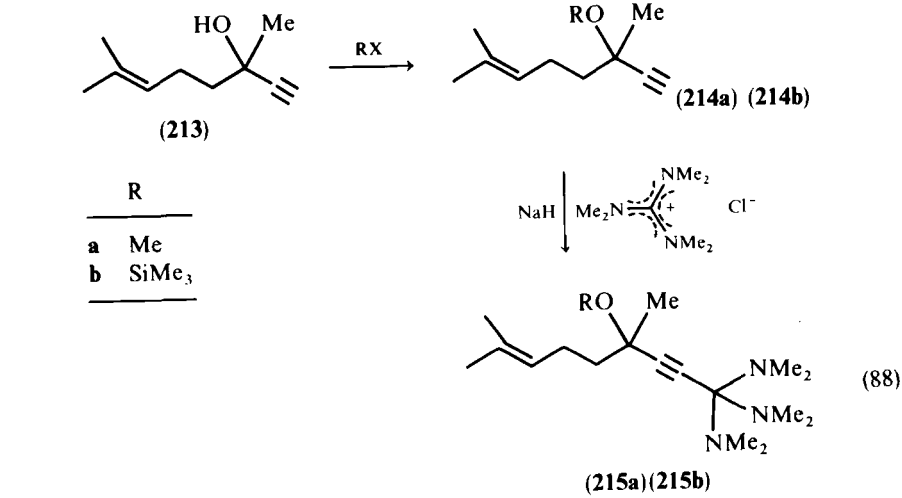
(86)

R^1 = H, Me, i-C_3H_7
R^2 = Me, Et

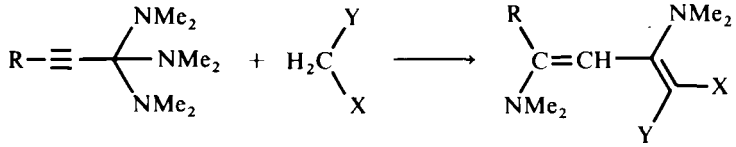
catalysis (equation 86)[179]. The products **209** can be metallated rapidily to furnish the 2-lithio derivatives which participate in highly regioselective reactions with a variety of electrophiles to produce further functionalized imidazoles[179].

Ortho amides are directly accessible from reactions of guanidinium salts with carbanionic reagents[180]. This method can also be used for the synthesis of the ortho amides of alkynoic acids. For example, the guanidinium chloride **210** reacts with sodium acetylide in tetrahydrofuran to furnish the propynoic acid ortho amide **211**, which undergoes a coupling reaction at 80 °C under vacuum to yield product **212** (equation 87)[181]. This product **212** can also be prepared from **210** and disodium acetylide[181]. The same method has also been used to introduce an ortho amide functionality into *O*-protected alkynols to furnish the *O*-protected dehydrolinolol derivatives **215a** and **b** (equation 88)[181].





Alkyne-functionalized ortho amides are highly reactive acceptor reagents: reactions of **216** with the carbon acids **217** give rise to the 'push pull' substituted butadienes **218** (equation 89)[181].

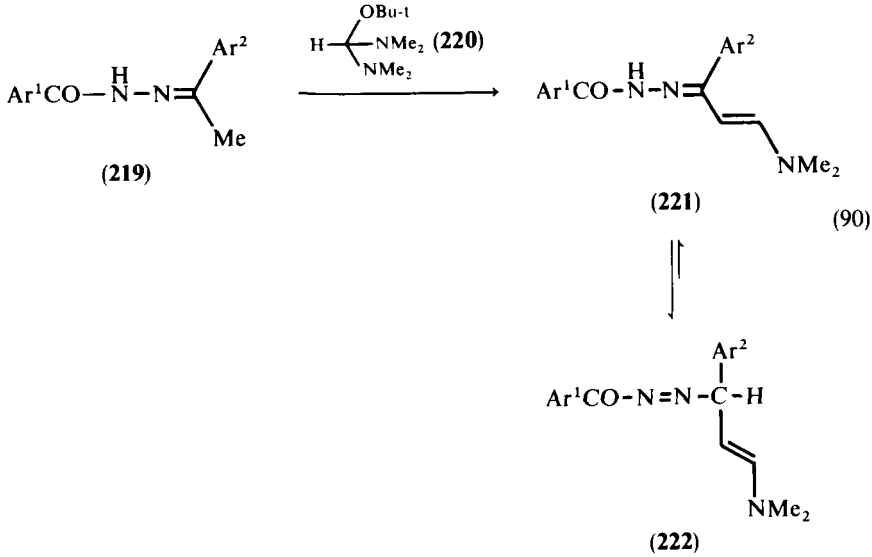


(89)

(216) (217) (218)

218	R	X	Y
a	H	CN	CO_2Me
b	H	CO_2Me	CO_2Me
c	Ph	CN	CN

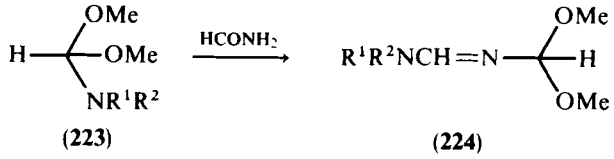
The synthetic applications of the formylation reactivity of formamide acetals or aminal esters of formic acid have been further extended. For example, aryl methyl ketone aroylhydrazones **219** react with the aminal ester **220** to furnish the aryl (β-dimethylamino)vinyl ketone aroylhydrazones **221** (equation 90)[182]. According to ^{1}H-NMR analysis, the tautomeric equilibrium in the liquid phase ($CDCl_3$ solution) is shifted to the side of **222** (equation 90)[182].



(90)

(219) (220) (221) (222)

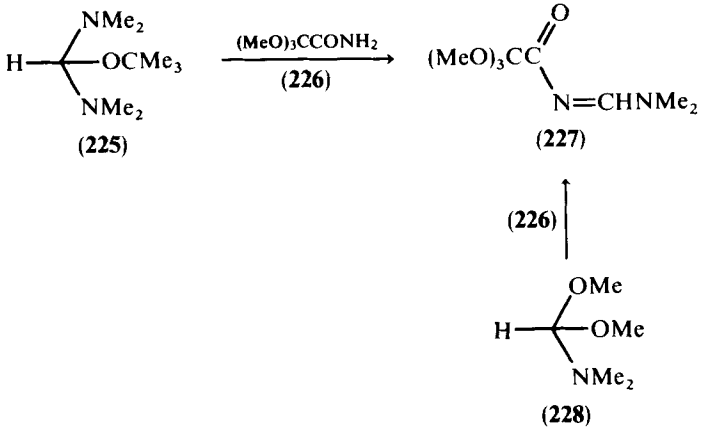
Acetamides and higher homologues as well as ureas and urethanes react with ortho amides (amide acetals, aminal esters) to yield *N*-acylformamidines[165,174]. However, formamide reacts with the dialkylformamide acetals **223** directly to furnish the azavinylogous amide acetals **224** in good yields (equation 91)[183].



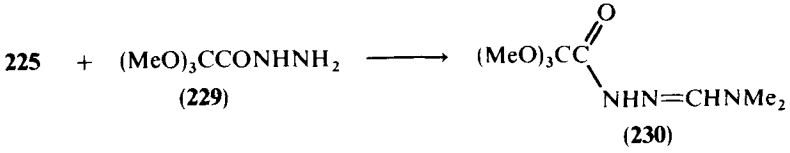
(223) (224) (91)

223, 224	a	b	c	d
R^1	Me	Et		
			$-(CH_2)_4-$	$-(CH_2)_2O(CH_2)_2-$
R^2	Me	Et		

Aminal esters of formic acid and formamide acetals are able to functionalize NH_2-acidic compounds such as carbonic acid amides or carbonic acid hydrazide derivatives; products of these reactions are formamidines or formamidrazones, respectively. In the same way, *t*-butoxy-(*N*,*N*,*N'*,*N'*-tetramethyl)-methanediamine (**225**) reacts with the amide **226** to furnish *N*,*N*-dimethyl-*N'*-(trimethoxyacetyl)formamidine (**227**) directly (equation 92)[24]. Use of *N*,*N*-dimethylformamide dimethyl acetal (**228**) results in the formation of the same product. The aminal ester **225** reacts with trimethoxyacetic acid hydrazide (**229**) to give *N*,*N*-dimethyl-*N'*-(trimethoxyacetyl)formamidrazone (**230**) in high yield (equation 93)[24].



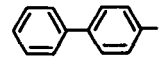
(225) (227) (228) (92)



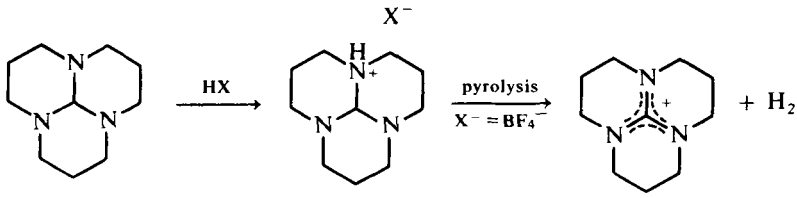
(230) (93)

The ortho amide derivative of carbonic acid (**232**) reacts with the weak carbon acids **231a–h** to furnish the ketene aminals **233a–h** (equation 94)[184]. In contrast, orthoformic acid derivatives react with *CH*-acidic ketones to produce vinylogous amides[165,172–174].

$$\underset{\textbf{(231a–h)}}{RCOMe} + \underset{\textbf{(232)}}{EtOC(NMe_2)_3} \longrightarrow \underset{\textbf{(233a–h)}}{RCOCH{=}C(NMe_2)_2} \qquad (94)$$

a	b	c	d	e	f	g	h
R = Me	Et	Me_2CH	$(MeO)_2CH$	Ph	Me-	MeO-	

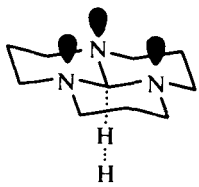
Treatment of perhydro-3*a*,6*a*,9*a*-triazaphenalene (**234**) with an equimolar amount of aqueous tetrafluoroboric or hydrochloric acid furnishes the simple salts **235a** or **b** from which the substrate **234** can be regenerated by neutralization (equation 95)[185]. Addition of excess hydrochloric acid to the ortho amide **234** causes precipitation of the bicyclic dichloride **237**. Pyrolysis of the solid tetrafluoroborate **235a** under nitrogen (110 °C/23 h) produces the guanidinium tetrafluoroborate **236** in a clean process. Hydrogen, the inevitable by-product, was captured by *trans*-stilbene in the presence of 10% palladium on carbon. It is suggested that this reaction takes place in two steps.



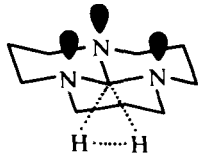
(95)

(234) **(235)** **(236)**

a ($X = BF_4^-$)
b ($X = Cl^-$)



(238)



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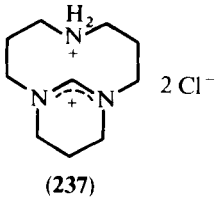
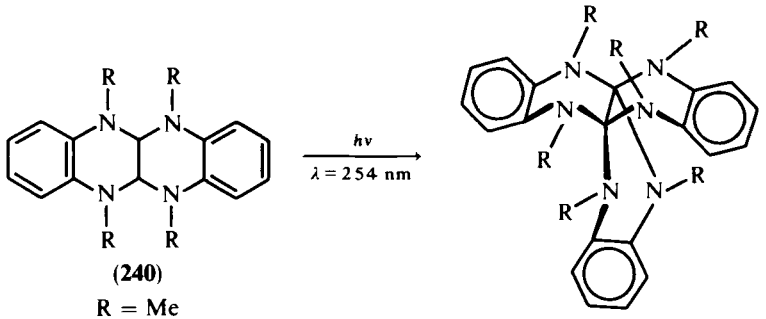


(237)

The first step is dissociation of the ammonium tetrafluoroborate **235a** into the ortho amide **234** and tetrafluoroboric acid while the second step is the oxidation of the ortho amide **234** by the Brönsted acid. Protonation of the central carbon–hydrogen bond of the ortho amide can produce a transition state or an intermediate with either the linear configuration **238** or the triangular configuration **239**. The former structure **238** was tentatively favoured by the authors[185].

A photochemically induced synthesis of a stable oxalic acid ortho amide possessing the propellane skeleton has been described[186]. The methylated hexahydroquinoxalino[2,3-*b*]quinoxaline derivative **240** extrudes nitrogen upon photochemical induction to furnish the stable oxalic acid ortho amide **241** (equation 96), a molecule belonging to



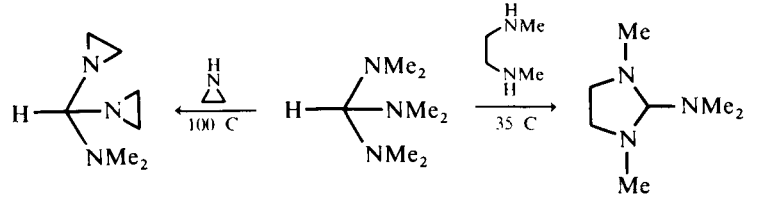
(240)
R = Me

(241)

(96)

the [4,4,4]propellane series. X-ray crystallographic analysis of **241** reveals D_3 symmetry in the solid state[186].

In contrast to the highly volatile dimethylamine, tris(dimethylamino)methane (**242**) can be employed for transamination reactions with higher boiling amines. Thus, **242** is easily converted to the imidazolidine derivative **243** by treatment with a 1,2-diamine and to the bis(aziridino)dimethylaminomethane **244** by treatment with aziridine (equation 97)[3,189].



(244) (242) (243)

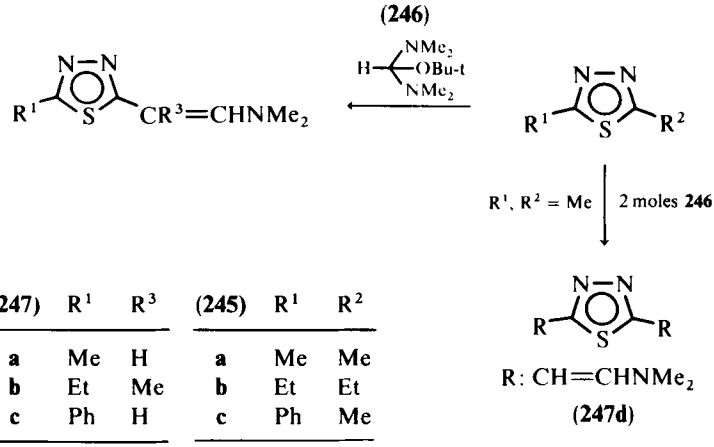
(97)

Ortho amides of formic acid are interesting reagents for the aminomethylenation of thiadiazoles and related heterocyclic systems containing acidic CH groups. Thus, the 1,3,4-thiadiazoles **245** react with the aminal ester **246** to furnish the enamines **247a–c** (equation 98)[187]. The amide acetals **249** and **250** are able to formylate the methyl group of the 1,3,5,6-dithiadiazepine **248** to yield the enamine **251** (equation 99)[187]. Treatment of **245a** or **248** with two moles of **246** affords the dienamine **247d** or **252**, respectively (equations 98 and 99).

In an analogous reaction with the amide acetals **249** and **250**, the 1,3,4-thiadiazolium salts **253** are readily formylated to furnish the corresponding thiadiazolium salts **254** (equation 100)[187].

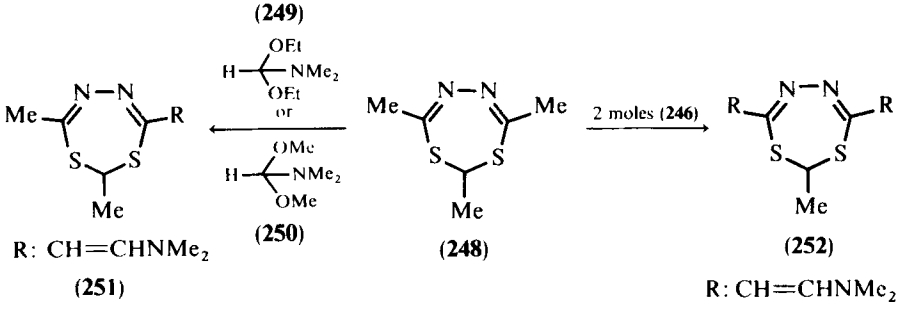
Reactions of orthoformamides with isocyanates, isothiocyanates and carbodiimides give rise to a wide range of five-membered heterocyclic systems[173]. Thus, the orthoformamide **255a**, the thio-analogue **255b** and tris(dialkylamino)methanes **255c** react with isocyanates to furnish the parabanic acid derivatives **256a–c** (equation 101)[188]. In some cases, isothiocyanates and the amide acetals **255a** also react to yield thioparabanic acid derivatives[188].

Amide acetal **257** also reacts with 5-imino-2,4-imidazolidinediones **258a** and **b** to furnish the parabanic acid derivatives **259a** and **b** (equation 102)[188]. The imino nitrogen

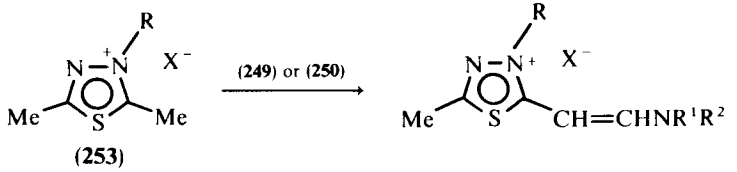


(247)	R^1	R^3	(245)	R^1	R^2
a	Me	H	**a**	Me	Me
b	Et	Me	**b**	Et	Et
c	Ph	H	**c**	Ph	Me

(98)



(99)

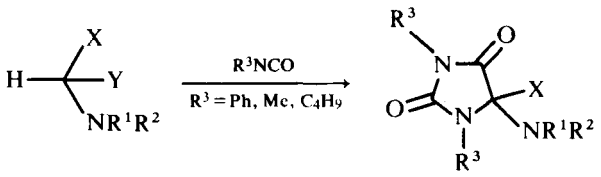


(100)

(254)	R	R^1	R^2	X
a	Me	Me	Me	$MeSO_4$
b	Bz	Me	Me	Br
c	C_8H_{17}	Me	Me	I

atom is probably involved first in the nucleophilic displacement reaction with compound **257**.

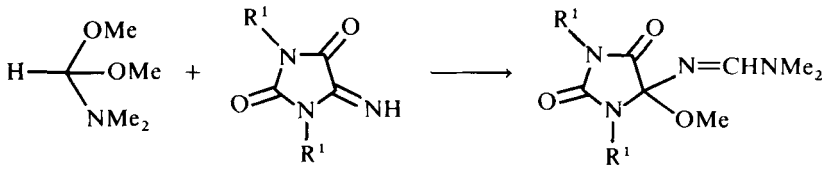
Ortho amide derivatives can be used in group transfer reactions for the synthesis of tetracarbonylferrates. In these reactions, the nucleophilic leaving group X is transferred



(101)

(255)	X	Y
a	OR	OR
b	SR	SR
c	$NAlk_2$	$NAlk_2$

(256)	X	R^1, R^2
a	OR	Alk
b	SR	Alk
c	$NAlk_2$	Alk

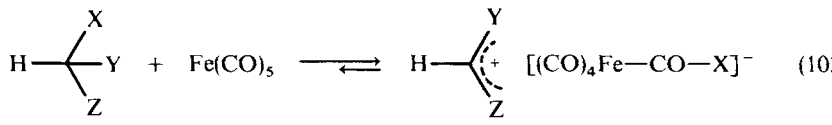


(102)

(257)

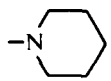
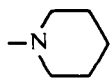
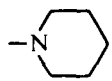
(258)	R^1
a	*p*-Tol
b	2,3-Cl₂C₆H₃

(259)	R^1
a	*p*-Tol
b	2,3-Cl₂C₆H₃



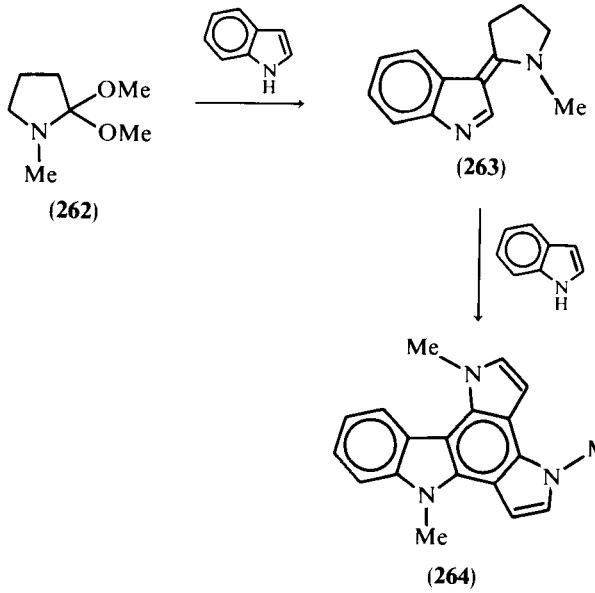
(103)

(260) (261a,b,c,d)

260	X	Y	Z
a	$-NMe_2$	$-NMe_2$	$-NMe_2$
b	$-NMe_2$	$-N(Me)CH_2CH_2N(Me)-$	
c			

from the orthoformic acid derivative **260** to the $Fe(CO)_5$ unit to furnish the salts **261** (equation 103)[189]. In the case of the reaction of tris(dimethylamino)methane (**260a**) with $Fe(CO)_5$, the equilibrium between the resultant amidinium–carbamoyltetracarbonylferrate complex **261a** and the starting materials was investigated[189] and found to be shifted completely to the side of the ionic compound **261a**.

Lactam acetals can easily be converted into interesting building blocks for heterocyclic synthesis by reaction with a variety of *NH*- and *CH*-nucleophiles[165]. Using this concept, a novel synthesis of 1,4,7-trimethyldipyrrolo[2,3-*a*: 2′,3′-*c*]carbazole (**264**) was developed[190]. Indole thus reacts with the lactam acetal **262** by way of a 1:1 condensation product **263** to furnish **264** (equation 104). Similarly, 2-oxoindolines react with **262** to yield related 1:1 condensation products[190]. Compounds of the type **264** are of interest as potential DNA intercalators with both mutagenic and anti-tumour activity.



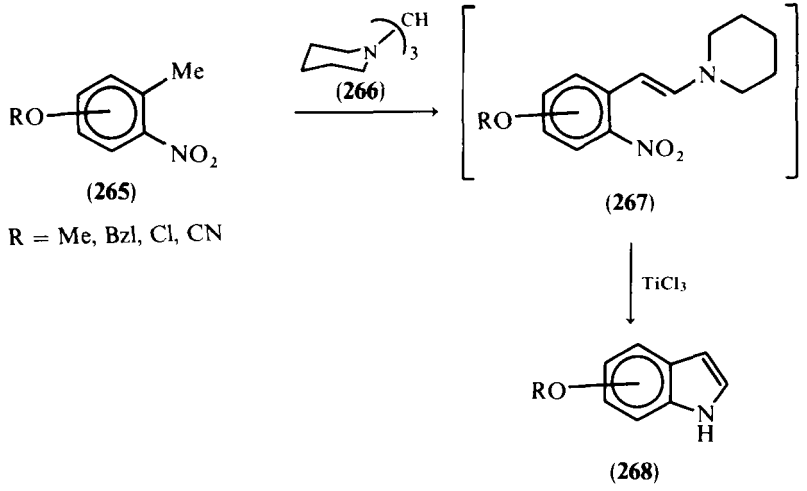
(104)

The indoles **268** can be prepared easily in 60–70% yields by condensation of the corresponding *o*-nitrotoluenes **265** with tripiperidinomethane (**266**) and subsequent reductive cyclization in the presence of aqueous titanium(III) chloride (equation 105)[191,192]. This method represents a further development of the Leimgruber and Batcho method[192] in which dimethylformamide acetals are used as a C_1-synthon.

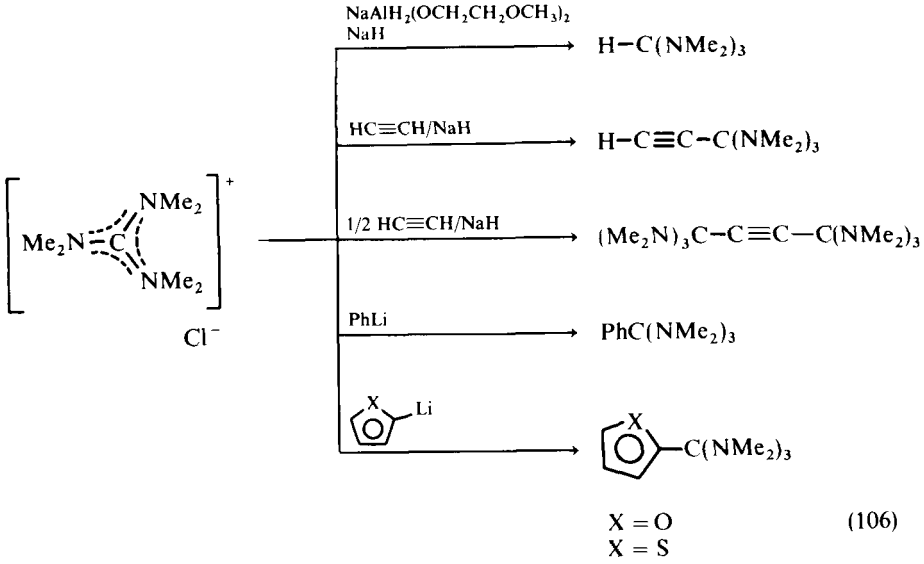
The nucleophilic addition of hydride ion or carbanions to guanidinium salts has been established as a versatile method for the syntheses of a variety of 1,1,1-tris(dialkylamino)alkanes[3,182]. Some examples of this procedure are illustrated in equation 106.

4-Amino-2-azabutadienes **270** are readily accessible by the reaction of the azomethines **269** with dimethylformamide diethyl acetal (equation 107)[193]. In the same way, the mixture of esters **271** can be converted to the 1-aminobutadiene **272** (equation 108)[193].

These compounds are interesting substrates for the preparation of functionalized benzenes, pyridines and azoles. Reaction of the 2-azavinamidinium salts **273** and **274** with dimethylformamide diethyl acetal give rise to the 2-aza- and 2,4-diazapentamethinium salts **275** and **276**, respectively (equation 109)[194]. Some of the salts **275** can



(105)



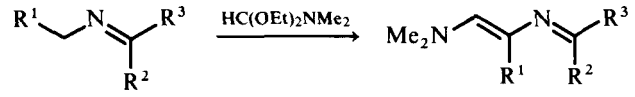
X = O
X = S

(106)

be readily transformed into pyrimidine derivatives by the action of ammonium acetate[194].

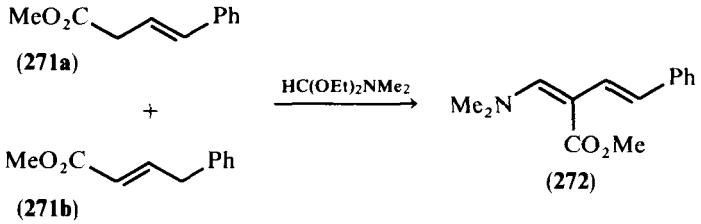
The general synthetic utility and reactivity of organyloxymethyleneiminium, amidinium and guanidinium salts has now been widely documented[3,165,173] and is further substantiated by the references cited in this review. However, some further interesting reactions in this area will be discussed in detail in the following paragraphs.

Succinic diimide (**277**) can be *O*-silylated by trimethylsilyl trifluoromethanesulphonate to furnish the bis(trimethylsilyloxymethylene)iminium trifluoromethanesulphonate (**278**) (equation 110)[42,194].

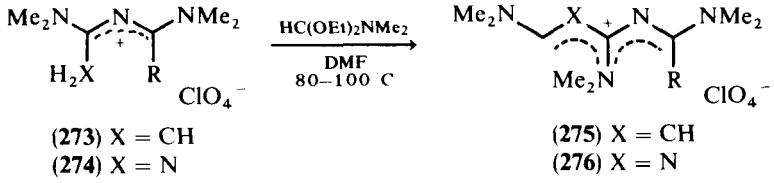


(269) (270) (107)

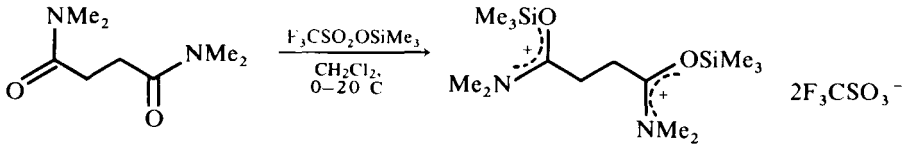
270	R^1	R^2	R^3
a	CO_2Me	H	Ph
b	CO_2Me	H	p-ClC_6H_4
c	CO_2Me	H	*p*-Tol



(108)



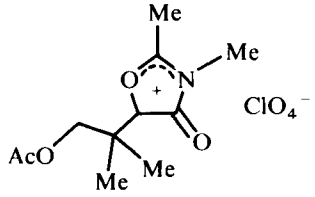
(273) X = CH
(274) X = N
(275) X = CH
(276) X = N
(109)



(277) (278) (110)

N-Alkylbenzanilides are also methylated at the carbonyl oxygen atom by treatment with methyl trifluoromethanesulphonate[196]. Cyclic and acyclic alkoxymethyleneiminium tetrafluoroborates are readily obtainable by selective *O*-alkylation of amides or lactams by trialkyloxonium tetrafluoroborates[3,197]. In the alkylation of *N*-alkyllactams, the product yield is only influenced to a minor degree by the size of the ring[197].

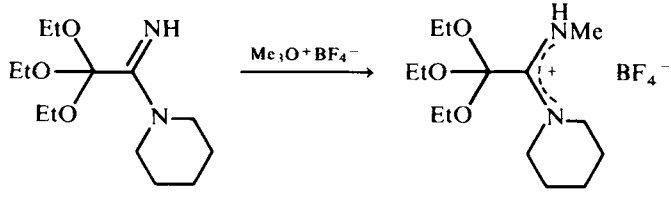
Cyclization reactions of 2,4-dihydroxy-3,3-dimethylbutanoic acid alkylamides give rise to cyclic products; for example, the substituted 1,3-oxazolidin-2-enium perchlorate **279** was prepared by this route[198].



(279)

The reaction of alkoxymethyleneiminium salts with secondary amines constitutes a useful method for the preparation of symmetrical *N,N,N',N'*-tetraalkylamidinium salts in high purity[199].

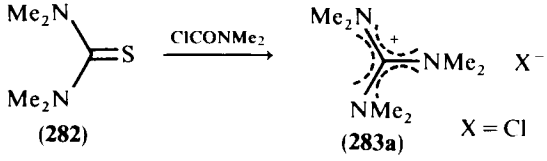
In contrast to the reaction of triethoxyacetic acid piperidide with triethyloxonium tetrafluoroborate (cleavage at the ortho ester function), the related amidine **280** was alkylated at the imino function by trimethyloxonium tetrafluoroborate to furnish the amidinium tetrafluoroborate **281** with high regioselectivity (equation 111)[200].



(280) (281) (111)

Peralkylated guanidinium salts represent an interesting group of reagents for a variety of chemical transformations: for example, for the synthesis of alkoxy-*N,N,N',N',N'',N''*-hexaalkylmethanetriamines[201]; these compounds can also serve as phase transfer catalysts[202].

N,N,N',N'-Tetramethylthiourea (**282**) reacts with *N,N*-dimethylaminocarbonyl chloride to furnish the guanidinium salt **283a** (equation 112)[203]. The carbenium salt **284**,

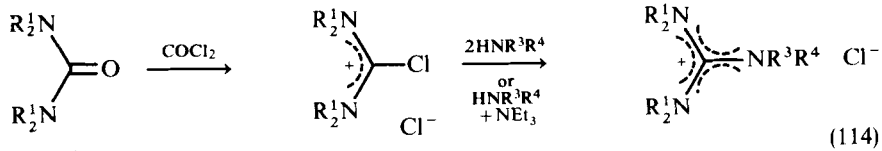


(282) (283a) X = Cl (112)

(284) (283b) X = $MeSO_4$ (113)

prepared from **282** and dimethyl sulphate, reacts with dimethylamine to yield the guanidinium salt **283b** (equation 113)[203].

Reactions of phosgene with the *N,N,N',N'*-tetraalkylureas **285** furnish the synthetically versatile chloroformamidinium chlorides **286**. Compounds **286** can be transformed into mixtures of the guanidinium salts **287** and ammonium salts by treatment with mixtures of primary, secondary and tertiary amines. The guanidinium salts **283** have been isolated by treatment of these mixtures with sodium hydroxide (equation 114)[203].

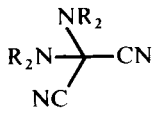


R^1—R^4 = Alkyl

(285) **(286)** **(287)** + $H_2\overset{+}{N}R^3R^4$ Cl^- or $HNEt_3$ Cl^-

(114)

As a consequence of their capto-dative substituent patterns, the bis(dialkylamino)malononitriles **288** are interesting building blocks for functionalization processes[204]. Compounds of this type are now readily available in good yields from the reaction of a chloroformamidinium chloride with sodium cyanide in the two-phase system diethyl ether/water. Subsequent transformations of the compounds **288** with amines give rise to guanidines. Urea acetals, orthocarbamic acid esters and ketene aminals are also accessible starting from the malononitriles **288** (in particular when R = Me)[204].



(228) R = Me, Et, $[CH_2]_4$, $[CH_2]_5$, $[CH_2]_2$ $O[CH_2]_2$

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CHAPTER 18

Recent developments concerning carboxyl groups in biochemistry

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ABBREVIATIONS

ADP	adenosine diphosphate
ALA	δ-aminolevulinic acid
AMP	adenosine monophosphate
ATP	adenosine triphosphate

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BGP	bone Gla protein
cDNA	complementary deoxyribonucleic acid (complementary to an mRNA that is used as a template by reverse transcriptase)
CoA	coenzyme A
FMN	flavin mononucleotide
Gla	γ-carboxyglutamic acid
GTP	guanosine triposphate
HGAD	hydroxyglycine amidating dealkylase
HMGCoA	β-hydroxy-β-methylglutaryl CoA
MGP	matrix Gla protein
mRNA	messenger ribonucleic acid (the RNA that carries genetic information to ribosomes and determines the order of incorporation of amino acids in proteins)
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	reduced NADP
NMT	*N*-myristyl transferase
PAM	peptidylglycine amidating enzyme
PP	inorganic pyrophosphate
RNase	ribonuclease
tRNA	transfer ribonucleic acid (small RNA molecules that are esterified with specific amino acids to form intermediates in protein synthesis)

I. INTRODUCTION

The prominent role of carboxyl groups in intermediary metabolism was the subject of a review by Doonan in this series[1]. The formation of amides and their biological reactions have also been reviewed by Reimann and Byerrum[2]. The topics discussed in these articles will be summarized briefly in relevant sections of this updating of biochemical reactions of free and derivatized carboxyl groups.

II. FORMATION OF CARBOXYL GROUPS BY CO_2 FIXATION

A. Photosynthesis

Carboxyl groups in biological material are formed by two general mechanisms: CO_2 fixation and oxidation. The most prominent fixation reaction is that of photosynthesis, catalyzed by ribulose bisphosphate carboxylase[3,4]. This reaction is energetically favorable because cleaving the carbon chain of the hypothetical enzyme-bound 6-carbon intermediate to two molecules of 3-phosphoglycerate occurs concomitant with the process of carboxylation (Figure 1).

B. Biotin-containing Carboxylases

In addition to this well-established reaction, a number of carboxylation reactions that form intermediates in the catabolism of specific amino acids and odd-chain fatty acids and in gluconeogenesis depend upon biotin-containing enzymes (Table 1). In these reactions a reactive CO_2 donor is carboxylated biotin, which is generated as a part of each enzyme in a reaction coupled with hydrolysis of ATP (Figure 2). The biotin in each enzyme is covalently attached to the protein through an amide bond to the ε-amino

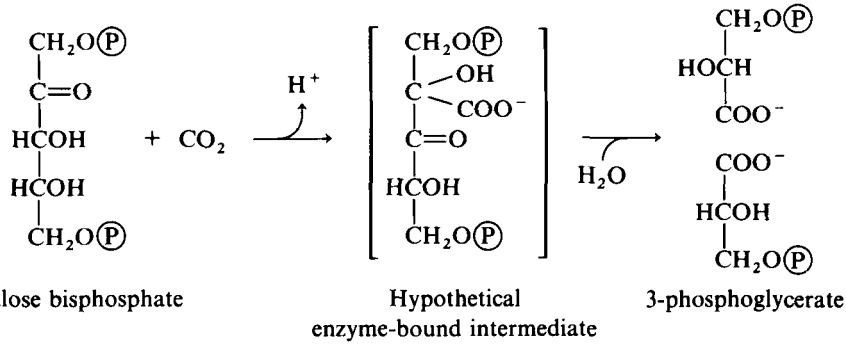


FIGURE 1. Carboxylation reaction of photosynthesis

group of a lysyl residue and the tethered biotin ring is capable of moving from one catalytic site, where it is carboxylated, to a second site, where the specific acceptor is bound[5].

C. Reversible Oxidative Decarboxylations

Several carboxylation reactions are prominent in intermediary metabolism as parts of complex reactions that do not require coupled reactions to supply free energy but are freely reversible under physiological conditions[6]. Of the three enzymes that catalyze reversible oxidative decarboxylations (see Table 2), the malic enzyme might function in some circumstances to fix CO_2, although the major function of all of these enzymes appears to be generation of reduced pyridine nucleotide coenzymes (NADH or NADPH). Phosphoenolpyruvate (PEP) carboxy kinase also catalyzes a reversible reaction (Figure 3) in which phosphate transfer balances the free energy change expected for the reaction involving CO_2[7].

D. Vitamin K-dependent Carboxylations

A new type of carboxylation reaction was discovered in 1975 as an enzyme that depends upon vitamin K and converts certain glutamic acid residues (Glu) in specific proteins to γ-carboxy glutamyl residues (Gla). The observations and reasoning involved in defining and characterizing this reaction will be summarized here.

The discovery of vitamin K and the early studies on its biological function gave no hint of the chemical mechanism by which it works. The vitamin was discovered as a nutritional factor that could prevent a deficiency disease in chickens characterized by

TABLE 1. Biotin-containing enzymes that catalyze net carboxylation reactions

Enzyme	Reaction
Acetyl-CoA carboxylase	Acetyl-CoA + CO_2 ⟶ malonyl-CoA
Propionyl-CoA carboxylase	Propionyl-CoA + CO_2 ⟶ methylmalonyl-CoA
Pyruvate carboxylase	Pyruvate + CO_2 ⟶ oxaloacetate
β-Methylcrotonyl-CoA carboxylase	β-Methylcrotonyl-CoA + CO_2 ⟶ β-methylglutaconyl-CoA

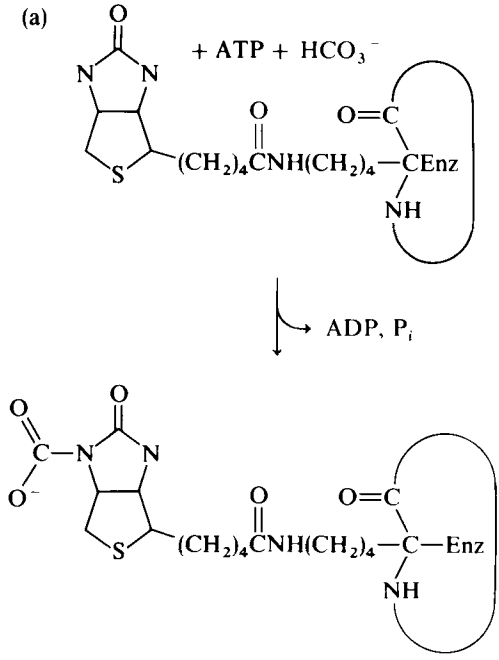


FIGURE 2. Reaction of biotin carboxylases. In the first step (a) 1-carboxy biotin is formed. In the second step (b), illustrated with acetyl CoA as the substrate, the carboxyl group is transferred to form malonyl CoA and to regenerate the biotinylated enzyme

excessive bleeding[8]. Schönheyder presented evidence in a thesis (referred to in a subsequent article[9]) that the excessive bleeding was a consequence of a prothrombin deficiency, a protein that is now known to be the precursor of the final enzyme in the cascade of reactions that result in the conversion of fibrinogen to fibrin, the material that forms the blood clot (Figure 4). A useful tool for the study of the mechanism of vitamin K action is the antagonist dicoumarol, identified by Link and coworkers as the agent in spoiled sweet clover responsible for a hemorrhagic disease of cattle also characterized by a deficiency of prothrombin[10]. A related synthetic compound, warfarin, has similar action (Figure 5).

Prothrombin was first isolated and purified in 1940[11] and shown to be convertible to another glycoprotein, thrombin, with distinguishable solubility characteristics. The function of vitamin K in production of prothrombin was indicated in experiments in which animals were first made deficient in prothrombin, either by deprivation of the vitamin or by treatment with dicoumarol. When vitamin K is administered to the deficient animals, after 30 to 60 minutes there is a rapid increase ('burst') of prothrombin in the blood. The size of the burst is only slightly affected by cycloheximide, which inhibits protein synthesis in animals. Therefore, it was concluded that vitamin K participates in the post-translational modification of a precursor of prothrombin. These studies are well reviewed by Suttie[12].

A demonstration of the hypothesized precursor of prothrombin *in vitro* was carried out by Suttie[13], who showed that a protein prepared from microsomes from livers of rats treated with dicoumarol was different from prothrombin, could not be activated to

(b)

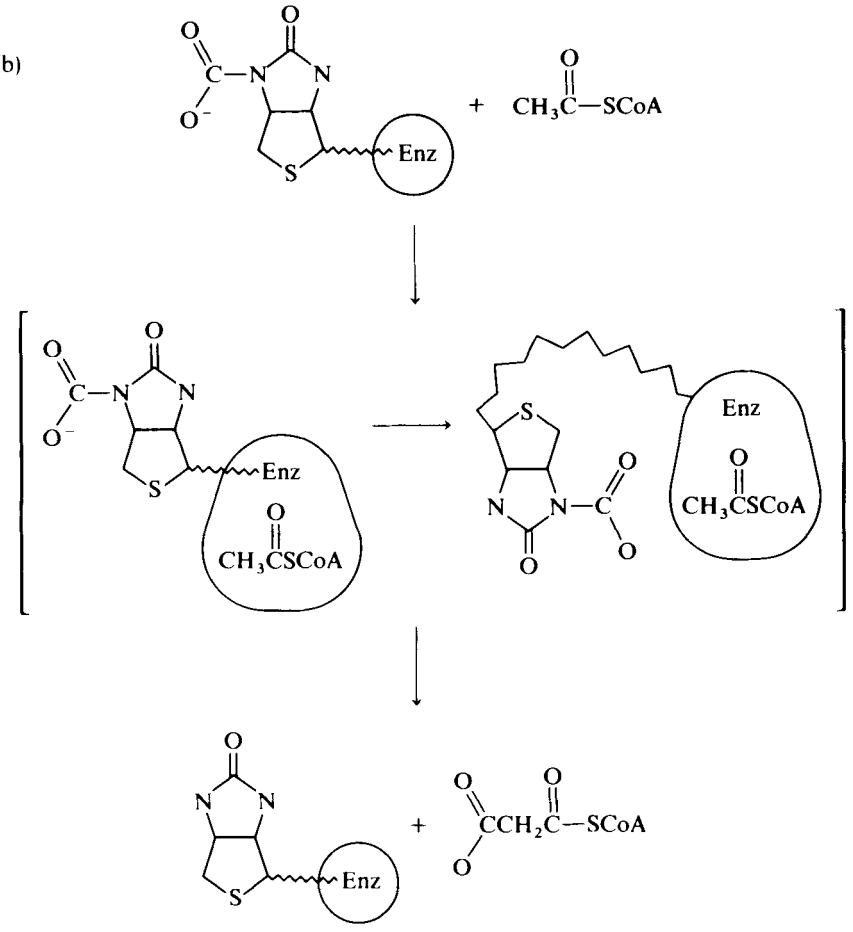
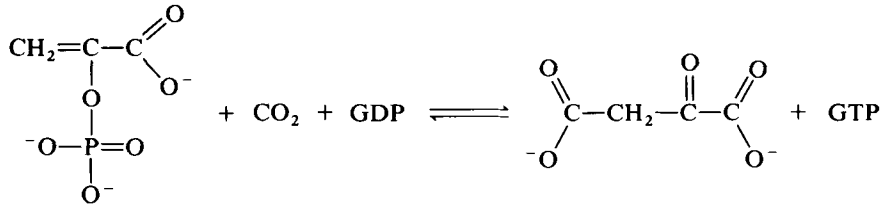


FIGURE 2(b)

TABLE 2. Reversible oxidative decarboxylations[a]

Enzyme	Reaction
Malic enzyme	Malate + NAD(P) $\rightleftharpoons$ pyruvate + CO_2 + NAD(P)H
Isocitrate dehydrogenase	Isocitrate + NAD(P) $\rightleftharpoons$ α-ketoglutarate + CO_2 + NAD(P)H
6-Phosphogluconate dehydrogenase	6-Phosphogluconate + NADP $\rightleftharpoons$ ribulose 5-phosphate + CO_2 + NADPH

[a] The enzymes that catalyze these reactions require divalent metal ions, but no other factors.



Phosphoenolpyruvate Oxaloacetate

FIGURE 3. Reaction of PEP carboxy kinase

form thrombin by enzymes of blood plasma, but was converted to thrombin by the action of an enzyme in the venom of a snake. A protein purified from blood plasma of prothrombin-deficient animals on the basis of reaction with antibodies to prothrombin[14] also appeared to be a precursor. This protein was highly purified and characterized independently by Stenflo[15] and by Nelsestuen and Suttie[16]. Both laboratories found that the protein had the same amino acid composition and carbohydrate content as prothrombin, but the two proteins differed in that prothrombin bound Ca^{++} more tightly, adsorbed to insoluble barium salts and was active in blood clotting.

These investigators[17,18] ultimately discovered simultaneously and independently the chemical basis for the difference between prothrombin and the homologous protein from vitamin K-deficient animals. Stenflo[17] purified a tetrapeptide from enzymatic digests of

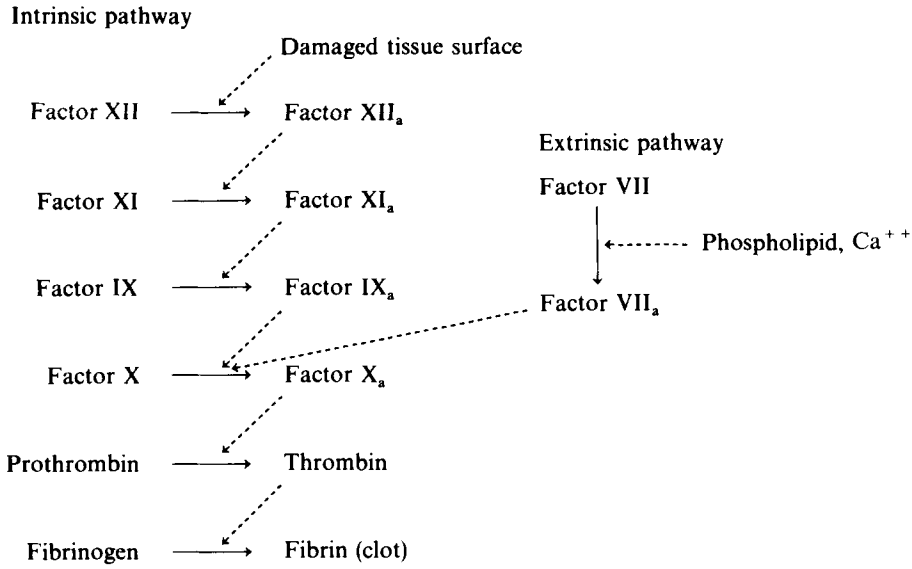
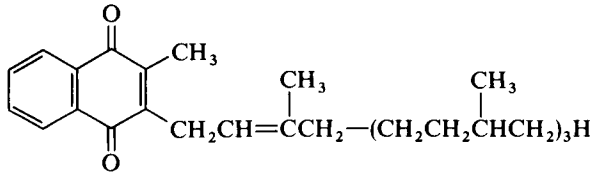
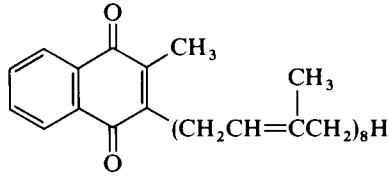


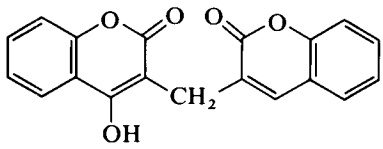
FIGURE 4. Blood clotting cascade. This outline shows the series of proteolytic reactions that are capable of enormous amplification as each step produces an enzyme. The final enzyme, thrombin, removes peptides from fibrinogen to leave a protein that aggregates strongly. The regulatory factors that prevent clot formation in the absence of injury and arrest the process when the wound is sealed are not shown



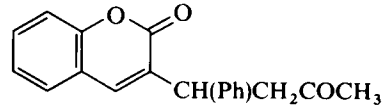
Vitamin K_1, phylloquinone (from green plants)



Vitamin K_3, menadione (from intestinal bacteria)



Dicoumarol

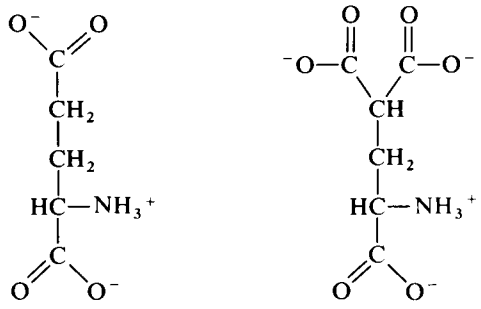


Warfarin

FIGURE 5. Vitamin K and antagonists

prothrombin with abnormally high electrophoretic nobility. Nelsestuen and collaborators[18] isolated a dipeptide from a fragment of prothrombin with high affinity for barium citrate. Both groups used mass spectrometry to show that their peptides included glutamic acid modified by the addition of a carboxyl group. The Swedish group relied upon NMR analysis to locate the new carboxyl group as a γ-substituent and the American group established the γ-position of the extra carboxyl group by decarboxylation of the new amino acid through heating with 6N DCl in D_2O and using mass spectrometry to locate the two deuterium atoms incorporated. Since the new amino acid, γ-carboxyglutamic acid (Gla), is a substituted malonic acid, it decarboxylates readily on heating in acid (Figure 6). The lability of this compound explains the failure to identify the novel amino acid during the many years that prothrombin was studied as a protein in numerous laboratories.

The observation that vitamin K is required for formation of prothrombin was followed by finding that three other blood-clotting factors are also decreased by administration of a vitamin K antagonist[19]. Factors VII, IX and X are diminished and inactive homologues that react with antibodies to these factors are found in the blood plasma. Other proteins that are not part of the clotting cascade but seem to play accessory or regulatory roles have also been found to be produced by a process that requires vitamin K[20]. All of these contain Gla residues[21]. In the most completely studied materials, the Gla residues occur in short N-terminal regions, which are cleaved from the proenzyme by more-or-less specific enzymes only when the Gla residues are complexed with Ca^{++}.



glutamate γ-carboxyglutamate

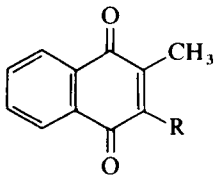
FIGURE 6

The occurrence of Gla residues is not restricted to blood-clotting proteins. A major site of proteins containing Gla is bone, where two proteins[22,23] osteocalcin (also known as bone Gla protein, BGP) and matrix Gla protein (MGP) are found. Similar proteins occur in the dentine of teeth[24], renal stones[25] and in other biological materials. Since the mRNA of osteocalcin has been found in soft tissues[26], the metabolic roles of Gla-containing proteins may be varied. At this time, however, except for the well-defined function of binding calcium to enable blood-clotting proteins to be processed, no precise role has been established.

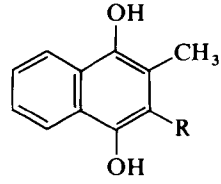
Evidence cited above that vitamin K-deficient livers produce a precursor of prothrombin led to several attempts to identify the enzyme system involved. An early report by the group of Johnson[27] cited unpublished results showing that a cell-free preparation of liver produced more prothrombin when bicarbonate buffer was used and demonstrated incorporation of CO_2 into an unidentified amino acid that moved on an ion exchange column in the region of the very acidic cysteic acid and was converted to glutamic acid on heating at pH 2. The subsequent work of Stenflo[17] and Nelsestuen[18] make it apparent that the liver system is capable of forming Gla from certain Glu residues.

The role of vitamin K in the carboxylating system was shown by Esmon, Sadowski and Suttie[28], who prepared microsomes from the livers of vitamin K-deficient rats and showed that both formation of prothrombin and incorporation of CO_2 into prothrombin were increased by the addition of vitamin K. The carboxylating system in cell-free preparations was found by several groups to be associated with cell membranes and the requirements of the reaction were not clearly defined until Esmon and Suttie[29] used a preparation solubilized with a detergent and showed that O_2, CO_2, a reduced pyridine nucleotide coenzyme (NADH or NADPH) and vitamin K were all involved but that ATP (required for biotin-dependent carboxylations) was not needed. The reduced pyridine nucleotide coenzyme does not play a direct role and is not needed if the vitamin K is replaced by its hydroquinone.

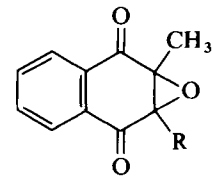
The mechanism of carboxylation of glutamyl residues does not resemble any known model. The lability of the product Gla indicates that, as is generally true, the free energy of the carboxylation is positive and the reaction must be coupled with an exergonic reaction. The nature of the coupled reaction is suggested by the finding that the hydroquinone of vitamin K is converted stoichiometrically to the 2,3-epoxide of the quinone during carboxylation[30]. The epoxide had been synthesized chemically much earlier and shown to have vitamin K activity *in vivo*[31]. Subsequently it was identified



Vitamin K



Vitamin K hydroquinone



Vitamin K epoxide

FIGURE 7

as a metabolite produced from vitamin K in the livers of rats pretreated with warfarin[32]. Studies from several laboratories suggested a relationship (Figure 7) between epoxide formation and carboxylation[33,34]. The relationship has been definitively established by the finding that a pure protein, MW 77,000, exhibits both carboxylation and epoxide formation[35].

There is a voluminous literature describing attempts to understand the mechanism of this complex reaction during the years that only crude enzyme systems were available to act on poorly defined substrates, often in the presence of inhibitors whose site of action was obscure. During this period many mechanisms were suggested, but these will not be reviewed at this time because they are not supported by current evidence; neither superoxide, hydroxide radical, hydrogen peroxide nor singlet oxygen appears to be involved[36]. However, chain breakers do inhibit, suggesting the formation of a radical, probably the semiquinone of vitamin K[37].

Although carboxylation and epoxide formation are coupled under optimal reaction conditions, in the absence of CO_2[38] or in the presence of CN^-[30], which inhibits carboxylation, the rate of epoxide formation is maintained or even increased. This

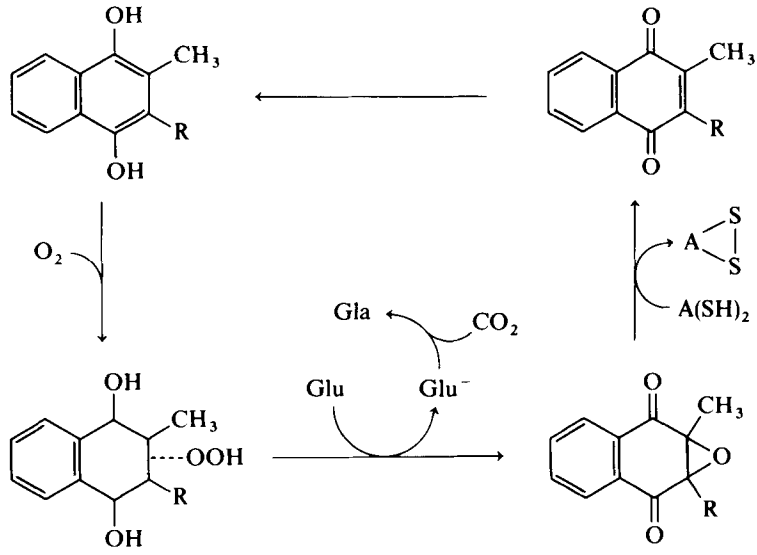


FIGURE 8. Hypothetical mechanism of vitamin K-dependent carboxylation

```
hPT       ANTFLGlaGlaVRKGNLGlaRGlaCVGlaGlaTCSYGlaGlaAFGlaALGlaSSTATDVFW-----
hFact X   ANSFLGlaGlaMKKGHLGlaRGlaCMGlaGlaTCSYGlaGlaARGlaVFGlaDSDKTNGlaFW-----
hFact IX  YNSGKLGlaGlaFVQGNLGlaRGlaCMGlaGlaKCSFGlaGlaARGlaVFGlaNTGlaKTTGlaFW-----
hFact VII ANAFLGlaGlaLRPGSLGlaRGlaCKGlaGlaQCSFGlaGlaARGlaIFKDAGlaRTKLFW-----
```

FIGURE 9. Homologous sequences of the N-termini of the carboxylated blood-clotting proteins[43]. The one-letter code for amino acids is used except for Gla, γ-carboxyglutamate. The h indicates that these sequences represent human proteins, PT is prothrombin and the other proteins are Factors X, IX and VII

suggests that the reaction proceeds stepwise and that an oxygenated vitamin K (a peroxide at position 2 or 3) is an enzyme-bound intermediate, which can be converted to the epoxide plus H_2O. In the absence of carboxylation this reaction is coupled with a rapid stereospecific exchange of hydrogen into the pro-S position of the γ-methylene group of glutamyl residues[39]. Suttie[36] has proposed the outline of reactions in Figure 8 as compatible with all current evidence. *In vivo* the epoxide is reduced to the quinone in the presence of dithiols. Either another enzyme using a dithiol or a flavoprotein, diaphorase[40], can reduce the quinone to the hydroquinone that is the substrate for the carboxylase.

The identity of the glutamyl residues that are the substrates for carboxylation in the precursor of prothrombin was established soon after the identification of Gla. Magnusson and collaborators[41] determined the sequence of the first 42 residues of prothrombin and showed that all 10 of the glutamyl residues were carboxylated. The complete sequence of this protein shows that the remaining 33 glutamyl residues are unchanged[42]. Similar analyses (Figure 9) of the blood clotting factors VII, IX and X, of other vitamin K-dependent plasma proteins and Gla-containing proteins from bone all show carboxylation only in the N-terminal portion of the protein and many structural homologies[43]. At this time it is not possible to define the basis for specificity of the carboxylase, but the availability of purified enzyme and synthetic substrates makes it reasonable to anticipate rapid increase in understanding. Substrates as small as pentapeptides (Phe-Leu-Glu-Glu-Leu) are carboxylated[44] but the K_m values† are in the millimolar range, in contrast to the micromolar values of natural substrates. A peptide containing only glutamyl residues corresponding to the first residues of prothrombin is a substrate, but much better substrates contain in addition the structure of the propeptides, the sequence of amino acid residues cleaved from the precursor protein after carboxylation, glycosylation and transport through cell membranes[45]. It remains to be determined which interactions are involved in recognition, which contribute nonspecifically to binding and what sort of positioning is required for activation by deprotonation of the methylene group of glutamyl residues.

III. REDUCTION OF CARBOXYL GROUPS

For many years the general outlines of intermediary metabolism have been well known and summarized in textbooks and metabolic maps. Every major component, carbohydrate, lipid, protein, nucleic acid and trace materials, includes both free carboxyl groups

† K_m is the Michaelis constant, the concentration of substrate at which the rate of an enzyme-catalyzed reaction is half the theoretical maximum velocity, V_{max}. Thus, the synthetic peptides with higher K_m values interact much less effectively with the carboxylating enzyme than the protein substrates.

and derivatives. Most of these materials and the reactions in which they are involved were described in earlier reviews[1,2]. Therefore, no mention will be made of the numerous decarboxylations, esterifications, amidations, thioesterifications, hydrolyses and transfers that are part of the common knowledge of biochemistry. However, a few novel processes have been described in recent years and will be summarized here. These are reduction of carboxylic acids, the formation of C-terminal peptide amides and the acylation of proteins.

A. Glyceraldehyde 3-Phosphate Dehydrogenase

The oxidative reactions referred to above that form carboxyl groups are generally irreversible and most organic acids that occur in biological systems cannot be reduced. Biological systems, however, have long been known to form derivatives of certain carboxylic acids that can be reduced. The only generally familiar reaction of this sort occurs in glycolysis, where the reversible oxidation of an aldehyde, glyceraldehyde 3-phosphate, by the enzyme glyceraldehyde phosphate dehydrogenase (triose phosphate dehydrogenase) requires the presence of inorganic phosphate to form the product 1,3-bisphosphoglycerate[46]. In the well established glycolytic pathway, the bisphosphate donated its anhydride phosphate to ADP in a reaction catalyzed by 3-phosphoglycerate kinase (Figure 10)[47]. This reaction is reversible and in the process of gluconeogenesis converts the free carboxyl group of 3-phosphoglycerate to the anhydride that is the substrate of reduction, i.e. the reversal of the triose phosphate dehydrogenase reaction.

The mechanism of triose phosphate dehydrogenase has been studied extensively[46] and involves an acyl-enzyme intermediate, a thioester of the carboxyl group with the sulfhydryl group of a cysteine residue. This is the actual reagent that accepts electrons from NADH. In most of the systems described below, such detailed information is lacking. What is apparent, however, is that the initial activation of the carboxyl group to be reduced occurs in diverse ways.

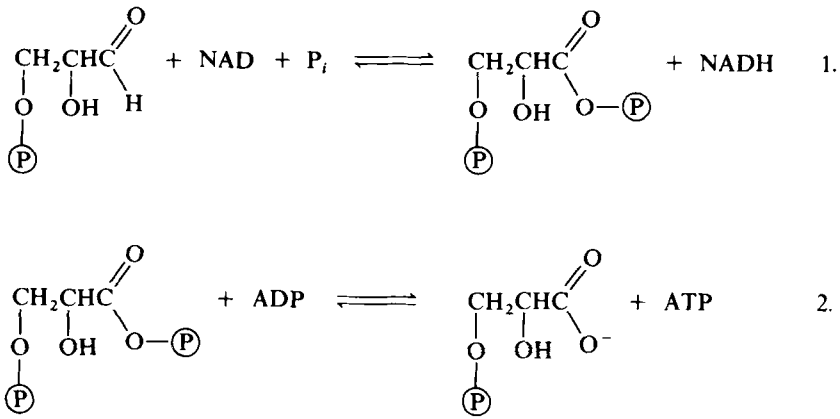


FIGURE 10. Reactions of triose phosphate dehydrogenase (1) and 3-phosphoglycerate kinase (2)

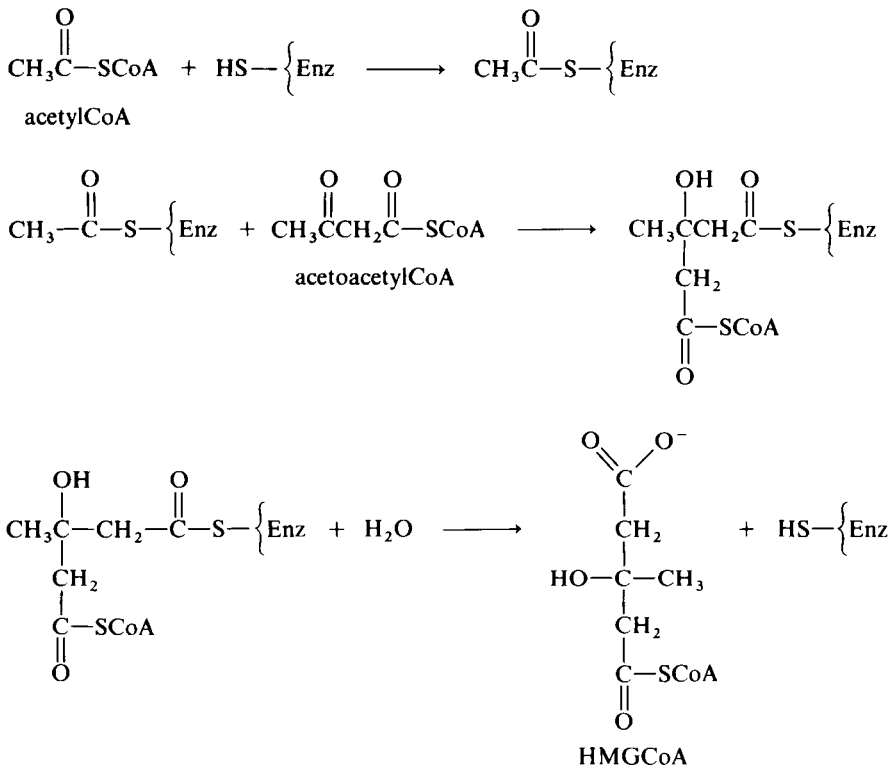
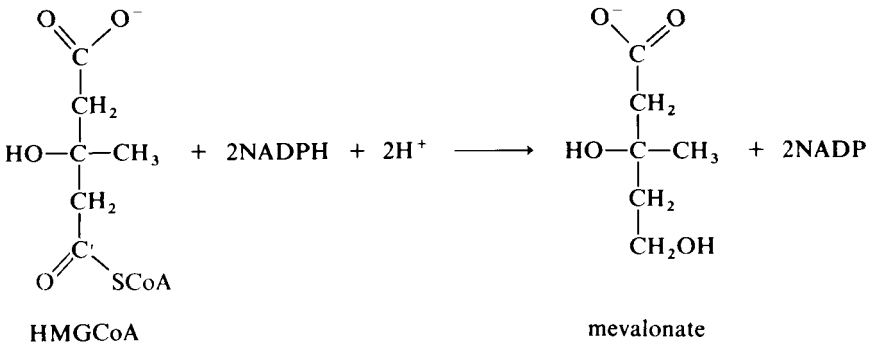


FIGURE 11. Condensation of acetylCoA and acetoacetylCoA catalyzed by HMGCoA synthetase

B. HMG CoA Reductase

A major metabolic pathway, the biosynthesis of cholesterol, is initiated by a reduction of a thioester. In this pathway β-hydroxy-β-methylglutaryl CoA (HMG CoA) is formed by the condensation of acetyl CoA and acetoacetyl CoA (Figure 11). HMG CoA is synthesized from acetoacetyl CoA and acetyl CoA, by distinguishable enzymes in mitochondria and cytosol, and the textbook picture indicates that the mitochondrial reaction leads to ketone bodies and the soluble system is used only for the synthesis of isoprene derivations. Teleological reasoning suggests that cytosolic HMG CoA may have another fate also because regulation of the pathway is exerted on the enzyme discussed below that uses HMG CoA, not on the enzyme that forms it. The condensation reaction that forms HMG CoA occurs between an acetyl thioester of the enzyme and acetoacetyl CoA to give an enzyme-linked HMG CoA, which is rapidly hydrolyzed to free HMG CoA and enzyme[48]. The reduction of the thioester to mevalonic acid catalyzed by HMG CoA reductase[49] is a reaction (Figure 12) that at this time is unique in biochemistry in that two equivalents of NADPH are used to form the alcohol with no evidence for the corresponding aldehyde as an intermediate. A few other dehydrogenases are known to carry out two-step oxidations of alcohols to acids[50,51] but no other is known to form an alcohol from an acyl group.



HMGCoA mevalonate

FIGURE 12. Reaction of HMG CoA reductase

In many simple dehydrogenase reactions, separate enzymes have been isolated that use aldehydes as substrates for reversible conversion to the corresponding alcohols or for oxidation to the corresponding acid (or derivative). In the case of HMG CoA reduction, the expected intermediate would be β-hydroxy-β-methylglutaric semialdehyde, in which the thioester has been replaced by an aldehyde group. This compound has been synthesized[52] and named mevaldic acid. The synthetic compound can serve as a substrate for reduction but cannot be isolated or trapped as an intermediate during reduction of HMG CoA[53]. The nature of the reaction is not yet resolved; it may be that the conformation of the enzyme with an intermediate so favors binding that the rate of dissociation is negligible or there may be a covalent intermediate, such as a thiohemiacetal.

The mevalonic acid that is produced by HMG CoA reductase is converted in several steps of phosphorylation, decarboxylation and elimination to isopentenyl pyrophosphate, the primary isoprene unit for synthesis of sterols (Figure 13). Although cholesterol is the major polyisoprene product in animals, other open-chain polyprenes are also of biological importance. One such product is dolichol, a family of compounds with 8 to 10 isoprene units that participate in transfer of oligosaccharides to glycoproteins (Figure 14). Recently, the sesquiterpene farnesol[54] and the diterpene geranylgeraniol[55,56] have been found to be incorporated in proteins as thioethers with cysteine sulfhydryl groups and to serve as anchors in lipid membranes. The cysteine residue that is prenylated is initially the fourth residue from the C-terminus, but further processing removes the three C-terminal amino acids and converts the carboxyl group of the cysteine to its methyl ester. In plants, myriads of terpenes are synthesized for functions that are in early stages of investigation.

C. Biosynthesis of Long-chain Alkanols

Plasmalogens (Figure 15) are lipids containing a long-chain alkyl ether of glycerol, which is also esterified to a fatty acid and a phosphoryl ethanolamine or choline. The name was created by Feulgen on the basis of his fuchsin-sulfurous acid stain; accidentally mishandled tissues were found to contain an aldehyde in their cytoplasm, 'plasmal', so the unknown precursor was named plasmalogen[57]. These compounds exist in varying amounts in the membranes of all animal cells and in some tissues, notably muscle and the white matter of brain, they are major lipids. Since the alkyl group is incorporated as the alcohol[58], the metabolic origins of the alcohols are of significance. A related

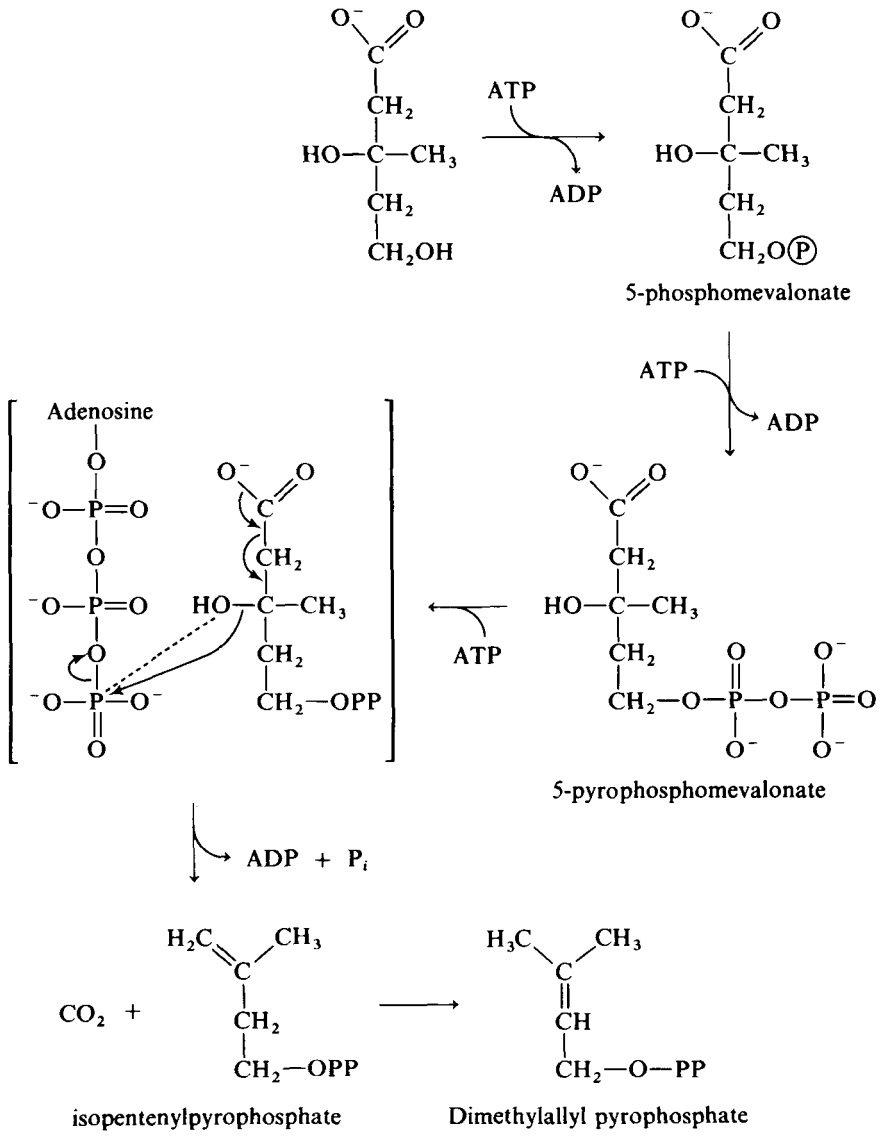
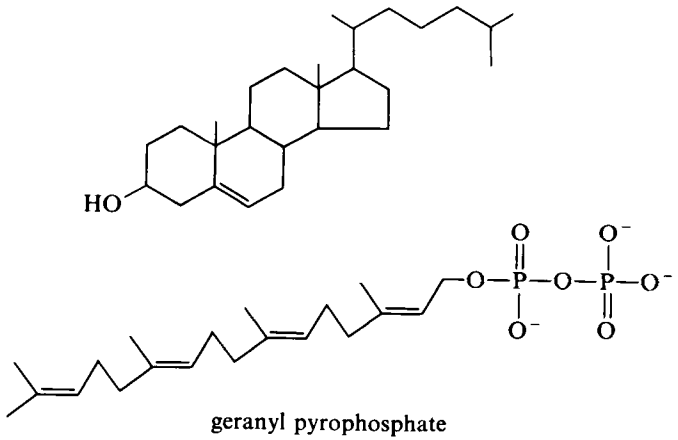


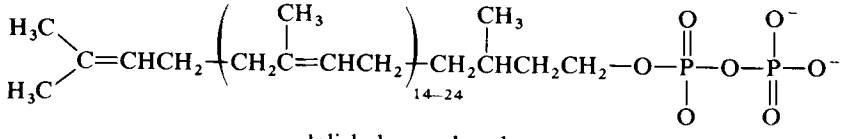
FIGURE 13. Outline of conversion of mevalonate to isoprene units

matter is the occurrence in various organisms of waxes (simple ethers) and also small amounts of free long-chain alcohols and aldehydes[59]. The general question is: What is the origin of the alcohols and aldehydes?

The biosynthesis of the alkyl ether linkage was shown by Hajra[60] to involve a unique reaction in which the acyl group of acyl dehydroxyactone phosphate is replaced by an alcohol. The major reaction appears to occur early in the biosynthesis of phospholipids



geranyl pyrophosphate

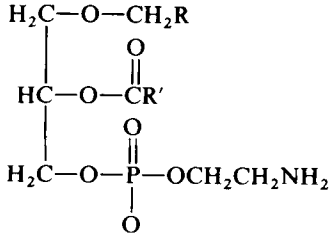


dolichol pyrophosphate

FIGURE 14. Some products of condensation of isoprene units

with an ester of dihydroxyacetone phosphate. The nature of the exchange reaction has not been elucidated. Subsequent reactions that result in the formation of plasmalogens are the same as those that form conventional phospholipids, with an additional reaction of a cytochrome P450 in animal cells that uses molecular oxygen to introduce an α,β-double bond adjacent to the ether linkage[61]. The alkenyl compounds readily decompose to give the aldehydes responsible for naming the plasmalogens.

Incorporation of isotopically labelled substrates indicated that the long-chain alcohols used for plasmalogen synthesis were derived from the corresponding fatty acids[62]. The first enzymatic reduction of fatty acids was demonstrated in plant extracts[63a], where the CoA thioesters of fatty acids were shown to be the substrates. Subsequently, reduction



A plasmalogen

FIGURE 15

of acyl CoA was demonstrated in a large variety of organisms from bacteria to mammals[63b]. In all cases the first step is formation of the aldehyde and the second enzyme, an alcohol dehydrogenase, reduces the aldehyde to the alkanol.

D. Bioluminescent Reactions

The production of light by a large variety of organisms has been a phenomenon of interest throughout recorded history. The early attempts to understand the process are summarized by Johnson[64]. In his review reference is made to the work of Dubois, who identified a heat labile and a heat stable component of a firefly (in 1885) and of a clam (in 1887) that produced light on mixing. The former he named luciferase and the latter, luciferin. The names are retained today for the enzyme and substrate, respectively, of bioluminescent systems.

The chemistry of producing the excited state is varied for different biological systems. Some luciferase reactions, described below, decarboxylate their substrates during oxidation. The light-producing reaction of bacteria, however, involves an activated prosthetic group on an enzyme, a flavin, that requires a long-chain aldehyde as its substrate. It is the production of the aldehyde that justifies inclusion of these reactions in this section.

The first luciferin to be identified was that of the firefly, *Photinus pyralis*[65], shown in Figure 16. The corresponding luciferase has been purified and crystallized[66]. The

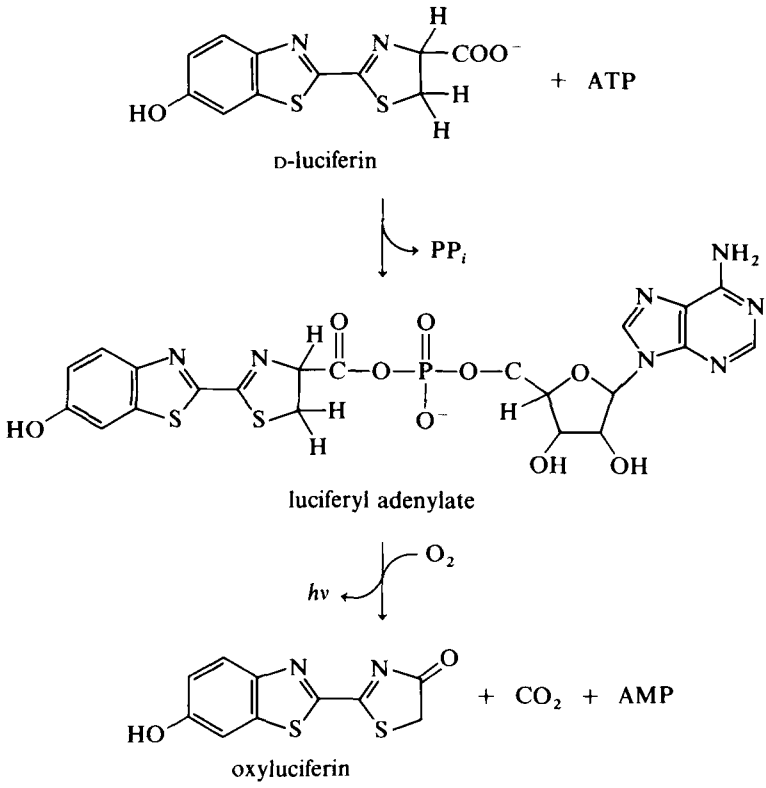


FIGURE 16. Reactions of firefly luciferase

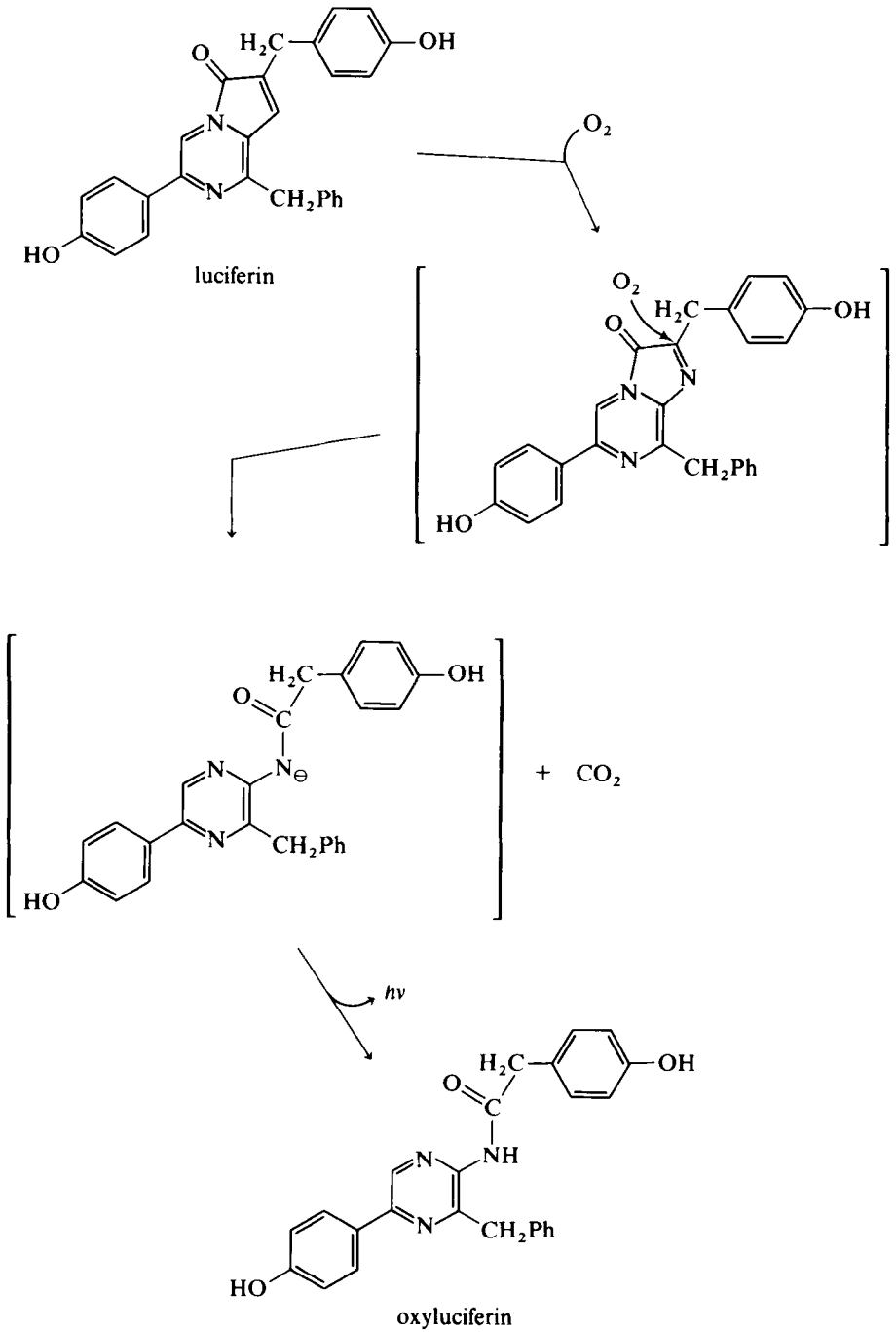


FIGURE 17. Reaction of Renilla luciferase

reaction involves the intermediate formation of an acyl adenylate, which is the substrate for oxygenation and subsequent decarboxylation[67]. Upon oxidation, several changes occur consistent with an attack of oxygen upon the carbon bearing the carboxyl-AMP. Elimination of the carboxyl group and formation of a peroxide would account for the emission of light, the appearance of a carboxyl group in oxyluciferin and the hydrolysis of the hypothetical carboxy-AMP to CO_2 and AMP. A very different derivative of a carboxyl group is involved in the luciferin of a coelenterate. In the case of the sea pansy, *Renilla reniformis*, the CO_2 is derived from the carboxyl group of a substituted imidazolone. The reaction of a purified luciferase from this organism[68] is explained by Cormier[69] by the mechanism in Figure 17. The crustacean *Cypridina* contains a similar luciferin and produces light and CO_2 by a similar mechanism[70].

Luminescence in bacteria involves a very different physiological system. Enzymes from luminous bacteria require riboflavin phosphate (FMN) and a long-chain aldehyde, the 14-carbon atom myristyl aldehyde, in addition to oxygen and a mechanism for reducing the flavin[71]. During the reaction the aldehyde is oxidized to the corresponding carboxylic acid[72] with the incorporation of an atom of oxygen from O_2[73]. The most probable reaction scheme (Figure 18) summarized by Hastings and coworkers[74] involves the formation of a reduced flavin peroxide with molecular oxygen and emission of light as the peroxide oxidizes an aldehyde and removes hydrogens from the flavin, forming H_2O_2 and oxidized riboflavin.

The formation of the aldehyde from long-chain fatty acids for bacterial luminescence requires ATP and NADPH[75]. In contrast to the reduction in other bacteria for the formation of alcohols, the system from luminous bacteria does not require CoA (Figure 19). Instead, the mixed anhydride, fatty acyl adenylate, is the activated intermediate[76].

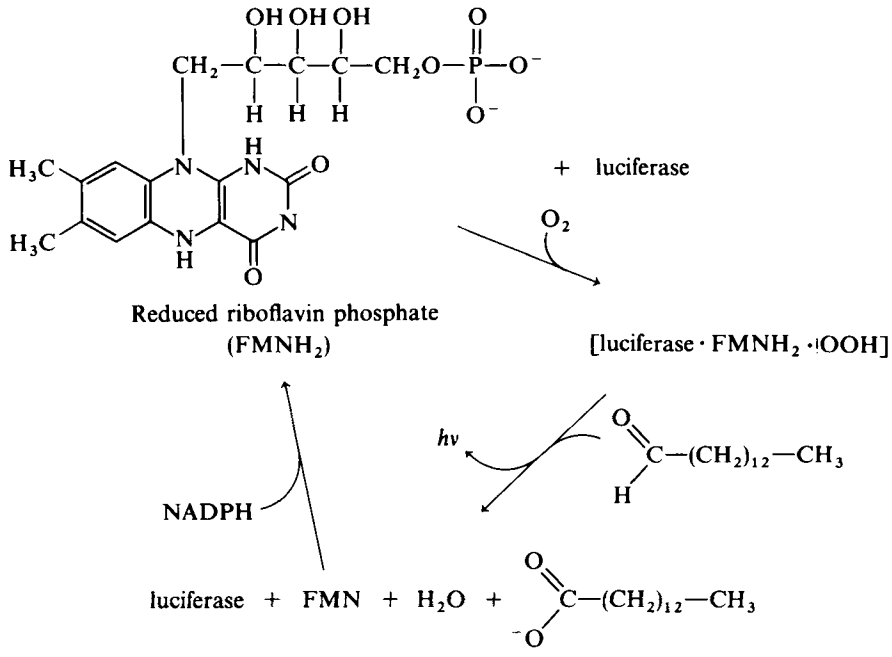


FIGURE 18. Outline of reactions of bacterial luciferase

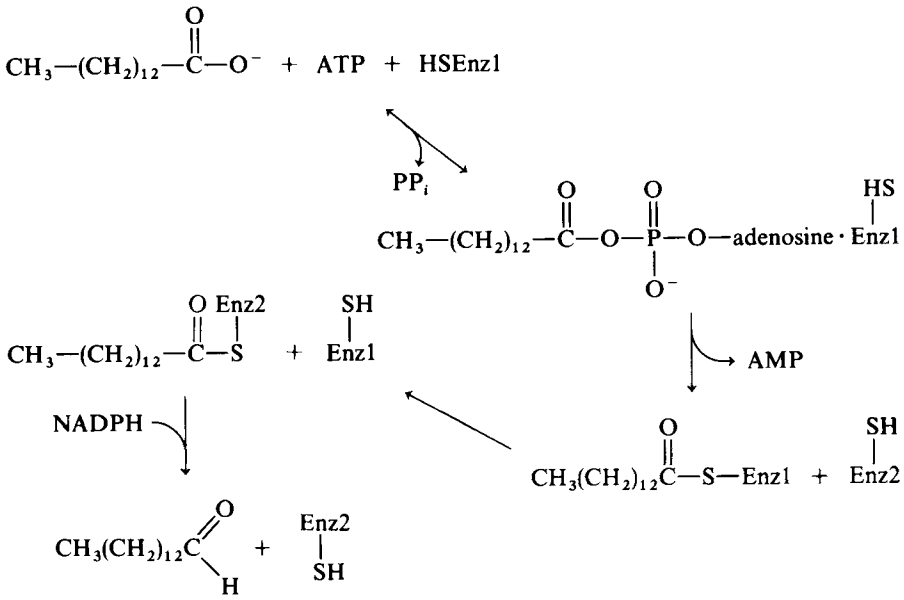


FIGURE 19. Reduction of myristic acid by luminescent bacteria

Again in contrast to other acid activating enzymes, the synthetase that forms the acyl adenylate is acylated and then transfers the acid to a second protein, the reductase[77]. The acylated reductase uses NADPH to reduce the acyl group to the aldehyde. Although transfer of the acyl groups from one protein to another can proceed *in vitro*, the transfer is accelerated by a third protein, the transferase, coded for by a gene essential for reduction of myristic acid *in vivo*[78]. In all cases, the acyl group is bound to the protein through a thioester with a cysteine residue[79].

E. Reduction of Dicarboxylic Amino Acids

1. Interconversion of amino acids

In microorganisms, a well-known series of reactions uses aspartic acid as a precursor of threonine, methionine and lysine[80]. The enzymes responsible for the first steps in these syntheses were elucidated by Black and Wright, who demonstrated the formation of β-aspartyl phosphate[82] and reduction of this compound to aspartic semialdehyde (Figure 20)[81]. The search for similar mechanisms in the conversion of glutamate to the five-carbon amino acids proline and ornithine was more difficult because the hypothetical γ-glutamyl phosphate is too reactive to be isolated and forms pyrrolidone 5-carboxylate. A pathway that eliminates this problem was described in *E. coli*[83]. In these reactions, the glutamate is first acetylated so that the kinase produces from acetyl glutamate and ATP a compound that reacts with hydroxylamine plus ADP; the reactive product is also a substrate for reduction to the semialdehyde by a dehydrogenase and NADPH. That the substrate for reduction was actually acetylglutamyl phosphate is supported by the requirement for reversal of the dehydrogenase of inorganic phosphate

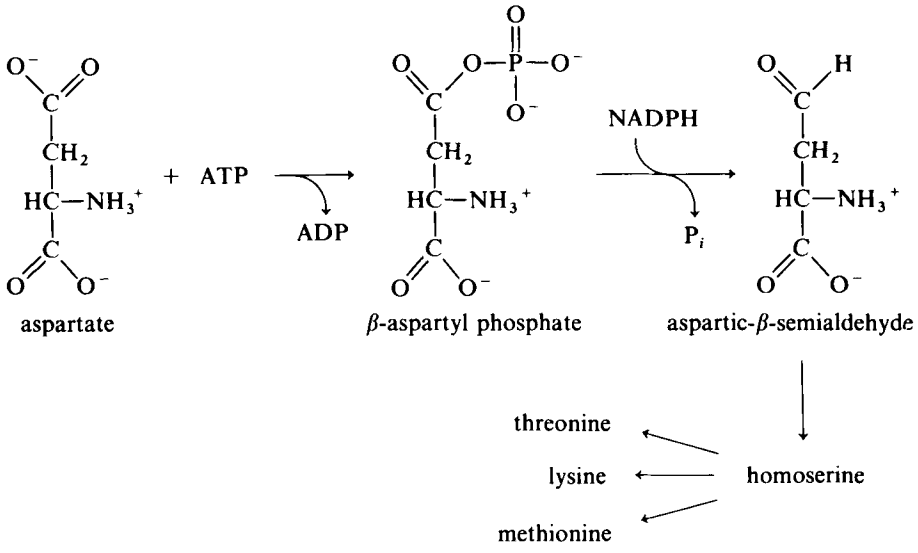


FIGURE 20. Reduction of aspartic acid

in addition to the semialdehyde and NADP.

The corresponding enzymes in *E. coli* that form proline do not use acetylated glutamate but require the free amino acid. A kinase was purified that formed γ-glutamic hydroxamic acid from glutamate, ATP and NH_2OH[84]. The relation of this reaction to proline formation was indicated by strong inhibition by proline (Figure 21). Since a stable activated carboxyl group was not available as a substrate for reduction, the enzyme was detected and purified by studying the reverse reaction, using pyrroline 5-carboxylate to generate a small amount of the open-chain glutamic semialdehyde. The dehydrogenase requires NADP and inorganic phosphate and produces pyrrolidone 5-carboxylate, although only NADPH was measured[85]. Subsequent reduction of pyrroline 5-carboxylate to proline by an enzyme using NADPH was also demonstrated[86]. In animals, the only reduction of glutamic acid follows the proline model for producing the semialdehyde via the putative (enzyme-bound?) γ-glutamyl phosphate. The reduction has been observed only in intestinal mucosa, where ornithine is synthesized[87]. Interconversion of proline and ornithine through pyrroline 5-carboxylate (glutamic semialdehyde) occurs in liver and other tissues[87].

2. *Alternative synthesis of porphyrins*

Early studies on the biosynthesis of heme by Shemin and Russell led to the discovery of δ-aminolevulinate as the precursor of all of the carbon and nitrogen atoms of the tetrapyrrole[88]. Studies in Granick's laboratory established that a common pathway used glycine and succinyl CoA to form porphobilinogen via δ-aminolevulinate (ALA) (see Figure 22) for synthesis of chlorophyll as well as for heme[89]. Until recently the reaction of ALA synthase was believed to be the universal mechanism for initiating the synthesis of all tetrapyrroles in all organisms. However, Beale and Castelfranco[90] found that glutamate and related 5-carbon compounds were incorporated into ALA much more efficiently than glycine and succinate and subsequent studies with isotopically labelled

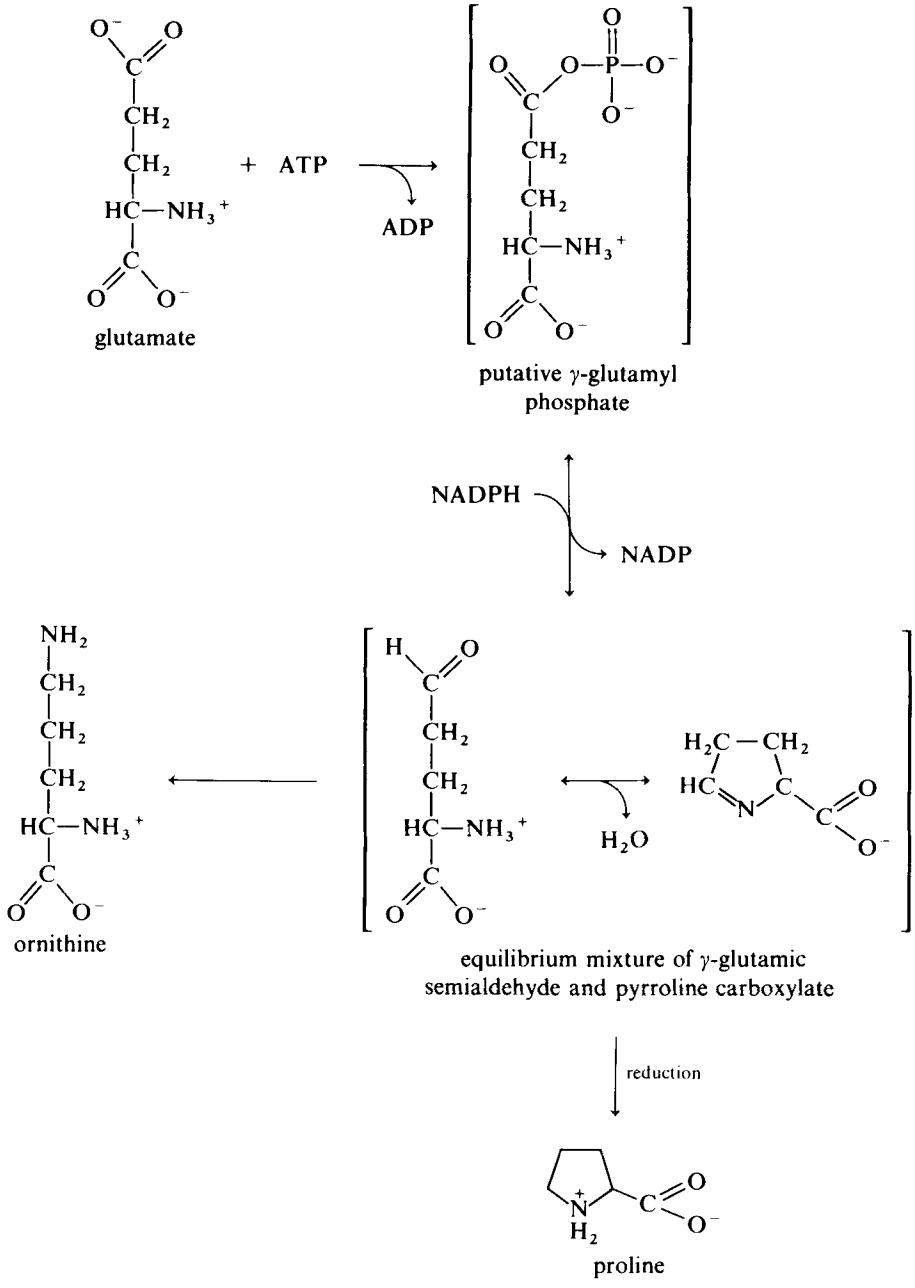
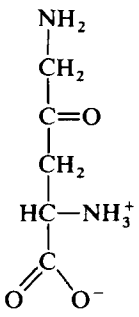
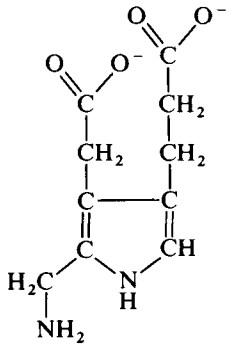


FIGURE 21. Reduction of glutamic acid in mammals and formation of proline and ornithine



δ-aminolevulinate



porphobilinogen

FIGURE 22

atoms of glutamate[91] showed that the carbon skeleton of glutamate is incorporated intact into the 5-carbon atom δ-aminolevulinate.

Glutamic acid α-semialdehyde was synthesized and shown to behave like an intermediate of glutamate metabolism[92]. Extracts of plant cells capable of forming ALA from glutamate were separated into three protein reactions, all required for the reaction[93]. These studies demonstrated requirements also for ATP and NADH and a novel sensitivity to ribonuclease. Subsequently[94] it was shown that the RNase-sensitive material is the tRNA for glutamic acid and that glutamyl-tRNA is the substrate that is reduced to glutamic semialdehyde (Figure 23). The reductase has been purified from plant[95] and bacterial[96] sources. Since these enzymes reduced glutamyl-tRNA from various organisms with different efficiencies, it is clear that there is specificity for some part of the tRNA structure, not merely for the glutamyl ester, but the determinants for the purified reductases have not yet been determined.

F. Overview of Reactions that Reduce Carboxyl Groups

In the two cases in which the detailed mechanism of enzyme action has been studied, glyceraldehyde 3-phosphate dehydrogenase and the reductase involved in the formation of the long-chain aldehyde of bacterial luminescence, reduction by a reduced pyridine nucleotide transfers electrons to a thioester of the enzyme. It is not known whether this is a general mechanism; that is, it remains to be determined whether other acyl reductases are themselves acylated by the substrates. It is of interest to note, however, that the substrates for the two established reactions are acids that have been activated in different ways by ATP. In the case of glyceraldehyde 3-phosphate dehydrogenase, the substrate is the acyl phosphate, 1,3-glyceric acid bisphosphate, whereas in the system of luminescent bacteria an acyl-AMP is the donor of the acyl group. In the reduction of fatty acids to the corresponding alcohols by other bacteria, plants and animals as well as in the production of mevalonic acid, the thioester of the carboxyl group with CoA is the substrate for the reductases. Although the thioester of the reductase of luminescent bacteria can exchange the acyl group reversibly with CoA, it remains to be determined whether such an exchange actually produces a protein thioester as the group that is reduced in the cases in which an acyl CoA is the primary substrate.

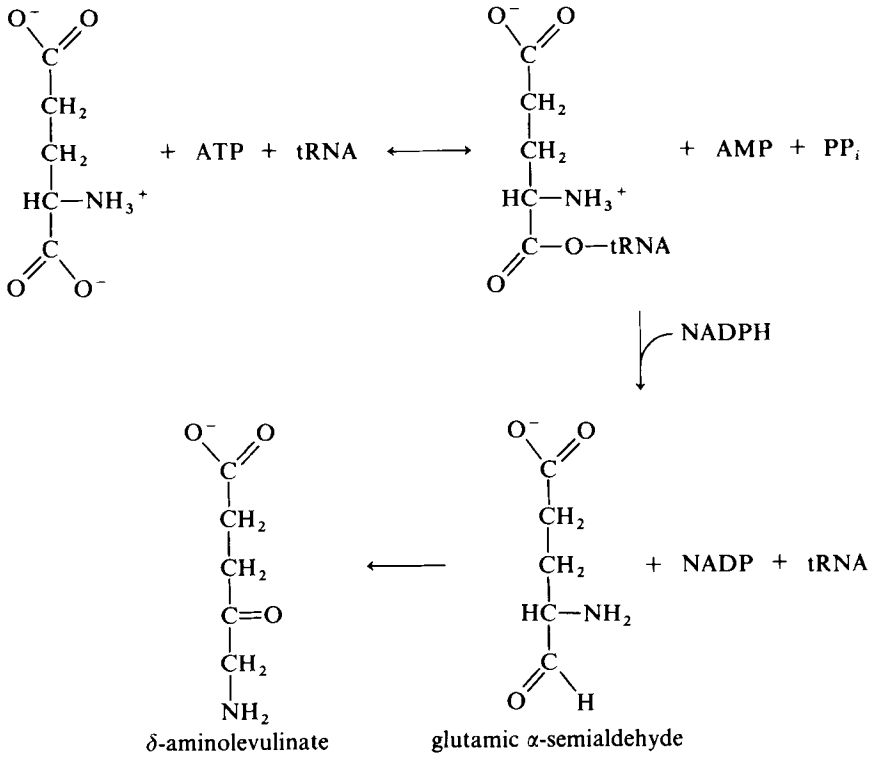


FIGURE 23. Alternative pathway of formation of δ-aminolevulinate

IV. ACYLATION OF PROTEINS

Reactions that form esters, amides and thioesters have been well known for many years and will not be reviewed here. However, two types of reaction have been described recently involving acylation of proteins by compounds that cause profound changes in the physiological properties of the proteins. One of these is attachment of a specific protein, ubiquitin; the other involves attachment of long-chain fatty acids.

A. Ubiquitin

Ubiquitin is a small protein composed of only 76 amino acid residues. It was discovered as a factor that appeared to stimulate differentiation of lymphocytes[97] and was purified on that basis, although this function appears to have been due to a contaminant[98]. Antibodies to the purified factor were found to react with similar material from other cell types and other organisms, including plants. Thus the ubiquitous distribution was recognized early. A few years later an independent investigation found a small protein bound to a histone by an isopeptide linkage and characterized it chemically[99]. Finally, one of the fractions needed for degradation of proteins by an ATP-requiring enzyme system from reticulocytes was found to be a heat-stable polypep-

tide[100], which was identified as the same small protein[101]. The sequence of amino acids in ubiquitin has been determined in a large variety of organisms and the structures show less variation than found in any other protein. In higher animals the sequences are identical and preparations from two plants showed only three residues different from the animal sequence[102].

The marking of proteins for degradation is the most thoroughly studied function of ubiquitin. It should be noted that there are at least two other mechanisms for degrading proteins in most cells, one involving cytosolic proteases that do not require ubiquitination and one occurring in lysosomes[103]. The ubiquitinating reaction starts with activation of the C-terminal carboxyl group of ubiquitin in a reaction that resembles the partial reaction that initiates activation of fatty acids and amino acids[104]:

$$\text{ubiquitin COO}^- + \text{ATP} \longrightarrow \text{ubiquitin CO-AMP} + \text{PP}$$

The ubiquitin is then transferred to a sulfhydryl group of the activating enzyme[104]. The acceptor of the activated carboxyl group is not CoA or a nucleic acid but a specific family of proteins, E_2, that also become thioesters[105]. A poorly defined group of enzymes, E_3, transfers the ubiquitin from the thioester of various E_2 carriers to amino groups on the proteins that are ubiquitinated, although for some simple amines transfer of ubiquitin from E_2 does not require the presence of E_3[106].

In general the acceptor of ubiquitin is the ε-amino group of a specific lysine residue[107]. For unknown reasons in some cases more than single ubiquitin molecules are added to acceptor proteins; in the limited studies so far available the extra ubiquitins are not added to new lysines but form branched ubiquitin polymers on a single lysine[107].

Many years earlier an enzyme was found by Soffer to catalyze a reaction in which arginine could be transferred from arginyl-tRNA to some soluble proteins with no involvement of ribosomes needed for normal protein synthesis[108]. The arginine is added only to the N-terminus and converts an otherwise stable protein to a good substrate for ubiquitination and degradation[109]. The specificity of the arginine transferase is still obscure although it can add arginine to compounds as small as dipeptides[110]. Ubiquitin is not degraded along with the protein to which it is attached but is released from peptides by hydrolysis[111].

Ubiquitination of proteins serves several apparently unrelated biological functions not related to turnover. The original finding of a ubiquitinated histone H2A[99] has been followed with the finding that approximately 10% of all histones contain ubiquitin residues, some of which are polyubiquitins, but the role of the modification in chromatin structure or function is still obscure[112]. Ubiquitin has also been found on proteins exposed on the outer surface of cells. These include the receptors for the platelet derived growth factor[113] and growth hormone[114] and a 'homing receptor' that mediates the binding of lymphocytes to high endothelial venules in lymph nodes[115].

B. Fatty Acylation of Proteins

The blocking of N-termini of proteins has been known for many years. Recently, two enzymes were found to add long-chain fatty acids to specific proteins. Myristic acid was found in 1982 to be the N-blocker of a protein kinase of bovine heart muscle[116]. Shortly after myristic acid was identified as the blocking group of a viral membrane protein[117]. The sequences of both proteins showed that the fatty acid was attached to a glycine residue. Towler and Glazer[118] noted that these and other myristylated proteins contained N-terminal glycine and purified an enzyme from yeast on the basis of amidation of an octapeptide with myristic acid in the presence of ATP and CoA. This enzyme, *N*-myristyl transferase, NMT, was subsequently purified to homogeneity and shown to have an absolute specificity for the terminal glycine and to have a strong preference for

alanine in the fifth position. Among simple fatty acids only myristic acid is a substrate[119]. The properties of the side-chain binding site of NMT have been explored with a large variety of substitutions, including sulfur and oxygen at various positions in the chain, double and triple bonds and phenyl groups[120]. The results suggest that the acyl chain is bent to fit the enzyme and that the enzyme is sensitive to chain length and steric volume, but a three-dimensional model will be needed to obtain a better understanding of the unusual specificity. A similar enzyme has been detected in rat tissues, with highest activity in brain[121]. This was studied with a peptide corresponding to the 16 N-terminal residues of the tyrosine kinase of the Rous sarcoma virus, $p60^{v\text{-}src}$. In this case also the enzyme shows high specificity for myristic acid, with some activity with shorter chains but not with longer. It also requires N-terminal glycine. Inhibition by several peptides indicates that the enzyme is influenced by as yet undefined internal amino acid residues.

Many proteins are isolated as palmityl derivatives[122]. The linkage may be either an ester with a serine residue or a thioester with cysteine. The enzymes responsible for palmitylation have not been well characterized with regard to specificity, but since substitution of serine for cysteine eliminated acylation in membrane protein[123], there is reason to expect different enzymes to form esters and thioesters.

V. FORMATION OF PEPTIDE AMIDES

A. Peptide Bond Formation in Proteins

The major constituent of most cells is protein, linear polymers of amino acids in amide linkages. Two of the twenty amino acids that are the primary elements of which most proteins are composed, glutamine and asparagine, contain amide groups in addition to the α-amino and α-carboxyl groups that participate in forming the backbone of the polymer, the so-called peptide bonds. The biosynthesis of glutamine was reviewed earlier[2]. At that time similar reactions in various organisms had been described for the synthesis of asparagine from aspartic acid and ammonia with the participation of ATP. However, direct synthesis of asparagine has not been demonstrated in higher animals. Instead, a transfer of the NH_2 group from glutamine to aspartate occurs[124]. It is important to note that this reaction, which has a free energy change near zero, cannot proceed without the stoichiometric hydrolysis of ATP to AMP and inorganic pyrophosphate since the β-carboxyl group of aspartate must be activated before it can be amidated. In animal metabolism, glutamine also serves as a nitrogen donor in many biosynthetic pathways.

The elaborate process by which amino acids are incorporated into proteins is outlined in every textbook of biochemistry published in the last ten years and only those features will be mentioned here that concern the mechanism of activation of the carboxyl groups and the release of the completed polypeptide with a free C-terminal carboxyl group. This is to define the problem recently solved of the mechanism by which some peptide hormones are produced with C-terminal amide groups.

The assembly of proteins occurs on ribosomes, large complex structures composed of approximately equal amounts of protein and nucleic acid. Several additional protein 'factors' also participate and GTP is used to provide energy in a poorly understood process. What is clear, however, is that the order in which the amino acids are assembled is determined by a sequence of bases in the nucleotides of mRNA. In order to translate the code of the message, nucleic acid 'transducers' are used to carry specific amino acids. Thus, the enzymatic basis for the specificity of protein synthesis is the specificity by

which twenty enzymes esterify the twenty primary amino acids to the 3'-end of specific acceptor molecules, tRNA. The reaction of esterification is:

$$\text{amino acid} + \text{ATP} + \text{tRNA} \longrightarrow \text{aminoacyl-tRNA} + \text{AMP} + \text{PPi}$$

Each of the tRNA species contains a sequence of three bases in a position (the anticodon) to form hydrogen bonds with a complementary sequence (the codon) in the mRNA in the ribosomal complex. The first amino acid specified by the mRNA is the N-terminal amino acid. It is bound to the ribosomal complex, esterified to its tRNA. A second aminoacyl tRNA is then bound to an adjacent part of the complex and the carboxyl group of the first amino acid is transferred from tRNA to the amino group of the second amino acid to form a peptidyl tRNA. The GTP is somehow used to shift the mRNA on the ribosome, so that the first tRNA dissociates and a third aminoacyl tRNA binds to the complex. This process is repeated until the complete polypeptide is formed as an ester of tRNA (Figure 24). The final step, when the message of mRNA is complete and the terminator codon is reached, is hydrolysis of the peptide from the tRNA of the C-terminal amino acid[125]. Thus, every completed peptide terminates with a free carboxyl group.

B. Peptide Amide Formation

The primary sequences of a number of peptide hormones, however, contain C-terminal amides, which are essential for their physiological activity. Bradbury, Finnie and Smythe[126] noticed that several of these hormones are derived from precursors in which the amino acid residue destined to become the C-terminal amide is followed by a glycine residue. These workers showed that an extract of secretory granules of porcine pituitary

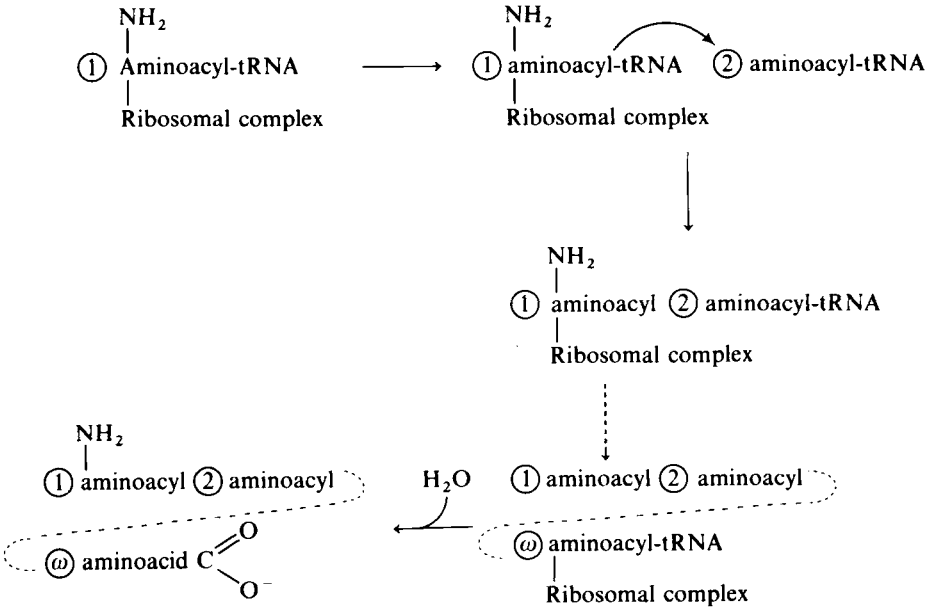


FIGURE 24. Outline of synthesis of polypeptides

gland was capable of converting peptides with C-terminal glycine to the corresponding desglycine peptide amide. They used [^{14}N]-glycine to demonstrate retention of the peptide N in the amide and identified the remainder of the glycine residue as glyoxalate.

Several investigators confirmed the findings of Bradbury and coworkers and purified peptidyl glycine amidating enzyme (PAM) from various sources. The activity was found to be dependent upon the presence of ascorbic acid, Cu^{++} and molecular oxygen[127,128]. Similar requirements had previously been found for dopamine-hydroxylase[129]. This latter enzyme is a monooxygenase and Young and Tamburini[130] presented evidence that PAM acts in a similar manner by synthesizing peptides with C-terminal α-hydroxyglycine residues, which were found to be split to yield the corresponding truncated amide and glyoxalate. Katopodis, Ping and May partially purified an enzyme that produces benzamide from α-hydroxy-benzoylglycine[131] and proposed that their enzyme is the α-hydroxyglycine amidating dealkylase (HGAD) that catalyzes a second step in the sequence initiated by hydroxylation (Figure 25). An independent series of studies in Japan led to a similar proposal: Noguchi and collaborators[132] separated PAM from rat brain into two fractions that were both needed for efficient amidation; the same group[133] showed that one of these fractions, 36k, produced an intermediate from a peptidyl glycine that was converted to the corresponding amide by the other fraction, 41k. Suzuki and coworkers[134] expressed the gene for a frog PAM with a baculovirus in cultured insect cells and showed that the enzyme produced acted on peptides with C-terminal glycine to produce the corresponding α-hydroxylated peptide and that another enzyme, separated from the first, formed the amide. The genes of the amidating enzymes are complex. Recently, cDNAs were made that show a family of enzymes can exist, probably as result of alternative splicing of mRNA[135]; some of the proteins are

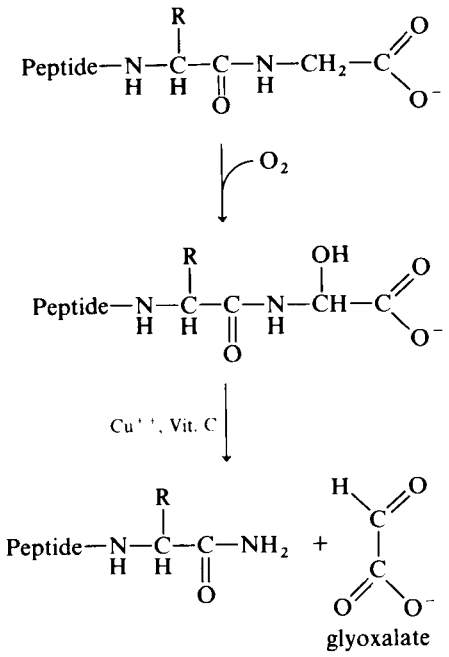


FIGURE 25. Mechanism of formation of peptide amides

encoded by sequences that contain a transmembrane structure that can anchor the enzyme, but other sequences apparently produce soluble proteins. A cDNA from rat atrium contains domains for both the hydroxylating activity and the elimination reaction, whereas another cDNA has information for only the initial hydroxylating activity. The existence of multiple forms of amidating enzymes suggests that the formation of peptide amides serves multiple biological purposes, as yet unidentified.

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CHAPTER **19**

Pharmacology of acid derivatives

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I. INTRODUCTION

Pharmacology is the science concerned with the study of chemicals that are capable of interacting with biological systems. These chemicals, referred to as drugs, may be endogenous substances or be foreign to the system. The nature, extent and outcome of such interactions are determined by the structure and physicochemical characteristics of the drug on the one hand, and the specific properties of the biological system on the other.

Drugs that are used either in therapeutics or experimentally are expected to produce specific effects, i.e. they should ideally affect only one discrete process in the physiology or biochemistry of the organism. The fact is that only seldom is such a degree of selectivity achieved. Often a drug may exert the desired effect, but in addition produce several other actions on the biological system or organism. In therapeutics these additional effects are considered adverse reactions or side effects[1]. The latter may be extensions of the main effect, for example a drug used to lower elevated blood pressure may reduce it to such an extent as to produce dizziness. Another drug that is used to prevent epileptic seizures may in addition cause sedation, because it reduces neuronal activity in the brain. Other adverse reactions may be unrelated to the major activity.

Consider an antibiotic that is used for its effect on bacterial cell wall sythesis, e.g. the semisynthetic penicillin methicillin (see Section VIII.A) that may also damage the kidney of the host through a totally unrelated mechanism[2]. For a drug to be useful, experimentally or clinically, the desired effect should be manifested at lower concentrations or doses than the untoward reactions, thus partially satisfying the quest for specificity. Larger than recommended doses may lead to toxicity and are considered under the heading of toxicology[3-5]. In the biochemical sense, a drug may inhibit one enzyme at one (low) concentration, but also influence the activity of another enzyme at higher concentrations. Thus, the antiinflammatory agent indomethacin, which is usually considered a specific inhibitor of cyclooxygenase (see Section VII), may at higher concentrations also inhibit the activity of phospholipase A_2[6].

The activity of most drugs depends on their interactions with specific macromolecules on the surface of or within cells. These molecules are called receptors. They are present in the organism as part of the signalling system that regulates the function of cells. Many drugs, therefore, mimic or interfere with the actions of endogenous substances. Consider a cell that contains receptors to, and responds to the neurotransmitter acetylcholine. One can manipulate this cell pharmacologically by either applying acetylcholine itself or one of several other choline esters, having the same activity as acetylcholine. Other modes of interference with the function of this system may involve inhibition of the synthesis or release of acetylcholine or, conversely, inhibition of its breakdown. The interaction of a drug with its receptor involves specific physicochemical binding that results in occupation of the receptor. For endogenous substances such bonding must be reversible, so that the system can be briefly activated and eventual dissociation terminates the action. The system is thus regenerated. Therefore, covalent binding to receptors is not expected to take place with endogenous substances and is, indeed, a rare occurrence even with foreign drugs. The binding of most drugs to their receptors is achieved through much weaker bonding, such as ionic, hydrogen and van der Waals bonds. For a drug to act on a receptor it must contain the molecular geometry and functional groups to fit as tightly as possible to the receptor structure. Thus the molecular structure of the drug *vis-à-vis* the receptor confers specificity. Upon binding of the drug substance to the receptor it may either activate it, i.e. act as an agonist, or occupy the receptor and prevent activation by the endogenous agonist. The latter situation describes an antagonist. One can envisage similar processes acting on enzymes, transport proteins etc. In all of these cases the specific structure and functional groups on the drug will determine its tightness of fit to the biological macromolecule. Through studying such structure–activity relationships better and more specific drugs can be synthesized.

Experimentally, drugs may be introduced directly to their target cells or subcellular structure of interest. More often drugs that are introduced into a system should cross biological membranes to reach their site of action. Similar processes carry the drugs to their sites of elimination, which eventually result in their excretion or biotransformation. The latter processes are dealt with under the heading of pharmacokinetics[7-11]. Eventually, at the site of action, the drug acts on a discrete biochemical or pysiological process to produce its pharmacological effects. The study of the various aspects of drug action is referred to as pharmacodynamics.

The present review is not intended to constitute an exhaustive survey of the pharmacology of any group of drugs. Rather, an attempt will be made to overview some of the fundamentals of pharmacology as they relate to drugs that are acid derivatives and to highlight some aspects of the specific pharmacology of several groups of such drugs, as examples. For extensive discussions of these and other aspects of the pharmacology of acid derivatives the reader is referred to various textbooks such as References 12, 13 and others. Most valuable and detailed information on individual drugs is available in Martindale's *Extra Pharmacopoeia*[14]. Particular emphasis is made in the latter text on

dosage and administration, pharmacokinetic behavior, indications and adverse reactions. Detailed references are cited in each monograph, making it a superb reference source. Comprehensive and authoritative reviews on drugs appear in the journal *Drugs* and up-to-date accounts of important developments in the field may be found in *Trends in Pharmacological Sciences*. Original research articles are published in numerous pharmacology journals and, in addition, clinical pharmacological investigations are published in specialized journals.

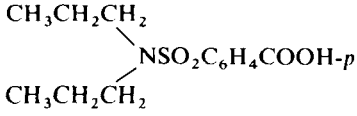
II. TRANSFER ACROSS MEMBRANES

Biological membranes are phospholipid bilayers in which cholesterol and, more importantly, protein and glycoprotein molecules are embedded. The latter may traverse the membrane and also protrude from it on either side. The proteins may form minute pores and channels, about 7 Å in diameter, to allow for the movement of small hydrophilic substances of molecular weight smaller than 100. Other substances have to interact with the membrane to get access through it. The membrane as a whole is fluid, allowing free movement of lipid-soluble molecules across it. One should note that bulk flow from capillaries to the extracellular fluid does not involve passage through membranes. It occurs through small pores between endothelial cells and allows almost free passage to most drug molecules[15,16]. In most instances drugs diffuse passively through biological membranes. Because of the lipid nature of such membranes, the rate and extent of diffusion depends on the lipid solubility of the drug in question. A common index of lipid solubility of a drug is its lipid-to-water partition coefficient. This is estimated by shaking the drug in a mixture of a lipid solvent such as heptane, octanol or butanol and an aqueous buffer, usually at pH 7.4.

Most drugs, being weak electrolytes, are partly ionized in a biological environment, depending on their pK_a and the pH of the system. Since only the nonionized entity can diffuse through the membrane, a weak acid will partition between the two sides of a lipid membrane in a manner dictated by its pK_a and the pH gradient across the membrane, as predicted by the Henderson–Hasselbalch equation (equation 1):

$$\log \frac{[\text{nonionized}]}{[\text{ionized}]} = \text{pH} - pK_a \tag{1}$$

will dissociate in the stomach (pH 1.4), whereas in the plasma (pH 7.4) the ratio between ionized and nonionized drug will be 10,000. Because the nonionized part can freely diffuse across the mucosal membrane, the equilibrium concentrations of this alone will



Probenecid

will dissociate in the stomach (pH 1.4), whereas in the plasma (pH 7.4) the ratio between ionized and nonionized drug will be 10,000. Because the nonionized part can freely diffuse across the mucosal membrane, the equilibrium concentrations of this alone will be equal on both sides of the membrane. The total drug concentration on the plasma side of the membrane will therefore be 10,001 (10,000 ionized + 1 nonionized) and only 1.01 (0.01 ionized + 1 nonionized) inside the stomach, some 10,000-fold difference. This 'ion trapping' mechanism can thus be very effective. Therefore, to the extent that solubility is not a limiting factor, weak acid drugs will be efficiently absorbed from the

stomach into the blood stream, and the reverse is true of weak bases[17]. Fortunately, as a drug travels down the gastrointestinal tract it encounters the nearly neutral intestinal contents. It is in the small intestines, the mucosal surface area of which is some 3 orders of magnitude larger than that of the stomach, that most drug absorption takes place[18].

The dual contribution to absorption of both the pH in relation to the pK_a of a drug molecule and its lipid solubility were clearly illustrated in a study of the buccal absorption of a congeneric series of *p*-n-alkyl substituted phenylacetic acids[19]. For all members of the series, absorption increased with decreasing pH (down to pH 3). In addition, the extent of absorption increased with the length of the alkyl chain, going from unsubstituted phenylacetic acid to the *p*-hexyl derivative. The same principles also apply to the renal tubular reabsorption of acidic drugs and may be manipulated to enhance the renal excretion of such substances, as discussed later.

Some of the drug transport mechanisms involve active transport or facilitated diffusion processes. Both require carrier proteins and are therefore selective and saturable processes. The first of these mechanisms requires energy and can transport drug molecules against concentration gradients. By contrast, facilitated diffusion can only proceed down a concentration gradient and, accordingly, is energy independent. Most of the available examples of transport of drugs involve active transport mechanisms. Such are the mechanisms involved in entry of water-soluble molecules such as amino acids, sugars etc. into cells and across biological barriers. Many of these hydrophilic drug molecules are acid derivatives. The intestinal brush-border contains a carrier-mediated transport system for some monocarboxylic acids. In a study by Simanjuntak and colleagues[20] several monocarboxylic acids competed for the carrier system, whereas structural analogs in which the carboxylic function was altered (nicotinamide and nicotinyl alcohol vs nicotinic acid) failed to compete.

III. ROLE OF THE KIDNEY

The renal handling of drugs is of the utmost importance in the economy of drugs in the body. The kidney is the major route of drug elimination and to a large extent it determines the length of sojourn of a drug in the body. Multiple processes in the kidney are responsible for effective elimination of many molecules on the one hand and for conservation of others on the other hand. Thus, following initial filtration of the blood flowing through the renal glomeruli, most of the water and solutes that had been filtered are reabsorbed. In addition, the epithelial cells of the proximal renal tubule perform both active reabsorption from the filtrate back into the blood and active secretion processes in the opposite direction. Further down the nephron, additional processes involving further water reabsorption and ion fluxes take place. Although these latter processes do not involve drug substances directly, they may exert influences secondary to changing urine volume and pH.

The passive reabsorption of drug molecules from the tubular urine back into the plasma tends to conserve part of the drug load that had been filtered in the glomeruli. For electrolyte drugs this process depends to a large extent on the pH of the urine, which in turn determines the degree of ionization of the drug molecule in question. Weak acids are ionized more at higher urinary pH, depending on their pK_a, according to the Henderson–Hasselbalch equation. Under such circumstances, therefore, less (nonionized) drug is available for reabsorption and consequently more is excreted. With some acidic drugs, forced alkaline diuresis can thus enhance their renal clearance as much as 100-fold. This principle has been applied in the treatment of poisonings, for example with 2,4-dichlorophenoxyacetic acid ($pK_a = 3.3$), which is used as a weed-killer[21]. In their study of a patient who had ingested a large quantity of this weedkiller, Prescott and colleagues documented a sharp increase in the renal clearance of the poison

with increasing urine pH. For each pH unit the renal clearance rose almost fivefold. For drugs to be so influenced they must be weak acids with a pK_a of 3–7.5 In addition, to be of clinical significance, their elimination must depend largely on the urinary excretion of unchanged drug.

Urine flow also influences the extent of reabsorption of lipid-soluble compounds or the nonionized fraction of weak electrolytes. As the process of passive reabsorption tends to equalize the drug concentrations in the urine and plasma, the renal clearance of such drugs will correlate with the rate of diuresis. Thus, some acidic drugs are better excreted with forced alkaline diuresis. For phenobarbital ($pK_a = 7.2$), for example, increasing alkaline urine flow causes proportional increases in the renal clearance of the drug. This principle is also exploited in the treatment of poisoning.

Organic anions have long been known to be actively secreted in the proximal tubular cells of the kidney. This carrier system transports acidic drugs such as probenecid, β-lactam antibiotics etc.[22–24]. The competition between such compounds has been exploited to reduce the renal excretion, thereby prolonging the half-life time, of substances such as penicillin. Similar organic acid transport systems operate across the blood–brain barrier[25]. One, with relatively low affinity and capacity, transports carboxylic acids from blood into the brain[26,27]. The other system, operating in the choroid plexus, is more powerful and serves to eliminate foreign substances from the cerebrospinal fluid[28].

IV. PLASMA PROTEIN BINDING

Many drugs, most notably acidic compounds, are transported in the blood while they are partly bound to plasma proteins[29]. The most abundant plasma protein, albumin, is also the major binding protein for acidic drugs as well as for endogenous substances such as free fatty acids, bilirubin etc. It has several binding sites, at each of which drugs may compete for binding. Because of the relatively nonspecific nature of the binding to albumin, competition interactions are often encountered clinically. This binding is reversible and initially involves electrostatic attraction and hydrogen bonds and eventually hydrophobic bonding. Some commonly used acidic drugs are bound to albumin as much as 90% or more, which leaves only a small fraction available for diffusion into, and equilibration with, tissue sites of action, or conversely, elimination. Because the binding is reversible, equilibrium is constantly readjusted, and as free drug is utilized or excreted, bound molecules dissociate and become available. Thus, bound drug can be regarded as a form of depot within the blood stream. The main pharmacokinetic implications of protein binding are thus that the volume of distribution of the drug that binds is decreased, in other words its tissue concentrations are lowered. The rate of elimination may also be effected by protein binding[30,31].

Attempts have been made to correlate albumin binding with the lipophilicity of drugs[32]. Laznicek and colleagues[33] compared the binding of several benzoic and phenylacetic acid derivatives in several species. They proposed a model which allows calculation of the extent of binding from the lipophilicity of structurally similar drugs.

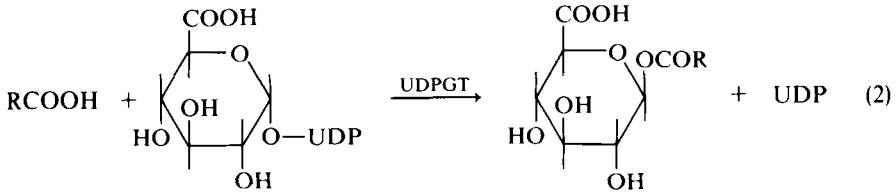
V. METABOLISM OF ORGANIC ACIDS

Drug molecules may undergo one or more metabolic reactions which usually serve to inactivate or detoxify them. Most metabolites are usually more water soluble than the parent compounds and are therefore rapidly excreted in the kidney. The major site of drug metabolism is the liver, although the lungs, kidneys, gut, adrenals and other organs may also contribute. Detoxification pathways are conventionally classified into two groups of reactions: phase I reactions consist of oxidation, reduction and hydrolysis, while phase II comprises conjugation reactions.

Endogenous as well as exogenous carboxylic acids are usually detoxified by two conjugation pathways (phase II reactions). The first and major route is conjugation with glucuronic acid to form glucuronides, while the second type of conjugation involves reaction with the amino acid glycine to form hippuric acid derivatives.

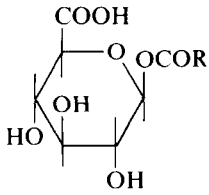
A. Glucuronide Formation

The formation of glucuronides is mediated by the enzyme(s) uridine diphosphoglucuronyl transferase (UDPGT) in the presence of the biological carrier of glucuronic acid, uridine diphosphoglucuronic acid (equation 2). The new glycoside bond formed between the hydroxylic hemiacetal of glucuronic acid and the carboxyl group of the drug is an

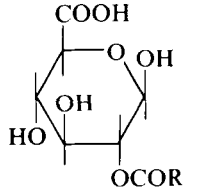


(2)

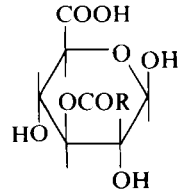
'ester type' glucuronide with β configuration. This is in contrast to 'ether type' glucuronides that are formed by alcohols and phenols. 'Ester type' glucuronides are the major metabolites of the endobiotic bilirubin[34] and a variety of xenobiotics such as iopanoic acid[35], valproic acid[36] (see Section XIII), 2-arylpropionic acids[37] (see Section VII.B.) and clofibrate[38] (see Section XVIII). These glucuronides can be hydrolyzed under alkaline conditions or enzymatically by β-glucuronidase to yield the original acid derivatives. Additionally, 'ester type' glucuronides may undergo, in mild alkaline conditions, intramolecular rearrangements to form 2,3 and 4-0-acylglucuronides[39].



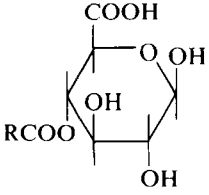
1-Acyl glucuronide



2-Acyl glucuronide

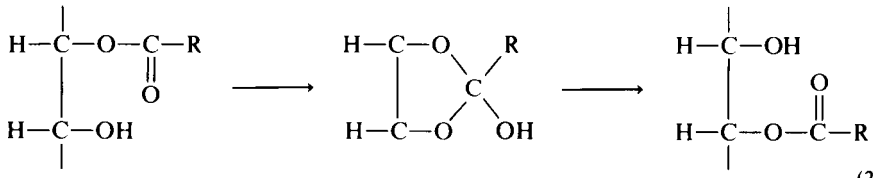


3-Acyl glucuronide



4-Acyl glucuronide

The mechanism of this rearrangement involves a nucleophilic attack of the neighboring hydroxyl on the carboxylic carbon atom to form an orthoacid intermediate (equation



(3)

3). The rearranged acyl glucuronides are sensitive to basic hydrolysis but not to enzymatic hydrolysis by β-glucuronidase[40]. This rearrangement may have important implications in terms of the disposition of glucuronides in certain disease states and in the application of analytical procedures to these conjugates.

'Ester type' glucuronides of acid derivatives may undergo transacylation reactions with the mercapto group of cysteine or the hydroxyl group of tyrosine in proteins, leading to covalent binding of acid derivatives to these proteins[41]. Irreversible binding of organic acid glucuronides such as tolmetin[42] and zomepirac[43] to albumin has been reported. This is different from the common reversible binding of drugs to plasma albumin (see Section IV) and probably has dissimilar biological implications.

B. Conjugation with Amino Acids

Aromatic acids such as benzoic acid are conjugated with glycine to form hippuric acid. This conjugation reaction involves the formation of an intermediate ester of the acid with adenosine monophosphate (AMP). The intermediate reacts with CoA-SH to form a second intermediate CoA-thioester of the organic acid. The CoA-thioester then reacts with glycine to form hippuric acid, as shown in equation 4:

$$\text{ArCOOH} \longrightarrow [\text{ArCOAMP} \longrightarrow \text{ArCO–S–CoA}] \longrightarrow \text{ArCONHCH}_2\text{COOH} \quad (4)$$

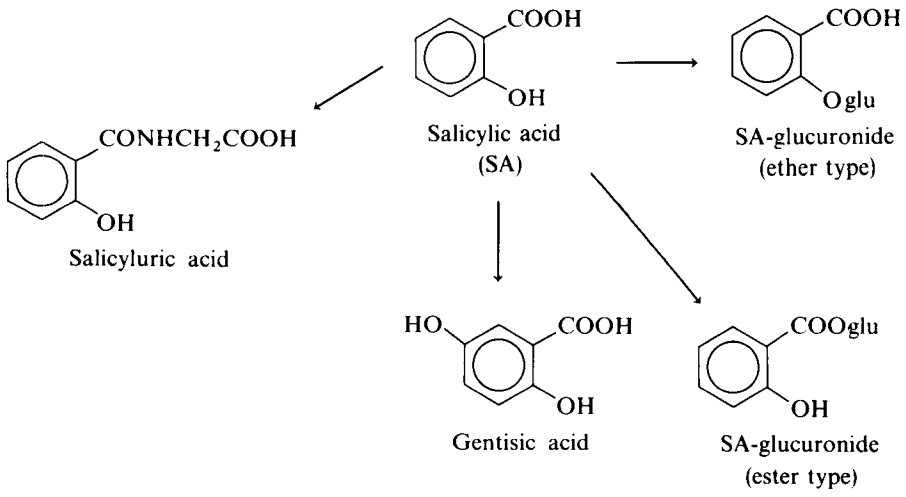
Amino acids can form conjugates with aliphatic acids, as in the case of bile acids. Thus, glycocholic and taurocholic acids are the amide conjugates of cholic acid with glycine and taurine, respectively.

C. Detoxification of Organic Acids at Sites Other than the Carboxyl

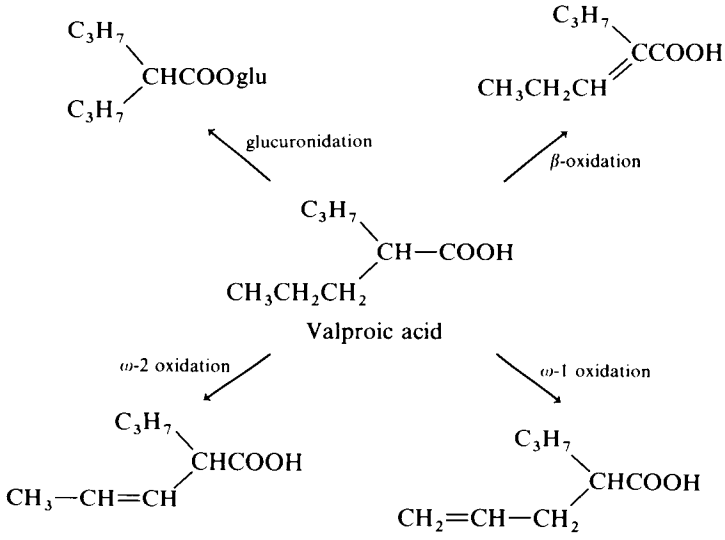
Organic acids can be detoxified by additional pathways unrelated to their acidic functional group. These pathways may include oxidative or conjugative reactions which lead to the formation of polar metabolites. For example, salicylic acid (see Section VII.A.2) is metabolized to the 'ester type' glucuronide and to salicyluric acid, and also to an 'ether type' glucuronide, a major metabolite, and to the minor metabolite gentisic acid (2,5 dihydroxybenzoic acid) (Scheme 1). Valproic acid (2-propylvaleric acid) (see Section XIII) also undergoes extensive oxidative metabolism in addition to the major metabolic pathway resulting in 'ester type' glucuronide formation[36] (Scheme 2).

D. Chiral Bioinversion of Arylpropionic Acids

The concept of stereoselectivity of drug action and disposition are well established with numerous natural as well as synthetic drugs[44–47]. Therefore, the observation that various [*S*] arylpropionic acid derivatives (see Section VII.B.1) are by far more active as antiinflammatory drugs in *in vitro* tests than the [*R*] enantiomers was not unique. However, in *in vivo* experiments the difference in activity between the enantiomers was

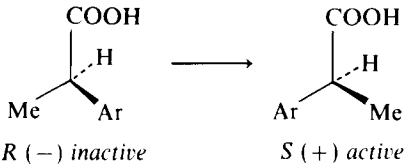


SCHEME 1



SCHEME 2

not as evident. Thus, while the *in vitro* [*S*]/[*R*] activity ratio of ibuprofen and naproxen, for example, was 130 and 160, the ratio for *in vivo* activity of these drugs was only 1.3 and 25, respectively[48,49]. Additionally, it was shown that the urinary metabolites of ibuprofen in humans are predominantly dextrorotatory [*S*], irrespective of the specific enantiomer or mixture that was administered[50]. These observations led to the hypothesis that certain [*R*] arylpropionic acid derivatives are bioinverted *in vivo* to the corresponding [*S*] enantiomers (equation 5).



R (−) *inactive* *S* (+) *active* (5)

The bioinversion of arylpropionic acids is a unique and novel biochemical pathway. With the development of analytical procedures for the separation and quantitation of arylpropionic acid enantiomers it became possible to determine the kinetics of the chiral bioinversion, as exemplified by ibuprofen in humans[51]. The extent of inversion varies between members of this family of drugs. In some, like ibuprofen, this phenomenon occurs very efficiently while in others, like indoprofen, it is hardly noticeable[37]. In addition to the enantiomeric bioinversion process, arylpropionic acids are of course biotransformed to different other metabolites via oxidative or conjugative pathways according to their chemical structures.

1. Species variation

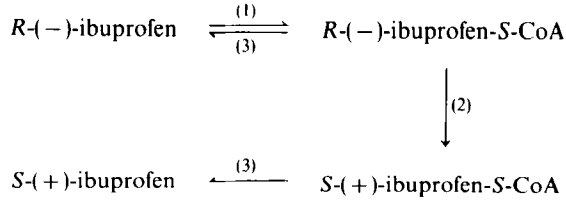
The extent of bioinversion varies among species. Some animal species are more active than others in bioinversion of certain arylpropionic acids. While in the rat, bioinversion of ketoprofen occurs to a very significant extent, the magnitude of inversion of this drug in humans and rabbits is very low[52,53]. 2-Phenylpropionic acid is bioinverted by humans, rats and rabbits but not by mice, while ibuprofen is inverted by all species so far investigated[37]. It may be concluded that it is difficult to predict the rate and extent of bioinversion of any specific drug in this group by any animal species.

2. Site of inversion

Following the documentation of *in vivo* inversion of arylpropionic acid derivatives, it was of interest to determine the site(s) of this reaction. Early studies failed to show any inversion with liver homogenates. Subsequently, Nakamura and Yamaguchi[54] and Knihinicki and colleagues[55] showed that liver homogenates fortified with ATP, coenzyme A and magnesium ions were capable of inverting [*R*]- to [*S*]-ibuprofen. The difficulty in showing chiral inversion by liver homogenates may thus be due to destruction of the hepatic cell structure during homogenization. Indeed, it was shown that other liver preparations, including hepatocytes, liver slices and isolated perfused liver, were capable of bioinverting various arylpropionates[56–58]. Simmonds and colleagues[59] also showed that the everted intestine preparation of the rat can epimerize [*R*]-benoxafen. Also, rat kidney slices were three times more active than liver slices in inverting phenylpropionic acid[54]. However, no inversion of ibuprofen was detected by kidney homogenates[55].

3. *Mechanism of bioinversion*

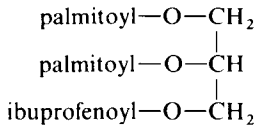
Preliminary studies that were carried out in an effort to elucidate the mechanism of the stereospecific epimerization of ibuprofen indicated that 2,3-dehydroibuprofen might be an intermediate in this process[60]. Later studies with [*R*]- [2-$^2H_1$] ibuprofen showed that deuterium was lost during the inversion process. When [*R*]-[3,3,3-$^2H_3$]ibuprofen was administered the [*S*]-ibuprofen that was isolated retained its three deuterium atoms. These observations preclude the formation of 2,3-dehydroibuprofen as an intermediate, because if the latter substance is formed, one deuterium atom from the methyl group would exchange with a hydrogen atom[61]. Recent studies showed that inversion of [*R*]-enantiomers of arylpropionic acids proceeded through the formation of coenzyme A (CoA) thioester[55,56]. Moreover, only [*R*]-enantiomers (but not [*S*]) could form this thioester with CoA[56]. Thus, it seems that the ester formation with CoA is an obligatory step in the bioinversion of arylpropionic acids. The esterification step with CoA is mediated by long-chain acyl CoA synthetase (also called long-chain acyl CoA ligase), the enzyme which catalyzes the formation of CoA esters with fatty acids such as palmitic acid[62,63]. The esterification with CoA is also an oligatory step in the formation of



(6)

(1) long-chain acyl-CoA synthetase
(2) racemase
(3) hydrolase

glycerol esters with fatty acids[62]. Indeed, [*R*]-ibuprofen forms, in the presence of palmitic acid, glycerol-CoA and long-chain acyl-CoA synthetase, a hybrid triglyceride in which ibuprofen is esterified to glycerol[63]:



Racemization of [*R*]-ibuprofen-CoA ester does not occur in buffer or plasma[55]. It is therefore assumed that the racemization is catalyzed by a racemase, an enzyme not completely characterized. Following racemization the [*R*] and [*S*] enantiomeric-CoA esters are probably hydrolyzed by a hydrolase. Although the nature of the hydrolase is not yet clear, it may be the same hydrolase catalyzing the hydrolysis of fatty acid CoA esters, namely palmitoyl-CoA hydrolase. The inversion process presented above is based on the scheme suggested by Williams[64].

VI. ESTERS AS PRODRUGS

Often in therapeutics valuable drugs may be limited by some unfavorable quality such as insufficient absorption from the gastrointestinal tract, acid lability or short half-life

in the body. In many instances esterification may produce a prodrug with better characteristics, which is eventually hydrolyzed in the body to yield the active drug molecule. Other advantages that may be gained from ester prodrugs could be better water solubility to allow preparation of solutions for parenteral injection. Inversely, an ester may reduce the aqueous solubility of a bitter compound, thus masking its taste and allowing a more acceptable oral dosage form. Esters can be hydrolyzed in the gut lumen by bacterial enzymes[65]. This may be followed by gut wall metabolism and finally by liver and blood esterases. Therefore the active hydrolysis product becomes readily available to the system.

Two types of ester prodrugs will be discussed. One, in which a carboxylic drug is esterified with an alcohol. The other type uses mainly fatty acids to esterify a hydroxy group in the drug of interest.

A. Ampicillin Esters

Several of these prodrugs have been prepared with the objective of improving the bioavailability of the broad spectrum penicillin, ampicillin (see Section VIII.A). An added advantage of such derivatization could be reduced antibiotic effect on the intestinal flora, constituting a disturbing side effect. The most widely exploited of these esters has been bacampicillin, the ethoxycarbonyloxyethyl ester of ampicillin[66]. After oral administration it produces higher serum concentrations than the parent compound, indicating some 40% greater bioavailability[67].

B. Indanyl Carbenicillin

Carbenicillin, an antipseudomonal semisynthetic penicillin (see Section VIII.A), is not absorbed from the gastrointestinal tract. However, the indanyl ester is readily absorbed following oral administration and undergoes hydrolysis to produce peak plasma concentrations of carbenicillin 1 to 2 hours after oral administration[68].

C. Methyldopate

This is the ethyl ester of methyldopa (see Section XIV.B), the hydrochloride of which is used as the injectable form of methyldopa for the treatment of hypertensive crisis. The ester is some 100-fold more water-soluble than the parent compound. Although the pharmacology and clinical response with both preparations are essentially similar, some pharmacokinetic differences between the two have been reported[69].

D. Erythromycin Esters

The antibiotic erythromycin is acid-labile and is easily destroyed by the gastric acid, unless it is administered in enteric-coated tablets (tablets that decompose only in the small intestines, thus protecting their contents from the gastric acid). Several fatty acid esters of erythromycin that are resistant to gastric acid decomposition have been manufactured, such as erythromycin stearate, estolate, palmitate etc., thus providing better bioavailability of erythromycin. Although it is assumed that such ester prodrugs release the active compound and eventually display similar characteristics, an exception has been noted with erythromycin estolate. This ester presents specific toxicity to the liver[70].

E. Depot Neuroleptics

Phenothiazines and butyrophenones are neuroleptic drugs used mainly for the treatment of psychiatric disease. In order to enable convenient long-term parenteral

treatment of psychiatric patients, some of these neuroleptics have been prepared as fatty acid esters for injection in an oil vehicle. These heptanoic, decanoic or palmitic acid esters are exceedingly lipid soluble and are released very slowly from the oil vehicle at the site of intramuscular injection. Once released, they are readily hydrolyzed to yield the active neuroleptic molecule. The rate of release of neuroleptics into the circulation depends both on the fatty acid used for esterification[71] and on the oil vehicle chosen[72]. Commonly available preparations are fluphenazine enanthate and decanoate and haloperidol decanoate. Such esters provide adequate therapy for as long as 2–4 weeks after a single injection.

F. Vidarabine Formate

Vidarabine is an antiviral analog of adenosine. Due to its low water solubility, over 2 liters of fluid are required to dissolve the clinically used dose for intravenous injection. The formate ester is 65-fold more water-soluble than the parent compound, thus enabling intravenous injections in a reasonable volume.

G. Chloramphenicol Esters

Chloramphenicol is a broad spectrum antibiotic. It has some water solubility (1 in 400) and, due to its very bitter taste, is unacceptable to children in liquid oral dosage form. The palmitate ester is practically insoluble in water and therefore has no taste. It is used as an oral suspension, out of which the active drug is rapidly hydrolyzed in the body. For parenteral administration chloramphenicol sodium succinate, a water soluble prodrug is used. The site where hydrolysis of the succinate takes place is not yet clear. Esterases of the liver, kidney and other organs are probably involved. The renal clearance of this prodrug is very rapid. On the other hand, decreased esterase activity may delay the hydrolysis of the succinate.

H. Steroid Esters

Steroid hormones have low water solubility. For those requiring intravenous injection, mostly glucocorticoids, water-soluble ester prodrugs have been prepared. Examples are prednisolone disodium phosphate, prednisolone sodium hemisuccinate or prednisolone sodium tetrahydrophthalate. The rate of hydrolysis of these esters may be different, as evidenced by higher peak plasma concentrations of prednisolone and larger area under the concentration–time curve after intravenous administration of prednisolone phosphate, compared with the phthalate ester[73,74]. Biological effects of the steroid that was administered as phthalate were smaller than with the phosphate ester, as were also cerebrospinal fluid concentrations of the active drug[75]. These data indicate that not only the rate of hydrolysis of different ester prodrugs may be different, but also some may not be completely hydrolyzed before they are excreted by the kidney.

VII. NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAID)

Drugs in this category share three major pharmacologic actions. They are analgesic, i.e. relieve pain, antipyretic, i.e. reduce fever, and, as their name implies, are anti-inflammatory[76]. Members of this group of drugs vary in their chemical structures and may be divided into several chemical categories, as detailed in the following discussion. Nevertheless, they all share inhibition of cyclooxygenase activity as their major mechanism of action[77]. Cyclooxygenase catalyzes the first reaction in the formation of prostaglandins from precursor polyunsaturated fatty acids, primarily arachidonic acid. The biosynthesis of prostaglandins is depicted in Scheme 3 (Section VII.A.1). Prostaglandins

constitute a group of ubiquitous lipid local hormones that, among other activities, regulate local blood flow, mediate inflammation and control platelet function[78]. According to the most widely accepted hypothesis of the mechanism of action of NSAID, all the major pharmacological effects of these drugs, as well as their most frequent adverse reactions, are explained on the basis of cyclooxygenase inhibition[79,80]. Prostaglandins are thus proinflammatory, they mediate the febrile effect of pyrogenic agents at the level of the hypothalamus, and they are essential for the generation of pain at the peripheral tissue level. Therefore, inhibition of prostaglandin synthesis results in the three major pharmacological actions of NSAID, as specified. Also, since prostaglandins exert a cytoprotective effect on the gastrointestinal mucosa, inhibition of their generation by NSAID may result in damage to the gastrointestinal mucosa. Thus, erosions of the stomach and ulcer production are the most frequently encountered adverse reactions of this group of drugs[81, 82]. Another adverse effect that is common to the NSAID is their ability to induce acute renal failure in susceptible patients[83, 84]. One of the physiological processes that regulate renal blood flow is the increased synthesis of prostaglandins in response to stimuli that may compromise renal blood flow. Thus, the renal function of patients with decreased kidney reserves depends to a large extent on the ability of this tissue to elaborate vasodilatory prostaglandins. In such patients, ingestion of NSAID may adversely affect renal function. Other adverse effects of NSAID have been reported and were recently reviewed[85].

Most of the NSAID are organic acids with pK_a ranging from 3–5. They may interact with cyclooxygenase in different ways, resulting in enzyme inactivation. Aspirin is unique in causing covalent modification of the enzyme by first binding to the active site and then acetylating a serine at position 530 of the enzyme[86,87]. This bulky group acts to modify the three-dimensional architecture of the arachidonic acid binding site of the cyclooxygenase, thereby preventing the binding of substrate. On the other hand, indomethacin competes with the substrate for binding to the enzyme and thus causes a yet undefined modification of the active site, leading to its irreversible inactivation[88]. Other NSAID may compete with arachidonic acid for binding to the enzyme, but their effects are fully reversible[89].

Apart from the different molecular mechanism of action of the various NSAID, these drugs have been known to influence prostaglandin synthesis in different tissues in an uneven manner[90, 91]. Two kinds of explanations have been proposed for this phenomenon. One, that cyclooxygenase could exist in different tissues as several isozymes, and therefore these isozymes could display different susceptibilities to inhibitors. However, to date only one gene for cyclooxygenase has been identified[92], making this hypothesis unlikely. Alternatively, tissue distribution, concentration and metabolism may be differential for the various NSAID, thus giving rise to quantitatively different levels of enzyme inhibition. For example, the acid nature of most NSAID would favor their distribution from the acidic environment of the stomach contents into the cells. Larger concentrations of NSAID in the gastric mucosa may therefore explain stronger inhibition of cyclooxygenase in that tissue than in others[93]. Similarly, lipid solubility of different NSAID could determine their penetration into the central nervous system through the blood–brain barrier. Since the antipyretic action is central, whereas the analgesic and anti-inflammatory effects are exerted at peripheral sites, brain penetration could account for some differences in activity. A further difference in the action of the various NSAID may result from the dissimilar environment at inflammatory sites compared with the hypothalamus. While the former may contain high concentrations of peroxides, the latter does not. This was offered as a possible explanation for the poor antiinflammatory action of paracetamol[94]. Some or all NSAID may exhibit additional mechanisms of action[95] which could contribute of their pharmacological profile. However, the precise significance of each of these presumed mechanisms has to be determined. Clinically, despite

the notion that all NSAID exert similar effects, differences between the various members of the group have been reported both in therapeutic effectiveness and in adverse reactions[96].

Another common feature of the NSAID is their high degree of binding to plasma albumin (see Section IV), in many cases in excess of 95%. Because NSAID are generally prescribed in large quantities, they tend at therapeutic concentrations to saturate albumin binding sites. This gives rise to a variety of drug–drug interactions, in which NSAID may displace other drugs from albumin. The resulting elevation in free drug concentrations has often produced clinically significant disturbances.

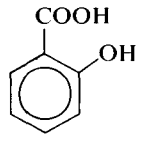
In the following discussion we will highlight several aspects of the pharmacology of the prototype NSAID, aspirin. We will later discuss some selected topics relating to other commonly used acidic NSAID, the pharmacology of which, as a group, was recently reviewed[97,98].

A. The Salicylates

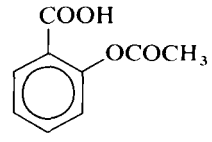
1. Aspirin

Acetylsalicylic acid, commonly known as aspirin (a proprietary name that has turned generic), was first synthesized in 1853 and is still one of the best selling drugs worldwide. It possesses all three major activities common to the NSAID. Lower doses are mainly antipyretic and analgesic, while larger doses are required for significant antiinflammatory activity. Recently, its use for the prevention of myocardial infarction has been promoted by numerous laboratory and clinical studies. It has been found effective in preventing myocardial infarction and other thrombotic diseases at very low doses[99,100]. The mechanism of this action is again related to inhibition of cyclooxygenase. Two prostanoids, thromboxane (TXA_2) and prostacyclin (PGI_2) (Scheme 3), are extremely potent regulators of platelet aggregation. Other prostaglandins, namely PGE_2, $PGF_{2\alpha}$ etc., are involved in inflammation and other processes. While thromboxane, produced by platelets, is a natural proaggregator and vasoconstrictor, prostacyclin which is synthesized in endothelial cells inhibits platelet aggregation and is a vasodilator. Although inhibition by aspirin of the first enzyme involved in prostanoid synthesis is expected to equally affect the production of prostacyclin and thromboxane, a remarkable degree of specificity is actually achieved. Thus, with low doses of aspirin *in vivo* significant reduction in platelet thromboxane synthesis follows, while endothelial prostacyclin production is actually spared. This differential effect is achieved because of the dissimilar biological characteristics of blood platelets and endothelial cells. The latter continuously synthesize new protein and can readily replace the cyclooxygenase that had been inactivated by aspirin. By contrast, blood platelets lack nucleus and hence are incapable of new protein synthesis. Therefore, the effect of aspirin on platelet thromboxane synthesis lasts for the life of the platelet, i.e. 7–10 days[101,102].

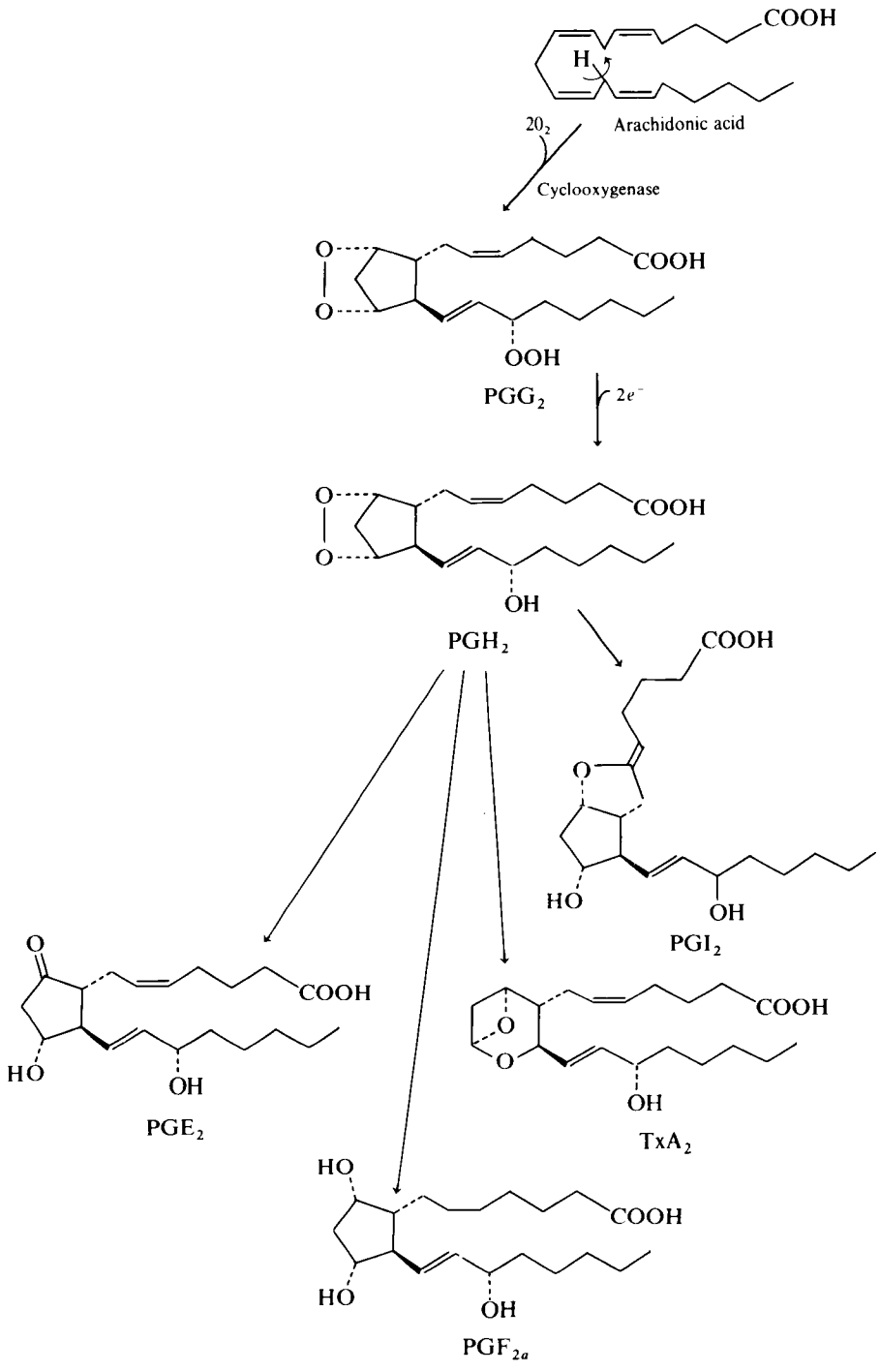
Aspirin is readily hydrolyzed *in vitro* and is therefore not available commercially in solution. *In vivo* it is also hydolyzed in the intestines, plasma and liver with a half-life of 15–20 min, resulting in circulating salicylate. The latter has a half-life of 2–20 hours



Salicylic acid



Aspirin


COOH
H
Arachidonic acid
$2O_2$
Cyclooxygenase
O
O
COOH
OOH
PGG_2
$2e^-$
O
O
COOH
OH
PGH_2
COOH
O
HO
OH
PGI_2
O
COOH
HO
OH
PGE_2
COOH
O
O
OH
TxA_2
HO
COOH
HO
OH
PGF_{2a}

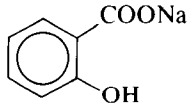
SCHEME 3

in humans, depending on the plasma concentrations. The main routes of metabolism are conjugation with glycine to yield salicyluric acid, and glucuronidation of either the phenol or carboxyl group. Both of these routes of metabolism are saturable at therapeutic doses of aspirin, which accounts for the dose-dependent metabolism and half-life[103]. This is in contrast to most drugs that at therapeutic concentrations manifest a nonsaturable metabolic behavior, therefore their half-lives are constant.

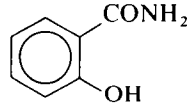
The most common adverse effects of aspirin, as is the case with other NSAID, are gastrointestinal. The incidence of gastric lesions varies with the method of observation, ranging from a few percent when spontaneous clinical reporting is used to alarming figures when gastroscopy is performed, even after a single dose[104, 105]. Attempts have been made to reduce the extent of upper gastointestinal damage by improved formulations such as buffered aspirin, which seem to decrease the incidence of gastrointestinal adverse reactions.

2. *Other salicylates*

Salicylates were used in the past as sodium or magnesium salicylate, choline salicylate and salicylamide. Also, after ingestion and hydrolysis of aspirin, salicylate stays in the body. Clinically, salicylates share most of the actions and adverse effects of aspirin. From

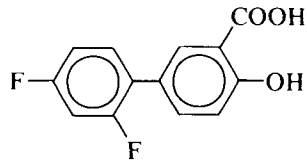


Sodium salicylate



Salicylamide

a mechanistic point of view this presents a difficulty, since we believe that acetylation of the cyclooxygenase enzyme is an important part of the mechnism of action of aspirin, and this obviously cannot be the case with salicylate. Indeed, salicylate is a poor inhibitor of prostaglandin synthesis *in vitro*. On the other hand, several *in vivo* studies suggest that the active antiinflammatory agent is probably the salicylate. Thus, Higgs and colleagues[106] observed sustained inhibition of prostaglandin E_2 production in the inflammatory exudates of rats that had been treated with aspirin long after aspirin was completely converted to salicylate. In a recent study on cultured endothelial cells, Wu and colleagues[107] reported that very small concentrations of salicylate (as sodium salicylate) inhibited interleukin 1-induced prostaglandin H synthase expression but not basal enzyme levels. Aspirin had a similar effect, and it was suggested that this was due to its salicylate content. If such observations are confirmed, they may revolutionize our understanding of the mechanism of action of NSAID and pave the way to more specific antiinflammatory therapy. Such drugs may thus inhibit inflammatory prostaglandin synthesis and spare basal levels that are necessary for normal physiological function.



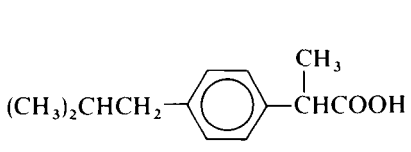
Diflunisal

A recent addition to the antiinflammatory armamentarium is diflunisal. This is the difluorophenyl derivative of salicylic acid[108,109]. The pharmacological activity of diflunisal probably resides in its specific molecular structure, since it is not converted to salicylate. Also, in contrast to the latter, it hardly possesses any antipyretic activity. Nevertheless, it is a potent antiinflammatory agent and shares the common mechanism of action of NSAID, namely cyclooxygenase inhibition. Clinically, it is characterized by a relatively long half-life in plasma, about 12 hours, and allows convenient dosage regimens.

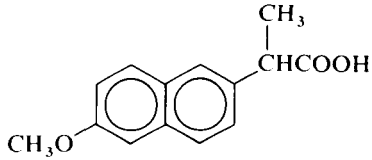
B. Arylalkanoic Acids

1. Arylpropionic acid derivatives

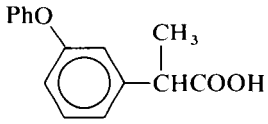
This is a relatively new class of antiinflammatory drugs that was introduced into therapeutics in the seventies. The number of useful drugs in this group is constantly increasing. Examples are ibuprofen[110], fenoprofen[111], naproxen[112], ketoprofen[113] etc.



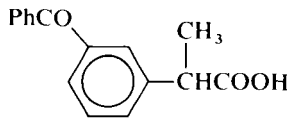
Ibuprofen



Naproxen



Fenoprofen



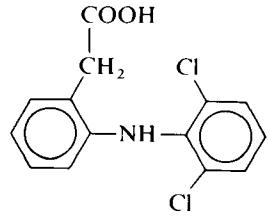
Ketoprofen

Some arylpropionic acid derivatives

They share most of the effects of other NSAID and are usually better tolerated[114]. Naproxen has the added advantage of a relatively long half-life (13 hours), which allows a twice daily regimen, compared with 3–4 times daily for the shorter acting drugs. Naproxen is available as the [*S*] enantiomer, but the other members of this group are marketed as the racemic mixtures. The bioinversion of these drugs was discussed in Section V.D.

2. Diclofenac

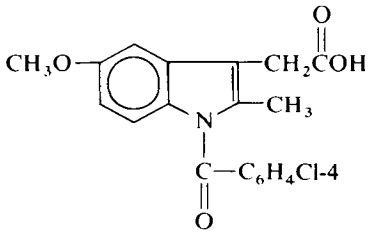
Diclofenac is a phenylacetic acid derivative that shares the analgesic, antiinflammatory and antipyretic actions of other NSAID[115,116]. It is generally used orally as enteric-coated tablets. More recently, a topical transdermal preparation of diclofenac (Voltaren emulgel) has been introduced for the treatment of local musculoskeletal pain. The drug is absorbed through the skin, yielding detectable blood-plasma levels, but higher concentrations were measured in underlying muscle and joints[117]. Thus, the transdermal route may exert local effects over aching joints and muscles and spare many of the side effects of systemic treatment.



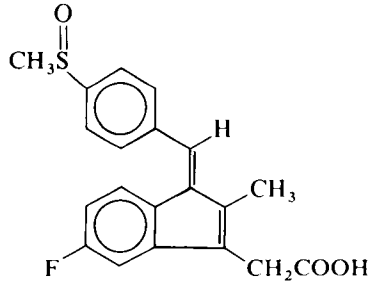
Diclofenac

3. Indoles and indenes

Indomethacin is an indole derivative with very potent and efficacious antiinflammatory activity. It also shows the analgesic–antipyretic activity of other NSAID, but has an alarming incidence of serious adverse reactions. It is a powerful irreversible inhibitor of cyclooxygenase and has been used in many investigations as a specific tool for making decisions on the possible involvement of this enzyme in biological systems. As implied earlier, this approach should be utilized very cautiously, because indomenthacin may, at higher than recommended concentrations, exert additional pharmacological effects[6].



Indomethacin

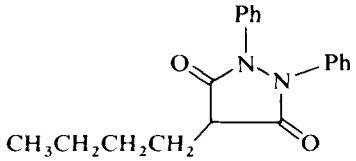


Sulindac

Sulindac is an indene derivative closely related to indomethacin. It is metabolized in the body to the active sulfide metabolite, and is therefore considered a prodrug. Because of this, initial expectations were that sulindac would exhibit considerably less gastrointestinal side effects than other NSAID. Unfortunately, these expectations materialized only partly.

C. Pyrazolon Derivatives

Drugs in this group, including phenylbutazone, oxyphenylbutazone, dipyrone and others, have been falling out of favor with the introduction of safer antiinflammatory medications. Dipyrone is used mainly for its powerful analgesic properties. Other members of this group, notably phenylbutazone and oxyphenylbutazone, exert very powerful antiinflammatory effects, but by many their toxicity is considered unacceptable. The most serious toxicity of these drugs is their propensity to cause bone marrow depression and agranulocytosis. Although this is a very rare occurrence, it may be a fatal event. More common adverse effects strike the gastrointestinal tract, the kidney, liver and the central nervous system.

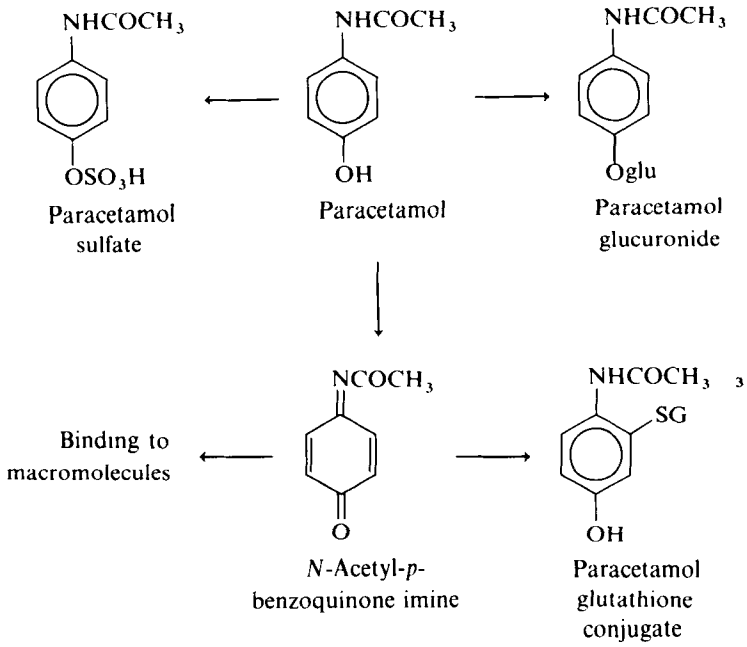


Phenylbutazone

D. *para*-Aminophenol Derivatives

Paracetamol (acetaminophen, *N*-acetyl-*p*-aminophenol) is the only member of this group that is currently widely used in clinical practice. It differs from most NSAID in that it is analgetic–antipyretic, but hardly antiinflammatory[118]. There has also been debate on whether and to what extent this drug acts via cyclooxygenase inhibition[90].

Paracetamol in conventional doses is extremely well tolerated. However, an acute overdose may cause severe hepatotoxicity, which is potentially fatal. The study of the mechanism of this liver toxicity has been most rewarding both in terms of unraveling the mechanism of this toxicity and of devising effective clinical antidotes. Paracetamol in small doses is metabolized in the liver to the inactive glucuronide and sulfate conjugates. In addition, minute amounts of a toxic metabolite are generated by the cytochrome P450 enzyme system, which are in turn rapidly detoxified by hepatic glutathione. However, following an acute overdose (usually in excess of 10 g), enough toxic metabolite is produced to deplete liver glutathione stores. At this point the toxic metabolite accumulates in liver cells and reacts with cellular macromolecules to cause massive necrosis (Scheme 4).



SCHEME 4

The antidotes for paracetamol-induced hepatotoxicity are sulfhydryl compounds (the most effective of which is *N*-acetylcysteine), which either restore glutathione levels or serve to inactivate the toxic metabolite directly. The effectiveness of such treatment, administered within 12–24 hours of the poisoning, has been documented in numerous animal and clinical trials[119].

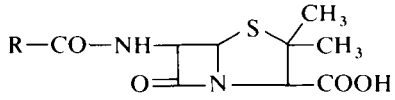
VIII. BETA-LACTAM ANTIBIOTICS

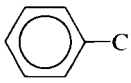
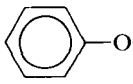
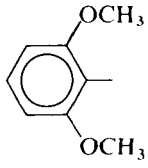
One of the major breakthroughs in pharmacology and medicine has been the discovery of antibiotics. Following the discovery of penicillin by Fleming in 1929, newer additions to this family of beta-lactam antibiotics followed since 1954, when the first semisynthetic penicillin was introduced. The beta-lactam antibiotics now include penicillins, cephalosporins, monobactams and carbapenems[120]. All contain a beta-lactam ring, which confers a bactericidal activity through inhibition of bacterial cell-wall synthesis. This is accomplished through binding to a group of enzymes on the inner surface of the bacterial cell membrane that catalyze the last stages of cell-wall synthesis. These enzymes are collectively referred to as penicillin-binding proteins (PBP). Such binding inactivates the specific PBP that are involved, ultimately causing bacterial cell death. For a more detailed account of the mechanism of action of beta-lactam antibiotics, the reader is referred to some recent publications[121–123]. Because these antibiotics are designed to interfere with a biochemical process that is specific to bacteria and has no counterpart in eukariotics, they are considered to have reached the highest degree of selectivity a drug can achieve. Unfortunately, even such selectivity does not preclude the occurrence of adverse reactions, as discussed later.

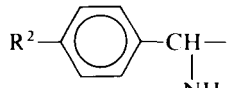
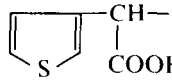
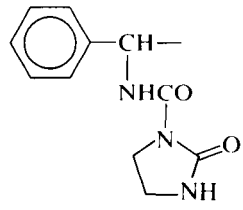
A. The Penicillins[124]

Common to all penicillins is a beta-lactam ring fused to a five-membered thiazolidine ring. Although the original penicillin G, or benzyl-penicillin, possesses marked *in vitro* and therapeutic activity against susceptible organisms, chemical modifications of this molecule have resulted in remarkable further advantages. Thus semisynthetic penicillins may possess extended spectrum of activity against a variety of bacteria, exhibit resistance to bacterial beta-lactamases, or have improved pharmacokinetic properties. Most of the modifications are made on the acyl side chain attached to carbon 6 of the penicillin.

The first semisynthetic penicillin, phenoxymethyl-penicillin, known as penicillin V, resolved the problem of acid lability of the original penicillin G. Because of this lability, penicillin G cannot be administered orally or it is rapidly destroyed by the acidity of the gastric juice. Penicillin V is more stable to acid and therefore displays better bioavailability after oral administration. Otherwise penicillin V shares all the properties of penicillin G. One limitation of both is their very short biological half-life, about 30 minutes. This rapid elimination results from a very efficient process of renal tubular secretion, in addition to glomerular filtration. The renal secretion of acids has been discussed earlier and may be slowed by concomitant administration of probenecid. A different approach is the formation of repository forms of penicillin G with very slight water solubility. Two such preparations are available for parenteral injection: Procaine–penicillin suspension has water solubility of 0.4% and is therefore slowly absorbed from its deep intramuscular injection site over a period of 12 hours or more. Benzathine–penicillin (N,N^1-dibenzylethylenediamine dipenicillin G) has water solubility of only 0.02% and is therefore used to provide very low systemic concentrations of penicillin over a period extending to one month. The utility of such preparations is limited to combating very susceptible bacteria, which can be eradicated with low penicillin concentrations.

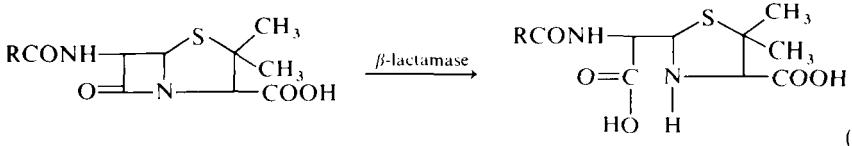


R	
	Penicillin G
	Penicillin V
	Methicillin

R	
	Ampicillin† (R^2 = H) Amoxycillin (R^2 = OH)
	Ticarcillin
	Azlocillin

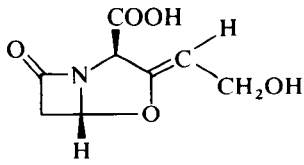
Some representative penicillins

Some bacteria possess enzymes which can destroy beta-lactam antibiotics. Beta-lactamases or penicillinases may be present in the chromosome of certain strains of bacteria or transferred as plasmids or transposons[125,126]. Therefore, bacterial resistance to the penicillins is spreading. For example, prior to the penicillin era, some 85% of Staphylococci were penicillin-sensitive, whereas most of these strains are now penicillin-resistant. Beta-lactamases, enzymes that hydrolyze the cyclic amide bond of the beta-lactam ring (equation 7), may exhibit different activities against different beta-lactams such as penicillins and cephalosporins. Several semisynthetic penicillins have been introduced for their relative resistance to penicillinase. The first of these, methicillin, was introduced as an antistaphylococcal agent. Oxacillin, cloxacillin, nafcillin and others share this resistance to cleavage by penicillinase and may offer additional advantages, such as oral absorption.



Penicillins Penicilloic acids (7)

A more recent strategy for dealing with the problem of beta-lactamases has been the use of beta-lactamase inhibitors in combination with penicillins. Clavulanic acid is a bicyclic beta-lactam isolated from cultures of streptomyces clauvigerms, having only weak antibacterial activity. However, it serves as 'suicide inhibitor' of beta-lactamase



Clavulanic acid

by virtue of its binding affinity and slow hydrolyzability. Thus, an otherwise beta-lactamase susceptible penicillin that is administered concomitantly can be protected and exert its bactericidal activity[127]. Newer beta-lactamase inhibitors have been synthesized. Sulbactam and tazobactam are sulfones and other are halogenated derivatives of penicillanic acid. The currently used combinations are ticarcillin plus clavulanic acid, amoxycillin plus clavulanic acid and ampicillin plus sulbactam[128–131].

A major determinant of the spectrum of action of the various penicillins is their penetrability through bacterial cell walls and affinity for binding to PBP. Penicillin G can penetrate the cell walls of many gram-positive bacteria, but is unable to do so with the more complex structure of the outer cell wall of gram-negative organisms[132]. The so-called broad-spectrum penicillins and, more recently, the extended-spectrum penicillins, have provided adequate solutions to this problem[133]. The very prevalent broad-spectrum penicillins ampicillin and amoxycillin are acid resistant and therefore suitable for oral use, but are readily destroyed by beta-lactamases. However, their spectrum of activity extends from gram-positive (albeit at a lower sensitivity than to penicillin G) to many gram-negative bacteria. Prominent among the latter are *H. influenzae*, some strains of *E. coli*, *Pr. mirabilis*, Salmonella and Shigella. The extended-spectrum penicillins are also known as antipseudomonal penicillins, although their spectrum also includes other aerobic gram-negative bacilli such as certain Proteus species and sometimes Klebsiella as well as anaerobes[134,135]. Two groups of extended-spectrum penicillin are available: the carboxy penicillins include carbenicillin and ticarcillin, and the ureido penicillins azlocillin, mezlocillin and piperacillin.

Enormous effort has been made to determine the structure–activity relationship of penicillins and other beta-lactams with very significant achievements[136]. In a recent critical review of this subject, however, Frere and colleagues[137] concluded that definition of the structure–activity relationship of beta-lactams was 'an impossible dream'. The reason for the difficulty in defining structure–activity relationships among members of this group of drugs is that at least three unrelated factors should contribute to such relationship. The authors discussed and defined these factors: first, the different sensitivities of target enzymes, namely PBP, in various bacteria; second, the different characteristics of beta-lactamases of bacteria; and third, the requirements for permeability of the drug through the outer membrane of gram-negative bacteria.

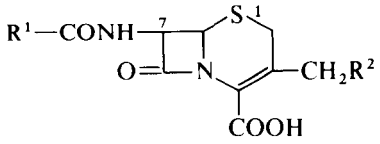
The most common side effects of the penicillins are hypersensitivity reactions or allergies. Between 1–10% of patients receiving a penicillin preparation may develop one form or another of drug allergy. Most frequently this is manifest as various forms of rash, but fever, bronchospasm and anaphylactic shock may also occur. The latter situation may be life threatening and is fortunately very rare[138]. The mechanism of penicillin allergy involves covalent reactions of penicillins or their breakdown products with body proteins. Thus penicillins act as haptens and the modified proteins as antigens. The major hapten is the penicilloyl moiety, obtained by opening the beta-lactam ring, but the unaltered penicillin molecule as well as other breakdown products may also serve as haptens. Because the penicilloyl moiety is common to all penicillins and indeed to all beta-lactams, there is considerable incidence of cross-sensitization. This means

that a patient who has aquired penicillin allergy after treatment with one particular penicillin preparation may be allergic to all penicillins and, furthermore, to other beta-lactams. There is, indeed, some 20% incidence of cross-allergy between penicillins and cephalosporins.

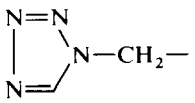
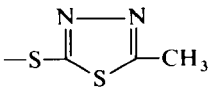
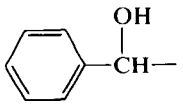
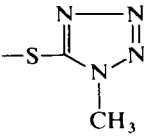
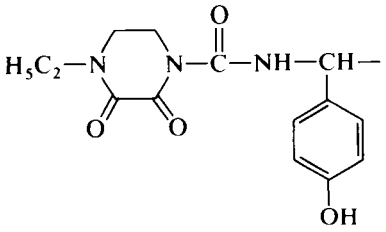
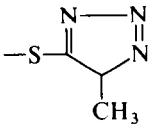
Skin tests have been used to determine and predict penicillin allergy[139] but with limited success. Although such tests may capture a large percentage of sensitive individuals, they are notorious for significant incidence of both false-positive and false-negative tests. Moreover, skin tests may occasionally present a hazard to sensitive individuals, who might develop an immediate hypersensitivity reaction to even the minute amount of antigen used for the test.

B. Cephalosporins[140–142]

Structually, the cephalosporins contain a beta-lactam ring attached to a six-membered dihydrothiazine ring. The first cephalosporins were isolated from the marine fungus *Cephalosporium acremonium*. However, all of the clinically useful cephalosporins to date



7-Aminocephalosporanic acid

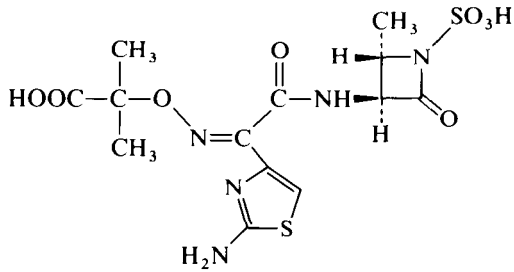
	R^1		R^2
First generation		Cephazolin	
Second generation		Cephamandole	
Third generation		Cefoperazone	

Some representative cephalosporins

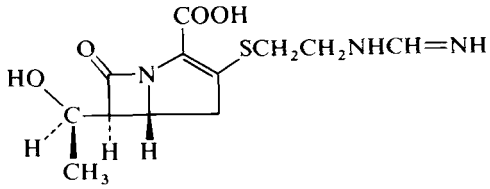
are semisynthetic compounds. Their mechanism of action is essentially similar to that of penicillins. As a group they are more resistant to beta-lactamases than are penicillins, although this property differs among different members of the group and depends on the bacterial source of the beta-lactamase. Cephalosporins have been categorized into 'generations': first, second and third. The definitions of antibiotic spectrum of each generation are not clear-cut, but some generalization can be made. All act against both gram-positive and gram-negative organisms, but their spectrum of activity against the latter broadens, going from first to second to third generation. Also, there is a tendency for increased resistance to beta-lactamase in the higher generations.

C. Monobactams[143-145] and Carbapenems[146,147]

Monobactams retain the beta-lactam ring but, as the name implies, are monocyclic. The only member of this group that is currently available for clinical use, aztreonam, exhibits a spectrum of antibacterial activity distinct from that of other beta-lactams: it acts only on gram-negative bacilli. It is also resistant to most beta-lactamases.



Aztreonam

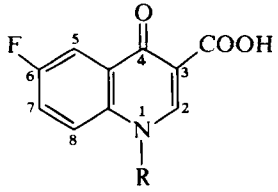


Imipenem

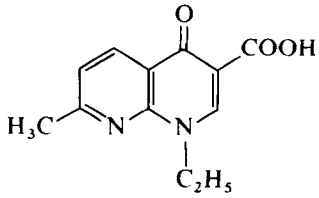
In carbapenems the beta-lactam ring is fused to a five-membered ring similar to that of the penicillins, except the sulfur is replaced with a carbon. In imipenem the side chain, in contrast with other beta-lactams, has a *trans* configuration which confers significant resistance to most bacterial beta-lactamases. Imipenem is considered to have the broadest spectrum of any antibiotic known. Its entire clinical usefulness has not yet been exploited.

IX. QUINOLONES

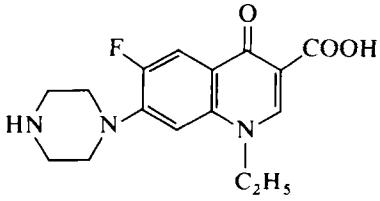
The quinolones are synthetic antibacterial agents. They are mostly 4-quinolones with a carboxyl in the 3 position and fluorine in position 6. The older prototype, nalidixic acid, lacked the fluorine and had very limited therapeutic utility. The newer fluoroquinolones,



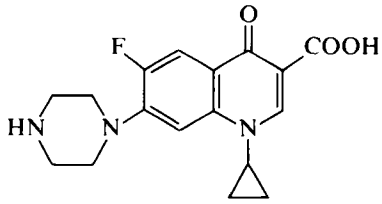
Fluoro-quinolone nucleus



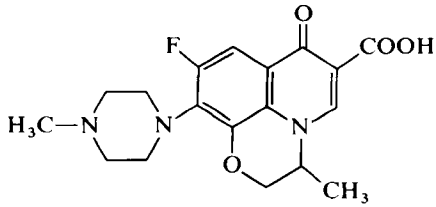
Nalidixic acid



Norfloxacin



Ciprofloxacin



Ofloxacin

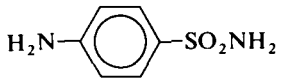
Some representative quinolones

however, are gaining increasing importance as broad spectrum antimicrobial agents for a variety of infections. Their unique mechanism of action involves inhibition of bacterial DNA gyrase, an enzyme not present in eukariotic cells[148]. The most common quinolones to date are norfloxacin, ciprofloxacin and ofloxacin and numerous additional congeners are emerging[149–151]. The various quinolones exhibit both different antimicrobial properties and diverse pharmacokinetic behavior.

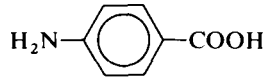
X. SULFONAMIDES

Sulfonamides are synthetic antimicrobial agents the mechanism of action of which is competitive inhibition of the incorporation of *p*-aminobenzoic acid into folic acid[152]. The latter, in its reduced form, tetrahydrofolate, is a coenzyme that is essential for one-carbon transfer reactions such as occur in the synthesis of purines, thymidine and certain amino acids. Because mammals do not synthesize folic acid but rather get it as a vitamin from their diets, sulfonamides show specific toxicity to microorganisms.

Numerous sulfonamides have been synthesized and many are of clinical utility. Substitutions are mainly made on the sulfonamide group, but some have also been made on the amino group. The resulting sulfonamides differ little in their antimicrobial activity. Differences are mainly in pharmacokinetic parameters and in solubility, which has a bearing on one of the typical side effects of sulfonamides, namely crystalluria (formation

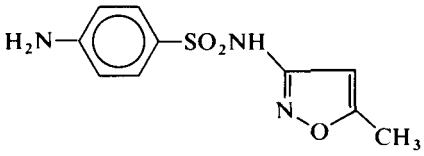


Sulfanilamide

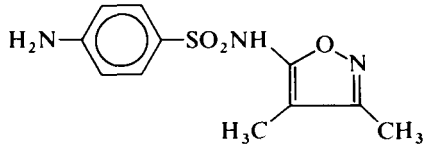


p-Aminobenzoic acid

of urinary crystals)[153]. The most widely used sulfonamides to date are sulfisoxazole and sulfamethoxazole (in combination with trimethoprim)[154].



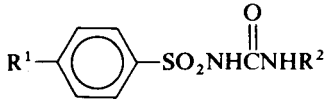
Sulfamethoxazole



Sulfisoxazole

XI. SULFONYLUREA HYPOGLYCEMIC DRUGS

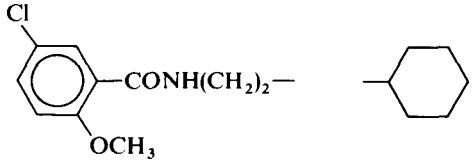
These drugs, used in the treatment of non-insulin-dependent diabetes, are related to the sulfonamides and were indeed developed from them. The important clinical observation that patients treated with high doses of sulfonamides for typhoid fever had decreased plasma glucose levels led to a search for new, related compounds, where this activity was more pronounced. Several of these compounds have been selected for clinical use and are the treatment of choice for non-insulin-dependent diabetes. Of the so-called first-generation agents the most important are tolbutamide and chlorpropamide. The



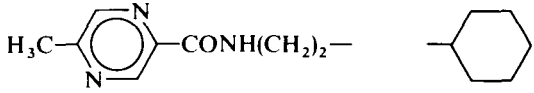
First generation	R^1	R^2
Tolbutamide	H_3C-	$-C_4H_9$
Chlorpropamide	Cl—	$-C_3H_7$

Second generation

Glyburide (Glibenclamide)



Glipizide



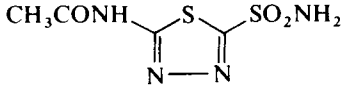
Representative sulfonylureas

most useful second-generation sulfonylureas are glibenclamide (glyburide) and glipizide. These latter drugs are not only much more potent but also display several advantages in terms of cardiovascular effects in diabetic patients[155–157]. The major mechanism of action of drugs in this group is stimulation of insulin release from the beta cells of the pancreas[158]. Therefore, functional beta cells are essential for the sulfonylureas to act.

XII. DIURETICS[159,160]

A. Carbonic Anhydrase Inhibitors[161]

These diuretics, exemplified by acetazolamide, are sulfonamide derivatives. They exhibit only a limited diuretic action, therefore their main current therapeutic use is not as diuretics but in the treatment of glaucoma. In the kidney, inhibition of the enzyme

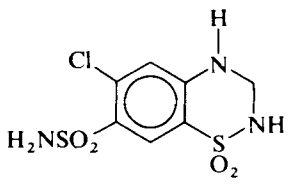


Acetazolamide

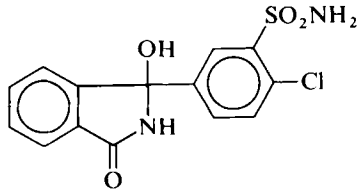
carbonic anhydrase decreases bicarbonate reabsorption, which is in turn accompanied by excretion of sodium and potassium ions and water[162, 163]. This diuresis produces major disturbances in acid–base balance and is self-limiting. Glaucoma is a disease state characterized by increased intraocular pressure. Formation of the aqueous humor in the eye also depends on the activity of carbonic anhydrase and can be decreased by acetazolamide[164].

B. Thiazide Diuretics

The first of this class of diuretics, chlorothiazide, was synthesized as part of a program to improve carbonic anhydrase inhibitors. It turned out that this and subsequent congeners, termed benzothiadiazides or thiazides for short, are better diuretics than the carbonic anhydrase inhibitors and act through a different mechanism, namely inhibition



Chlorothiazide



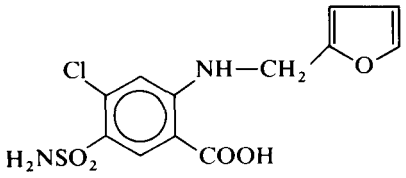
Chlorthalidone

of electroneutral $Na^+ + Cl^-$ transport[165]. They exhibit higher efficacy and fewer side effects. They are therefore used for the treatment of congestive heart failure and edema of other causes and of hypertension. Other nonthiazide compounds, such as chlorthalidone, act via a similar mechanism.

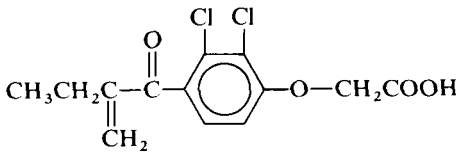
C. High Ceiling Diuretics

This category includes two chemically unrelated groups of compounds, probably sharing a common mechanism. Furosemide and bumetanide retain the sulfamyl group

and are therefore related to the thiazides while ethacrynic acid has a different structure. Both groups act on the ascending limb of the loop of Henle, hence their additional name, loop diuretics[166,167]. They are the most efficacious of all diuretics and exhibit



Furosemide

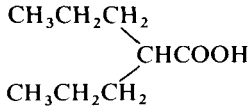


Ethacrynic acid

few adverse reactions, most of which are related to excessive diuretic action, i.e. water and electrolyte imbalance[168,169].

XIII. VALPROATE AND ANALOGS

The antiepileptic properties of valproic acid (2-propylpentanoic acid) were discovered serendipitously when this compound was used as a solvent for lipophilic antiepileptic drugs. It is now accepted that valproic acid and sodium valproate are effective antiepileptic agents in their own right. They equal carbamazepine and diphenylhydantoin (phenytoin), the leading therapy for treatment of tonic–clonic convulsions. Moreover, valproate is the drug of choice for treatment of petit mal and tonic–clonic convulsions in children and is also used in infantile spasms.



Valproic acid

A. Mechanism of Action

The precise mechanism of antiepileptic action of valproate and its analogs is not completely understood. However, there is evidence for the involvement of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and other endogenous amino acids in the antiepileptic activity of these drugs. *In vitro* valproate and its analogs inhibit the metabolism of GABA in the brain and thus cause accumulation of GABA. Valproate and most of its active analogs have also been shown to elevate brain concentrations of GABA in mice, although this elevation was of a relatively small magnitude (30%). However, 2-ethylbutyric acid, which also has considerable antiepileptic activity, is an exception in not causing any elevation of GABA[170–172]. Other antiepileptic drugs, namely phenobarbital and various benzodiazepines, may also exert their antiepileptic activity by modulation of the brain GABA system.

Good correlations between the antiepileptic activity of valproate analogs and the ability to reduce aspartic acid levels were also shown[170]. Aspartic acid is an excitatory amino acid, therefore reduction of its brain levels may conceivably mediate the antiepileptic activity of this group of drugs[173]. More recently the antiepileptic activity of valproate was linked to reduction in brain levels of gamma hydroxybutyric acid, which is considered an endogenous modulator of convulsant activity in the central nervous system[174].

B. Disposition of Valproate

Valproate is well absorbed when administered orally. The rate, but not the extent of absorption, is slowed by food. In humans valproate is highly bound to plasma proteins. It is completely metabolized and the metabolites are mainly excreted in the urine. In rodents, an appreciable fraction of valproate and metabolites is excreted in the bile[175]. Also, valproate and its analogs are choleretic agents in rodents[176].

The major metabolic pathway of valproate is formation of acyl glucuronide. However, about 50 additional metabolites, the products of several oxidative pathways, have been suggested[177]. The major metabolic pathways and primary metabolites are depicted in Scheme 2 (Section V.C). These primary metabolites are further metabolized to the final breakdown products, mainly dicarboxylic and keto-acids. Analogs of valproate are detoxified quantitatively by the same metabolic pathways. As mentioned earlier glucuronides, like many other organic acids, are eliminated by renal excretion.

C. Drug Interactions with Valproate

Valproate, in contrast to most other antiepileptic drugs, inhibits the activity of the major enzyme involved in drug metabolism, cytochrome P450. Thus when given concomitantly with other antiepileptic drugs like phenobarbital, valproate may cause elevation of their plasma concentration[178]. On the other hand, because the major antiepileptic drugs phenytoin and phenobarbital are inducers of cytochrome P450, concomitant administration of these drugs with valproate may give rise to faster disposition of the latter. Valproate can also cause displacement of other drugs from their albumin binding sites, thus producing elevation of their plasma levels, as shown for phenytoin[179] and other antiepileptic drugs[180]. Valproate itself may be displaced by other drugs from its binding sites, resulting in elevated plasma levels of free valproate. This, however, may be offset by faster hepatic detoxification of valproate[18]. Valpromide, but not valproic acid, was shown to inhibit the enzymatic hydration of the antiepileptic drug metabolite carbamazepine epoxide to carbamazepine *trans* dihydrodiol[182]. This inhibition can be of therapeutic importance, because carbamazepine epoxide is the major metabolite of carbamazepine and has antiepileptic potency similar to that of carbamazepine itself. Other interactions of valproate have been documented, such as the interaction of valproate with chlorpromazine or amitriptyline, but these are probably of minor therapeutic significance[180].

Like other antiepileptic drugs valproate has a narrow therapeutic index and numerous side effects. The most common of these include tremor, sedation, drowsiness, ataxia, appetite stimulation, and ankle swelling. One of the most severe side effects is hepatotoxicity, which may be fatal in approximately one out of 10000 cases. Valproate may be teratogenic in about 1% of exposed pregnant women, the major malformation being spina bifida[183].

D. Structure–Activity Relationship

1. Aliphatic acids

In order to improve the drug, detailed investigations have been initiated on the structure–antiepileptic activity relationship of normal and branched short-chain fatty acids as well as their related amides.

The following general conclusions relating to the structure–antiepileptic activity can be drawn from these studies (Table 1).

(a) The anticonvulsant activity of straight short-chain fatty acids (4–8 carbons) was very weak or even absent[172,184,185].

TABLE 1. Antiepileptic and teratogenic activity of valproic acid analogs

Acid	MES test[a]	Teratogenic activity[b]
Valproic acid	1	+
Butanoic acid	0	−
Octanoic acid	0	±
2-Ethylbutanoic acid	0.22	−
2-Butylhexanoic acid	1.6	ND[c]
2-Methyl-2-ethylpentanoic acid	2.7	+
3-Propylhexanoic acid	3.7	+
Cyclohexanoic acid	0.11	ND[c]
1-Methyl cyclohexanoic acid	0.88	ND[c]
Spiro[4,6]undecane-2-carboxylic acid	1	ND[c]
2-Propyl-4-pentenoic acid	0.87	+
2-propyl-2-pentenoic acid (*trans*)	0.87	−
2-propyl-2-pentenoic acid (*cis*)	0.56	−

[a] MES test: relative potency compared to valproic acid in maximal electroshock seizure test, data from References 172, 184, 185 and 188 190.
[b] Data from DiCarlo[187,188].
[c] ND denotes not determined.

(b) Branching at carbon 2 (α carbon to the carboxyl) of the fatty acid resulted in increased protection against electroshock, chemical convulsions (pentyltetrazol), or audiogenic convulsions[184,188].

(c) Analogs of valproic acid with side chains shorter than propyl had only weak activity[184].

(d) Analogs with side chains longer than propyl were more potent than valproate[172,184,185].

(e) Substances with additional branching of carbon 2 had increased activity[184].

(f) Derivatives of propionic acid with two side chains longer than propyl had activities comparable to or higher than valproate.

(g) Cyclic acids (5-, 6-, 7-membered rings) had very weak activity, if at all[184].

(h) Additional alkylation at carbon α to the carboxyl (1-methylcyclohexanoic acid) increased the activity very significantly[184].

(i) Spiro [4.6] undecane-2-carboxylic acid, an analog of cyclopentanoic acid, was as potent as valproate[189,190].

(j) Introducing unsaturation in the valproate molecule caused some reduction in antiepileptic activity, although most was still retained. It may be of interest that some of these analogs are *in vivo* metabolites of valproate[184].

All analogs of valproic acid tested had narrow therapeutic index and were as toxic as valproic acid itself. Keane and colleagues[172] showed that the antiepileptic activity of valproate analogs was directly related to their lipophilicity. Analogs that had antiepileptic activity comparable to or higher than valproate, as for example 2-butylhexanoic acid and 2-phenylpentanoic acid, had octanol-to-water partition coefficients higher than 550.

2. Aliphatic acid amides

Valpromide has also been used therapeutically as an anticonvulsant and is 5 times more potent than valproic acid in protection against maximal electroshock in mice[184]. Valnoctamide, an isomer of valpromide, is also used occasionally as anticonvulsant.

TABLE 2. Antiepileptic properties of primary amide analogs of valproic acid[a]

Amide	Hydrolysis	MES test[b]	PI[c]
2,2-Dipropyl acetamide (valpromide)	Complete	3.6	1.4
2-Ethyl-2-(1'-methylpropyl) acetamide (valnoctamide)	Partial	3.4	1.4
2-Ethyl-2-butyl acetamide	Partial	2.6	1.5
2-Methyl-2-pentyl acetamide	Complete	1.2	1.2
2-Propyl-2-isopropyl acetamide	None	3.4	1.7
2-Propyl-2-allyl acetamide	Complete	3.0	1.4
2,2-Diisopropyl acetamide	None	2.3	0.5
2,2-Diallyl acetamide	Complete	1.6	1.5
Octanamide	Complete	0	

[a] Data from Haj-Yehia and Bialer[185,186].
[b] MES test: relative potency compared to valproic acid in maximal electroshock seizure test.
[c] PI: protective index, the ratio between the median toxic dose TD50 and median effective dose ED50 in maximal electroshock seizure test.

These two drugs are different in their hydrolyzability *in vivo*. While valpromide is completely hydrolized to valproic acid and is considered a prodrug of the latter, valnoctamide is not hydrolyzed to an appreciable extent to valnoctic acid.

Studies of the structure–anticonvulsant activity and kinetic relationships of a series of isomers and analogs of valpromide have been undertaken[185,186]. It was found (Table 2) that, except for the amide of n-octanoic acid, all the amides investigated were more active than valproic acid in protecting mice against maximal electroshock. However, the toxicities of these analogs were also increased, thus leaving the therapeutic index as narrow as that of valproic acid. Most of the amides investigated were stable in blood and plasma and the major site of their hydrolysis in the dog was the liver. Exceptions to this rule were the normal chain amide octanamide and 2-methyl-2-pentyl acetamide, the least branched analogs of valpromide, which were hydrolyzed very quickly in various sites in the body, including blood plasma. In dogs, all amides were poorly extracted by the liver and did not have an appreciable first-pass effect. Valpromide, however, underwent rapid first-pass metabolism in humans[191]. Plasma protein binding of the amides in dogs was usually moderate, not exceeding 60%, as was also reported in humans for valpromide[191].

As mentioned, valnoctamide is hardly hydrolyzed *in vivo*. Other amides with branching at the β carbon, diisopropyl acetamide and propyl isopropyl acetamide were hydrolyzed to a very small extent. It was thus suggested that substitution at the β position prevents or substantially slows the rate and extent of hydrolysis. Substitution at carbon α as in the case of 2,2-dimethyl-2-butyl acetamide or at carbon γ as in 2-ethyl-2-isobutyl acetamide did not affect the rate of hydrolysis of these amides to the corresponding acids.

In addition to the antiepileptic activity common to all branched amides and acids, valpromide and valnoctamide have other pharmacological activities. Valpromide has antipsychotic activities, and is also used in the treatment of sleep disorders and neurosis[182]. Valnoctamide is used as anxiolytic in addition to its use in epilepsy. The different pharmacological profiles of the amides could arise from the fact that the amides are more lipophilic drugs and can better penetrate the blood–brain barrier. It is conceivable that, in the initial phase after its administration, valpromide may thus reach the central nervous system and exert its special activity as an amide. Because of its lipophilicity it may reside there for an appreciable length of time.

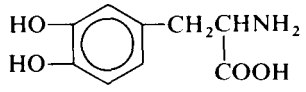
Large species differences in the pharmacokinetic behavior of valpromide in humans, dogs and rats have been observed. Thus clearance, half-life of elimination and the fraction of the amide hydrolyzed vary among these species. Because of these differences between species it could be that the antiepileptic activity measured in mice does not directly reflect the real activity in humans or in dogs.

XIV. AMINO ACID DRUGS

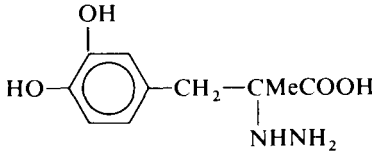
A. Levodopa and Related Drugs

Levodopa is used in the treatment of Parkinson's disease. Its use has been prompted by the realization in the 1950s and 1960s that the key defect in Parkinson's disease is dopamine deficiency in the brain basal ganglia[192]. Because direct dopamine replacement is not feasible, since it does not cross the blood–brain barrier, levodopa (L-dopa) was chosen as its precursor. Levodopa is physiologically decarboxylated in dopaminergic neurons to dopamine, the natural neurotransmitter of the basal ganglia. Unfortunately, rapid decarboxylation also occurs at peripheral sites such as the gut, liver and heart. Peripheral decarboxylation reduces the amount of levodopa that reaches its site of action in the brain and also produces unnecessary adverse reactions, mostly gestrointestinal and cardiovascular[193]. This problem has been solved by the addition to the therapeutic regimen of inhibitors of L-aromatic amino acid decarboxylase that do not cross the blood–brain barrier. Two such compounds, carbidopa and benserazide, in combination with smaller doses of levodopa provide the treatment of choice for Parkinson's disease[194,195]. The therapeutic dose of levodopa is thus reduced some 20-fold and many of the disturbing adverse reactions are spared.

Levodopa, being an amino acid, is transported across the membranes of the gastrointestinal epithelium and also into the brain by active transport processes (see Section II). As these are saturable processes, multiple interactions have been observed clinically with dietary amino acids. Careful dietary instructions have been used to circumvent these interactions.



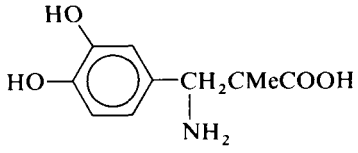
Levodopa



Carbidopa

B. Alpha Methyldopa

This agent is used in the treatment of hypertension[196]. Being an analog of the natural precursor of the neurotransmitter noradrenaline (norepinephrine), methyldopa gets access into central adrenergic neurons and is converted by neuronal enzymes to methyl dopamine and then to methyl noradrenaline. It thus acts as a 'false transmitter', being

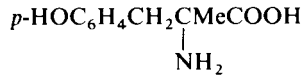


Methyldopa

released from adrenergic neurons and acting on the natural receptors. Because methyl-noradrenaline is a more potent agonist than noradrenaline itself on alpha-2 receptors in the brainstem, it acts as a feedback regulator, reducing overall sympathetic activity[197]. Consequently, blood pressure is reduced.

C. Metyrosine

Alpha-methyl-L-tyrosine, also called metyrosine, inhibits the first and rate-limiting enzyme that is involved in noradrenaline synthesis, tyrosine hydroxylase. It is thus capable of decreasing overall catecholamine synthesis in the sympathetic nervous system.

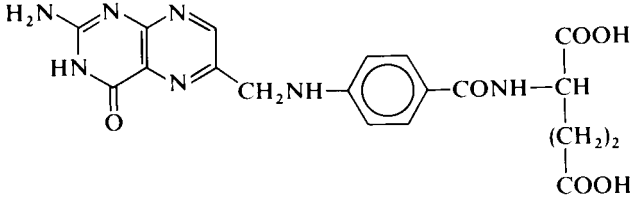


Metyrosine

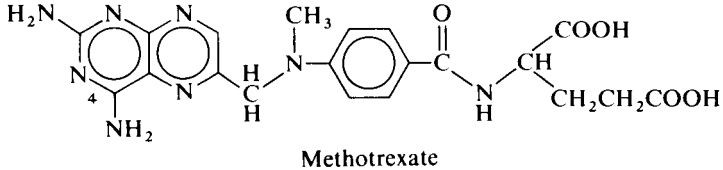
Because of serious adverse reactions, the use of metyrosine is mostly investigational and clinically it is restricted to the treatment of a specific catecholamine-producing tumor of the adrenal medulla, pheochromocytoma[198].

XV. ANTIFOLATES

Methotrexate and several newer analogs are very closely related to folic acid and therefore act as folate antagonists or antimetabolites. They bind to dihydrofolate reductase, competing with the natural substrate, folic acid. The latter must be reduced by this enzyme before it can fulfil its metabolic function as cofactor in the synthesis of purines, thymidine and the amino acids glycine and methionine[199,200]. This is the basis of methotrexate's action in certain kinds of cancer. As is true for other anticancer drugs,



Folic acid

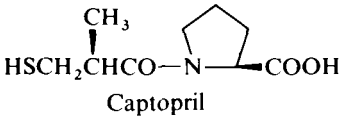


Methotrexate

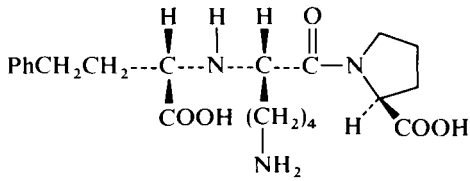
the specificity of such agents is limited and their use results in high incidence of alarming side effects. The systems most affected are the blood cell-forming elements, the gastro-intestinal tract and hair follicles, all characterized by high rates of cell division. Resistance to folate antagonists in a variety of cancer cells has led to a continued search for new analogs that would provide solutions to the resistance problem[201].

XVI. ACE INHIBITORS

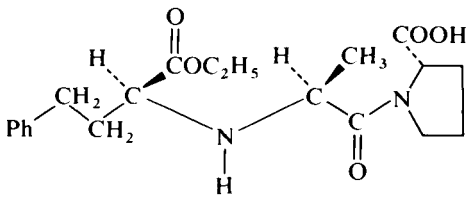
Angiotensin converting enzyme (ACE) inhibitors are a relatively recent but very worthwhile addition to the treatment of two common diseases: hypertension and congestive heart failure[202]. Angiotensin II is a hormone produced by a two-step reaction. The first involves cleavage by the enzyme renin of a substrate angiotensinogen to yield the decapeptide angiotensin I. The latter is then cleaved by ACE to yield the active octapeptide, angiotensin II. This hormone is a potent vasoconstrictor and also regulates electolyte and water balance through the synthesis of aldosterone by the adrenal cortex as well as by other mechanisms. ACE inhibitors are thus used in pathophysiologic situations where angiotensin II is thought to act excessively, namely in congestive heart failure and hypertension[203–205]. Because the active site of ACE contains a zinc ion that is important in the catalytic process, inhibitors that can bind to this zinc ion have been synthesized. They contain either a carboxyl, a sulfhydryl or a phosphoryl group as the zinc-binding ligand. The most widely used members of this group of drugs to date are captopril[206], lisinopril and enalapril[207]. The latter is a prodrug affording better bioavailability, and is hydrolyzed by serum esterases to a dicarboxylic acid, enalaprilate[208–210]. The clinical pharmacokinetics of ACE inhibitor were recently reviewed[211]. Numerous new ACE inhibitors are being currently tested clinically in many countries[212].



Captopril



Lisinopril



Enalapril

Some representative ACE inhibitors

XVII. HYPOLIPIDEMIC DRUGS

Plasma lipids are carried in the blood as complex lipoprotein molecules. They are partly derived from the diet and partly from *de novo* synthesis in the liver. Plasma levels depend on intake and production, on the one hand, and on utilization on the other. The latter depends mainly on low-density lipoprotein (LDL) receptors. The hyperlipidemias have been classified into several types, depending on the lipoprotein abnormality.These biochemical abnormalities constitute disease entities in themselves and also predispose patients to other risks, such as atherosclerosis with increased incidence of heart attacks.

Three major strategies have been used in the treatment of hyperlipidemias:

(a) Dietary modifications to lower fat and carbohydrate contents.

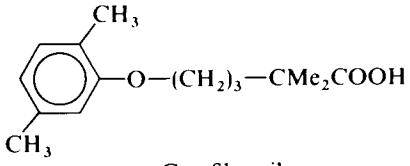
(b) Elimination of additional risk factors for cardiovascular disease by treatment of certain associated diseases or cessation of smoking that might aggravate the atherosclerotic process.

(c) Drug treatment of hyperlipidemias with one of four major groups of drugs. The first consists of resins such as cholestyramine and cholestipol that bind bile acids and therefore decrease the absorption of dietary fat. The other three groups of drugs are carboxylic acid derivatives, namely fibric acid derivatives, nicotinic acid and hydroxymethyl glutaryl (HMG) CoA reductase inhibitors.

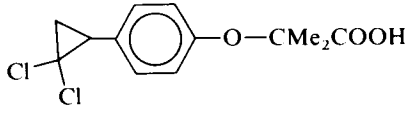
A. Fibric Acid Derivatives

This group consists of derivatives of aryloxyisobutyric acid. The first of these drugs that became useful for lowering blood levels of triglycerides and cholesterol was clofibrate, developed in the early sixties[213]. Additional derivatives followed, namely ciprofibrate, fenofibrate and bezafibrate and the fibric acid analog gemfibrozil. These drugs may lower plasma cholesterol and triglycerides by as much as 50% and 80%, respectively, in patients with familial type III hyperlipidemia[214]. The newer derivatives are more potent than clofibrate, therefore smaller doses than those of clofibrate are used. The mechanism by which fibric acid derivatives lower plasma cholesterol and triglyceride

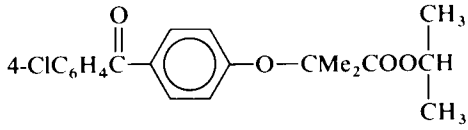
Clofibrate



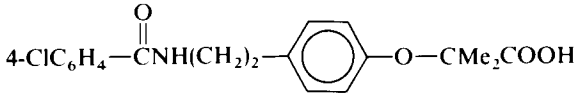
Gemfibrozil



Ciprofibrate



Fenofibrate



Bezafibrate

levels is thought to be increased activity of lipoprotein lipase, an enzyme that participates in the metabolism of very low density lipoprotein (VLDL) and LDL, although the precise mechanism is not yet understood[215]. Some of the fibrates are administered as esters which are hydrolyzed to yield the active free acids[216] (see Section VI). The fibric acid

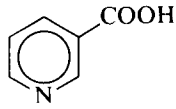
derivatives are well absorbed following oral administration and are excreted in the urine following glucuronidation to acyl glucuronides (see Section V.A).

Fibric acid derivatives may cause nausea and diarrhea in about 5% of patients and other side effects are encountered less frequently. Secondary to increased cholesterol concentration in the bile, the fibric acid derivatives may also augment the incidence of gallstones[217].

Fibric acid derivatives bind to a high extent to serum albumin, therefore drug–drug interactions due to binding displacement are not uncommon. Thus, cases in which clofibrate potentiated the activity of oral anticoagulants by displacing them from their plasma protein binding site have been reported[218].

B. Nicotinic Acid (Niacin)

Nicotinic acid along with nicotinamide are vitamins of the B complex. The hypolipidemic action of nicotinic acid was discovered in the fifties and it was determined to require high doses and be specific for the acid and not shared by the amide. Thus, the mechanism of this effect is unrelated to the vitamin action of the nicotinic acid. At



Nicotinic acid

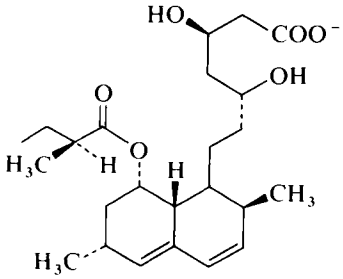
adequate doses nicotinic acid can lower plasma concentrations of triglycerides, the major constituent of VLDL[219], by as much as 80%. Cholesterol lowering activity is much smaller, about 15% reduction. The precise mechanism of action of this drug is not well understood.

The major side effects of nicotinic acid are gastrointestinal disturbances, palpitations and flushing. At high doses, liver function disorders may also occur.

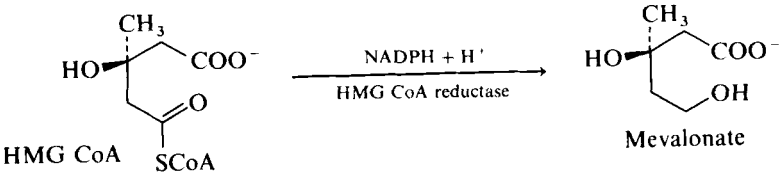
C. HMG CoA Reductase Inhibitors

This group of drugs is the newest addition to the antihyperlipidemic drugs. The first two drugs in this group, mevastatin and lovastatin, were isolated from fungus cultures[220]. Later semisynthetic analogs followed, of which pravastatin and simvastatin have been more thoroughly studied.

Lovastatin, mevastatin and simvastatin contain a lactone group and are actually prodrugs. Following hydrolysis of the lactone, which occurs in the liver, the active species is obtained [221,222], and that derived from lovastatin is shown below:

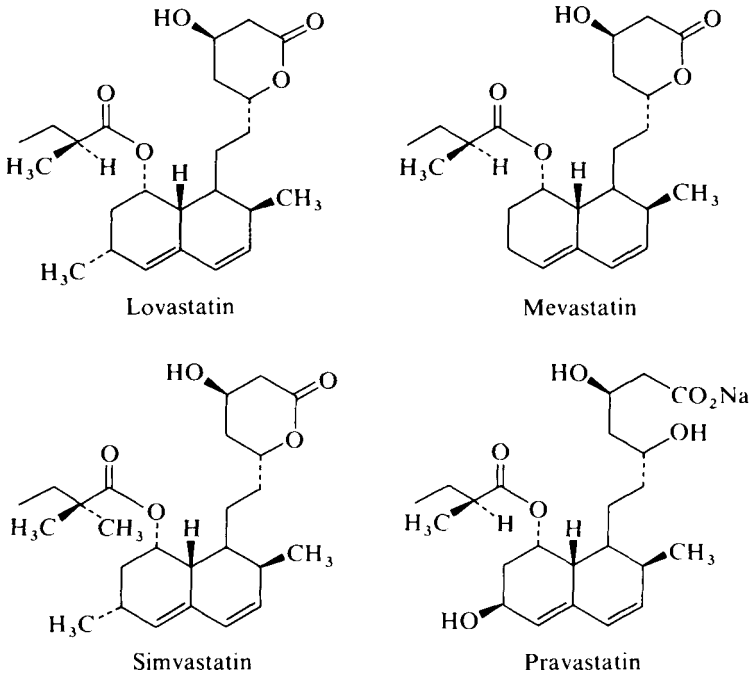


Lovastatin and other members of this group may lower cholesterol plasma levels by up to 40%[223]. These drugs were originally developed as inhibitors of the rate-limiting enzyme in cholesterol synthesis, hydroxymethyl glutaryl (HMG) CoA reductase, which catalyzes the step shown in equation 8. Because this is a rate-limiting step in cholesterol



(8)

biosynthesis, its inhibition is expected to decrease cholesterol levels. Studies in cell cultures showed, however, that following the application of these drugs, large amounts of new enzyme are synthesized which overcome the partial inhibition of HMG CoA reductase activity by the drug[224]. Thus, inhibition of HMG CoA reductase cannot account for the therapeutic effects of these drugs. It is currently believed that lovastatin and its congeners increase the hepatic clearance of LDL rich in cholesterol by increasing the number of hepatic LDL receptors[225,226].



Some HMG CoA reductase inhibitors

The drugs in this group are usually well tolerated and their side effects are generally mild. The most frequent side effects are gastrointestinal disturbances. Other adverse reactions include asymptomatic biochemical abnormalities and, more rarely, jaundice and myopathy.

XVIII. ACKNOWLEDGMENT

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CHAPTER **20**

Photochemistry of esters, lactones and their thio analogues

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Please note that in this chapter the numbering of the references starts from 1 in each main section, and the corresponding references are located immediately after these main sections (and not, as is usual, at the end of the chapter).

Similarly, the numbering of figures, structures, schemes and tables starts from 1 in each main section.

Esters and lactones, as ketones and cyclic ketones, constitute one of the most common classes of molecules in organic chemistry. Study of the photochemistry of saturated esters and lactones, however, has been considerably less common than that of the ketones and cyclic ketones. This lack of research activity has apparently been due to the characteristics of the ester chromophore, which exhibits only very weak absorption ($\varepsilon \sim 100$) in a region around 215 nm, where most of the commonly used mercury-vapour arc lamps exhibit very weak emission and where most of the quenchers show strong absorption. Moreover, the ester group exhibits neither fluorescence nor phosphorescence. Thus, carboxylic acid esters are common products arising from photochemical α-cleavage of cycloalkanones in alcohol as a solvent, and are unreactive under standard photolytic conditions. The direct photochemical reactions of simple saturated esters and lactones, which were adequately reviewed by Givens and Levi[5] in this series, have therefore seldom been exploited in synthetic organic chemistry.

There have, however, been significant new developments in the photochemistry of these classes of compounds since 1978, particularly in the photochemistry of conjugated esters and lactones where the transformation of molecules having an —O—CO group takes place mainly at the conjugated chromophore. These reactions have been utilized for certain synthetic problems and have considerable potential in future syntheses. Moreover, new developments concerning the photoreactions of phosphate esters were proven to be useful in synthesis.

I. ESTERS

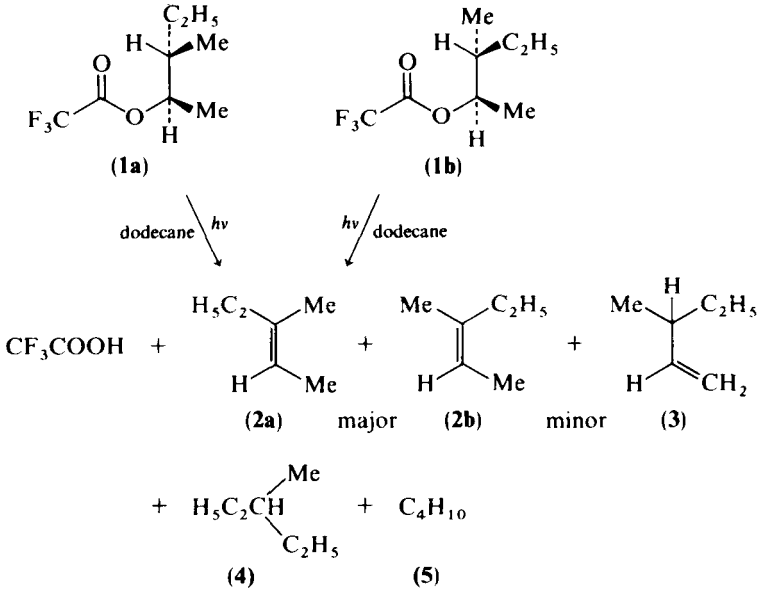
A. Carboxylic Acid Esters

1. Esters of aliphatic alcohols

The photoelimination of relatively simple esters of aliphatic alcohols in solution has been studied by Gano[1], Saunders[2], Eadon[3] and their colleagues since Ausloos' classical studies[4] on the photoelimination of esters in the 1960s. Studies concerning the stereochemistry of type-II elimination from some cyclohexyl phenyl acetates and their deuterium-labelled derivatives by Saunders[2] as well as Eadon[3] have already been reviewed by Givens and Levi[5] in this series.

Subsequent to these studies, type-II elimination has been studied in some detail by Gano and colleagues using racemic (*R,S*; *S,R*)- and (*R,R*; *S,S*)-1,2-dimethylbutyl trifluoroacetates **1** and **2**. They also compared this elimination with that of similar ketones. Thus, a solution of **1a** or **1b** was irradiated with an unfiltered medium-pressure mercury-arc lamp in order to form the anticipated alkenes **2a** and **2b** (major), alkene **3**, alkanes **4** and **5** (minor), as outlined in Scheme 1.

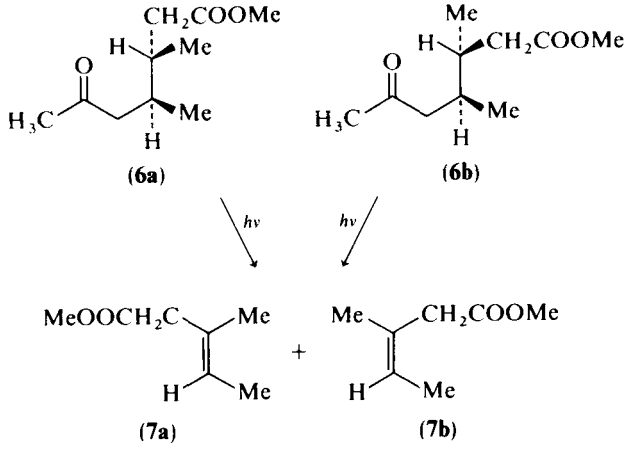
A similar photolysis of stereoisomeric ketones **6a** and **6b** gave olefins **7a** and **7b** arising from type-II eliminations (Scheme 2).



SCHEME 1

Quenching experiments (1-dodecene) gave the triplet excited-state lifetimes (0.4 and 2.1 ns) for **1a** and **1b**. The regioselectivities and stereospecificities in photoelimination reactions of **1a**, **1b**, **6a** and **6b**, obtained by Gano and colleagues, are summarized in Table 1. These results have indicated that the type-II photoelimination reaction is markedly similar to an analogous reaction in ketones.

The regioselectivity of type-II photoelimination in 1-decalylphenyl acetates **8a** and **8b** (see Scheme 3) was investigated by Eadon and colleagues[3b] in order to compare it with the behaviour of electron-impact-induced fragmentation. An inspection of Dreiding



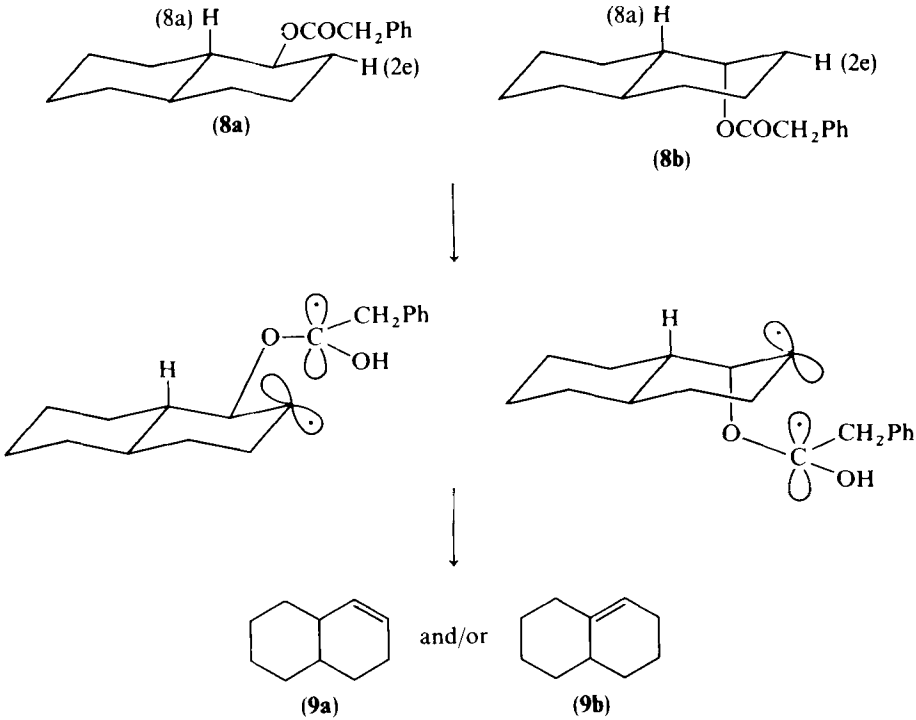
SCHEME 2

TABLE 1

Ester ketone	Product	Regioselectivty		Stereoselectivity	
		singlet	triplet	singlet	triplet
1a	**2a** + **2b**	7.38	6.6	0.88	0.56
	3a	7.38	6.6		
6a	**7a** + **7b**		>50	1.03	0.62
1a	**2a** + **2b**	4.32	3.5	0.74	0.02
	3	4.39	3.5		
6b	**7a** + **7b**	>50	>50	1.02	0.53

models of acetate **8a** has indicated that the C-2 equatorial hydrogen is accessible to the carbonyl oxygen in the chair conformer. However, this same hydrogen is either far beyond the requisite 1.8 Å O—H internuclear distance required for hydrogen abstraction, or less accessible to the carbonyl oxygen than the axial hydrogens at C-2 or C-8a in any boat conformer. Therefore, a determination of the stereochemistry of hydrogen abstraction from C-2 or C-8a should offer direct proof of the conformation of the phenylacetate-bearing cyclohexyl ring in hydrogen abstraction.

Models of the phenylacetate **8b** have indicated that the C-2 equatorial hydrogen is the only hydrogen accessible for abstraction from the chair conformer, even though the

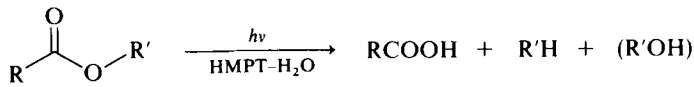


SCHEME 3

abstraction of the C-2 or C-8a axial hydrogen in some boatlike conformers could compete with abstraction of the C-2 equatorial hydrogen on the basis of the 1.8 Å criterion.

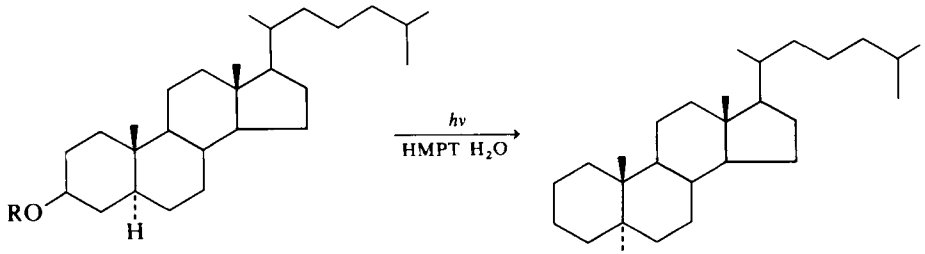
Photolysis of these phenylacetates **8a** and **8b** in hexane with 253.7 nm light resulted in an elimination of phenylacetic acid and formation of the corresponding alkenes, **9a** and **9b**, through a 6-membered-ring transition state (Scheme 3). They reported that the axial phenylacetates **8b** exhibit nearly complete abstraction of a C-2 hydrogen (C_{8a} abstraction/C_2 abstraction ratio of 0.01), as is observed in the mass spectrum of the acetate **8b** (C_{8a} abstraction/C_2 abstraction ratio of 0.08). Moreover, the equatorial phenylacetate **8a** undergoes photolysis with preferential C-2 hydrogen abstraction (C_{8a} abstraction/C-2 abstraction ratio of 0.37), while the acetate **8a** exhibits a similar preference in its electron-impact-induced fragmentation (C_{8a} abstraction/C-2 abstraction ratio of 0.38).

In addition, several synthetically useful photochemical transformations of saturated carboxylic acid esters have recently been reported. Pete and colleagues[6] have reported that alkanes were obtained in 52–79% yields by the irradiation of solutions of carboxylic acid esters in HMPT (hexamethylphosphonic triamide)–H_2O (95:5) with ultraviolet light (254 nm) (Scheme 4). This photochemical reduction seems to be quite general for carboxylic esters, since formates, acetates and benzoates were reported to give good yields of the corresponding alkanes.



SCHEME 4

In a typical example, the irradiation of 5α-cholestan-3β-yl acetate **10a** in HMPT–H_2O for 3 h gave 5α-cholestane **11** in 80% yield. A similar photolysis of formate **10b** and benzoate **10c** gave 5α-cholestane in 79 and 52% yields with the accompanying formation of 5α-cholestan-3-ol in 19 and 36% yields (Scheme 5).



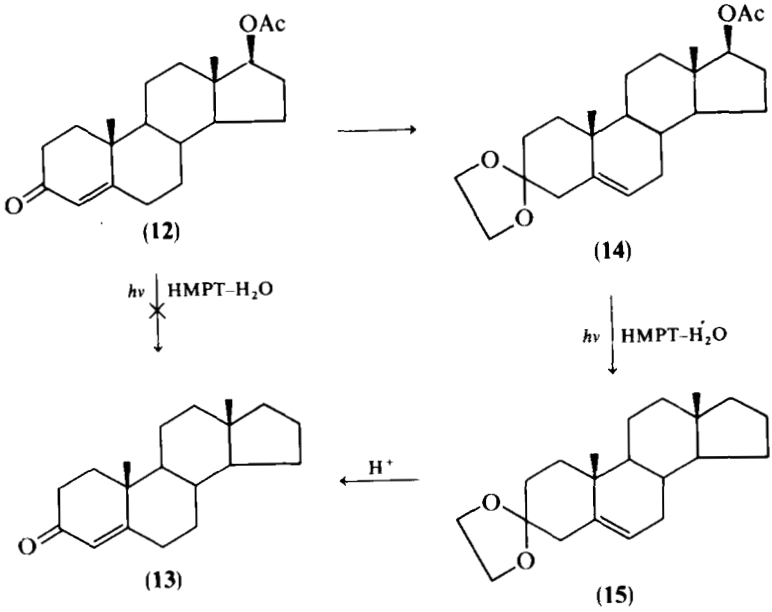
(10a) R = Ac
(10b) R = CHO
(10c) R = COC_6H_5

(11)

SCHEME 5

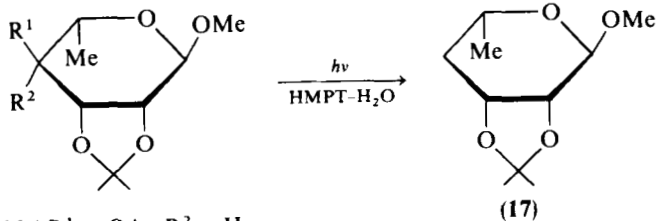
Esters derived from primary, secondary and tertiary alcohols, as well as from neopentyl alcohol, are reduced to the corresponding alkanes in good yields by this method; nonyl acetate, *cis*- and *trans*-1-acetoxy-4-*t*-butylcyclohexanes gave nonane and *t*-butylcyclohexane in 70% yield when a solution of these esters in HMPT–H_2O was irradiated for 4 h. Although the C—C double-bond, hydroxyl, ether, carboxyl and acetal

groups are not attacked by this procedure, a carbonyl group is reduced to a hydroxyl group and a carbon–halogen bond is cleaved to give a hydrocarbon under these conditions. One example is outlined in Scheme 6; although no clean reduction products can be obtained if testosterone acetate **1** in HMPT–H_2O is irradiated, androst-4-en-3-one **13** is obtained in 60% yield through the reduction of a protected testosterone acetate **14** to steroid **15** by this method.



SCHEME 6

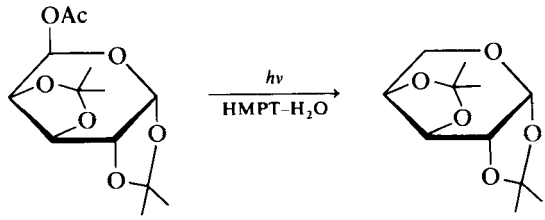
Application of this photochemical deoxygenation to sugar area has been published[7]; *irradiation of methyl 4-O-acetyl-6-deoxy-2,3-O-isopropylidene-α-L-mannopyranoside* **16a** in HMPT–H_2O with ultraviolet light for 60 h gave the corresponding 4,6-dideoxy derivative **17** in 70% yields. The same product was similarly obtained from the C-4 epimeric acetate **16b** (Scheme 7). Irradiation of carbohydrate **18** similarly gives a deoxy sugar **19**[8] (Scheme 8).



(**16a**) R^1 = OAc, R^2 = H
(**16b**) R^1 = H, R^2 = OAc

(**17**)

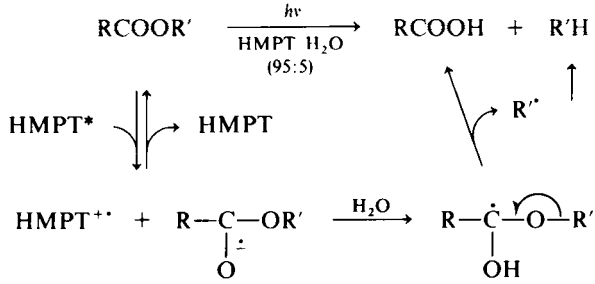
SCHEME 7



(18) (19)

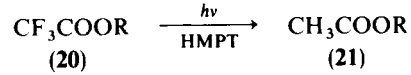
SCHEME 8

The photochemical reduction of carboxylic acid esters in HMPT–D_2O indicated that no deuterium is incorporated into the hydrocarbons[9,10]. The path of this deoxygenation, which involves an electron transfer from an excited HMPT molecule to the esters, proposed by Pete and colleagues[9,10] is outlined in Scheme 9: anion radical intermediates are generated by electron transfer from an excited HMPT to an ester function.



SCHEME 9

Protonation and β-scission of the resulting radicals give an alkyl radical which abstracts hydrogen from the solvent, thus furnishing the deoxygenated product. Using α-fluorocarboxylic acid esters **20** in dry HMPT defluorination takes place to give the carboxylic acid esters **21**[11] (Scheme 10). A pathway involving an electron transfer was proposed as outlined in Scheme 11.

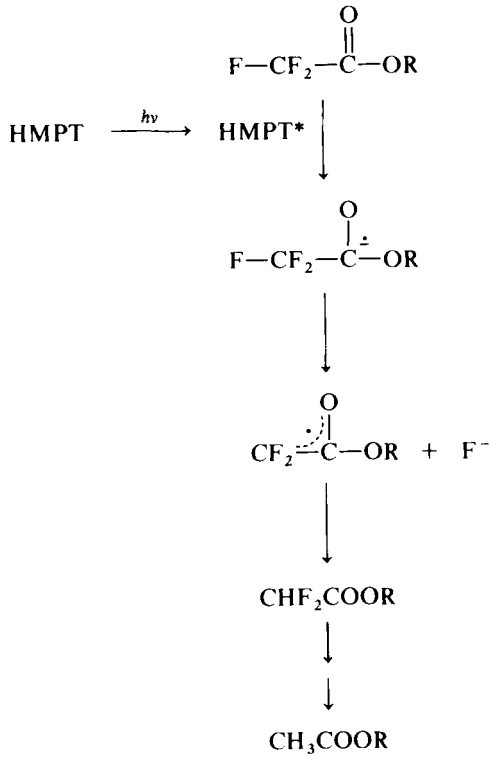


(20) (21)

SCHEME 10

Saito and colleagues[12] have reported that the irradiation of a 10:1 THF–water solution of *m*-(trifluoromethyl)benzoate **22a** and *N*-methylcarbazole (MCZ) through a Pyrex filter with a 100-W high-pressure Hg arc gave 1,3-diphenylpropane **23** in 91% yield, together with *m*-(trifluoromethyl)benzoic acid (95%) (Scheme 12). The irradiation of other esters, **22b** and **22c**, also gave **23**, though the yields were low.

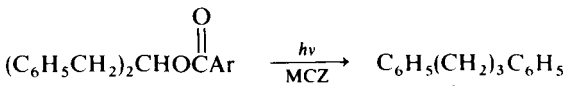
Irradiation of diester **24** and MCZ in 10:1 isopropyl alcohol–water led to selective deoxygenation of the ester of the tertiary alcohol moiety to give a 1:1 mixture of two primary alcohol benzoates, **25** and **26**, at a combined yield of 85% (Scheme 13). The results indicated that the aroyloxy group attached to the tertiary carbon is more readily deoxygenated under photosensitized irradiation.



SCHEME 11

Dideoxygenation of 1,2-diols can be readily achieved by this method. Thus, the irradiation of 2',3',5'-tri-*O*-[*m*-(trifluoromethyl)benzoyl]-adenosine **27** in the presence of MCZ in isopropyl alcohol–water gave 2',3'-dideoxyadenosine **28** in 73% yield. This result indicates that the aroyloxy groups attached to the secondary carbons are more readily deoxygenated by this method than is the aroyloxy group attached to the primary carbon (Scheme 14).

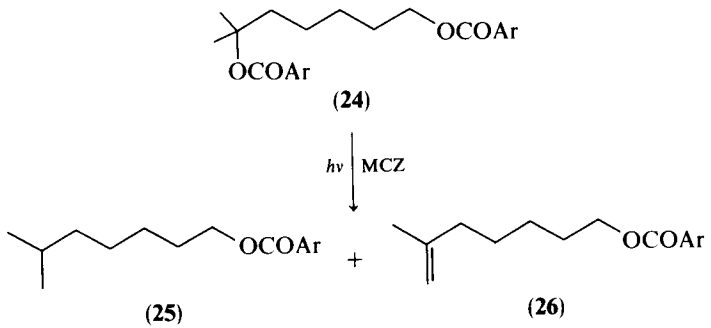
The free-energy change (ΔG) associated with the electron-transfer process obtained by the Rehm–Weller equation showed large negative values of ΔG, thus suggesting an electron transfer from singlet MCZ to the ester (e.g. **22**, Scheme 12). Saito and coworkers[12] proposed a pathway for this selective photosensitized deoxygenation of



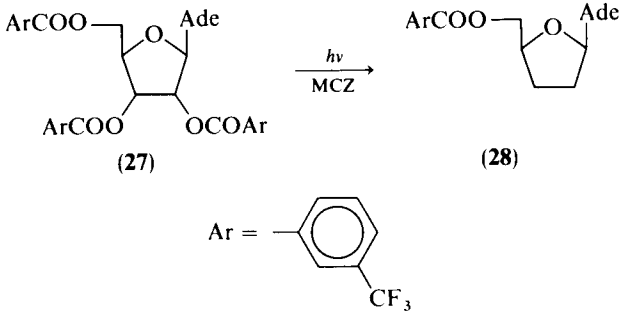
(22) **(23)**

(a) Ar = *m*-$CF_3C_6H_4$
(b) Ar = *p*-ClC_6H_4
(c) Ar = C_6H_5

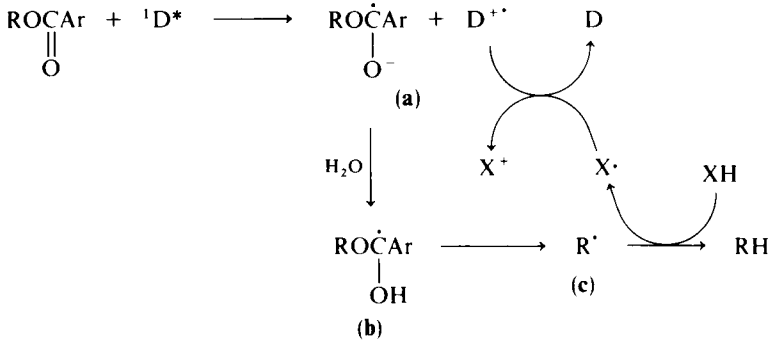
SCHEME 12



SCHEME 13



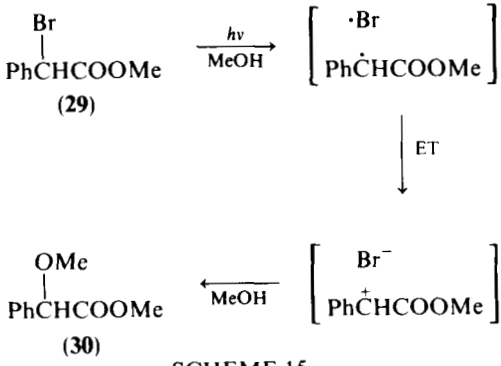
SCHEME 14



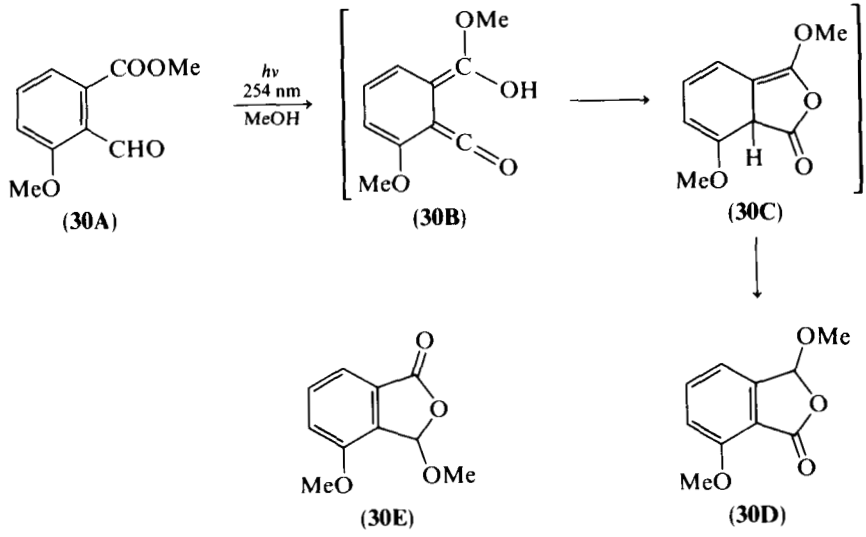
SCHEME 15

benzoates of secondary alcohols, as outlined in Scheme 15. Thus, electron transfer from a singlet MCZ as an electron donor to an aromatic ester generates the radical (**b**) via protonation of the primarily formed anion radical (**a**) in an aqueous solvent. The radical (**b**) generated from the esters of secondary or tertiary alcohols undergoes a β-scission to generate stabilized secondary or tertiary alkyl radicals which can abstract hydrogen from a solvent to give a deoxygenated product. This reaction may be useful for the selective deoxygenation of secondary hydroxyl groups under mild conditions.

As part of an investigation concerning the effect of the structure on the photoalcoholysis of aromatic α-haloketones, Izawa and colleagues have disclosed that the irradiation of α-bromophenyl acetate **29** resulted in a smooth photomethanolysis to give α-methoxyphenyl acetate **30** in 80% yield[13]. The mechanism for the formation of **30** is believed to involve an initial homolysis of C—Br, followed by an electron transfer (ET) from the carbon-centred radical to ·Br, resulting in the formation of a keto cation[14–16a], as outlined in Scheme 16.



SCHEME 15



SCHEME 16A

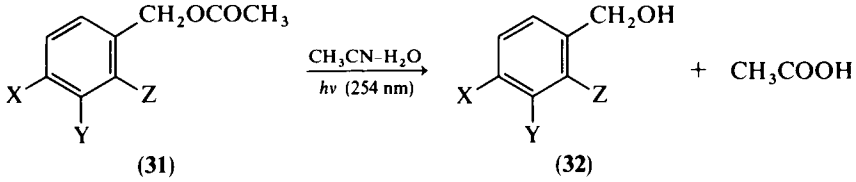
An efficient photochemical cyclization of phthalaldehydic esters to a phthalide has been reported. Thus, irradiation of a solution of an ester **30A** in methanol with 254 nm light under nitrogen gave a 6:1 mixture of **30D** and **30E** in a quantitative yield. Chromatography afforded the pure phthalide **30D** in 82% isolated yield (Scheme 16A)[16b].

A probable mechanism proposed by Jung and Blum[16b] involves the formation of a bisketene monohemiacetal **30B** by a photoenolization followed by internal trapping of the hydroxyl group by the ketone to give the lactone **30C**. Aromatization of the lactone **30C** gives the observed phthalide **30D** (Scheme 16A).

2. *Esters of benzyl alcohols*

The photosolvolysis of benzyl esters has been an area of much interest. The results of these investigations were reviewed by Cristol and Bindel[17].

One of the first substrates studied were the methoxy-substituted benzyl acetates; Zimmerman and Sandel[18] showed that a *m*-CH_3O substituent has a much better electron-donating effect than does the *p*-CH_3O substituent. This difference of reactivity was subsequently studied on a quantitative basis by Wan and coworkers[19]. The relative reactivity of the photosolvolysis of a number of substituted benzyl acetates **31** to the corresponding benzyl alcohols **32** was found to be in the order: *ortho* > *meta* > *para*; these substituent effects were apparently additive, as proven by the relative reactivity of the photomethanolysis of several dimethoxy-substituted benzyl acetates (Scheme 17).



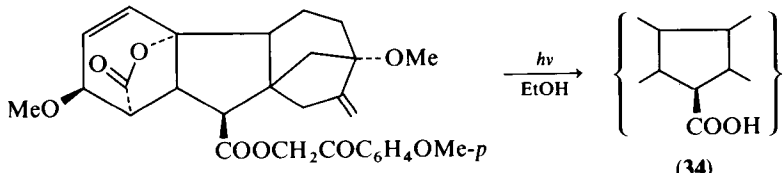
(31) **(32)**

X, Y, Z = Me, Cl, H, F

SCHEME 17

3. *Esters of phenacyl alcohols*

Phenacyl esters are photolabile. Serebryakov and colleagues[20] have recently reported that these can be used as a photolabile protecting group of the carboxyl function attached to a complex molecule. Thus, irradiation of *p*-methoxyphenacyl esters **33** of the gibberellin derivative in ethanol with ultraviolet light regenerated the corresponding carboxylic acid **34** in good yield (Scheme 18).

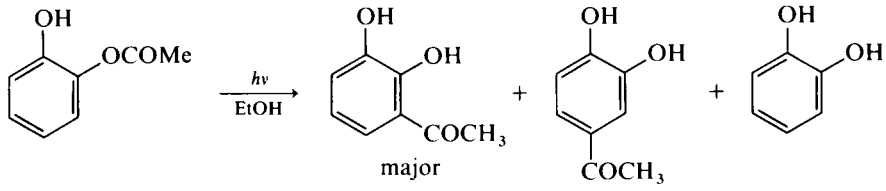


(33) **(34)**

SCHEME 18

4. *Esters of enols*

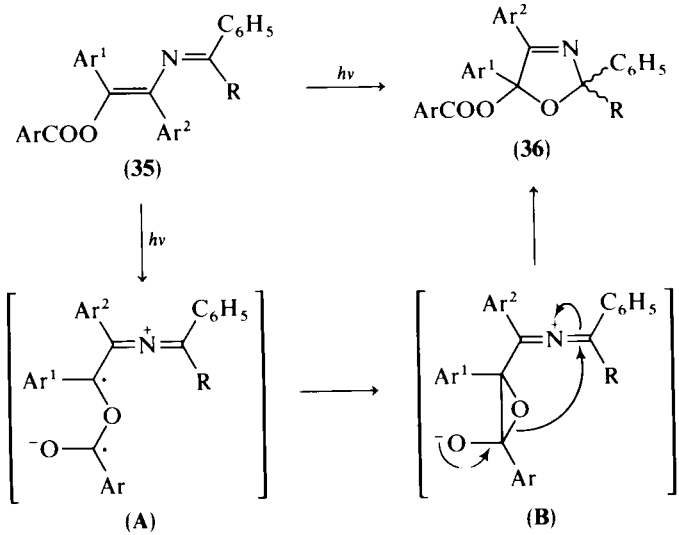
The photochemistry of enol esters has been known to be dominated by the [1,3]-acyl migration[21]. Some examples of the photorearrangements are outlined in Scheme 19. Thus, photo-Fries rearrangements of aryl esters[22] and photorearrangements of vinyl benzoates[23] gave predominantly products arising from [1,3]-acyl migration, as outlined in Scheme 19.



$$PhCOOCH{=}CH_2 \xrightarrow[EtOH]{h\nu} \underset{\text{major}}{PhCOCH_2CHO} + PhCOCH_3 + PhCOOH$$

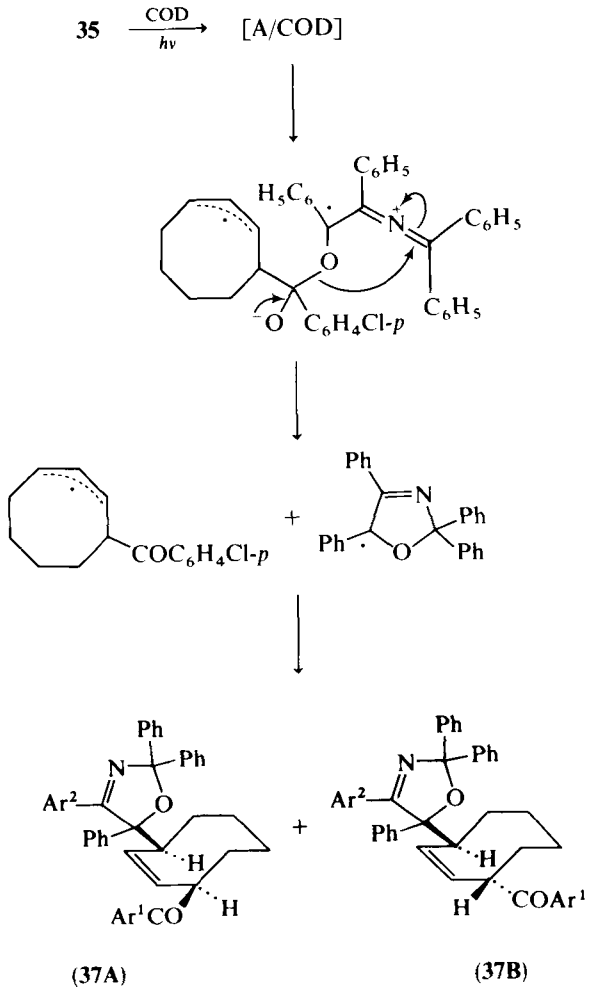
SCHEME 19

A novel [1,2] photorearrangement of enol esters, 4-acyloxy-2-azabuta-1,3-dienes, to dihydrooxazoles has been reported by Armesto and coworkers[24]. For example, 4-benzoyloxy-1,1,3,4-tetraphenyl-2-azabuta-1,3-diene **35** rearranges into 5-benzoyl-2,3,4,5-tetraphenyl-2,5-dihydrooxazole **36**. The authors propose that this rearrangement takes place via an oxa-di-π-methane-type process involving intermediates **A** and **B**, and cyclization to the observed products (Scheme 20).



R = C_6H_5, Ar = C_6H_5, Ar^1 = C_6H_5, Ar^2 = C_6H_4Cl-*p*

SCHEME 20



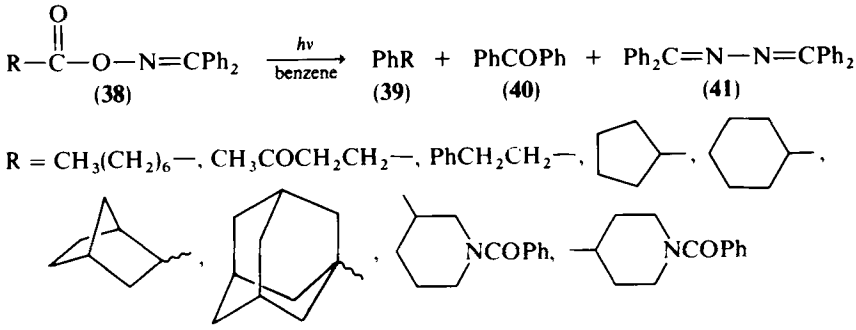
(37A) (37B)

SCHEME 21

A quenching study of this unprecedented photoreaction by an added diene, such as cycloocta-1,3-diene (COD), resulted in the formation of *cis*- and *trans*-isomers of 4-aryl-2,2,4-triphenyl-5(4'-aroyl-*cis*-cycloocta-2'-enyl)-2,5-dihydrooxazole derivatives, **37A** and **37B**[25] (Scheme 21).

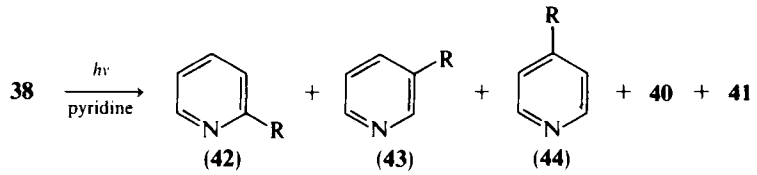
5. *Esters of oximes*

The photolysis of benzophenone oxime esters appears to be a good source of alkyl radicals by virtue of the ready homolysis of their O—N bond[26,27]. The irradiation of benzophenone oxime esters (**38**) in benzene or in pyridine with light of wavelength longer than 300 nm gave the corresponding alkylbenzenes (**39**) in 59–90% yields, together with benzophenone (**40**, 70–95%) and benzophenone azine (**41**, 5–22%), as outlined in Scheme

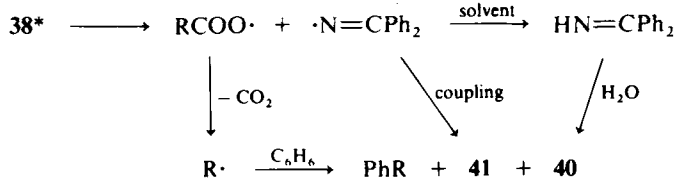


SCHEME 22

22[26]. A similar photolysis of benzophenone oxime esters (**38**) in pyridine gave a mixture of three isomers of alkylpyridines (**42–44**) in high combined yields (66–95%), together with **40** (75–90%) and **41**, (7–8%) (Scheme 23).



SCHEME 23

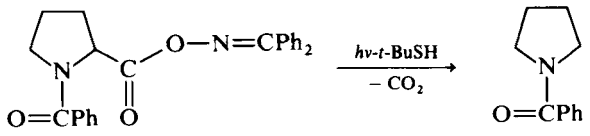


SCHEME 24

The pathway leading to alkylbenzenes or alkylpyridines is outlined in Scheme 24. Thus, the homolysis of the N—O bond of triplet excited oxime esters generates alkylcarboxylyl radicals which expel carbon dioxide to give alkyl radicals. The reaction of these radicals with the solvent benzene or pyridine gives the observed alkylbenzene or alkylpyridines.

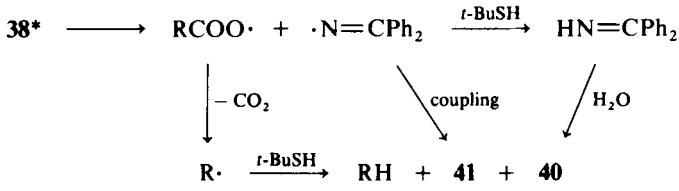
In an extension of this reaction, Hasebe and Tsuchiya[27] have reported that if the photolysis of benzophenone oxime esters is carried out in isopropanol containing a hydrogen donor, such as *t*-BuSH, the products derived from reductive decarboxylation of the parent carboxylic acids are formed in 73–98% yields.

The reductive decarboxylation of a variety of carboxylic acids including α-, β- and γ-amino acids can be achieved by this method. The amide **46**, for example, can be obtained by irradiation of the α-amino acid ester **45** in 88% yield, together with benzophenone, benzophenone azine and *t*-butyl disulphide, as outlined in Scheme 25. This method is useful, since the decarboxylation of β- and γ-amino acids is difficult.



(45) (46)

SCHEME 25

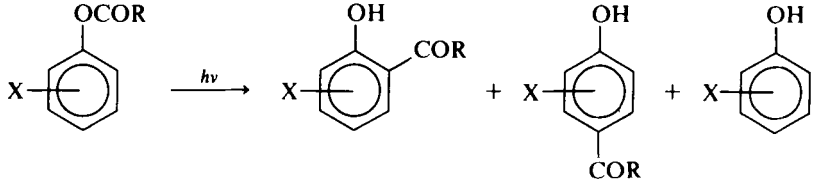


SCHEME 26

The authors also found that although primary, secondary and tertiary carboxylic acids can be readily decarboxylated by this method, decarboxylation of aromatic acids is difficult. The pathway of the reaction is outlined in Scheme 26.

6. *Aryl esters*

The principal photochemical reaction of aryl esters is the photo-Fries rearrangement[22], a photochemical conversion of aryl esters into α-aroylphenols (Scheme 27), which was much studied in the 1960s, and summarized in several review articles[28–31].

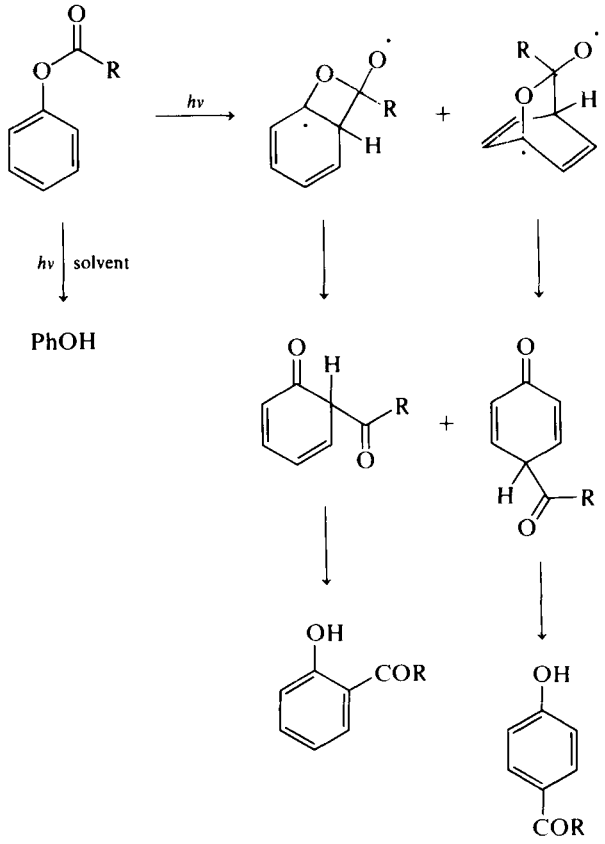


SCHEME 27

Two alternative mechanistic pathways have been proposed as outlined in Schemes 28 and 29. Thus, according to Scheme 28, the excited ester gives 2- and 4-acylcyclohexadienones by a concerted symmetry-allowed 1,3- or 1,5-sigmatropic shift. The acyl and phenoxy portions of the ester are bonded to each other throughout the rearrangement. The acylcyclohexadienones thus formed rapidly enolize to give the observed 2- and 4-hydroxyketones.

Phenols always accompany the photo-Fries rearrangement, and are considered to be produced through a separate, competing reaction with the solvent.

The mechanism outlined in Scheme 29 is a solvent-cage recombination mechanism; acyl and phenoxy radical pairs which are held in close proximity in the solvent cage are produced from the excited esters. The radical pairs either regenerate the starting ester, or undergo recombination of the acyl radical at either the 2 or 4 positions of the phenoxy radical to give acyl cyclohexadienones. Some of the phenoxy radicals escape from the



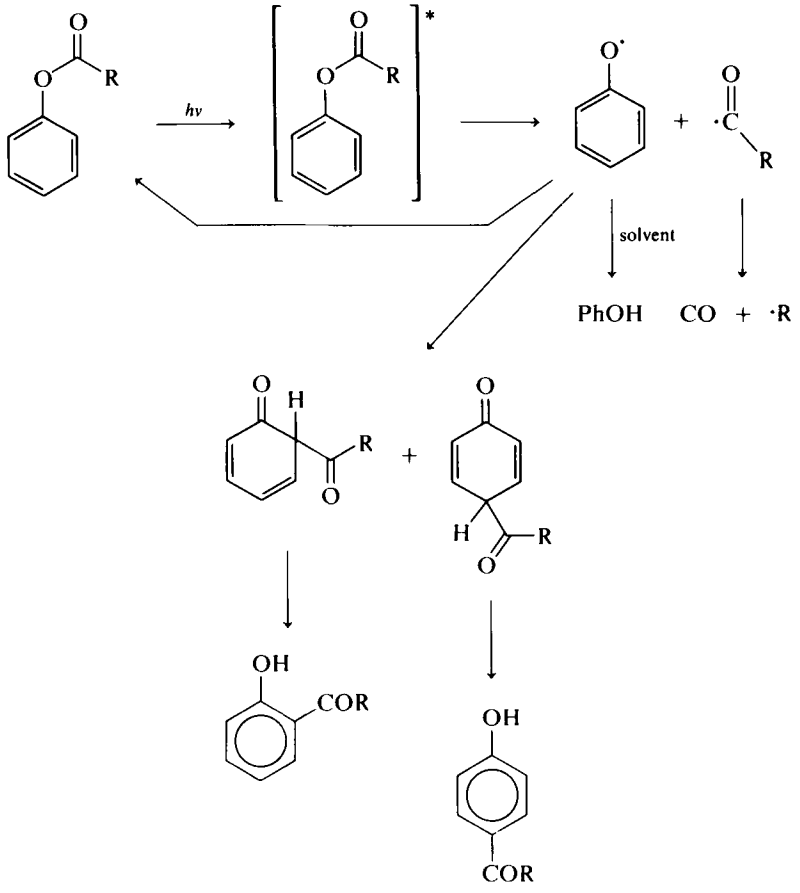
SCHEME 28

solvent cage and become kinetically free radicals furnishing phenols by hydrogen abstraction.

This mechanism differs from that outlined in Scheme 28, in that the hydroxyketones and the phenol are formed in closely related processes.

The photolysis of phenyl acetate in the vapour phase in a flow system with nitrogen used as a carrier gas and isobutane as a hydrogen donor has been investigated[31] in connection with the above-mentioned conflicting mechanisms of phenyl esters in solution. The products identified were phenol, *o*- and *p*-cresol, *o*- and *p*-hydroxydiphenyl ether and *p*-benzoquinone. All these products can be accounted for in terms of a free-radical mechanism. The authors[31] believe that these results are consistent with a common primary mechanism involving fragmentation to give free radicals both in the gas phase and in solution.

Only sporadic studies seem to have been carried out concerning the exploitation of this photorearrangement for synthesis. This was perhaps because the reaction usually gives poor yields of the hydroxyketones. However, there have been some investigations concerning the synthetic exploitation of this photorearrangement during the last two decades. For example, the photo-Fries rearrangement of esters of 1-naphthol and 5-methoxy-1-naphthol to the corresponding 1-hydroxy-2-acetylnaphthalenes were in-



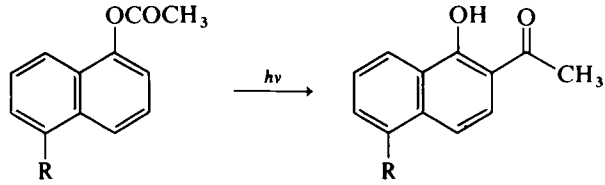
SCHEME 29

vestigated[32] in connection with the synthesis of analogues of the antibiotic daunomycinone (Scheme 30). Thus, the best yield (70%) of 1-hydroxy-5-methoxy-2-acetylnaphthalene **48** was obtained by the photolysis of 5-methoxy-1-naphthyl acetate **47** in ethyl acetate, while the yield of 1-hydroxy-2-acetylnaphthalene **50** was 40% in the photolysis of 1-naphthyl acetate **49** under similar conditions[32] (Scheme 30).

The photo-Fries rearrangement was used for the synthesis of some benzoxanthone derivatives[33,34] (Schemes 31–33) and 4-azaxanthone derivative (Scheme 34)[35].

Irradiation of the diacyloxynaphthalene derivative **51** in ethanol gave two products, **52** and **53**, arising from photo-Fries rearrangements in 19 and 27% yields. Treatment with a base (KOH–EtOH or Me_4NOH–pyridine) gave a linear benzoxanthone **54** and/or an angular isomer **55**. The photo-Fries rearrangement of the diacyloxynaphthalene derivative **56** under similar conditions gave a rearranged product **57** in 40% yield. The benzoxanthones, **54** and **55**, were used for the synthesis of bikaverin.

More recently, the photo-Fries rearrangement was applied to the syntheses of 9-acetyl-6,7α,9α,11-tetrahydroxy-12-oxoxantho[2,3-*g*]tetralin **62**, as outlined in Scheme

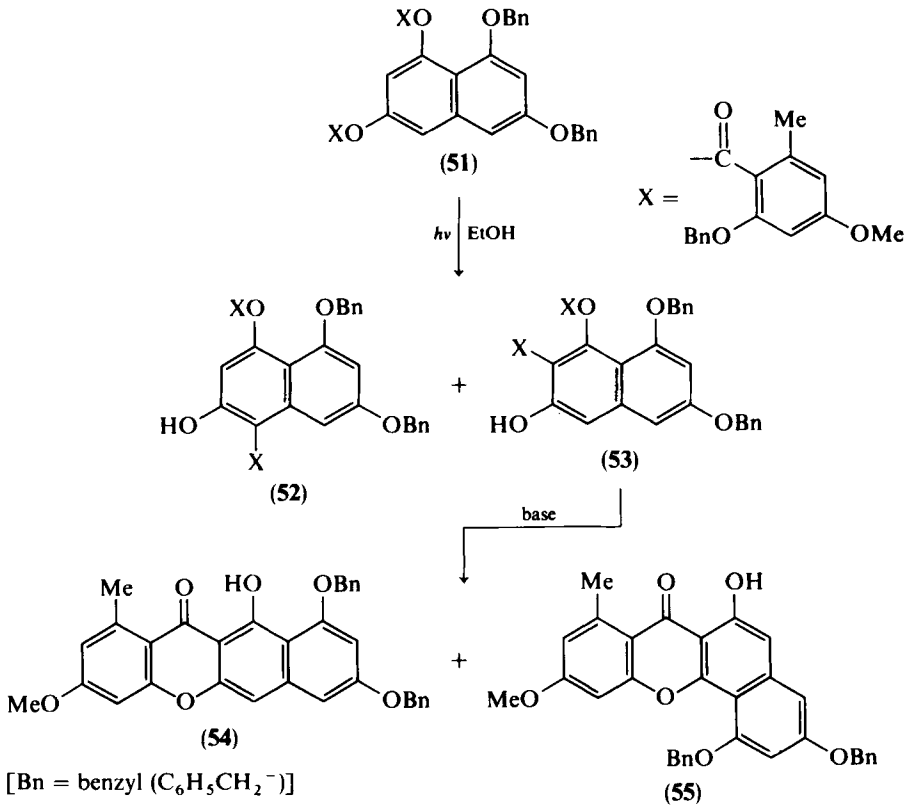


(47) R = OMe (48) R = OMe
(49) R = H (50) R = H

SCHEME 30

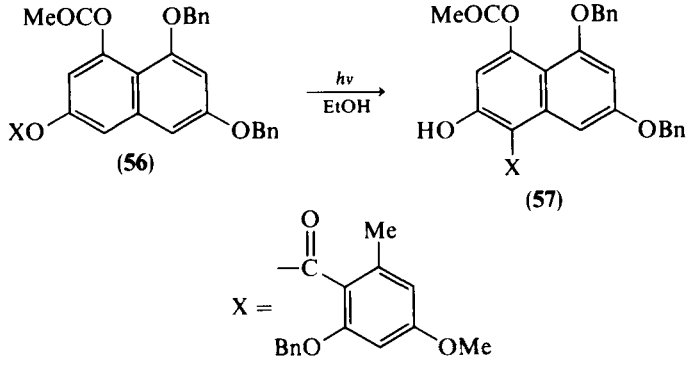
33[34]. Thus, **58** gave the rearranged product **59** (25%) together with **60** (5%) and **61** (36%), arising from coupling of the radicals produced upon photoextrusion of carbon dioxide, and from a regeneration of the phenol, respectively. The photo-Fries product **59** was then transformed into the xanthone derivative **62**, in 6 steps.

On the other hand, the irradiation of a benzene solution of the aryl-2-chloronicotinate **63** gave a photo-Fries product **64** and 4-azaxanthone **65**[35]. **64** also gave **65** upon either irradiation or heating[35]. Photo-Fries rearrangement of salicylonitrile benzoate **66** gave 3-cyano-4-hydroxybenzophenone **67** (12%) and 3-cyano-2-hydroxybenzophenone **68** (14%)[36] (Scheme 35).



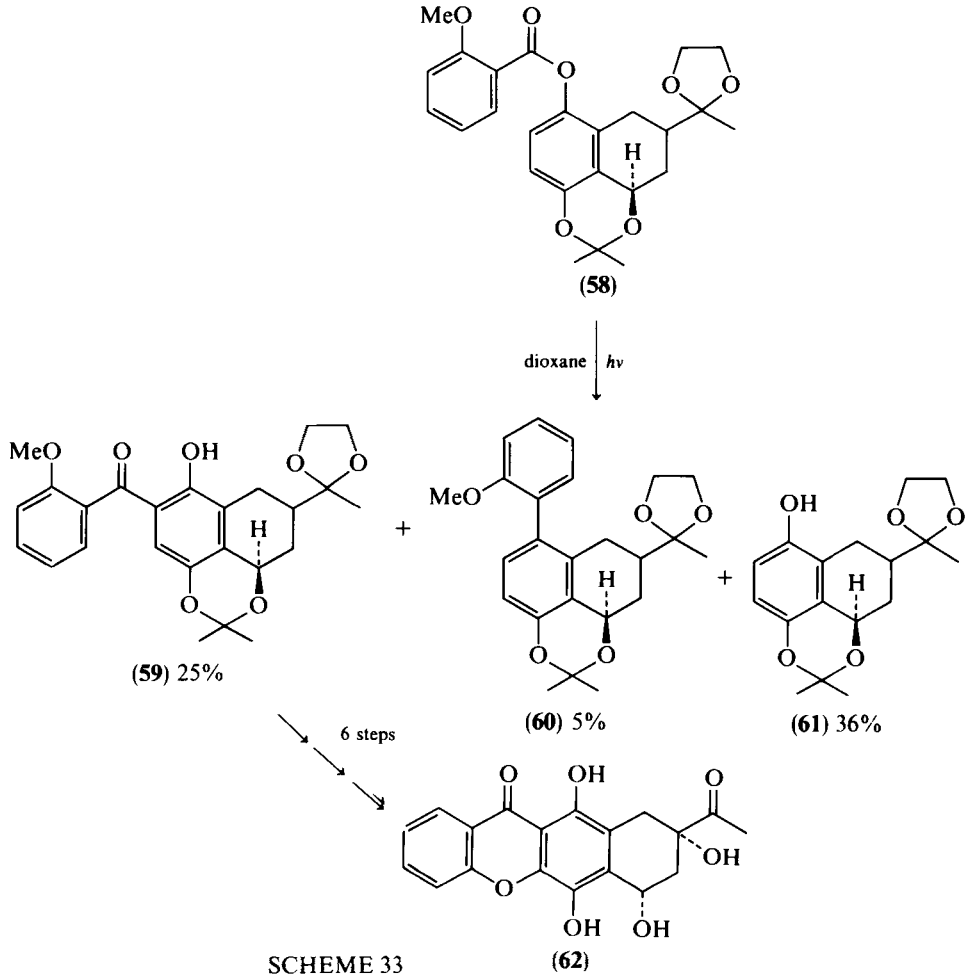
[Bn = benzyl ($C_6H_5CH_2^-$)]

SCHEME 31



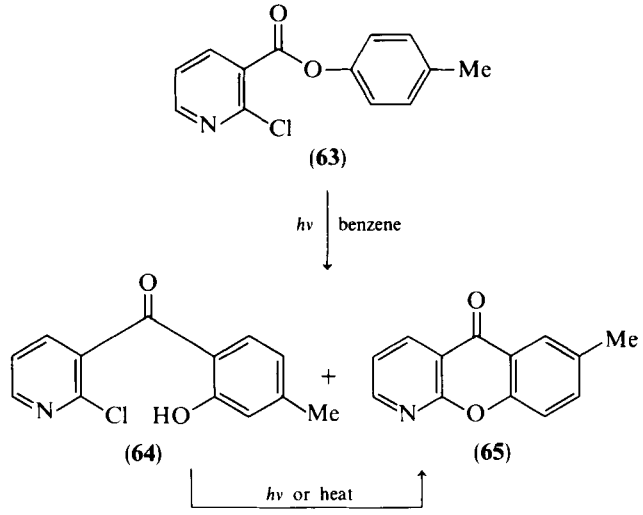
(56) (57)

SCHEME 32

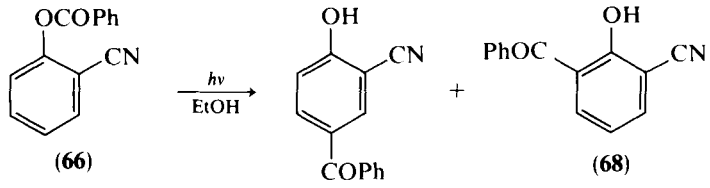


(58) (59) 25% (60) 5% (61) 36% (62)

SCHEME 33

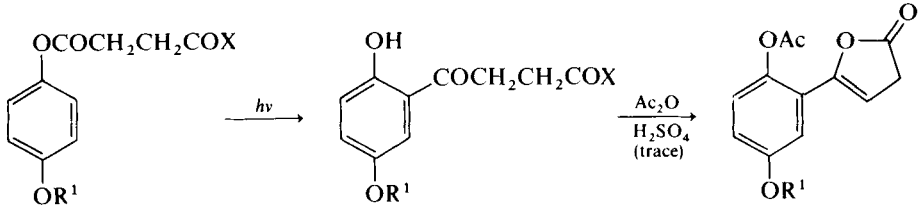


SCHEME 34



SCHEME 35

Photo-Fries rearrangements of hydroquinone succinates **69** gave the corresponding hydroxyketones **70** in 55–60% yields[37]. The treatment of **70** with acetic anhydride and a trace amount of sulphuric acid quantitatively afforded furanones **71** or **72**, as outlined in Scheme 36.



(69a) R^1 = Me, X = OH
(69b) R^1 = H, X = OH
(69c) R^1 = Me, X = OMe

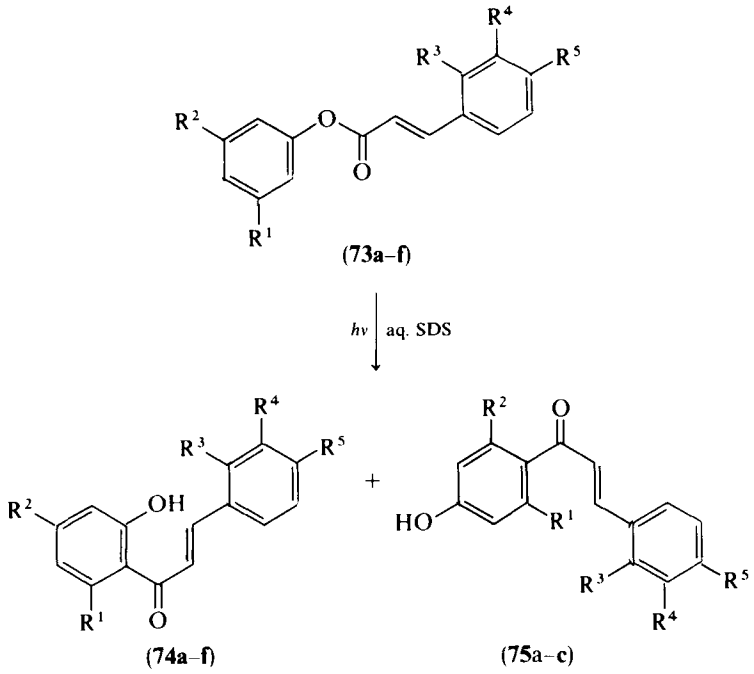
(70a) R^1 = Me, X = OH
(70b) R^1 = H, X = OH
(70c) R^1 = Me, X = OMe

(71) R^1 = Me
(72) R^1 = Ac

SCHEME 36

A study of the photo-Fries rearrangement in a micellar environment has recently been published by Singh and Raghuraman[38]. Reactions in a micellar environment may result in transformations of molecules with high efficiency and selectivity by virtue of the high local concentration, longer lifetime and reduced translational freedom of the reactive species generated in the micelles.

The photo-Fries rearrangement of phenyl cinnamates was used a long time ago for the synthesis of 2′-hydroxychalcones in 20–30% yield[39]. The reaction required long photolysis times with low conversions of the starting material, since the produced chalcones act as internal filters, as well as other factors. In contrast to this, Singh and Raghuraman[38] have found that the photolysis of phenyl cinnamates **73** in an aqueous SDS (sodium dodecyl sulphate) solution results in an efficient, clean, high-yield transformation into the corresponding 2′-hydroxychalcones **75** (Scheme 37).



(a) $R^1 = R^2 = R^3 = R^4 = R^5 = H$
(b) $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Me$
(c) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$
(d) $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = OH$
(e) $R^1 = R^2 = OH$, $R^3 = R^4 = R^5 = H$
(f) $R^1 = R^2 = OH$, $R^3 = H$, $R^4 = R^5 = OMe$

SCHEME 37

Thus, 10^{-4} M micellar solutions of the cinnamates **73** in a 10^{-2} M aqueous SDS solution on irradiation with 254 nm light for 5–8 h gave 2′-hydroxychalcones **74a–f** in 70–75% yields. While the photolysis of **73a–c** gave also 4′-hydroxychalcones as by-products in 15–20% yields, no isomers were formed on irradiation of the cinnamates

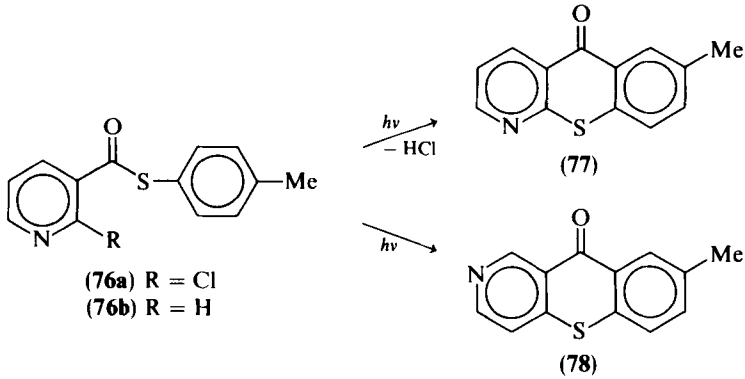
73d–f. There was no indication of any formation of phenols, which is also in contrast to the results of photo-Fries rearrangement in solution.

The high yield, selectivity and short duration of the photolysis can be attributed to the effects of the micelles which give protection of the excited state, since the molecules are located in the interface region with the aromatic group toward the hydrophobic core, with reduced translational freedom of the substrate.

7. S-Aryl esters

Photoreactions of a number of *S*-aryl esters of thionicotinic acids and thiophencarbothioic acids have been investigated by Praefcke and colleagues[40,41]. These reactions are of utility for preparing some molecules having a thiopyrone nucleus.

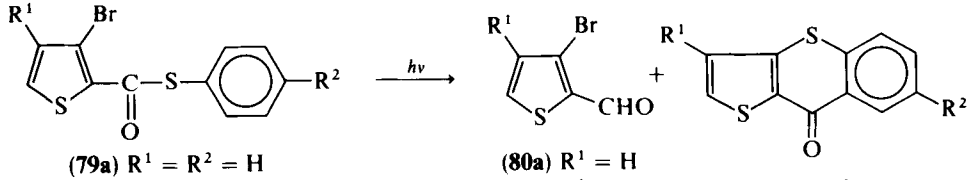
Thus, UV irradiation of the thionicotinic acid aryl ester **76a** gave the thiopyrone **77** arising from a photo-Fries-type rearrangement and cyclization (Scheme 38). Similar irradiation of the ester **76b** gave the thiopyrone **78**, in which the thio function underwent cyclization at the *para* position to the pyridine ring.



(**76a**) R = Cl
(**76b**) R = H

SCHEME 38

S-Aryl esters of thiophene-2-thiocarboxylic acids bearing a bromine atom at the 3-position, **79a–79c**, and those of thiophene-3-carbothioic acids **82a–82c** upon irradiation in benzene gave thiopyrones, although the yields were low and the major products were aldehydes arising from S—O fission (Schemes 39 and 40); the *S*-aryl ester **79a** gave thiopyrone (**81a**) exclusively in 8% yield, while the esters **79b** and **79c** gave thiopyrones **81b** and **81c** in 17–6% yields, together with aldehydes **80a** and **80b** in 79–20% yields.

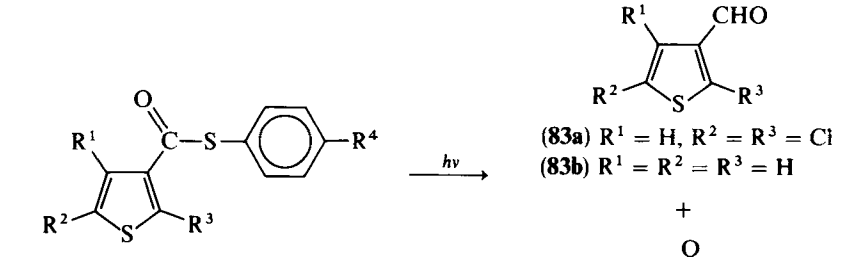


(**79a**) $R^1 = R^2 = H$
(**79b**) $R^1 = H$, $R^2 = Me$
(**79c**) $R^1 = Br$, $R^2 = Me$

(**80a**) $R^1 = H$
(**80b**) $R^1 = Br$

(**81a**) $R^1 = R^2 = H$
(**81b**) $R^1 = H$, $R^2 = Me$
(**81c**) $R^1 = Br$, $R^2 = Me$

SCHEME 39



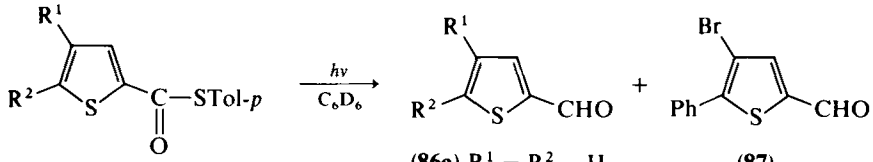
(82a) $R^1 = H$, $R^2 = R^3 = Cl$, $R^4 = Me$
(82b) $R^1 = R^2 = R^3 = H$, $R^4 = Me$
(82c) $R^1 = R^2 = R^3 = R^4 = H$

(83a) $R^1 = H$, $R^2 = R^3 = Cl$
(83b) $R^1 = R^2 = R^3 = H$

(84a) $R^1 = H$, $R^2 = Cl$, $R^4 = Me$
(84b) $R^1 = R^2 = H$, $R^4 = Me$
(84c) $R^1 = R^2 = R^4 = H$

SCHEME 40

An unsubstituted *S*-aryl ester **82c** afforded thiopyrone **84c** in 13% yield, while the *S*-aryl esters **82a** and **82b** gave thiopyrones **84a** and **84b** in 11 and 10% yields, as well as aldehydes **83a** and **83b** in 36 and 70% yields. The photoreaction of *S*-aryl esters of thiophene-2-thiocarboxylic acids **85a** or **85b**, unsubstituted at the 3-position, on the other hand, afforded no thiopyrones and gave aldehydes **86a** or **86b**, respectively, in 80 and 44% yields. Aldehyde **87** was an accompanying product in the photoreaction of ester **85b** (Scheme 41). The synthesis of thio-azaheterocycles **89** (7%) and **89b** (19%) from *S*-aryl esters, **88a** and **88b**, by the above-mentioned method is outlined in Scheme 42.

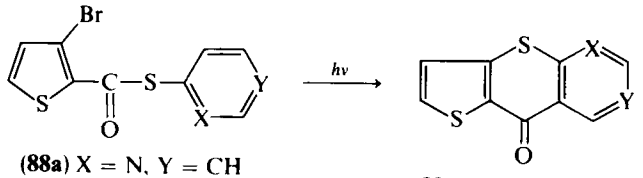


(85a) $R^1 = R^2 = H$
(85b) $R^1 = R^2 = Br$

(86a) $R^1 = R^2 = H$
(86b) $R^1 = R^2 = Br$

(87)

SCHEME 41



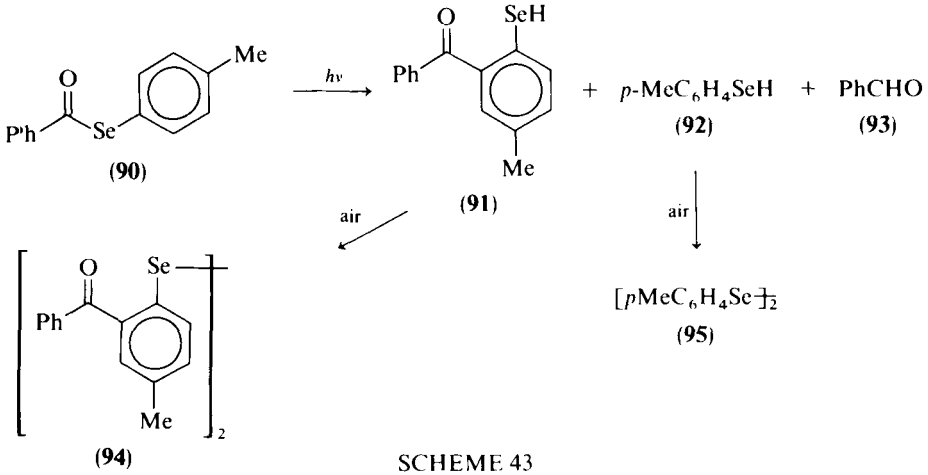
(88a) X = N, Y = CH
(88b) X = CH, Y = N

(89a) X = N, Y = CH
(89b) X = CH, Y = N

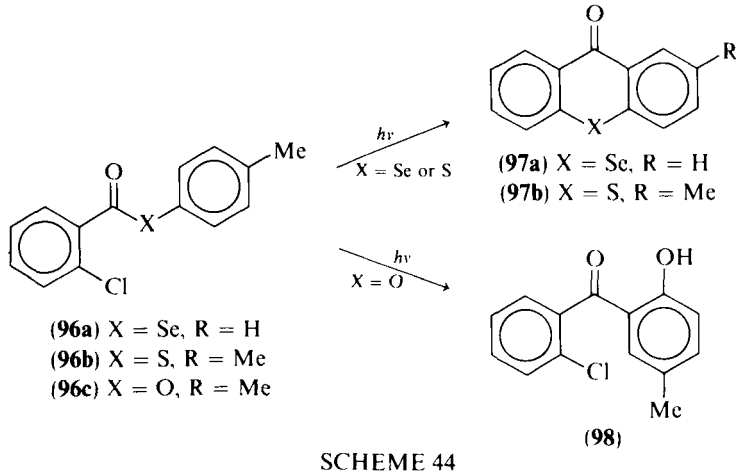
SCHEME 42

8. Esters of selenols and tellurols

The preparations and photochemical reactions of certain selenols and tellurols have been reported by Praefcke and colleagues, who are responsible for much of the current understanding of the photochemistry of organic selenium and tellurium compounds[42]. The photoreaction of Se-aryl carboselenoates was first reported by Praefcke and colleagues in 1976[43]. Thus, the irradiation of Se-(4-methylphenyl)selenobenzoate **90** in benzene with ultraviolet light gave a seleno-photo-Fries-type product **91**, selenocresol **92** and benzaldehyde **93**. Products **91** and **92** were air-sensitive and were only detectable immediately after the photolysis in the crude degassed solution by NMR spectroscopy. After isolation by chromatography, these two products were obtained as dimers **94** and **95** in 33 and 46% yields, respectively (Scheme 43).

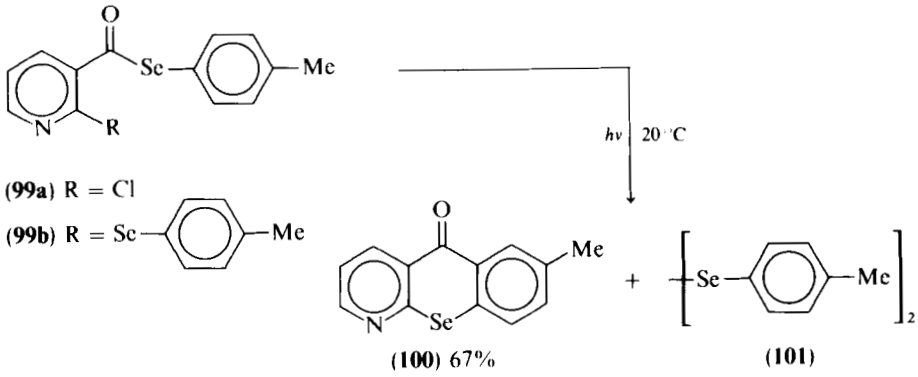


SCHEME 43

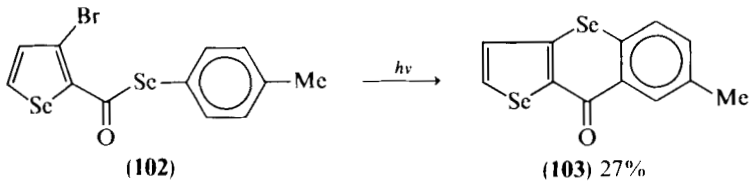


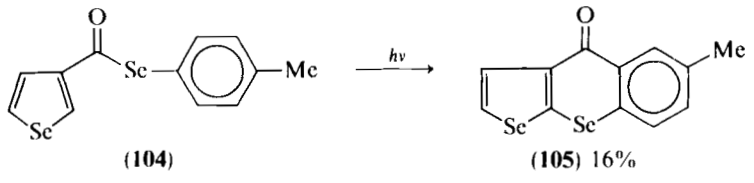
SCHEME 44

Selenoxanthone **97a** is formed in 19% yield when Se-phenyl-2-chloroselenobenzoate **96a** is photolysed, as in the case of the photo-Fries-type reaction of the thiophenol ester **96b**. The formation of the xanthone skeleton can be contrasted to the photo-Fries

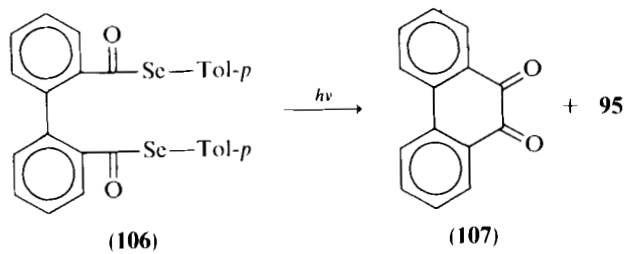


SCHEME 45





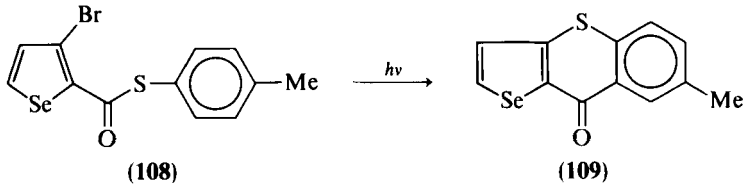
SCHEME 46



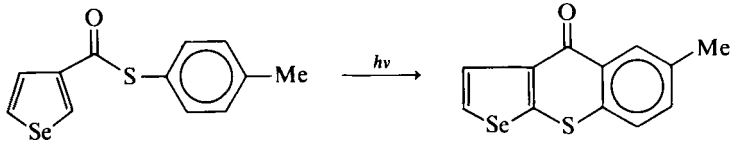
SCHEME 47

rearrangement of aryl 2-chlorobenzoate **96c**, which results only in the formation of the benzophenone derivative **98** (Scheme 44).

Several new heterocyclic ring systems, such as 5*H*-[1]benzoseleno[2,3-*b*]pyridine **100**[44] and 9*H*-selenolo[3,2-*b*][1]benzoselenine **103**[45], were synthesized for the first time by such photoinduced selenol ester–seleninone transformations (Schemes 45 and 46). The irradiation of diselenol ester **106** has been reported to give both phenanthraquinone **107** and diselenide **95** in good yields[43] (Scheme 47).

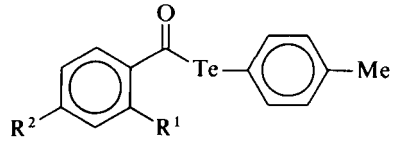


(108) (109)

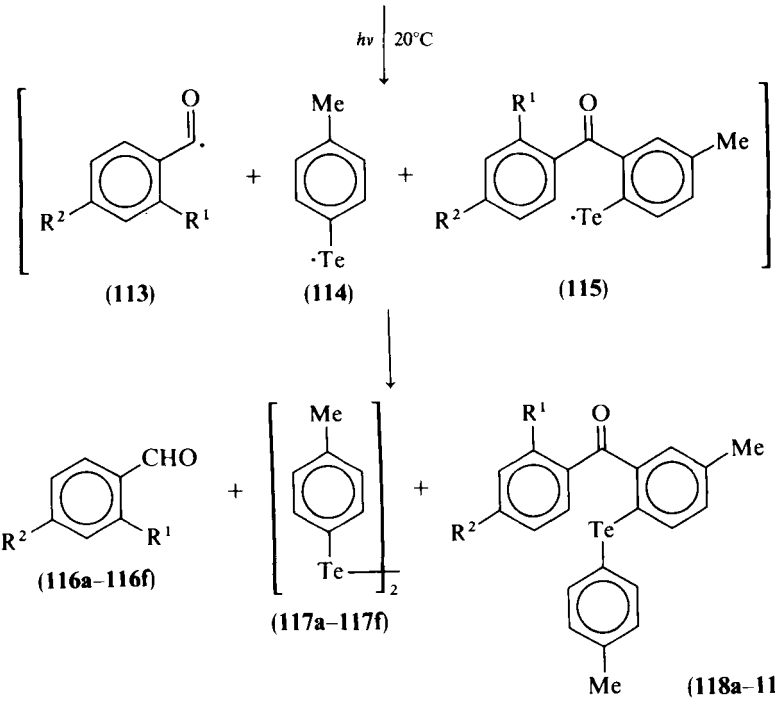


(110) (111)

SCHEME 48



(112a–112f)



(113) (114) (115)

(116a–116f) (117a–117f) (118a–118f)

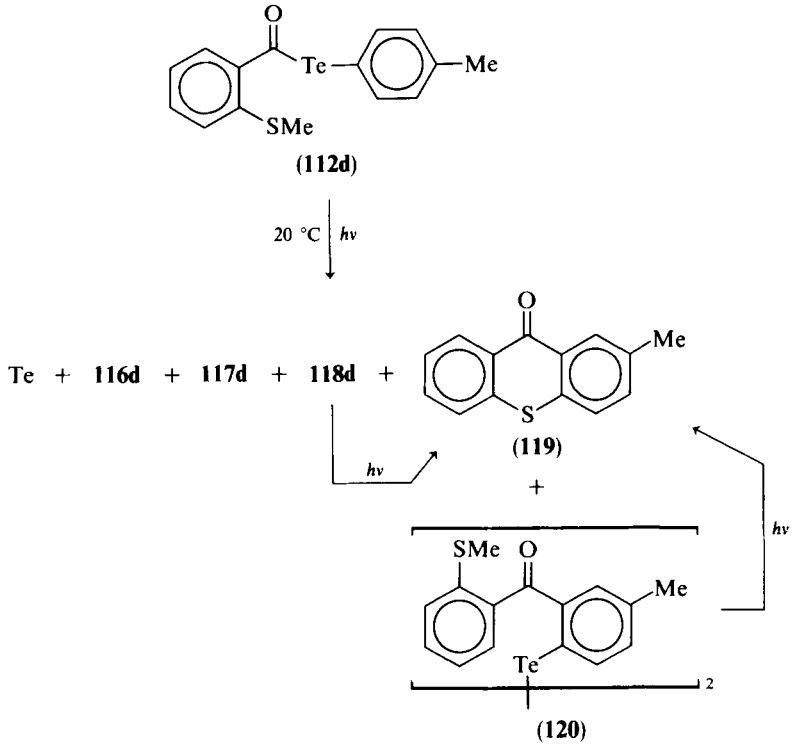
(a) $R^1 = R^2 = H$, (b) $R^1 = H$, $R^2 = OMe$, (c) $R^1 = Cl$, $R^2 = H$,
(d) $R^1 = SMe$, $R^2 = H$, (e) $R^1 = -SO_2Me$, $R^2 = H$, (f) $R^1 = OMe$, $R^2 = H$

SCHEME 49

The synthesis of several sulphur analogues of xanthones **103** and **105** were similarly achieved by Praefcke and colleagues[46]. For instance, the thio analogue **109** of **103** was prepared by the photolysis of 3-bromoselenophene-2-thiocarboxylic acid-*S*-(*p*-tolylester), **108**, in 18% yield. Likewise, the thio analogue **111** of **105** was prepared in 3% yield by the photolysis of **110** (Scheme 48).

The photoreaction of the telluro esters of aromatic carboxylic acids has also been studied by Praefcke and colleagues since 1978[47,48]. Photoinduced reactions of telluro esters **112a–112f** thus gave elemental tellurium, aldehydes **116a–116f** (6–22% yields) and ditellurides **117a–117f** (26–62% yields) through radicals **113**, **114** and **115** arising from cleavage of the carbonyl–tellurium bond. In addition to these products, the photolysis of telluroesters **112d**, **112e** and **112f**[48] gave photo-Fries-type products **118d**, **118e** and **118f** in 2–10% yields (Scheme 49).

The photolysis of telluro ester **112d**[48], substituted by a methylthio group at the *ortho* position of the benzoyl group, gave thioxanthone **119** (22%) and ditelluride **120** (11%) in addition to the above-mentioned four types of the products: Te, **116d**, **117d** and **118d** (Scheme 50). Thioxanthone **119** was proved to be a secondary product, since independent irradiation of either **118** or **120** gave thioxanthone **119**.



SCHEME 50

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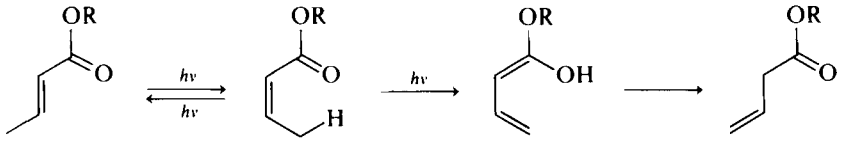
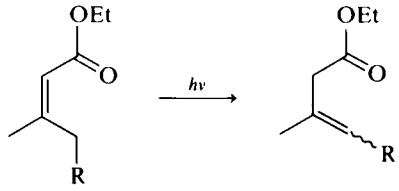
B. α,β-Unsaturated Carboxylic Acid Esters

Direct photochemical excitation of α,β-unsaturated esters results in *E–Z* isomerization; the quantum efficiency of this process was reported to be 5–10%[1]. If the esters possess hydrogens attached to the γ-position oriented *syn* with respect to the ester carbonyl, they can be abstracted in competition with the *E–Z* isomerization to form dienol intermediates which can revert to give a less stable β,γ-unsaturated esters by protonation (Scheme 1). This photoenolization reaction appears to proceed via the



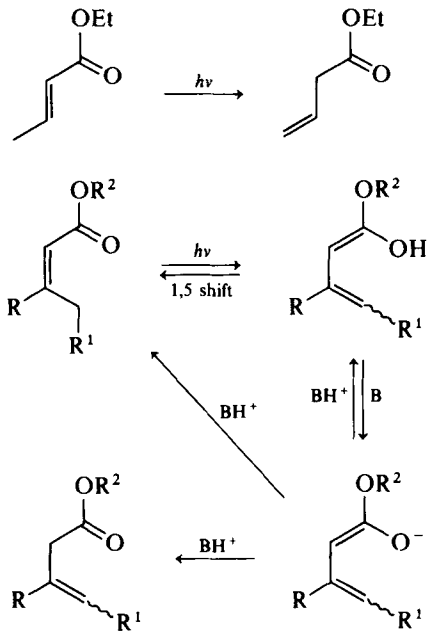
SCHEME 1

singlet state[2,3]. A number of examples of this photodeconjugation, which is of utility for the synthesis of less readily available β,γ-unsaturated esters, have been reported[4]. Thus photochemical conversion of α,β-unsaturated esters to their β,γ-isomers takes place efficiently with esters possessing substituents in the γ-position. In the absence of γ-substituents (Scheme 2, R = H), however, the esters were found to be rather unreactive, and underwent a slow deconjugation to give a low yield of the products. For example, ethyl *trans*-butenoate is incompletely converted into the deconjugated isomer at a much slower rate than is its homologues, having an alkyl substituent in the γ-position[4g,4b].



SCHEME 2

Weedon and colleagues[5,6] have recently investigated the pathway of this deconjugation in some detail. The formation of the dienol is viewed by them as being a photochemically allowed antarafacial 1,5-sigmatropic hydrogen shift, rather than a non-concerted hydrogen abstraction process. They suggested that the photochemically produced dienol, as outlined in Scheme 3, can revert to the keto form via a thermal suprafacial 1,5-sigmatropic hydrogen shift. In competition with this reversion to the keto form, the dienol can be intercepted by a base (this can be solvent, impurities in the solvent, or added base) to give a dienolate. The dienolate can then re-ketonize to give the β,γ-unsaturated isomer or the conjugated ester.

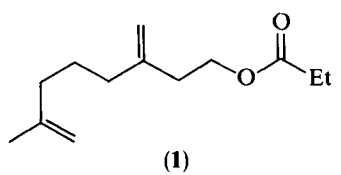


SCHEME 3

The pathways outlined in Scheme 3 suggest that the deliberate addition of a base to α,β-unsaturated esters may accelerate the formation of the dienolate in competition with reverting to the keto form by a 1,5-sigmatropic shift, and may increase the efficiency of photochemical deconjugation.

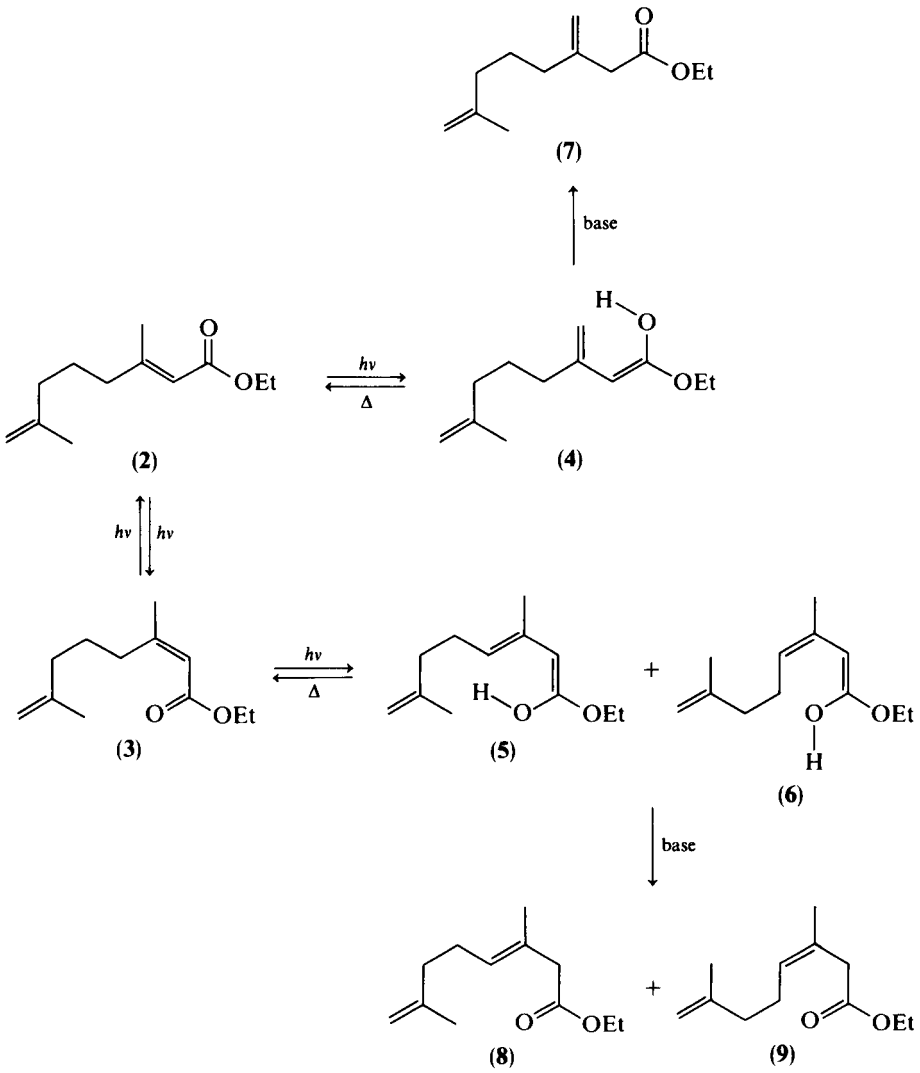
Weedon and colleagues in fact found that these esters, which are photochemically inert to deconjugation, can be converted to their β,γ-isomers in good yields if the irradiation is performed in the presence of a catalytic amount of a weak base, such as 1,2-dimethylimidazole[6].

The authors have suggested[6] that some control over the regiochemistry of the photochemical deconjugation can be achieved via interception of the intermediate dienol by adding a weak organic base, considering the details of the pathways of the deconjugation outlined in Scheme 3. They then demonstrated this control of the regiochemistry of the photochemical deconjugation by synthesizing one of the components of a natural pheromone **1**[7].



(1)

Thus, irradiation of the *E*-ester **2**, prepared in six steps from 3-methyl-2-butenoate in diethyl ether in the presence of 1,2-dimethylimidazole, resulted in rapid *E*-**2**–*Z*-**3** isomerization followed by the formation of three deconjugated products, (**7**, **8** and **9**) in the ratio 2.7:1.8:1.0 and in a combined yield of 83% at 100% conversion (Scheme 4).



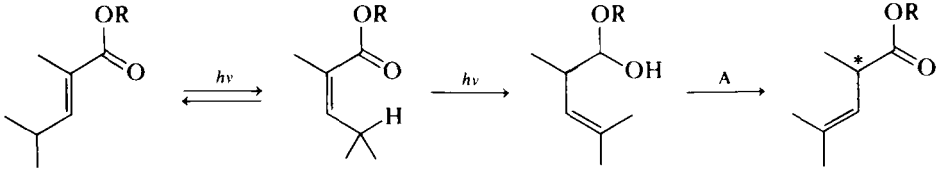
SCHEME 4

Reduction of the reaction mixture followed by a treatment of the resulting alcohols with propionyl chloride gave a mixture of esters with pheromone **1** as the major component. Irradiation of the ester **2** under the same conditions with no added base produced an *E–Z* mixture of **2** and **3** containing less than 10% of the deconjugated isomers, **8** and **9**.

According to the authors, these results are consistent with the proposed mechanism; the irradiation of **2** results in rapid *E–Z* isomerization from both the singlet and triplet excited states; a slower photoenolization of the *E* and *Z* isomers from their singlet excited states gives dienols **4**, **5** and **6**. In the absence of an added base, the dienol **4** efficiently reverts to the conjugated ester by a thermal 1,5-sigmatropic hydrogen shift; this process

is made more efficient by the side chain, which helps to maintain the dienol in the *cisoid* conformation necessary for the 1,5-hydrogen shift. However, when a base is added to the reaction mixture, this dienol **4** is intercepted and equilibrated with its dienolate, which is rapidly reprotonated to give the deconjugated ester. In the case of the dienols **5** and **6**, the same arguments apply, except that the side chain now inhibits the adoption of the *cisoid* conformation of the dienol necessary for reversion to the conjugated ester. This makes the dienol lifetime longer, and the solvent can catalyse the conversion of the dienol to the deconjugated ester via the dienolate anion. The increased proportion of the *E* deconjugated ester **8** formed in the reaction in the presence of base supports this, since the dienol **5** can revert to **3** by a 1,5-hydrogen shift more readily than can dienol **6**.

Pete and coworkers[8] have reported that enantioselective deconjugation can be achieved when α,β-unsaturated esters with an alkyl substituent and hydrogens attached to the α- and γ-positions are irradiated in the presence of a catalytic amount of β-amino alcohols as a chiral inductor (Scheme 5).



(10) **(11)**

R = Me, Et, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$—, $C_6H_5(CH_2)_3$—, $(CH_3)_2C{=}CHCH_2$—

(A) chiral amino alcohols

SCHEME 5

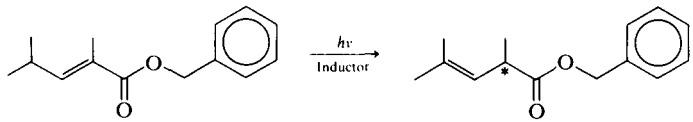
For example, the irradiation of the α,β-unsaturated ester **10** (R = Et) in dichloromethane containing 0.1 equivalent of (−)-ephedrine at −78°C gave the (*R*)-β,γ-unsaturated isomer **11** (R = Et) in 68% yield[2] with an enantiomeric excess of 16%[9]. Subsequent extensive investigations on this enantioselective photodeconjugation with other chiral β-amino alcohols prepared from norephedrine resulted in the enhanced enantioselectivity reaching 70%[10].

More recently, Pete and colleagues reported that enantioselectivities of up to 91% have been reached in the photodeconjugation of α,β-unsaturated esters or lactones using new chiral cyclic inductors (**12**, **13** and **14**) derived from (+)-camphor[11]. The results of the enantioselective deconjugation of ester **10** in dry dichloromethane in the presence of 0.15 equivalents of three new chiral β-amino alcohols (**12**, **13** and **14**) are summarized in Table 1.

No optical activity of the β,γ-isomer **11** was observed if **12a** was used. This result can be explained by the low basicity of the anilino moiety, which did not allow any strong interaction of the enolic proton with a basic site of the inductor.

Exo,exo-isomers **13** were also found to be rather inactive as inductors. The *endo,endo*-isomer (**14**), however, was found to be an efficient inductor. The substituent attached to the nitrogen was found to influence the enantioselectivity considerably; the isopropylamino-, hexylamino- and benzylamino groups gave the β,γ-isomer with an *R* configuration while the amino group gave the β,γ-isomer with an *S* configuration. The best enantioselectivity was achieved by **14** with a benzylamino group (91%) or with an isopropylamino group (89%).

TABLE 1



(10) (11)

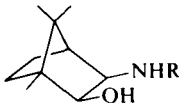
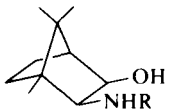
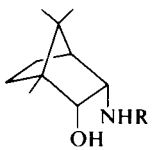
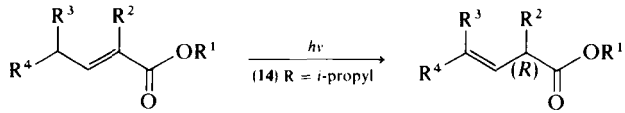
Inductor	R	°C	Yield (%)	e.e (%)	Configuration
 (12)	(a) C_6H_5	−45	61	0	—
	(b) hexyl	−45	52	40	*S*
 (13)	H	−52	72	10	*R*
	i-propyl	−50	74	16	*S*
 (14)	H	−45	57	54	*S*
	Me	−45	61	<5	*S*
	i-propyl	−45	71	83	*R*
	i-propyl	−55	76	89	*R*
	i-propyl	−84	76	86	*R*
	hexyl	−45	70	70	*R*
	hexyl	−55	73	80	*R*
	benzyl	−55	75	91	*R*

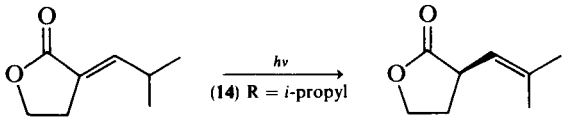
TABLE 2



Substituents

R^1	R^2	R^3	R^4	Yield (%)	e.e (%)
Et	Me	Me	Me	56	61
Me	Et	Me	Me	53	56
Et	Me	—$(CH_2)_4$—		73	59
Et	Me	—$(CH_2)_5$—		54	77
Me	Me	H	C_7H_{15}	56	44

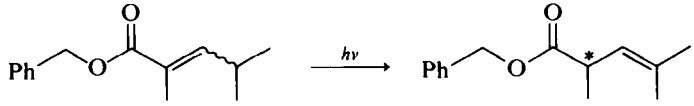
Table 2 summarizes the results of the enantioselective deconjugation of α,β-unsaturated esters with a different alkyl substitution. The enantioselectivity was enhanced when the γ-position of the esters was substituted with two alkyl groups. The alkylidene lactone **15** was similarly deconjugated by irradiation with an enantioselectivity of 43% to give the β,γ-isomer **16** (Scheme 6).



(15) **(16)**

SCHEME 6

The efficiency of various inductors on the enantioselective photodeconjugation and the mechanism of the asymmetric induction has been investigated by Pete and colleagues using benzyl-2,4-dimethyl-2-pentanoate as a model substrate[12]. Dichloromethane was used as a solvent in order to avoid any competition of the solvent, having either acidic or basic properties, with the chiral catalyst (Scheme 7).



SCHEME 7

They found that while (−)-ephedrine (0.1 equivalents) induced an enantio selectivity (e.e. = 28%) to give the predominant enantiomer with an (*R*) configuration, no chiral induction was observed involving a chiral alcohol. Moreover, the chiral amines bearing no hydroxyl group, such as *O*-methyl (+)-ephedrine, lowered the e.e. by a factor of 4. Although replacement of the secondary amino group of (−)-ephedrine or of the tertiary amino group in (−)-*N*-methylephedrine decreased the enantioselectivity, the use of cinchonidine as a chiral inductor enhanced the enantioselectivity up to 37%.

As a whole, the e.e. was found to be improved when the chiral inductor possesses both amino and hydroxyl groups. The configuration of the predominant enantiomer appears to depend only on the configuration of the carbon atom carrying the nitrogen atom; a deconjugated isomer having an (*R*) configuration is obtained when the configuration of the carbon carrying the nitrogen of the inductor has an (*S*) configuration, regardless of the configuration of the carbon atom carrying the hydroxyl group of the inductor. The authors consider that the synergistic effect of the amino and hydroxyl groups of the chiral inductor on the enantioselectivity can be explained by assuming that removing the enolic proton by the basic amine and protonation of the double bond by the hydroxyl group of the β-aminoalcohol is a concerted process (Figure 1). Chiral discrimination would result from differences in the steric interaction in the two diastereoisomeric transition states involving each face of the prochiral enol.

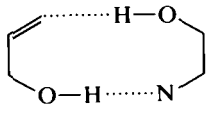


FIGURE 1

Pete and colleagues further examined the effect of the substituents of the starting unsaturated ester on the absolute configuration of the deconjugated isomer, and on the enantiomeric excess using (+)- and (−)-ephedrine as the chiral catalysts[13]. They found that whatever the size of the alkoxyl group of the starting ester, a deconjugated isomer with an (*S*) configuration is formed with (+)-ephedrine. Moreover, this configuration is still the same when the α-methyl group is replaced by an ethyl substituent. A modification of the substituents attached to the acid part of the starting ester had a far more appreciable effect on the enantioselectivity. On the basis of these results, they explained chiral discrimination by assuming competition between the two diastereoisomeric transition states represented in Figure 2.

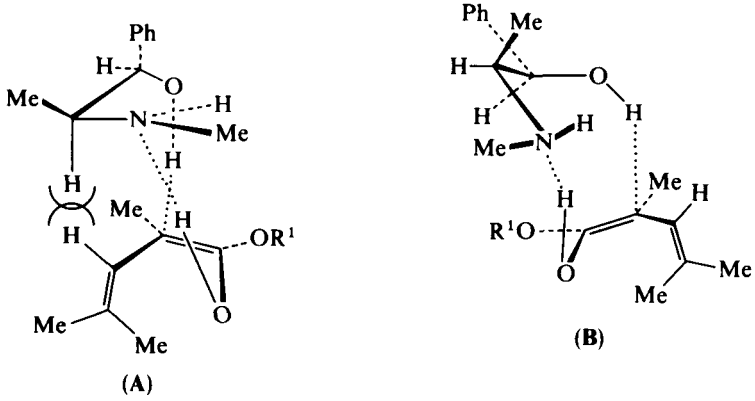
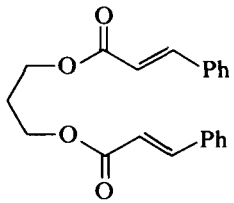


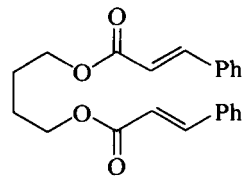
FIGURE 2

Among the two transition states [**A** and **B** leading to the (2*S*) and (2*R*) configurations] **A** has a greater steric interaction between the vinylic β-hydrogen of the dienol and the C—H bond of the carbon attached to the nitrogen atom of ephedrine.This consideration of the conformation of the transition state may explain why the enantiomer with an (*R*) configuration is predominantly formed with (−)-ephedrine as the inductor[14].

An intramolecular photochemical [2 + 2] addition between two chromophores bridged by more than eight bonds has been reported. Thus, Rennart and colleagues[15] have reported that the irradiation of a solution of α,ω-dicinnamate **17**, in which two chromophores are separated by eight bonds, gave a mixture of the internal diesters of β-truxinic acid (90%) and δ-truxinic acid (10%), while α,ω-dicinnamate **18** gave the diester of the δ acid exclusively.



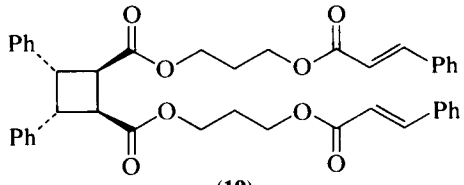
(17)



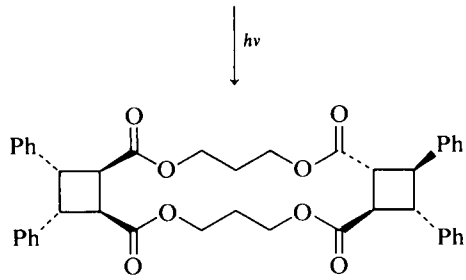
(18)

More recently, a successful internal photochemical [2 + 2] addition in a α,ω-dicinnamate **19**, leading to a tricyclic molecule **20**, has been reported by Ors and Srinivasan[16].

The reaction represents a photoaddition between chromophores separated by 17 bonds. Thus, the direct irradiation of **19** in diethyl ether with 300 nm light in the presence of cuprous chloride as a catalyst gave **20** in 32% isolated yield. Although the quantum yields for the ring formation and the *trans–cis* isomerization of **19** in the absence of CuCl were 0.90 and 0.02, respectively, the quantum yield of the cyclization in the presence of CuCl was 0.20. Cyclization in the absence of CuCl takes place from an excited singlet state of **19**. Cuprous chloride may function by enhancing the intersystem crossing through a heavy-atom effect. It is of interest to note that in contrast to solution photochemistry, in which δ-truxinic ester is a product of the photocyclization of **19** and is the only product from **18**, in the solid state a [2 + 2] photoaddition between cinnamate groups leads to give α-truxillic or β-truxinic acids or their derivatives exclusively (Scheme 8).



(19)



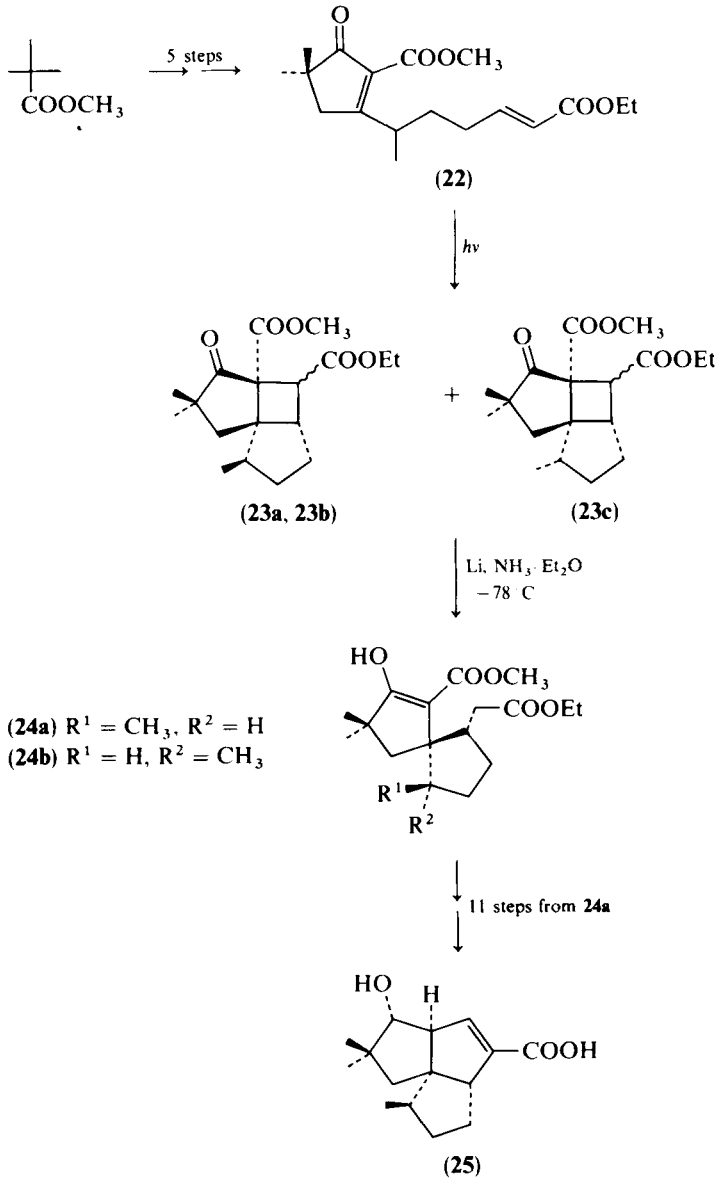
(20)

SCHEME 8

An intramolecular photochemical [2 + 2] addition of an α,β-unsaturated ester **22** has been used as the key reaction in an efficient total synthesis of (±)-pentalenic acid **25**, a tricyclic natural product as outlined in Scheme 9[17]. Thus, irradiation of a hexane solution of diester **22** gave cyclobutane photoadducts in 72% yield as a 10:3:1 mixture of diastereoisomers: **23a**, **23b** and **23c**. Cleavage of the cyclobutane ring of **23** with lithium–ammonia at − 78 °C led to a 13:1 mixture of spirofused esters, **24a** and **24b**, in 90% yield. The major isomer **24a** was then converted to (±)-pentalenic acid **25** in 11 steps.

The authors state that the excellent stereoselectivity in the photoannulation might be explained on thermodynamic grounds, even though kinetic control cannot be excluded.

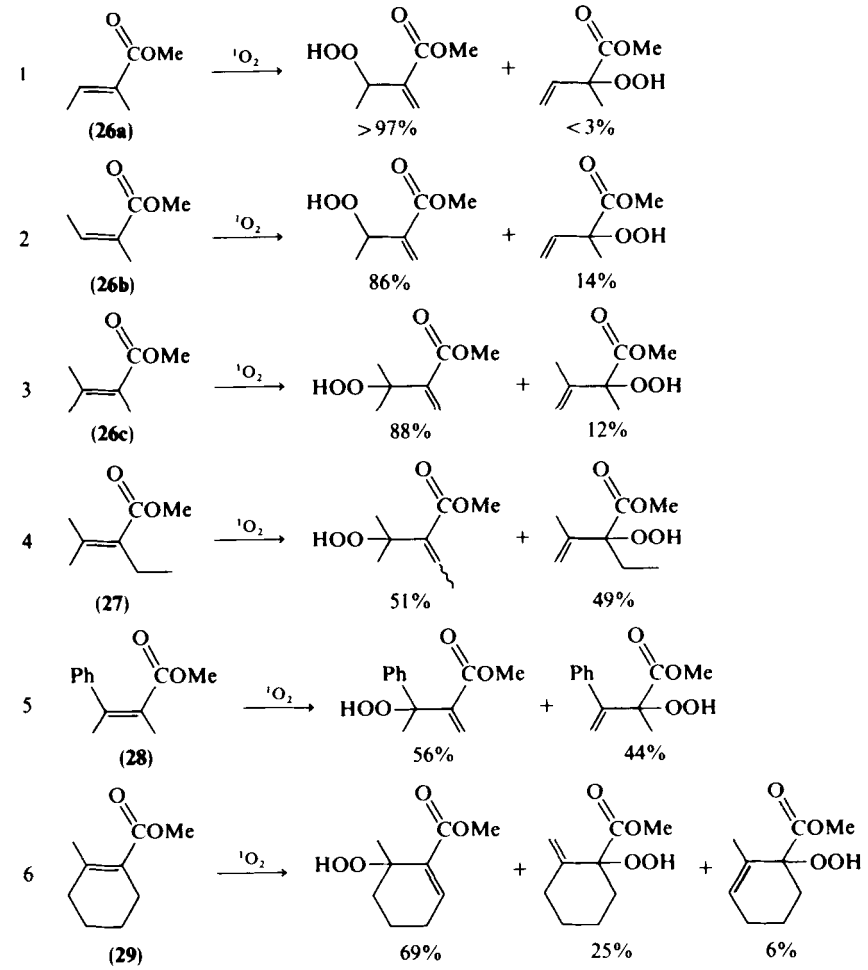
Extensive studies have been carried out on the 'ene' reaction of singlet oxygen with olefins[18,19]. It has recently been reported[20] that the reaction of singlet oxygen with α,β-unsaturated esters takes place in a regioselective manner, as in the case of the reaction of singlet oxygen with α,β-unsaturated ketones[20]. The results of the reaction of singlet oxygen with α,β-unsaturated esters are summarized in Table 3.



SCHEME 9

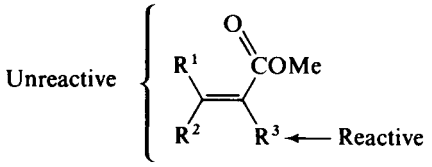
As with the reaction of singlet oxygen with ketones, this reaction shows a preferential abstraction of the allylic hydrogens geminal to the ester functionality. For example, the α,β-unsaturated ester gives $>97\%$ hydrogen abstraction from the R^3 methyl group and only $<3\%$ from the R^2 methyl group (Scheme 10).

TABLE 3



Thus, the ester group activates the geminal hydrogens, whether or not this group is on the crowded side of the double bond. This differs from enol ethers or simple olefins, where the most crowded side of the alkene is the most reactive.

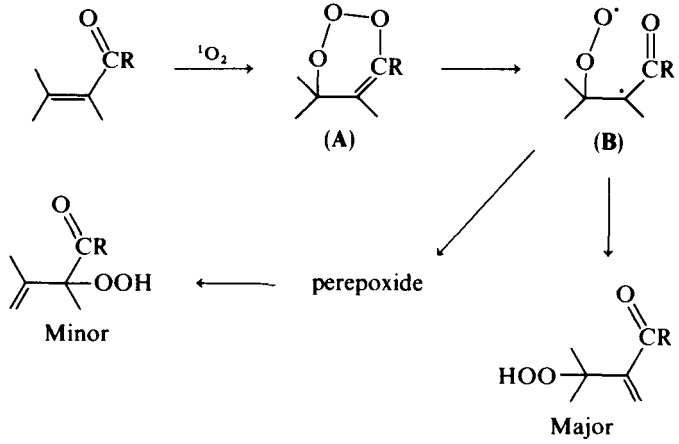
Orfanopoulos and Foote[20] suggested that this geminal effect may be attributed to the formation of a trioxene intermediate, similar to that proposed by Ensley and colleagues[21]. The formation of trioxene **A**, followed by a rupture of the weak O—O



	R^1	R^2	R^3
(26a)	H	Me	Me
(26b)	Me	H	Me
(26c)	Me	Me	Me

SCHEME 10

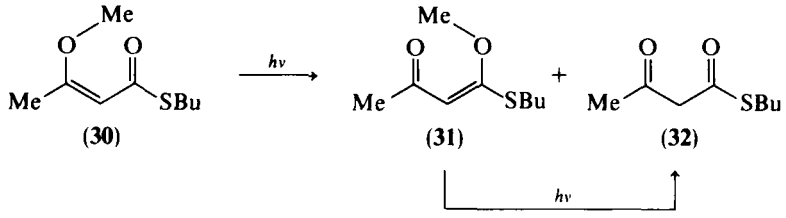
bond, might lead to intermediate **B**, forcing geminal hydrogen abstraction (Scheme 11). A minor product may result from a rearrangement of **B** to perepoxide, or in a competing normal ene reaction.



SCHEME 11

An unusual 1,5-methyl migration and *O*-demethylation were found in the photoreaction of *S*-butyl- (*Z*)-3-methoxy-2-butenethioate (**30**)[22]. Thus, irradiation of **30** gave 4-butylthio-4-methoxy-3-butene-2-one **31** (65%) and 5-butyl-3-oxobutanethioate **32** (25%) (see Scheme 12).

Time-conversion curves have indicated that migration of the methyl group competes with demethylation. The formation of both **31** and **32** were found to be equally quenched with 1,3-pentadiene, and to be sensitized with *p*-methoxyacetophenone. These results have suggested that the formation of **31** and **32** takes place from the excited triplet state



SCHEME 12

of **30**. Prolonged irradiation in a non-degassed benzene solution was found to convert **31** into **32**. Ethyl bromide accelerated the photoreaction **30** and the secondary photoreaction of **31**. The authors suggest that this external heavy-atom effect is an indication of the involvement of the π,π^* excited triplet state in the transformation of **30** into products **31** and **32**, and in the transformation of **31** into **32**. The authors also suggest that the rearrangement from **30** to **31** takes place via a non-concerted radical cleavage, rather than through concerted 1,5-sigmatropic migration.

It is of interest to note that the irradiation of the *E*-isomer of **30** in benzene gave no **31**, but the *O*-demethylated product **32** (58%).

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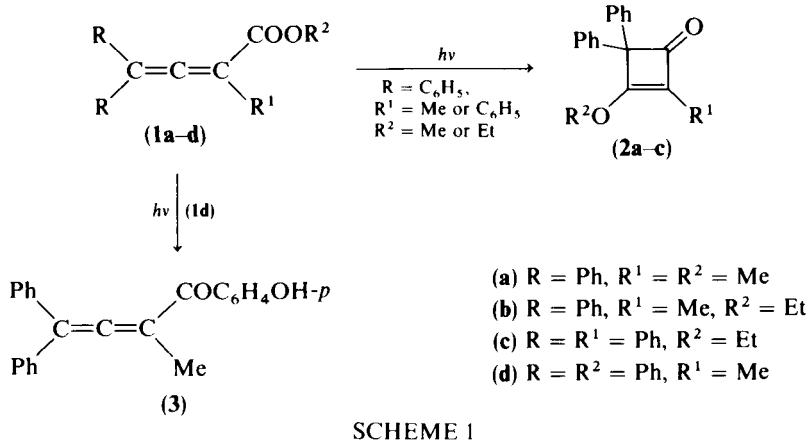
C. Allenic Esters

Although the photochemistry of allenes has been the subject of intense studies[1] there have been no early investigations concerning allenic esters.

Orahovats and colleagues have recently studied the photochemistry of some alkyl and phenyl allenic esters[2]. They found that the irradiation of alkyl allenic esters **1a–c**

in hexane with a high-pressure mercury arc at room temperature gives cyclobutenones **2a–c** in low yields, while the irradiation of the phenyl allenic ester **1d** under the same conditions results in the formation of a photo-Fries product **3** in low yield (Scheme 1).



SCHEME 1

The authors have suggested that the cyclobutenones may arise through a 1,3-transfer of the alkoxyl group from an excited triplet of the allenes, or through a C—O bond cleavage of the ester function to give a radical pair.

References to Section I.C

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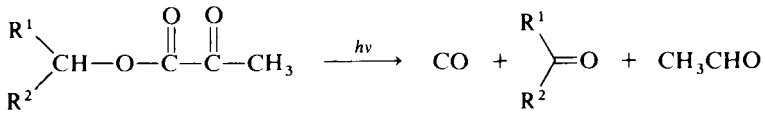
D. α- and β-Oxocarboxylic Acid Esters

1. α-Oxocarboxylic acid esters

The photochemistry of α- and β-oxocarboxylic acid esters received little attention until the 1980s[1–3]. The few reports which were published dealt mostly with the synthetic application of the photochemical properties of this class of compounds.

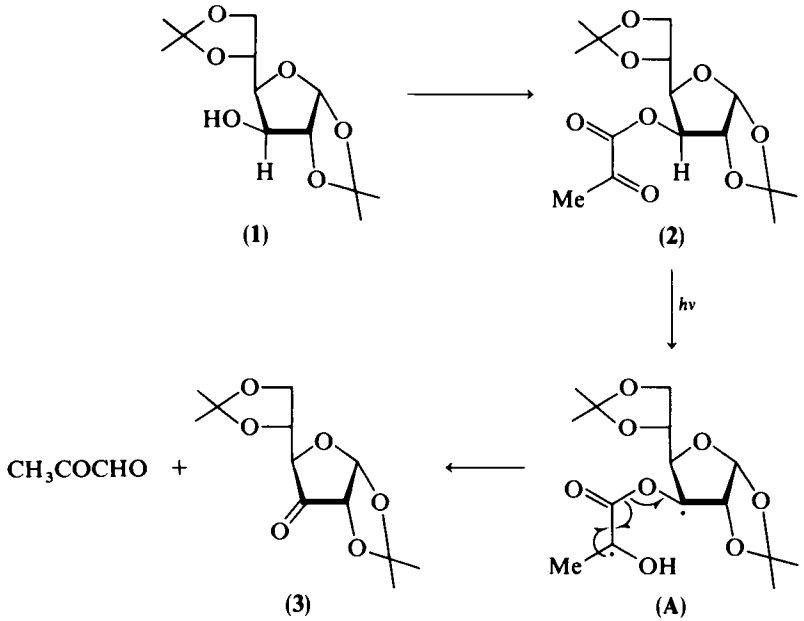
The photochemistry of simple pyruvic esters was investigated[1] during the first half of the sixties, but only in 1976 did Binkley[2] report a synthetically useful photochemical elimination of pyruvic esters. He found that the irradiation of esters of pyruvic acid with primary or secondary alcohols in benzene at room temperature resulted in the formation of the corresponding ketones arising from type-II photoelimination in acceptable yields (Scheme 1). The usefulness of this new process for a mild, selective oxidation of a hydroxyl



SCHEME 1

group to a carbonyl group has been demonstrated by Binkley also in the oxidation of partially protected carbohydrates.

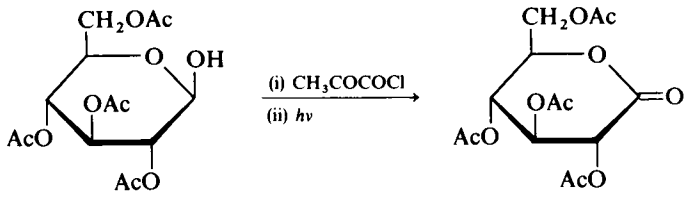
Typically, the pyruvoyl ester **2** of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** was prepared from pyruvoyl chloride and the protected carbohydrate, and **2** was irradiated at 25 °C to give the corresponding ketone **3** through **A** in 71% yield[2,4] (Scheme 2).



(1) (2) (3) (A)

SCHEME 2

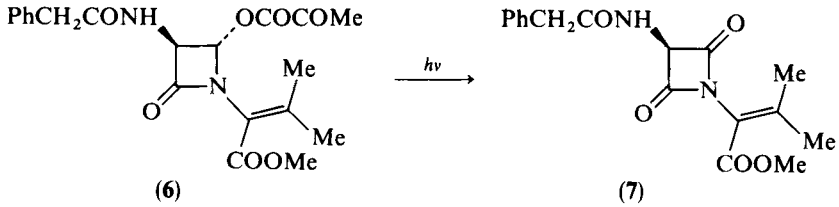
Several partially protected monosaccharides were oxidized and found to give good yields of the corresponding carbonyl compounds. It is worth noting that even the extremely sensitive anomeric hydroxyl groups of carbohydrates[2] can be oxidized to carbonyl groups by this method, which can be carried out under neutral conditions (Scheme 3).



(4) (5)

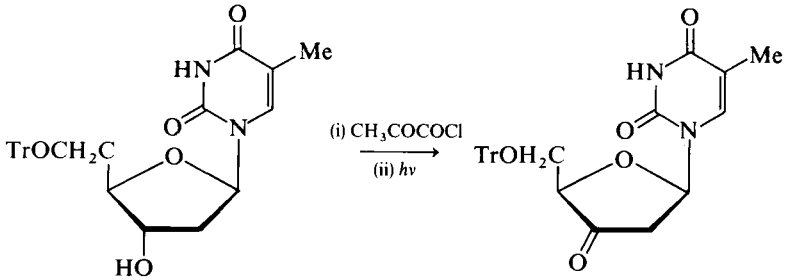
SCHEME 3

The method has been successfully used to generate a carbonyl group adjacent to a β-lactam nitrogen atom[3] (Scheme 4). Binkley has also reported that this method can be applied to the oxidation of a nucleoside, 5′-*O*-tritylthymidine **8**, to the 3′-keto derivative **9** in 61% yield (Scheme 5). Aoyama and colleagues[5,6] have reported that hydroxy-



(6) (7)

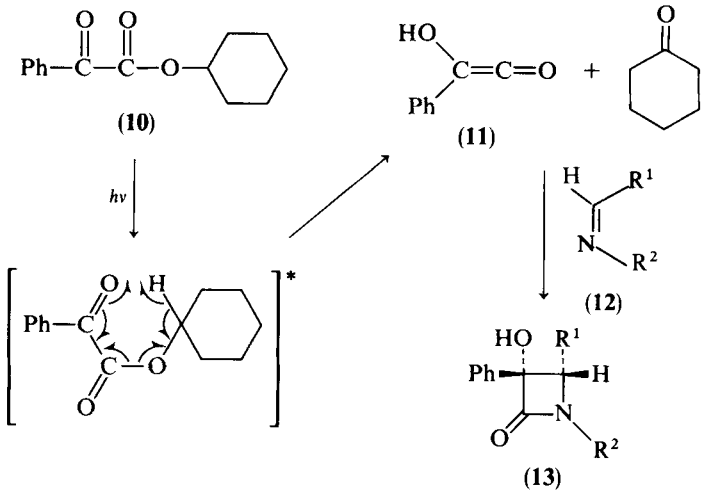
SCHEME 4



(8) (9)

SCHEME 5

phenylketene **11** is generated by the photolysis of cyclohexyl benzoylformate **10** and that **11** reacts with imines to form β-lactams in 27–73% yield (Scheme 6).



(10) (11) (12) (13)

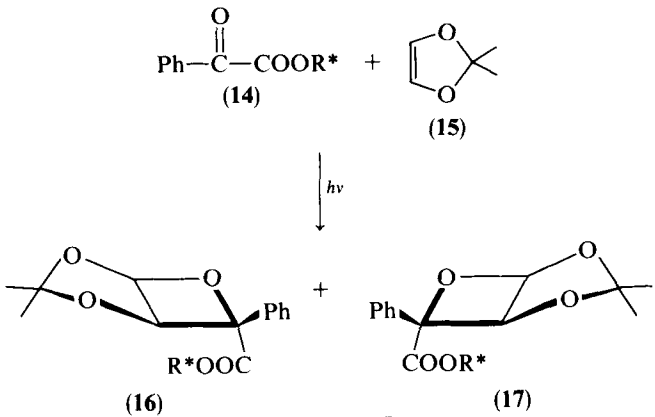
R^1 = Ph, *p*-Tol, *p*-CNC_6H_4, *p*-ClC_6H_4
R^2 = Bn, *p*-$MeC_6H_4CH_2$—, *p*-$ClC_6H_4CH_2$—, Et, *i*-Pr, *t*-Bu

SCHEME 6

Typically, the photolysis of ester **10** in the presence of *N*-benzylidenebenzylamine **12** (R^1 = Ph, R^2 = CH_2Ph) in benzene at 80 °C stereoselectively gave 3,4-diphenyl-1-benzyl-3-hydroxyazetidin-2-one **13** (R^1 = Ph, R^2 = CH_2Ph) in 73% yield. In most cases, however, only small amounts of the stereoisomers were reported to be formed in these reactions. The reaction apparently involves a γ-hydrogen abstraction by the excited benzoyl carbonyl group, as outlined in Scheme 6.

The mode of the photodecomposition of several alkyl benzoylformates has been studied in some detail by Encinas and colleagues by laser-flash photolysis techniques[7]. They concluded that the type-II reaction is a major triplet deactivation path in all alkyl benzoylformates having γ-hydrogen atoms.

Scharf and colleagues have reported[8] that excited chiral phenylglyoxylates **14** add to electron-rich olefins to give oxetanes with high diastereomeric excesses. Thus, the irradiation of (1*R*, 3*R*, 4*S*)-(−)-8-phenylmenthyl phenylglyoxylate **14a** and 2,2-dimethyl-1,3-dioxole **15** gave oxetane **17a** with high exo (>99%) and diastereoselectivity (≥96%), as outlined in Scheme 7[9]. When the (−)-menthyl ester **14b** or the (+)-menthyl ester **14c** were used, the diastereoselectivities were 57 and 56%, respectively, as summarized in Table 1. The observed exo selectivity is not attributable to the chiral ester grouping, since photoaddition of the chiral methyl ester (**14**, R* = Me) with olefin **15** also gave the racemate of exo-oxetanes **16** and **17**.

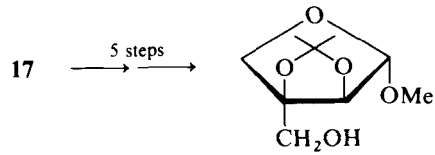


SCHEME 7

Three chiral centres have been established in a single face-differentiation reaction step in this photochemical chiral induction. Of these three centres, two centres remain when oxetane enantiomers **16** and **17** are regarded as being masked aldols. The preparation

TABLE 1. Chemical yields and diastereomeric excess (*de*) in the Paterno–Buchi reaction of the phenyl glyoxylates **14a–14c**

Alcohol R*OH	R*	Chem. yield of oxetane	*de*	Excess oxetane
14a	(−)-8-Phenylmenthyl	99%	≥96%	**17a**
14b	(−)-Menthyl	99%	57%	**17b**
14c	(+)-Menthyl	99%	56%	**16c**

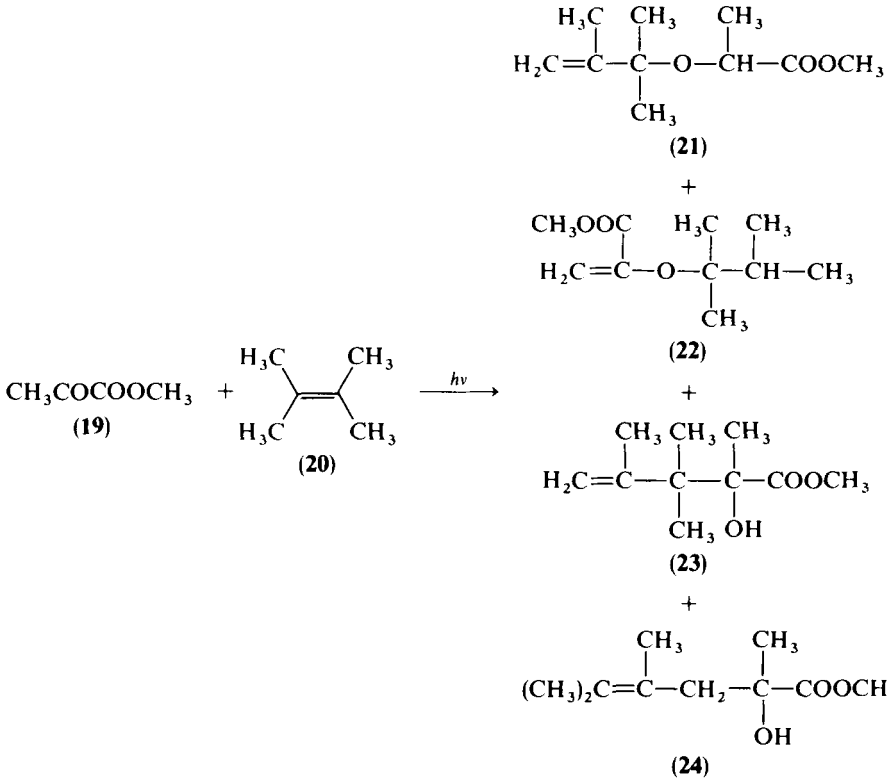


(18)

SCHEME 8

of methyl 2,3-*O*-isopropylidene-β-L-apio-L-furanoside **18** was then achieved in 5 steps from oxetane **17** (Scheme 8).

The reaction of an excited carbonyl group with alkenes carrying alkyl groups was reported to give both unsaturated ethers and unsaturated alcohols[10,12] rather than the Paterno–Büchi products[11]. Shima and colleagues have reported that the irradiation of a solution of methyl pyruvate **19** and 2,3-dimethyl-2-butene **20** in acetonitrile with ultraviolet light afforded 4 adducts, **21**–**24** (Scheme 9)[10,12].

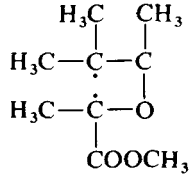


SCHEME 9

Mechanistic studies carried out by Shima and colleagues[12] have indicated that the allylic ether **21** and the enol ether **22** arise from a disproportionation of the biradical intermediate **25**, and that the two tertiary alcohols, **23** and **24**, are formed via a hydrogen

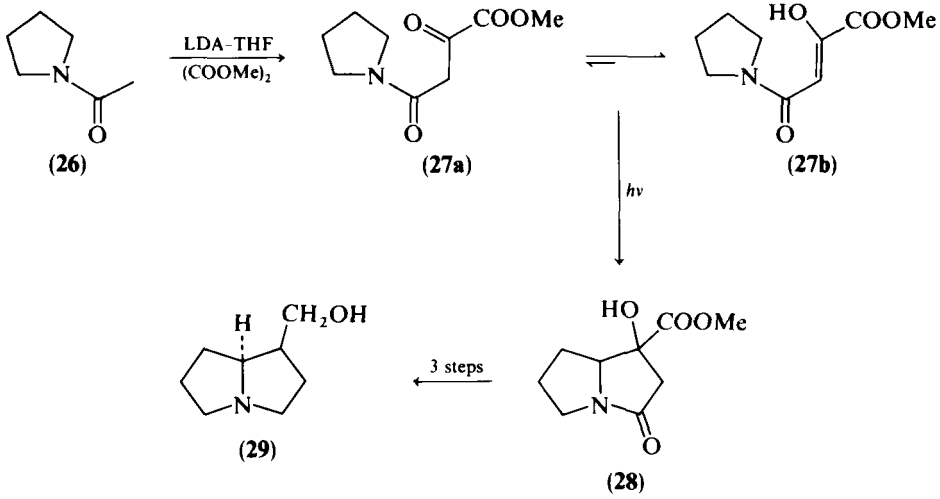
abstraction of the excited carbonyl group of methyl pyruvate from 2,3-dimethyl-2-butene.

The effects of the concentration of the alkenes on the quantum yield of product formation, as well as quenching studies, have suggested that ethers **21** and **22** are formed from an excited triplet state of the methyl pyruvate, while alcohols **23** and **24** are formed from an excited singlet.



(25)

Intramolecular reductive photocyclization of α-keto esters **27** has been used as a key reaction in a short, efficient (32% overall yield) synthesis of isoretronecarol **29**, a pyrrolizidine alkaloid[13]. The irradiation of **27**, being an equilibrated mixture of the keto (**27a**) and the enol form (**27b**) in *t*-butyl alcohol, gave the pyrrolizidine derivative **28** as a mixture of two diastereoisomers in a 1:1 ratio (Scheme 10).



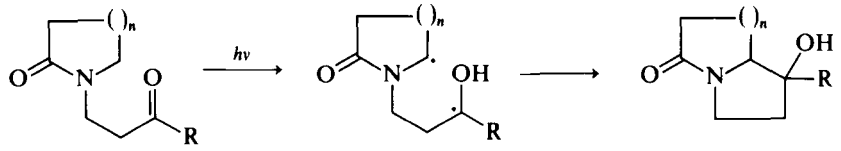
(26) **(27a)** **(27b)** **(28)** **(29)**

SCHEME 10

The second ring in this photocyclization is formed through intramolecular abstraction of a hydrogen atom α to the nitrogen of the amide function by the excited carbonyl group, followed by ring closure of the resulting biradical, **31** to **32** (Scheme 11). This reaction is analogous to the formation of 1-azabicyclo[*x*.3.*O*]alkanes **35** through a biradical **34** by the irradiation of the phenyl ketone **33**, reported by the same authors (Scheme 11)[14].

The keto ester **27** in acetonitrile or in benzene is completely enolized and no reductive photochemical cyclization of **27** took place in these solvents.

Gallucci and Jones[15] studied the photoreaction of alkyl 3-diazo-2-oxopropionates. Thus, the photolysis of methyl 3-diazo-2-oxopropionate **36** in benzene and an excess of



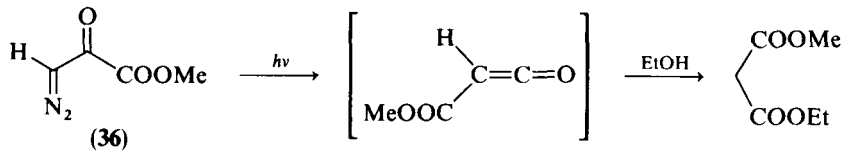
(30) $n = 1$, R = COOMe
(33) R = Ph

(31) $n = 1$, R = COOMe
(34) R = Ph

(32) $n = 1$, R = COOMe
(35) R = Ph

SCHEME 11

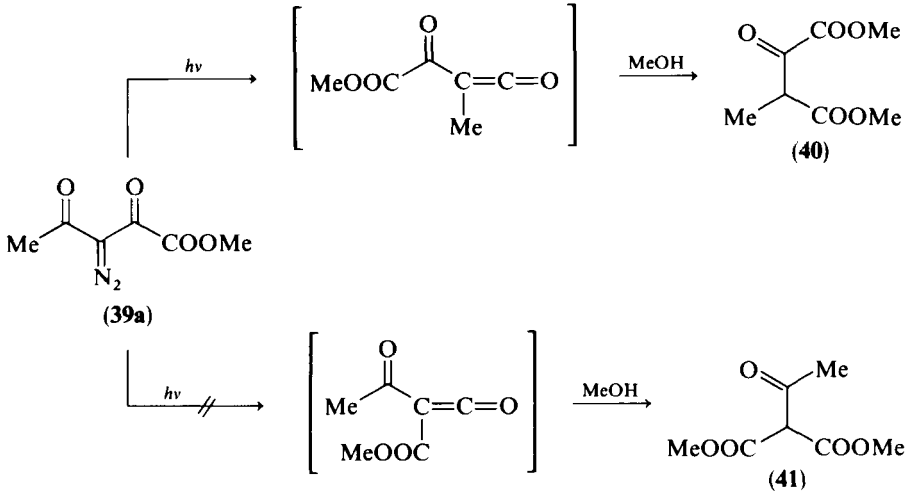
ethanol led to the formation of ethyl methyl malonate **38** as a single major product in 37% yield (Scheme 12). The path from **36** to **38** clearly involves a Wolff rearrangement of the carbomethoxy group, followed by capture of the resulting ketene **37** by ethanol.



(36) (37) (38)

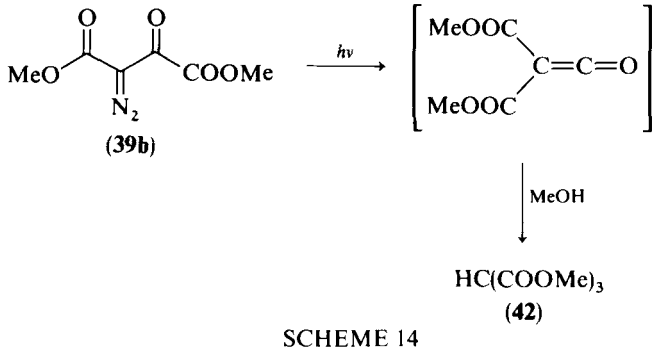
SCHEME 12

The migratory aptitude of a relatively efficient migrating group, methyl, and an inefficient group, carbomethoxy, was compared by using diazoesters **39a** in a benzene solution containing methanol, which led to the formation of **40** as a single major product with no accompanying formation of the product **41** that would arise from ester migration (Scheme 13). This experiment proved that the methyl group migrates to the exclusion



(39a) (40) (41)

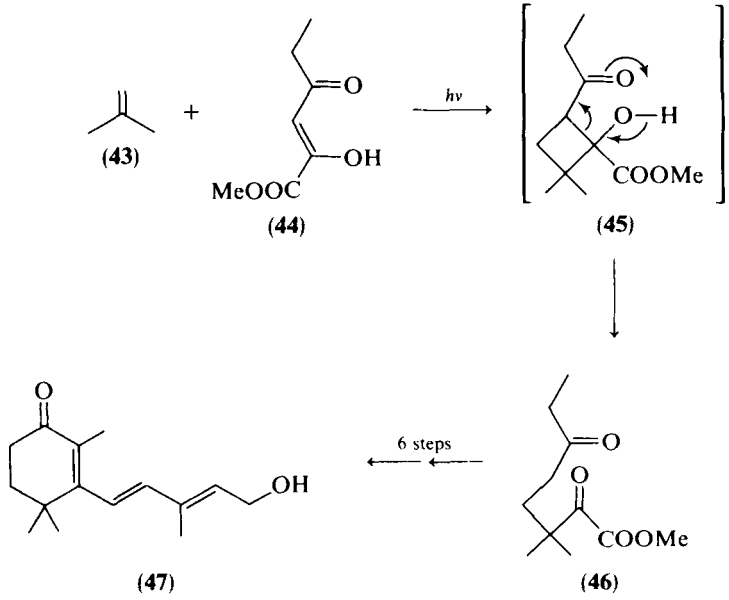
SCHEME 13



SCHEME 14

of the carbomethoxy group. Irradiation of **39b** in benzene containing methanol gave trimethyl methanetricarboxylate **42**, a product of ester migration, as a major product (Scheme 14). These results indicate that the order of migratory aptitudes in the Wolff rearrangement is Me > COOR > OMe.

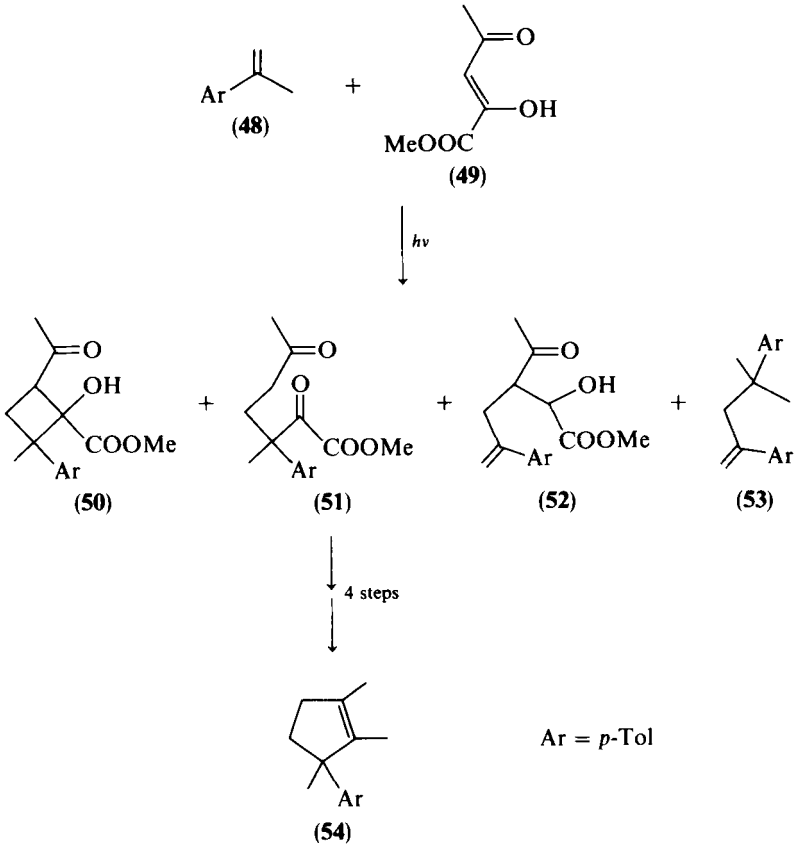
A de Mayo [2 + 2] photocycloaddition of enolized α,γ-diketocarboxylic acid esters with olefins was reported by Takeshita and colleagues as a route to the synthesis of some natural products. Thus, a [2 + 2] photocycloaddition of 2-methylpropene **43** with methyl 2,4-dioxohexanoate **44** gave photoadduct **46** via a retro-aldol condensation of the initial photoadduct **45** in 56% yield[16]. The photoadduct **46** was then converted to deoxytrisporone **47** (Scheme 15)[16].



SCHEME 15

The photocycloaddition of 4-isopropenyltoluene **48** with 2,4-dioxopentanoate **49** in ethyl acetate gave four products (**50**–**53**) in 0.2, 48, 10 and 23% yields[17]. The major

adduct **51** is apparently formed by a retro-aldol reaction of photoadduct **50**. The by-products, **52** and **53**, are formed by disproportionations of a biradical intermediate in the photodimerization of olefin **48**. The major cycloadduct **51** was then transformed into isolaurene **54** via four steps, as outlined in Scheme 16[17].

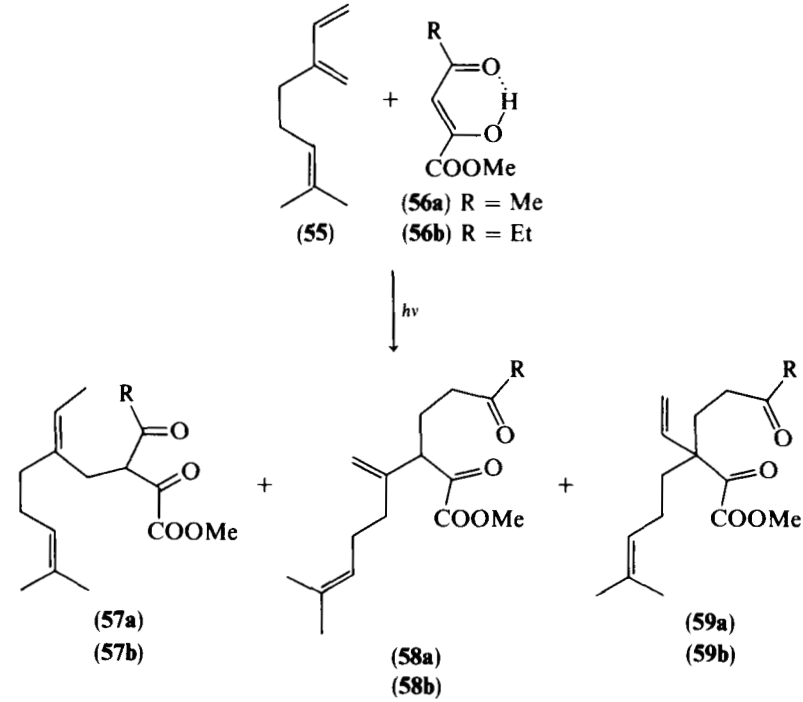


SCHEME 16

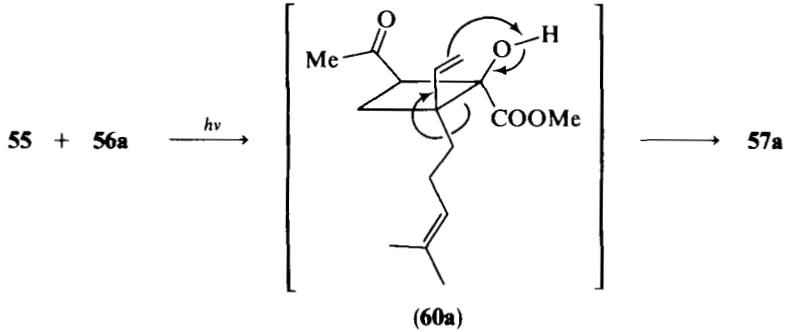
The photocycloadditions of the conjugated monoterpene diene, myrcene **55**, with methyl 2,4-dioxopentanoate **56a**, and with methyl 2,4-dioxohexanoate **56b**, were studied[18]. **56a** gave three products (**57a**, **58a** and **59a**), with the latter two being the major ones (Scheme 17). The photoaddition of **55** with **56b** gave parallel results with the formation of **57b**, **58b** and **59b**. The formation of the minor products **57a** and **57b** was enhanced at low temperatures (28% at *ca* 35 °C). According to the authors, **57a** is formed through a 1,5-hydrogen shift of the metastable $[2 + 2]\pi$ adduct **60a**, as outlined in Scheme 18.

2. β-Oxocarboxylic acid esters

Type-1 photochemical cleavage of α-alkylated β-keto esters is a simple approach to bifunctional synthons, which has already been exploited in the synthesis of some natural

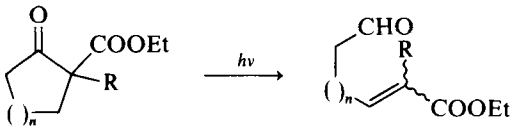


SCHEME 17



SCHEME 18

products[19]. Photochemical preparations of ω-formylalkenoates **63** or **64** from β-keto esters **61** or **62** have been reported[20], and cyclopentanone derivatives **61** gave a mixture of (*E*)- and (*Z*)-forms of formylalkenoates in combined yields of 68–85% (Scheme 19). Similar irradiation of the cyclohexanone derivatives **62** also gave a mixture of two geometrical isomers of formylalkenoates, but in low yields. The type-1 photocleavage of six-membered rings is complicated by two side reactions: a type-2 elimination of the

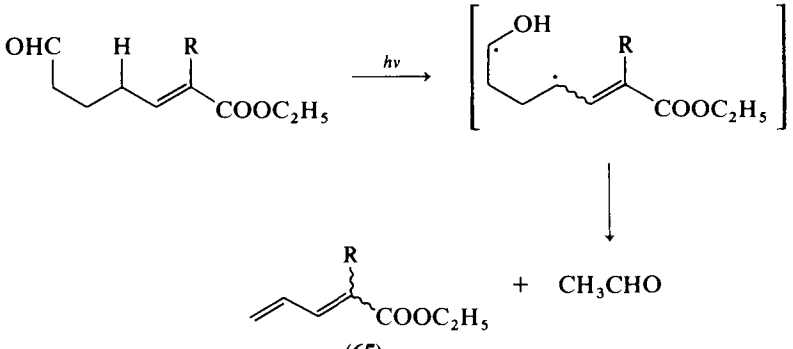


(**61**) $n = 1$ (**63**) $n = 1$
(**62**) $n = 2$ (**64**) $n = 2$

R = H, Me, Et, Pr, Bu

SCHEME 19

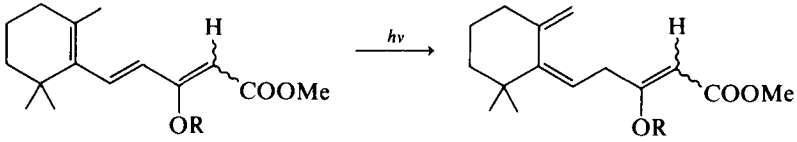
side chain R (when R is ethyl or alkyl higher than ethyl) and a type-2 elimination of an aldehyde to give dienic esters **65** (Scheme 20).



(**65**)

SCHEME 20

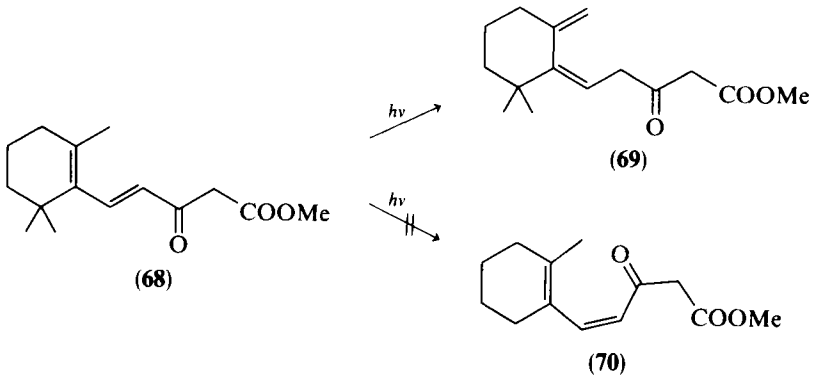
Photochemical reactions of certain olefinic β-keto esters and their enol ethers have been reported by White and colleagues in connection with the synthesis of certain carbocyclic structures by cyclization of 1,5-dienes[21]. Thus, the irradiation of *E*- and *Z*-isomers of the trimethylsilyl enol ether **66a** of a β-keto ester gave a mixture of geometrical isomers **67a** with an exo-methylene group in quantitative yield. Similar results were obtained when the *E*- or *Z*-isomer of the enol acetate **66b** was irradiated. The transformation of **66** into **67** involves a 1,5-hydrogen migration (Scheme 21).



(**66a**) R = $SiMe_3$ (**67a**) R = $SiMe_3$
(**66b**) R = OAc (**67b**) R = OAc

SCHEME 21

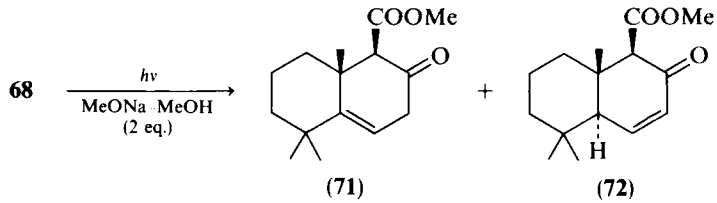
Irradiation of the parent β-keto ester **68** in tetrahydrofuran or methanol also resulted in the formation of a deconjugated β-keto ester **69**, arising from 1,5-hydrogen migration, in 60% yield (Scheme 22). Thus, the predominant photochemical paths from **66a**, **66b**



SCHEME 22

and **68** appear to be 1,5-hydrogen migrations, and not *trans*-**68**–*cis*-**70** isomerization or carbocycle formation.

The same authors[21] have reported the synthesis of a thermodynamically equilibrated mixture of bicyclic compounds **71** and **72** in 36 and 30% yields by irradiating the β-keto ester **68** in methanol containing sodium methoxide (Scheme 23). The initial product of this photoreaction is probably **71**, but the mechanism of the formation is obscure.

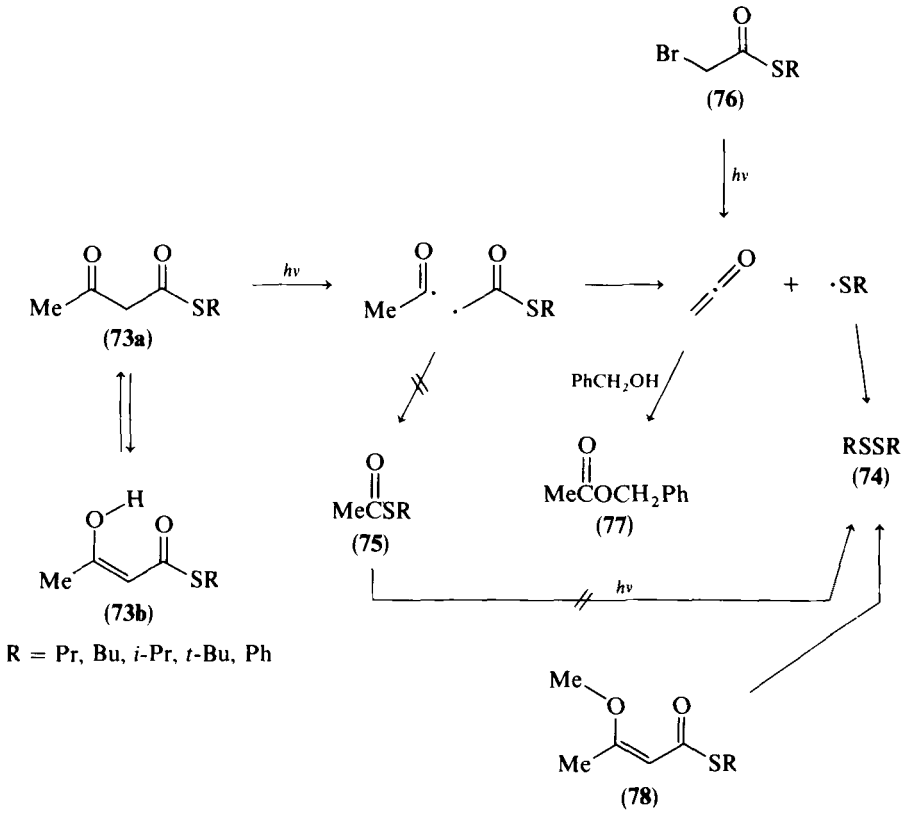


SCHEME 23

Photoreactions of some β-ketocarboxylic acid esters of thiols have been reported[22]. Thus, the irradiation of a benzene solution of *S*-alkyl-3-oxobutanethioate (**73a**), which is in equilibrium with the enol **72b**, gave dialkyl disulphides (**74**) (2–59%) arising from a type-1 cleavage of the 3-oxo group (Scheme 24). No *S*-alkyl thioacetates (**75**) or thiolactones, which are expected to be formed through the type-1 reaction and δ-hydrogen abstraction by the β-oxo group, respectively, were formed in this photoreaction. Irradiation of *S*-butyl α-bromothioacetate (**76**) in benzene also gave dibutyl disulphide **74** in 37% yield.

The pathway for the formation of the disulphide **74** can be explained by assuming a type-1 cleavage of 3-oxobutanethioates **73a**, followed by expulsion of a thiyl radical from the resulting radical $\cdot CH_2COSR$ (Scheme 24). The intermediate ketone can be trapped as benzyl acetate **77** when butyl 3-oxobutanethioate is irradiated in benzene containing 20% benzyl alcohol. The type-1 cleavage seems to take place from the n,π^* triplet state of the keto form of the 3-oxobutanethioate **73a**, since formation of the disulphides **74** is suppressed by the addition of 1,3-pentadiene.

An alternative pathway for the formation of disulphides **74** involving a cleavage of the sulphur–acyl bond of the excited 3-oxobutanethioate (**73a**) was excluded, since neither direct nor acetone-sensitized irradiation of *S*-propyl thioacetate (**75**; R = propyl) gave the disulphide **74** (R = propyl).



SCHEME 24

The formation of disulphide **74** from an excited enol form **73b** is also excluded, since no disulphides (**74**) are formed when a benzene solution of *S*-butyl-3-methoxy-2-butanethioate **78** is irradiated under the above-mentioned conditions.

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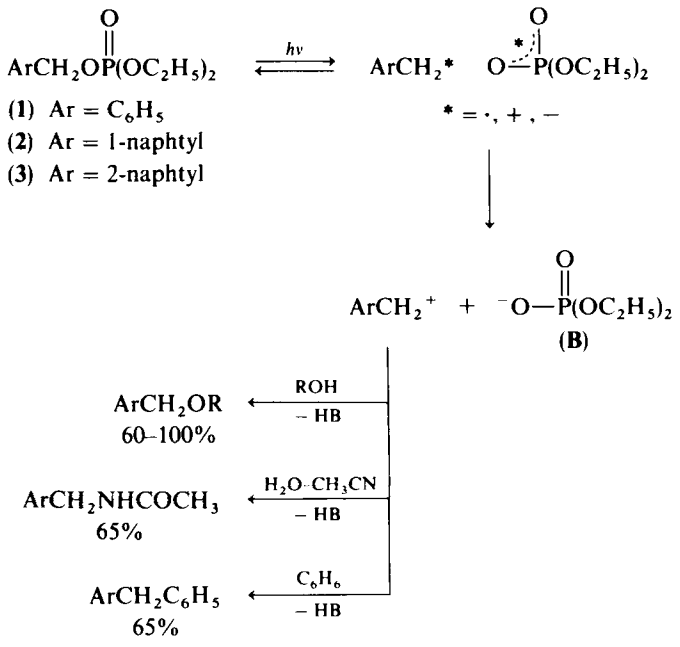
E. Phosphoric Esters

Since arylmethyl and phenacyl phosphates are photolabile, their photochemical reactions have attracted much attention in connection with problems involving functional group protection, phosphorylation and the generation of electrophiles.

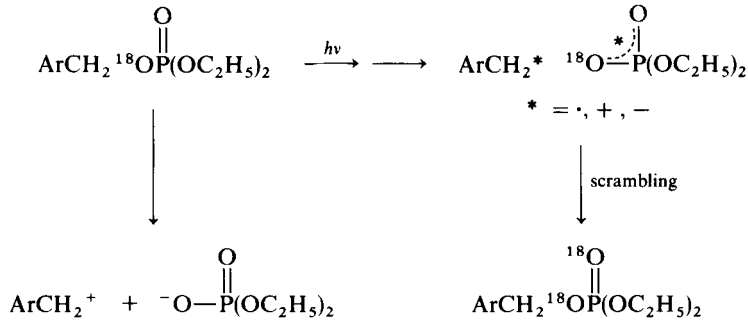
Givens and Matuszewski[1] have reported that excited arylmethyl phosphates readily expel the dialkyl phosphate anion. For example, benzyl phosphate (**1**), 1-naphthyl phosphate (**2**) and 2-naphthyl phosphate (**3**) undergo efficient photofragmentation to give the phosphate anion, as well as the corresponding reactive electrophiles upon irradiation (Scheme 1).



SCHEME 1

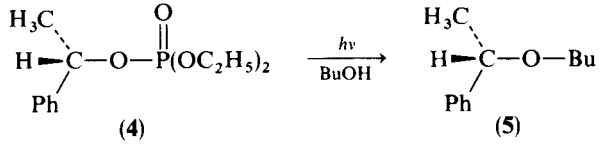
These photogenerated electrophilic benzylic carbocations then attack the solvent through nucleophilic substitution (in alcohol or acetonitrile), or by electrophilic aromatic substitution (in benzene), resulting in the major products shown in Scheme 1 while the corresponding ethyl ether and radical coupling products are often minor accompanying products. The naphthylmethyl phosphates, **2** and **3**, were reported to undergo especially efficient and clean photofragmentations, which as shown by sensitization experiments take place from their excited singlet state.

A mechanistic path for the arylmethyl phosphate ester photolysis, supported by oxygen-18 labelling, stereochemical and substituent effect studies, is outlined in Scheme 2; the ^{18}O-labelling and stereochemical studies indicated the intervention of an equilibrating intermediate, possibly an ion pair, capable of scrambling the benzylic and phosphoryl oxygens (Scheme 2). Measurements involving the quantum efficiencies for an oxygen-label exchange have indicated the importance of the recombination pathway for the energy dissipation of the excited ester. Moreover, the sum of the quantum efficiencies for all photochemical reactions established almost unit efficiency for this bond-dissociation process.



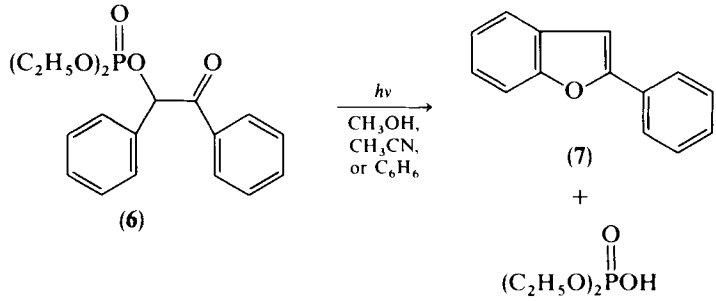
SCHEME 2

This ion-pair mechanism was also supported by the photoracemization of the optically active phenylethyl phosphate ester (**4**). Thus, the photolysis of (*S*)-(−)-**4** in butanol was discontinued at 77% conversion of the starting optically active phosphate ester (**4**). Examination of the recovered ester (**4**) indicated 28% net racemization. Moreover, the product of ether (**5**) was largely racemic with a slight preference for net retention (5.5%) of the configuration (Scheme 3). According to Givens and Matuszewski, the weakly basic phosphonate anion delivers the nucleophile to the front face of the carbocation by a general-base catalyzed deprotonation of the solvent, resulting in the formation of a slight excess of the retention product (**5**). They also found that the irradiation of benzoin diethyl



(**4**) 28% net racemization (**5**) 5.5% net retention

SCHEME 3

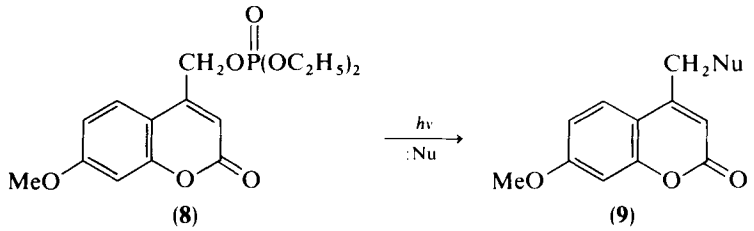


SCHEME 4

phosphate gave exclusively 2-phenylbenzo[*b*]furan (**7**), arising from an intramolecular rearrangement, regardless of the solvent, as outlined in Scheme 4.

In contrast to the arylmethyl phosphate esters (**1**, **2** and **3**), the photolysis of the phosphate (**6**) takes place via a triplet manifold, as proved by the efficient quenching in the formation of the product with triplet quenchers. This photoreaction appears to be a good method for the generation of α-keto carbocations. It may also provide a potential photoprotection group for the phosphate moiety.

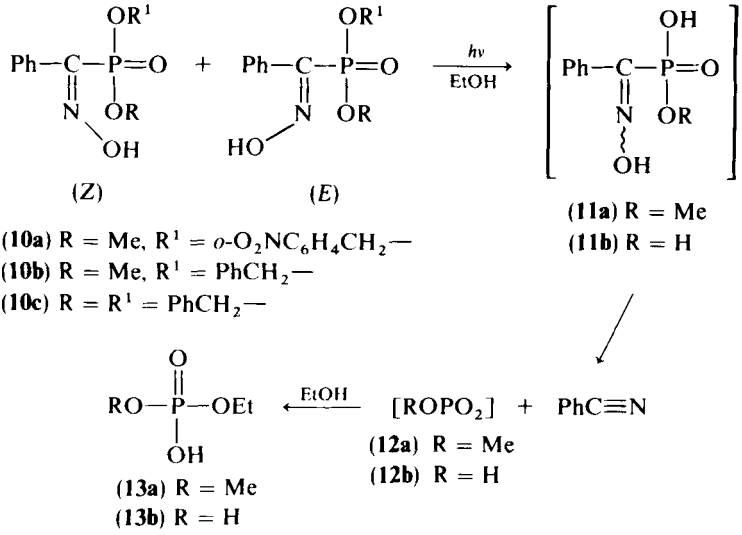
A useful application of the photoreaction of phosphate esters was demonstrated with coumaryl diethyl phosphate (**8**) (Scheme 5). Irradiation of the phosphate **8** with 360 nm light in the presence of a wide variety of such nucleophiles as methanol, piperidine, cysteine, tyrosine, α-chymotrypsin and HMT gave product **9**. As outlined in Scheme 5, several organic substrates, including such enzymes as α-chymotrypsin and histamine *N*-methyltransferase (HMT), can be covalently 'tagged' with the highly fluorescent coumaryl moiety. The phosphate **8** may therefore be applied to affinity labelling.



SCHEME 5

This photochemical cleavage of the arylmethyl group of arylmethyl phosphates was recently used for the synthesis of some benzyl esters of [α-(hydroxyimino)benzyl]phosphonic acid[2]. This reaction is of utility for photoinduced phosphorylation through fragmentation to monomeric metaphosphates. Thus, the irradiation of *o*-nitrobenzylmethyl[α-(hydroxyimino)benzyl]phosphonate **10a** (as a 1:1 mixture of *E*,*Z*-isomers) gave ethyl methyl hydrogen phosphate (**13**) in over 90% yield. Identical results were obtained when the *o*-nitrobenzyl group was replaced by a benzyl group: irradiation of benzylmethyl[α-(hydroxyimino)benzyl]phosphonate (**10b**) in ethanol gave ethyl methyl hydrogen phosphate **13a** (Scheme 6).

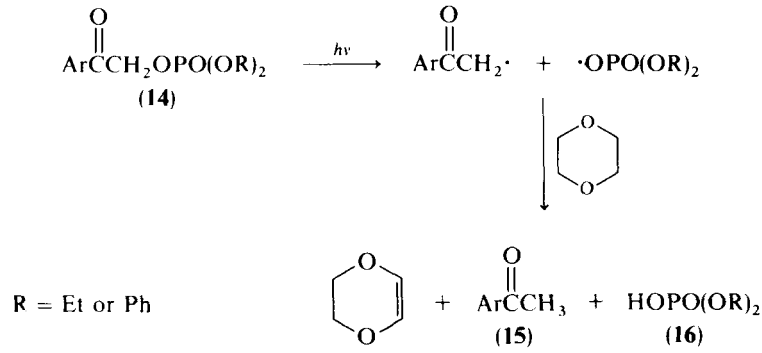
The formation of phosphate **12a** in these experiments indicates that the photolysis resulted in the debenzylation to give methyl hydrogen[α-(hydroxyimino)benzyl]phosphonate **11a**. This in turn fragmented to methyl metaphosphate (**12a**) which then phosphorylated ethanol.



SCHEME 6

While these results indicated that reagents such as **10a** and **10b** can be used for the synthesis of phosphodiesters under mild conditions, Breuer and colleagues further extended their method to the synthesis of phosphomonoesters; irradiation of dibenzyl[α-(hydroxyimino)benzyl]phosphonate (**10c**, $E:Z$ = 8:2) in ethanol gave, via the consecutive intermediacy of **11b** and of metaphosphoric acid (**12b**), ethyl dihydrogen phosphate (**13b**) and benzonitrile in nearly quantitative yields. Benzyl α-hydroxyimino phosphonates may thus be used as novel, mild phosphorylating agents via photogenerated acids.

Epstein and Garrossian[3] have reported that excited *p*-methoxyphenacyl esters of substituted phosphates readily fragment at their C—O bond, and that the phenacyl group can be used as a photosensitive protecting group of phosphates useful in the synthesis of phosphates of biological importance[1] (Scheme 7). Thus, the photolysis of *p*-methoxyphenacyl phosphates (**14**) in dioxane leads to homolysis of the C—O bond to give arylmethyl ketones **15** (84–91%) and diphenyl or diethyl phosphate **16** in 74–86% yields.



SCHEME 7

References to Section I.E

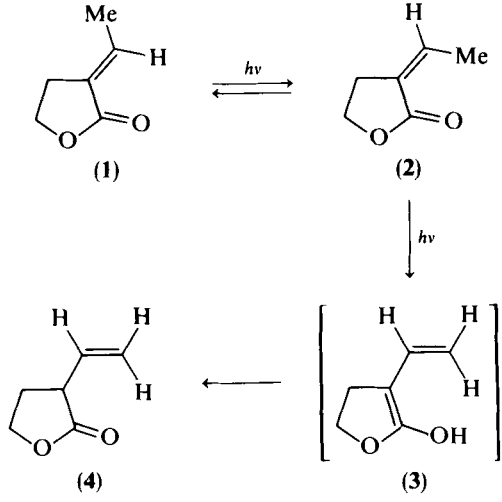
1. R. S. Givens and B. Matuszewski, *J. Am. Chem. Soc.*, **106**, 6860 (1984) and references cited therein.
2. E. Breuer, M. Mahajna, L. D. Quin and G. S. Quin, *J. Org. Chem.*, **56**, 4791 (1991).
3. W. W. Epstein and M. Garrossian, *J. Chem. Soc., Chem. Commun.*, 533 (1987).

II. LACTONES

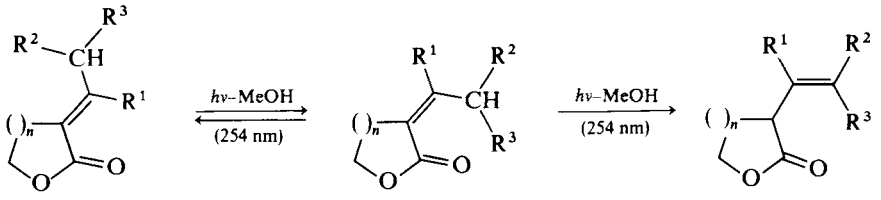
Early studies of the primary photochemical reactions of saturated lactones, such as photodecarbonylations and photodecarboxylations were adequately reviewed by Givens and Levi[1] in the previous volume of this series. Subsequent progress in the photochemical transformation of lactones has been made mainly in the area of unsaturated lactones, thiolactones and related compounds. Some of these photoreactions have considerable synthetic utility.

A. α,β-Unsaturated γ- and δ-Lactones

If the α-alkylidene lactones (e.g. **1**) possess hydrogens attached to the γ-position oriented *syn* with respect to the lactone carbonyl, they can be intramolecularly abstracted by the excited carbonyl in competition with *E–Z* isomerization (e.g. **1** ⇄ **2**) to form dienol intermediates (e.g. **3**) which can revert to give β,γ-unsaturated lactones (e.g. **4**) by protonation (Scheme 1). This photodeconjugation of conjugated lactones, which is entirely analogous to the photoisomerization of α,β-unsaturated esters into the β,γ-unsaturated isomers[2], was reported by Ohga and Matsuo[3]. On the basis of the solvent effect on the quantum yield and the wavelength dependence of the photoreactions they concluded that the photoisomerization and *cis–trans* isomerization took place from the n,π* triplet (T_2) and π,π* triplet (T_1) states, respectively.



SCHEME 1



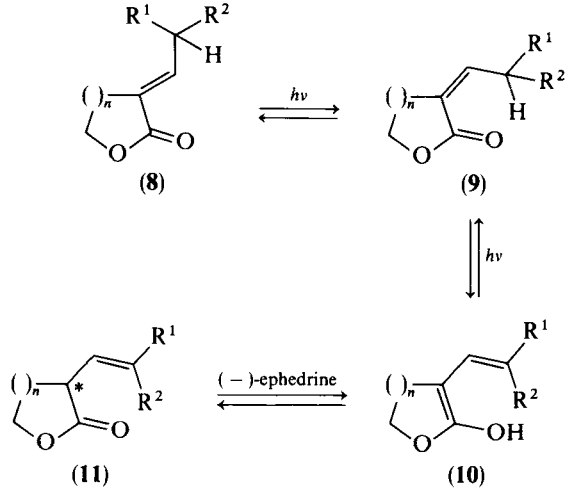
(5a–f) (6a–f) (7a–f)

(a) $R^1 = R^2 = R^3 = H$, $n = 1$
(b) $R^1 = R^2 = H$; $R^3 = Me$, $n = 1$
(c) $R^1 = R^2 = H$; $R^3 = Et$, $n = 1$
(d) $R^1 = H$; $R^2 = R^3 = Me$, $n = 1$
(e) $R^1 = Me$; $R^2 = R^3 = H$, $n = 1$
(f) $R^1 = R^2 = R^3 = H$, $n = 2$

SCHEME 2

The photodeconjugation of α,β-unsaturated lactones has recently been applied to the preparation of some α-vinyl lactones[4]. Thus, irradiation of α-alkylidene-butyrolactones **5a–f** gave the corresponding 3-alkenyl compounds **7a–f** in 72–83% yields (Scheme 2). The formation of **7a–f** is independent of the initial geometry of the C—C double bond of the α-alkylidene lactones **5** since *E–Z* photoisomerization is a very fast process.

Pete and colleagues have also reported that the photodeconjugation of alkylidenelactones in the presence of catalytic amounts of (−)-ephedrine led to the formation of an enantiomeric excess of photodeconjugated lactones having the 3-(*R*) configuration[5] (Scheme 3). They reported that the enantioselectivity in this photodeconjugation depends on the structure of the starting conjugated lactones, and that diastereotopic discrimination increased when the reaction was carried out at a low temperature.



(8) (9) (11) (10)

SCHEME 3

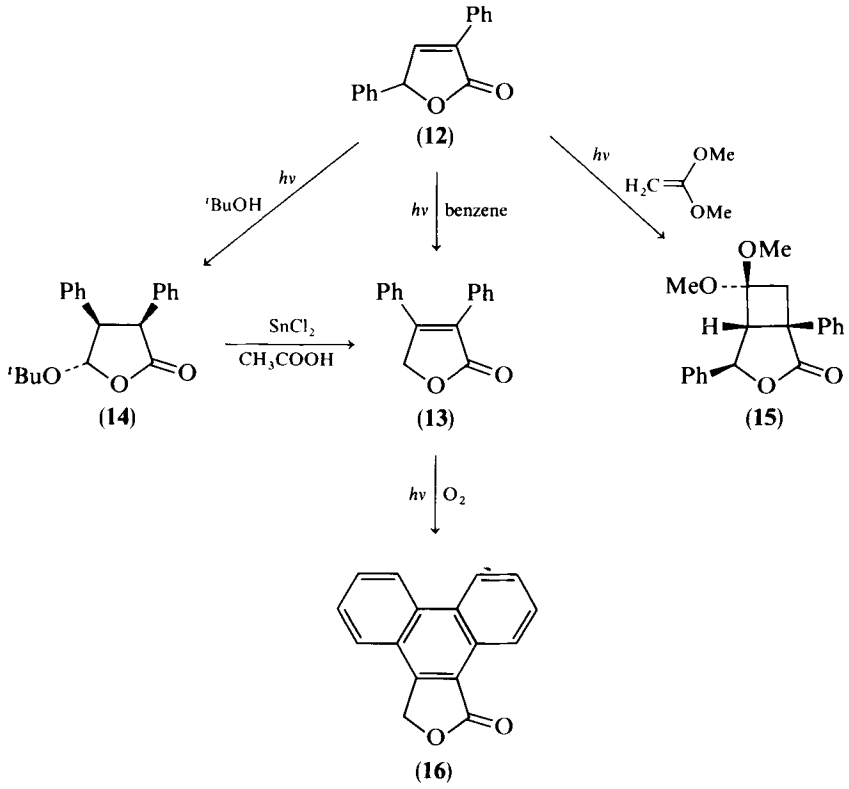
The results of enantioselective deconjugation are summarized in Table 1. This reaction is entirely analogous to the photodeconjugation of α,β-unsaturated acid esters described in Section I.B.

TABLE 1

	n	R^1	R^2	Conditions[a]	Yield (%)	Configuration	e.e. (%)
8a	1	H	H	A	100	*R*	2.2
8a	1	H	H	B	100	*R*	26.7
8b	0	H	H	B	100	*R*	—
8c	0	Me	H	C	80	*R*	10
8d	0	Me	Me	D	64	*R*	5
8d	0	Me	Me	C	85	*R*	25.1

[a] A: pentane–diethyl ether (90:10), 25 °C. B: pentane–CH_2Cl_2 (95:5), −78 °C. C: CH_2Cl_2, −78 °C. D: CH_2Cl_2, 25 °C.

Apart from these type-II photoreactions of the excited carbonyl group of the exocyclic α,β-unsaturated lactones, several intriguing reports concerning photochemical rearrangements as well as intra- and intermolecular [2 + 2]π photocycloadditions were made in the eighties.

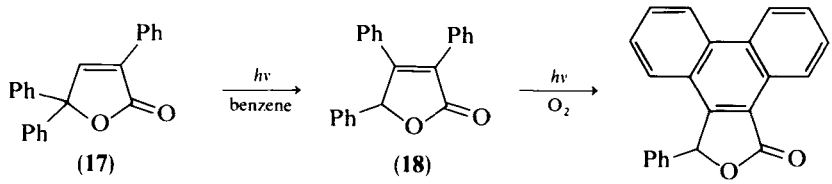


SCHEME 4

Padwa and Dehm have reported that irradiation of 3,5-diphenyl-2(5*H*)-furanone (**12**) gave 3,4-diphenyl-2(5*H*)-furanone (**13**) in quantitative yield (Scheme 4)[6]. If this reaction was carried out in the presence of molecular oxygen, furanone **13** reacts further by the well-known stilbene–phenanthrene cyclization route to produce phenanthro[9,10-*c*]furanone **16** (Scheme 4). Interestingly, the only product isolated (87%) in the photoreaction of furanone **12** in *t*-butyl alcohol was *cis*-3,4-diphenyl-*trans*-5-*tert*-butoxy-γ-lactone **14**, which was transformed into **13** by treatment with stannous chloride in refluxing acetic acid (Scheme 4).

The photochemical reaction of furanone **12** with excess 1,1-dimethoxyethylene in benzene, on the other hand, gave a single [2 + 2]photoadduct **15** in nearly quantitative yield. The photochemical rearrangement of **12** → **13** was completely suppressed in this case (Scheme 4).

Similar irradiation of 3,5,5-triphenyl-2(5*H*)-furanone (**17**) gave 3,4,5-triphenyl-2(5*H*)-furanone (**18**) as the initial product with a quantum yield 0.47 (78% yield). Prolonged irradiation led to the formation of phenylphenanthro[9,10-*c*]furanone (**19**) in high yield (Scheme 5).

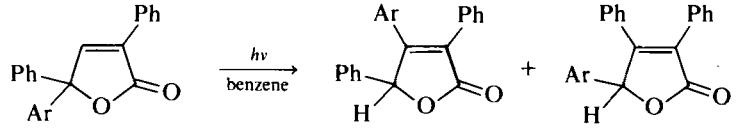


(**17**) (**18**) (**19**)

SCHEME 5

Photolysis of furanone **17** in benzene sensitized with acetophenone gave also **18** with the same quantum yield (0.47). The equivalence of the direct and sensitized quantum yields, together with quenching by piperylene, provided strong evidence for the involvement of a triplet excited state.

Photolysis of the 5-(4′-anisyl)- (**20**) and 5-(4′-cyanophenyl)-3,5-diphenyl-2(5*H*)-furanone (**21**) indicated (Scheme 6) that the *p*-anisyl group migrated in strong preference to phenyl (**22**/**23** = 16/1) as did also the *p*-cyanophenyl group (ratio **22**/**23** = 3.5/1). These rearrangements were sensitized by propiophenone and were quenched by piperylene, indicating the involvement of a triplet state upon direct irradiation. According to Padwa, the preference of cyanophenyl over phenyl clearly suggests that the β-carbon atom of the 2(5*H*)-furanone system does not exhibit electron-deficient reactivity. Similarly, he suggested that the preferential migration of the *p*-anisyl group over phenyl is a clear indication of the unlikeliness of a contribution from $^{-}CC{=}CO^{+}$ as a representation of the excited state of the 2(5*H*)-furanone system in non-polar solvents. The results could



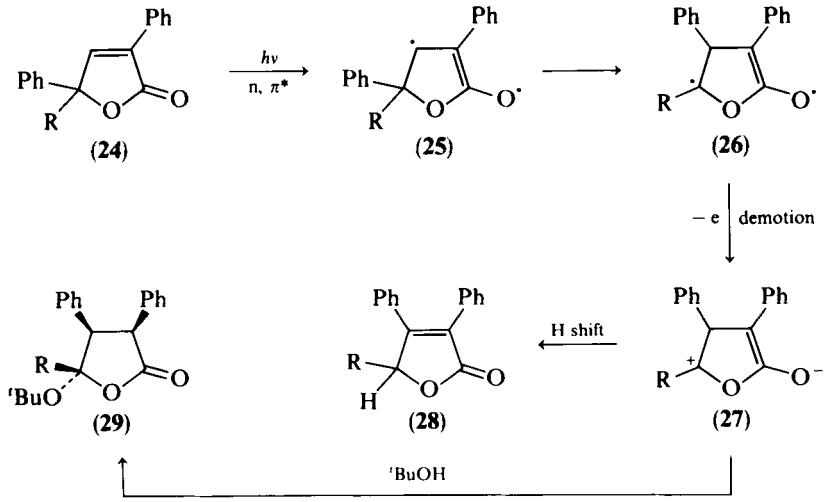
(**20**) Ar = *p*-$CH_3OC_6H_4$
(**21**) Ar = *p*-NCC_6H_4

(**22**) (**23**)

SCHEME 6

therefore be explained by invoking a low-lying n-π^* triplet as the reactive electronic state involved in these rearrangements.

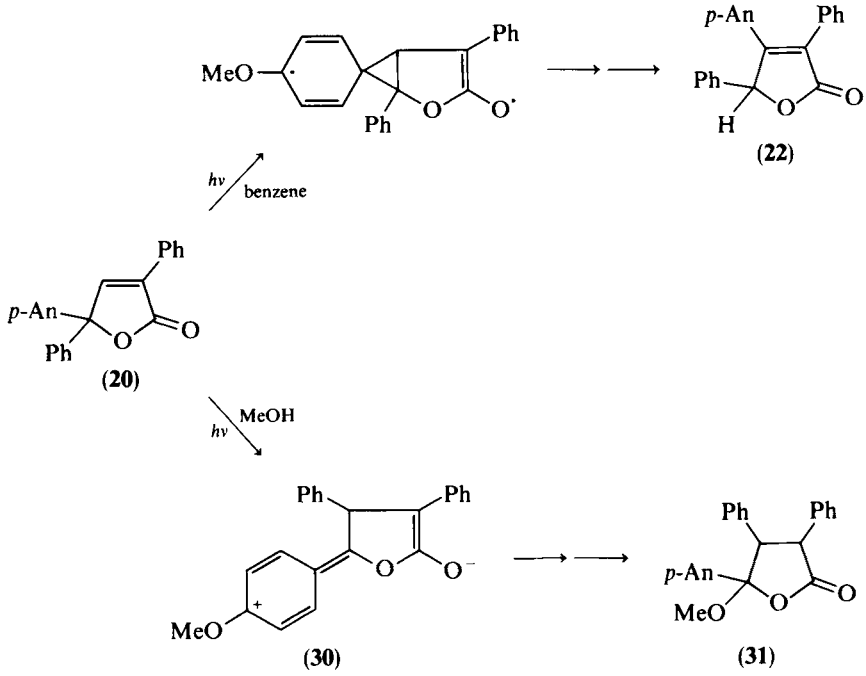
The proposed mechanism for the photoreactions of furanones is outlined in Scheme 7. Thus, excitation of furanone **24** generates the n,π^* triplet state **25** by an efficient intersystem crossing. Bridging of the phenyl group and a subsequent cleavage, analogous to a di-π-methane rearrangement, gives **26**. Electron demotion through the divalent oxygen atom proceeds to give a zwitterion **27**, which is trapped by the alcoholic solvent. In the absence of a hydroxylic solvent the zwitterion undergoes a hydride shift to give **28**.



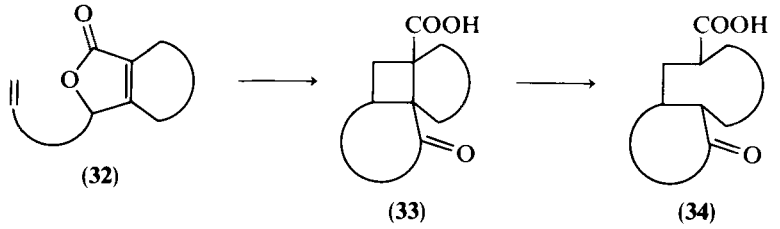
SCHEME 7

Padwa and colleagues have investigated more precisely the migratory aptitudes in the photochemical rearrangements of 2(5*H*)-furanones[7]. They found that, in certain instances, the excited migratory aptitudes in 5,5-diaryl-2(5*H*)-furanones can be controlled by stabilizing the non-migrating aryl group. They estimated the rate constants of aryl group migration (triplet reaction) for furanones **17**, **20** and **21**, by quenching studies using piperylene, as being 0.18×10^{10}, 1.3×10^{10} and 0.9×10^{10} s^{-1} for the migration of phenyl, *p*-anisyl and *p*-cyanophenyl groups in benzene. Thus, *p*-anisyl and *p*-cyanophenyl are more reactive migrating groups than phenyl by factors of 7.2 and 5.0, respectively. They also found that the rate of phenyl migration is accelerated 1.4-fold by non-migrating *p*-cyanophenyl and is decreased twofold by a non-migrating *p*-anisyl group when benzene is used as the solvent. They obtained quantum yields, rate data and migratory aptitudes for compounds **17**, **20** and **21** in both benzene and methanol. An interesting feature of these rearrangements is that a substantial crossover in migratory aptitude occurs upon changing the solvent from benzene to methanol. According to Padwa, these results suggest that the photoreaction of the *p*-anisyl furanone **20** proceeds from a diradical state in benzene to give **22**, while in methanol the rearrangement occurs from the zwitterionic state **30** to give **31** (Scheme 8).

The combination of intramolecular photochemical [2 + 2] cycloaddition of α,β-unsaturated lactones bearing a side chain such as but-3-enyl, with a ring opening of the resulting photoadduct via a retro-aldol or reductive cleavage reaction has been investigated by Coates and colleagues, and has proved to be a useful synthetic method



SCHEME 8

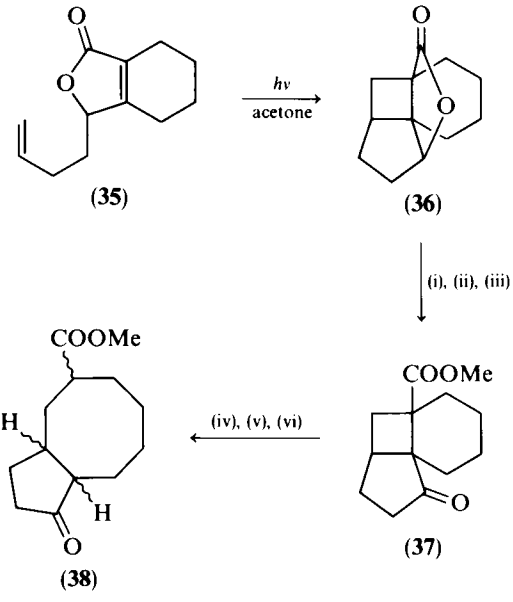


SCHEME 9

for constructing polycarbocyclic rings[8]. This method, outlined in Scheme 9, is essentially a new variation of the intramolecular de Mayo reaction[9].

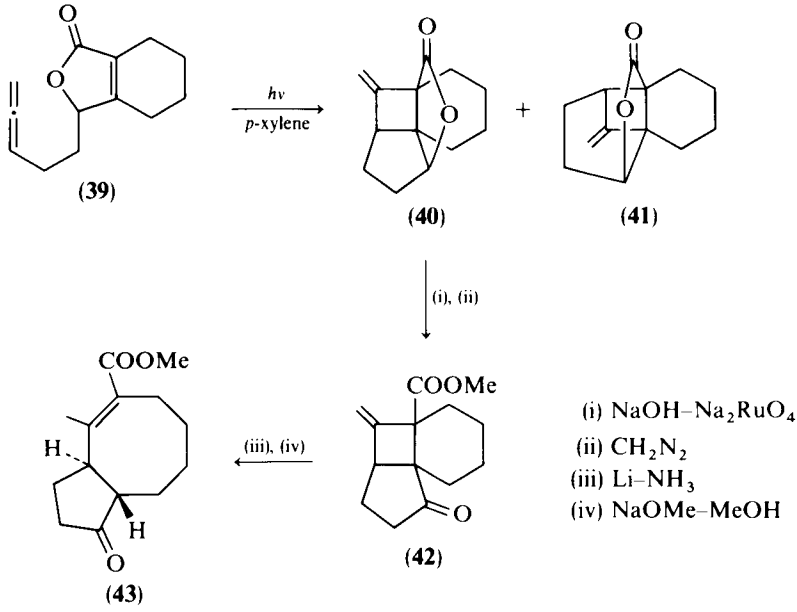
Thus, intramolecular photochemical [2 + 2] cycloaddition of fused α,β-unsaturated γ-lactones **32** bearing alkenyl side chains in the γ-position and oxidation of the resulting cyclobutylcarbinol gives a γ-keto acid **33**. Subsequent reductive cleavage of the cyclobutane ring gives rise to bicyclic ε-keto acids with differentially functionalized rings. Coates and colleagues have applied this annelation procedure to the synthesis of methyl decahydro- and octahydro-1-oxo-1*H*-cyclopentacyclooctene-5-carboxylates. Two examples of this method are outlined in Schemes 10 and 11.

Irradiation of butenolide **35** in acetone gave the tricyclic lactone **36** in 77% yield. Subsequent hydrolysis and oxidation gave the keto acid **37** (50%). Three further steps gave decahydro-1-oxo-1*H*-cyclopentacyclooctene-5-carboxylate **38** in 44% yield.



(i) $NaOH–H_2O$ (iv) $Li–NH_3$
(ii) Na_2RuO_4 (v) H_2CrO_4
(iii) CH_2N_2 (vi) CH_2N_2

SCHEME 10

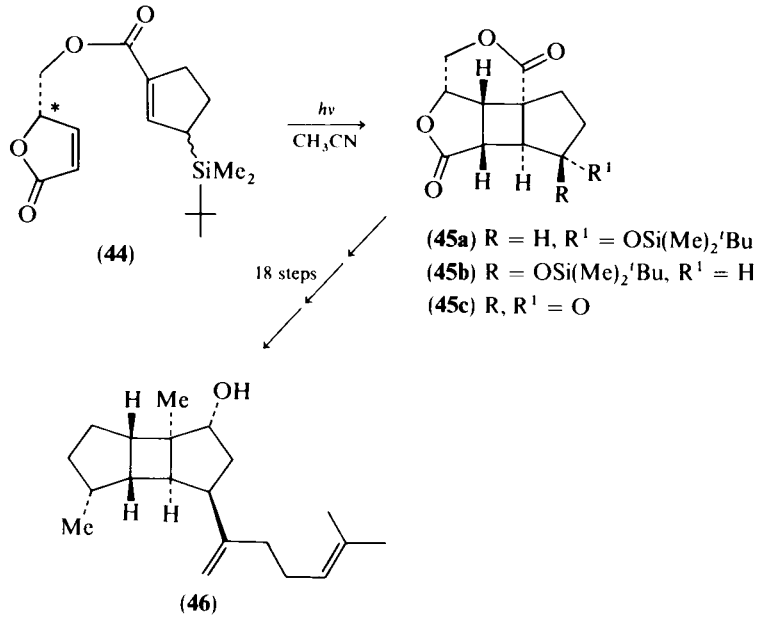


(i) $NaOH–Na_2RuO_4$
(ii) CH_2N_2
(iii) $Li–NH_3$
(iv) NaOMe–MeOH

SCHEME 11

Similar irradiation of the 3,4-pentadienyl lactone **39** in *p*-xylene gave a 2:1 ratio of fused and bridged cycloadducts **40** and **41** in 33% and 16% yields. Transformation of the tricyclic lactone **40** gave the conjugated ester **43** through the keto ester **42** in 54% overall yield.

The intramolecular [2 + 2] photocycloaddition of the α,β-unsaturated lactone has also been used as the key step in the first total synthesis of stoechospermol **46**, a representative spatane diterpene by Koga and colleagues (Scheme 12)[10]. Thus, irradiation of a mixture of butenolide diastereomers in acetonitrile afforded a 1:1 mixture of epimers **45a** and **45b**, both of which gave the same ketone **45c** after desilylation, followed by Jones oxidation. This indicated that the intramolecular cycloaddition is stereo- and regioselective, and is fully controlled by the chiral centre of the butenolide portion. The ketone **45c** was transformed into stoechospermol **46** in 18 steps (Scheme 12).



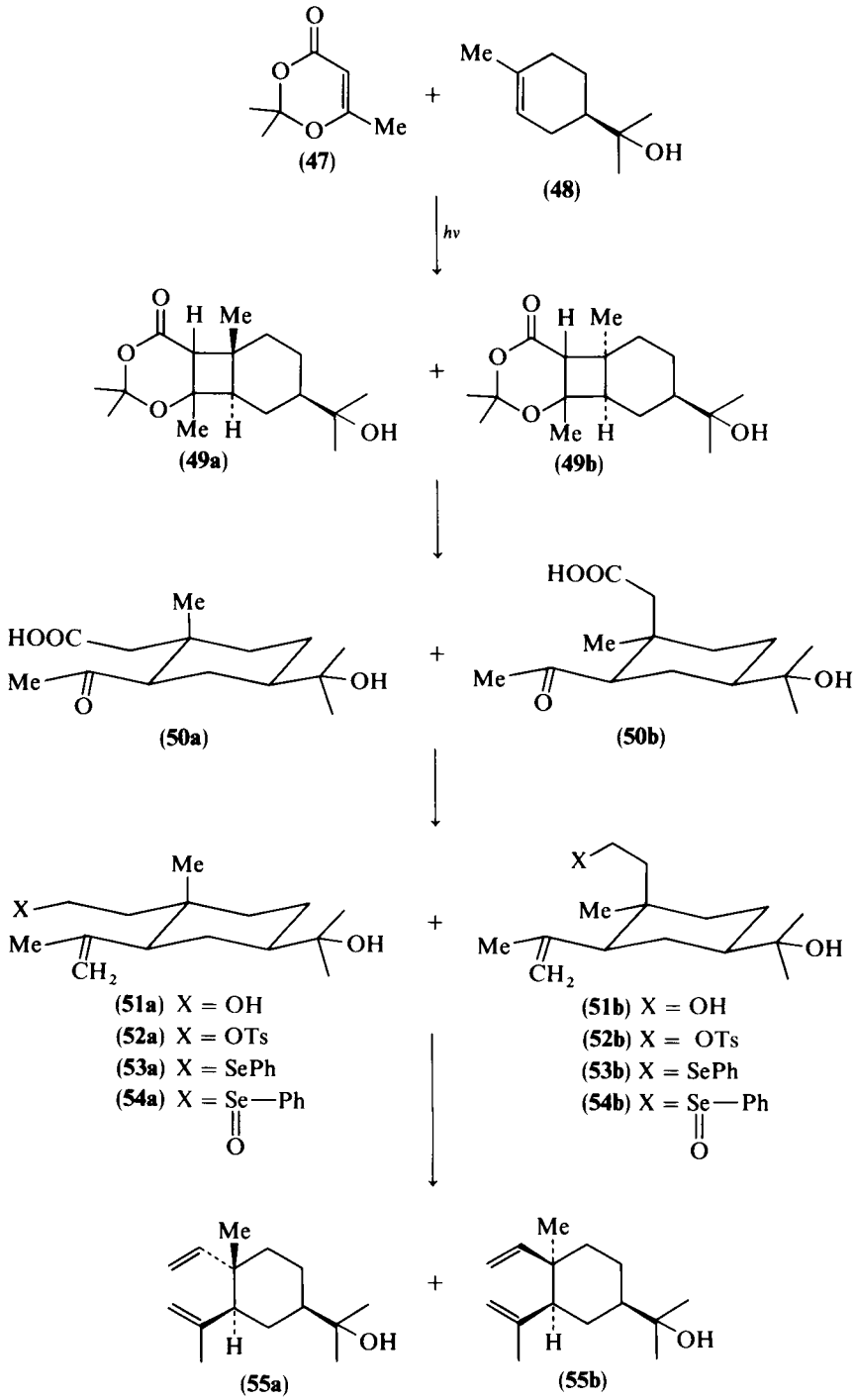
(44)

(45a) R = H, R¹ = OSi(Me)₂ᵗBu
(45b) R = OSi(Me)₂ᵗBu, R¹ = H
(45c) R, R¹ = O

(46)

SCHEME 12

The intermolecular photochemical [2 + 2] cycloadditions of various α,β-unsaturated γ- and δ-lactones with alkenes have been studied[11,12]. The cycloaddition of α,β-unsaturated butenolides with cyclopentene proceeds through the triplet state of the lactone, since it was sensitized by acetone and quenched by piperylene. More recently, an intermolecular [2 + 2] photochemical cycloaddition between a six-membered α,β-unsaturated lactone and an optically active cyclohexene derivative was used as the key step in a total synthesis of (+)-elemol by Baldwin and colleagues, as outlined in Scheme 13[13]. Irradiation of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**47**) and (−)-α-terpineol (**48**) in acetone actonitrile gave a mixture of four stereoisomers of photoadducts in 88–94% yield. Of these isomers, the majority comprised head-to-head adducts **49a** and **49b**, which on basic hydrolysis gave a mixture of keto acids **50a** and **50b** in the approximate ratio of 3.5/1. Exposure of the keto acid mixture **50** to 3 equivalents of methylenetriphenylphosphorane, followed by reduction afforded the alkanediols **51a** and **51b**. Conversion of

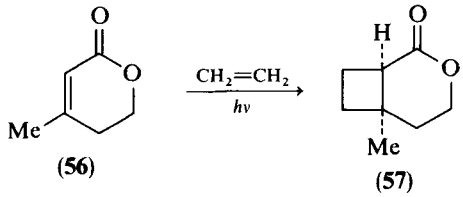

(47)
(48)
hv
(49a)
(49b)
(50a)
(50b)
(51a) X = OH
(52a) X = OTs
(53a) X = SePh
(54a) X = Se—Ph
(51b) X = OH
(52b) X = OTs
(53b) X = SePh
(54b) X = Se—Ph
(55a)
(55b)

SCHEME 13

the major diol **51a** (42.6%) to elemol was accomplished by elimination of the selenide **53a** via the tosylate **52a** derived from the primary alcohol **51a**. Thus, oxidation of **53a** with *t*-butyl hydroperoxide in THF followed by flash chromatography afforded 54% of (+)-elemol **55a**. Similar treatment of the minor diol isomer (**51b**) gave diene **55b** in 23% yield for the three steps. (−)-α-Terpineol has thus been converted to (+)-elemol in seven steps and 16.7% overall yield.

The [2 + 2] photocycloaddition of allene to anhydromevalonolactone **56** was the key step in the synthesis of (±)-lineatin, the aggregation pheromone of an ambrosia beetle[14].

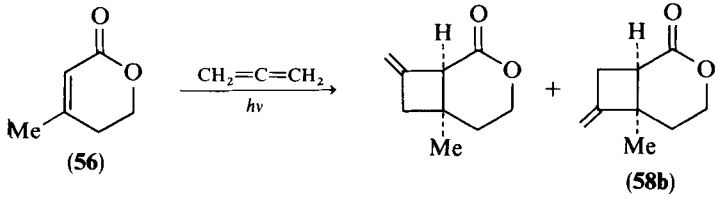
It had already been reported in the seventies that the photocycloaddition of lactone **56** and ethylene gave the cycloadduct **57** in 70% yield (Scheme 14)[12b,15]. Weiler and



(**56**) (**57**)

SCHEME 14

colleagues[14] have found that irradiation of an acetone solution of lactone **56** and allene gave a 3:2 mixture of 1:1 cycloaddition products **58a** and **58b** in 80% yield (Scheme 15). An effort to improve the low regioselectivity in the photoaddition (temperature, polarity of solvent and sensitizer) was unsuccessful. On treatment with excess methyl-

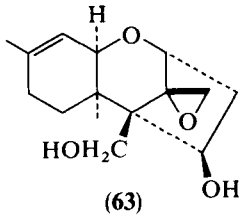


(**56**) (**58b**)

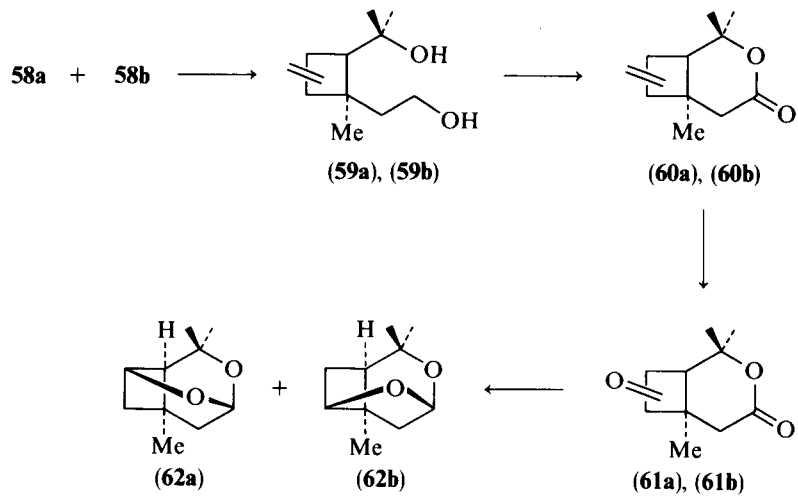
SCHEME 15

lithium, a mixture of the adducts gave the diols **59a** and **59b** in 97% yield. These diols were oxidized to the lactones **60a** and **60b** in 70–75% yield, which were then ozonized to give the keto lactones **61a** and **61b** in *ca* 70% yield. DIBAL reduction of **61a** and **61b** followed by work-up by acid gave a mixture of (±)-lineatin **62a** and its isomer **62b** in *ca* 95% yield. These were readily separated by column chromatography (Scheme 16).

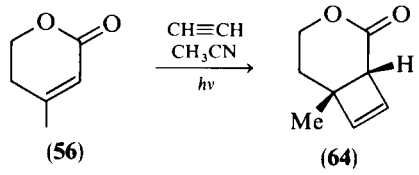
The photochemical cycloaddition of an α,β-unsaturated δ-lactone having a structural unit of anhydromevalonolactone **56** with acetylene was used to prepare a substance possessing the ABC rings of verrucarol **63**[16].



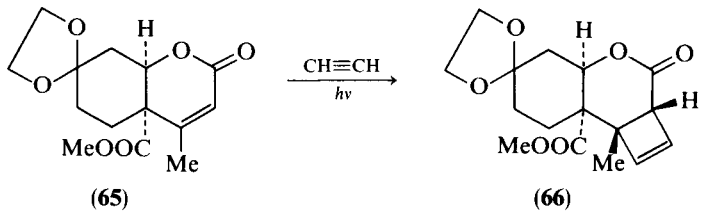
(**63**)



SCHEME 16

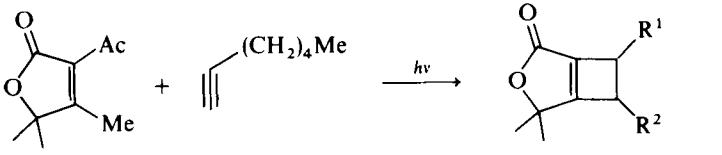


SCHEME 17



SCHEME 18

Irradiation of **56** in acetonitrile saturated with a stream of acetylene gave the cyclobutane **64** in 73% yield (Scheme 17). A similar cycloaddition with lactone **65** gave adduct **66** in 62% yield by stereospecific addition of acetylene from the exo (α) direction (Scheme 18). Selective reduction of the lactone carbonyl of **66** with DIBAL to a pair of epimeric hemiacetals **67a** and **67b** (84%) followed by treatment with pyridine–acetic anhydride, gave the corresponding acetate **68** (80%). When acetate **67** was exposed to *p*-toluenesulphonic acid in wet benzene containing acetic acid at 50 °C, a rapid rearrangement took place to give **68**, as a mixture with a 2.5:1 ratio of *endo* and *exo* epimers in 46% yield.



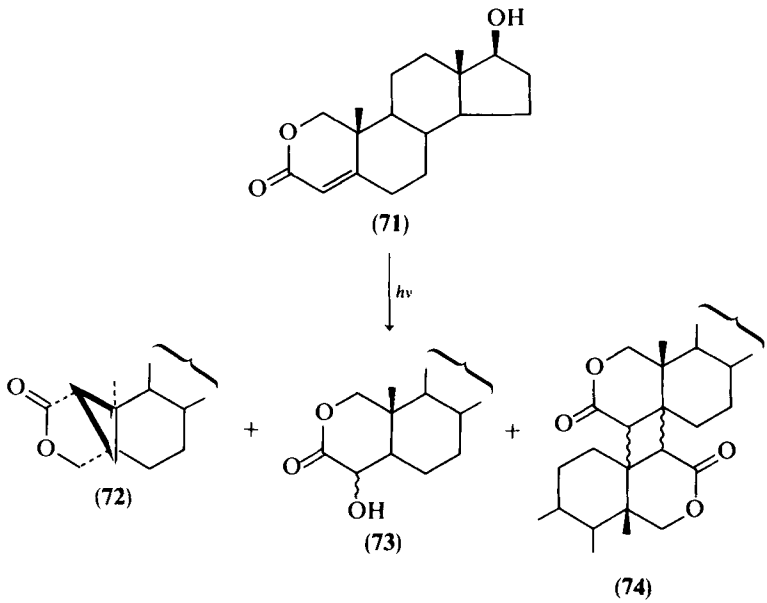
(69)

(70a) R^1 = pentyl, R^2 = H
(70b) R^1 = H, R^2 = pentyl

SCHEME 19

The intermolecular [2 + 2] photoaddition of butenolide **69** with 1-heptyne has also been reported to give oxabicycloheptenes **70a** and **70b** as the major products (68–70%) (Scheme 19)[17].

Photochemical skeletal rearrangements of unsaturated lactones have been considerably less common than that of the corresponding ketones. Some photorearrangements formally analogous to those of the enones have been found in steroidal systems by Bonet and colleagues[18].



(71)

(72)

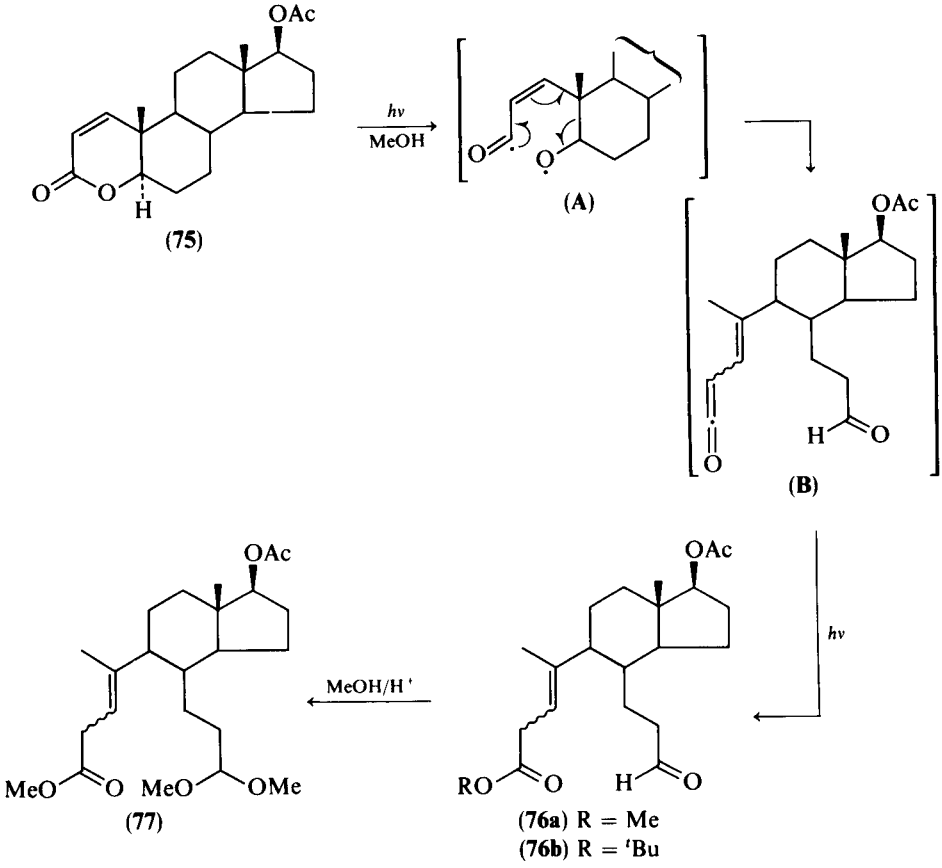
(73)

(74)

SCHEME 20

Thus, the irradiation of 17β-hydroxy-2-oxaandrost-4-en-3-one **71** in *t*-butyl alcohol, under similar conditions as those used in the testosterone rearrangement, gave three products (**72**, **73** and **74**) in 10.1%, 3.2% and 27.2% together with the recovered starting material (36.1%) as outlined in Scheme 20. The photorearrangement **71** → **72** is a new type of photochemical reaction of α,β-unsaturated δ-lactones and is categorized as belonging to the well-established 'type A rearrangements' in cyclic enones[19].

Subsequent to this investigation, Bonet and colleagues have reported both a di-π-methane photorearrangement[20] and a type I cleavage[21] in the photolysis of steroidal α,β-unsaturated δ-lactone, which are similar to their carbocyclic counterparts.

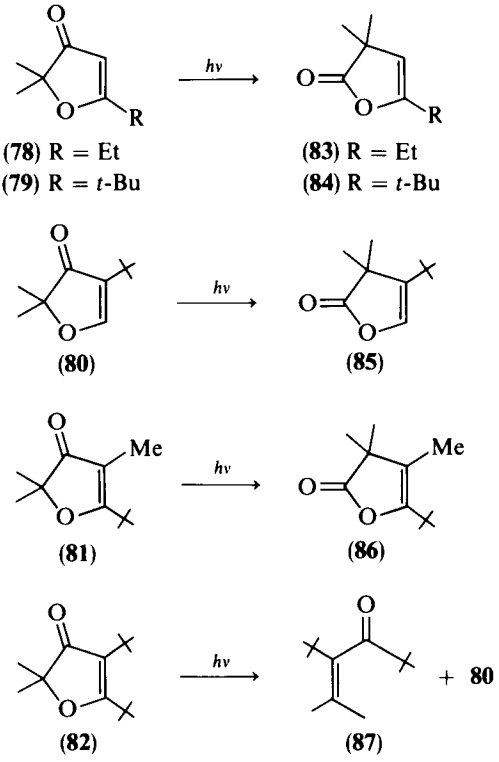


SCHEME 21

The irradiation of 17β-acetoxy-4-oxa-5α-androst-1-en-3-one **75** gave a mixture of the aldehyde ester **76a** and its acetal **77** in 50 and 6% yields together with recovered starting material (13%) as outlined in Scheme 21. When the photolysis was carried out in *t*-butyl alcohol, only the ester **76b** (34%) was isolated[21]. The ester is probably formed via **A** and **B**, arising from a type I cleavage of the C—O bond. The acetal **77** is a product of a thermal reaction catalysed by a trace of formic acid formed by the irradiation of methanol in the presence of air.

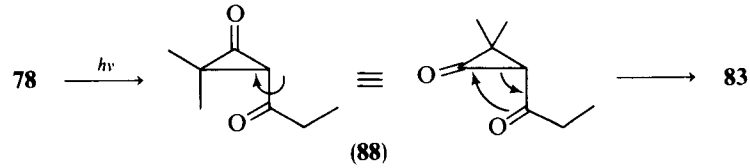
B. 3(2*H*)-Furanones

The photochemistry of 3(2*H*)-furanones has received much less attention than that of α,β-butenolides. Wolff and Agosta have reported that irradiation of 3(2*H*)-furanones leads to photorearrangements giving enol lactones **83–86** in 20–40% yield, while, the di-*t*-butyl-substituted derivative **82** underwent decarbonylation to produce **87** (50%) and **80** (5%) as outlined in Scheme 22[22]. The rearrangement of **81** as well as the photoreaction of **82** are efficiently quenched by added 2,3-dimethyl-1,3-butadiene indicating that these transformations take place from a triplet state: a two-step mechanism for the rearrangements of **78–81** proposed by Wolff and Agosta is outlined for **78** in Scheme 23.



(**78**) R = Et
(**79**) R = *t*-Bu
(**83**) R = Et
(**84**) R = *t*-Bu
(**80**)
(**85**)
(**81**)
(**86**)
(**82**)
(**87**)

SCHEME 22

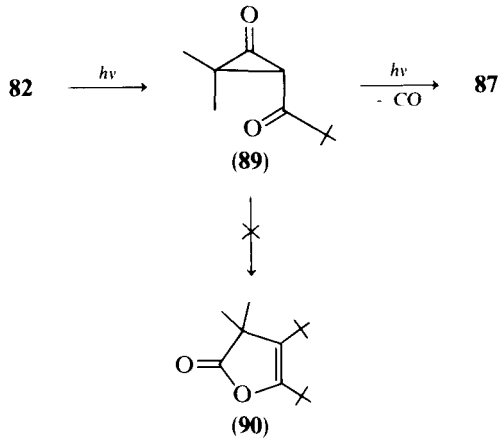


(**88**)

SCHEME 23

Photoisomerization of **78** to **88** is formally a familiar cyclopentane–vinylcyclopropane rearrangement, although such reactions leading to cyclopropanones are rare and no direct evidence for the intermediacy of acylcyclopropanones is available. Conversion of **88** to **83** is merely the reverse process involving of the other cyclopropane centre.

The pathway leading from **82** to **87** is outlined in Scheme 24. In this case, decarbonylation rather than isomerization to the β,γ-butenolide **90** is considered to be the preferred process which can take place from a conformation that minimizes crowding of the *t*-butyl groups.

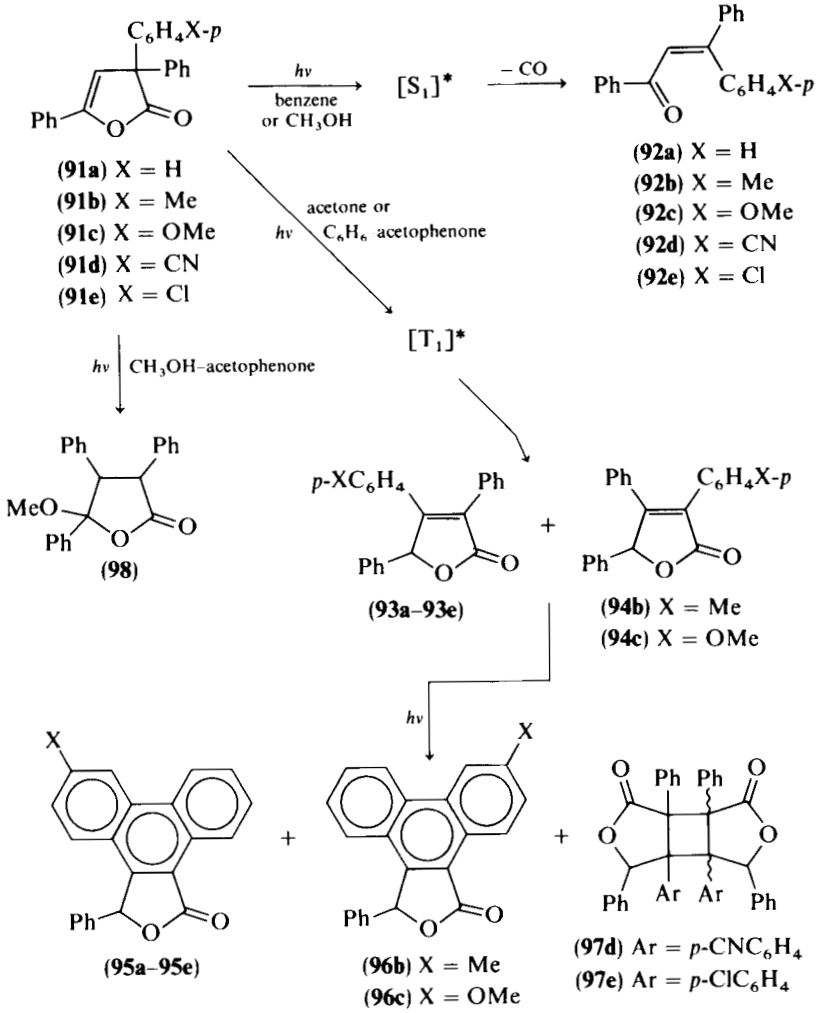


SCHEME 24

C. 2(3*H*)-Furanones

Photorearrangements of 2(3*H*)-furanones substituted by aryl groups have been reported by George and colleagues[23a]. Typically, acetophenone-sensitized irradiation of the 2(3*H*)-furanone **91a** gave the photorearranged 2(5*H*)-furanone **93a** (20%) and the corresponding phenanthrofuranone **95a** (51%). Irradiation of **91a** in acetone similarly gave furanone **93a** (15%) and the phenanthrofuranone **95a** (65%). On the other hand, when sensitized irradiation was carried out in methanol, the product obtained was *cis*-5-methoxy-4,5-dihydro-3,4,5-triphenyl-2(3*H*)-furanone (**98**) in 75% yield.

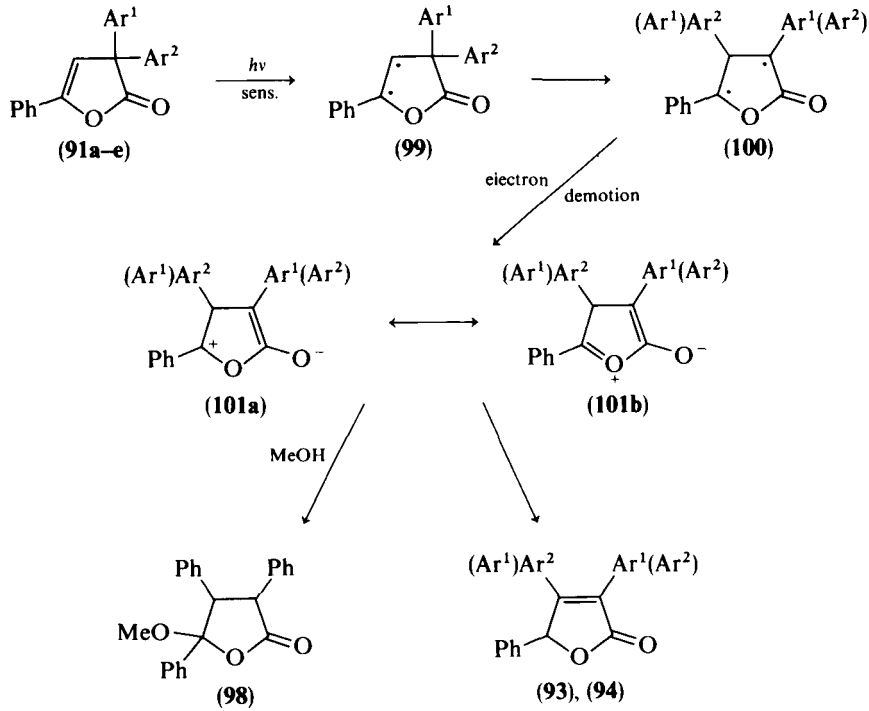
In contrast, direct irradiation of a solution of **91a** in benzene or methanol gave the decarbonylated product 1,3,3-triphenylprop-2-en-1-one (**92a**) in 87 and 66% yields as outlined in Scheme 25. Further examination was carried out on photoreactions of other furanones **91b–e** containing both electron-withdrawing and -donating substituents. Thus, it was found that sensitized irradiation of 3,3,5-triaryl-2(3*H*)-furanones **91a–91e** in benzene gave generally gives a mixture of the photorearranged 2(5*H*)-furanones **93** and **94**, along with the corresponding phenanthrofuranones **95** and **96**, respectively. In contrast, the direct irradiation of **91a–91c** in benzene or methanol gave generally the corresponding decarbonylated products **92a–92c** as outlined in Scheme 25. These studies on the migratory aptitudes of different substituted aryl groups at the C-3 position of the furanones showed that *p*-chlorophenyl, *p*-cyanophenyl and *p*-tolyl groups were better migrating groups than phenyl from the C-3 carbon, whereas the *p*-anisyl group showed a smaller migratory aptitude than did phenyl. These migration aptitudes as well as the



SCHEME 25

formation of the methanol adduct **98** in the acetophenone-sensitized irradiation of **91a** in methanol suggest the involvement of photointermediates with significant ionic character.

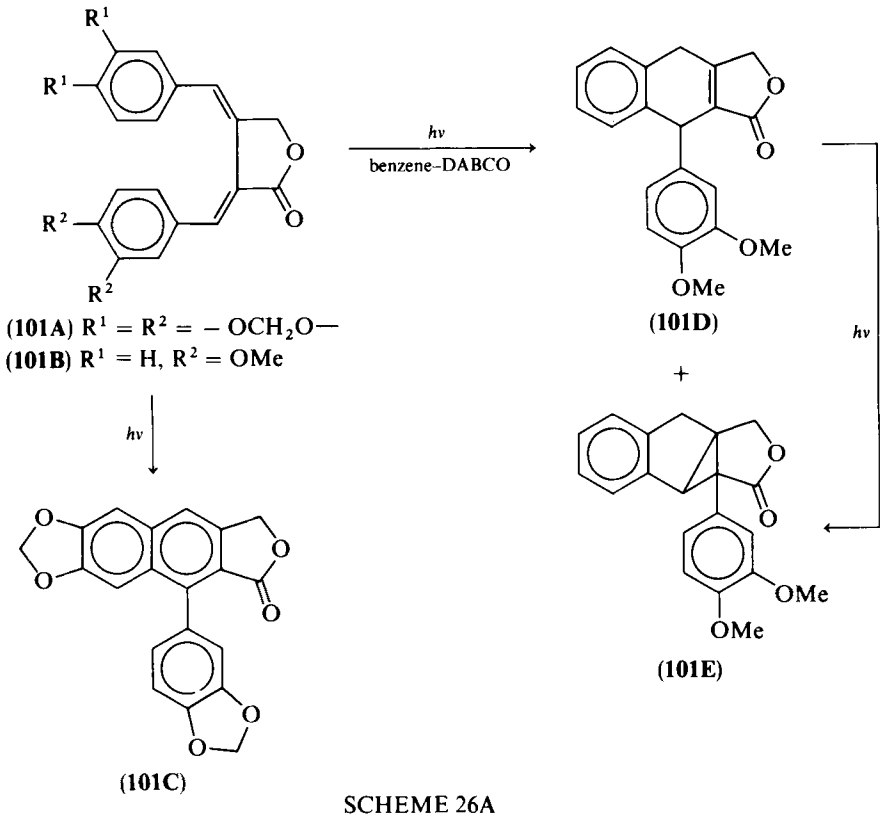
In order to shed light on the precursors and intermediates that lead to the photoproducts obtained, the authors also subjected 2(3*H*)-furanones **91a–c** to laser-flash photolysis studies. On the basis of direct observations of the 2(3*H*)-furanone triplets by laser-flash photolysis, they estimated the aryl group migrating rates at $\leq 1.5 \times 10^6\ s^{-1}$, except for the *p*-cyanophenyl group for which the rate is higher by an order of magnitude.



SCHEME 26

The pathways of the photochemical rearrangement of the 2(3*H*)-furanones **91** to the corresponding 2(5*H*)-furanones **93** and **94** and the subsequent formation of the phenanthrofuranones **95** and **96** proposed by George and colleagues[23a] are outlined in Scheme 26. Thus, one of the C-3 aryl groups in the triplet-excited furanone **99** migrates through a bridged transition state to give the rearranged diradical intermediate **100**. Electron demotion in **100** may result in the formation of a zwitterionic intermediate which is trapped by methanol to give adduct **98**. In the absence of the alcohol, the intermediate **101** undergoes a hydride shift to give rearranged 2(5*H*)-furanones **93** and **94**. These furanones absorb light and undergo further photocyclization to give dihydrophenanthrofuranones which are converted, in turn, into the phenanthrofuranones **95** and **96** through air oxidation. Alternatively, these 2(5*H*)-furanones can undergo [2 + 2] photocycloaddition to give the dimers **97**. The observed migratory aptitudes of the various aryl groups attached to C-3 are in accord with the pathway outlined in Scheme 26.

It has been known that irradiation of taiwanin A **101A**, a natural phthalide lignane, in solution results in selective cyclization to give the 1-aryl-2,3-naphthalide **101C**[23b]. Momose and colleagues[23c] have reported that irradiation of a solution of 3,4-bisarylmethylenedihydro-2(3*H*)-furanone **101B** gives cyclized products **101D** and **101E** each in 24% yield (Scheme 26A). The formation of the rearranged product **101E** through **101D** was evidenced by the quantitative formation of **101E** in the independent irradiation of **101D**, by photoinduced 1,2-aryl migration.

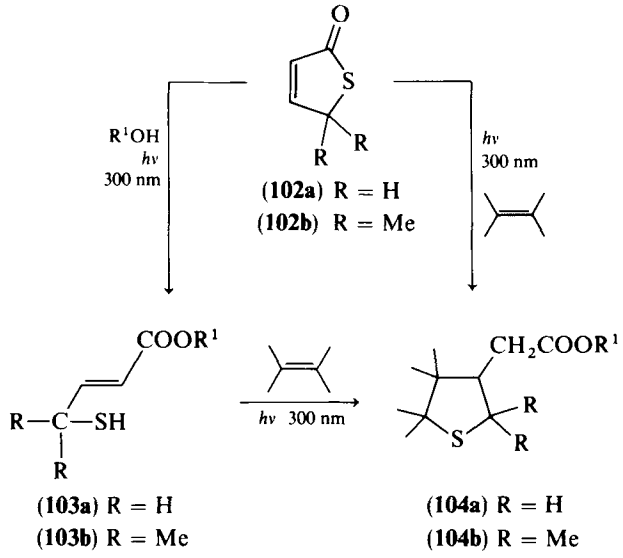


SCHEME 26A

D. 2(5*H*)-Thiophenones and 3(2*H*)-Thiophenones

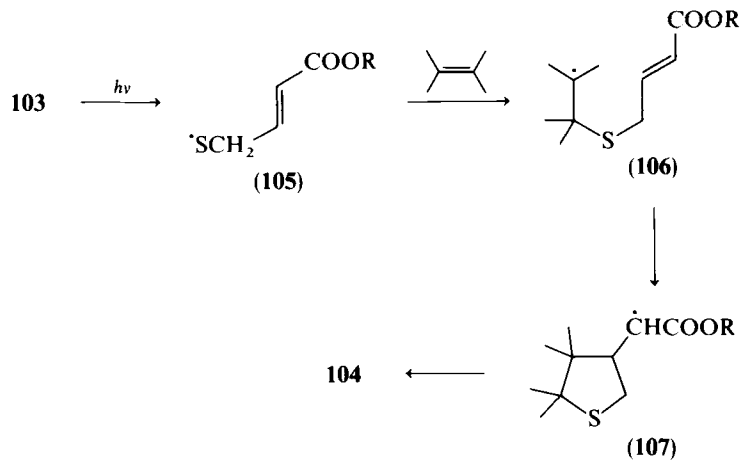
Extensive studies on the photochemical reaction of thiolactones carried out by Margaretha and colleagues[24] have indicated that 2(5*H*)-thiophenones behave quite differently from their oxygen counterparts. Irradiation of 2(5*H*)-thiophenone **102a**, or its 5,5-dimethyl derivative **102b**, in benzene or cyclohexane in either the presence or absence of olefins, yields neither cycloadducts nor other products. In contrast, irradiation of **102a** and **102b** in alcohols gave 4-mercaptocrotonates **103a** or the dimethyl derivatives **103b** in good yields. The photoreaction likely proceeds from the singlet state of **102**, since the addition of 2,5-dimethyl-2,4-hexadiene does not lower the rate of the formation of **103**.

Irradiation of **102a** or **102b** in alcohols in the presence of 2,3-dimethyl-2-butene was found to lead to the formation of 4,4,5,5-tetramethyltetrahydro-3-thienylacetates **104a** (80–85%) or the dimethyl derivatives (10–36%) (Scheme 27). The product **104** can also be obtained when the α,β-unsaturated carboxylic acid ester **103** is irradiated in the presence of the olefin. The path of the formation of tetrahydrothiophene **104** from ester **103** and the olefin is outlined in Scheme 28. Photosolvolysis of 2(5*H*)-thiophenone gives ester **103** from which the alkylthio radical **105** is generated by homolysis of the SH bond

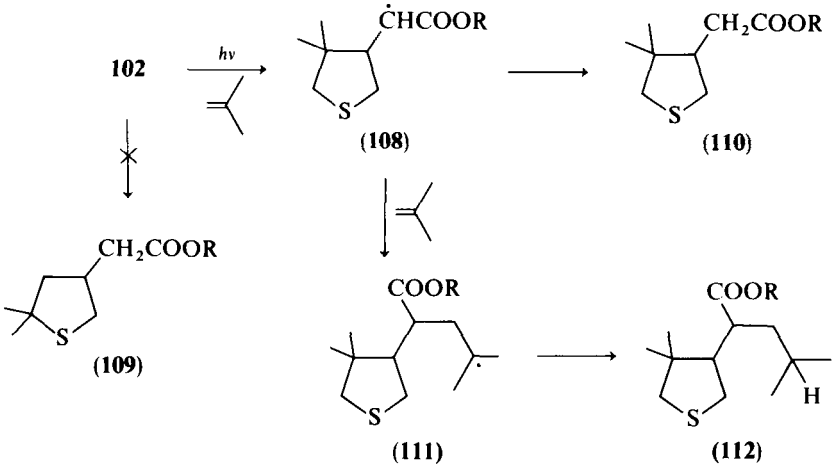


SCHEME 27

in the excited thiol, or by abstraction of hydrogen by the carbonyl oxygen from the ester group. [3 + 2] Cycloaddition between **105** and the olefin via **106** may give radical **107**. The reaction of **107** with **103** then gives the product **104** with simultaneous generation of radical **105**. This mechanism is supported by the results on the photoreaction of **102** with a large excess 2-methylpropene (Scheme 29) giving 2-(tetrahydro-3-thienyl)-4-methylpentanoic acid esters **112** together with **110**. Exclusive formation of **110** and **112**, but not of the regioisomer **109**, suggests the involvement of the alkylthio radical as the



SCHEME 28

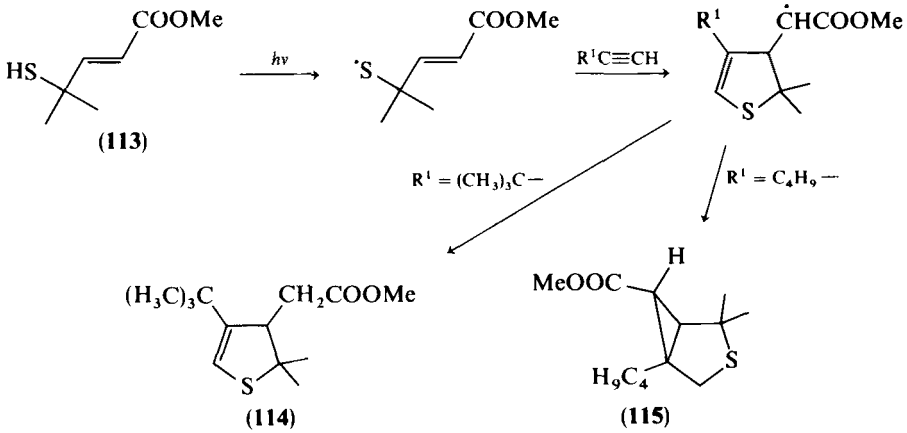


SCHEME 29

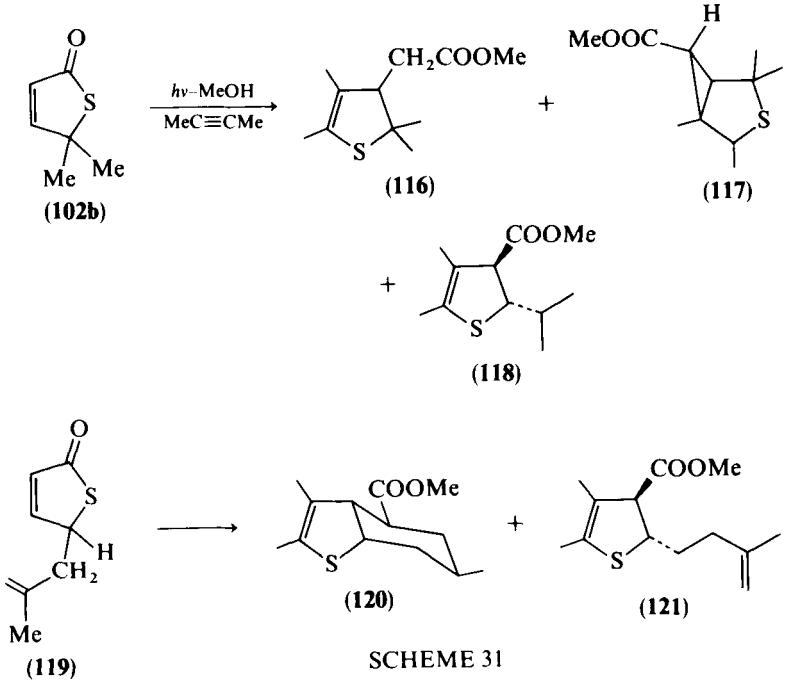
intermediate. The radical **108**, however, also reacts with 2-methylpropene to give **111** and then **112**.

Irradiation of (*E*)-4-mercapto-4-methyl-2-pentenoates **113** in the presence of 3,3-dimethyl-1-butyne gave 2,3-dihydrothiophenes **114**, while the photoreaction of **113** with 1-hexyne gave **115** having a cyclopropane ring (Scheme 30)[25]. In contrast to 5,5-dimethyl-2(5*H*)-thiophenone **102b**, 3,4-dimethyl-2(5*H*)-thiophenone was not converted to the corresponding mercapto ester even after prolonged irradiation.

The same group also examined the photoreaction of 2(5*H*)-thiophenes **102b** and **119** with 2-butyne[26] (Scheme 31). Thus, irradiation of the 2(5*H*)-thiophenone **102b** in methanol saturated with 2-butyne afforded 2,3-dihydrothiophene-3-acetate **116** (22%), 3-thiabicyclo[3.1.0]hexane **117** (20%) and 2,3-dihydrothiophene-3-carboxylate **118** (20%).



SCHEME 30



SCHEME 31

Similar photoreaction of the 2(5*H*)-thiophenone **119** with 2-butyne gave the *trans*-fused 3a,4,5,6,7,7a-hexahydrobenzo[*b*]thiophene **120** (29%) and the 2,3-dihydrothiophene-3-carboxylate **121** (51%). The probable pathways leading to products which involve successive radical reactions, proposed by Margaretha, are outlined in Scheme 32.

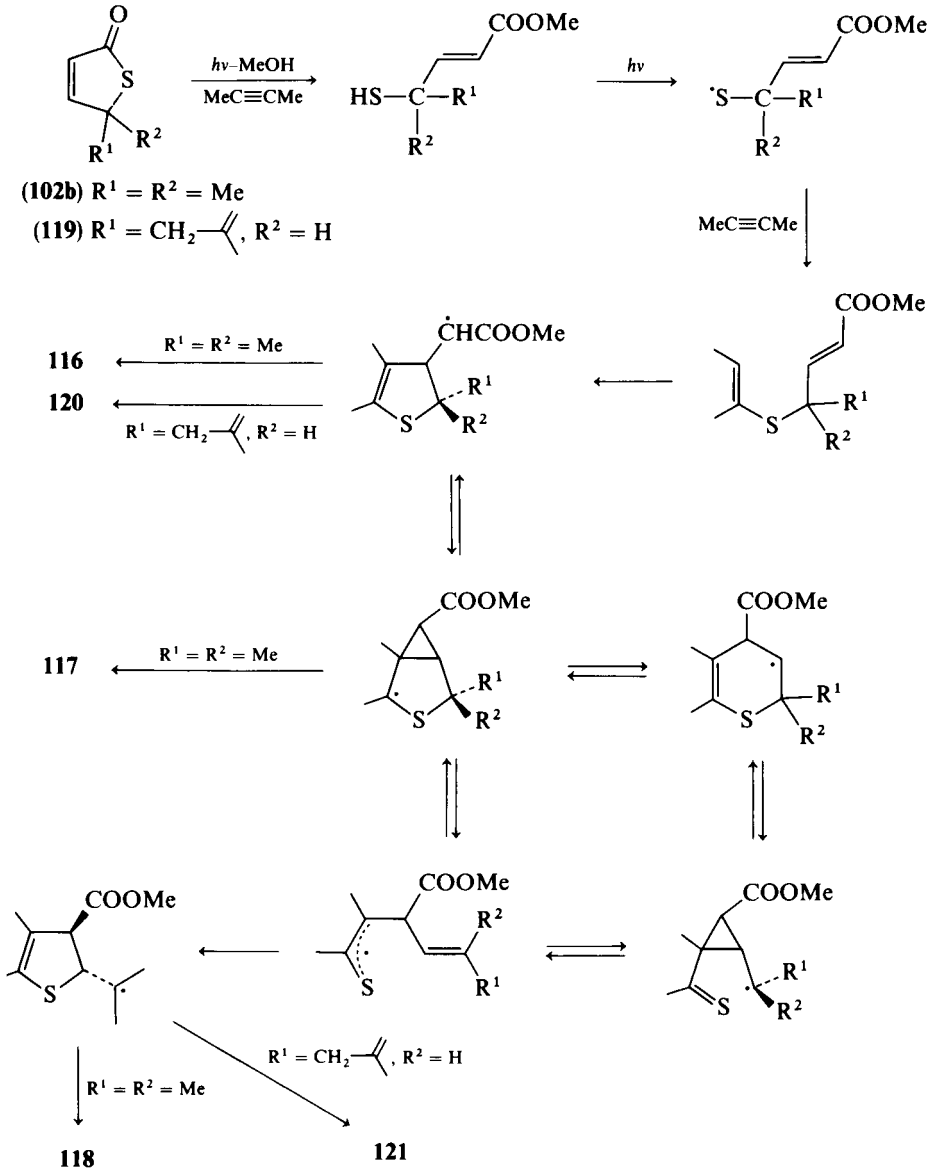
The 3(2*H*)-thiophenone **122** exhibited a totally different photochemical behaviour to that of 2-(5*H*)-thiophenone. The photochemical behaviour was analogous to the corresponding lactone[27]. Thus, irradiation of 2,2-dimethyl-3(2*H*)-thiophenone **122** gave a 10:1 mixture of two dimers **123** and **124** while the photoreaction in isopropyl alcohol gave the head-to-head dimer **123** in 90% yield exclusively.

Irradiation of **122** in the presence of 2,3-dimethyl-2-butene or 2-methylpropene afforded the thiabicyclo[3.2.0]heptanones **125** (90%) and **126** (88%), respectively (Scheme 33).

Intramolecular [2 + 2] photocycloaddition was also found in the 3(2*H*)-thiophenone system[28]. Irradiation of methyl 2-allyl-3-oxo-2,3-dihydrothiophene-2-carboxylate **127** in benzene, acetonitrile or isopropyl alcohol gave the [2 + 2] adduct **128** in a quantum yield of 0.21 (benzene) and in 91% chemical yield (Scheme 34).

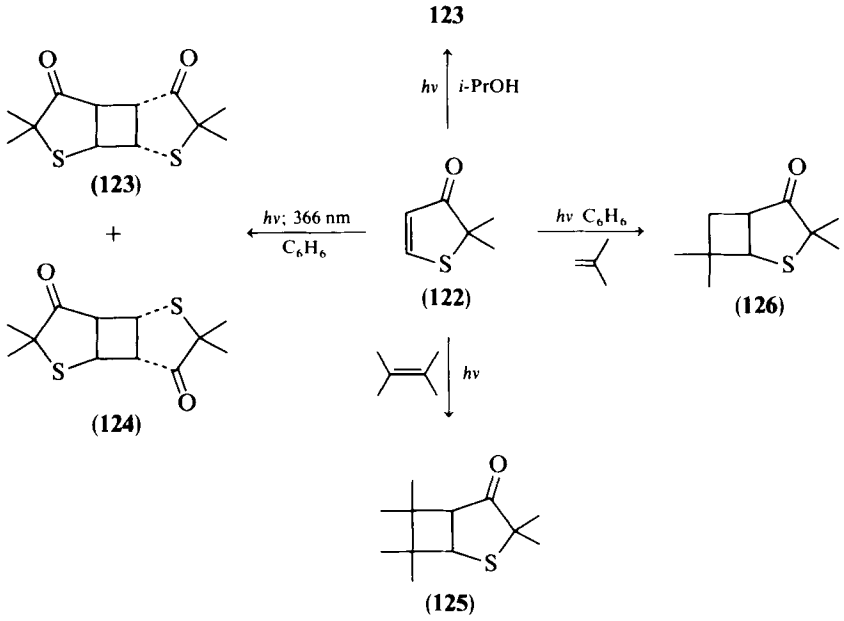
The photochemistry of 4-thia-2-cyclohexenone **129** has also been examined by Margaretha and colleagues, and was found to be less efficient than that of the five-membered analogue[27]. Enone **129** gave only a low yield (10%) of the head-to-head, *cis–transoid–cis* photodimer **130** after prolonged irradiation. Irradiation of **129** in the presence of an excess of 2-methylpropene afforded the two products **131** and **132** in 25% yield. Irradiation of **129** in isopropyl alcohol gave the product **133** in 25% yield (Scheme 35).

Photoreaction of 5-(2-propenyl)-2(5*H*)-thiophenone **134** resulted in the formation of interesting cycloalkane-annelated thiolanes and dihydrothiophenes (Scheme 36). Thus,



SCHEME 32

irradiation of **134** in methanol gave (*E*)-4-mercapto-2,6-heptadianoate **135** (12%), and methyl (*E*)-3-(thiolan-2-yl)-2-propenoate **137** (15%). The ester **135** is transformed into **137** via **136** upon irradiation. Irradiation of **134** in the presence of 2,3-dimethyl-2-butene gave methyl octahydro-2,3,3,3-tetramethyl-*trans*-benzo[*b*]thiophene-4-carboxylate **140**

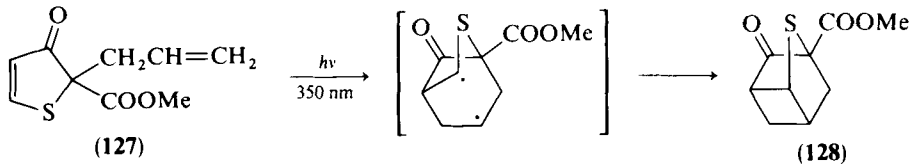


SCHEME 33

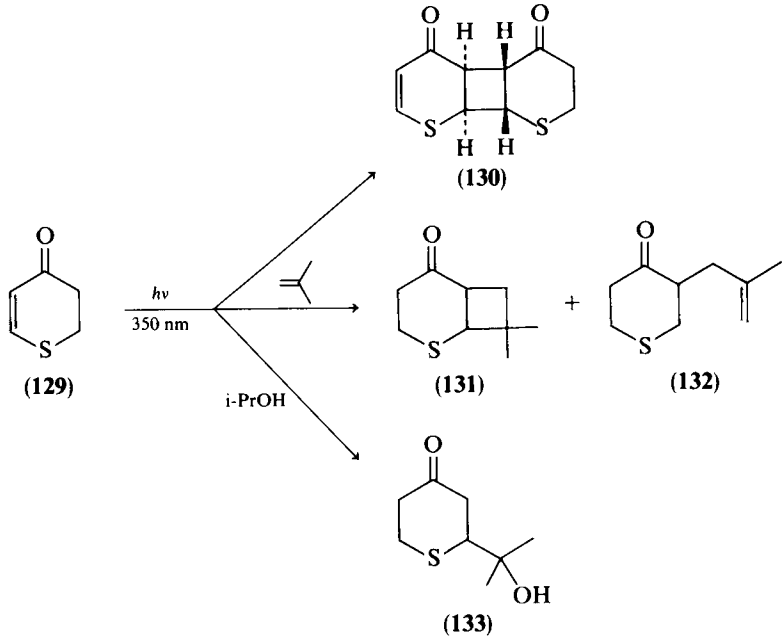
(18%) and methyl hexahydro-2,2,3,3,5-pentamethyl-2*H*-*trans*-cyclopenta[*b*]thiophene-4-carboxylate **141** (3%) (Scheme 37).

Irradiation of **134** in the presence of 2-butyne gave methyl 3a,4,5,6,7,7a-hexahydro-2,3-dimethyl-*trans*-benzo[*b*]thiophene-4-carboxylate **142** (43%) and methyl 5,6-dimethyl-4-thiatricyclo[4.2.1.$0^{3,7}$]nonane-8-carboxylate **143** (11%) via consecutive radical ring closures as outlined in Scheme 38[29].

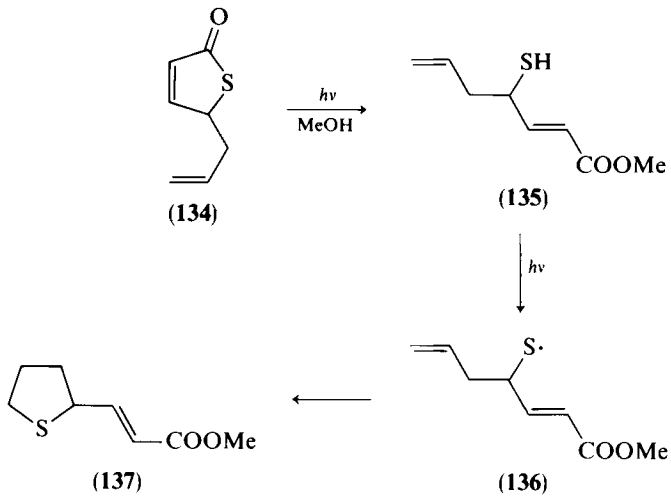
More recently, Margaretha and colleagues[30] reported that irradiation of 5-(2-propynyl)-2(5*H*)-thiophenone **144** and cyclopentene in methanol gave a 3:1 mixture of diastereoisomeric methyl 7-thiatricyclo[6.4.0.$0^{2,6}$]dodec-10-ene-12-carboxylates **145a** and **145b** while irradiation of 3,5-di(2-propenyl)-2(5*H*)-thiophenone **146** in methanol saturated with 2-methylpropene gave a 3:2 mixture of the diastereoisomers **147a** and **147b** of methyl 3,3,9-trimethyl-5-thiatricyclo[6.2.1.$0^{2,6}$]undecane-1-carboxylates (Scheme 39).



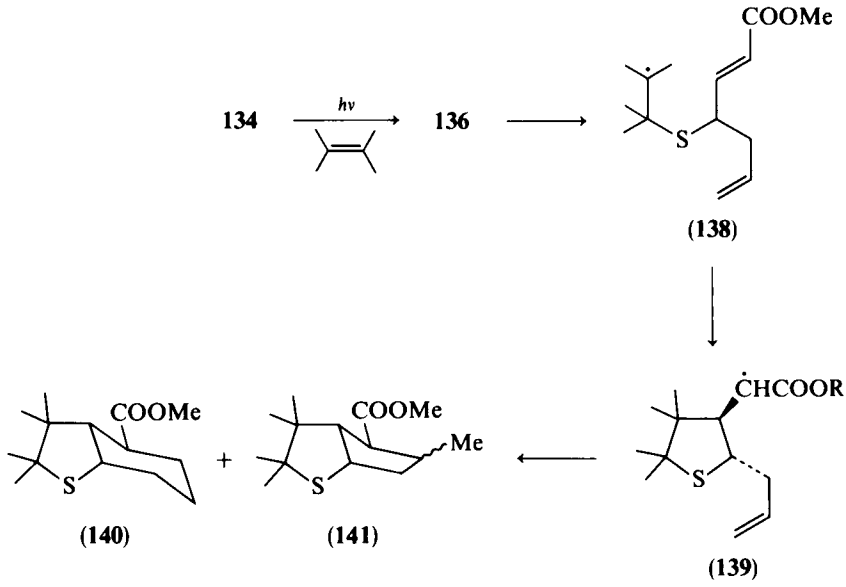
SCHEME 34



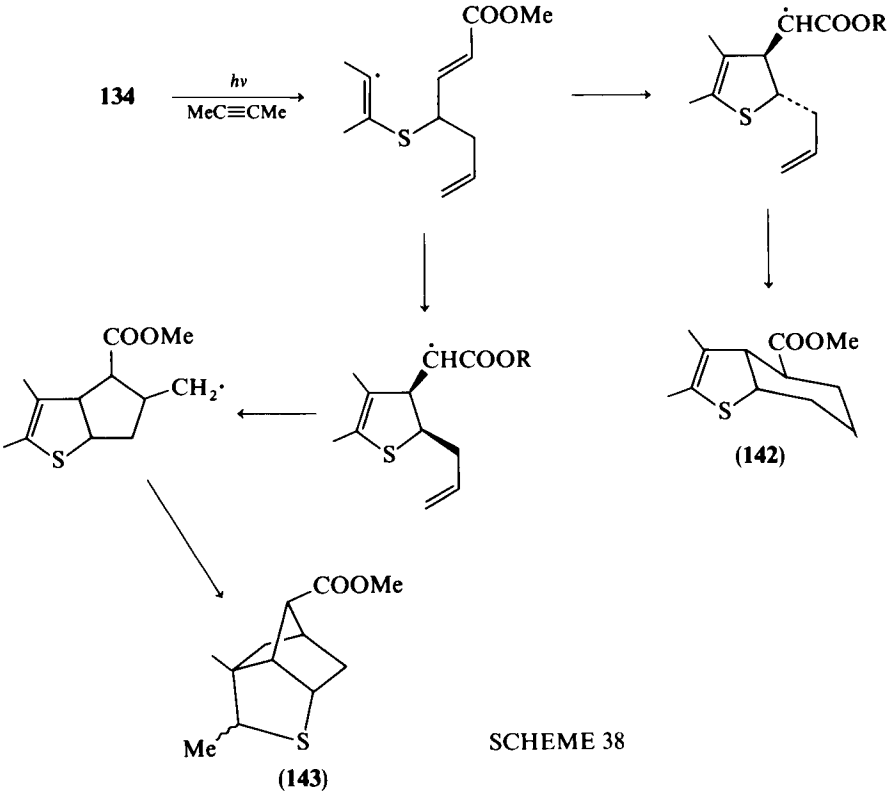
SCHEME 35



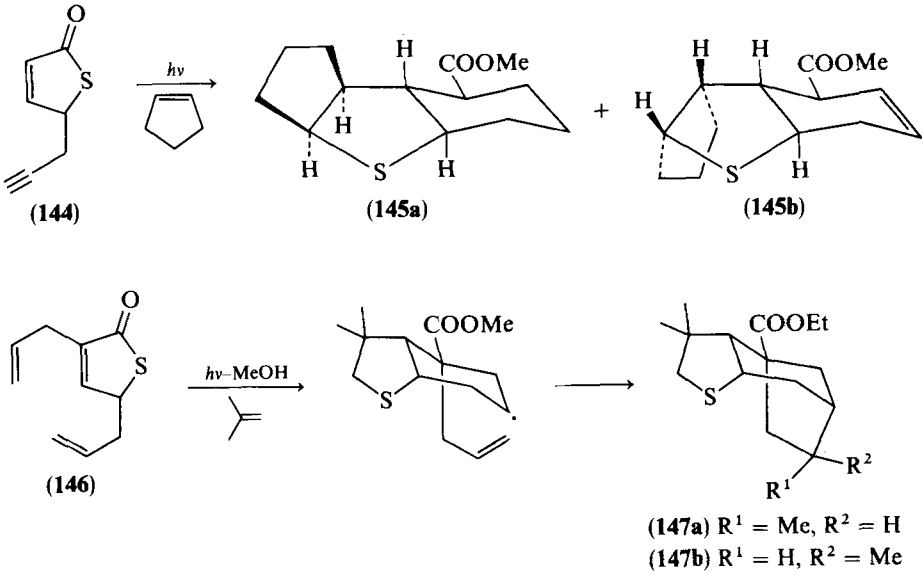
SCHEME 36



SCHEME 37



SCHEME 38

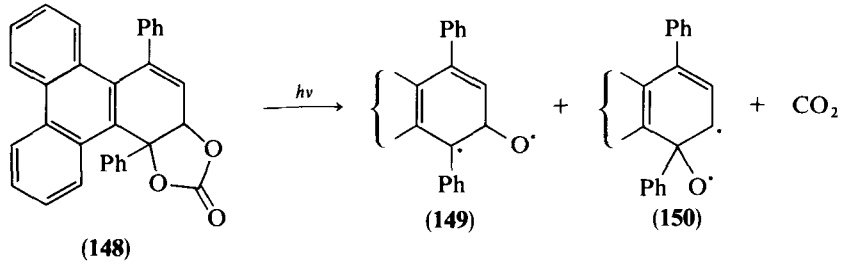


SCHEME 39

E. Cyclic Carbonate Esters

The photoextrusion of carbon dioxide from esters and lactones that have radical stabilizing groups in the appropriate position is a general process; this subject has been reviewed[1,31].

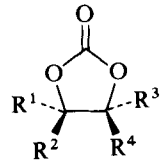
The photolysis of cyclic carbonate esters similarly proceeds with a loss of carbon dioxide. Harrison and Ammon reported that the photolysis of the carbonate **148** proceeds with loss of carbon dioxide to form two isomeric 1,3-diradicals **149** and **150** (Scheme 40), which undergo further reactions[32].



SCHEME 40

Griffin and colleagues have reported that cyclic aryl pinacol carbonates **151** generally undergo photoinduced [5 → 2 + 2 + 1] cycloelimination to give arylcarbenes **152**, as outlined in Scheme 41[33].

Typically, photolysis of the benzopinacol carbonate **153** in methanol gave diphenylcarbene, as proved by the formation of benzhydryl methyl ether **154** in 60% yield. Benzophenone (15%) and 9,10-diphenylphenanthrene **156** (10%), which was formed from dehydrophotocyclization of tetraphenylethylene **155** initially formed, were accompanying products (Scheme 42).



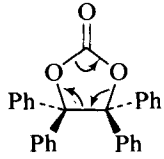
R^1, R^2, R^3, R^4; H, Me, Ph

(151)

$\xrightarrow{h\nu}$ CO_2 + $R^1R^2C{=}O$ + R^3R^4C:

(152)

SCHEME 41



(153)

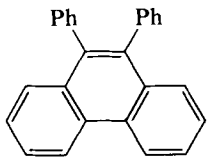
$\xrightarrow{h\nu\text{–MeOH}}$ CO_2 + $Ph_2C{=}O$ + Ph_2C:

MeOH ↓

Ph_2CHOMe + $[Ph_2C{=}CPh_2]$

(154) **(155)**

$h\nu$ ↓



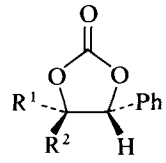
(156)

SCHEME 42

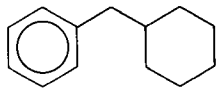
$PhCH_2OMe$ + PhCHO + CO_2

(159)

$h\nu$–MeOH



$h\nu$–cyclohexane



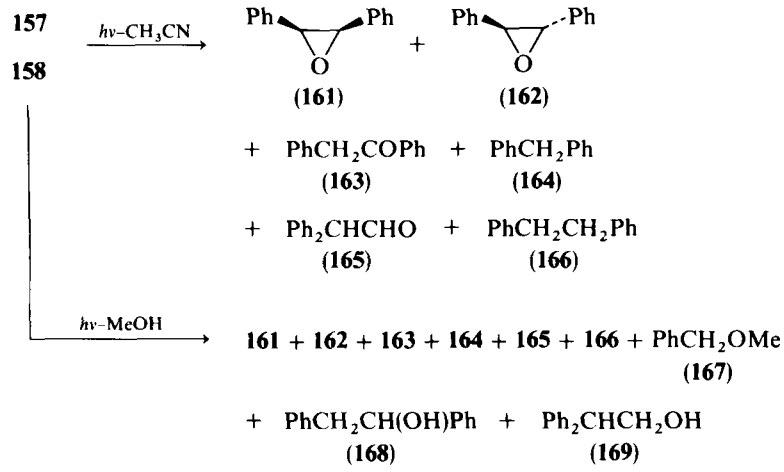
+ PhCHO + CO_2

(157) R^1 = Ph, R^2 = H

(158) R^1 = H, R^2 = Ph

SCHEME 43

(160)



SCHEME 44

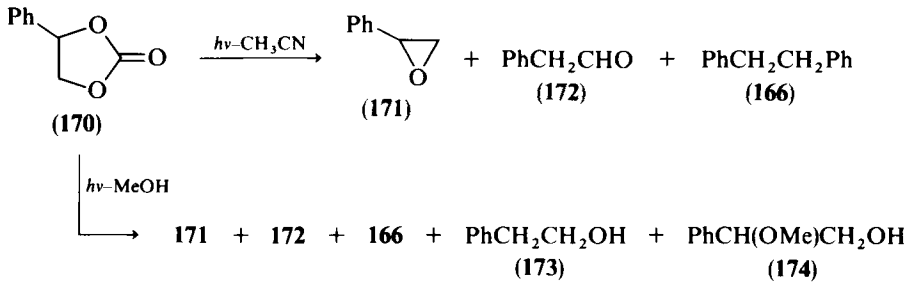
Similar photolysis of the *meso*- and *d,l*-hydrobenzoin carbonates **157** and **158** in methanol with 254 nm light gave benzyl methyl ether **159**, benzaldehyde and CO_2, while photolysis in cyclohexane gave benzylcyclohexane **160** with unspecified yields (Scheme 43). Recently, White and Rix have re-examined the products in the photolysis of *meso*- and *dl*-hydrobenzoin carbonate in greater detail[34a]. They found that the direct irradiation of *meso*-hydrobenzoin in acetonitrile produced *cis*-stilbene oxide (**161**), *trans*-stilbene oxide (**162**), deoxybenzoin (**163**) and diphenylmethane (**164**), along with smaller amounts of diphenylacetaldehyde (**165**) and bibenzyl (**166**). The photolysis of the *trans*-isomer **158** under the same conditions produced the same products, except that the *trans*-oxirane **162** is the major oxirane formed (Scheme 44). The yields of the products are summarized in Table 2.

When the photolysis of **157** was executed in methanol, again the same products were obtained with accompanying formation of benzyl methyl ether (**167**), 1,2-diphenylethanol (**168**) and 2,2-diphenylethanol (**169**). The yields of the main products are summarized in Table 2. Study of the initial phases of the photolysis of **157** in acetonitrile indicated that **163** and **164** are, respectively, the primary photoproducts formed from **157**.

White and Ma further examined the photolysis of 4-phenyl-1,3-dioxolan-2-one **170** to compare its photochemistry with that of **157** and **158**[35]. Direct irradiation of **170** gave styrene oxide **171**, phenylacetaldehyde **172** and bibenzyl **166**, while the same reaction in methanol gave **171**, **172** and **166** along with phenethyl alcohol **173** and

TABLE 2

Carbonate	Solvent	Conversion (%)	Yield (%)				
			161	**162**	**163**	**164**	**167**
157	MeCN	35	37	4	19	7	
158	MeCN	44	16	28	32	7	
157	MeOH	61	29	4	4	6	10
158	MeOH	65	4	16	5	4	11



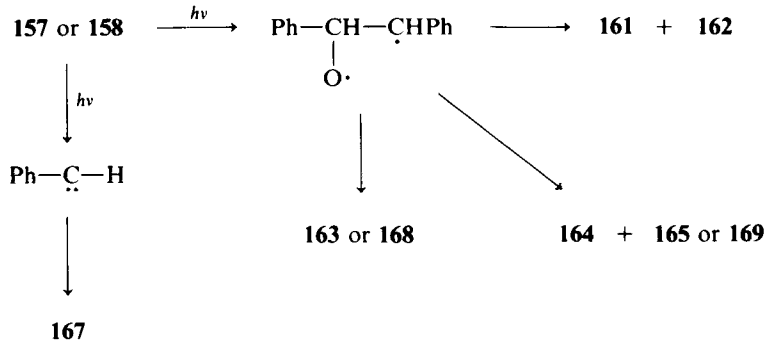
SCHEME 45

2-methoxy-2-phenylethanol **174** (Scheme 45). The photolysis of **170** under sensitized conditions in acetone–acetonitrile with 300 nm light gave **166** as the nearly exclusive product, while in acetone–methanol **174** was the only major product. In the triplet-state reaction, the intermediate diradical (*vide supra*) does not undergo cyclization but rather rearranges to **172** and then decarbonylates to benzyl radicals, which either dimerize or react with solvent radicals. The yields of these products are summarized in Table 3.

TABLE 3

			Yield (%)				
Carbonate	Solvent	Conversion (%)	**171**	**172**	**166**	**173**	**174**
170	MeCN	65	16	30	17		
170	MeOH	70	21	15	10	8	5
170	MeCN –Sens.	56			67		
170	MeOH –Sens.	58			trace	52	

These results can be accommodated in terms of the involvement of biradical intermediates in Scheme 45 (*vide supra*), since the formation of products **172**, **166**, **173** and



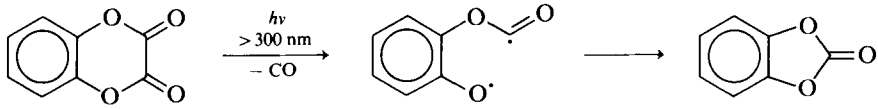
SCHEME 46

174 subsequent to the concerted formation of styrene oxide was excluded by analysis of the reaction products in the initial period of the reaction.

Fragmentation pathways in the photolysis of **157** and **158** proposed by White are outlined in Scheme 46. Thus, the photoextrusion of carbon dioxide from carbonates appears to generate carbenes and/or 1,3-biradicals, depending on the substrate structure and solvent.

F. α-Phenylene Oxalate

Photolysis of acyclic aryl oxalates have been reported to give products arising from photo-Fries rearrangements with simultaneous formation of phenols[34b,c]. In contrast to the photolysis of aryl esters, including acyclic oxalate esters, the photolysis of *O*-phenylene oxalate **174A** has been found to give a product arising from decarbonylation in nearly quantitative yields[34c]. Thus, irradiation of a de-aerated hexane solution of



(174A) (174B) (174C)

SCHEME 46A

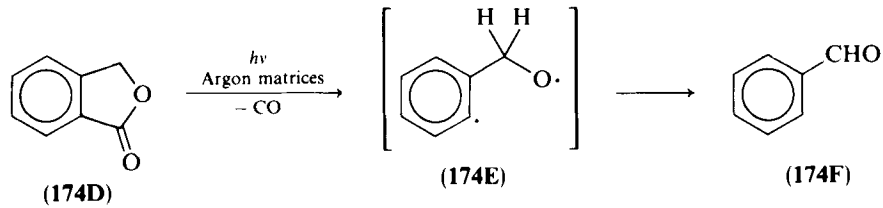
174A afforded *O*-phenylene oxalate **175c** as the only observed product (94%) (Scheme 46A).

The primary photochemical reaction in this decarbonylation is an α-cleavage of either the acyl–oxygen bond as in the case of aryl esters or the acyl–acyl bond as in the case of α-dicarbonyl compounds[34e]. Decarbonylation of the biradical intermediate followed by reclosure of **174B** leads to the observed carbonate **174c**. The formation of a photo-Fries product is probably suppressed by geometrical constraints.

G. Phthalides

Phthalides in solution are unreactive under normal photolytic conditions and therefore their photochemistry has received little attention.

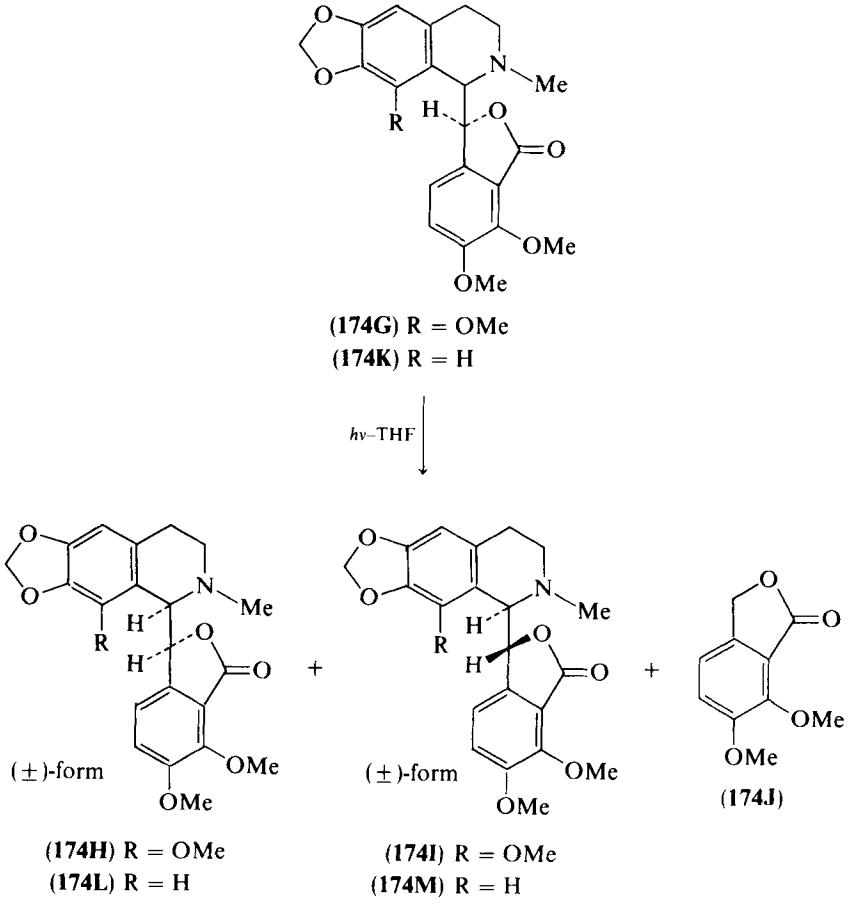
The photofragmentation of phthalide in low-temperature matrices was reported recently[34f]. Thus, phthalide **174D** was isolated in N_2 and Ar matrices by sublimation onto a CSI window at 12 K, with simultaneous deposition of the matrix host gas. Irradiation of the resulting matrices resulted in a decrease of the IR bands due to the phthalide while the IR bands of CO, CO_2 and of benzaldehyde **174F** grew. According to the authors, the benzaldehyde is probably formed by loss of CO from phthalide **174D** followed by a 1,3-hydrogen shift in the intermediate biradical **174E** (Scheme 46B).



(174D) (174E) (174F)

SCHEME 46B

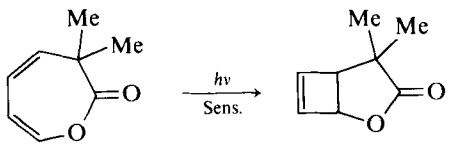
Kametani and colleagues[34g] have reported that irradiation of (−)-α-narcotine in tetrahydrofuran with a Pyrex-filtered light **174G** gave a mixture of racemates of two epimers, (±)-α-narcotine **174H** and (±)-β-narcotine along with a small amount of 6,7-dimethoxyphthalide **174J**. Irradiation of (−)-β-hydrastine **174K** under the same conditions similarly gave two isomeric compounds **174L** and **174M** in their racemic form (Scheme 46C).



(174H) R = OMe
(174L) R = H

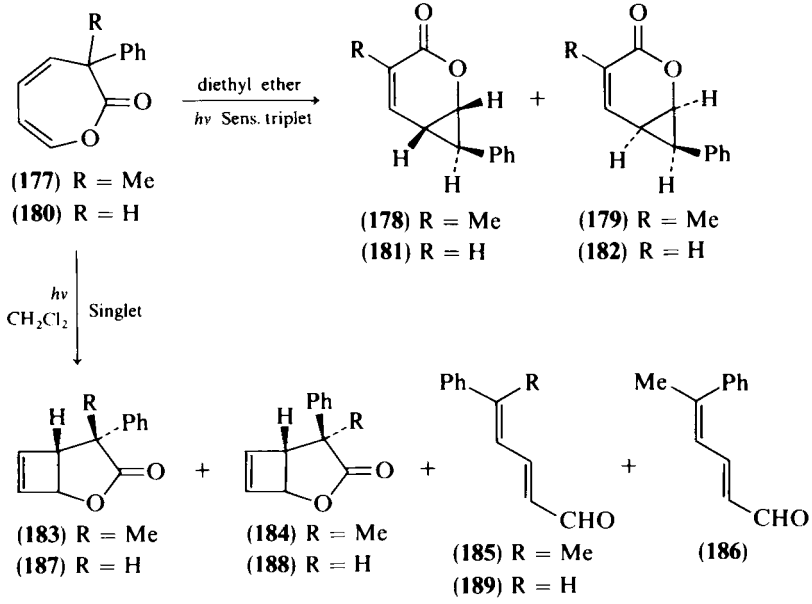
(174I) R = OMe
(174M) R = H

SCHEME 46C

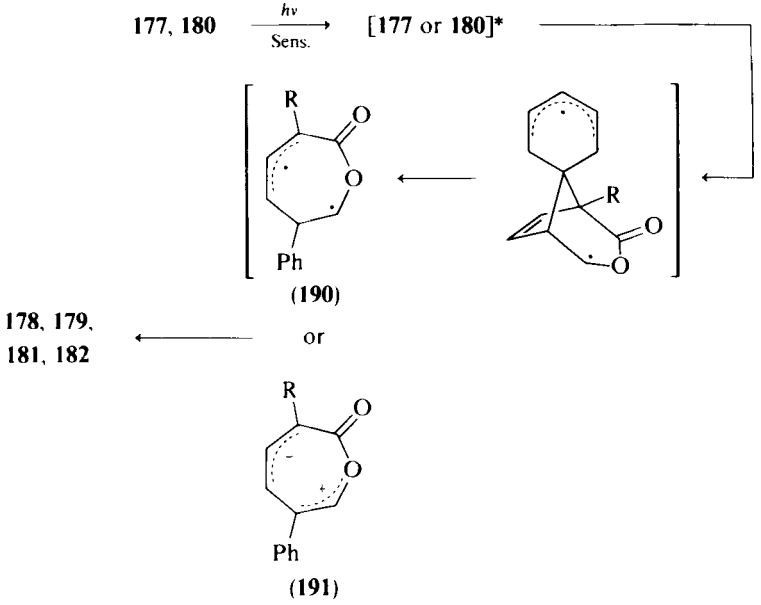


(175) **(176)**

SCHEME 47



SCHEME 48



SCHEME 49

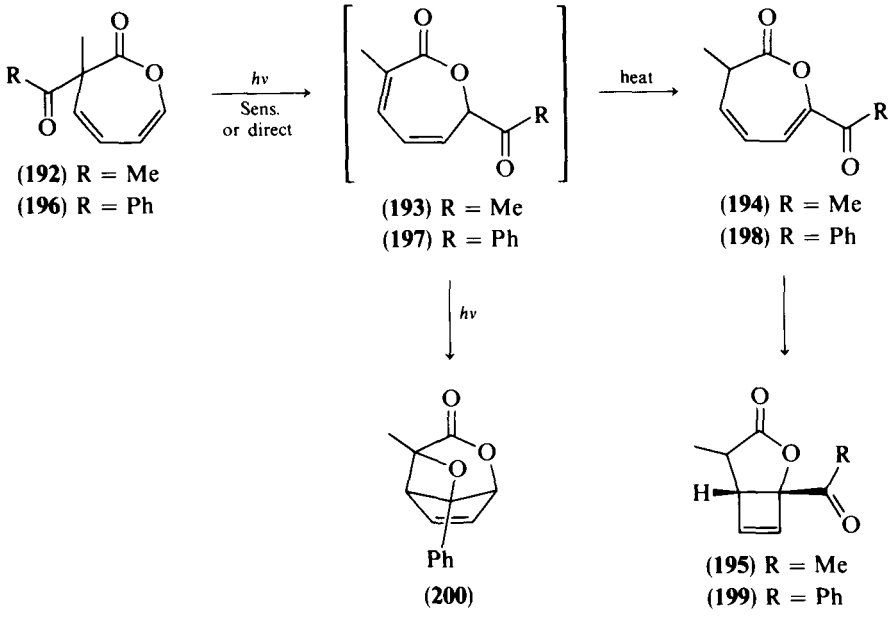
H. 2(3*H*)-Oxepinones

Several new valence-bond isomerizations of substituted 2(3*H*)-oxepinones induced by irradiation have been reported by Uda and colleagues[36,37]. Sensitized photolysis of 3,3-dimethyl-2(3*H*)-oxepinone **175** in the presence of β-acetonaphthone gave the cyclization product **176** (Scheme 47). In contrast, the sensitized photolysis of 3-methyl-3-phenyl-2(3*H*)-oxepinone **177** gave two rearranged products **178** (65%) and **179** (2.5%). No products arising from valence-bond isomerization were formed[36] (Scheme 48).

Direct irradiation of **177** in dichloromethane, on the other hand, gave a mixture of the cyclization products **183** and **184** (44%) and two geometrically isomeric unsaturated aldehydes **185** (36%) and **186** (20%). Similar results were obtained in the photolysis of 3-phenyl-2(3*H*)-oxepinone **180**. It is thus apparent that the phenyl group attached to the 3-position of 2(3*H*)-oxepinones significantly affects the pathway of the triplet reaction, and that cyclization and decarbonylation take place competitively in the singlet reaction.

The pathway leading to the rearranged products involving a 1,4-bridging step of the excited species proposed by Uda and colleagues is outlined in Scheme 49. This pathway is apparently a vinylogous analogue of the first two formal steps of a di-π-methane rearrangement. Recombination of the biradical **190** or of the zwitterionic species **191** yields the observed rearranged products. The products **178** and **181** are the predominant ones, since they are probably thermodynamically more stable than are **179** and **182**.

Uda and colleagues have also examined the photochemistry of 3-acyl- and 3-allyl-2(3*H*)-oxepinones[37]. Thus, the sensitized photolysis of 3-acetyl-3-methyloxepin-2(3*H*)-one **192** in diethyl ether in the presence of methyl 2-naphthyl ketone gave 7-acetyl-3-methyloxepin-2(3*H*)-one **194** (42%) and 1-acetyl-4-*endo*-methyl-2-oxabicyclo[3.2.0]hept-6-en-3-one **195** (24%), as outlined in Scheme 50. The formation of **194** can be accounted



(192) R = Me
(196) R = Ph

(193) R = Me
(197) R = Ph

(194) R = Me
(198) R = Ph

(200)

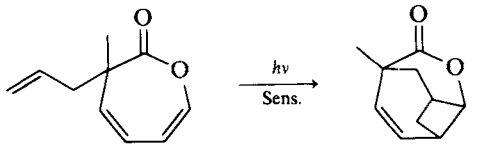
(195) R = Me
(199) R = Ph

SCHEME 50

for by an initial 1,5-acetyl shift which is analogous to the case of the 3-phenyl derivatives **177** and **180**, and a subsequent thermal isomerization of the double bond of the resulting 7-acetyl-2(7*H*) isomer **193**. Subsequent photochemical cyclization of **194** gives the observed product **195**. When then photolysis is carried out at −60 °C, **193** was formed and is thermally isomerized to **194** (89% yield).

Similarly sensitized photolysis of the 3-benzoyl derivative **196** in the presence of 2-naphthyl ketone in dichloromethane gave the corresponding cyclobutene γ-lactone **199** in 63% yield. When the photoreaction was conducted in acetone as solvent as well as a sensitizer at −60 °C, 4-methyl-6-phenyl-2,5-dioxatricyclo[4.3.0.$0^{4,7}$]non-8-en-3-one (**200**) arising from Paterno–Büchi reaction of an intermediate **197** was observed in 30% yield. The 3-acyloxepinones **192** and **196** underwent a 1,5-acyl shift under direct irradiation to give products **194**, **195** and **199**. These results can be accounted for by self-sensitization caused by excitation of the acetyl or benzoyl group.

Irradiation of 3-allyl-3-methyloxepin-2(3*H*)-one **201** in the presence of a sensitizer afforded the intramolecular [2 + 2] photocycloadduct **202** nearly quantitatively (Scheme 51).

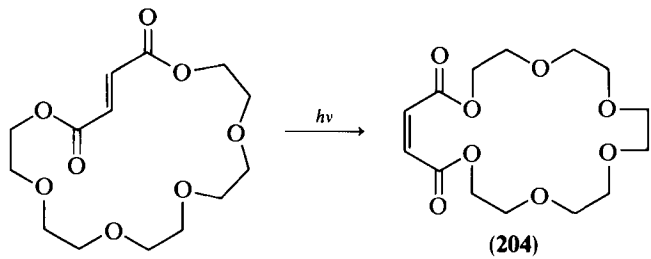


(201) **(202)**

SCHEME 51

I. Macrolides

Benzophenone-sensitized photoisomerization of a macrocyclic fumarate lactone **203** was reported to give a macrocyclic maleate lactone **204** (Scheme 52)[38]. The latter showed an enhanced cation binding ability, probably by virtue of the appropriate geometry of oxygen atoms in the polyether linkage.



(203) **(204)**

SCHEME 52

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CHAPTER 21

Radiation chemistry of fatty and amino acids

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I. INTRODUCTION

The radiation chemistry of simple aliphatic carboxylic acids and their derivatives was extensively reviewed in 1978[1]. New developments have been scarce since then and were, in fact, extensions of the earlier studies, rather than breakthroughs[2]. Similar reasoning applies to aromatic carboxylic acids.

Conversely, the radiation chemistry of biological systems and biocomponents developed rapidly in the last decade. Interest in these studies is prompted by the growing consensus that free radicals are involved in degenerative diseases in general, and in cancer initiation and promotion in particular[3]. In addition, the application of radiation technology in food industry has been investigated in detail in connection with quality control and detection of irradiated foods[4]. The radiation chemistry of fatty, amino and nucleic acids in model systems of various degrees of complexity has been investigated to understand better the free radical mechanisms of damage and repair of these important biocomponents. This review is concerned with fatty and amino acids, since nucleic acids, strictly speaking, do not belong to the carboxylic acids. In addition, the radiation chemistry of nucleic acids was extensively reviewed recently[2].

Absorption of ionizing radiation in any material results in the ionization and excitation[5] of the molecules. The process of energy deposition results in the formation of microscopic spatial inhomogeneities of the energy deposited, called spurs, which contain high local concentrations of primary species. Within these spurs (diameter 20 to 50 Å) a very rapid interaction occurs among the species they contain, concurrent with the diffusive expansion of the spurs, which have essentially lost their identity in about 40 ns. Ionization leads to the formation of geminate ion pairs, cations and electrons, which may either recombine ('cage' effect) or escape and get solvated. Excited states may dissociate into molecular fragments, react with neutral molecules or undergo deactivation by emission of energy. Consequently, the energy deposition in the irradiated system produces highly unstable species, which are excited states, ions and free radicals, in addition to 'primary' stable products. In principle, heavy charged particles, with higher LET, produce high density of reactive species along the track, which favors their mutual reactions that lead to their inactivation to stable products. Conversely, low LET electrons produce local inhomogeneities of unstable intermediates at lower density, which results in more free radical products. The number of species formed per 100 eV ionizing radiation energy absorbed by the unit mass or volume of the system is called the radiation chemical yield and denoted as the *G*-value.

Radiation chemistry of fatty and amino acids is mostly investigated in aqueous solutions. Absorption of ionizing radiation energy in water results in the formation of ionized and excited water molecules, which decompose into primary water radicals. Primary water radicals are formed in spurs, where they partially recombine to stable products or escape and get hydrated. Therefore, the radiolysis of water may be depicted as follows[6]:

$$H_2O \rightsquigarrow {}^{\bullet}H(0.55),\ {}^{\bullet}OH(2.8),\ e_{aq}^{-}(2.7),\ H_3O^{+}(2.7),\ H_2(0.65),\ \text{and}\ H_2O_2(0.7)$$

The radiation chemical yields are given in parentheses. Primary water radicals are unstable and often react at diffusion-controlled rates[7]. Hydrated electrons, e_{aq}^{-}, are the strongest known reducing agents, whereas ${}^{\bullet}OH$ radicals are strong oxidants. Hydrated electrons may be converted to ${}^{\bullet}OH$ radicals in the reaction with nitrogen suboxide, N_2O[6,7]:

$$e_{aq}^{-} + N_2O + H_2O \longrightarrow N_2 + {}^{\bullet}OH + OH^{-}$$
$$k = 9 \times 10^9\ M^{-1}\ s^{-1}$$

The field of 'OH radicals is effectively doubled, and they are major reacting species ($G_{OH} = 5.5$ vs $G_H = 0.55$). 'OH radicals and H-atoms, however, react predominantly by H-abstraction and addition to unsaturated systems.

II. FATTY ACIDS AND THEIR DERIVATIVES

The radiation chemistry of fatty acids and their derivatives has been extensively studied in the past decade. The focus was on the free radical chemistry of fatty acid radicals at various states of aggregation in aqueous and organic solutions and on the stable products of irradiation of fatty acids as food components. Underlying these studies are increasing interest in free radical (predominantly oxy radical) mechanisms of aging and cancer[3a,8-13], where fatty acid peroxidation plays a role, and various aspects of the use of radiation technology in food industry, such as quality control in food irradiation and detection of irradiated foodstuffs[4,14,15].

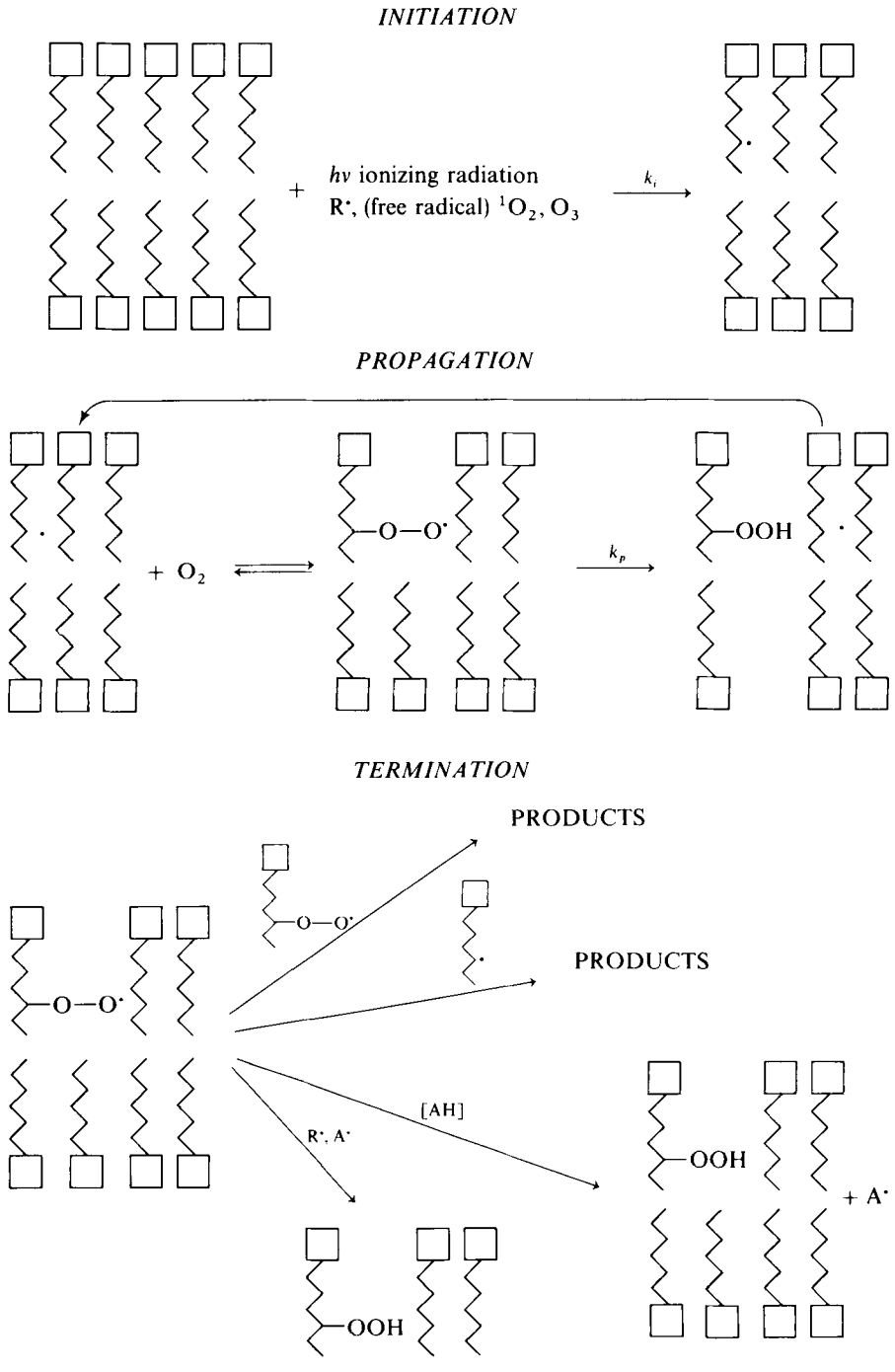
Kinetics and mechanisms of fatty acid radical generation and inactivation were studied by fast time-resolved techniques of pulse radiolysis and flash photolysis[16-22], whereas the kinetics of slower chain autoxidation was monitored by oxygen uptake measurements using automatic apparatus in which the pressure change was continuously recorded with a pressure transducer[23,24] or an oxygen electrode[25]. Electron spin resonance[26-30] was also used to monitor fatty acid radical reactions, because of the relatively high rise time of an ESR spectrometer, rapid radical reactions had to be studied at low temperatures, typically 77–180 K, and the data were then extrapolated to more relevant higher temperatures.

Various analytical techniques were used for identification and quantification of stable products of fatty acid radical reactions. These techniques range from fairly general, such as thiobarbituric acid reaction (malondialdehyde formation)[24], diene conjugation[24], chemiluminiscence[31,32] or hydroperoxide formation, to more specific and often more reliable ones, such as cold-finger isolation followed by derivatization and gas chromatography[4,14,33,34], HPLC[3c,3d,14,34] and GC/MS methods[14,34].

The radiation chemistry of fatty acids and their derivatives is, in fact, the chemistry of fatty acid free radicals.

In general, the state of aggregation of fatty acids, from monomer or dimer structures at low concentrations to micelles, vesicles and other aggregates at higher concentrations, determines the extent of chemical changes induced by free radical reactions. Another important structural parameter is the degree of unsaturation and the number of bis-allylic C—H bonds, by far the most reactive moieties in the fatty acid molecule. The major process upon absorption of ionizing radiation energy in saturated fatty acids is decarboxylation and subsequent formation of the *n*-1 hydrocarbon[1,15,35]*. Irrespective of the initiating agent, which may be the absorption of energy from a UV or ionizing radiation source, free radicals from smog or some free radical generating system, e.g. metal–organic peroxide or xanthine–xanthine oxidase, polyunsaturated fatty acids (PUFAs) and their derivatives, undergo autoxidation, which is a free radical mediated chain-oxidation, leading to the formation of hydroperoxides, peroxides, aldehydes, alcohols and *n*-1 and lower hydrocarbons. There are important differences in the relative yields of various stable products depending on the nature and energy of the initiating agent, which are useful in identification of this agent. However, the effects of all these agents are similar, which enables the use of diverse methods of free radical generation

* Saturated fatty acids are more important as food components, and will be dealt with in more detail in section II.B.


INITIATION
hν ionizing radiation
R•, (free radical) $^1O_2$, O_3
k_i
PROPAGATION
+ O_2
O—O•
k_p
OOH
TERMINATION
PRODUCTS
O—O•
PRODUCTS
O—O•
[AH]
R•, A•
OOH
+ A•
OOH

SCHEME 1

in the studies of mechanistic aspects of fatty acid peroxidation as well as antioxidant protection. Scheme 1 summarizes some processes known to be involved in autoxidation of unsaturated fatty acids and their derivatives.

A. Autoxidation of Unsaturated Fatty Acids

1. Formation and characteristics of pentadienyl radicals

In diluted aqueous and organic solutions of fatty acids, the radiation energy is deposited mainly by forming solvent free radicals[5]. These solvent radicals may react with unsaturated fatty acids directly or may be converted into other radicals in reactions with selected solutes and with fatty acids. The mechanisms and rates of reactions of free radicals with fatty acids depend on the properties of free radicals, such as nucleophilicity, one-electron redox potential and the difference in bond strengths of the bonds being broken and formed in the reaction, on the one hand, and on the state of aggregation of the fatty acids on the other. Some representative initiation rate constants of reactions of radiolytically and photochemically generated free radicals with PUFAs in homogeneous solutions and in aggregates are summarized in Table 1.

Selective organic and inorganic free radicals, such as hydroperoxy, $HO_2^{\bullet}$, *t*-butoxy, *t*-BuO$^{\bullet}$, sulfite, $SO_3^{-\bullet}$, and glutathione radicals, GS$^{\bullet}$, and singlet oxygen, $^1O_2$, react with PUFA predominantly at the bis-allylic CH_2 group:

$$X^{\bullet} + RCH{=}CHCH_2CH{=}CHR' \longrightarrow \overset{\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots}{RCH{-}CH{-}CH{-}CH{-}CHR'} + XH \text{ (or } X^- + H^+) \quad (1)$$

This is reflected in a relatively regular increase in the rates of the reactions with linolenate (two bis-allylic CH_2 groups) and arachidonate (three bis-allylic CH_2 groups) as compared with those of the reactions with linoleate (one bis-allylic CH_2 group), i.e.

$$k(X^{\bullet} + \text{Arachidonate}) \sim 3 \times k(X^{\bullet} + \text{Linoleate}) \text{ and}$$

$$k(X^{\bullet} + \text{Linolenate}) \sim 2 \times k(X^{\bullet} + \text{Linoleate})$$

Nucleophilic radicals, such as *t*-BuO$^{\bullet}$ and GS$^{\bullet}$, react with unsaturated fatty acids very likely by an H-atom abstraction from the bis-allylic C—H bond. However, oxidizing free radicals, such as $HO_2^{\bullet}$ and $SO_3^{\bullet -}$, may also react by one-electron oxidation of PUFA. The important difference between these two mechanisms is the requirement for the solvation of charged transition state and incipient (transient) products in the electron transfer mechanism, which might effectively slow down one-electron transfer reactions in nonpolar environments, such as PUFA aggregates or biological membranes[42].

The superoxide radical anion, $O_2^{\bullet -}$, was found to be unreactive with PUFA both in homogeneous solutions[36] and in aggregates[49]. Consequently, in order to damage biological membranes (as, for example, occurs during phagocytosis) this radical would need an 'activation', such as the conversion to $^{\bullet}OH$ radical via the Haber–Weiss–Fenton reaction[43].

The data on the reactions of halide and pseudohalide radical anions with fatty acids are inconsistent. Some authors reported sensitized autoxidation of PUFA in the presence of bromide, thiocyanate and azide radicals[44,45a]. The rates of the reactions of these radicals with linoleate were measured at both c < cmc and c > cmc[46]. Others claim that bromide, thiocyanate and azide radicals were unreactive with linoleate even at c < cmc[47]. The finding[47] that sulfite, a considerably milder oxidant than either bromide, thiocyanate or azide[48], reacted with linoleate, whereas these strong radical oxidants did not, seems surprising, unless other than an outer-sphere electron transfer mechanism is postulated for the sulfite-carried oxidations. On the other hand, the observed sensitiza-

TABLE 1. Initiation rate constants, $k(X^{\cdot} + S)$ in $M^{-1} s^{-1}$, of fatty acid oxidation in homogeneous solutions

Substrate, S	$^{\cdot}OH$[a]	$^{\cdot}O^{-}$[b]	$HO_2^{\cdot}$[c]	O_3[d]	t-BuO$^{\cdot}$[e]	$SO_3^{\cdot -}$[f]	GS$^{\cdot}$[g]	$^1O_2$[h]
Oleic acid Methyl oleate			unr.	9.5×10^5 9.0×10^5 (6.0×10^5)	3.8×10^6		($< 2 \times 10^6$)	0.74×10^5
Linoleic acid	1.0×10^{10}	2.5×10^9	1.18×10^3	11×10^5	8.8×10^6	1.8×10^6	8×10^6 (1.3×10^7)	1.3×10^5
Methyl linoleate				11.1×10^5 (7×10^5)	9.1×10^6			
Linolenic acid	7.3×10^9		1.7×10^3		13×10^6	2.8×10^6	1.9×10^7 (1.9×10^7)	1.9×10^5
Arachidonic acid			3.05×10^3		20.5×10^6	3.9×10^6	3.1×10^7 (2.2×10^7)	2.4×10^5

[a] From Reference 7. The value for linoleic acid is the mean of 8×10^9 $M^{-1} s^{-1}$ [17] and 1.15×10^{10} $M^{-1} s^{-1}$ [19], measured at pH 7–10.5 at c(Linoleate) < *c*ritical *m*icelle *c*oncentration (cmc).
[b] In aqueous solutions at pH 11.9–12.5, c(Linoleate) < cmc[19].
[c] In 85% (v/v) ethanol/water[36].
[d] In aqueous 140–160 mM *S*odium *D*odecyl *S*ulfate (SDS) solutions at 25 °C, the values obtained in homogeneous CCl_4 solutions are given in parentheses[37].
[e] In benzene/di-*t*-butyl peroxide 1/1[18].
[f] In aqueous solution at pH 11.5, c(Linoleate) < cmc[38].
[g] In ethanol/water 1/1 at pH 5.1[39]. The values[40] obtained in 60% aqueous methanol at pH 6 are given in parentheses.
[h] In pyridine[41].

TABLE 2. Rate constants of reactions of primary radicals from water with fatty acid functional groups or relevant compounds in aqueous solutions at 20 °C (from Reference 7)

Reactants, S	k ($M^{-1} s^{-1}$)		
	$e_{aq}^- + S$	$^{\bullet}OH + S$	$^{\bullet}H + S$
C_nH_{2n}	$<1 \times 10^7$	1.1×10^a	2.3×10^6
CH_3OH	$<1 \times 10^4$	9.7×10^8	2.6×10^6
CH_3COOH	2.0×10^8	8.5×10^7	9.8×10^4
CH_3COO^-	1.1×10^6	1.6×10^7	3.5×10^5
>C=C< [a] (Ethylene)	$<3 \times 10^5$	4.4×10^9	3×10^9
>C=CH—CH_2—CH=C< [b] (1,4-cyclohexadiene)	$<7.5 \times 10^5$	3.5×10^9	2.1×10^9
O_2	1.8×10^{10}	$<10^6$	2.1×10^{10}

[a] Any double bond, data given for ethylene.
[b] Any bis-allylic C—H bond, data given for 1,4-cyclohexadiene.

tion[44,45a] may not be taken as a conclusive evidence for the attack of halide and pseudohalide radicals on PUFA, since other mechanisms of sensitization are possible, e.g. the involvement of these radicals in secondary reactions with the radicals and/or products of PUFA autoxidation.

Very reactive primary radicals from water, $^{\bullet}OH$, and its conjugate base $^{\bullet}O^-$, e_{aq}^-, and $^{\bullet}H$, react rapidly with unsaturated fatty acids and their derivatives[7,35]. Interestingly, except rates of $^{\bullet}OH$ radical reactions with linoleate and linolenate[7], and that of e_{aq}^- reaction with oleate ion[7], the absolute rate constants are still missing. The data on average rates for the reactions of primary radical species from water with unsaturated fatty acid structural components are presented in Table 2.

The rates of reactions of primary radicals from water radiolysis with fatty acids in homogeneous solution are diffusion controlled, which is characteristic of these highly reactive nonselective free radicals.

The reactions of hydrated electron, e_{aq}, with PUFA in either homogeneous solutions or aggregates have not been systematically studied, as opposed to the reactions of the $^{\bullet}OH$ radical. The reason may be the well-known rapid reaction of hydrated electrons with oxygen[7],

$$e_{aq}^- + O_2 \longrightarrow O_2^{\bullet -} \qquad (2)$$
$$k = 2 \times 10^{10}\ M^{-1} s^{-1}$$

which effectively removes these potent reducing agents from the system.

At low oxygen concentrations, however, hydrated electrons may add to the protonated or esterified carboxy group[35],

$$e_{aq}^- + RCOOR' \longrightarrow RC^{\bullet}(O^-)OR' \xrightarrow{H^+} RC^{\bullet}(OH)OR' \qquad (3)$$

where R' = H or alkyl. The electron adducts in neutral solutions are usually protonated. The electron adducts to the acid may undergo water elimination, as found for pure formic acid at low pH[35],

$$R\dot{C}(O^-)OH \longrightarrow R\dot{C}{=}O + OH^- \qquad (4)$$

However, electrons react slowly with acetate ions (see Table 2), and under the conditions normally encountered in autoxidation of PUFA ($P_{O_2} > 100$ mbar) they will be converted to relatively unreactive superoxide radicals via reaction 2.

The $^{\bullet}OH$ radical and H-atom react predominantly by addition to double bonds, e.g.

$$^{\bullet}OH + RCH{=}CHCH_2CH{=}CHR' \longrightarrow RCH(OH)\dot{C}HCH_2CH{=}CHR' \quad (5)$$

and to a considerably lesser extent by H-abstraction from a bis-allylic CH_2 group,

$$^{\bullet}OH + RCH{=}CHCH_2CH{=}CHR' \longrightarrow$$

$$RCH{-}CH{-}\dot{C}H{-}CH{-}CH{-}CHR' + H_2O \quad (6)$$

or some other C—H bond,

$$^{\bullet}OH + R''CH_2R' \longrightarrow R''\dot{C}HR' + H_2O \quad (7)$$

$$k_{overall} = 1.0 \times 10^{10}\ M^{-1}\ s^{-1}\ ^{17,19}$$

The observation that less than 10% of $^{\bullet}OH$ radicals undergo reaction 6 in linoleate solutions below cmc[17] may be rationalized on the basis of average rates for addition to double bonds and H-abstraction (Table 2), and relative concentrations of methylene, bis-allylic C—H and saturated C—H bonds.

The oxide radical ion, $^{\bullet}O^-$, is, in general, a more selective H-abstracting agent than $^{\bullet}OH$ radical. The yield of PUFA pentadienyl radicals is markedly enhanced at pH 13 for linoleate, linolenate and arachidonate[17,49], where $^{\bullet}O^-$ is more abundant than $^{\bullet}OH$ due to

$$^{\bullet}OH + OH^- \rightleftharpoons {}^{\bullet}O^- + H_2O \quad (8)$$

$$pK_a = 11.9^7$$

and

$$^{\bullet}O^- + RCH{=}CHCH_2CH{=}CHR' \longrightarrow R\dot{C}H{-}CH{-}CH{-}CH{-}CHR' + OH^-$$

$$k = 2.5 \times 10^9\ M^{-1}\ s^{-1}\ ^{19} \quad (9)$$

Reaction 9 is in competition with reactions 5, 6 and 7. The full yield of pentadienyl radicals was not obtained at pH 13 in spite of the fact that $[^{\bullet}O^-]/[^{\bullet}OH] > 9{:}1$. Because of unfavorable reactivities of $^{\bullet}OH$ and $^{\bullet}O^-$ with PUFA only 20% of the initially produced $^{\bullet}OH$ react by reaction 9.

In monomeric solutions ([PUFA] < cmc), the carbon-centered radical OH or H-adduct from reaction 5, and $R\dot{C}HR'$ radical from reaction 7, may abstract an H-atom from a bis-allylic C—H via an intramolecular process[49], i.e.

$$RCH(OH)\dot{C}HCH_2CH{=}CHR' \longrightarrow RCH(OH)\dot{C}H{-}CH{-}CH{-}CH{-}CH{-}R' \quad (10)$$

Figure 1 shows, as an example, the growth of the pentadienyl radical in monomeric arachidonate following $^{\bullet}OH$ attack. A rough half-life of this process is $> 10\ \mu s$[17]. In the micelles, close packing of PUFA molecules enables alkyl radicals to undergo intermolecular H-abstraction from a neighboring PUFA molecule. This results in greater yield of the pentadienyl radicals, which approaches unity within ~ 2 ms at low dose rates[50]. Recombination of alkyl radicals ($k \sim 2 \times 10^8\ M^{-1}\ s^{-1}$ [50]) is concurrent with the formation of pentadienyl radicals.

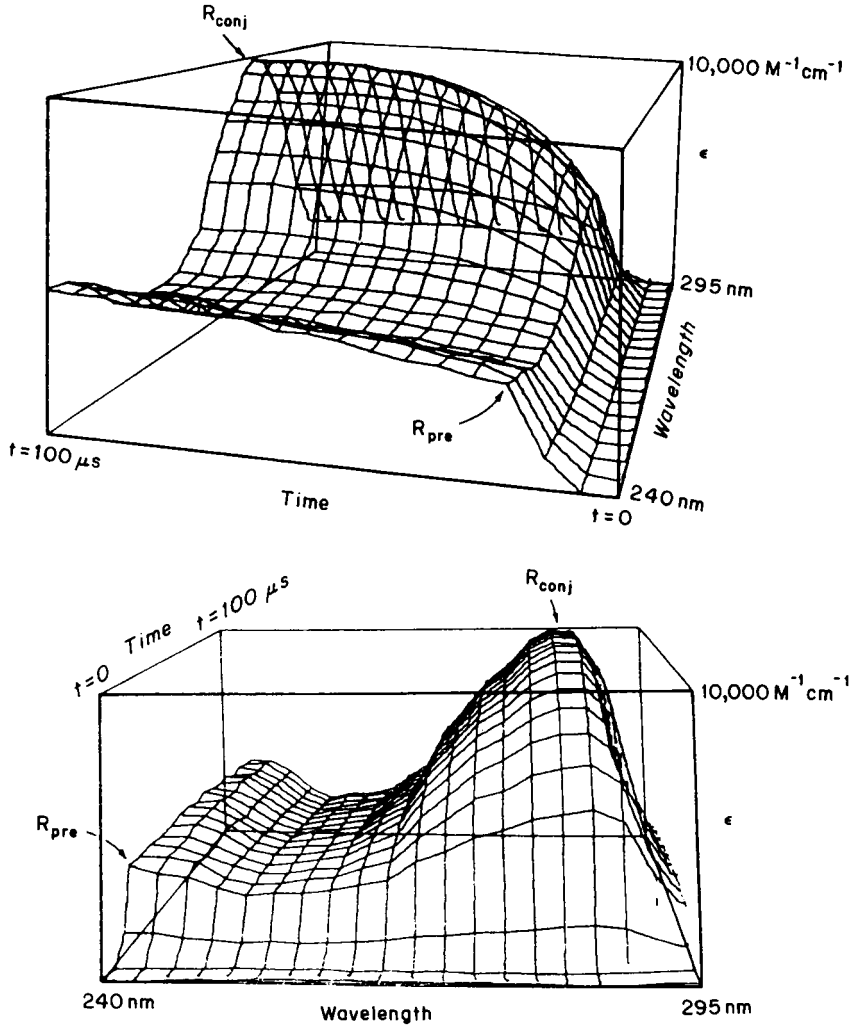


FIGURE 1. The growth of the cyclopentadienyl radical following 'OH attack on monomeric arachidonate in N_2O saturated aqueous solution at pH 10.5[49]. Reprinted with permission from Hasegawa and Patterson, *Photochem. Photobiol.*, **28**, 817 (1978). Copyright (1978) Pergamon Press PLC

At oxygen pressures > 100 mbar, intramolecular H-abstraction from the bis-allylic C—H by carbon-centered OH- and H-adducts and radicals R‴·CHR′ from reaction 7 is in competition with the addition of oxygen to the radical site,

$$R''\dot{C}HR' + O_2 \longrightarrow R''CH(R')OO^{\cdot} \qquad (11)$$

$$k \sim 10^9\ M^{-1}\ s^{-1}$$

The resulting peroxyl radical R″CH(R′)OO• may then abstract an H-atom from the bis-allylic C—H,

$$R''CH(R')OO^{\bullet} + RCH{=}CHCH_2CH{=}CHR' \longrightarrow \overset{\cdots\cdots\cdots\cdots\cdots\cdots\cdots}{RCH{-}CH{-}CH{-}CH{-}CHR'} + R''CH(R')OOH \quad (12)$$

The rate of reaction 12 has not been accurately determined for alkyl peroxy radicals, but should be in the range from $k[HO_2^{\bullet} + PUFA] \sim 10^3\ M^{-1}\ s^{-1}$ [36] to $k_p(ROO^{\bullet} + PUFA) = 36.1\ M^{-1}\ s^{-1}$ [21]. Halogenated peroxy radicals, however, react with PUFA many orders of magnitude faster, i.e. $k = 10^6$–$10^7\ M^{-1}\ s^{-1}$ [51], due to their considerably higher reduction potential ($E_7 > 1.1\ V$[3f]).

2. *Reactions of pentadienyl radicals*

The pentadienyl radical, $\overset{\cdots\cdots\cdots\cdots\cdots}{RCH{-}CH{-}CH{-}CHR'}$, absorbs strongly at 280–286 nm, $\varepsilon \sim 30{,}000\ M^{-1}\ cm^{-1}$, due to its highly resonant nature. ESR studies[13,23,27,28,52–54] showed that an unpaired electron is delocalized over four C—C bonds. A typical ESR spectrum of the pentadienyl radical is presented in Figure 2.

Because of the resonance stabilization of the pentadienyl radical, its reaction with oxygen is almost an order of magnitude slower,

$$\overset{\cdots\cdots\cdots\cdots\cdots\cdots\cdots}{RCH{-}CH{-}CH{-}CH{-}CHR'} + O_2 \longrightarrow RCH(OO^{\bullet})CH{=}CHCH{=}CHR' \qquad k = 1.4 \times 10^8\ M^{-1}\ s^{-1}\ [55] \quad (13)$$

than the corresponding rate of oxygen addition to the carbon-centered radical (reaction 11) and significantly reversible under normal autoxidation conditions. An apparent activation energy of $E_a = 24\ kJ\ mol^{-1}$ was measured for reaction 13 in the ESR study of low-temperature autoxidation of glycerides of unsaturated lipids[27].

The β-scission of the pentadienyl radical, i.e.

$$RCH(OO^{\bullet})CH{=}CH{-}CH{=}CHR' \longrightarrow \overset{\cdots\cdots\cdots\cdots\cdots\cdots\cdots}{RCH{-}CH{-}CH{-}CH{-}CHR'} + O_2 \quad (14)$$

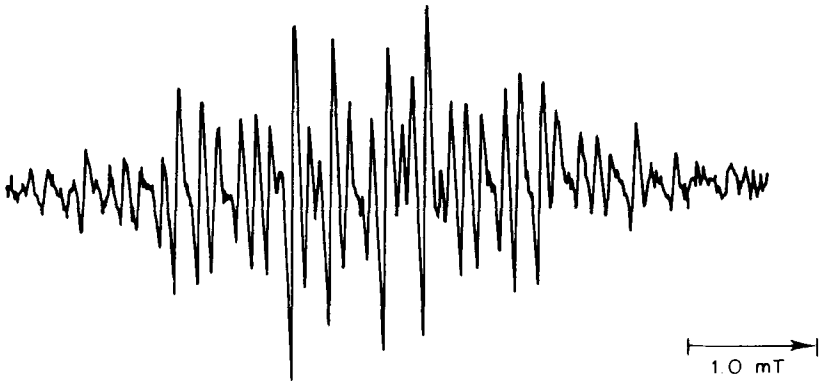


FIGURE 2. ESR spectrum of the pentadienyl radical at ambient temperature[28]. Reproduced by permission of the Royal Society of Chemistry

is in fact a reverse of reaction 13. In the Porter mechanism[56], the rate of conversion of an sp^3 radical center on the peroxy radical, $k_\beta = 430\ s^{-1}$, to a transoid sp^2 radical center is considerably faster than when peroxy radical decomposes to give cisoid sp^2 radical center, $k_\beta = 27\ s^{-1}$. Oxygen addition at the transoid end of the pentadienyl radical occurs more readily than at the cisoid end of the radical. Consequently, a transoid terminus of a pentadienyl radical is kinetically more labile than a cisoid center. ESR results[29], which suggest that there is a higher spin density at a transoid pentadienyl radical, substantiate the above mechanism.

Similarly to alkyl peroxy radicals[23], the unpaired electron in the pentadienyl peroxy radical is ~60% on the terminal and 40% on the inner oxygen,

$$\underset{(\mathbf{A} = 56\text{–}57\%)}{R{-}\ddot{O}{-}\dot{O}} \longleftrightarrow \underset{(\mathbf{B} = 43\text{–}44\%)}{R{-}\overset{+}{O}{-}\ddot{\underset{-}{O}}}, \qquad \mu = 2.6\ D$$

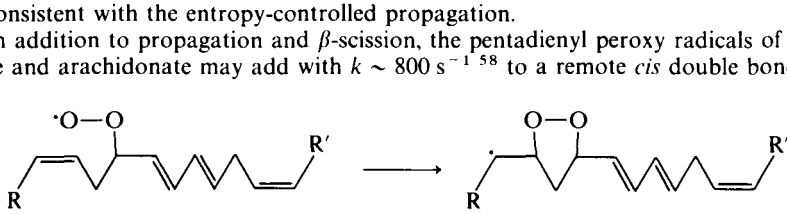
This structure of the pentadienyl peroxy radical makes it both a nucleophile (structure **A**), which may add to an unsaturated system or abstract an H-atom, and an electrophile (structure **B**), which may undergo electron transfer reactions with suitable electron donors.

Peroxy pentadienyl radical may abstract an H-atom from bis-allylic C—H on the neighboring PUFA molecule, which leads to the formation of another pentadienyl radical, and propagates the autoxidation chain,

$$RCH(OO^{\cdot})CH{=}CHCH{=}CHR' + RCH{=}CHCH_2CH{=}CHR' \longrightarrow$$
$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$
$$RCH{-}CH{-}CH{-}CH{-}CHR' + RCH(OOH)CH{=}CHCH{=}CHR' \qquad (15)$$

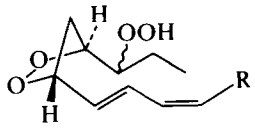
The rate of this reaction in SDS micelles, $k = 36.1\ M^{-1}\ s^{-1}$ [23,57], is low compared with the rates of free radical reactions (e.g. rates of initiation—Table 1). However, because of the close packing of PUFA molecules in micelles, bilayers or in biological membranes, the propagation of the chain reaction is very efficient, and the kinetic chain length may reach ~120[55]. The propagation rate constants increase regularly with the number of bis-allylic CH_2 groups in the molecule, thus k_p (arachidonic) ~ 3 × k_p (linoleic), and k_p (linolenic) ~ 2 × k_p (linoleic). The activation energies of the decay of lipid peroxy radicals into allylic and pentadienyl radicals[66] are $E_a = 9\ kJ\ mol^{-1}$ for trilinolenin, $34\ kJ\ mol^{-1}$ for trilinolein and $88\ kJ\ mol^{-1}$ for triolein. The low activation energy in trilinolenin indicates that the propagation is entropy-controlled in this highly unsaturated system, i.e. the proximity of the reaction centers and polarity of the peroxy radicals play a role. This is substantiated by the finding[50] that the yield of hydroperoxide drops in radiation-induced peroxidation of linolenate and arachidonate micelles as compared with the linoleate system. The latter result was interpreted[50] to suggest that the more extensive *cis*-double-bond structure in linolenate and arachidonate prevents close packing of molecules and decreases the probability of the propagation step, which is consistent with the entropy-controlled propagation.

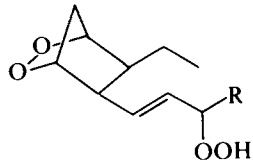
In addition to propagation and β-scission, the pentadienyl peroxy radicals of linolenate and arachidonate may add with $k \sim 800\ s^{-1}$ [58] to a remote *cis* double bond,



(16)

This reaction leads to the formation of prostaglandin-like cyclic peroxides, i.e.





The mutual reaction of two peroxy pentadienyl radicals,

$$2RCH(OO^{\cdot})CH{=}CHCH{=}CHR' \longrightarrow \text{nonradical products} \qquad (17)$$

terminates the chain propagation. The rate of decay of linoleic peroxy radical, $2k = 2.4 \times 10^7\ M^{-1}\ s^{-1}$, was measured in monomeric solutions with an Arrhenius activation energy of 9.5 kJ mol^{-1} [55].

The generation of pentadienyl radical, subsequent reversible addition of oxygen and termination of pentadienyl peroxy radicals constitute the classical mechanism of PUFA autoxidation. If we, for simplicity, designate k_i, k_p and $2k_t$ as the rate constants of, respectively, the initiation (reactions 6, 9, 10, 12), propagation (reaction 15) and termination (reaction 17), then the rate of oxygen consumption in the autoxidation of any PUFA is[55]

$$-(d[O_2]/dt) = k_p/\{(2k_i)^{1/2}[RH]k_t^{1/2}\}$$

where [RH] represents the concentration of PUFA. This expression is also known as the classical rate law of autoxidation, which holds for any initiating agent and autoxidizing system. When ionizing radiation is an initiating agent, the radiation-chemical yield of oxygen consumption in an aqueous micellar or liposomal PUFA solution, $G(-O_2)$, is related to the yield of free radicals, G_{in} ($R^{\cdot}$), to the density of the solution, d, and to the dose rate, D_r, by the following equation:

$$G(-O_2) = G_{in}(R^{\cdot})/2 + k_p\{G_{in}(R^{\cdot})/(2k_t d)\}^{1/2}[RH]/D_r^{1/2}$$

The two above expressions are similar, except that the radiation-chemical yield of oxygen consumption has a nonzero value, $G(-O_2) = G_{in}(R^{\cdot})/2$, when there is no chain reaction ($k_p = 0$).

The ratio of the rate of propagation and the rate of recombination of peroxy radicals, that is $k_p/2k_t$, is referred to as oxidizability, which is characteristic for a substrate undergoing autoxidation, in given conditions (pressure, temperature and reaction medium). Some representative data on oxidizability of unsaturated fatty acids in various systems are presented in Table 3.

The oxidizabilities of various phosphatidyl cholines (PC) were higher in homogeneous solutions than in aggregates, e.g. oxidizabilities of egg phosphatidyl choline in various organic solvents $\sim 0.2\ M^{-1/2}\ s^{-1/2}$ decreased to $0.0027\ M^{-1/2}\ s^{-1/2}$ in 0.1 M NaCl[24]. This effect was attributed to the decrease in the rate of propagation and increase in the rate of termination in aggregates[57], as a consequence of the tendency of polar peroxy radicals to migrate towards the aqueous phase and escape from the aggregates. However, the process of peroxy radical escape would reduce the chain propagation length, which was not observed[55]. An alternative explanation for the increase in oxidizability of phosphatidyl cholines in solutions in organic solvents is the formation of reverse-phase micelles[24].

Chemiluminiscence is known to be associated with oxidation reactions of fatty acids and oils[31,32]. Figure 3 exemplifies chemiluminiscence spectra obtained in model lipid

TABLE 3. Oxidizability of PUFA in various systems

PUFA	t (°C)	Solvent	Oxidizability $k_p/(2k_t)^{1/2}(M^{-1/2}\,s^{-1/2})$	Reference
Linoleic acid	30	0.5 M SDS aq	0.04	59
	37	0.5 M SDS aq	0.05 (k_p = 39.1)	57
	30	0.5 M SDS aq	0.06 (k_p = 36.2)	21
	30	Acetonitrile	0.05 (k_p = 94)	21
	30	*t*-BuOH	0.02 (k_p = 76)	21
Methyl linoleate	30	Chlorobenzene	0.02 (k_p = 31)	60
Methyl linolenate	30	Chlorobenzene	0.039 (k_p = 59)	60
1,4-Cyclohexadiene	30	Chlorobenzene	0.039 (k_p = 370)	60
Egg PC	50	Benzene	0.28	24
	50	CCl_4	0.16	24
	50	Chlorobenzene	0.21	24
	50	*o*-$C_6H_4Cl_2$	0.22	24
	50	0.1 M NaCl aq	0.0027	24
Soyabean PC	50	*t*-BuOH	0.15	24
	50	0.1 M NaCl aq	0.0064	24
Egg lecithin	30	Chlorobenzene	0.61	23
	30	Water	0.0165	23
Tetralin	30	Neat	0.0028	23
Dilinoleyl PC	37	Water	0.1 (k_p = 36.1)	57

systems[32]. The emission spectra from oxidized rat liver homogenates induced by feeding of animals with oxidized linseed oil[32] indicated that $^1O_2$ is the major emitting species in addition to triplet carbonyls. This was substantiated by diminishing of the chemiluminiscence spectrum of homogenates upon addition of $^1O_2$-quenchers, especially β-carotene. The source of $^1O_2$ and triplet carbonyls is most likely the decomposition of lipid hydroperoxides induced by light or metal[61], although the termination reactions of lipid peroxy radicals (reaction 16) cannot be excluded[32].

In radiation-induced oxidation of fatty acids, superoxide radical is generated[62], probably via elimination from the PUFA peroxy radicals. The yield of $O_2^{\cdot -}$, measured as the yield of nitroform anion, increased linearly with the number of double bonds present in the fatty acid [i.e. $G(O_2^{\cdot -}) = 1.1$ for oleic, 2.2 for linoleic and 4.7 for arachidonic acid]. It is not clear which PUFA radical eliminates the superoxide radical ion, and whether the superoxide radical elimination occurs in the systems where PUFA autoxidation is induced by another initiating agent.

3. *Stable products*

Autoxidation of unsaturated fatty acids leads to the formation of stable products, such as hydroperoxides and peroxides, aldehydes and volatile products. The analytical techniques used in the analysis of the stable products have been extensively reviewed (see References 3c, 3d, 3e, 14 and 34).

The major products of fatty acid autoxidation in chlorobenzene are conjugated diene hydroperoxides. These products account for over 97% of oxygen consumed in the process[56]. In the case of linoleate autoxidation in chlorobenzene, four isomeric hydroperoxides are formed[52,56], i.e. 13-*trans,cis*, 13-*trans,trans*, 9-*trans,cis* and 9-*trans,trans* in

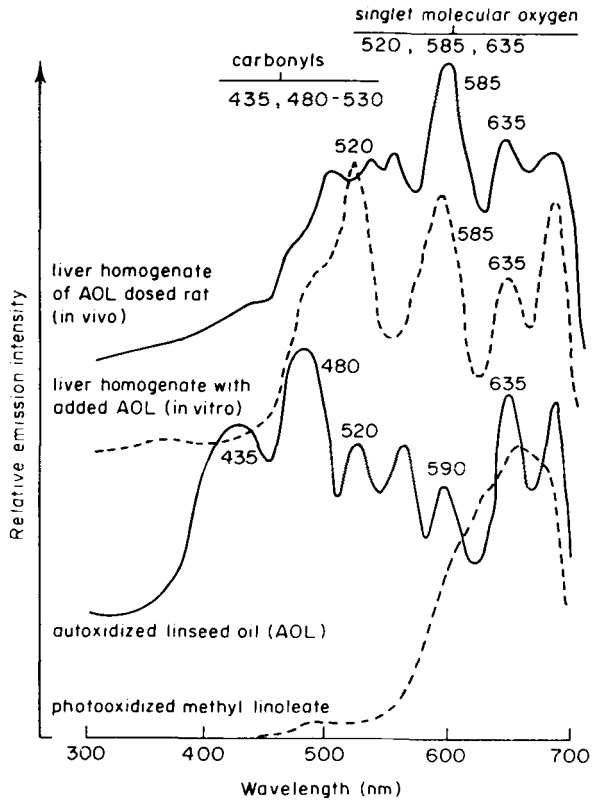
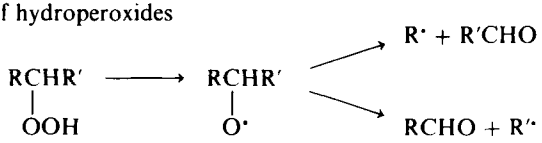


FIGURE 3. Chemiluminescence spectra of liver homogenates of rats fed with autoxidized linseed oil (peroxide value 2000 meq/kg) and photooxidized methyl linoleate[32]. Reproduced by permission of the American Oil Chemists' Society

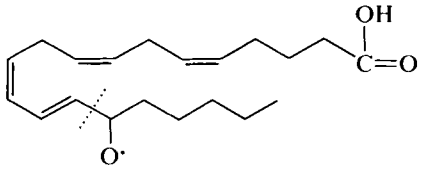
approximately equal amounts. The ratio of *trans,cis* to *trans,trans* hydroperoxides is higher for higher linoleate concentrations (kinetic control), since increasing concentrations of H-atom donors favor conversion of the initially formed *trans,cis* linoleate peroxy radical. At higher temperatures, β-fragmentation pathways become competitive with H-atom transfer reactions and more *trans,trans* products are formed (thermodynamic control). These premises constitute the Porter mechanism[52,56], which is based on the isomerization of PUFA peroxy radicals as a consequence of the reversible addition of oxygen on the pentadienyl radical. An alternative mechanism to explain the stereochemistry of product distribution is the isomerization of the pentadienyl radicals proposed by Frankel[3d]. The ESR results[28,29] favor the Porter mechanisms, since no isomerization of the pentadienyl radicals was detected under the conditions of photoinduced autoxidation of methyl linoleate in neat *t*-butyl peroxide.

Aldehydes are secondary products of lipid peroxidation, which cause off-flavor in oxidized foodstuffs, and are highly cytotoxic and mutagenic[10]. For example, the fluorescent products in the aging-pigment lipofuscin are thought to be formed by malondialdehyde (a mutagen and carcinogen and a major end-product of rancidity) crosslinking proteins and lipids[9]. Scheme 2 summarizes the major pathways of the

1. Dismutation of hydroperoxides

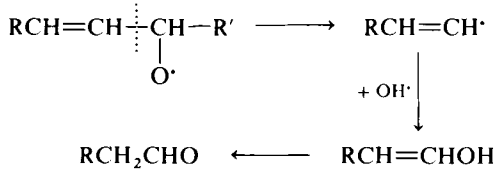


Example: 15-hydroperoxyarachidonic acid ⟶ hexanal



⟶ n-hexanal

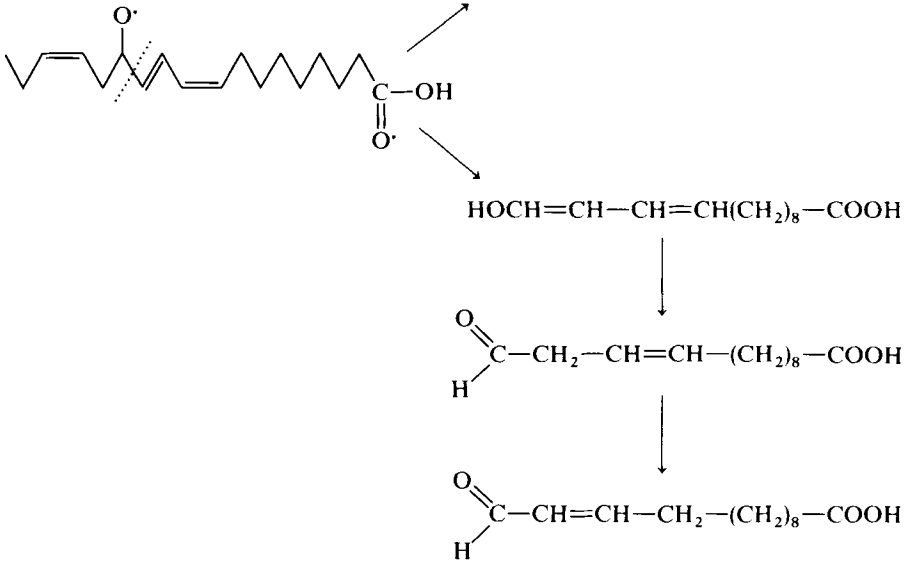
2. Rearrangement of an enol:



Example: 13-hydroxylineolenic acid ⟶ 12-oxo-10-*trans*-dodecanoic acid ("traumatic half aldehyde")[10]

+ 2-*trans*-hexenal

3-*cis*-hexenal ⟶ 2-*trans*-hexenal



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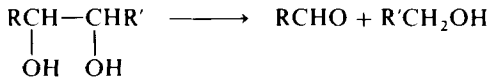
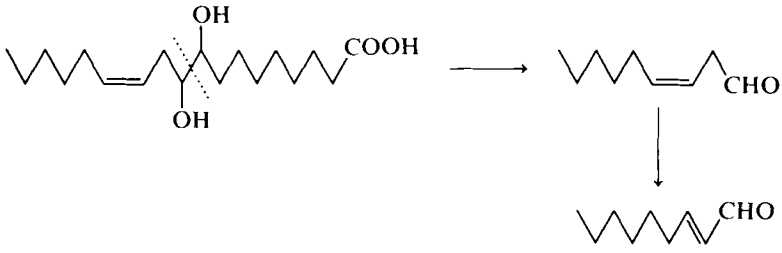
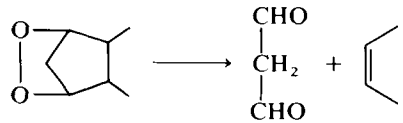
3. Reversible aldol condensation of vicinal hydroxy groups



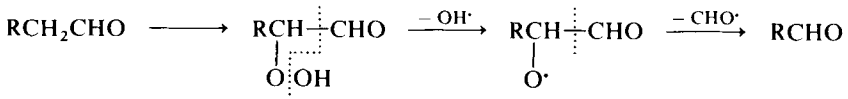
Example: 9,10-dihydroxy-12-octadecanoic acid ⟶ 2-*trans*-nonenal



4. Malonaldehyde formation through cleavage of cyclic endoperoxide



5. Recurrent autoxidation and dismutation



SCHEME 2

production of aldehydes from the primary products of PUFA autoxidation (cf Reference 10).

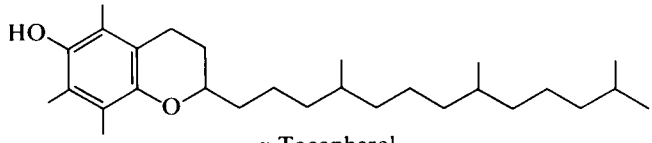
4. Reactions of pentadienyl radicals with antioxidants

Biological consequences of lipid peroxidation, such as cancer and aging, originate from membrane damage and disfunction. Peroxidative damage to membrane lipids is widely held as a major underlying mechanism for cell injury and death from oxidative stress[11]. The brain uses 20% of the oxygen consumed by man and contains an appreciable amount of unsaturated fat. Lipid peroxidation is known to occur readily in the brain, and possible consequences could be senile dementia or other brain abnormalities[9]. It has been found recently[54] that the water-soluble radical initiator 2,2-azobis(2-amidinopropane)dihydrochloride (AAPH) administered intraperitoneally to mice causes toxicological effects in biological tissues, such as degeneration, swelling and disruption of the endothelial lining cells of capillaries in various organs, the death of lymphocytes in the lymphoid tissues and the fatty degeneration of the liver and kidneys. Deleterious effects of lipid peroxidation may be suppressed by antioxidants. Ascorbate, vitamin C and α-tocopherol, vitamin E, are well-known natural antioxidants. For example, there is a high concentration of ascorbic acid in the gray and white matter of the central nervous system. The concentration is second only to the level found in the adrenal glands[8]. The brain has a specific active transport system for ascorbic acid in the choroid

plexus which elevates the concentration of ascorbate in the cerebrospinal fluid 100-fold above the plasma level. Furthermore, neuronal tissue cells have a second transport system that concentrates intracellular ascorbate an additional 10-fold. In states of leukocyte activation and other types of acute or chronic oxidative stress, controlled ascorbate supplementation could prove helpful in preventing formation of lipid hydroperoxides[63].

The obvious strategy in the prevention of lipid peroxidation is the inactivation of pentadienyl peroxy radicals, that is inhibition of the propagation of chain oxidation. In order to effectively compete with the chain propagation, with k_p [PUFA] $\sim 100\ s^{-1}$, an antioxidant, typically present at 0.01–1% (i.e. $c \sim 0.6$–6 mM for ascorbate and $c \sim 0.2$–2 mM for α-tocopherol) should have high reactivity, $k > 10^6\ M^{-1}\ s^{-1}$, with the peroxy radical. In addition, antioxidant radicals should be fairly unreactive with fatty acids and oxygen, so that their radicals do not propagate chain oxidation. The representative rate constants of the reactions of selected antioxidants with alkyl peroxy radicals are summarized in Table 4.

On the basis of the mode of action antioxidants may be divided into peroxide-decomposing (preventive) and chain-breaking antioxidants[64]. In biological systems, peroxide-decomposing antioxidants are enzymes[11], such as catalase and glutathione peroxidase, whereas chain-breaking antioxidants are generally phenols, aromatic amines or thiols



α-Tocopherol

Vitamin E, α-tocopherol, has long been known as the most efficient natural lipid-soluble chain-breaking antioxidant. Peroxy radicals react with the active part of the molecule, which is the chromane ring, whereas the phytyl side-chain is an anchor in the hydrophobic inner structure of fatty acid aggregates.

Site-specific action of vitamin E has been elegantly investigated by Niki and colleagues[65], who used a spin probe *N*-oxyl-4,4′-dimethyloxazolidine attached to C5, C7, C10, C12 and C16 of stearic acid. The spin probe reacted with the fatty acid peroxy radicals inhibiting chain autoxidation in a manner similar to α-tocopherol. α-Tocopherol was found to protect more efficiently the spin probe with radical site at C5 than those where the radical was buried deeper in the hydrophobic interior of the phosphatidyl choline liposome. Consequently, the above study clearly shows that vitamin E is better suited for action against oxidants from the aqueous phase. The efficiency of scavenging decreases below 50% for the radicals residing deeper than 5 to 6 C—H bonds in the membrane[65]. It was suggested[74] that the higher antioxidant activity of bilirubin in radiation-induced oxidation of micellar linoleate, as compared to that of α-tocopherol, resulted from its deeper penetration of the hydrophobic interior (buried in the micelle up to C11).

At present there are two mechanisms, either an H-atom or a one-electron donation to the peroxy radical[75]. The major difference between the two mechanisms is in the driving force of the reaction, which is proportional to the difference in energies of bonds being broken and formed in the case of an H-atom transfer, but to the redox potential difference between a peroxy radical and an antioxidant in the one-electron transfer. H-atom transfer reactions are considerably slower than electron transfer reactions, and strongly thermodynamically controlled. For example, the reaction of the fatty acid peroxy radical with the bis-allylic C—H (reaction 15), which is responsible for chain

TABLE 4. Rates of inactivation of peroxy radicals with selected antioxidants

Antioxidant AH^-	Peroxy radical, $ROO^\cdot$, from	$k(ROO^\cdot + AH^-)$ $(M^{-1} s^{-1})$	Reference
α-Tocopherol	Linoleic acid in 0.5 SDS, 37 °C	3.7×10^4	66
	Methyl linoleate, 37 °C	5.1×10^5	54
	Cyclohexane, air, r.t.[a]	5.7×10^6	67
	$^1O_2$ in pyridine, r.t.	2.5×10^8	68
	$HO_2^\cdot$	2.0×10^5	67
	$O_2^{\cdot -}$	6	67
	DLPCaq[b], initiated by DMVN[c] at 37 °C	3900	57
	DLPCaq, photoinitiated at 37 °C	2900	57
	Styrene, 24 °C	2.9×10^6	69
	O_3 in aqueous 0.5 M SDS, 37 °C, pH 7	7.1×10^5	37
β-Tocopherol	Linoleic acid, 0.5 M SDS, 37 °C	2.2×10^4	66
γ-Tocopherol	Linoleic acid, 0.5 M SDS, 37 °C	2.2×10^4	66
δ-Tocopherol	Linoleic acid, 0.5 M SDS, 37 °C	0.89×10^4	66
BHT[d]	Linoleic acid, 0.5 M SDS, 37 °C	1.1×10^4	66
	DLPCaq, initiated by DMVN at 37 °C	2700	57
	DLPCaq, photoinitiated at 37 °C	1900	57
	Cyclohexane, air, r.t.	$\sim 10^4$	45
BHA[e]	Linoleic acid, 0.5 M SDS, 37 °C	1.0×10^4	66
	Cyclohexane, air, r.t.	3.4×10^6	45
Probucol	Linoleic acid, 0.5 M SDS, 37 °C	0.52×10^4	66
Ascorbate	$(CH_3)_2SO$aq, N_2O: O_2 = 4:1 r.t., pH 7	1.7×10^6	71
	Aqueous cyclohexanol, N_2O:O_2 = 4:1, pH 7, 20 °C	2.2×10^6	70
Uric acid	$(CH_3)_2SO$aq, N_2O:O_2 = 4:1 r.t., pH 13	8.8×10^6	71
	CCl_4 aqueous, r.t., pH 7	3.2×10^8	72
5-Hydroxytryptophan	$(CH_3)_2SO$aq, N_2O:O_2 = 4:1 r.t., pH 13	7.0×10^6	71
Trolox C[f]	Linoleic acid, 0.5 M SDS, 37 °C	11×10^4	66
	DLPCaq, initiated by DMVN at 37 °C	6500	57
	DLPCaq, photoinitiated 37 °C	2500	57
	Styrene, 20 °C	1.1×10^6	69

(*continued*)

TABLE 4. (*continued*)

Antioxidant AH^-	Peroxy radical, ROO·, from	$k(ROO^\cdot + AH^-)$ ($M^{-1} s^{-1}$)	Reference
	Aqueous cyclohexanol, $N_2O:O_2 = 4:1$, pH 9, 20 °C	6×10^5	70
4-$CH_3OC_6H_4OH$	Chlorobenzene, 60 °C	2.42×10^5 ($k_r = 650$)	73
Kaempferol	Linoleate hydroperoxide, $^\cdot N_3$ pH 11.5, 20 °C	2.1×10^8	20
Quercetin	Linoleate hydroperoxide, $^\cdot N_3$, pH 11.5, 20 °C	3.5×10^8	20

[a] Room temperature.
[b] Dilinoleyl phosphatidylcholine.
[c] 2,2'azobis(2,4-dimethylvaleronitrile).
[d] Butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol).
[e] Butylated hydroxyanisole (a mixture of 2-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

propagation, is very slow, $k_p = 36.1$–$59\ M^{-1} s^{-1}$, in spite of a considerable driving force of the bond strengths (BS) (BS(ROO—H) − BS(bis-allylic C—H) = 443 − 314 = 129 kJ mol^{-1} [70]. Conversely, $k \sim 10^6\ M^{-1} s^{-1}$ for one-electron oxidation of well-known electron-donors ascorbate, urate and trolox by peroxy radicals[67,70], with relatively low activation enthalpy and negative activation entropy (e.g. for c-C_6H_{10}(OH)OO· + ascorbate, $\Delta H^+ = 77$ kJ mol^{-1}, $\Delta S^+ = -59$ J mol K^{-1} [70]).

In the case of phenolic antioxidants, such as α-tocopherol, one-electron transfer to the fatty acid peroxy radical is the most probable mechanism in polar solvents, which are good proton-donors[3f,13,20,42,67,70,71,75], such as water and alcohols. In the reaction of the peroxy radical with any phenolic antioxidant a proton is exchanged in addition to an electron, that is,

$$ROO^\cdot + Ph{-}OH \longrightarrow (Ph{-}OH^{\cdot+} + ROO^-) \longrightarrow Ph{-}O^\cdot + ROOH \quad (18)$$

The solvent mediates the proton exchange between the phenoxy radical cation and the hydroperoxide anion, very probably through a hydrogen-bonded transition state[42]. The requirement for this type of mechanism is the negative activation entropy, because of the pronounced reorganization in the solvent shell. As a consequence of this requirement, under conditions of low polarity or poor proton donicity, as in membranes, reaction by electron transfer is likely to be considerably slowed down, giving H-atom transfer a chance to dominate.

Synergistic action of vitamin C and vitamin E was first postulated by Tappel[76]. The reaction of the vitamin E radical (Chromanoxyl or Chr-O·) with ascorbate, AH^-, was later demonstrated in homogeneous solution[77], i.e.

$$Chr{-}O^\cdot + AH^- \longrightarrow Chr{-}OH + A^{\cdot-} \quad (19)$$
$$k = 2 \times 10^6\ M^{-1} s^{-1}$$

A clear synergistic effect of vitamin C in antioxidant action of vitamin E was reported by Niki and colleagues[78]. They found that in the oxidation of egg PC liposomes initiated by the lipid-soluble free radical generator, the lag period due to antioxidant protection of vitamin E and C was longer than the sum of the individual effects (Figure 4).

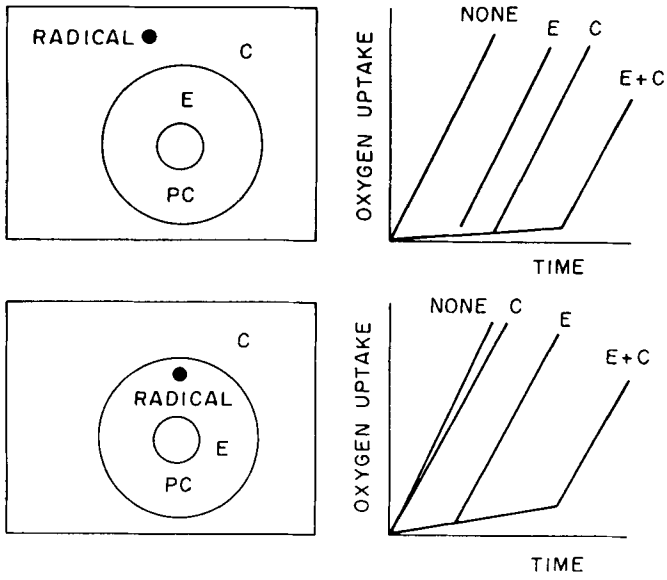


FIGURE 4. Oxidation of liposomal membrane induced by water-soluble and lipid-soluble initiators and inhibition by vitamin E, vitamin C and mixture of vitamin E and C[54]. Reproduced by permission of Elsevier Science Publishers from Niki, *Chem. Phys. Lipids*, **44**, 227 (1987)

In addition to their physiological receptor binding functions, most commonly used cardiovascular drugs, being amphophylic by nature, partition readily into the hydrophobic regions of the cell membrane and thus may exert antioxidant prevention of free-radical injury[79]. *In vitro* studies[79,80], using autoxidation of highly purified sarcolemal membranes initiated by the dihydroxyfumarate + Fe-ADP free radical generating system, showed that selected beta-blockers inhibit lipid peroxidation in a concentration-dependent manner. The order of relative antioxidant potency of some of these drugs was: propranolol > pindolol > metoprolol > atenolol > sotalol, which correlates well with their lipophilicity[79]. Probucol is a drug developed for treatment of hypercholesterolemia and atherosclerosis, which shows potent antioxidant activity, comparable to that of α-tocopherol[80,81]. This antioxidant activity is associated with the conjugated phenolic groups. In fact, the structure of probucol consists of two 2,5-di-*t*-butylphenol molecules, BHT, which are well-known man-made antioxidants, linked by a $-S-CMe_2-S-$ linkage.

Several metabolites, which occur during normal metabolism, have been tested as endogenous antioxidants. These include uric acid[3e,54,72,82], bilirubin[74,83], female hormones (e.g. estrogens[54,84], which are phenolic-type antioxidants), 5-hydroxytryptophan and its derivatives[3f,85,86], and 3,4-dihydroxyphenylalanine (DOPA)[3f]. The rationale of these studies was to investigate the ability of metabolites, which are already present in biological systems because of their definite metabolic functions, to inactivate peroxy radicals and/or repair damaged biomolecules. Water-soluble endogenous antioxidants, such as uric acid, 5-hydroxytryptophan and its derivatives, and DOPA, reacted with peroxy radicals by a one-electron transfer mechanism[3f]. However, the redox potentials of these compounds[76,87] are higher than that of α-tocopherol, which means that their radicals may be repaired at the expense of α-tocopherol. Estrogens were found to be

excellent scavengers of substituted phenolic radicals in benzene solution and potential repair agents of the α-tocopherol phenoxy radical[84]. Bilirubin showed potent antioxidant activity, even higher than vitamin E[74,83], due to its highly unsaturated structure and penetration into the hydrophobic interior of membranes.

The reactions in which peroxy radicals are inactivated by antioxidants are irreversible in homogeneous solutions. This is a consequence of (1) the low and finite lifetime of antioxidant radicals, and (2) low concentrations of antioxidants and hydroperoxides. However, the lifetime of antioxidant radicals in membranes is many orders of magnitude higher, and hydroperoxides may accumulate during the autoxidation process. Consequently, the reverse of the repair reaction has a chance and was, in fact, observed[88,89]

B. Fatty Acids as Food Components

The radiation chemistry of fats and oils has been studied in relation to the assessment of the wholesomeness and safety of irradiated foods, as well as to the detection of radiation treatment. Consequently, the radiation doses used in most of these studies matched those normally encountered in radiation applications, that is, up to 50 kGy for sterilization, or less than 10 kGy for pasteurization, and other applications. Substrates vary from model systems of fatty acids, esters and triglycerides to natural fats or fat-containing foods. Irradiations were carried out under diverse conditions of temperature, pressure, atmosphere, dose rate, etc.

1. Neat fatty acids and derivatives

The major compounds formed in saturated fatty acids upon irradiation in the absence of oxygen are hydrogen gas, carbon dioxide, carbon monoxide, a series of hydrocarbons (n-alkanes and 1-alkenes) and an aldehyde[1,2,15,35,90,91]. The formation of carbon dioxide and *n*-1 alkane may be explained by the reaction sequence 20–23. Ionization of a fatty acid molecule leads to the formation of the radical cation and an electron[1,2,35]:

$$\sim CH_2COOH \quad \rightsquigarrow \quad CH_2COOH^{\cdot +} + e^- \tag{20}$$

The radical cation undergoes rapid proton transfer reaction with its hydrogen-bonded neighbor:

$$\sim CH_2COOH^{\cdot +} + \sim CH_2COOH \longrightarrow \sim CH_2COO^{\cdot} + \sim CH_2OOH_2^{+} \tag{21}$$

The resulting alkylcarboxyl radical is known to decarboxylate easily:

$$\sim CH_2COO^{\cdot} \longrightarrow \sim CH_2^{\cdot} + CO_2 \tag{22}$$

$$\sim CH_2^{\cdot} + (\text{H-donor}) \longrightarrow \sim CH_3\ (n-1\ \text{alkane}) \tag{23}$$

Table 5 and Figure 5 illustrate the yields of *n*-1 alkanes and CO_2 obtained upon irradiation of saturated fatty acids.

It can be seen from Figure 5 that the yield CO_2 decreases for longer-chain fatty acids and alternates from even and uneven solid saturated acids with the number of C-atoms higher than 10 irradiated at 77 K. These interesting phenomena have still to be elucidated.

Decarboxylation is not a major radiolytic pathway in irradiated unsaturated acids. For example, dimeric products are predominantly produced upon the radiolysis of oleic acid[1,2,15,35]. It has been proposed[2] that the dimerization is due to the reaction of initially formed radical cation with a neighboring molecule followed by the neutralization of the dimer radical cation (equation 24).

TABLE 5. $n-1$ Alkanes in saturated fatty acids irradiated at room temperature with 60 kGy[15]

Fatty acid (FA)	$n-1$ alkane	Quantity of $n-1$ alkane formed (nmol/mol FA)
Lauric	Undecane	6.91
Myristic	Tridecane	6.00
Palmitic	Pentadecane	5.20
Stearic	Heptadecane	4.62

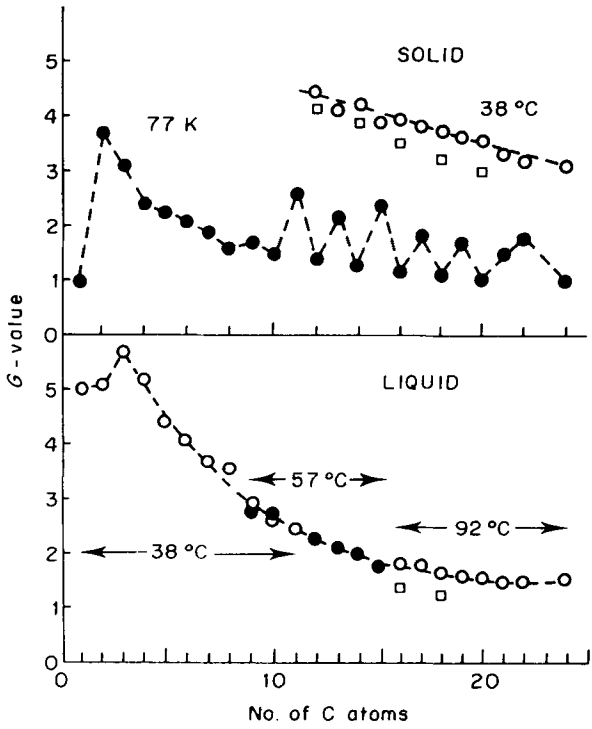
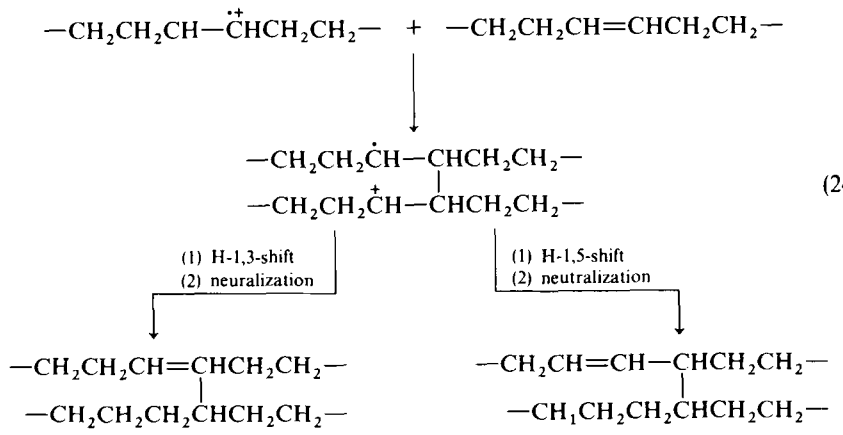


FIGURE 5. Radiolytic products of saturated aliphatic fatty acids at different temperatures in liquid and solid state as a function of the number of C atoms: ○ and ●—CO_2; □—C_{n-1} saturated hydrocarbon[35]. Reproduced by permission of the American Oil Chemists' Society



(24)

The yields of $n-1$ hydrocarbons are ~20 times lower in irradiated triglycerides than in the corresponding fatty acids[91]. In a triglyceride molecule,

radiolytic cleavage preferentially occurs at five locations in the vicinity of the carbonyl groups (solid lines) and randomly at all the remaining carbon–carbon bonds in the fatty acid moiety (dotted lines)[15]. In addition to cleavage at (c) and (d), which respectively produce *n*-1 and *n*-2 hydrocarbons, cleavage at (b) produces *n* aldehydes, alkylcyclobutanones, diglycerides and oxo-alkanediol esters, at (a) *n* fatty acids and propanediol and propenediol esters, and at (e) methyl esters and ethanediol diesters. The competition between the above processes reduces the yield of *n*-1 alkanes in irradiated triglycerides.

2. Fats and fat-containing foods

The content of essential PUFA is significantly reduced upon irradiation, as a result of their radiosensitivity, which affects the nutritional value of irradiated foods. In addition, the antioxidant content, especially that of chain-breaking antioxidants such as vitamin E and C, is depleted during irradiation. As a result of protective antioxidant action, less hydroperoxides and aldehydes are formed[92] in irradiated synthetic diets. Similarly, it was suggested[93] that milk fat globule membranes were less sensitive to radiation decomposition than whole milk and milk fat globules, because of the presence of proteins, vitamin E and cholesterol, which are known to inhibit lipid peroxidation (see Section II.A.4).

Irradiation of fats and fat-containing foods results in the formation of a complex mixture of radiolytic products, which consists of the products of radiolysis of individual components as well as the products of cross-reactions of all free radicals generated in the irradiated material. The yields of carcinogenic and mutagenic peroxides and aldehydes in artificial food models[94,95], as well as in whole grain of rye, wheat and

rice[96], were considerably higher if the samples were oxygenated prior to irradiation, and for higher water content of irradiated samples. Oxygen concentration above ~100 mbar is necessary to propagate chain peroxidation of polyunsaturated fatty acid components in the samples, whereas the effect of water content was attributed to the formation of OH radicals, known as one of the most efficient initiating agents of lipid peroxidation. It was also found[95] that the species generated during radiation-induced oxidation of unsaturated fats can react with polycyclic aromatic hydrocarbons, such as the environmental carcinogen benzo[*a*]pyrene, and convert them into active mutagenic and toxic products. All these effects may be reversed by the addition of appropriate antioxidants. The accumulation of carcinogenic products, and serious depletion of the nutritional value of irradiated foodstuffs occur at higher doses than those normally encountered in food irradiation[94–96].

The possibility of using lipid-derived hydrocarbons as indicators of irradiation of food was first proposed by Nawar and Balboni[97]. The rationale of this approach was that fatty acid food components yield *n*-1 alkane and *n*-2 alkene upon irradiation in a dose-dependent manner, irrespective of the conditions of irradiation (i.e. dose rate, oxygen). In the original publication[97], the feasibility of using six 'key' hydrocarbons, i.e. heptadecene, hexadecadiene, pentadecane, tetradecane, heptadecane and hexadecene (radiolytic products of oleic, palmitic and stearic acid), in the detection of irradiation of pork meat was investigated. Later, this approach was extended to chicken, pork and beef gamma-irradiated at room temperature with 0.25, 0.5, 1 and 2 kGy[33]. Relatively good linear correlations of the yields of radiolytically generated hydrocarbons with absorbed doses were obtained for 15:0, 14:1, 15:1, 14:2, 17:0, 16:1, 17:1, 16:2, 17:2 and 16:3 hydrocarbons. The best correlations were those of 17:1, 16:2 and 14:1 hydrocarbons.† It was also demonstrated that an unknown dose could be determined from standard yield–dose plots for these hydrocarbons.

The specificity of radiation treatment is reflected in different yields of products, as well as in the formation of certain products which are claimed to be unique to the radiation treatment. The *n*-1 alkanes and *n*-2 alkenes, and *n* aldehydes are considered specific for radiation treatment[4], as illustrated in Figure 6. In addition, the 2-alkylcyclobutanones[4] have not been reported in heated or oxidized fat.

III. AMINO ACIDS

The chemical changes induced in amino acids by high-energy radiation have been most extensively studied in aqueous solutions[2,98–102]. This is understandable because amino acids are constituents of proteins and enzymes which are present in almost all biological and biochemical systems. Some investigations were also carried out in the solid state[2,298–102].

In aqueous solutions, in the reactions with primary water radicals, different short-lived intermediates are formed, depending on the structure of amino acids and the pH of solution. It is now well established that the reaction of e_{aq}^- with simple aliphatic amino acids leads to deamination and to the formation of $^{\cdot}H$ atoms[2,98–102]:

$$e_{aq}^- + {}^+NH_3CH_2COO^- \longrightarrow NH_3 + \dot{C}H_2COO^- \quad (25)$$

$$e_{aq}^- + {}^+NH_3CH_2COO^- \longrightarrow {}^{\cdot}H + \dot{N}H_2CH_2COO^- \quad (26)$$

† The first number is the number of C atoms in the molecule, and the second is the number of double bonds in it. For example, 18:2 is linoleic acid.

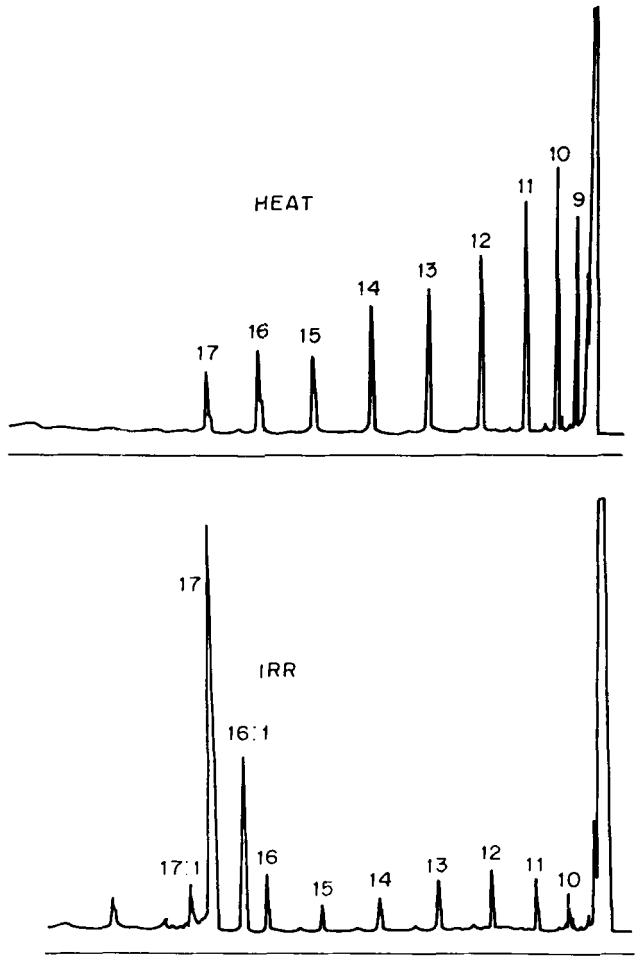


FIGURE 6. Nonpolar volatile products formed from ethyl linoleate by heat and irradiation[4]. Numbers over peaks indicate the number of C atoms in the hydrocarbon. Reproduced by permission of the Bundesgesundheitsamt, München

$^{\cdot}H$ and $^{\cdot}OH$ radicals react by abstracting hydrogen atoms from the α-carbon, as indicated by the following reaction:

$$^{\cdot}OH(H) + {}^{+}NH_3CH_2COO^{-} \longrightarrow {}^{+}NH_3\dot{C}H_2COO^{-} + H_2O(H_2) \quad (27)$$

Ammonia, carboxylic acids and keto acids are the main products formed in reactions 25–27[98]. Decarboxylation of simple amino acids is very efficient in alkaline solutions where the amino group is deprotonated[103]. Under these conditions the $^{\cdot}OH$ radicals oxidize amino-nitrogen:

$$NH_2CH_2COO^{-} + {}^{\cdot}OH \longrightarrow {}^{\cdot}{}^{+}NH_2CH(R)COO^{-} + OH^{-} \quad (28)$$

followed by the decarboxylation of the radical cation:

$$^{+\cdot}NH_2CH_2COO^- \longrightarrow NH_2CH_2 + CO_2 \quad (29)$$

In the gamma radiolysis of 13 amino acids in alkaline media the measured yield of CO_2 accounted for about 60–100% of G_{OH}[103]. For example, at pH 10, $G(CO_2) = 4$ for glycine, $G(CO_2) = 5$ for α-alanine and $G(CO_2) = 4.5$ for serine should be compared with $G_{OH} = 5.5$[6].

Both e_{aq}^- and $^{\cdot}OH$ radicals react with amino acid disulfides at diffusion-controlled rates[7]. The addition of e_{aq}^- to a disulfide bridge results in the formation of the disulfide radical anion:

$$e_{aq}^- + RSSR \longrightarrow RSSR^{-\cdot} \quad (30)$$

$$k = 1.6 \times 10^{10}\ M^{-1}\ s^{-1}\ ^{7}$$

which absorbs strongly near 410 nm, $\varepsilon = 10^4\ M^{-1}\ cm^{-1}$ [2,100,101]. The disulfide radical anion is in equilibrium with the thiolate anion, RS^-, and a neutral thio-radical:

$$RSSR^- \rightleftharpoons RS^{\cdot} + RS^- \quad (31)$$

$$k_f = 4.9 \times 10^9\ M^{-1}\ s^{-1},\ k_r = 8 \times 10^5\ s^{-1},\ K = 1.2 \times 10^4\ M^{-1}\ ^{104}$$

$^{\cdot}OH$ radicals oxidize the disulfide bridge in amino acid disulfides to the disulfide radical cation, $RSSR^+$:

$$RSSR + {}^{\cdot}OH \longrightarrow RSSR^{+\cdot} + OH^- \quad (32)$$

$$k = 2.1 \times 10^9\ M^{-1}\ s^{-1}\ ^{7}$$

This transient absorbs in the visible region with $\lambda_{max} = 420$ nm and $\varepsilon_{420} = 2000\ M^{-1}\ cmu^{-1}$ [2,100,101]. The products of decomposition of the disulfide radical cation are RSSR, RS, RSOH and RSO. It should be pointed out that radiation-induced changes in sulfur-containing amino acids differ considerably from those in other amino acids, where mainly carbon-centered radicals are initially formed. Sulfur radical chemistry has been extensively reviewed recently[2]. This review is therefore predominantly concerned with the radiation chemistry of aromatic amino acids.

A. Aromatic Amino Acids in Aqueous Solutions

1. Reactions of e_{aq}^-, $^{\cdot}OH$ and $^{\cdot}H$

Aromatic amino acids often react with primary water radicals at diffusion-controlled rates[7]. The rate constants of aromatic amino acids with e_{aq}^-, $H^{\cdot}$ and $^{\cdot}OH$ are given in Table 6.

According to the rate constants with e_{aq}^-, phenylalanine, tyrosine and tryptophan are of moderate reactivity, whereas histidine is of high reactivity[105].

Among amino acids, the aromatic ones are the most reactive with $^{\cdot}OH$ radicals, because the $^{\cdot}OH$ radical can easily add to the π-electron system of the ring. The rate constants are in the range 10^9–$10^{10}\ M^{-1}\ s^{-1}$. Since the $^{\cdot}OH$ radical has been implicated as the most damaging oxidizing free radical, its reactions with aromatic amino acids have been extensively studied.

Due to the low yield of hydrogen atoms in neural solutions, $G_H = 0.55$[6], their reactions are less important.

The aromatic moiety is generally assumed to dominate the radiation chemistry of phenylalanine, tyrosine, tryptophan and histidine. Primary water radicals, e_{aq}^-, $^{\cdot}OH$

TABLE 6. Rate constants for the reactions of aromatic amino acids with e_{aq}^-, H· and ·OH radicals[7] and $\cdot OH_2$ and $O_2^{-\cdot}$ radicals[153]

		k ($M^{-1} s^{-1}$)			
Radical	pH	Phe	TyrOH	TrpH	His
e_{aq}^-	4.8	—	—	—	2.8×10^9
	~7	1.4×10^8	3.4×10^8	2.9×10^8	6.4×10^7
	11	$< 1.6 \times 10^7$	$< 1.7 \times 10^7$	—	$< 1.4 \times 10^6$
	12.5	9.6×10^7	—	—	—
H·	1	7.4×10^8	2×10^9	7.4×10^9	4.4×10^7
	6–7	7.1×10^8	4×10^8	2×10^9	2.3×10^8
·OH	1–2	—	1.2×10^{10}	1.2×10^{10}	—
	6–8	6.5×10^9	1.3×10^{10}	1.3×10^{10}	5×10^9
	11	9×10^9	1.3×10^{10}	—	—
$\cdot OH_2$	1–2	< 180.00	—	—	< 95.00
$O_2^{-\cdot}$	~10	< 0.36	< 10.00	< 24.00	< 1.00

and ·H, react by addition at different positions of the aromatic system, producing H- and OH-adducts. The exception is phenylalanine, where the yield of ammonia both in solid state[98] and in aqueous solution[106,107] is surprisingly high, showing that deamination is a significant process in the radiolysis of this amino acid.

In proteins aromatic amino acids were also found to be the most reactive. The covalent bonds in radiation aggregates are formed predominantly between radicals of tyrosine, phenylalanine and tryptophan residues[108]. This means that the radiation-induced crosslinking of proteins takes place at specific sites. There are numerous examples of crosslinking in nature which are promoted by autoxidation of phenols and their derivatives integrated in macromolecules. For example, autoxidation of eye-lens proteins induces crosslinks, which lead to cataract. It was suggested that the crosslinking was induced by photooxidation of tyrosyl residues in lens proteins[109].

The ESR spectroscopy coupled with the spin-trapping technique has also been used to study the free radical chemistry of aromatic amino acids in aqueous solutions[110–112]. The results are in some cases difficult to correlate with the reaction mechanism based on pulse radiolytic data. Contrary to the pulse radiolysis results, which suggest that few, if any, ·OH radicals react with the alanine side-chain in aromatic amino acids, a radical produced by H-abstraction from the α-carbon was observed[110–112].

Deamination was not detected in irradiated frozen solutions of L-tryptophan[113], and the ESR spectrum observed at 77 K was explained by the delocalization of an unpaired electron over the indole ring of tryptophan. At higher temperatures three species are formed: the tryptophan radical cation with characteristic absorption around 600 nm; the neutral tryptophan radical formed by H-abstraction at the indole N—H, which absorbs around 550 nm; and the radical formed by H-addition at C7. Some of these results agree well with those obtained in the pulse radiolysis of tryptophan[114].

a. Phenylalanine. Pulse radiolytic data[115] indicate that ~50% of e_{aq}^- reacts with the aliphatic side-chain by deamination, whereas the other half adds to the benzene ring (equations 33 and 34). The electron adduct protonates rapidly to produce a hydrocyclohexadienyl radical.

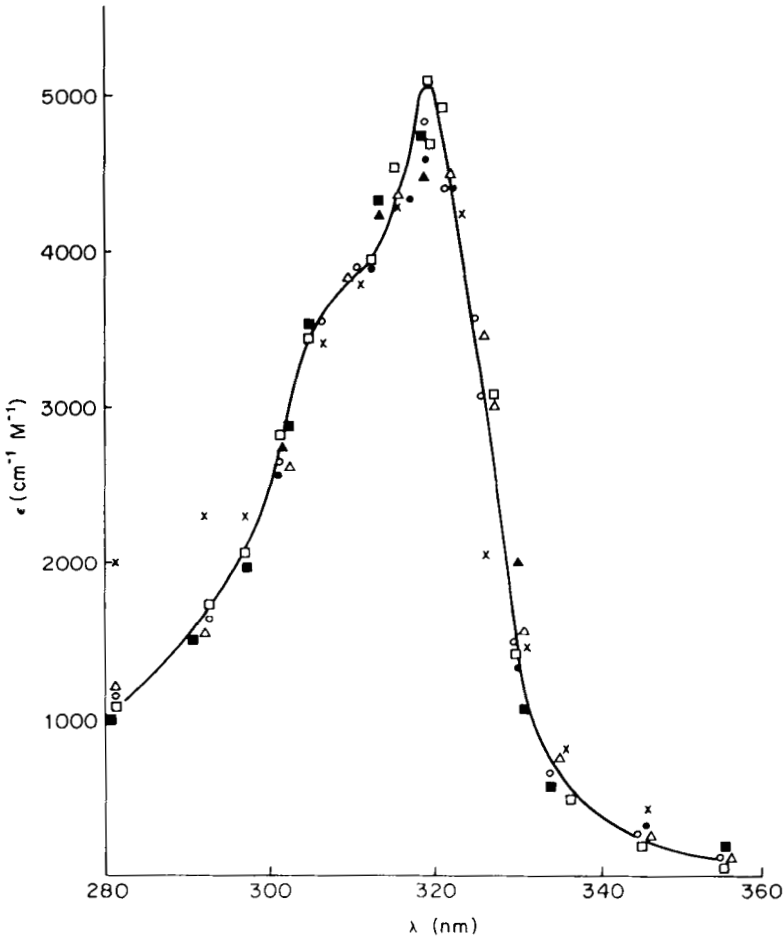
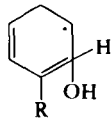
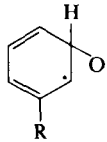
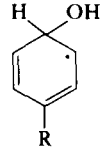
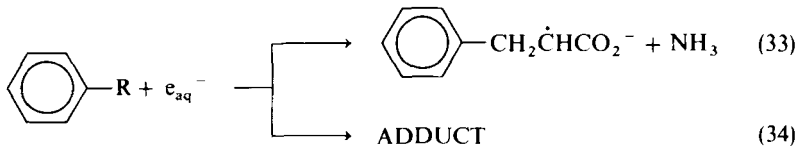


FIGURE 7. Transient absorption spectra of phenylalanine, *N*-acetylphenylalanine and *N*-acetylphenylalanylamide obtained by pulse radiolysis of deaerated aqueous solutions. pH 2, Phe □; AcPhe—△; $AcPheNH_2$—○; pH 6.4, Phe—■; Phe (N_2O)×; AcPhe—▲; $AcPheNH_2$ ●. Reproduced by permission of Academic Press, Inc., from Lichtin and Schafferman, *Radiat. Res.*, **60**, 432 (1974).

$$R = -CH_2CHCOO^-$$
$$\quad\quad\quad

TABLE 7. OH-adducts produced in aqueous solutions of phenylalanine at pH 7.5[123]

OH—Adducts		λ_{max} (nm)	ε_{max} ($M^{-1} cm^{-1}$)	Decay $2k$ ($M^{-1} s^{-1}$)
	*ortho*	305	3800	1×10^9
	*meta*	315 540	3500 3200	1.3×10^9
	*para*	320	4100	1.5×10^9



around 310 nm may be due to the formation of at least two isomeric hydrocyclohexadienyl radicals, which result from ·H-addition in different positions of the benzene ring. The spectra were independent of the pH and the substitution in the side-chain. This is understandable because ·H-atoms do not react with the side-chain of phenylalanine. The decay of the hydrocyclohexadienyl radical follows strictly second-order kinetics with $2k = 8.8 \times 10^8\ M^{-1} s^1$ at pH 2 and $2k = 6.9 \times 10^8\ M^{-1} s^{-1}$ at pH 6.4[116]. The product of this decay is a dimer with spectral characteristics $\lambda_{max} = 260$ nm, $\varepsilon_{max} = 2500\ M^{-1} cm^{-1}$. Similar spectral characteristics were reported for dimers produced upon the recombination of cyclohexadienyl radicals formed in the gamma-radiolysis of aqueous benzene[118].

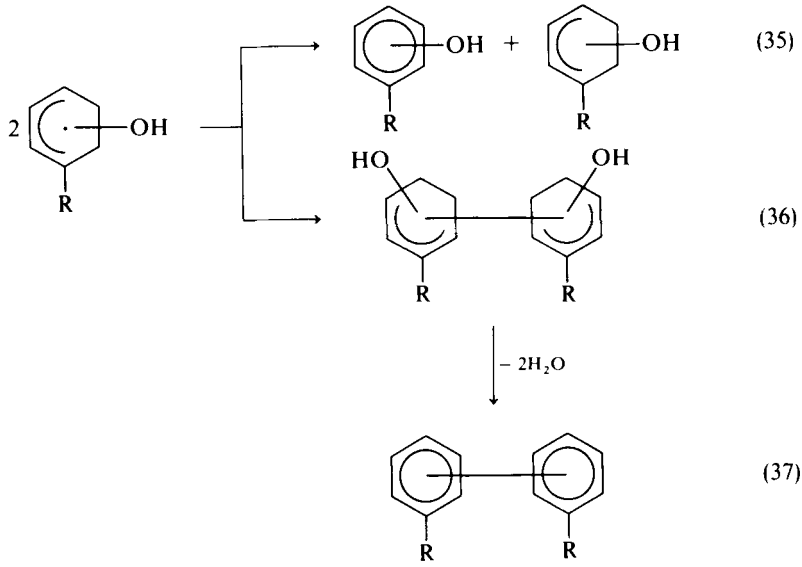
The transient absorption spectrum produced upon the reaction of ·OH radicals with phenylalanine (a broad absorption band with $\lambda_{max} = 320$ nm at pH 10) was first reported by Chrysochoos[119]. The transient product was assigned to the hydroxycyclohexadienyl radical, which was also observed in the pulse radiolysis of benzene[120] and its derivatives[121]. It was assumed that the spectrum was an overlap of two closely spaced bands originating from the *ortho*- and *meta*-substituted radicals.

The multisite ·OH attack on phenylalanine was studied by pulse radiolysis in neutral N_2O-saturated solution[122,123]. The spectrum of the radicals obtained upon the ·OH-

radical reaction is similar to that in Figure 7. It exhibited an absorption band below 250 nm, a maximum at 320 nm, a shoulder at ~310 nm and a weak absorption around 540 nm. The kinetics of the decay of this transient was investigated at several concentrations of phenylalanine and at different wavelengths (240, 260, 280, 310, 320 and 540 nm)[123]. At all wavelengths the transient disappeared by the second-order kinetics. It was assumed that the mechanism of the radical decay was disproportionation and/or dimerization, whereas cross-reactions of radicals were not taken into account. The decay rates were slightly different among each other and a decrease of $2k/\varepsilon$ was observed in sequences 327 > 300 and 325 > 312 mm indicating that more than one OH adduct were formed. To resolve the composite kinetic and spectroscopic data a semilinear optimization procedure was applied[123]. The resolved absorption spectrum revealed three different OH-adducts. It was also shown that 94% of $^{\cdot}$OH radicals added to the aromatic ring whereas 6% might be involved in H-abstraction from the side-chain. The $^{\cdot}$OH radicals preferentially add in the sequence *ortho* > *para* > *meta* positions. The isomeric hydrocyclohexadienyl radicals derived from phenylalanine, their spectral characteristics and decay rates are summarized in Table 7.

Phenylalanine hydroxycyclohexadienyl radicals do not eliminate water but undergo various bimolecular reactions[122].

They are expected to disproportionate and to dimerize (equations 35–37). *Ortho*, *meta* and *para* tyrosines (reaction 35) are formed in the ratio 1:0.6:1[122]. The yield of tyrosines was found to be very low (G = 0.5, 0.3 and 0.5)[122], showing that the main reaction of hydrocyclohexadienyl radicals is dimerization (reaction 36). Reaction 36 is followed by elimination of water to give biphenyl-type dimers[122], G(dimers) = 1.5 (reaction 37).



(35)

(36)

(37)

b. Tyrosine. Hydrated electrons, $^{\cdot}$H and $^{\cdot}$OH radicals add to the phenol ring of tyrosine. The low yield of ammonia, $G(NH_3) < 0.5$[124,125] indicates that the attack of e_{aq}^- on the alanine side-chain of tyrosine is not significant. The hydrocyclohexadienyl radical produced upon e_{aq}^- addition to the phenol ring, and subsequent protonation, exhibits an absorption with λ_{max} = 330 nm (ε = 3800 M^{-1} cm^{-1})[121]. An absorption spectrum with identical characteristics was observed in the reaction of tyrosine with $^{\cdot}$H

$$R = -CH_2CHCOO^-$$
$$\quad\quad\quad

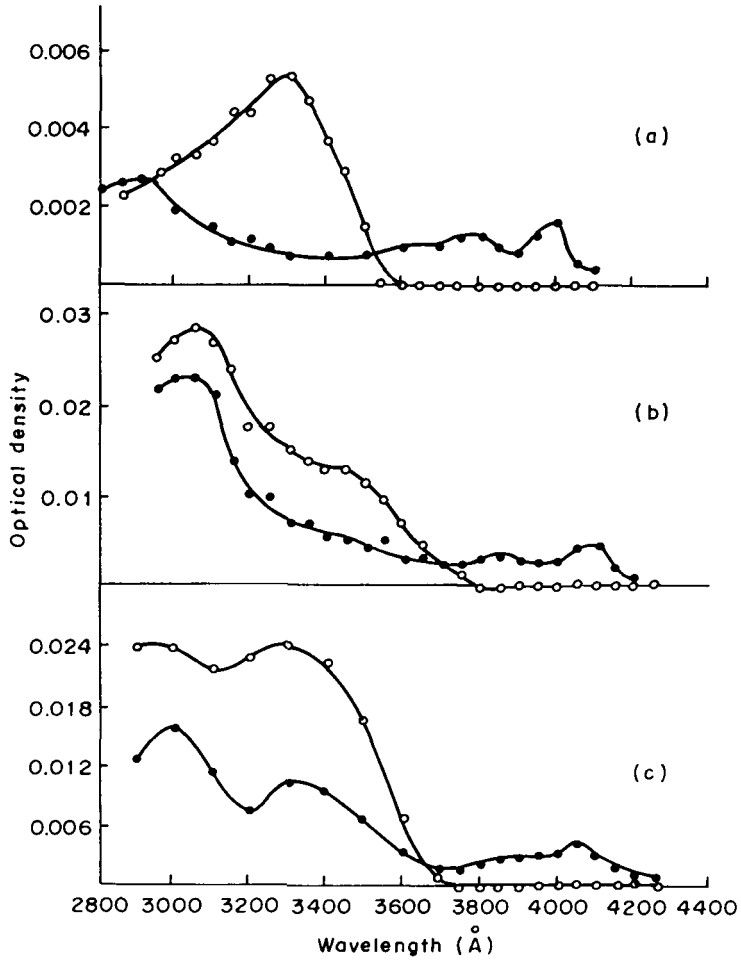


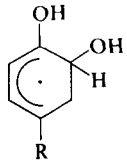
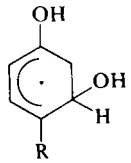
FIGURE 8. Transient absorption spectra of phenol, and *p*-cresol and tyrosine in N_2O-saturated aqueous solutions at pH ~ 6: (a) phenol, ○—immediately after the pulse, ●—at 400 μs; (b) *p*-cresol, ○—immediately after the pulse, ●—at 200 μs; (c) tyrosine, ○—immediately after the pulse, ●—at 400 μs[121]. Reproduced by permission of the Royal Society of Chemistry

OH-adduct is oxidized by the phenoxyl radical is also proposed for the production of DOPA[134]:

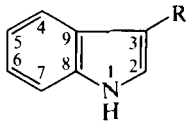
$$\text{PheOH(OH)}^{\cdot} + \text{PheO}^{\cdot} \longrightarrow \text{PheOH} + \text{DOPA} \qquad (40)$$

c. Tryptophan. Primary radicals generated in the radiolysis of water react rapidly with tryptophan mainly by addition at various positions in the indole ring. According to Armstrong and Swallow[114] hydroxyl radicals are the least selective and form three adducts, at C2, C3 and C5 or C7 positions of the indole ring. Hydrogen atoms form two adducts, at C2 and at the benzene ring, while hydrated electrons add at N1 giving

TABLE 8. OH—adducts produced in neutral aqueous solutions of tyrosine[131]

OH—adduct		λ_{max} (nm)	ε_{max} ($M^{-1}cm^{-1}$)	Decay $2k$ ($M^{-1}s^{-1}$)
	*ortho*	330	3000	3×10^8
	*meta*	305 540	2800 230	2×10^9

a radical anion which protonates to a H-adduct at C2 position. On the basis of these findings, essentially two classes of tryptophan radicals are initially formed, i.e. tryptophan OH- (TrpH—OH) and tryptophan H- (TrpH—H) adducts. The decay of tryptophan adducts follows second-order kinetics, with $2k = 7.7 \times 10^8\ M^{-1}\ s^{-1}$ for OH adducts at pH 7, and with a composite rate constant $2k = 1.1 \times 10^8\ M^{-1}\ s^1$ for OH- and H-adducts at pH 1.



$R = -CH_2CHCOO^-$
$\quad\quad\quad

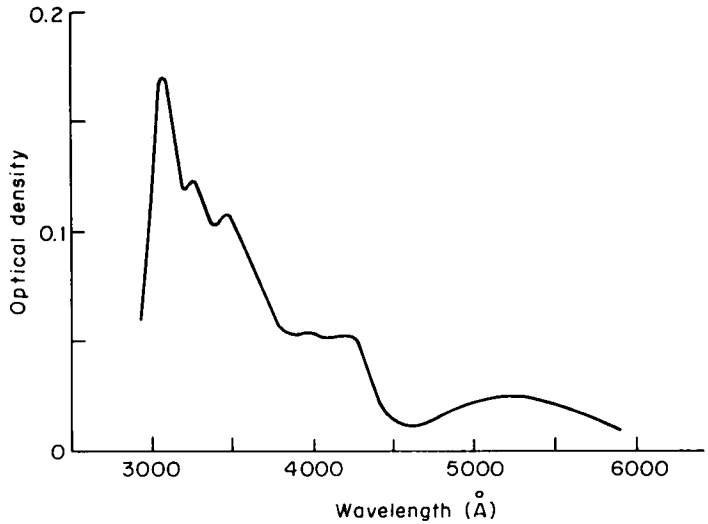


FIGURE 9. Transient absorption spectra of tryptophan OH-adducts at pH 7. Reproduced by permission of Academic Press, Inc., from Armstrong and Swallow, *Radiat. Res.*, **40**, 563 (1969)

330 and 560 nm appeared, and the spectrum was ascribed to the tryptophan radical cation:

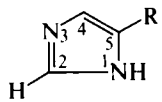
$$\text{TrpH—OH}^{\cdot} \rightleftharpoons \text{TrpH}^{+\cdot} + \text{H}_2\text{O} \qquad (41)$$

$$pK = 3.5^{114,136}$$

The tryptophan radicals formed in reactions with $^{\cdot}OH$, $^{\cdot}H$ and e_{aq}^- and their spectral characteristics are summarized in Table 9.

In the reactions of tryptophan OH- and H-adducts a number of stable products are very likely to be produced in a rather low yield. In deaerated tryptophan solutions pulse irradiated at high dose rates (260 kGy h^{-1}), the decomposition yield of tryptophan was found to be G(-TrpH) = 1.7[114], indicating that dimers were not formed. However, at low dose rates, where radical-radical reaction are disfavored, tryptophan is lost only with $G \sim 0.7$. To explain this very low decomposition yield Armstrong and Swallow[114] suggested that under steady-state conditions of irradiation the tryptophan radicals reacted with stable products to regenerate tryptophan. It was also suggested that small yields of highly reduced products were formed in these reactions. These products did not acquire resonance stability by elimination of hydrogen since the measured yield of hydrogen equals G_{H_2}. This effect was less pronounced in N_2O-saturated solutions, which was explained by the formation of a relatively stable hydroxylated product, OH—TrpH.

d. Histidine. A few studies available in the literature show that primary radicals produced in the radiolysis of water add to the imidazole ring, but their reactions with histidine have not been examined in detail.



$$R = -CH_2\underset{\displaystyle NH_3^+}{\underset{|}{C}}HCOO^-$$

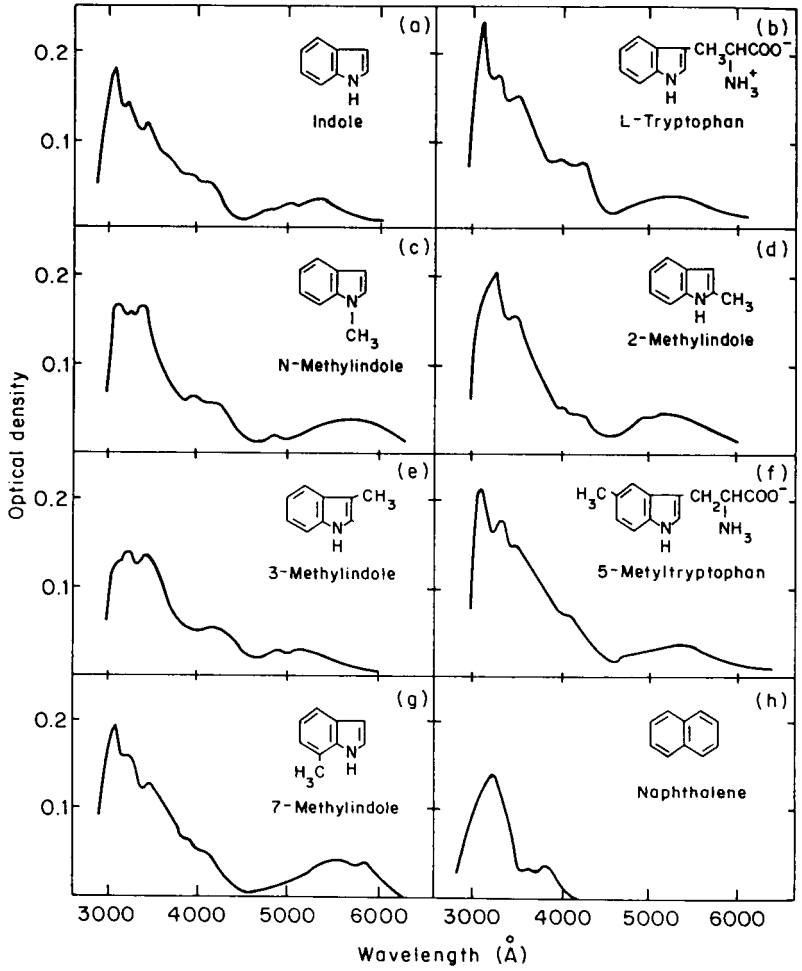


FIGURE 10. Transient absorption spectra of the OH-adducts of various indole derivatives at pH 7. Reproduced by permission of Academic Press, Inc., from Armstrong and Swallow, *Radiat. Res.*, **40**, 563 (1969)

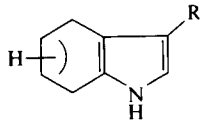
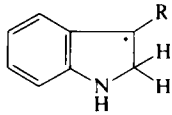
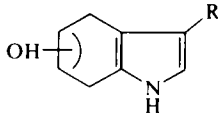
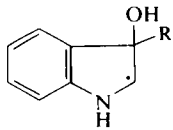
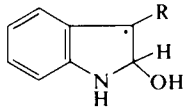
The rate constant of histidine with e_{aq}^- shows a very strong dependence on pH (Table 6). Histidine has two amino groups, one in the imidazole ring ($pK_a = 6$) and the other in the side-chain ($pK_a = 9.17$), but the decrease of its rate constant with e_{aq}^- over the pH range from 6 to 9 was related to the ionization of the amino group in the imidazole ring[105]. The following data were obtained for the contributions of e_{aq}^- reactivities with the ionic states of histidine to the overall rate constant:

$$k \text{ (positive ion)} = 7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

$$k \text{ (zwitterion)} = 6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

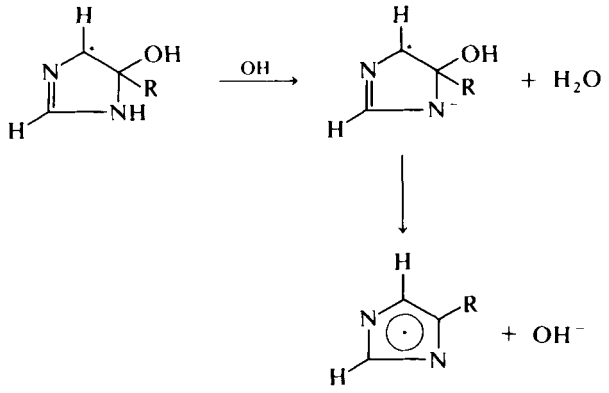
$$k \text{ (negative ion)} = 7 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$

TABLE 9. Free radicals produced in neutral aqueous solutions of tryptophan[114]

Reacting species	Radical formed	λ_{max} (nm)
H·		310
H·, e_{aq}^-		325
·OH		310
		325
		320, 520

The absorption spectrum of the transient produced upon the reaction of e_{aq}^- with histidine at pH 5.2 exhibits maxima at 295 nm ($\varepsilon = 4700\ M^{-1}\ cm^{-1}$) and 360 nm ($\varepsilon = 1700\ M^{-1}\ cm^{-1}$)[137]. A similar spectrum with the maxima at 300 nm and 360 nm was observed upon e_{aq}^- reaction with imidazole. On the basis of this finding, it was concluded that the majority of hydrated electrons add to the imidazole ring of histidine producing the $HisH_2$· radical. The electron adduct of histidine decays by second-order kinetics with $2k = 8.0 \times 10^8\ M^{-1}\ s^{-1}$.

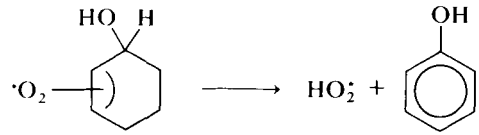
The ·OH radical adds to the imidazole ring preferentially at the C5 and C2 positions. Both adducts yield allylic-type radicals[138]. The absorption spectrum of histidine OH-adducts in the pH range from 3 to 10 exhibits maxima near 300 and 390 nm. Rao and coworkers[137] ascribed this spectrum to the $OH—HisH_2^{+}$· radical in acidic media and to the OH-HisH· radical in alkaline media. The spectral characteristics of the cation and neutral histidinyl radicals are, respectively; at pH 3.5, $\lambda_{max} = 300$ nm ($\varepsilon = 4200\ M^{-1}\ s^{-1}$) and 410 nm ($\varepsilon = 1400\ M^{-1}\ s^{-1}$); at pH 9.2, $\lambda_{max} = 310$ nm ($\varepsilon = 6200\ M^{-1}\ s^{-1}$) and 410 nm ($\varepsilon = 2300\ M^{-1}\ cm^{-1}$). At pH 9.2 the radicals decay by second-order kinetics with $2k = 1.2 \times 10^9\ M^{-1}\ s^{-1}$. At higher pH the decay becomes first order[138]. This latter effect was attributed to a base-catalyzed water elimination. Water elimination from the OH-adduct on C5 of histidine is illustrated by the scheme in equations 42 and 43. The



rate-determining process is reaction 43 with $k = 1.3 \times 10^4\ s^{-1}$ at pH 11.55; $k = 1.6 \times 10^4\ s^{-1}$ at pH 11.78; $k = 3.6 \times 10^4\ s^{-1}$ at pH 12.

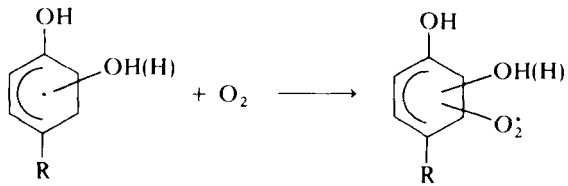
2. *Aromatic amino acid peroxy radicals*

The reaction of hydrocyclohexadienyl radical with oxygen was investigated in aqueous solution of benzene[3a,139,140]. It is now well established that the formation of hydrocyclohexadienyl radical is in oxygenated solution followed by addition of oxygen to the free radical sites with $k = 5 \times 10^8\ M^{-1}\ s^{-1}$ [120]. The equilibria between the hydrocyclohexadienyl radicals, oxygen and peroxy radicals was observed at room temperature[141], and the overall forward ($k = 3.1 \times 10^8\ M^{-1}\ s^{-1}$) and reverse ($k = 1.2 \times 10^4\ M^{-1}\ s^{-1}$) rates were determined. The peroxyhydrocyclohexadienyl radicals eliminate $HO_2^{\cdot}$ which leads to the formation of phenol[120] (equation 44).



In oxygenated solutions of phenylalanine similar reactions must occur and the expected products (*ortho*, *meta* and *para* tyrosines) were indeed observed[142]. Due to the low yield of H atoms in neutral media, $G_H = 0.55$, the cyclohexadienyl peroxy radical plays a minor role. In benzene this peroxy radical eliminates HO_2 regenerating benzene in 60% yield[141].

Similar to phenol OH- and H-adducts[143], tyrosine H- and OH-adducts react with oxygen to give peroxy radicals (equation 45). The constants for the reaction of phenol H- and OH-adducts with oxygen are[143] $k(C_6H_5OH(H) + O_2) = 2.65 \times 10^9\ M^{-1}\ s^{-1}$ and



$k(C_6H_5OH(OH) + O_2) = 1.5 \times 10^9\ M^{-1}\ s^{-1}$. $C_6H_5OH(OH)O_2$ and $C_6H_5OH(H)O_2$ radicals undergo rapid $HO_2^{\cdot}$ elimination, with $k = 8 \times 10^3\ s^{-1}$ and $k = 2.2 \times 10^4\ s^{-1}$, respectively. Similar reactions are expected in the case of tyrosine peroxy radicals. Relatively high yields of 3,4-DOPA are produced upon $HO_2^{\cdot}$ elimination from the *ortho* OH-adduct peroxy radical. Tyrosine peroxy radical from *ortho* H-adduct eliminates $HO_2^{\cdot}$ regenerating tyrosine.

$$\text{PheOH(OH)OO}^{\cdot} \longrightarrow \text{DOPA} + HO_2^{\cdot} \quad (46)$$

$$\text{PheOH(H)OO}^{\cdot} \longrightarrow \text{PheOH} + HO_2^{\cdot} \quad (47)$$

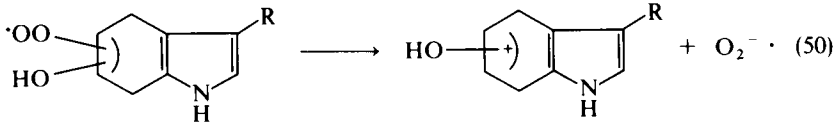
The loss of tyrosine under irradiation in oxygenated solutions and the yields of stable products—hydrogen peroxide and DOPA—were determined in a pH range from 1 to 9[144]. It was found that in slightly acidic and neutral media G(-Tyr) = G(DOPA) = G_{OH}, showing that all initially formed tyrosine OH-adducts reacted with oxygen to give peroxy radicals. The excess of hydrogen peroxide was accounted for with $HO_2^{\cdot}$ eliminated in reaction 46, i.e $G(H_2O_2) = \frac{1}{2} G_{OH}$. These results are at variance with the findings that G-values of both the loss of tyrosine and the formation of DOPA were lower than G_{OH} in neutral media[134,145,146], and are very probably due to the conditions of irradiation, i.e. only aerated solutions were analyzed where all oxygen is consumed in the early stage of irradiation. Furthermore, in these early studies, no attention was paid to the presence of hydrogen peroxide in irradiated solutions, which could interfere with the determination of tyrosine and DOPA[147]. In acid and alkaline media all measured yields decreased, and $G(H_2O_2) < \frac{1}{2} G_{OH}$ was observed. This is caused by the formation of phenoxyl radicals which react with $O_2^{-\cdot}$ ($HO_2^{\cdot}$) to regenerate tyrosine.

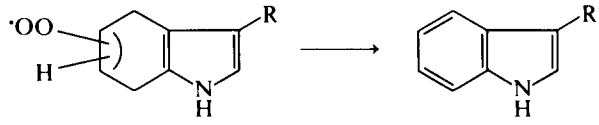
In the presence of oxygen tryptophan H- and OH-adducts react with oxygen to give peroxy radicals[148].

$$\text{TrpH—H} + O_2 \longrightarrow \text{TrpH—(H)OO}^{\cdot} \quad (48)$$

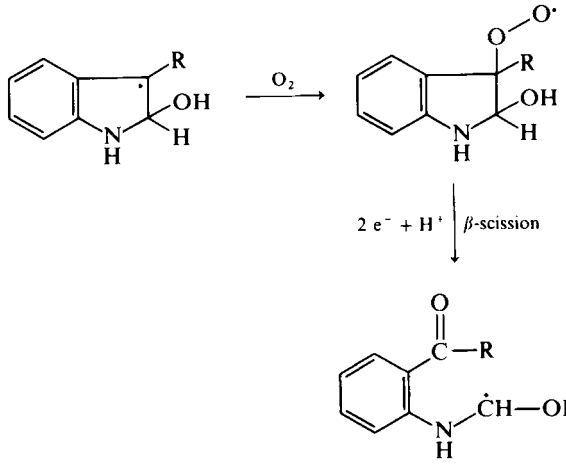
$$\text{TrpH—OH} + O_2 \longrightarrow \text{TrpH(OH)OO}^{\cdot} \quad (49)$$

The reactions of C-centered radicals with oxygen are normally fast with rate constants close to diffusion-controlled[5a]. Similarly to peroxy radicals of phenylalanine, tyrosine and some other aromatic compounds[2], rapid elimination of $HO_2^{\cdot}$ or $O_2^{-\cdot}$ from tryptophan peroxy radicals is also expected. We suggest that peroxy radicals at the benzene ring of tryptophan eliminate $O_2^{-\cdot}$ and $HO_2^{\cdot}$ according to equations 50 and 51. The yield





of $O_2^{-\cdot}$ measured by pulse radiolysis corresponds to 25% of $^{\cdot}OH$ radicals[149] showing that only some of Trp(OH)OO$^{\cdot}$ peroxy radicals react by reaction 50. It might be suggested that the reactions of peroxy radicals at the C2 position of the indole ring lead to the formation of *N*-formylkynurenine, a stable product observed by several authors[148,150–152]. Based on the previously proposed mechanism[148,152] the formation of *N*-formylkynurenine may be described by the reactions[85] in equations 52 and 53.



The reactions of tryptophan peroxy radicals were also followed by measuring the oxygen uptake during gamma-radiolysis[85]. In tryptophan solutions at pH 8 and dose rate 0.01 Gy s^{-1}, $G(-O_2) > 6$ was observed, i.e. $G(-O_2) = 15$, 22 and 30 were measured in 1×10^{-3} M, 5×10^{-3} M and 1×10^{-2} M solutions of tryptophan, respectively. The dependence of the G-value of the oxygen uptake on the concentration of tryptophan indicated that short-chain reactions of tryptophan peroxy radicals propagate oxidation of tryptophan. The reaction of peroxy radicals with tryptophan could not be observed directly because of its slowness. However, a reaction with a stronger oxidant, namely the trichlormethyl peroxy radical, was reported[153].

In oxygenated solutions, besides ·OH radicals, superoxide anion ($O_2^{-\cdot}$) and hydroperoxy radicals ($HO_2^{\cdot}$) are formed[6] in reactions with e_{aq}^- and ·H. The $O_2^{-\cdot}$ radical is the simplest peroxy radical, and is generated in metabolic processes. It was found that aromatic amino acids, as well as other amino acids, are relatively unreactive toward both $O_2^{-\cdot}$ and $HO_2^{\cdot}$[154]. Although very small rate constants were determined (Table 6), these reactions are important with regard to the oxygen toxicity in biological systems.

3. *One-electron transfer reactions*

A number of oxidizing radical anions, such as $Br_2^{-\cdot}$, $I_2^{-\cdot}$, $(SCN)_2^{-\cdot}$[155], as well as the azide radical, $^{\cdot}N_3$[156], were found to react more selectively with aromatic amino acids than ·OH radicals. These selective free radical oxidants are widely used to investigate functional amino acid residues of proteins and enzymes. For example, direct oxidation of tyrosine by inorganic radicals prevents the formation of different OH-adducts and facilitates the investigation of the tyrosine phenoxyl radical reactions:

$$OH^{\cdot} + X^- \longrightarrow X^{\cdot} + OH^- \tag{54}$$

$$X^{\cdot} + X^- \rightleftharpoons X_2^{-\cdot}$$

$$(X^- = Cl^-, Br^-, I^-, SCN^-, N_3^-)$$

$$X_2^{-\cdot} + TyrOH \longrightarrow TyrO^{\cdot} + H^+ + 2X^- \tag{55}$$

The rate constants for the reaction of aromatic amino acids with some inorganic radicals are given in Table 10.

TABLE 10. Rate constants for the reactions of aromatic amino acids with some inorganic radicals

Radical	pH	k ($M^{-1} s^{-1}$)				Reference
		Phenylalanine	Tyrosine	Tryptophan	Histidine	
$Br_2^{-\cdot}$	3	—	—	1.4×10^9	—	157
	7	—	2×10^7	7.7×10^8	1.5×10^8	155
$Cl_2^{-\cdot}$	1.8	—	2.7×10^8	2.6×10^9	1.4×10^7	155
$I_2^{-\cdot}$	7	—	$<10^6$	$<10^6$	$<10^6$	155
$(SCN)_2^{-\cdot}$	7	—	5×10^6	2.7×10^8	10^6	155
$SO_4^{-\cdot}$	7	—	3.2×10^9	$\sim 2.3 \times 10^9$		158
$CO_3^{-\cdot}$	7	5×10^4	4.5×10^7	7×10^8	5.6×10^6	159
	11	—	2.9×10^8	4×10^8	7×10^6	155
$N_3^{\cdot}$	3	—	—	4.2×10^9	—	157
	~ 7	$<10^6$	1×10^8	4.1×10^9	$<10^6$	156
	7–10	—	—	4.3×10^9	—	157
	11	—	—	—	1.7×10^7	156

a. Phenoxyl radical. This is selectively produced in the reaction of tyrosine with oxidizing radical anions[155,160] or with the azide radical[156,161]. The characteristic spectrum of the phenoxyl radical was also observed in the flash photolysis of phenolic compounds[133,162]. The absorption characteristics of the tyrosine phenoxyl radical are summarized in Table 11.

In the early pulse radiolysis studies[121,158], only one absorption maximum around 400 nm was observed in the spectrum of the phenoxyl radical, However, a better resolved spectrum recorded later[160] exhibited two maxima, at 407 nm and at 395 nm. The $\varepsilon_{407} = 3200\ M^{-1} cm^{-1}$ determined in the same work is adopted for the extinction coefficient of the tyrosine phenoxyl radical, the absorption spectrum of which is

TABLE 11. Absorption characteristics of tyrosine phenoxyl radical

Method	Reactive species	λ_{max} (nm)	ε ($M^{-1} cm^{-1}$)	Reference
Pulse radiolysis	$^{\cdot}OH$	405	—	119
		400	—	121
		410	—	134
		410, 260	2600, 6000	132
Pulse radiolysis	$(CNS)^{-\cdot}$, $CO_3^{-\cdot}$	410	—	155
	$Br_2^{-\cdot}$, $Cl_3^{-\cdot}$, $Cl_2^{-\cdot}$	420	—	155
	$SO_4^{-\cdot}$	407, 395	— —	158
	$SO_4^{-\cdot}$, $Br_2^{-\cdot}$	407, 395	3200, 2400	160
	$N_3^{\cdot}$	407	—	156
Flash photolysis		410, 390	2750, —	133
		410	2600	163

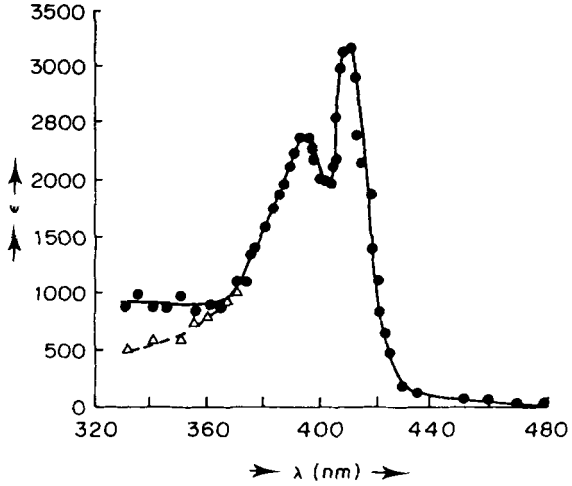


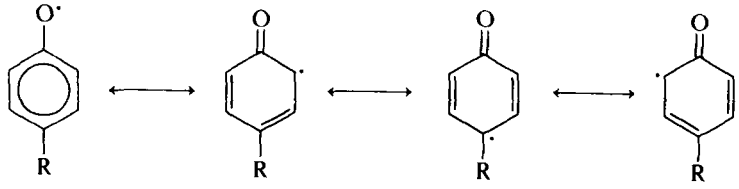
FIGURE 11. Transient absorption spectrum of the tyrosine phenoxyl radical. Reproduced by permission of Academic Press, Inc., from Bansal and Fesenden, *Radiat. Res.*, **67**, 1 (1976)

presented in Figure 11. The tyrosine phenoxyl radical is relatively unreactive with oxygen. In the pulse radiolysis k (TyrO + O_2) < 2×10^5 M^{-1} s^{-1} [144], whereas the lack of oxygen uptake during gamma-radiolysis indicates that the upper limit of this rate constant is $<10^3$ M^{-1} s^{-1} [164]. Tyrosine phenoxyl radicals react rapidly with $O_2^{-\cdot}$ radicals, $k = 1.7 \times 10^9$ M^{-1} s^{-1} [144]. Tyrosine is regenerated in this reaction[165],

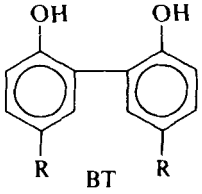
$$\text{PheO}^{\cdot} + O_2^{-\cdot} \longrightarrow \text{PheOH} + O_2 \qquad (56)$$

The tyrosine phenoxyl radical has various resonance structures[165] (Scheme 3). The lack of reactivity with oxygen may be explained by this high stabilization of the radical.

Recombination of tyrosine phenoxyl radicals results in the formation of a biphenyl-type linkage[164–168], leading to the formation of bityrosine (BT):



SCHEME 3



Bityrosine can be easily identified by its characteristic blue fluorescence[169]. The rate constant for the dimerization process has been determined at several pH values. In the pH range from 7 to 11, the rate constant does not depend on pH. The following values were determined by various groups: $2k = 4 \times 10^8\ M^{-1}\ s^{-1}$ at pH 6.8[132]; $2k = 6.1 \times 10^8\ M^{-1}\ s^{-1}$ at pH 10.2[161]; $2k = 6 \times 10^8\ M^{-1}\ s^{-1}$ at pH 7–11[170].

b. $TrpH^{+\cdot}$ and Trp$^{\cdot}$ radicals. Free radical oxidants such as $Br_2^{-\cdot}$[136,155], $Cl_2^{-\cdot}$[155], $(SCN)_2^{-\cdot}$[136,155], $SeO_3^{-\cdot}$[136], $SO_4^{-\cdot}$[158] and $N_3^{\cdot}$[156,161] react with tryptophan by one-electron transfer yielding tryptophan cation radical, which is in equilibrium with the neutral tryptophan radical (equation 57).

(57)

The absorption spectra of $TrpH^{\cdot+}$ and Trp$^{\cdot}$ radicals observed in reactions with different inorganic radicals are presented in Figure 12. The transient spectra in acid and neutral solutions (Figure 12) are similar to those observed in the flash photolysis of tryptophan[171]. The tryptophan radical in both systems is a species with the electron localized on the indole nitrogen[172]. The spectral characteristics and decay rates of $TrpH^{+\cdot}$ and Trp$^{\cdot}$ radicals are summarized in Table 12.

$TrpH^{+\cdot}$ and Trp$^{\cdot}$ radicals are both unreactive with oxygen[149,174], but react rapidly with $HO_2^{\cdot}$ and $O_2^{-\cdot}$, respectively—$k(TrpH^{+\cdot} + HO_2^{\cdot}) = 3.8 \times 10^9\ M^{-1}\ s^{-1}$ and $k(Trp^{\cdot} + O_2^{-\cdot}) = 4.5 \times 10^9\ M^{-1}\ s^{-1}$ were determined[149].

The Trp$^{\cdot}$ radical oxidizes tyrosine in many peptides and proteins via intramolecular electron transfer. This efficient long-range electron transfer has been implicated in free radical damage and oxygen toxicity in biological systems. Hence the electron transfer between tryptophan and tyrosine residues in proteins has been extensively studied[175–182].

The tryptophan radical was produced by azide radical oxidation of the Trp-X-Tyr peptides[175–178], where X is any amino acid residue, such as glycyl.

$$N_3^{\cdot} + TrpH{-}X{-}TyrOH \longrightarrow Trp^{\cdot}{-}X{-}TyrOH + N_3^{-} + H^{+} \quad (58)$$

The Trp$^{\cdot}$ radical, having a reduction potential of 1.05 V at pH 7[183–185], rapidly oxidizes the tyrosine residue to the phenoxyl radical, TyrO$^{\cdot}$,

$$Trp^{\cdot}{-}X{-}TyrOH \longrightarrow TrpH{-}X{-}TyrO^{\cdot} \quad (59)$$

In peptides containing both tryptophan and tyrosine, one-electron oxidation of tryptophan is the predominant process[175], since this has a rate constant higher by more than one order of magnitude (Table 11).

The redox potential values for the Trp$^{\cdot}$/TrpH couple at pH 7 reported recently are $E_7 = 1.08$[183], 1.05[184] and 1.03[185] (mean value 1.05), whereas those of the TyrO$^{\cdot}$/TyrOH couple are $E_7 = 0.85$ and 0.94[178,181,186]. The differences in the potentials of the tryptophan and tyrosine redox couples indicates that equilibria of reaction 57 lies toward the right.

B. Solid State Reactions

The extensive work on glycine and alanine led Henriksen and coworkers[187] to propose a reaction scheme for crystalline amino acids, which involves an initial formation of

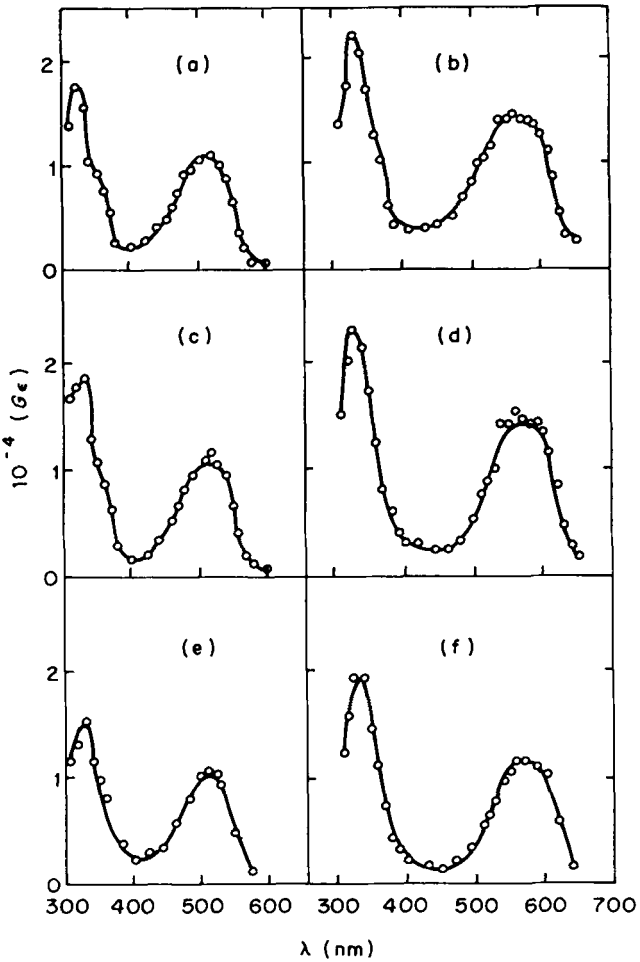


FIGURE 12. Transient absorption spectra of one-electron oxidized tryptophan by $(SCN)_2^{\cdot -}$ at (a) pH 6.7 and (b) pH 3.4; by $Br_2^{\cdot -}$ at (c) pH 6.3 and (d) pH 3.0; and by $SeO_3^{-\cdot}$ at (e) pH 7.4 and (f) pH 3.2[136]. Reproduced by permission of the Royal Society of Chemistry

ionic species—cations and anions. These reactive ionic species are trapped at very low temperatures and, on warming, decompose or react with neighboring molecules producing other radicals or stable products. It was suggested that cation and anion radicals decompose by decarboxylation and deamination, respectively[187]. A radical anion with the unpaired spin density localized on the carboxyl group was identified in single crystals of glycine[188], but cations of amino acids were not observed at that time. In crystals of glycine and alanine a cation which is deprotonated at the amino group was identified later[189,190], but no evidence for decarboxylation was obtained. In glycine and alanine irradiated in the solid state, ammonia with $G \sim 5$ was found to be a major product, while CO_2 was formed in glycine with only $G = 0.2$[98]. These results support the

TABLE 12. Absorption characteristics of $Trp^{\bullet}$ and $Trp^{+\bullet}$ radicals

Radical anion	pH	Radical formed	λ_{max} (nm)	ε ($M^{-1}cm^{-1}$)	Reference
$Br_2^{-\bullet}$	6.3	$Trp^{\bullet}$	320, 520	2990, 1930	136
	7	Trp	320, 510	2800, 1750	172
$(SCN)_2^{-\bullet}$	6.7	$Trp^{\bullet}$	320, 520	3030,1870	136
$Br_2^{-\bullet}$,$(SCN)_2^{-\bullet}$	7–10	$Trp^{\bullet}$	325, 510	3670, 2300	157
$SeO_3^{-\bullet}$	7.4	$Trp^{\bullet}$	320, 520	2690, 1800	136
$N_3^{\bullet}$	6.1	$Trp^{\bullet}$	320, 520	— 1960	173
	7–10	$Trp^{\bullet}$	325, 510	3670, 2300	157
Flash photolysis	7–12	$Trp^{\bullet}$	330, 510	3100, 1800	163
$Br_2^{-\bullet}$	3.1	$Trp^{+\bullet}$	330, 570	3860, 2450	136
$(SCN)_2^{-\bullet}$	3.4	$Trp^{+\bullet}$	330, 570	3780, 2520	136
$Br_2^{-\bullet}$, $(SCN)_2^{-\bullet}$	3	$Trp^{+\bullet}$	335, 560	4750, 3000	157
$N_3^{\bullet}$	3	$Trp^{+\bullet}$	330, 570	4750, 3000	157

assumption that deamination of the anion radical is a major process in single crystals of glycine and alanine and that decarboxylation does not occur in these amino acids. Consequently, a revised scheme for radical reactions in irradiated amino acids involves deprotonated cations and protonated anions, rearrangement of the cation and reductive deamination[191]:

$$^{2+}NH_3—CH_2—COO^- \rightsquigarrow {}^{\bullet+}NH_2—CH_2—COO^- + {}^{+}NH_3—CH_2—\dot{C}OOH^- \quad (60)$$

$$^{\bullet+}NH_2—CH_2—COO^- \longrightarrow {}^{\bullet+}NH_3—{}^{\bullet}CH—COO^- + H^{\bullet} \quad (61)$$

$$^{+}NH_3—CH_2—\dot{C}OOH^- \longrightarrow {}^{\bullet}CH_2—COOH + NH_3 \quad (62)$$

Assuming that the primary step (reaction 60) is the same for all amino acids, the secondary reactions might be different from those given by equations 60 and 61.

In the case of aromatic amino acids the formation of radicals on the benzene, indole and imidazole rings is expected. Contrary to simple aliphatic amino acids for which the radiation chemistry in solid state and aqueous solutions is quite similar, the radiation-induced changes in aromatic amino acids in the solid state differ much from those observed by pulse and gamma radiolysis in aqueous solutions. In single crystals of aromatic amino acids, beside the radicals localized on the aromatic moiety, deamination, decarboxylation and radicals formed by addition to the carboxyl group were also observed. Anions of the carboxyl group[192–194], deamination radicals[192,195] and decarboxylation radicals[193–195] were observed in histidine and tyrosine. The deamination radical was also found in single crystals of tryptophan[196]. In addition, the following aromatic amino acid radicals on the aromatic part of the molecule were observed in histidine and tyrosine, imidazole[193] and phenol ring[194] cation radicals, as well as the radical formed by the H-addition at the C5 position in the imidazole ring[197], and the radical produced by H-abstraction of the OH group at the phenol ring[195,198]. In tryptophan two species were observed[191]: one was assigned to the radical anion with the unpaired spin density localized on the indole moiety, and the other which was stable up to room temperature was assumed to be produced by protonation of the anion radical.

The radicals observed in single crystals of aromatic amino acids were examined either at low temperature (77 K) or at higher temperatures in order to follow the formation

of secondary radicals. However, the precursors of a number of secondary radicals observed are not identified, and therefore the mechanism of the aromatic amino acids in the solid state is still poorly understood. Nevertheless, the results obtained show clearly that in single crystals of aromatic amino acids, contrary to the processes in aqueous solutions, the carboxyl group competes with the aromatic ring for the stabilization of radicals formed under irradiation.

1. Alanine as a dosimeter

Alanine was first used as a dosimeter for special applications by Bradshow and coworkers[199]. Alanine was selected because of its high sensitivity to radiation damage, post-irradiation stability, dose-rate independent response and small effect of irradiation temperature. The dosimeter samples are nontoxic and insensitive to surface contamination, and can be prepared homogeneously and inexpensively in large batches. The similarity of the atomic composition of alanine to that of biological tissues is important for biological dosimetry applications. In addition, alanine can be used for dosimetric measurements over a wide temperature range from -40 to $+90°C$[200,201].

Stable free radicals formed in alanine under irradiation are easily measured quantitatively by the ESR technique[199–202]. In particular, the $CH_3\dot{C}HCOOH$ radical, predominant at room temperature, with a long-term stability of the ESR signal, is used as a measure of the absorbed dose over a wide range from 1 to 10^5 Gy. The other methods used to determine the concentration of radicals are lyoluminescence and color complexometry with spectrometric readout. Some other techniques using titrations, ion-selective electrodes, polarography, chromatography and spectrophotometric determination of ammonia produced upon dissolution in a basic aqueous solution are at present under investigation[202]. Numerous studies have proved that, compared to these other techniques, the ESR readout is superior with respect to precision. The dose response of the DL-alanine samples from 0.3 to 300 kGy, recorded by ESR spectroscopy within 2 weeks after irradiation, is presented in Figure 13. It should be pointed out, however, that the disadvantage of the ESR technique is that very expensive equipment is needed. Therefore, other methods, such as ammonia determination, are proposed for routine dosimetry,

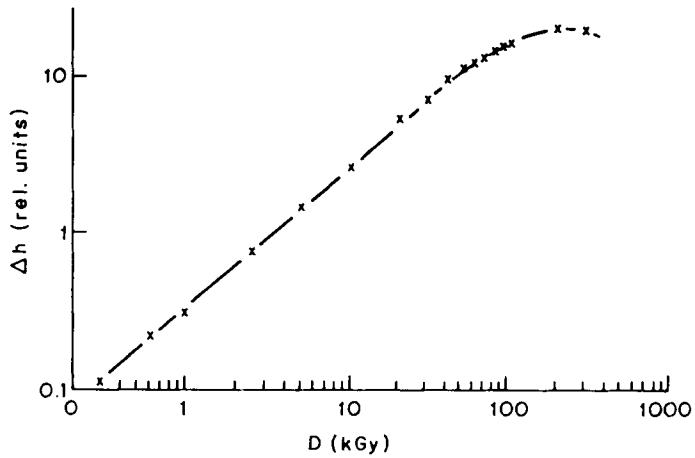


FIGURE 13. Dose response of DL-alanine from 0.3 to 300 kGy. ESR peak-to-peak measurements[201]. Reprinted with permission from van Laere, Buysse and Berkvens, *Appl. Radiat. Isot.*, **40**, 1885 (1989). Copyright (1989) Pergamon Press PLC

whereas the ESR readout is suggested for application in radiotherapy and as a reference dosimeter.

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CHAPTER 22

Electrochemistry of carboxylic acids: mechanistic aspects of Kolbe-type reactions

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I. INTRODUCTION

This chapter on the electrochemistry of carboxylic acids and derivatives will be limited to mechanistic aspects of the oxidation reactions. In a recent review, Schäfer[1] summarized the synthetic aspects of the Kolbe reaction. It is shown that a variety of compounds can be synthesized and that it is possible to control the pathway towards either radicals or carbocations by a proper choice of reaction conditions. The simplicity of carrying out the Kolbe electrosynthesis will contribute towards increasing use of this synthetic method in many important applications, like the preparation of pheromones and organosilicon compounds or for the synthesis of a prostaglandin intermediate by intramolecular radical addition. The carbocation route is used to prepare cyclic olefins and to enlargement of medium-sized rings[2].

The mechanistic aspects of the oxidation of carboxylic acids have been treated in several reviews, both from an organic[3–6] and a physical[7] point of view. However, during the last 10–15 years a renewed interest in the reaction mechanism of the oxidation of carboxylic acids arose. The recent contributions to the knowledge of the mechanism are mainly focused on the adsorption properties of organic substances like the acid or its anion, acid derivatives and additives like ethylene. The results of these studies have been used to explain many of the peculiar results obtained in the past. Even the existence of carbocations has been challenged[8] (see below).

In the latest edition of *Organic Electrochemistry*[9], a chapter on the cathodic reduction of carboxylic acids and their derivatives is given. Both the synthetic and the mechanistic aspects are treated up-to-date.

A number of exciting areas within the field of oxidation of carboxylic acids and derivatives will, however, be treated from a mechanistic viewpoint. These areas include the photo-Kolbe reaction, addition of olefins and polymer formation. In order to obtain a complete picture of the reactions of interest a brief summary of earlier work will be given.

II. RETROSPECT

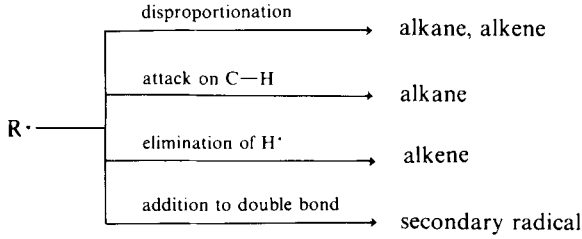
A. Definitions

The oxidation of a carboxylic acid, or rather its anion, with subsequent decarboxylation and dimerization of the radical formed is known as the classical Kolbe reaction[10], exemplified below by the decarboxylation of acetate to form ethane and carbon dioxide:

$$CH_3COO^- \longrightarrow CH_3COO\cdot \longrightarrow CH_3\cdot + CO_2 \quad (1)$$

$$2CH_3\cdot \longrightarrow C_2H_6 \quad (2)$$

Instead of dimerising, the radical can disproportionate to form alkane and alkene, attack a C—H bond in the substrate or the solvent to form an alkane, eliminate a hydrogen atom to form an alkene and be added to a double bond yielding a secondary radical (equation 3).



(3)

Depending on the processing parameters (current density, electrode material, solvent, electrolyte etc.) the radical can also be further oxidized to the corresponding carbocation:

$$R\cdot \longrightarrow R^+ \quad (4)$$

This carbocation will react with the carboxylate anion to form the corresponding ester:

$$R^+ + R'COO^- \longrightarrow R'COOR \quad (5)$$

In aqueous solution the carbocation will react with hydroxide anions to form an alcohol. The reactions deriving from the carbocation are called the Hofer-Moest[11] reactions (in aqueous solution) or, more generally, non-Kolbe reactions. The existence of a carbocation is especially proved in systems where rearrangements of the carbon skeleton are observed. Recently, however, Vassiliev and Grinberg[8] pointed out that no experimental evidence for the existence of carbocations could be found from electroanalytical measurements. For example, in aqueous solution methanol can also be formed by a radical coupling mechanism from hydroxyl radicals formed in the oxygen evolution reaction (equations 6 and 7) and methyl radicals formed in the Kolbe reaction (equation 8).

$$OH^- \longrightarrow OH\cdot + e \quad (6)$$

$$H_2O \longrightarrow OH\cdot + H^+ + e \quad (7)$$

$$CH_3\cdot + OH\cdot \longrightarrow CH_3OH \quad (8)$$

The Brown-Walker[12] version of the Kolbe electrosynthesis is one of the most universal methods to obtain dibasic saturated acids of normal structure and has no analog in traditional preparative organic chemistry. It consists of the dimerization of half-esters of dicarboxylic acids to form diesters (equations 9–11).

$$ROOC{-}(CH_2)_n{-}COO^- \longrightarrow ROOC{-}(CH_2)_n{-}COO\cdot \quad (9)$$

$$ROOC{-}(CH_2)_n{-}COO\cdot \longrightarrow ROOC{-}(CH_2)_n\cdot \quad (10)$$

$$2ROOC{-}(CH_2)_n\cdot \longrightarrow ROOC{-}(CH_2)_{2n}{-}COOR \quad (11)$$

B. Mechanisms

As studies on the mechanism of the Kolbe reaction started to appear[3,5,7,13–50] mainly two different views were dominating. The physical chemists preferred a mechanism involving adsorbed intermediates, while the organic chemists favoured free intermediates. The cause of disparity of opinions was due to the different methods used to investigate the reaction mechanism. The conclusions drawn by organic chemists derive from product analysis. The physical chemists, on the other hand, rely on electrode kinetic measurements.

The following questions are of particular interest and have been debated lively:

(i) Why is the Kolbe electrosynthesis at all possible in aqueous solutions, where the oxygen evolution starts at a much lower potential than the decarboxylation reaction?

(ii) What is the role of surface oxide layers and adsorption of carboxylate anions and intermediates formed?

(iii) What is the rate-determining step of the reaction?

(iv) Is the dimerization reaction homogeneous or heterogeneous?

(v) Why is the choice of anode material of vital importance for the distribution of products formed?

1. Electrode kinetics

In relation to (i) and (ii), most of the electrochemical studies show that the Kolbe reaction takes place on a modified electrode surface. At potentials where the Kolbe

reaction takes place, the platinum electrode will be covered by an oxide layer in aqueous solution. Since the Kolbe reaction can also proceed in non-aqueous solutions (in most cases with better efficiency), where oxide is not formed on the platinum surface, this reaction is not a necessity for the Kolbe reaction to occur. In aqueous solution the modification of the surface has been ascribed to the formation of an adsorbed monolayer of acetate radicals on top of the platinum oxide[7]. Other explanations are based on an adsorbed peroxide compound[40], adsorption of the acid or its anion[8,51-66] and polymer formation[67,68].

By steady-state and non-steady-state techniques it was concluded that the reaction mechanism for decarboxylation of acetic acid at a platinum electrode can be written in the form of equations 12–15. Thus, an electrochemical discharge step (equation 12) followed by either a fast chemical decarboxylation (equation 13) forming an alkyl radical, or an electrochemical decarboxylation (equation 15) forming the dimeric product. Direct coupling of alkoxyl or alkyl radicals (equation 14) to form the Kolbe dimer is also possible.

$$RCOO^- \longrightarrow RCOO^{\cdot}_{ads} + e \quad (12)$$

$$RCOO^{\cdot}_{ads} \longrightarrow R^{\cdot}_{ads} + CO_2 \quad (13)$$

$$2R^{\cdot}_{ads} \longrightarrow R{-}R \quad (14)$$

$$RCOO^{\cdot}_{ads} + RCOO^- \longrightarrow R{-}R + 2CO_2 + e \quad (15)$$

The adsorption characteristics, polarization and capacitance behaviours are of utmost importance for the kinetic description of the Kolbe reactions. In Figure 1 three schematic diagrams are given on the same potential scale in order to facilitate comparison. The curves correspond to similar experimental conditions, i.e. aqueous solution and platinum electrode. In Figure 1(a) the adsorption characteristics of carboxylic acids are shown[66] and will be discussed further in Section IIIA. In Figure 1(b) the anodic polarization curves of platinum in sulphuric acid are shown in the absence (1) and presence (2) of acetate and in pure acetate solution (3)[69]. Finally, in Figure 1(c) the capacitance, measured in sulphuric acid (1) and in acetate/acetic acid (2), is plotted as a function of potential[70].

The anodic polarization curve of acetate on a platinum electrode exhibits a complex feature with one Tafel region at low potentials, where mainly the oxidation of solvent takes place (Figure 1b). This Tafel region is followed by a transition region in which the current is more or less independent of the potential. At higher potentials (>2.3 V vs NHE) a second Tafel region appears and the decarboxylation takes place with good efficiency. The Tafel slope in this region is high ($>2F/RT$) and was explained by the concept of a dipole layer on the electrode surface[7]. A Tafel region together with a large coverage of alkoxy or alkyl radicals can only be achieved if the electrochemical desorption reaction (equation 15) is rate determining, as proposed by Vijh and Conway[7,27,30]. Recently, however, it was shown by capacitance measurements that the coverage of the alkoxy radical could not be detected[70]. With the discharging step rate determining, a Tafel slope of 120 mV will be expected. The surface coverage of alkoxy and alkyl radicals will be low. Thus it seems as though the first electron transfer is likely to be the rate-determining step in the reaction sequence.This is also in agreement with the absence of systematic changes in the discharge potential for different aliphatic carboxylic acids[5].

2. Physical organic approach

Eberson[20,35] proposed a concerted mechanism in which the electron transfer and decarboxylation takes place at the same time. Taking into account the position of the carboxylate anions with the oxygen atoms pointing towards the surface, it follows that the alkyl radical is formed in the solution. Most of the studies made by organic chemists

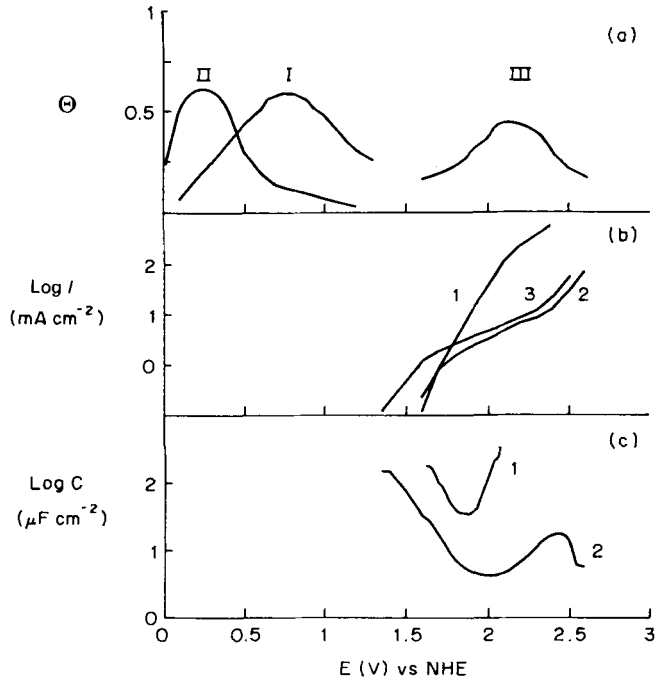


FIGURE 1. A comparison of adsorption, polarization and capacitance measurements at platinum electrodes in aqueous solutions: (a) surface coverage, Θ, of adsorbed species in 1 M CH_3COOH + 0.5 M H_2SO_4[66]. Reproduced by permission of Elsevier Sequoia S. A. (b) Polarization curves in 0.5 M H_2SO_4 (1), 0.5 M H_2SO_4 + 1 M CH_3COOK (2) and 1 M CH_3COOK[69] (3). Reproduced by permission of Plenum Publishing Corporation. (c) Capacitance curves in 0.1 M H_4SO_4 (1) and 0.1 M CH_3COOH + 1 M CH_3COONa (2)[70]. Reproduced by permission of Elsevier Sequoia S.A.

support the 'free' radical hypothesis. For example, studies of product distributions arising from different radicals electrogenerated by the Kolbe reaction show only minor differences with similar reactions of the same radicals homogeneously generated in solution[3,36,37,50,71]. Stereochemical experiments involving Kolbe electrosynthesis starting with an optically active α-carbon in the carboxylate show total racemization of saturated carboxylates[35,47,48,72–74]. If the intermediates are irreversibly adsorbed on the electrode surface with subsequent heterogeneous coupling, one would expect retention of optical activity. If, on the other hand, the adsorption process is dynamic with a fast exchange between the solution and the surface, the product will be more or less racemic, depending on the relative rates of coupling and exchange. Also, if the radical is totally free, a racemic product is expected to be formed. For unsaturated compounds some retention is found, indicating that adsorption plays a role in these cases. For saturated compounds no decisive conclusions can be drawn as to the question of 'free' or adsorbed intermediate radicals.

One reason for favouring adsorbed intermediates is the dramatic change in the mechanism that appears using different anode materials. Koehl[21] found that for anodic oxidation of aliphatic acids at carbon anodes in aqueous solution, only small amounts of dimeric products were formed. It was believed that the carbocation formation was promoted by paramagnetic centres at the carbon surface. These centres would bind the radicals more closely and thus impede desorption[75]. However, detailed studies on

different types of carbon electrodes have revealed that the difference can be attributed to the different adsorption properties[76–78]. Thus Brennan and Brettle[76] showed that in protic solvents the Kolbe dimer was the major product at vitreous or baked carbon as well as on platinum, while the major product on a graphite electrode was instead the ester. Large differences in the product distribution were found by electrolysing at the edge compared to the face surface of pyrolytic graphite. The number of adsorption sites is much larger for a pyrolytic edge electrode and the radical coupling is found to be promoted. In non-aqueous solvents the choice of anode material is not so critical[3].

Another possible explanation of the dramatic difference is product distribution between platinum and graphite may be the actual current density, which will differ due to roughness of the surface. It is well known that a high current density will promote the radical coupling reaction[3].

Also, the fact that addition of anions promotes the formation of carbonium ions in the Kolbe reaction points to participation of adsorbed intermediates in the Kolbe reaction. Coleman and coworkers[45] showed that the addition of only one hundredth part of perchlorate anions, relative to the phenylacetate ion, completely suppressed the formation of the Kolbe dimer. The phenylacetate ion is well electrosorbed on the anode surface both through the aromatic ring π-bonds as well as due to the positive charge of the electrode[79]. Upon oxidation the radical formed will remain electrosorbed, but to a lesser extent than the negatively charged anion. In the absence of perchlorate anions the dimer is formed in good yield at the inner Helmholtz layer. Solvent molecules cannot interfere, because they are displaced by the aromatic molecules. With the addition of perchlorate a competition towards the surface sites arises, resulting in a displacement of the phenylacetate radical by perchlorate ion at the inner Helmholtz layer. Instead of the dimer, dibenzyl, the monomeric benzyl methyl ether is preferentially formed.

For an aliphatic carboxylic acid the condition for electrosorption at the inner Helmholtz layer becomes even less favourable. In this case the solvent, especially water, can displace part of the carboxylate and competition between the oxygen evolution reaction and the Kolbe electrosynthesis will occur lowering the yield of dimer in the Kolbe reaction.

III. ADSORPTION AND KINETICS

As pointed out in Section II, the Kolbe electrosynthesis reaction has been the subject of numerous publications from both an organic chemical and an electrochemical point of view, and the mechanism of the Kolbe reaction has been debated. Recently, further studies on the kinetics and the adsorption in relation to the Kolbe electrosynthesis reaction have appeared[8,51–66,70,80–82]. It must, however, be stated that there is agreement neither about the nature of intermediates nor about the rate-determining step of the reaction[81]. The same uncertainty extends to the type of interactions of the intermediates with the electrode surface and the type of surface oxide layer at the high anodic potential at which the Kolbe reaction takes place[81,82]. Recent adsorption studies of carboxylic acids at high anodic potentials reveal that the Kolbe reaction takes place at an oxide-covered electrode and that this oxide in turn is covered by adsorbed acetate anions. However, it is still uncertain whether the methyl radical is adsorbed on the surface, incorporated in the oxide or free in solution.

A. The Role of Adsorption

The role of adsorption in the course of the Kolbe synthesis has been discussed[8] based on adsorption studies of carboxylic acids, dicarboxylic acids and other organic compounds such as ethylene and its derivatives[51–66], especially the adsorption at high anodic

potentials where the Kolbe reaction takes place[51,54,55,57–60,66]. The findings can be summarized as follows:

Carboxylic acids are adsorbed on the platinum surface in the entire potential region studied, from 0 to 3 V vs NHE. In aqueous solution three different regions are observed (Figure 1a)[66].

Region II. At low potentials, from 0 to 0.5 V, an irreversible destructive chemisorption takes place. The adsorbed species result from dehydrogenation or dehalogenation at the α-carbon atom.

Region I. In the potential range from potential of zero charge to about 1.5 V, a reversible adsorption takes place. In this region the adsorption is similar to the adsorption of inorganic anions and is believed to be due to adsorption of acetate anions.

Region III. The anions in region I are displaced by adsorbed oxygen as the potential becomes more positive. However, in the potential range from 1.6 to 3 V with a maximum at 2.3 V, a new type of adsorption arises. The adsorption is largely reversible and is due to acetate anions adsorbing on top of the surface oxide layer.

The decrease in the adsorption at potentials >2.3 V is associated with the discharge of anions and the occurrence of the Kolbe electrosynthesis. Based on the appearance of the adsorption isotherm, indicating considerable forces of mutual repulsion, it was concluded that no formation of discharged adsorbed acetate radicals is observed on the surface of a platinum electrode in this potential region[66]. This is also in agreement with the results obtained by Conway and Liu[70], who measured the double-layer capacitance as a function of potential (Figure 1c). A minimum in the capacitance value was observed at 2 V with a value of only 4 μF cm^{-2}. This low value might be associated with the physical adsorption of ethane or the adsorption of intermediates like the methyl radical, claimed to be electro-inactive. This is in agreement with the radiotracer study by Yakovleva[53], which show that at potentials >2.3 V the adsorption of labelled methyl carbon is almost 50 times higher than the adsorption of labelled carboxylate carbon. At more positive values the capacitance increases to about 18 μF cm^{-2} indicating that no pseudo-capacitance due to the adsorption of an electro-active species, such as the carboxyl radical $CH_3COO\cdot$, occurs. Below 2 V the capacitance rises to rather high values with a maximum at about 1.4 V (region I). The chemisorbed species in region I do not participate directly in the electrode process, as evidenced by the fractional concentration dependence of the current in this region. The characteristics of the capacitance curve [Figure 1c, (1) and (2)] also show that the Kolbe process in aqueous media inhibits anodic oxygen evolution, a well-known fact. Also, the yield of oxygen, methane, carbon dioxide and ethane as well as the electrode resistance was measured as a function of potential[80]. These results confirm that different electrochemical reactions take place in the various potential regions. In the potential region up to 2.4 V mainly methane and oxygen evolve, due to the competition between the oxygen evolution and oxidation of carboxylic acid. At potentials above 2.5 V mainly carbon dioxide and ethane are formed. The shape of the electrode resistance curve as a function of potential indicates that an insulating film is formed at the surface prior to the Kolbe reaction. This film is thought to be responsible for the total inhibition of the oxygen evolution. It was supposed that the film consists of methyl radicals that can dimerize if their concentration becomes sufficiently high. This should be compared to the work by Vasini and Giordano[81,82], discussed in Section IIIB.

It is interesting to note that Modulated Reflectance Spectroscopy was used to study the changes occurring at a platinum electrode at conditions for the Kolbe reaction in aqueous solution[83]. The optical effects were interpreted as oxide formation followed by the adsorption of a primary layer of radicals. This layer was formed at potentials cathodic to the dimer formation (cf type I). A secondary layer of adsorbed radicals was found at potentials in the Kolbe region (cf type III).

Whether the adsorbed species in region III is a true anion or partially discharged is rather difficult to decide. Quantum chemical calculations were made recently[84] to obtain quantitative parameters characterizing the activity of carboxyl radicals and their disproportionation products. It was shown that the C—O and C=O bond lengths are practically indentical and that there is a strong charge delocalization at the oxygen atoms. The overall charge at the oxygen atoms in the anion was found to be higher than unity. Most interesting is the result that the charge delocalization at the oxygen atoms of the carboxyl group is even somewhat higher in the case of the carboxyl radical than of the anion. In a homologous series of carboxylates, ranging from C_1 to C_7, there is a systematic increase in the overall charge, both for anions and for radicals. The influence of the hydrocarbon group can be explained in terms of an inductive σ-effect. This effect is not restricted to the α-carbon bond. This is also in accordance with the linear increase of the dipole moment in the homologous series found for both carboxylate anions and radicals[84].

The decarboxylation appears as a spontaneous process and it was stated that the alkyl radicals are the active species in the dimerization and polymerization. Note that the calculations refer to free radicals outside an external field and that a good correlation between the theoretical parameters and the experimental kinetic parameters was stated[84]. The presence of free radicals in the cause of the Kolbe reaction has been proved by ESR measurements[85]. The radicals of $CF_3\cdot$ have been detected, using a radical scavenger, which upon radical coupling forms the stable radical $C[CF(CF_3)_2]_3$[86]. Free radicals are also indirectly proved in the photo-Kolbe reaction (see Section VI) and in the addition reaction of radicals to ethylene (see Section III.A.3).

It has been argued that it is the undissociated molecule of acetic acid that is responsible for the adsorption in region I on the bare platinum surface[87]. In acidic solutions the concentration of acetate anions is very low and the adsorption of the undissociated molecule takes place owing to the dipole nature of the molecule. It has been emphasized that acetic acid and other saturated aliphatic acids[87–90] belong to the group of organic substances where adsorption is of 'anion-like' character. The adsorption characteristics of acetate on platinum, gold and rhodium were studied and it was concluded that the character of adsorption was similar for the different metals[56]. In this particular work the reversible adsorption (region I) at intermediate potentials was shown to take place on top of a monolayer of water, i.e. at the outer Helmholtz plane, which is the focus of the nearest solvated ions on the solution side of the double layer. Also in this study it was assumed that the undissociated molecule was adsorbed, because in alkaline solution, where acetate ions are dominating, no adsorption could be detected. This is in agreement with a recent investigation, where a combined infrared spectroscopic and radiotracer study on the adsorption of acetic acid at platinum and gold electrodes was carried out[62]. Extensive adsorption occurs at both platinum and gold, and the adsorption increases at more positive potentials and reaches a maximum at the onset of anodic oxide formation, i.e. type I adsorption. Adsorption at high potentials in the range where the Kolbe reaction proceeds was not investigated. For the type I adsorption it was concluded that the most likely modes of acetic acid adsorption involve hydrogen bonding between the carbonyl oxygen and inner-layer water molecules, or by self-association to form dimers or chain structures.

The electrode process in organic solvents is entirely analogous to the process in aqueous solutions. The transition from solvent oxidation to the Kolbe electrosynthesis becomes possible as a result of inhibition of the solvent oxidation, due to adsorption of the carboxylate anions[49]. In absolute methanol solution no destructive adsorption could be detected. A monotonic growth of the surface coverage with the reversibly adsorbed carboxylic acid anions is observed up to the moment when the process of Kolbe electrosynthesis starts[66]. The competition of solvent and carboxylate anions for a place

on the surface of the anode is one of the factors determining the direction and rate of the electrode process[49].

1. The influence of carboxylic acid structure

It is well known that substituents at the α-carbon atom have most important effects on the yield and product distribution of the Kolbe electrosynthesis. Most investigators did not observe any important difference in the behaviour of different monocarboxylic acids in the first electrochemical step of the anion oxidation[5] and it was concluded that the differences in product yield and distribution follow from the nature of the different radicals formed. In the light of the adsorption studies the influence of carboxylic acid structure on the Kolbe electrosynthesis have been examined. With acetic acid as a reference, the experimental data show the following[91]:

(i) There is a change in the rate of destructive adsorption and destructive oxidation of the carboxylic acid molecule.

(ii) There is a change in competition for the platinum electrode surface between the solvent and the carboxylic anions in the region of high anodic potential.

(iii) There is a change in the route of the radical reactions because of changes in the nature of the radicals formed.

As an example the reaction kinetics and the adsorption behaviour of chloroacetic acid have been studied[92]. It is well known that the halogenated derivatives of acetic acid do not form any characteristic Kolbe products upon oxidation in aqueous solution[55,93]. However, the adsorption of halogenated acetic acid derivatives on platinum proved to be analogous to that of acetic acid[66]. Three characteristic regions are again observed. The main differences in adsorption characteristics occur in the low potential region, where destructive adsorption takes place. For the anion-like adsorption at intermediate potentials and for acetate adsorption on the oxidized platinum surface, the influence of the halogen as a substituent is very weak. The lack of Kolbe dimer in the electrolysis of chloroacetic acid was shown recently[92] to be due to the special reaction features of the secondary chloroalkyl radicals formed. The dimerization reaction is made unlikely by the relatively weak C—Cl bond present in the chloroalkyl radical, so that disproportionation and other processes involving detachment of chlorine are preferred.

For aqueous trifluoroacetic acid the situation is different. The lack of the Kolbe dimer is in this case dependent on the weak adsorption of the trifluoroacetate anion on the surface. This means that the water molecules can more easily displace trifluoroacetate ions from the surface, resulting in a competing oxygen evolution reaction. Thus the rate of the oxidation of trifluoroacetic acid will be lower and the radical concentration correspondingly low[55]. The adsorption region III is shifted to more positive potentials, also enhancing the rate of oxygen evolution compared to oxidation of the trifluoroacetate[66]. Dimeric products can be obtained by displacement of water from the surface with the aid of adsorbates like acetonitrile or by electrolysing in non-aqueous solution, for example in acetonitrile or in anhydrous trifluoroacetic acid[91,93].

2. Dicarboxylic acids

During the course of developing an industrial process for the production of sebacic acid, systematic investigations of the Brown–Walker reaction were undertaken[59,60]. The Brown–Walker synthesis is one of the most universal methods to obtain dibasic saturated acids of normal structure and it has no analogs in traditional preparative organic chemistry. An advantage of the electrochemical method is its universal character, i.e. the possibility to obtain practically all dicarboxylic acids by the same scheme[59,60]. Owing to the high selectivity of the process, dicarboxylic acids thus formed are very

pure[59]. The characteristics of the anodic polarization curves on platinum in aqueous methanol solution of mono-alkyl esters of dicarboxylic acids is fully analogous to the polarization curves for acetates (cf. Figure 1b). This means that a transition from mainly solvent oxidation at low potentials to the discharge of monoester anions at high potentials occurs. The slow-down of the solvent oxidation is connected to the adsorption of the monoester. For example, the adsorption of the monomethyl ester of adipic acid is similar to the adsorption of carboxylates[60] (cf Figure 1a). In analogy with acetate adsorption three different regions can be observed. At low potentials a destructive irreversible adsorption takes place (region II). In region I a reversible anion-like adsorption is observed. In this region the organic species is displaced from the surface as oxygen starts to chemisorb. At still higher potentials, where the Brown–Walker reaction proceeds, a third type of adsorption takes place (region III). In this case the monoalkyl adipate anion is adsorbed on top of the first layer of adsorbed oxygen. Besides these reactions a degradation of the platinum electrode is observable. It is shown that the Kolbe and Brown–Walker reactions are analogous not only in the sense of the identity of the electrochemical route, but also because of the similar character of the chemical and adsorption features[59,60].

The influence of different processing parameters, such as the anode material, current density, structure and concentration of dicarboxylic acid, solvent and temperature, upon the kinetics of the electrode processes and the yield and the current efficiency of the electrosynthesis product was investigated[59].

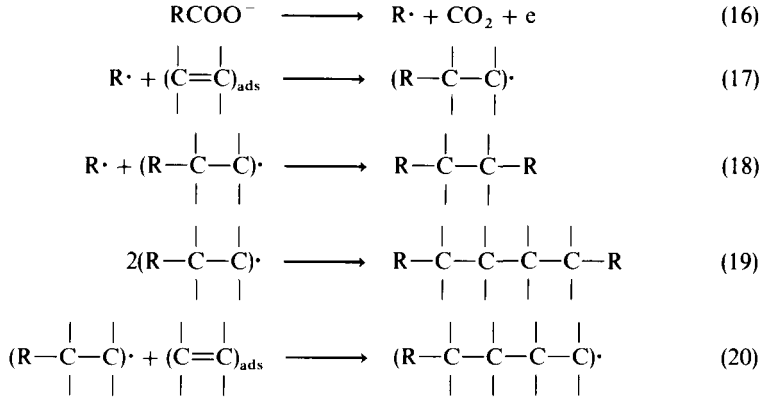
The adsorption of oxalic acid has been studied at low potentials (<0.8 V) on single-crystal and stepped surfaces of platinum. A specific adsorption is observed, which influences the hydrogen adsorption. The characteristics of adsorption are similar to the adsorption of inorganic ions. The potential was limited to 0.8 V, since oxidation of oxalic acid starts at this potential. No irreversible adsorption could be detected, thus showing the stability of the carbon–carbon bond. On Pt(110) only, a blocking of the surface was observed due to dissociative adsorption of products formed by reduction. Single-crystal surfaces of gold were used in the study of the adsorption of succinate and maleate[63,94]. In this case also the adsorption study was limited to low potentials.

3. Addition of olefins

The reaction between hydrocarbons with conjugated or isolated double bonds and the reactive radical formed in the Kolbe or in the Brown–Walker electrosynthesis is of great importance from both a synthetic and a mechanistic point of view. The major feature of electrochemical additive dimerization in the case of dienes (e.g. butadiene) is the retention of double bonds in the products of electrolysis. It is known that the free radicals formed during the Kolbe and Brown–Walker reaction can be added to different compounds with conjugated double bonds[1]. It was earlier supposed that only the electrogenerated radicals could react with activated (conjugated) double bonds. However, it was shown by Vassiliev and coworkers[54,57,58,95–98] that electrochemical additive dimerization, with the participation of ethylene under pressure, was possible forming products without double bonds. Thus it became possible to obtain higher saturated carboxylic acid derivatives from inexpensive materials.

Experimental data[58] show that ethylene is adsorbed on a platinum electrode in two different potential regions. At low potentials from 0 to 1.2 V a destructive adsorption on the clean platinum surface takes place. In this case adsorption is due to the breaking of C—C and C—H bonds in the molecule and the formation of new C—Pt and H—Pt bonds. In the second potential region from 1.5 V ethylene adsorption takes place upon a monolayer of adsorbed oxygen on Pt. The investigation showed that in this range the adsorption of ethylene is of the chemisorption type, i.e. it proceeds via complete or

partial opening of the double C=C bond with the formation of two new C—O bonds. This second, non-destructive type of adsorption increases as the anodic potential increases, passing through a maximum at 2.0 V and then slightly drops as the potential is further increased. Similar dependences are observed for the adsorption of other organic compounds. Thus, ethylene and other acceptors are adsorbed on a platinum electrode surface at high anodic potentials, i.e. in the region where the Kolbe and Brown–Walker electrosyntheses take place. However, ethylene and other acceptors are not directly involved in the electrode process, but due to their adsorption on the electrode the overpotential increases both for the solvent oxidation and for the discharge of carboxylate or diacid monoester, reducing their rate of oxidation. The rate of the electrode processes at constant potential drops with increasing ethylene pressure and exhibits a fractional dependence on the pressure. This is typical of particles adsorbed on uniformly inhomogeneous surfaces but not participating in the electrochemical process. The acceptor itself participates in the secondary radical reactions.



(16)

(17)

(18)

(19)

(20)

and so on

With the use of a rotating ring-disk electrode[58] it was shown that the generated radicals react in the surface layer. This can be due to either strong adsorption at the electrode surface or to very short life-time. It is known that the life-time of the radicals is indeed short and by the use of a rotating ring disk electrode it will not be possible to establish the state of the formed radicals, whether free or adsorbed. From comparative measurements on glassy carbon and platinum, where the concentration of ethylene and radicals were the same, it was concluded that the radicals formed in the Kolbe or Brown–Walker synthesis only react with adsorbed ethylene. On glassy carbon noticeable adsorption has not been obtained, and products of addition of radicals to ethylene are almost not observed. Thus it can be concluded that the adsorption characteristics at high potentials are of fundamental importance for the addition reactions[58].

B. Kinetics

Recent voltammetric studies[81,82] are interpreted through a reaction model in which the Kolbe reaction takes place on a modified Pt surface involving Pt-bonded carbon species. The adsorption studies by Vassiliev and coworkers have shown that three different potential regions exists with different types of adsorbed species; see Section IIIA. In relation to the voltammetric data by Vasini and Giordano[81,82] region III is discussed and divided into three parts.

(i) Just below the critical Kolbe potential ($E = 2.45$ V vs reversible hydrogen electrode), an unstable surface layer of Pt-oxide with a high number of adsorbed organic anions is formed. This layer is highly hydrated and can be detached from the surface under strong stirring conditions.

(ii) At 2.5 V vs RHE decarboxylation of anions adsorbed on the hydrated surface oxide starts, with the formation of a structure containing methyl groups bonded to the hydrous Pt-oxide.

(iii) At the same time a more stable layer is formed by dehydration of the hydrated surface oxide and incorporation of the carbon species into the surface layer (0.4 methyl groups per Pt surface atom).

The proposal of an unstable surface film in part (i) is interesting in the light of recent studies on Sonoelectrochemistry[69]. It was shown that when the Kolbe electrosynthesis of several carboxylic acids was performed under ultrasonic irradiation, the yield of the Kolbe dimer decreased dramatically. It was further noticed that the surface of the platinum electrode remained bright throughout the synthesis. This can be interpreted as a destruction of the hydrated layer formed, which will obstruct the formation of the stable layer upon which the Kolbe reaction can proceed efficiently.

In the adsorption studies referred to above, no methyl radicals could be detected in the potential region III, where the Kolbe reaction takes place[66]. However, with labelled acetate it was shown that the surface concentration of labelled methyl carbon is up to 50 times higher than that of labelled carboxyl carbon at Kolbe potentials[53]. The interpretation of the voltammetric data involves both adsorption and incorporation of methyl radicals[81]. The most interesting fact is that a strongly adsorbed intermediate can be detected in the potential region 0.9–0.99 V vs RHE on a normal positive potentiodynamic scan after polarization at potentials where the Kolbe reaction takes place. The strongly adsorbed intermediate must come from $CH_3\cdot$ radicals, which remain trapped in the oxide matrix in a rather low concentration. Similar voltammetric peaks are observed in the electroadsorption of different organic materials[81].

IV. POLYMER FORMATION

Three different kinds of phenomena are reported under this heading:

(i) Formation of a polymer, responsible for the inhibition of oxygen evolution and oxide growth.

(ii) Polymerization of dicarboxylic acids.

(iii) Electro-initiated polymerization.

(i) One of the most remarkable features of the Kolbe electrosynthesis in aqueous solution is its ability to totally inhibit oxygen evolution. The reasons for this inhibition have been discussed through the years; see Section II. One reason is due to the formation of a covering layer of methyl radicals on the platinum oxide, inhibiting both the oxygen evolution and further oxide growth. These radicals are supposed to dimerize yielding ethane. Another explanation is the formation of a polymer film on the electrode. The Kolbe reaction is supposed to take place on top of this polymer layer. Polaromicrotribometry[67] was used to establish the existence of such a film. At the critical potential for the Kolbe electrosynthesis the friction coefficient was found to diminish, indicating the formation of a hydrophobic film on the surface. Analysis of the film shows that it is a polyethylene-type polymer with acetate and methoxy groups as end groups. Radiotracer studies[68] confirm the existence of a polymer on the surface. However, it was stressed that the inhibition of oxygen evolution takes place prior to the polymer formation[68].

(ii) It is possible to form polymeric compounds by the Kolbe electrosynthesis reaction

of dicarboxylic acids, like adipic acid[100]. These acids, having two carboxyl groups that can undergo decarboxylation, have a potential for stepwise condensation polymerization to form hydrocarbon polymers. In order to avoid blocking of the electrode it was necessary to add a surface-active compound. Under these conditions the polymer was peeled off the electrode. The structural formula is dependent on the solvent used. The mechanism proposed involves both the radical and the cationic pathway. The cationic mechanism leads to formation of ester groups in the polymer. These ester groups are sensitive to hydrolysis which degrades the polymer. The amount of ester groups in the polymer is dependent on the solvent system. Furthermore, the solvent participates by incorporation in the polymer, resulting in methoxy groups from methanol and amide groups from acetonitrile via an ionic reaction, while pyridine is attached to the polymer through a free radical reaction.

(iii) The Kolbe electrosynthesis has also been used to initiate polymerization[101–103]. The radical formed can react with the monomer, such as acrylamide, forming a secondary radical. If the termination reactions can be avoided by stabilizing the radical[101], oligomers or polymers can be formed. It was shown that the reaction takes place close to the electrode in a region corresponding to the roughness of the electrode surface[102].

V. ELECTROCATALYSIS

A. Ad-atoms

The deposition of submonolayers of foreign metal ad-atoms† is a relatively simple way to modify the electrocatalytic properties of an electrode[104]. The catalytic effect of these ad-atoms depends on the electrochemical process taking place at the electrode. It is believed that the underpotential deposits form an organized array on the surface and that the mixed Pt/M surface can act as a promotor for some reactions and as a poison for others. Some studies have appeared in which this concept has been utilized for the oxidation of carboxylic acids[105,106]. For example, it was shown that the oxidation of glyoxylic acid is enhanced by oxygen adsorbing ad-atoms[106]. The main oxidation of glyoxylic acid at a potential more negative than 0.8 V on a Pt electrode proceeds via a hydroxyl radical at the surface[107]:

$$\text{HOOC—CHO} \longrightarrow [\text{HOOC—CO}]_{ads} + \text{H}^+ + \text{e} \qquad (21)$$

$$[\text{HOOC—CO}]_{ads} + \text{OH}\cdot \longrightarrow [\text{HOOC—COOH}] \qquad (22)$$

This is a radical coupling reaction where the carboxylate group remains unoxidized and where the dimer is formed by radical coupling with hydroxide radicals. By using ad-electrodes with oxygen-adsorbing ad-atoms the reaction is facilitated. Oxygen atoms adsorbed by the ad-atoms can be donated to a reaction intermediate adsorbed by Pt sites adjacent to the ad-atoms, resulting in an enhancement of the oxidation[106].

B. Mediators

Through indirect electrolysis by electrochemically regenerable electron transfer reagents, a redox reaction of a substrate may be initiated at a potential with a lower absolute value than that required for the direct process at the electrode. A prerequisite for such a catalytic process is a fast and irreversible chemical follow-up reaction of the

† An ad-atom is a metal atom deposited on a different substrate material. An ad-electrode consists of a substrate material covered by less than a monolayer of metal atoms, so-called ad-atoms.

substrate after the homogeneous electron transfer with the mediator. The oxidation of carboxylic acids fulfils these requirements, since the decarboxylation reaction is extremely fast[108]. Schmidt and Steckhan[109] showed that tris-(*p*-bromophenyl)amine could act as a mediator (Med) for the oxidation of aliphatic carboxylates:

$$\text{Med} \longrightarrow \text{Med}^{+\cdot} + \text{e} \tag{23}$$

$$\text{Med}^{+\cdot} + \text{RCOO}^- \rightleftharpoons \text{Med} + \text{RCOO}\cdot\,(K_{eq}) \tag{24}$$

$$\text{RCOO}\cdot \longrightarrow \text{R}\cdot + \text{CO}_2 \tag{25}$$

Since the oxidation process is performed by a homogeneous electron transfer, the reaction rate is mainly controlled by the standard potential difference of the carboxylate and the mediator. Tris-(*p*-bromophenyl)amine has a standard potential of 1.3 V vs NHE and from the experimental data the standard potential for the oxidation of carboxylate could be calculated to be 1.8 V vs the normal hydrogen electrode. Only low concentrations of the alkyl radicals are generated and therefore, in contrast to the normal Kolbe electrolysis, radical coupling is not favoured. The main products of the controlled potential electrolysis are esters formed by further oxidation of the alkyl radical to its corresponding carbocation, which then reacts with the carboxylate ion.

Polymer modified electrodes have also been used to mediate the electron transfer to carboxylate anions[110]. Unfortunately, the stability of the electrode (4,4'-dibromo-4''-vinyl triphenylamine, VTPA, on glassy carbon) was poor, resulting in degradation[110].

VI. THE PHOTO-KOLBE REACTION

A. Liquid–Solid Interfaces

In 1977[111] Kraeutler and Bard reported on photoelectrosynthesis of ethane from acetate and called it the photo-Kolbe reaction. It was shown that under illumination of an n-type TiO_2 electrode, acetate in acetonitrile can be oxidized at potentials about 2.4 V negative of which acetate oxidation occurs on Pt. Also, in aqueous MeCN and HOAc solutions the main products of the photo-oxidation on n-type TiO_2 were ethane and carbon dioxide[112].

A new reaction pathway of the Kolbe reaction was observed at platinized n-type TiO_2 powder under illumination[113]. The main product of the acetate oxidation was methane, which was rather suprising, in view of the usual dimeric products of the Kolbe reaction. It was later shown that this was common for a number of saturated carboxylic acids, i.e. under photocatalytic decarboxylation the corresponding alkanes are formed[114].

The mechanism discussed followed that suggested for other photoassisted oxidations at semiconductor electrodes. Light of energy greater than the semiconductor band gap excites an electron from the valence band into the conduction band, creating an electron–hole pair. When the redox potential of the solution is positive of the flat-band potential, the bands at the interface will be bent upwards and the electric field in the space-charge region will promote separation of the electron and hole. The hole will migrate to the surface and adsorbed acetate anions can provide a site for trapping this hole. The electron will move to the bulk of the material. The holes, at energies characteristic of the valence band, are effectively strong oxidizing agents (Figure 2). The chemical irreversibility of the overall process prevents back-donation of electrons from the electrode and leads to an overall high efficiency for the process. Short-circuiting the semiconductor with a metal makes the cathodic reaction more efficient.

Since the photooxidation of acetic acid takes place at potentials where the reduction of acetic acid protons is possible, it was suggested that the new pathway involved a combination between methyl radicals formed at the TiO_2 surface and adsorbed hydrogen at Pt. Measurements with monodeuterated acetic acid support these suggestions[114].

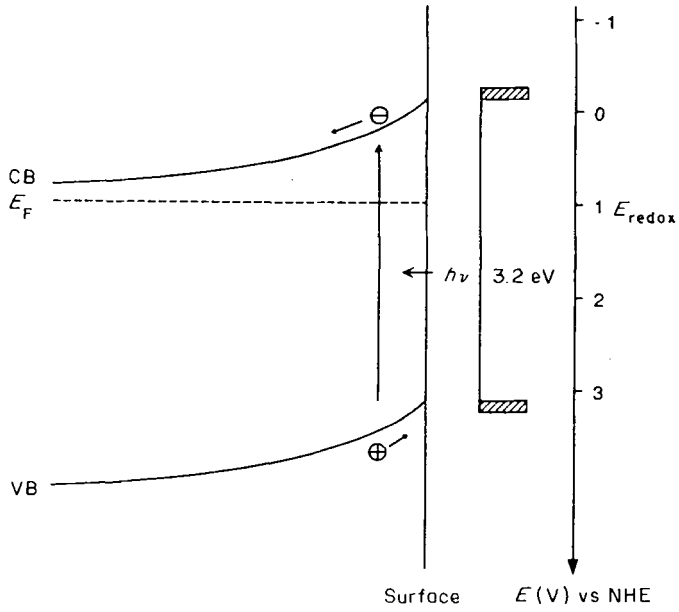


FIGURE 2. Schematic representation of the semiconductor model for the photo-Kolbe reaction. The position of the bandgap on the potential scale relates to a solution pH of 1. The E_{redox} is chosen arbitrarily

The influence of solution composition, reaction temperature, light intensity and semiconductor properties was also investigated[114]. A general reaction scheme was formulated and, in the absence of oxygen, the following steps are involved (h^+ symbolizes a positive hole):

$$RCOO_2^- + h^+ \longrightarrow R\cdot + CO_2 \quad (26)$$

$$RCOOH + e^- \longrightarrow H_{ads} + RCOO_2^- \quad (27)$$

$$RCOOH + R\cdot + e^- \longrightarrow RH + RCOO_2^- \quad (28)$$

$$2R\cdot \longrightarrow R_2 \quad (29)$$

$$2H_{ads} \longrightarrow H_2 \quad (30)$$

$$R\cdot + H_{ads} \longrightarrow RH \quad (31)$$

At platinized TiO_2 mainly RH is formed and only very small amounts of the dimer. A possible reason for this is that, since the catalyst surface is large, the radical concentration at the surface will be low. Furthermore, the radicals are produced near reducing sites on the powder, in contrast to radical production at a separate TiO_2 electrode[111] where ethane is the major product. By ESR it was possible to show the existence of methyl radicals as heterogeneously photogenerated radical intermediates in the photo-Kolbe reaction[115]. There is a close mechanistic parallel between the oxidation step in the electrochemical and photo-Kolbe reactions. In the electrochemical reaction it has not until recently[85] been possible to detect an intermediate radical. The difficulty in observing the intermediate radicals in the electrochemical path is probably due to the very fast follow-up reactions and further oxidation to the carbonium ion.

Later, it was found that not only gaseous products were formed but also alcohol and some aldehyde were found in the solution[116,117]. Furthermore, the reaction was shown to be pH-dependent and in alkaline solutions only hydrogen is observed[117]. The total product distribution was explained by competing reactions with hydroxyl radicals, OH·, formed in aqueous solutions:

$$H_2O + h^+ \longrightarrow OH\cdot + H^+ \quad (32)$$

The oxidation of acetate competes with water for photo-generated holes on n-TiO_2[118]. The reaction route with hydroxyl radicals (equation 33) can also explain the formation of methane at potentials where the hydrogen evolution reaction is totally depressed[116].

$$RCOOH + OH\cdot \longrightarrow R\cdot + CO_2 + H_2O \quad (33)$$

The heterogeneous photocatalytic decomposition of benzoic acid in oxygen containing solution at platinized TiO_2 resulted in a breakdown of the benzene ring through the addition of hydroxide radicals to the aromatic ring, while the electrochemical route yields biphenyl and phenyl benzoate[119]. Also, for the photocatalytic decomposition of adipic acid the products formed, CO_2 and butane, differ from the products found under electrochemical decarboxylation. The electrolysis of dicarboxylic acid has been reported to occur via carbocations and to produce alcohols, lactones and olefins[1]. The difference in product distribution is explained by the formation of OH·, which has strong oxidizing capability.

Kraeutler and Bard[114] suggested that photo-oxidation at platinized n-TiO_2 could be used to treat waste flux containing saturated carboxylic acids. In such a flux, principally those derived from biomass, polyfunctional carboxylic acids can be present. An example of this is the photocatalytic decomposition of levulinic acid on platinized n-TiO_2 powders[120]. Levulinic acid is the major product of controlled degradation of cellulose by acids. The product distribution was shown to be complex, with methyl ethyl ketone, propionic acid, acetic acid, acetone and acetaldehyde as major products, and dependent on the crystallographic phase of n-TiO_2 and the level of platinization of the semiconductor powder[120].

B. Gas–Solid Interfaces

It is also possible to study the photo-Kolbe reaction at the gas–solid interphase[121,122]. The photodecarboxylation of gaseous acetic acid over Pt/TiO_2 produces carbon dioxide, methane, ethane and hydrogen. The reaction rate and the relative yields of products are dependent upon the pressure of acetic acid. The reaction rate for ethane increases selectively with increasing acetic acid pressure, due to the increasing surface concentration of methyl radicals. The gas-phase photo-Kolbe reaction is accelerated by the addition of gaseous H_2O (Figure 3). At low pressures of acetic acid a selective increase in the dimeric product is observed on introducing gaseous water. At high pressures, however, the increase is not so dramatic. This difference can be due to the relative coverage of methyl radicals formed by oxidation of acetic acid and hydroxide radicals formed from water. Thus also for the gas-phase photo-Kolbe reaction the participation of hydroxide radicals have large effects. However, it was shown that the reaction also takes place in the absence of water, implying that the carboxylate ion is certainly discharged. The reaction sequence follows the one proposed for the liquid–solid reaction (equations 26–33).

The selectivity for ethane in the liquid-phase reaction is less than in the gas-phase reaction even if the reaction rate is higher. A possible explanation is that, since the gaseous acetic acid is present as a dimer, the latter would under decomposition produce two methyl radicals adjacent to each other, which will favour coupling[122].

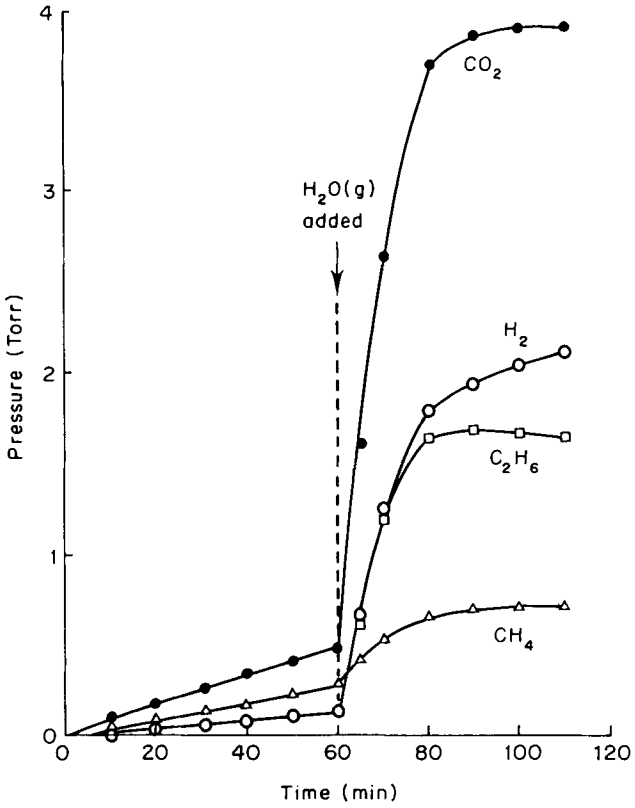


FIGURE 3. The effect of added gaseous water on the product yield and distribution of the photo-Kolbe reaction at a gas/solid interface[121]. Reproduced by permission of The Royal Society of Chemistry

The photo-Kolbe reaction is very attractive, since it only needs low polarization and since sunlight is a sufficient source of irradiation. Even if synthetic applications have not appeared, the study of the photo-Kolbe reaction has shed light on the reaction mechanism of the Kolbe reaction.

VII. MISCELLANEOUS

A. Molten Electrolytes

A few examples of organic preparative electrolysis in molten electrolytes have appeared[123,124]. The binary system CF_3COOK–CF_3COONa has been shown to be sufficiently stable to allow its use as an electrolytic solvent[125]. Electrolysis with a platinum electrode in a molten CF_3COOK–CF_3COONa mixture yields mainly CO_2 and C_2F_6, the normal Kolbe products. The reaction is not, as in aqueous solution, dependent on the electrode material used as an anode. Thus both on gold and pyrolytic graphite electrodes the main product of the anodic oxidation is that of coupling[124].

B. Special Electrode Materials

One of the most fascinating features in the Kolbe reaction is the strong influence of the anode material. To obtain the Kolbe dimer in aqueous solution, smooth platinum or iridium electrodes are normally used[3,6]. Other metals like gold, nickel and platinized platinum support only oxygen evolution. Carbon electrodes promote further oxidation to the carbocation. In non-aqueous solutions the choice of electrode material is not so critical. There exist different opinions whether further oxidation is promoted by specific adsorption of the radical on the electrode[75,126], or if the adsorption characteristics of the anion can explain the differences; see Section II.B.2. From an industrial point of view it is of interest to use cheaper electrode material, since some degradation of platinum takes place at these extreme potentials in non-aqueous solutions[3], hence especially different carbon electrodes have been tested[76].

Other electrode materials are, for example, dimensionally stable anodes, such as titanium anodes coated with titanium or ruthenium oxide[127]. It was found that in non-aqueous solution the titanium base corroded severely. By addition of only small amounts of water this dissolution could be suppressed without changing the Kolbe reaction. The discharge of acetate was found to be rate determining with a Tafel slope of about 120 mV for Ti/RuO_x and Ti/PdO_x and with a first order reaction with respect to acetate anions[127].

Conducting polypyrrole was used as electrode material for the Kolbe reaction of phenyl acetate and *p*-chlorophenyl acetate, both as a free film and as a coating on platinum electrodes[126]. The product distribution was found to change compared to the electrosynthesis on bare platinum.

The possibility of using the solid polymer electrolyte (SPE) method for Kolbe-type reaction has been investigated[129]. The study is motivated by the problems arising from the addition of supporting electrolyte, which is necessary in the electrochemical method, leading to difficulties in product purification. These problems are eliminated by the use of a solid polymer electrolyte. It was shown that the Kolbe reaction of acetic acid proceeds effectively on Pt-SPE composed with nafion membrane and platinum. The method was also applied successfully to the Brown–Walker reaction[129].

C. Pressure Dependence

Electrochemical oxidation of n-alkanoic acids in aqueous solution at a smooth platinum anode gives higher yields of alkane dimer product when performed at elevated pressures than in an equivalent experiment at atmospheric pressure[130]. One reason for this is that, under high-pressure conditions, the olefins are liquids and can accumulate at the anode and thereby prevent the water from reaching the surface. It is interesting to note that the alkane dimer only becomes the major product at room temperature and atmospheric pressure in aqueous solution when the acid used is n-hexanoic or longer. The olefinic side-products from these acids are liquids at room temperature. As a consequence of these results it should be possible to improve the yield of the dimer from acids with few carbons ($C_2 - C_6$) by addition of acids with higher molecular weight. Indeed, the dimer yield from butanoic acid is strongly increased in the presence of hexanoic acid[131]. This is explained by formation of a lipophilic layer on the electrode surface, excluding water from the anode.

VIII. CONCLUDING REMARKS

The Kolbe electrosynthesis is a simple and useful method for synthetic applications. The processing parameters have been investigated in detail and it is possible to direct the

reaction via the radical or carbocation path by choosing proper experimental conditions. However, to explain *why* and *how* the reactions proceed is a much more difficult task. Recent studies on the mechanism and kinetics of Kolbe-type reactions have emphasized the role of adsorption and have proved to be effective in answering some of the questions that were formulated in Section II.B of this chapter.

Thus the entire course of the Kolbe reaction in aqueous solution (i) can be rationalized according to the adsorption characteristics, i.e. the transition from mainly solvent oxidation to decarboxylation becomes possible due to anion adsorption. In aqueous solution at a platinum electrode, this adsorption takes place on top of the surface oxide, inhibiting both oxygen evolution and further oxide growth. The role of the oxide is not well established (ii), since in non-aqueous solvents, where platinum oxide is not supposed to be formed, the reaction proceeds more efficiently. Also, in this case an adsorption of the anion precedes decarboxylation. Whether it is truly the anion or a partially discharged species was discussed in relation to some quantum chemical calculations.

The question of homogeneous or heterogeneous coupling (iv) has been debated lively during the years. In recent years most investigators tend to support the view of a homogeneous dimerization reaction. This is also the most satisfactory explanation according to product analyses. It does not, however, depreciate the role of adsorption in these reactions, but rather points to the nature of the adsorbates. The effect of electrode material (v) on the product distribution is an outstanding example of this. The relative rates of the solvent oxidation and the Kolbe reaction can be explained by competitive adsorption of species participating in the respective reactions.

Now to the questions of the rate-determining step (iii). Since the surface coverage of intermediates in the Kolbe reaction is low, and it has not been possible to prove their existence, the experimental results point to the electron transfer reaction as the rate-determining step. This will also explain the lack of dependence of carboxylic acid structure on the oxidation potential.

Finally, the complexity of heterogeneous reactions sets limits to the degree to which the mechanisms can be analysed.

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CHAPTER **23**

Rearrangements

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The number of reports dealing with rearrangements in which carboxylic acids or their derivatives are involved, either as starting materials or as final products, is very large. When writing this chapter, we have tried to focus our attention on the most important theoretical advances and synthetic applications published during the last decade, especially when a carboxyl-derived functional group is directly involved in the rearrangement. Because of space limitations, we have not attempted to perform an extensive coverage of the topic, but concentrated on rearrangements which received the most

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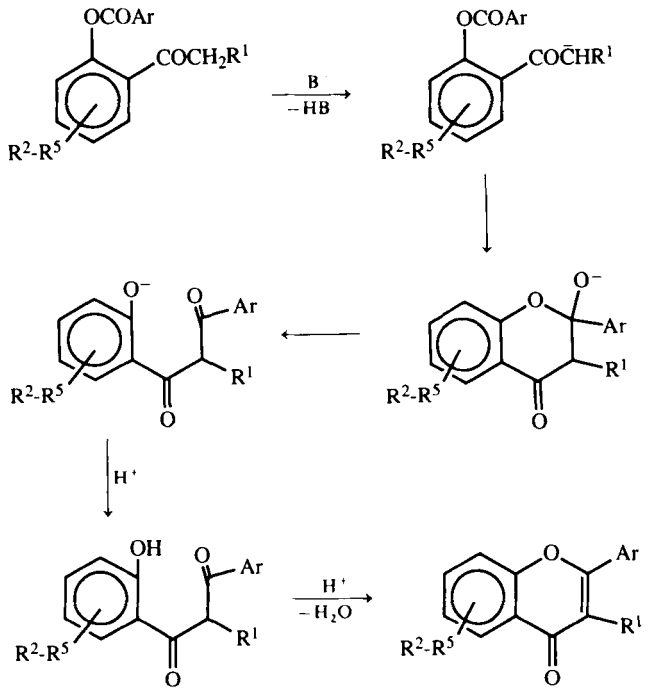
attention over the years, due to their scope and synthetic versatility. Not surprisingly, a systematic survey of the recent literature shows that the currently 'best selling' rearrangements are still the classic name reactions (Beckmann, Claisen, Fries, etc.) generally included in the textbooks. These have been taken, therefore, as the key items of our review, which has been arranged according to whether the acid derivatives play the part of starting materials (Section I) or final products (Section II). Section III, called 'Other Rearrangements', contains these processes where the functional groups of interest can be found not only at the beginning, but also at the end of the rearrangement. This includes, besides interconversions, the Schmidt reaction, which can be performed with carboxylic acids, with many similarities to the Curtius or Hofmann procedures, or with ketones, involving nitrogen insertion, like in the Beckmann rearrangement.

I. REARRANGEMENTS OF CARBOXYLIC ACIDS AND DERIVATIVES

A. Baker–Venkataraman Rearrangement

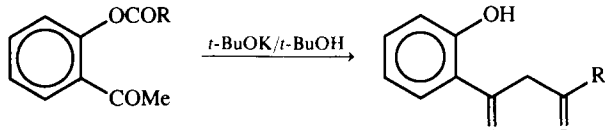
The Baker–Venkataraman rearrangement[1] is a classical reaction, extensively employed in flavonoid chemistry, consisting in the intramolecular acylation of an aromatic ketone enolate by an aryl ester group attached to the *ortho* position. It is, therefore, a base-mediated conversion of *o*-acylaryl benzoates into *o*-hydroxydiaroylmethanes, whose subsequent cyclization under acidic conditions affords the corresponding flavones (equation 1).



(1)

In spite of being known for more than fifty years, the Baker–Venkataraman rearrangement has not been subjected to systematic mechanistic study until very recently[2,3]. Careful kinetic work including substituent effects has allowed one to confirm the pathway shown in equation 1, which involves pre-equilibrium formation of the carbanion, followed by rate-determining intramolecular nucleophilic attack.

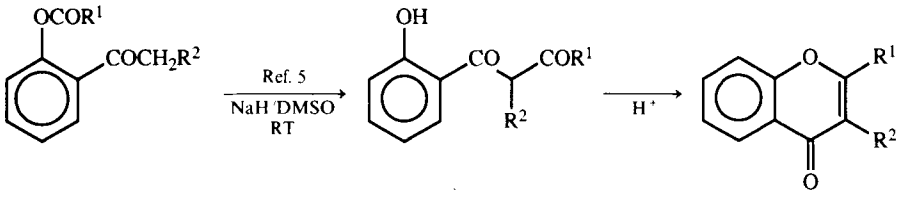
Recent interest in this rearrangement stems from the lack of systematic studies devoted to the transfer of aliphatic acyl groups, as opposed to the large number of reports dealing with the transfer of aromatic or heteroaromatic acyl groups. In this context, it has been found that treatment of a series of ketoesters with the potassium *tert*-butoxide/*tert*-butyl alcohol complex at 0 °C produces the rearranged diketones with acceptable yields[4]. In view of the vigorous conditions often employed in the traditional Baker–Venkataraman reaction, this modification appears advantageous in that it is compatible with more sensitive functionalities, allowing in principle its extension to more elaborate benzopyrones. However, as a general limitation, when α-deprotonation of the aliphatic ester group can compete with the desired α-deprotonation of the aromatic ketone, the major products are those derived from the ester enolate. Some examples of the application of this procedure are given in equation 2.



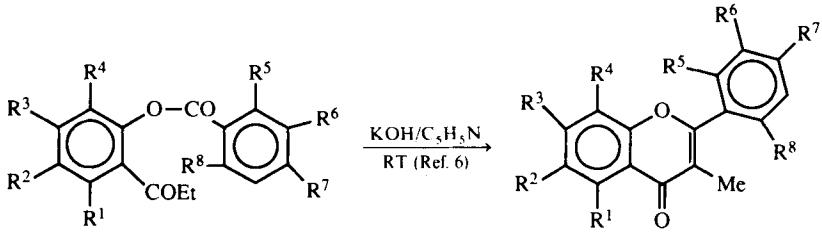
(2)

R = CH=CHMe (54%)
R = CH=CHPh (61%)
R = Me (28%)

Another possibility to achieve the transfer of aliphatic acyl groups is to use sodium hydride in DMSO at room temperature[5]. Under these conditions a number of 2- and 2,3-substituted chromones have been obtained. In this context, the introduction of a



(3)

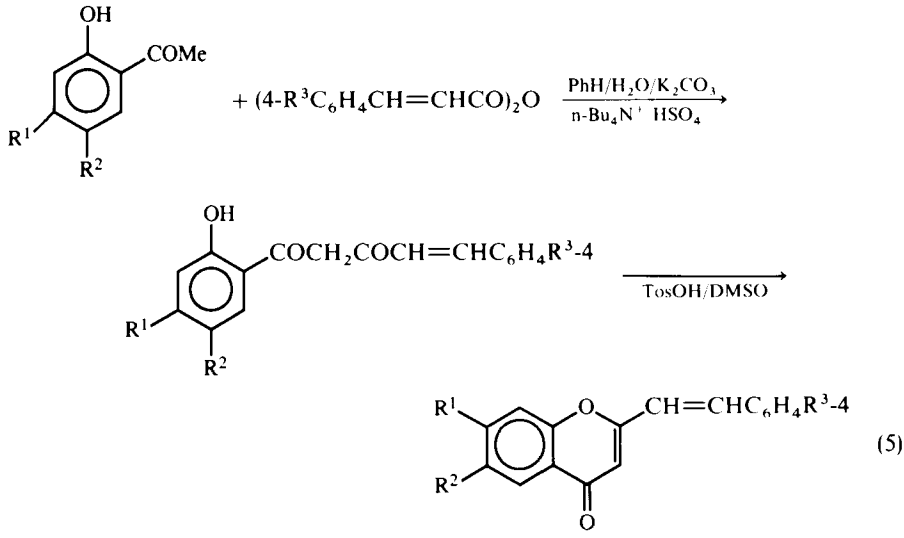


(4)

R^1-R^4 = Br, Cl, F, Me or H
R^5-R^8 = Br, Cl, I, F, Me, OMe, NO_2 or H

methyl group at the 3-position of the flavone skeleton is not always easy to perform by the general method[6]. Thus, the use of potassium hydroxide in pyridine at 60 °C or *t*-BuOK in *t*-BuOH at 60 °C fails to yield 3-methylflavones from the corresponding *o*-benzoyloxypropiophenone precursors, due to competing hydrolysis of the benzoate. This can be prevented by carrying out the reaction with potassium hydroxide at room temperature[6,7]. Some applications of the Baker–Venkataraman rearrangement at room temperature can be found in equations 3 and 4.

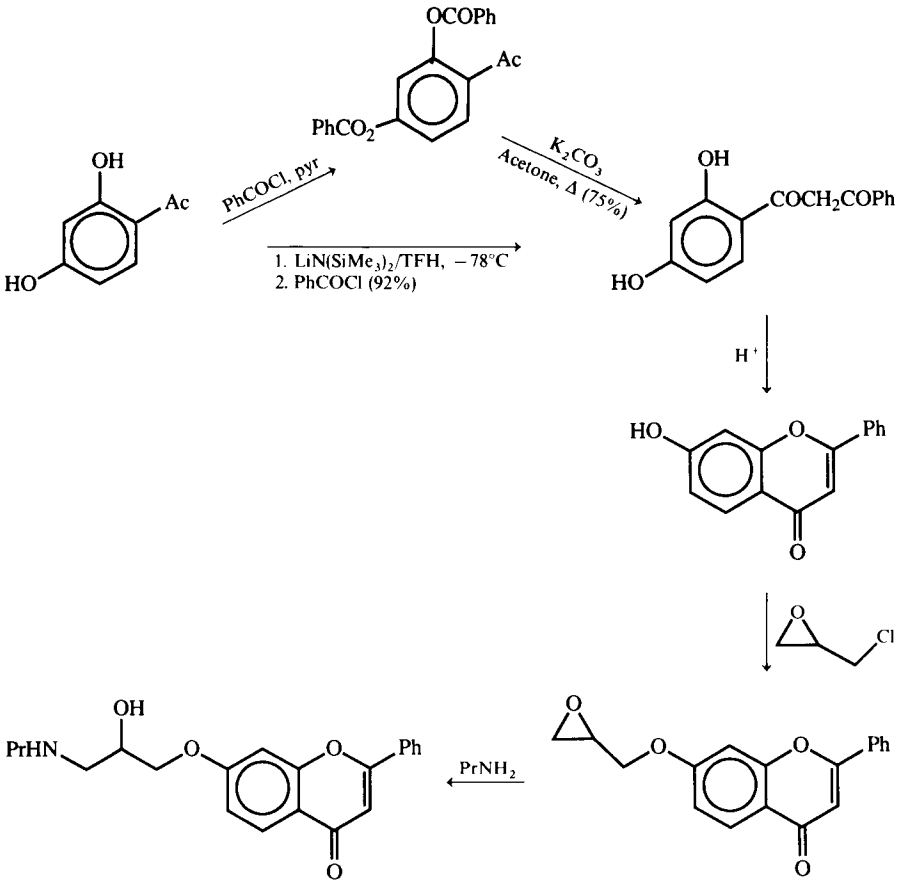
An interesting modification of the Baker–Venkataraman rearrangement involves the use of phase-transfer catalysis conditions[8–10]. Thus, treatment of *o*-hydroxyacetophenones with aroyl chlorides in benzene solution, in the presence of aqueous potassium carbonate or hydroxide and n-tetrabutylammonium hydrogen sulfate, results in the formation of *o*-hydroxydibenzoylmethanes, via the intermediate *o*-benzoyloxyacetophenones[8]. This method has been extended to the synthesis of 2-styrylchromones from cinnamic acid derivatives, which have also been performed by the classical procedure, in the absence of phase-transfer catalyst[11–13] (equation 5).



(5)

Direct reaction of the lithium dianions of *o*-hydroxyacetophenones with acyl chlorides at low temperature affords diketones identical to those obtained by the Baker–Venkataraman pathway[14]. Although the two-step procedure is usually more convenient, the above-mentioned direct acylation becomes the method of choice for obtaining ring-A hydroxylated or polyhydroxylated flavones, provided that the lithium polyanions of the corresponding acetophenones are prepared using enough base to ensure generation of the ketone enolates. Thus, 7-hydroxyflavone can be obtained from resacetophenone, by treatment with three equivalents of lithium bis(trimethyl)silyl amide and subsequently with benzoyl chloride or, alternatively, by Baker–Venkataraman rearrangement of resacetophenone dibenzoate[15]. Reaction of 7-hydroxyflavone with epichlorohydrin in ethanol containing sodium hydroxide, followed by ring opening of the epoxide with *n*-propylamine, affords flavodilol, a new antihypertensive agent with catecholamine depleting properties[15] (equation 6).

Finally, it is worth mentioning that the *o*-hydroxyketones obtained by the Baker–



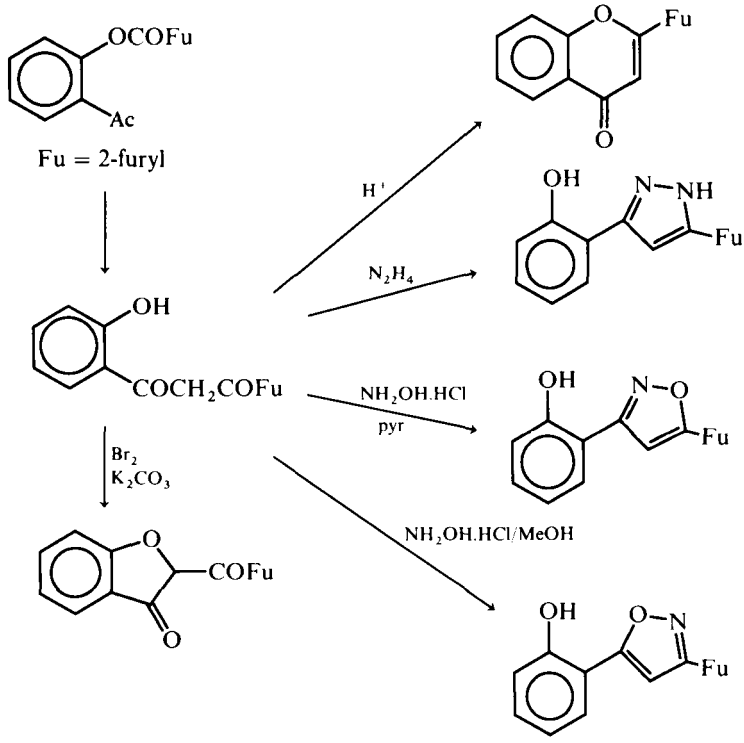
(6)

Venkataraman rearrangement have also been used for obtaining heterocycles different from chromones or flavones[16–18]. Some examples can be found in equation 7.

B. Curtius Rearrangement

Essentially, this rearrangement involves the thermal transformation of acyl azides into isocyanates (equation 8). The latter can be isolated in good yields when the reaction is carried out in an inert solvent, but it is also possible to use nucleophilic solvents, whereupon the corresponding trapping products are obtained[19–22].

Recently, the Curtius rearrangement has been performed under phase-transfer catalysis conditions[23–26]. Indeed, this approach is useful for the preparation of acyl azides rather than for the rearrangement step. The quaternary ammonium salts form ion pairs with azide anions, which are extracted into the organic solvent, where they react with acyl chlorides to form the required acyl azide precursors. The activity of the quaternary ammonium halides strongly depends on their structures[24], increasing with the length of the alkyl side chains and also in the order I < Br < Cl.



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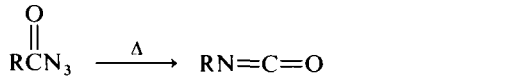
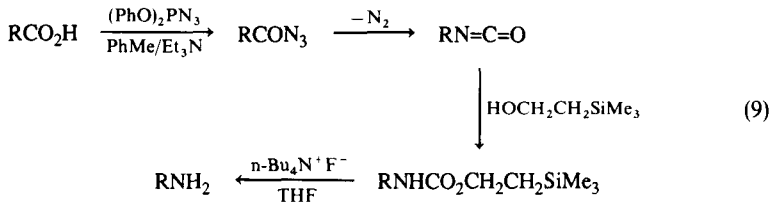


(8)

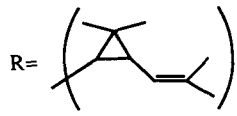
Diphenylphosphoryl azide[27–31] and trimethylsilyl azide[28,32] can be used to convert carboxylic acids into the corresponding acyl azides. An interesting application of this modification[29] involves subsequent addition of (trimethylsilyl)ethanol, to yield carbamates which are easily cleaved with Bu_4NF, the amines being finally isolated in good yields (equation 9).

Most current uses of the Curtius rearrangement involve trapping of the isocyanates by water or alcohols, to give amines or carbamates, respectively. However, difficulties arise sometimes in the presence of sensitive functionalities, such as cyclopropyl or polyunsaturated systems, due to the vigorous conditions needed to achieve the cleavage of carbamates to amines in the last step. Another method to circumvent such problems appears to be trapping of the isocyanates by means of trifluoroacetic acid, to give trifluoroacetamides which are easily cleaved to the desired amines[23].

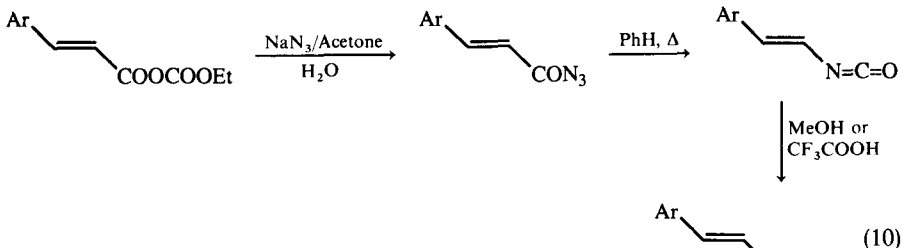
In the search for a stereospecific route to enamides in which the geometry of the double bond is retained from the beginning of the synthetic sequence, a series of cinnamic acid derivatives have been converted into the acyl azides, via reaction of mixed carbonic anhydrides with sodium azide in aqueous acetone[33]. Thermal decomposition of the cinnamoyl azides give the corresponding isocyanates with retention of configuration. Subsequent treatment of the latter with trifluoroacetic acid affords the expected trifluoroacetamides but, unfortunately, in the case of the (*Z*)-isocyanates partial isomerization



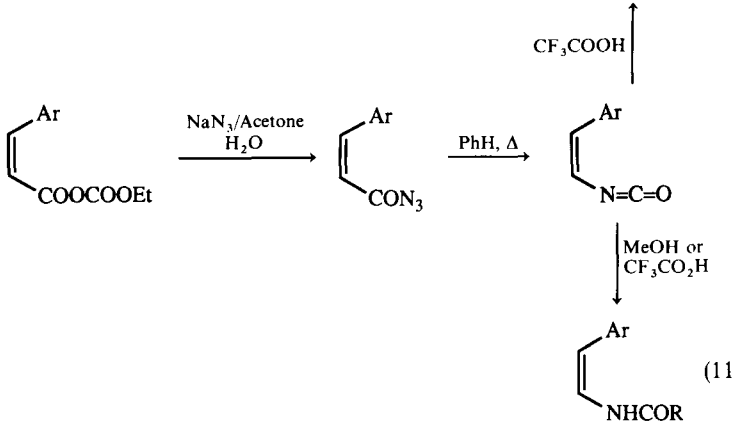
(9)



to the (*E*)-enamides has been observed to take place. This difficulty has been circumvented by converting the isocyanates into methyl carbamates, using anhydrous methanol at room temperature to carry out the reaction (equations 10 and 11).

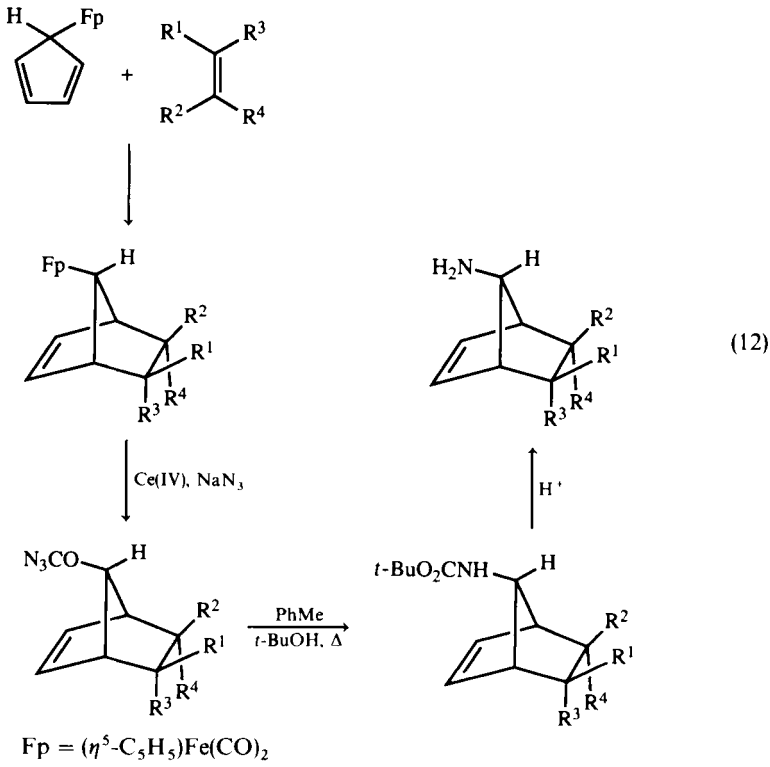


(10)



(11)

Recently, cerium(IV)-promoted one-electron oxidation of iron(II) complexes to iron(III) complexes has been shown[34] to result in rearrangement of the latter to acyl iron(III) complexes, which can be intermolecularly trapped by azide ion to give acyl azides. Thermolysis of these compounds in toluene/*tert*-butyl alcohol, followed by



(12)

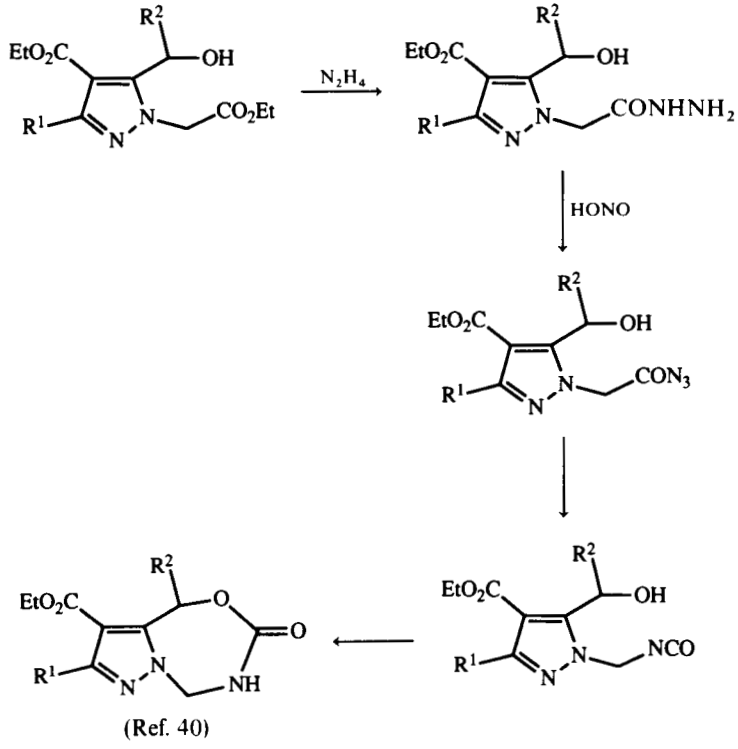
Fp = $(\eta^5\text{-}C_5H_5)Fe(CO)_2$

cleavage of the resulting carbamates, affords amines in good yields. This idea has been applied to the development of a useful synthetic equivalent of 5-amino-1,3-cyclopentadiene in cycloaddition reactions (equation 12).

The above method constitutes a rather unconventional approach for the generation of the acyl azides necessary to carry out the Curtius rearrangement. However, it shares with most of the more conventional methods the need for an azide source (sodium azide, trimethylsilyl azide[28,32] or diphenylphosphoryl azide[27–31, 35–39]) as already mentioned. By contrast, treatment of hydrazine derivatives with nitrous acid[40–44] constitutes an alternative approach to carry out the Curtius rearrangement without using azide reagents. Some applications of this methodology are illustrated in equations 13–15.

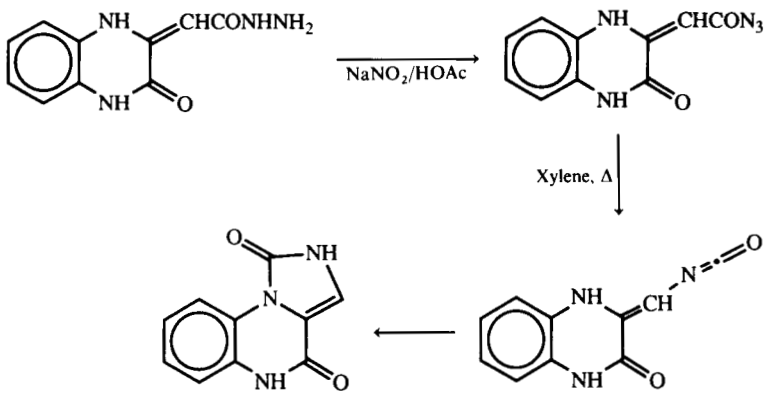
Intramolecular trapping of the isocyanate formed as a consequence of the Curtius rearrangement as in equations 13 and 14 has been used as a general principle for heterocyclization[19, 45–49]. Thus, treatment of phthalisoimidium perchlorates with sodium azide gives *o*-carbamoylbenzoyl azides, which upon heating yield *o*-carbamoylphenyl isocyanates. Depending on the substitution of the amide nitrogen, cyclization occurs readily to quinazoline-2,4-(1*H*, 3*H*)-diones or can be promoted by the action of perchloric acid, giving rise to benzoxazinone derivatives[46] (equation 16).

Likewise, α,β-epoxyacyl azides obtained from the corresponding activated carboxylic acids (mixed anhydrides or acyl chlorides) undergo Curtius rearrangement to epoxyisocyanates upon gentle heating in an inert dry solvent. Spontaneous ring expansion of the latter compounds leads to 3-oxazolin-2-ones, which, depending on the substitution at the β-position, undergo a prototropic tautomerization or, in the presence of adventitious moisture, water addition to the double bond[48] (equation 17).



(13)

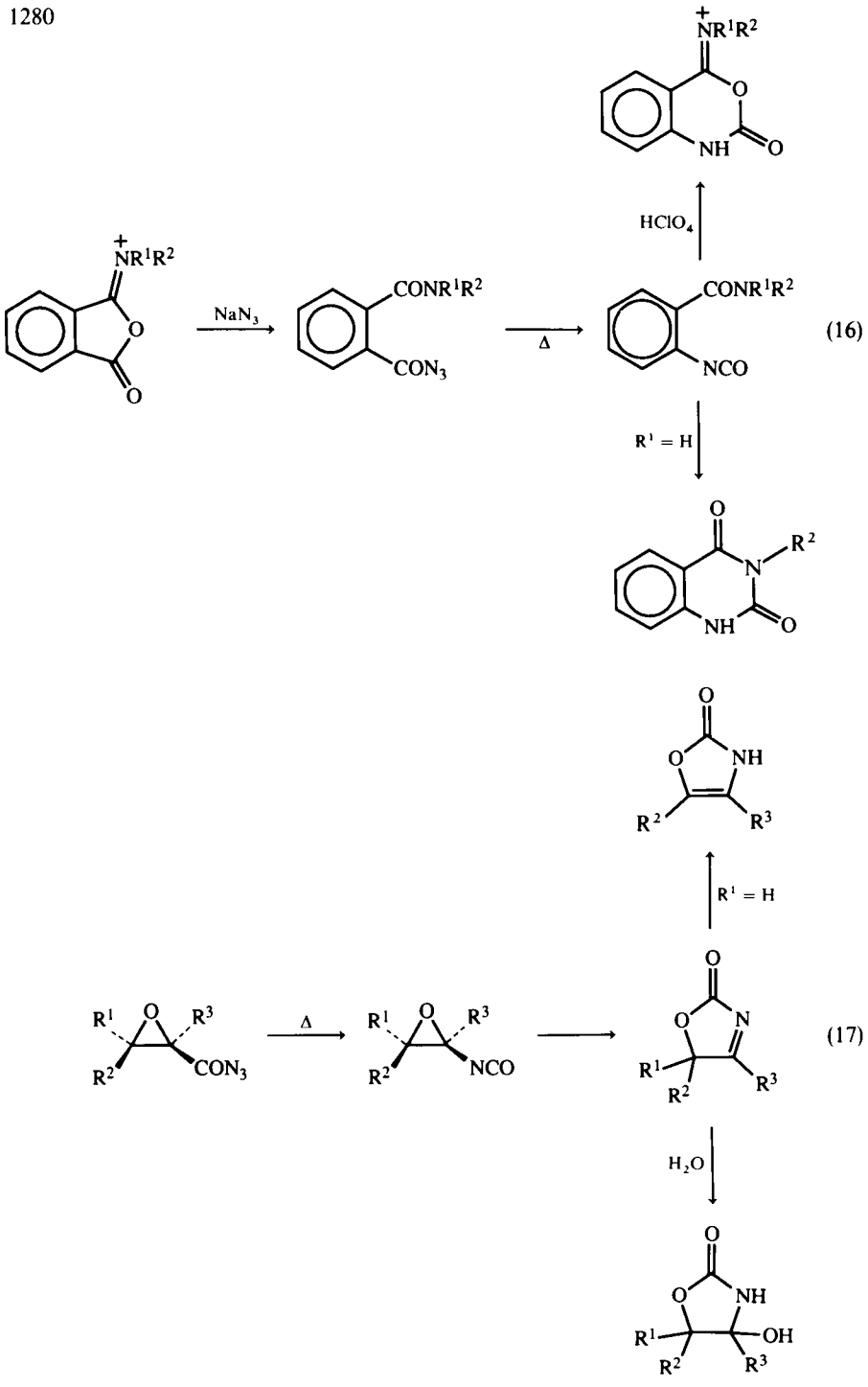
(Ref. 40)



(14)

$$RCONHNHCONH_2 \xrightarrow{HONO} RCON_3 \longrightarrow RNCO \xrightarrow[(Ref.\ 44)]{t\text{-}BuOH} RNHCOOCMe_3 \quad (15)$$

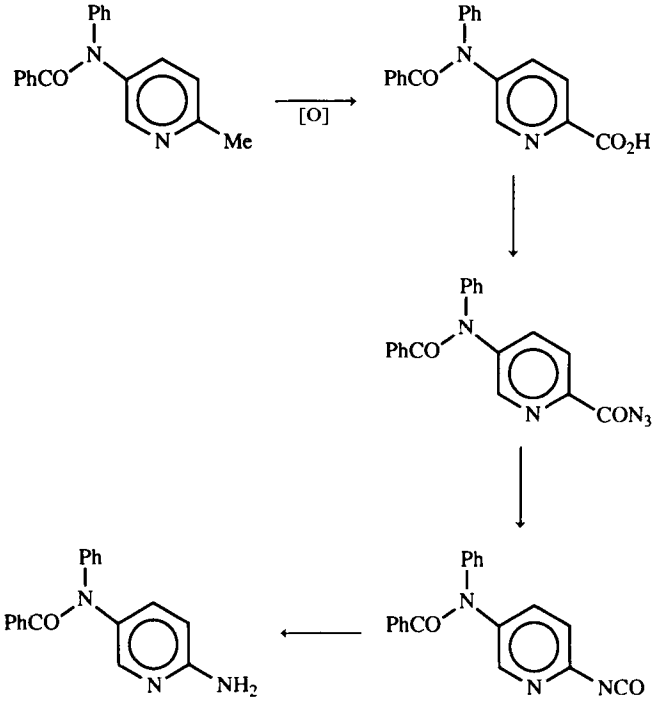
R = Ph, $PhCH_2$ or 3-pyr



(16)

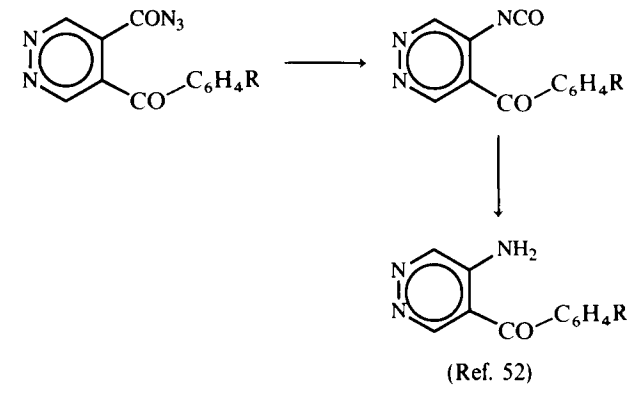
(17)

Besides its use in the ring-formation step, the Curtius rearrangement has also found wide application in the field of heterocyclic chemistry for the functionalization of heteroaromatic systems[50–54]. Two typical examples are given in equations 18 and 19.



(18)

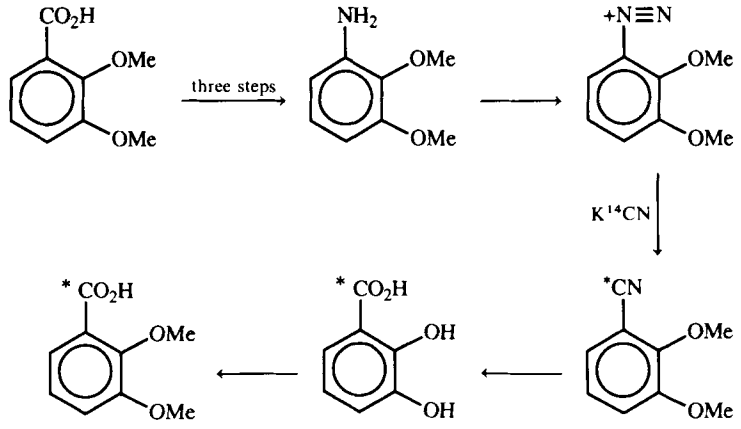
(Ref. 50)



(19)

(Ref. 52)

New developments still continue to appear concerning the Curtius rearrangement in benzenoid systems[31, 55–58]. Among them, the obtention of ^{14}C-labelled 2,3-dihydroxy-



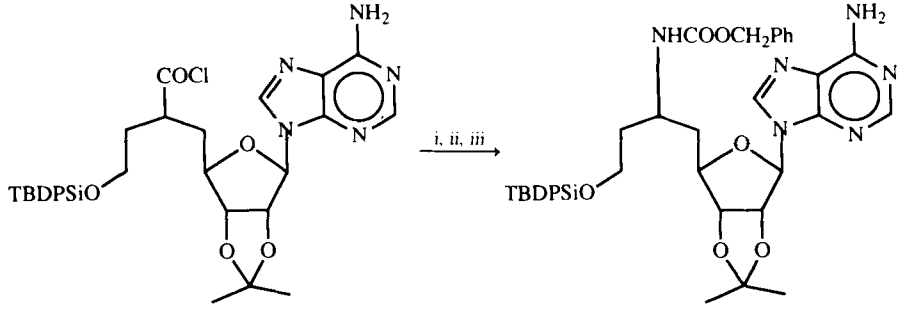
(20)

$$R_2Si(C_6H_4CON_3\text{-}p)_2 \xrightarrow[\text{(Ref. 58)}]{} R_2Si(C_6H_4NCO\text{-}p)_2 \qquad (21)$$

R = Me or Ph

benzoic acid[55] and the conversion of bis(azidocarbonylphenyl) silicon compounds into the corresponding isocyanates[58] are worthy of mention (equations 20 and 21).

Perhaps, the synthesis and/or structural modification of organic compounds of biological interest, such as nucleosides[28,59], amino acids or peptides[30,36,37,39,42,60–64], is the field which has attracted the most attention among the applications of the Curtius rearrangement. Thus, in the course of studies directed to the synthesis of the nucleoside antibiotic sinefungin, a $C_{(6')}$ amino group (blocked as urethane) has been introduced in three steps[28] (equation 22).

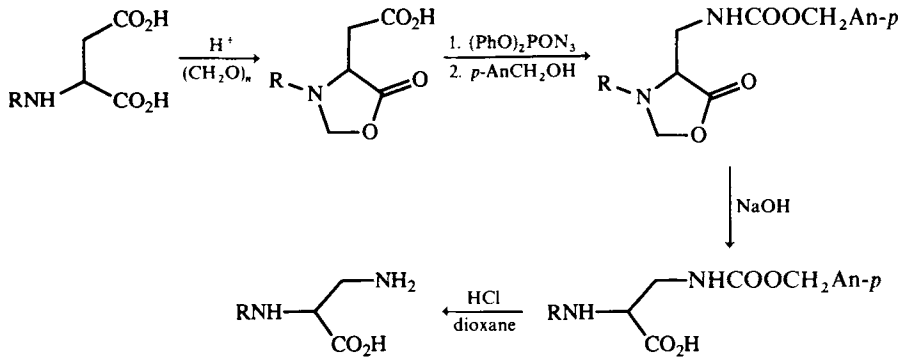


TBDP = *t*-butyldiphenyl

Reagents: i = NaN_3, acetone/H_2O
ii = PhMe, Δ
iii = $PhCH_2OH$

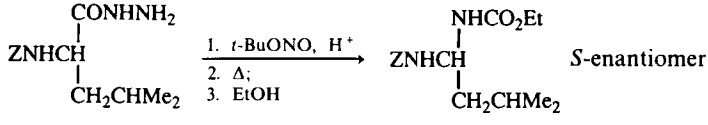
(22)

In the case of amino acids and peptides, the reaction has been used to prepare *gem*-diamino derivatives and partially modified retro-inverso peptides. Some representative processes[37,42,39] are outlined in equations 23–25.



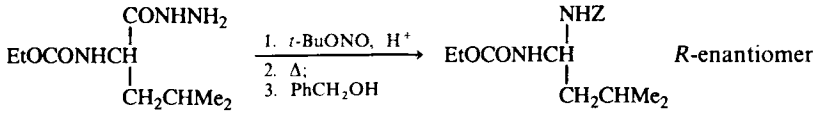
R = Cl_3CCH_2OCO or $PhCH_2OCO$ (Ref. 37)

(23)



L-enantiomer (Ref. 42)

(24)



L-enantiomer

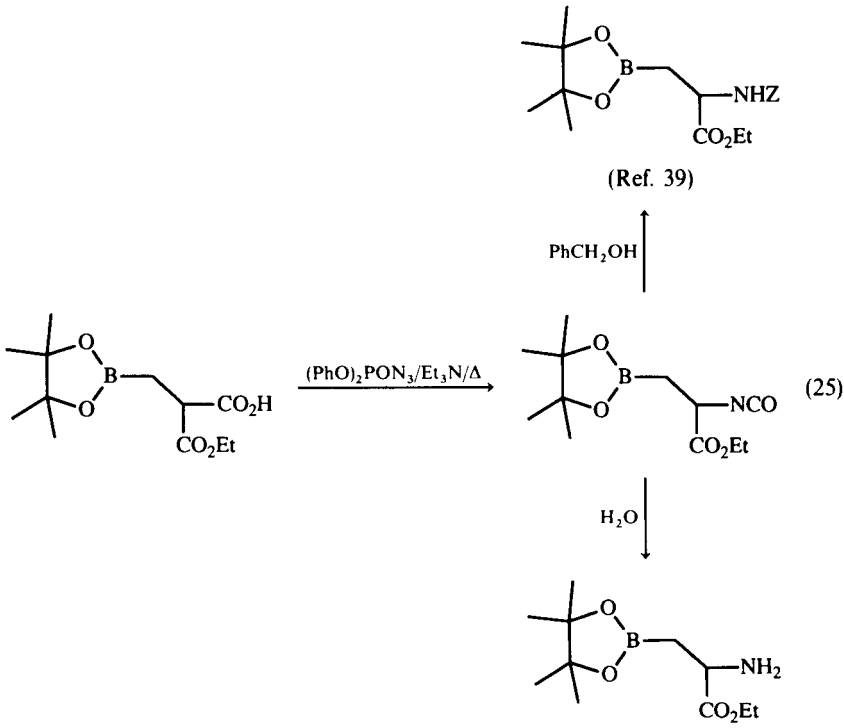
Z = $PHCH_2OCO$

Although the conversion of acyl azides into isocyanates has been generally achieved by thermal activation, a small number of reports have appeared during the period of coverage dealing with the photochemical Curtius rearrangement[19,65–68]. Unfortunately, this process is limited by the competitive formation of acyl nitrenes alongside with the desired isocyanates. Thus, photolysis of bicyclo[4.1.0]hept-3-en-*endo*-7-carboxylic acid azide affords a mixture of products derived from acyl nitrene and isocyanate intermediates[65] (equation 26).

A recent study on the photochemistry of a series of aroyl azides has shown that the formation of isocyanates occurs from a higher excited singlet state, which can be reached by irradiation at 254 nm, involving the $\pi\pi^*$ band. By contrast, no isocyanate is formed upon irradiation into the $n\pi^*$ band ($\lambda > 345$ nm), which results in the formation of products rationalizable as arising from singlet aroyl nitrenes[68] (equation 27).

Finally, it must be mentioned that the Curtius rearrangement of acyl azides has been extended to analogues of the heavier main group elements, such as tetracoordinated pentavalent phosphorus azides[69,70]. Equation 28 shows the products obtained upon irradiation of the oxide of diphenylphosphine azide, clearly demonstrating that the migration of a phenyl group from phosphorus to nitrogen occurs with loss of nitrogen.

The transient oxoiminophosphoranes are the phosphorus analogues of isocyanates.



(25)

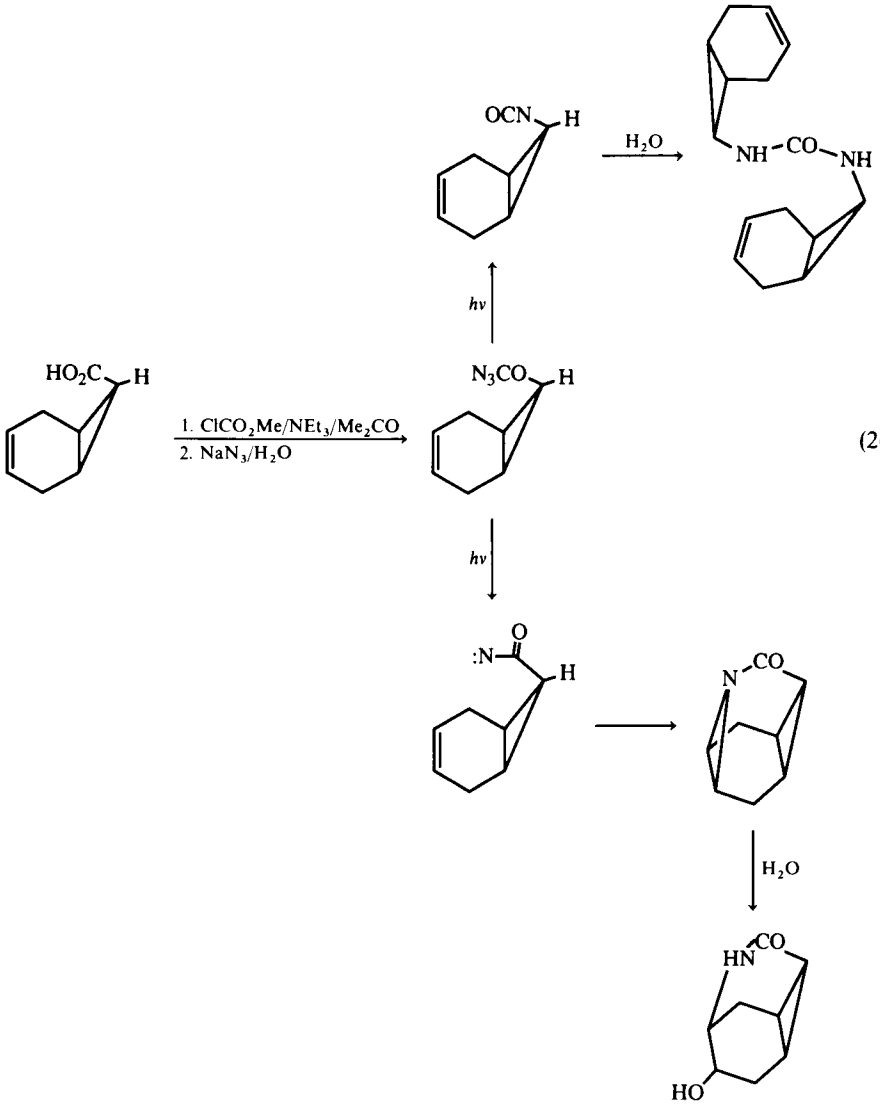
Very often, competitive nitrene-type reactions are observed, usually as a minor pathways. In some cases only nitrene-derived products are observed (equation 29).

C. Fries Rearrangement

This reaction, first studied by Fries in 1908[71], is the acid catalysed rearrangement of phenyl esters to mixtures of *o*- and *p*-acylphenols, as illustrated in equation 30 for phenyl acetate.

During the last decade, a number of reports appeared which clarified some controversial mechanistic aspects. Thus, it has been established beyond any doubt that the Fries rearrangement is reversible[72,73], similar to other electrophilic reactions such as sulfonations or alkylations. Thus, the rearrangement of phenyl benzoate in 1,2-dichloroethane, using trifluoromethanesulfonic acid as catalyst, to give *o*- and *p*-hydroxybenzophenones is reversible at high temperatures[72]. At 160–170 °C equilibrium mixtures are obtained whose compositions do not depend on the starting compound (aryl ester, *o*- or *p*-hydroxyketone) (equation 31). Another striking observation is the almost complete disappearance of 2-methyl-4-hydroxybenzophenone after heating during 20 minutes at 170 °C in the above-mentioned acidic medium, with formation of *m*-cresyl benzoate as the main product, together with minor amounts of 4-methyl-2-hydroxybenzophenone. Higher reaction times lead to equimolar mixtures of both products.

More recently[73], the successful synthesis of 4-acylcyclohexa-2,5-dienones, which have been postulated as intermediates for the formation of *p*-acylphenols, have allowed one to study their behaviour under acid catalysis. This work has shown that, in CD_2Cl_2



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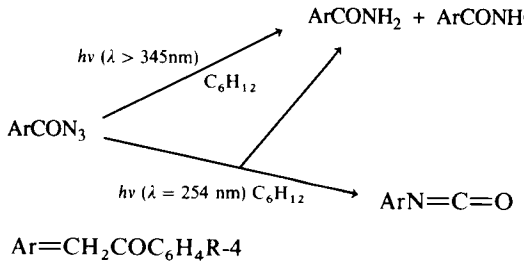
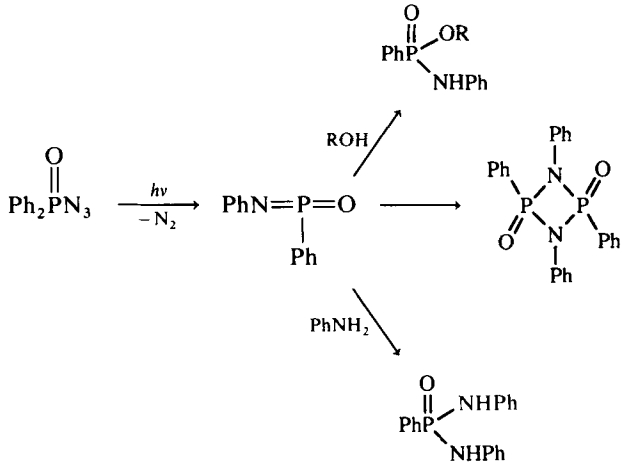
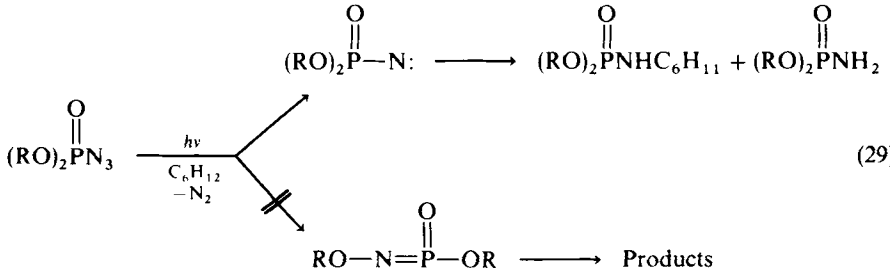


(27)

$Ar{=}CH_2COC_6H_4R\text{-}4$

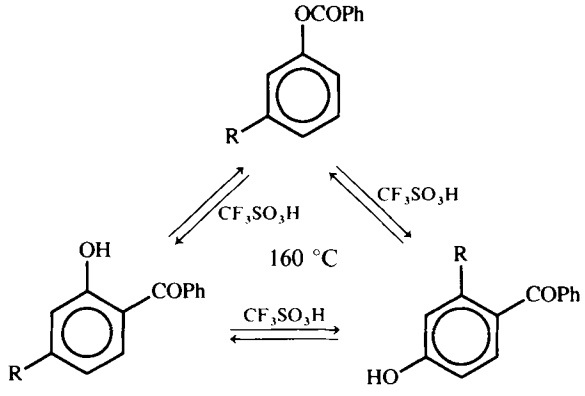


(28)



(29)

(30)



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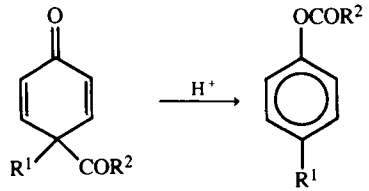
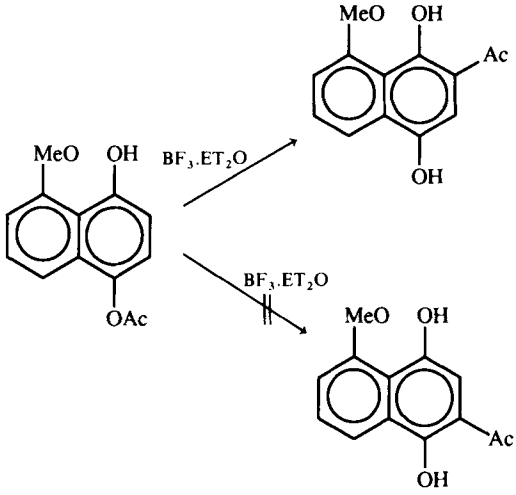


(32)

containing trifluoroacetic acid, a quantitative retro-Fries rearrangement to phenyl esters takes place instantaneously at room temperature (equation 32).

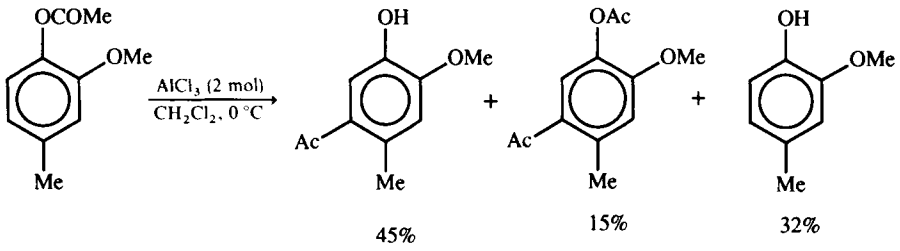
Another controversial point has been the intra- or intermolecular nature of the Fries rearrangement. The experimental evidence accumulated during the last years strongly supports the intermolecular mechanism, and there is currently general agreement on this question[72–80]. Thus, the formation in some cases of *meta*-rearranged products (equation 33) has been interpreted as resulting from intermolecular acylation at the most activated ring position[75,76,78].



(33)

A more convincing argument is the formation of ketoesters[72,78,81,82], which evidently occurs through electrophilic attack at the ring of the phenyl ester by an acylium ion arising from cleavage of a second molecule of the substrate (equation 34).

In the heterocyclic series, similar results have been obtained with 6-acetoxybenzo[*b*] thiophen[83], which undergoes intermolecular transfer of an acetyl group to give a mixture



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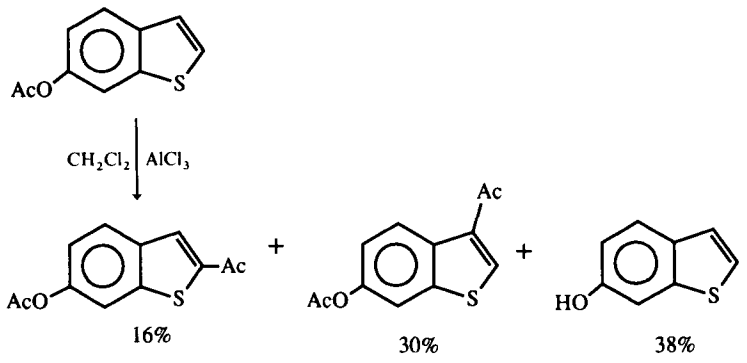
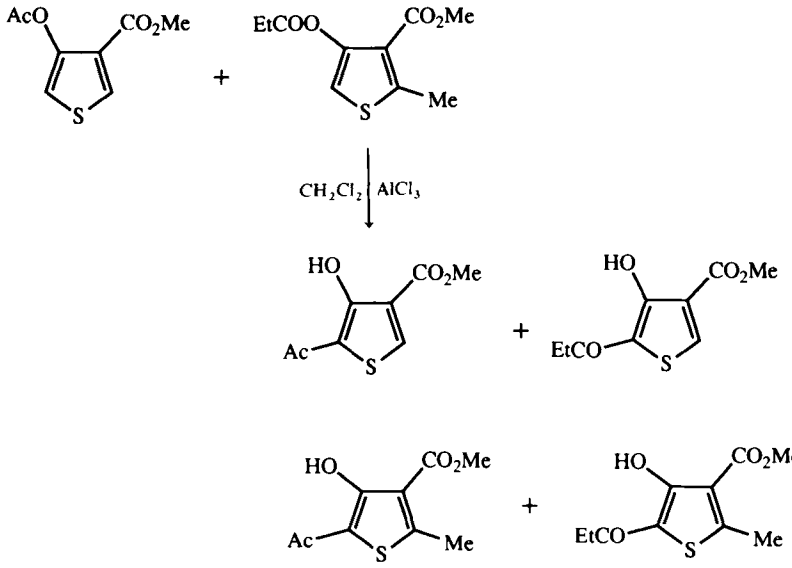


(35)

of 6-acetoxy-2- and 3-acetylbenzo[*b*]thiophens and 6-hydroxybenzo[*b*]thiophen (equation 35).

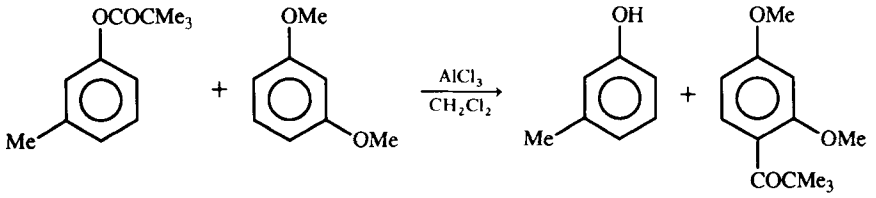
A third piece of evidence in favour of the intermolecular nature of the Fries rearrangement is the observation of mixed products in crossover experiments. Thus, treatment of a mixture of 3-acyloxythiophenes with aluminium chloride in methylene chloride has been reported[77] to give all possible mixed products in approximately equal proportions (equation 36).



(36)

Likewise, when *m*-cresyl pivalate is submitted to the conditions of the Fries rearrangement in the presence of 1,3-dimethoxybenzene, the latter compound quantitatively fixes the acylium ion formed by cleavage of the ester[74] (equation 37).

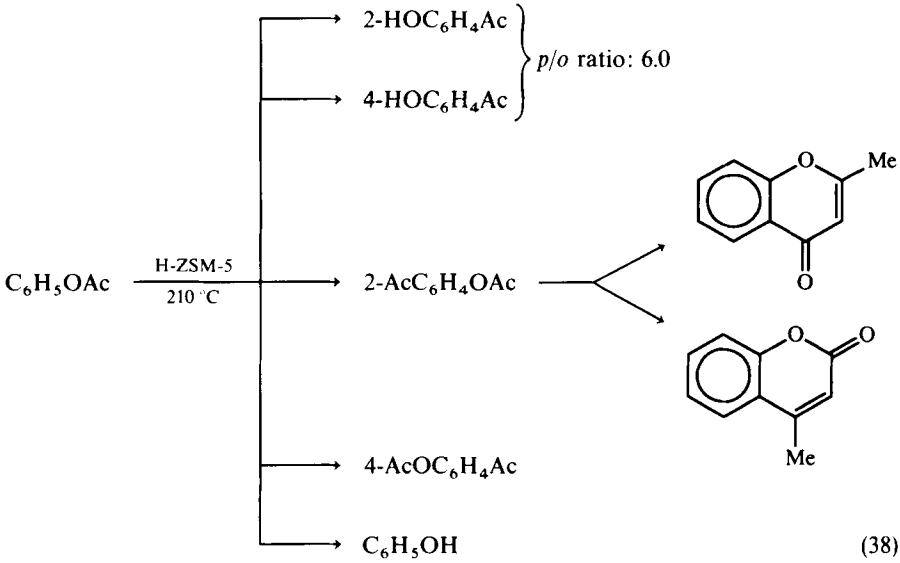
The most widely employed catalyst for the Fries rearrangement has been aluminium chloride; however, a variety of other Lewis acids ($AlBr_3$[80,84], AlI_3[85], $BF_3 \cdot Et_2O$[75,76,86,87], $ZnCl_2$[88], $SnCl_4$[74,89], $TiCl_4$[90,91], etc.) and Brönsted acids ($MeSO_3H$[88,92], CF_3SO_3H[72], polyphosphoric acid[92], etc.) have been found to be useful. Special mention is deserved by the recent introduction of solid acids to achieve the transformation[82,93,94].



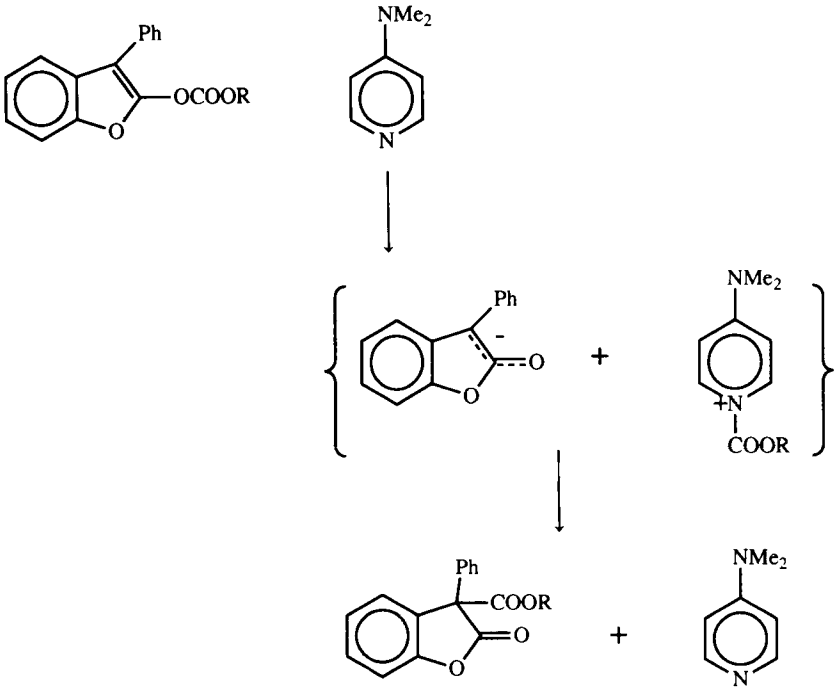
(37)

This approach has the advantage of requiring only catalytic amounts of the solid acid, instead of stoichiometric amounts. Also, the workup usually needed to decompose the substrate–catalyst complex is avoided and the catalyst is really recoverable. Thus, phenyl esters of aromatic carboxylic acids are refluxed in nitrobenzene, in the presence of small amounts of a polymeric perfluorinated sulfonic acid resin (Nafion-H) whereby a smooth conversion to *o*- and *p*-hydroxybenzophenones is achieved[93]. The workup involves filtration of the solid catalyst, extraction with aqueous sodium hydroxide and acidification. The catalyst can be regenerated without loss of activity.

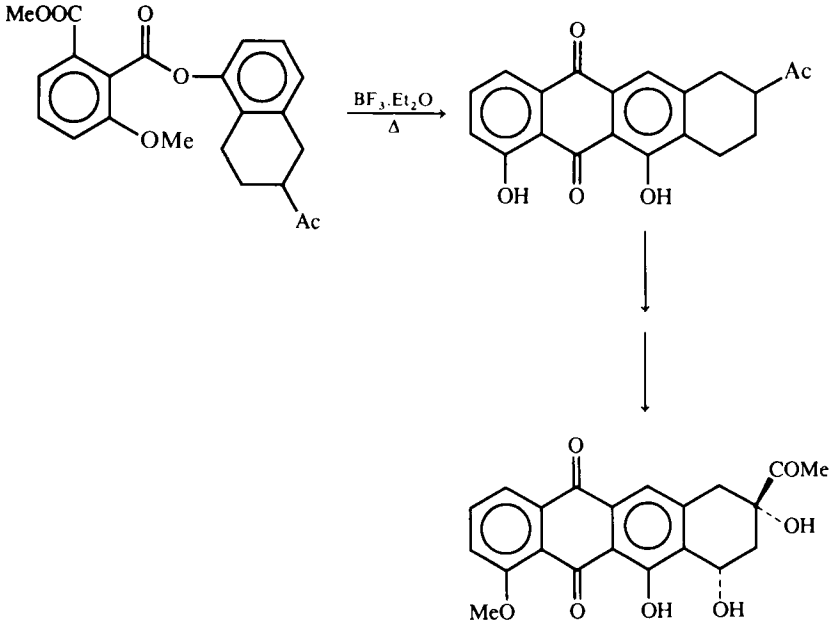
Initially[93], the reaction with acetate esters was unsuccessful; however, a more recent re-examination[82] has reported that Nafion-H does catalyse the Fries rearrangement of phenyl acetate, although the preparative yield is much lower than in the case of the analogous benzoate. In the same work[82], better results are reported for zeolite molecular sieves. Heating of a slurry of phenyl acetate with various zeolites leads to the expected *o*- and *p*-hydroxyacetophenones with a remarkable *para* selectivity (attributed to constraints of the zeolite void space), especially when the H-ZSM-5 zeolite is employed. Traces of *p*-acetoxyacetophenone, 2-methylchromone and 4-methylcoumarin are also formed, a fact that supports the intermolecular nature of the rearrangement under these conditions (equation 38).



(38)


Ph
OCOOR
O
NMe2
N
Ph
O
O
+
NMe2
+N
COOR
Ph
COOR
O
O
+
NMe2
N

(39)

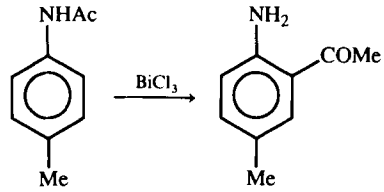

MeOOC
O
O
OMe
Ac
BF3.Et2O
Δ
O
Ac
OH
O
OH
COMe
OH
MeO
O
OH
OH

(40)

A conceptually different type of catalyst to achieve oxygen-to-carbon acyl migration in aromatic systems is 4-(dimethylamino)pyridine[95,96]. This catalyst, which has been found to be effective in benzofuranes, operates through an intermolecular mechanism involving the intermediacy of an acylated pyridinium species (equation 39).

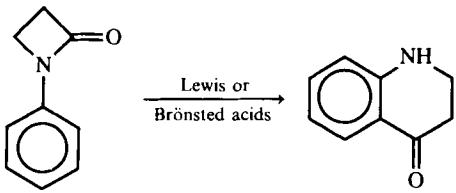
In addition to the considerable attention paid to the mechanistic aspects of the Fries rearrangement and to the introduction of alternative and more convenient catalysts, research efforts have also been directed to find new synthetic[86,97,98] or industrial[99] applications and to extend the scope of the reaction[100–102]. Among the applications, the Fries rearrangement has been used to achieve the total synthesis of the linear acylated coumarins geijerin and dehydrogeyjerin[98], to obtain selectively substituted *p*-acylcalixarenes[98] and to develop a simple and regiospecific synthesis of 11-deoxydaunomicinone[86]. The latter compound belongs to the family of anthracycline antibiotics, having a marked antitumor activity. Its synthesis is based on the BF_3-catalysed Fries rearrangement of a tetrahydronaphthyl phthalate derivative (equation 40).

Concerning the scope of the reaction, a few reports have appeared on the extension of the Fries rearrangement of phenyl esters to the analogous anilides[100–102]. Indeed, a high-yield acyl migration from nitrogen to carbon has been found to occur in *p*-toluidine upon treatment with bismuth chloride[102] (equation 41).



(41)

A similar reaction takes place in the case of 1-arylazetidin-2-ones[100,101], to afford 2,3-dihydroquinolones (equation 42). This transformation is catalysed by Lewis acids as well as by Brönsted acids.

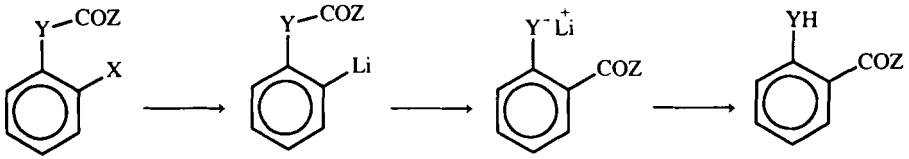


(42)

The 1,3 oxygen-to-carbon or nitrogen-to-carbon acyl migration characteristic of the Fries rearrangement can also be achieved without acid catalysis, through metallation (anionic Fries rearrangement) or photochemical activation (photo-Fries rearrangement). The mechanisms of these processes are completely different from that of the classical reaction catalysed by acids; however, the synthetic result is equivalent and therefore we deal with all these variations in this section.

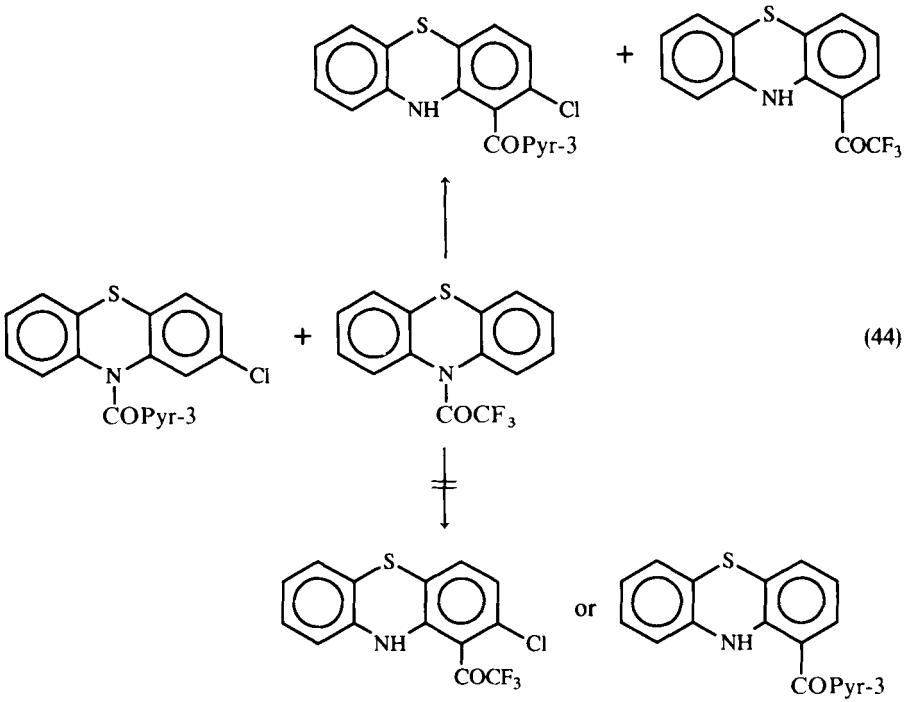
The anionic modification was first reported in 1983[103,104] and has received further attention in more recent years[105–108]. It has been applied to carbamates[103,107,108], esters[104,106] or amides[104,105], giving rise to *o*-hydroxyamides, *o*-hydroxyketones or *o*-aminoketones, respectively (equation 43).

The yields reported for the rearrangement products depend on the structure of the precursors and the reaction conditions, but values of 70–90% are rather usual. Specific features of this version of the Fries rearrangement are the complete *ortho* selectivity and



(43)

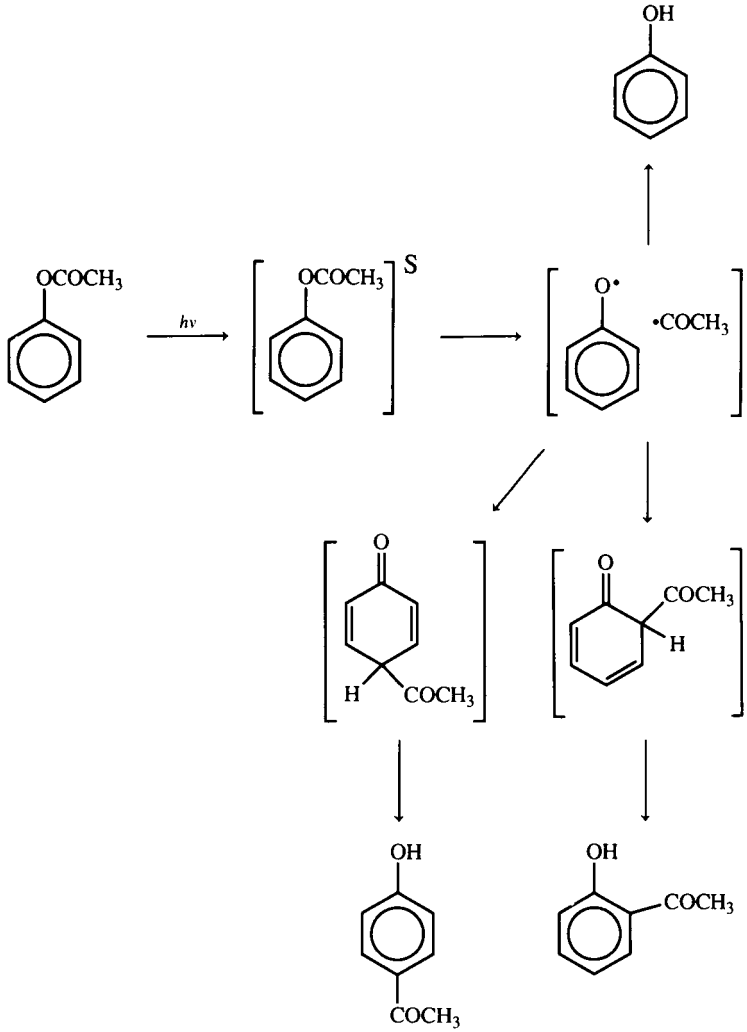
the intramolecular nature of the process, which has been proven by crossover experiments[105,106]. Thus, reaction of a mixture of *N*-acylphenothiazines with LDA at −78 °C affords none of the intermolecular reaction products (equation 44).



(44)

Concerning the photochemically induced Fries rearrangement, a considerable number of reports have appeared during the last years in connection with its mechanistic as well as synthetic aspects. Recent contributions to the understanding of the mechanism include: (a) detection of a phenoxy radical intermediate (and presumably 2- and 4-acetylcyclohexadienones) in the photolysis of phenyl acetate, by means of Raman spectroscopy[109], (b) spin trapping of acyl radicals (acetyl or benzoyl) in the photolysis of phenyl acetate, phenyl benzoate and acetanilide, using 2-methyl-2-nitrosopropane[110], (c) measurement of magnetic isotope effects and external magnetic field effects upon the photo-Fries rearrangement of 1-naphthyl acetate and its ^{13}C-carbonyl labelled analogue[111], (d) measurement of kinetic isotope effects (^{18}O at the phenolic oxygen, ^{14}C at the α-carbon and ^{14}C at the *ortho*-carbon) as well as magnetic isotope effects (^{13}C at the α-carbon) in the photo-Fries rearrangement of *p*-methoxyphenyl acetate[112], and (e) systematic studies on the actual source of hydrogen atoms leading to the formation

of phenol in the photolysis of phenyl benzoate[113]. The above contributions have confirmed that photo-Fries rearrangement occurs from an excited singlet state, through homolysis of the carbonyl–aryloxy bond, to give a radical pair enclosed in a solvent cage. Radical recombination leads to the rearranged acyl migration products, while hydrogen abstraction by the aryloxy radical leads to the formation of phenols. This is summarized for phenyl acetate in equation 45.



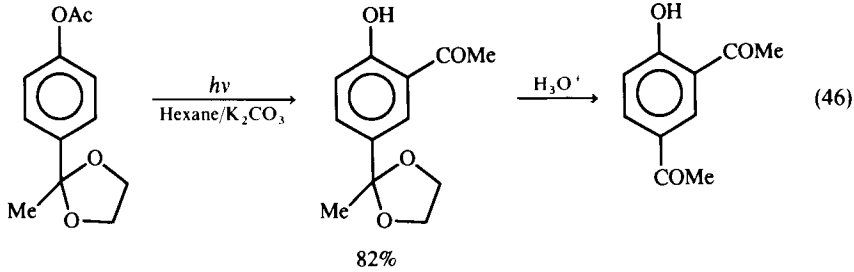
(45)

Being the prototype for geminate cage recombination and escape of relatively large molecular radicals, the photo-Fries rearrangement has attracted recent attention as a model reaction to study the influence of certain interacting added materials as modifiers of the reactivity and the selectivity. Earlier work tested this concept on the photo-Fries rearrangement of aryl esters on the surface of silica gel[114], and later work has extended this study to the analogous anilides[115], in which a slight decrease in reactivity and an

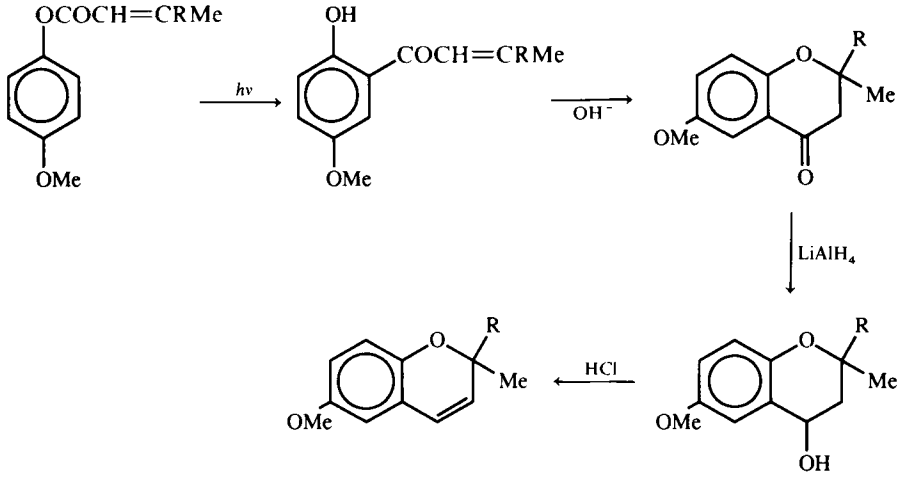
enhanced selectivity to the product of *para*-acyl migration has been associated with adsorption on silica gel. Under these conditions, crossover experiments show that the photo-Fries rearrangement of anilides is an intramolecular process[115].

Cyclodextrins have also been employed as restricted environments to carry out the photo-Fries rearrangement of aryl esters[116–119] and anilides[118,120,121]. The initial studies[116,117,120] appeared to support enhanced *para* selectivity as a consequence of cyclodextrin complexation; however, more recent reports[118,119,121] are consistent with increase in the *ortho* product, especially when β-cyclodextrin is used as complexing agent. There is no agreement concerning the magnitude of this effect and there are also some differences in the reported conversions and the isolation of undesired by-products, such as phenols (or anilines) and polymers.

Other modified photo-Fries rearrangements involve the addition of starch[117], amylose[117], sodium dodecyl sulphate[122] or potassium carbonate[123,124] to the irradiation system. The latter conditions have allowed the use of cyclic acetals as carbonyl blocking groups, in order to obtain diacylphenols[124,125]. In this way, the basicity of potassium carbonate prevents hydrolysis of the acetal moiety, circumventing the deactivating effect of the first acyl group (equation 46). Thus, the advantages of the photo-Fries rearrangement over the classical acid-catalysed process are due to the different mechanisms involved and to the mildness of the reaction conditions.



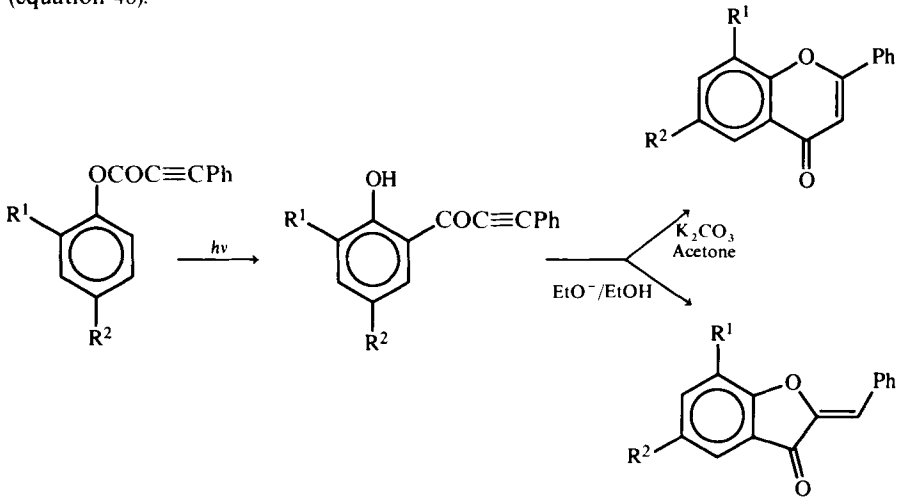
82% (46)



R = H or Me (47)

Many synthetic applications have been used for the construction of heterocyclic ring systems such as furanones[126,127], chromones[128–130], chromenes[92,131,132], flavones[133–135], aurones[135], xanthones[136–139], thioxanthones[140] or acridones[141a]. For instance, *p*-methoxyphenyl esters of α,β-unsaturated carboxylic acids undergo photorearrangement, followed by basic cyclization, to give 4-chromanones. Using a two-phase benzene/aqueous sodium hydroxide system, chromanones are directly obtained in excellent yields (82–91%). Subsequent reduction/dehydration affords 2*H*-chromenes, interesting because of their antijuvenile hormone activity[131] (equation 47).

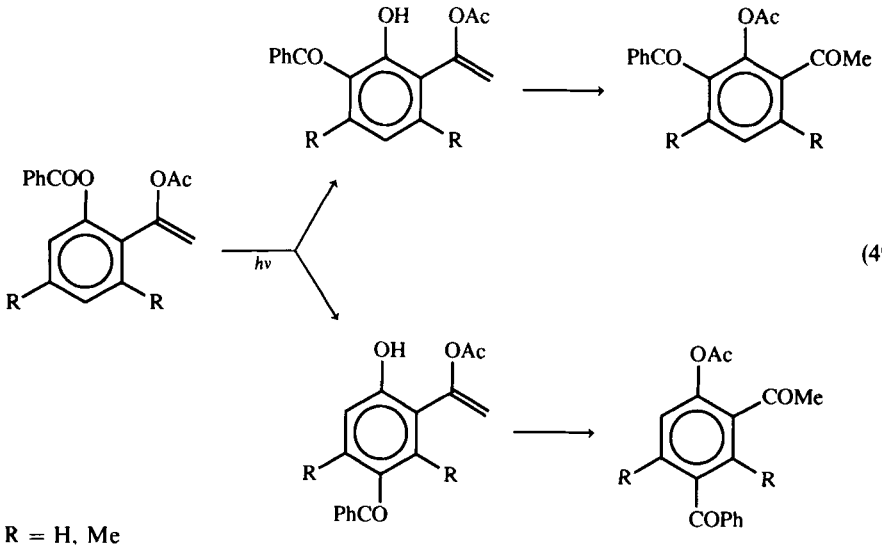
Similarly, aryl esters of phenylpropiolic acid yield *o*-hydroxyaryl phenylethynyl ketones. The mode of cyclization of the latter compounds can be controlled by changing the reaction conditions[141b]: the use of potassium carbonate in acetone favours the 6-*endo*-dig process, to give flavones, while with sodium ethoxide in ethanol the 5-*exo*-dig process becomes clearly enhanced, aurones being formed as the major products[135] (equation 48).



R^1,R^2 = H, Me, OMe (48)

The photo-Fries rearrangement has also been used for the functionalization of heterocyclic compounds, without modification of the ring system. This approach has been found to be superior, in many cases, to the Lewis acid-catalysed process, which often results in the formation of unwanted by-products. Some applications are the oxygen-to-carbon migration in acyloxy derivatives of coumarines[142], benzopyrans[143], indoles[144] and dihydrobenzofurans[145], as well as the nitrogen-to-carbon migration in benzoxazolones[146] and benzocarbazoles[147]. It is beyond the scope of this review to give details of these studies, however, those on naphthyl esters[148–150] and allenic esters[151] can be cited among the most significant work.

Finally, it is worth mentioning that the analogous photochemical 1,3 acyl migration in enol esters[152–154] and enamides[155,156] has been the subject of some publications in recent years. When the phenyl ester and enol ester moieties are part of the same molecule, the photoreactivity depends on the nature of the acyl groups[157,158]. For instance, enol acetates of *o*-benzoyloxyacetophenones undergo photo-Fries rearrangement of the aryl ester, followed by transacylation, to give diacyl derivatives (equation 49). By contrast, in the irradiation of enol acetates of *o*-acetoxyacetophenones the enol ester group cleaves first.

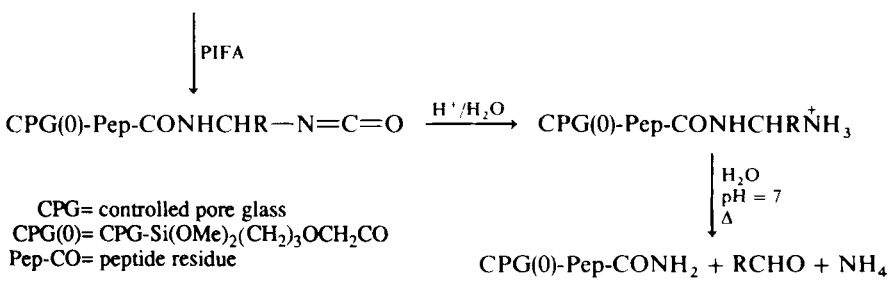


(49)

R = H, Me

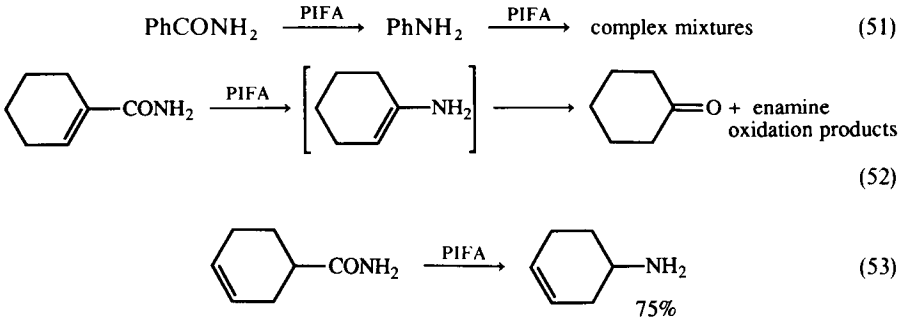
D. Hofmann Rearrangement

The classical amide-to-amine conversion has been typically carried out with sodium hypobromite (or sodium hydroxide and bromine). In the last decade *I,I*-bis(trifluoroacetoxy)iodobenzene (PIFA) has been used as an excellent reagent to achieve this transformation[159–166]. Initially, the reagent found application for the carboxyl-terminal sequential degradation of peptides, using solid-phase methodology[159,160] (equation 50).

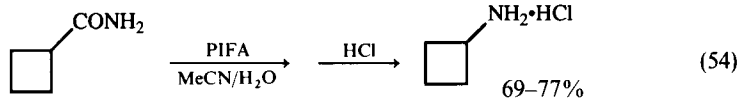


(50)

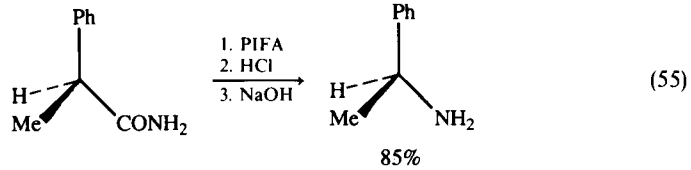
The reaction has been extended to a wide variety of primary amides (secondary and tertiary amides do not react with PIFA)[162,163]. However, aromatic amides cannot be converted into anilines by this procedure, due to the oxidizing character of the reagent, which is not compatible with the aniline functionality[162,163]. Another limitation is that the treatment of α,β-unsaturated amides does not afford the expected enamines, due to hydrolysis to the corresponding carbonyl compounds under the reaction conditions[163]. By contrast, amides containing isolated double bonds are rearranged in excellent yields (equations 51–53).



The latter examples show that PIFA is a comparatively weak oxidizing reagent, which does not attack isolated C=C bonds (as well as other labile functionalities) provided that only one equivalent of the reagent is employed. A detailed procedure for the conversion of cyclobutanecarboxamide into cyclobutylamine (equation 54) has been recently published[166].



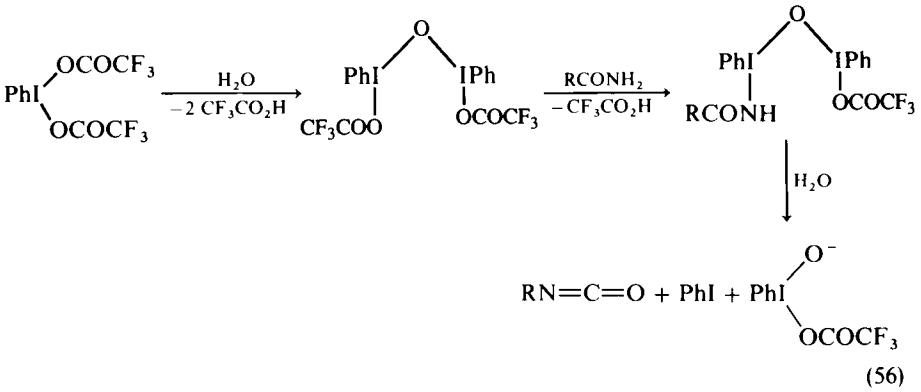
It has been established that the Hofmann rearrangement with PIFA proceeds with nearly complete stereoretention at the migrating carbon[163]. Thus, the (*S*)-(+)-amide of hydratropic acid undergoes rearrangement with PIFA, to afford (*R*)-(−)-α-phenethylamine (equation 55). The optical purity of these compounds was assessed by observing their specific rotation and also by NMR, using europium chiral shift reagents.



During the rearrangement of hexanamide, n-pentylisocyanate could be isolated from the reaction mixture in reasonable yield (29%) after *ca* 60% completion. This shows that the PIFA promoted reaction is a true Hofmann rearrangement, which is known to proceed through isocyanate intermediates. A more detailed study on the mechanism of PIFA promoted rearrangement of hexanamide[164] has allowed one to propose that the sequence of events is as follows: dimerization of PIFA, complexation of the dimer with the amide, releasing acid, and final rate-limiting rearrangement of the amide–dimer complex (equations 56 and 57).

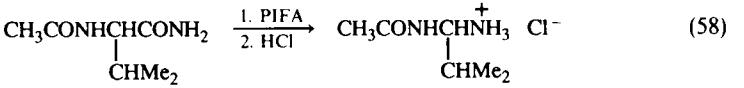
Geminal diamines are a particularly interesting class of compounds obtained from the PIFA rearrangement of the amides of α-acylaminoacids. The reaction is satisfactory for a variety of derivatives, but it does not work with cyclopropanecarboxamides, due to ring opening[165] (equations 58 and 59).

The possibility of obtaining geminal diamine products by the Hofmann rearrangement of carboxamides derived from α-amino acids has been applied to the synthesis of partially modified retro-inverso peptides[167–174]. These compounds are isomers of linear peptides

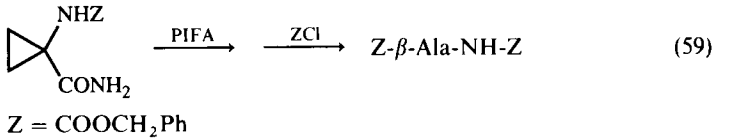


(56)

$$RN{=}C{=}O \xrightarrow[(-CO_2)]{H_2O} RNH_2 \qquad (57)$$

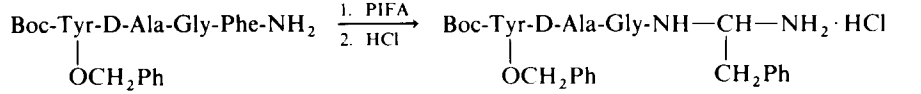


(58)



(59)

whose sequence is reversed in part. The chirality of the amino acid residues in the altered portion is reversed, but the biological activity can be maintained, due to retention of the general topochemistry of the parent molecule. Some examples are given in equations 60–63.

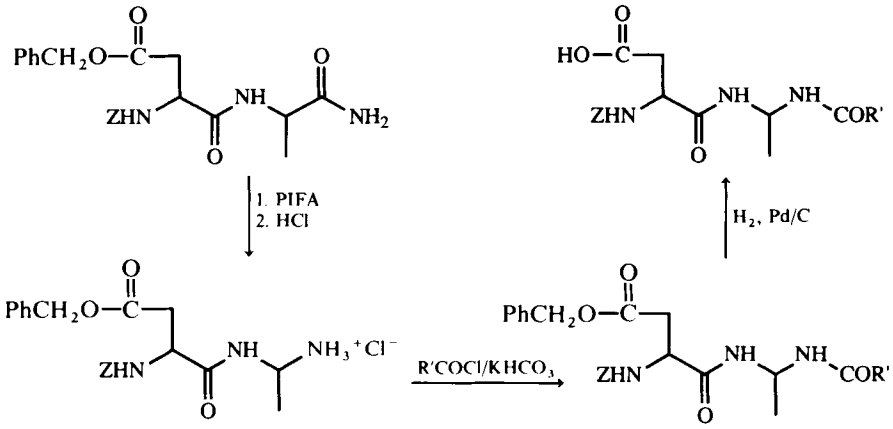


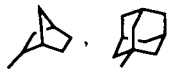
(Ref. 170) (60)

Besides PIFA, some other hypervalent iodine reagents have been used to achieve the Hofmann rearrangement. For instance, [hydroxy(tosyloxy)iodo]benzene in acetonitrile converts aliphatic primary carboxamides into the corresponding amines[175,176]. This reagent is readily available and fairly stable under ambient conditions; the progress of the reaction can be followed by the decolourization of the initially yellow solutions and the final products (alkylammonium tosylates) precipitate when the reaction mixtures are cooled[175]. The proposed mechanism of this rearrangement is indicated in equation 64.

However, the [hydroxy(tosyloxy)iodo]benzene-promoted conversion fails with benzamide, cyclopropanecarboxamide, chloroacetamide and 2-cyclopenteneacetamide. In the case of malonamide the 2-tosyloxy derivative is obtained[175].

The Hofmann rearrangement has also been achieved by means of NBS or dibromantin



R' = CMe_3, Ph,  , etc. (61)

Z = $-COOCH_2Ph$

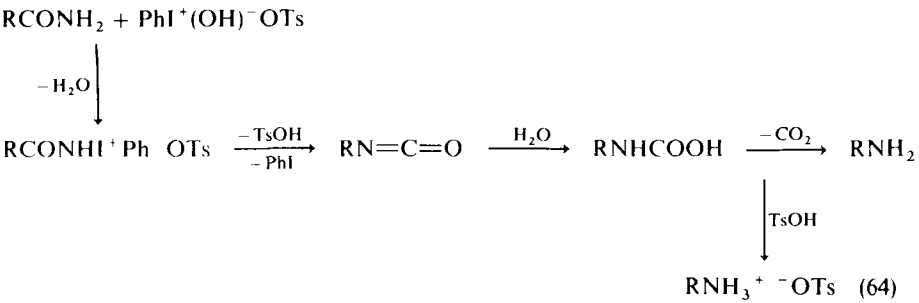
Boc-Tyr(Bzl)-Nle-NH_2 $\xrightarrow{PIFA/CH_3CN/H_2O}$ Boc-Tyr(Bzl)-gNle-H.TFA (62)

(Ref. 172)

Boc-Nle-Asp(OBzl)-NH_2 $\xrightarrow[2.\ H_2NCOCH(CH_2Ph)COOSu]{1.\ PIFA}$

Boc-Nle-gAsp(OBzl)-m(R,S)Phe-NH_2 (63)

(Ref. 174)



(64)

in the presence of mercury or silver acetate. In alcoholic solvents, carbamates resulting from trapping of the intermediate isocyanates are obtained in almost quantitative yields[177]. Another approach consists in the use of electroorganic methods, with potassium bromide as mediator[178].

An interesting modification of the Hofmann rearrangement involves phase-transfer catalysis[179–181]. Under these conditions the isocyanates can be obtained in good yield, while in the classical method these intermediates are readily hydrolysed to carbamic acids, whose spontaneous decarboxylation affords the commonly isolated amines. Thus, cyclohexanecarboxamide is converted into cyclohexyl isocyanate in 80% yield in a two-phase system, using tetra-butylammonium hydrogen sulphate to facilitate the transfer of the ionic species between the phases[179]. *n*-Alkanecarboxamides afford poor yields of the corresponding primary isocyanates, due to the formation of *N*-acylalkylureas (equations 65 and 66). This intermolecular process can be minimized by operating at high dilutions, when the yield of isocyanates increases. In the absence of phase-transfer catalyst only trace amounts of the isocyanates are obtained.

$$\text{c-HexCONH}_2 \xrightarrow[Bu_4N^+HSO_4^-]{Br_2,\ NaOH/CH_2Cl_2/H_2O} \underset{80\%}{\text{C-HexN=C=O}} \tag{65}$$

$$\text{n-HexCONH}_2 \xrightarrow[Bu_4N^+HSO_4^-]{Br_2,\ NaOH/CH_2Cl_2/H_2O} \underset{16\%}{\text{n-HexN=C=O}} + \text{N-HexC(=O)NHC(=O)NHHex-n} \tag{66}$$

While during the last years, considerable efforts have been devoted to introduce alternative reagents, the 'classical' conditions of carrying out the Hofmann rearrangement still continue to be employed, and a number of interesting applications have been found recently for the reaction[182–191]. Thus, the Hofmann rearrangement of *N,N*-disubstituted ureas affords the corresponding hydrazines in good yields[182,187] (equation 67).

$$\text{RR'NCONH}_2 \longrightarrow \text{RR'NNH}_2 \tag{67}$$

In the course of studies aimed at the synthesis of the antitumor antibiotic bleomycin, the preparation of L-2,3-diaminopropionamide with the two amino groups suitably differentiated by protection was desirable for further elaboration. This was accomplished by treatment of Boc-L-asparagine with sodium hypobromite followed by a sequence of reactions as outlined in equation 68[188].

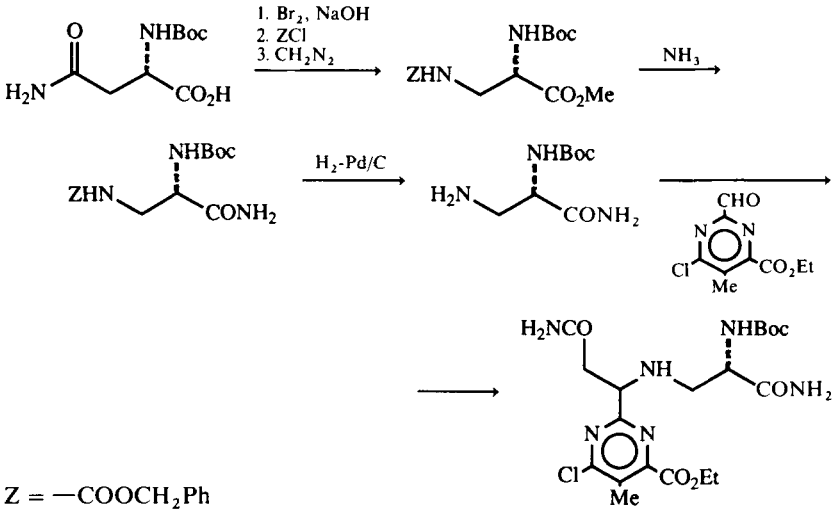
Amino substituted oxacage compounds have also been obtained by Hofmann rearrangement of the corresponding amides (equation 69).

Glutaric acid diamides, upon treatment with chlorine and subsequently with dry bases, are converted into 2,4-dioxohexahydro-1,3-diazepines[185]. However, the diesters, after enantioselective hydrolysis with pig liver esterase, can be converted into the (*R*) or the (*S*) isomer of γ-amino acids[191] (equations 70 and 71).

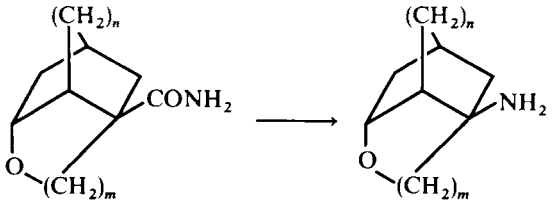
Finally, a fact that deserves a special comment is the discovery of the carbon analogue of the Hofmann rearrangement ten years ago[192]. This reaction involves deprotonation of an α-bromoketone and subsequent rearrangement with loss of bromide to afford a ketene anion, which can also be envisaged as an alkynolate ion (equation 72).

Ketene anions can be hydrolysed to the rearranged carboxylic acids or, in the presence of carbonyl compounds, act as nucleophiles to afford β-lactones or α,β-unsaturated carboxylic acids (equation 73).

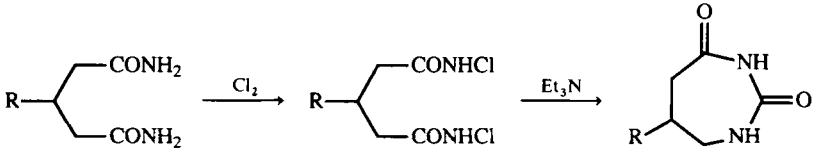
That the rearrangement involves carbon migration and not oxygen migration, was convincingly demonstrated by isotopically labelling with ^{13}C at the carbonyl carbon. Thus, it has been clearly established that this reaction parallels the Hofmann rearrangement, being formally isoelectronic with that process.


1. Br_2, NaOH
2. ZCl
3. CH_2N_2
NH_3
H_2-Pd/C
NHBoc
H_2N
ZHN
CO_2H
CO_2Me
$CONH_2$
CHO
N
Cl
CO_2Et
Me
H_2NCO
NH
Z = —$COOCH_2Ph$

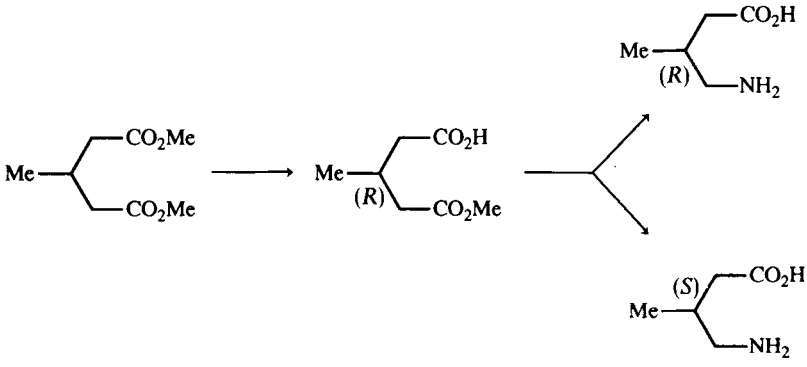
(68)


$(CH_2)_n$
$CONH_2$
NH_2
O
$(CH_2)_m$
n = 1, 2
m = 1, 2

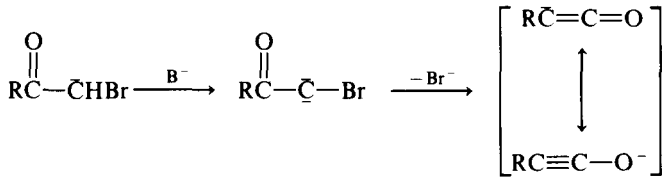
(69)


R
$CONH_2$
Cl_2
CONHCl
Et_3N
O
NH

(70)


Me
CO_2Me
CO_2H
(R)
NH_2
(S)

(71)



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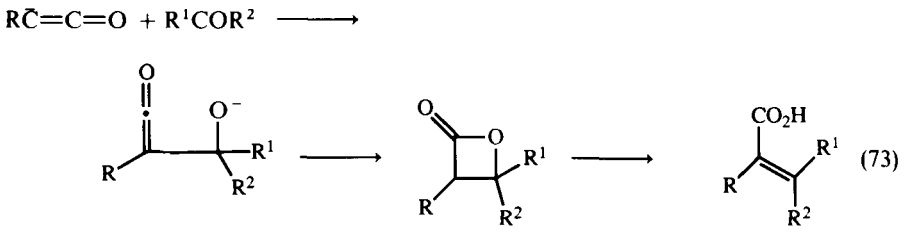
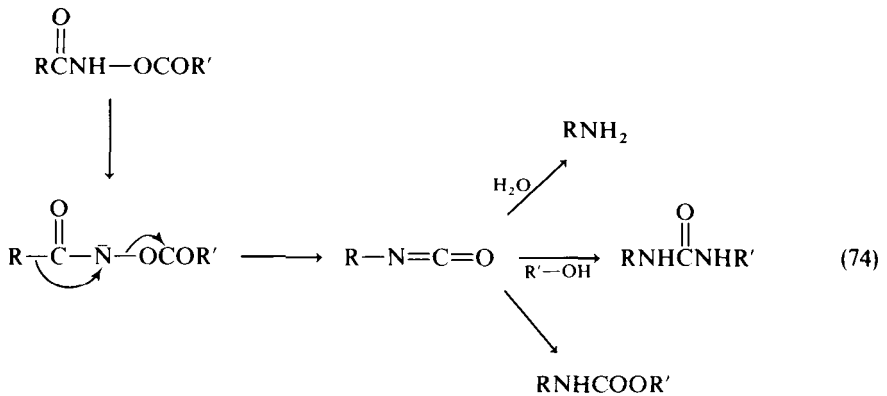


(73)

E. Lossen Rearrangement

In the Lossen rearrangement, *O*-acyl derivatives of hydroxamic acids are converted into the corresponding isocyanates, which are trapped by water or other nucleophiles present in the medium, giving rise to amines, amides, ureas or carbamates. The overall result and the mechanism of this reaction are closely related to those of the Hofmann and Curtius rearrangements; however, the scope of the Lossen rearrangement is somewhat restricted by the accessibility of the starting materials (equation 74).

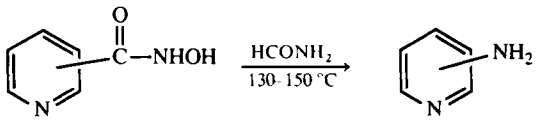


(74)

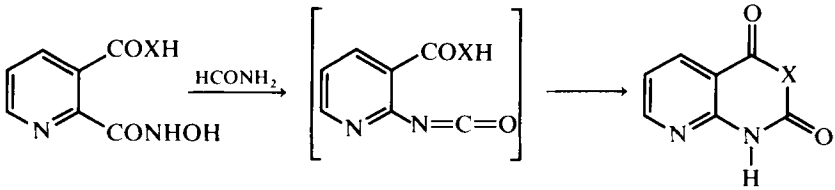
Although the reaction is usually carried out by treatment of the precursors with bases, it can also be effected thermally under neutral conditions. Thus, 2-, 3- and 4-(*N*-hydroxyaminocarbonyl)pyridines[193], as well as 4-quinolinecarbohydroxamic acid[194] directly rearrange to the corresponding amines, without a previous *O*-acylation step, just

by simple heating in formamide at about 150 °C. If a large amount of the latter is used, it is sometimes possible to obtain the *N*-heteroaryl urea.

It has been assumed that isocyanates are intermediates in the above reactions, and the formations of *N*-hydroxyquinazolinedione and benzoxazinedione have been attributed to intramolecular amino or hydroxy addition to the N=C=O group during the reaction of 2,3-bis(*N*-hydroxyaminocarbonyl)- and 2-*N*-hydroxaminocarbonyl-3-hydroxycarbonylpyridines (equations 75 and 76).



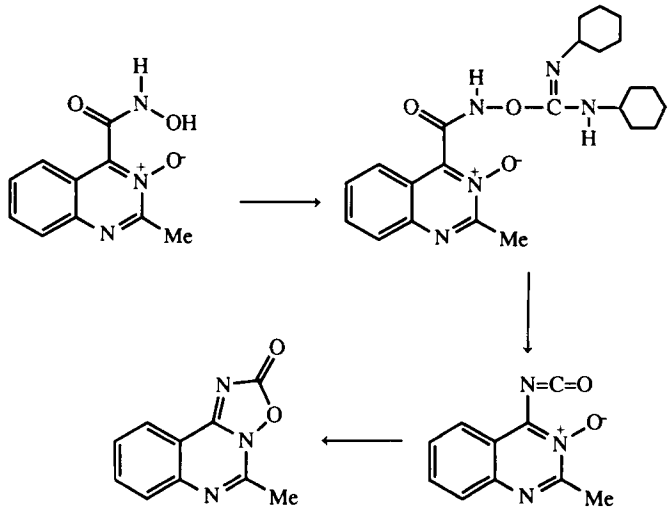
(75)



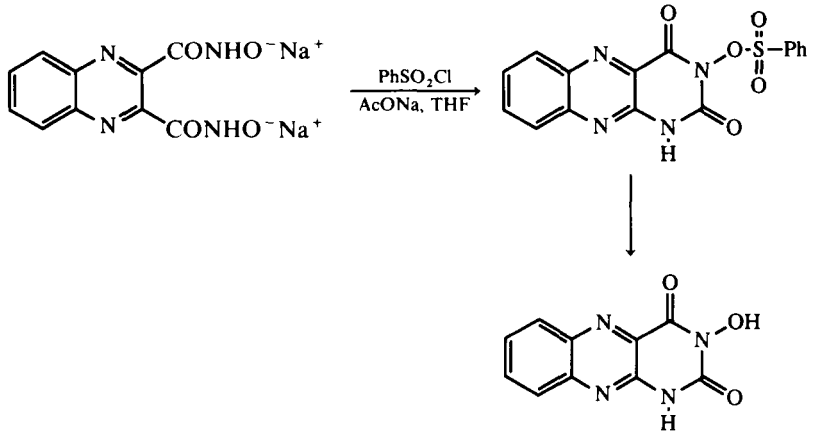
(76)

X = NOH or O

Likewise, anthranilohydroxamic acids, when heated in formamide at 100 °C, undergo a Lossen rearrangement with participation of *ortho* amino groups, to afford benzimidazol-2-ones in quantitative yields[195]. This procedure gives better results and is more convenient than the Hofmann and Curtius alternatives. In fact, the Lossen rearrangement of *O*-acyl derivatives of hydroxamic acids, followed by cyclization through intramolecular trapping of the isocyanate intermediate, has been successfully applied to the synthesis of other five- and six-membered nitrogen heterocycles comprising carbamate[196] and urea[197] moieties (equations 77 and 78).



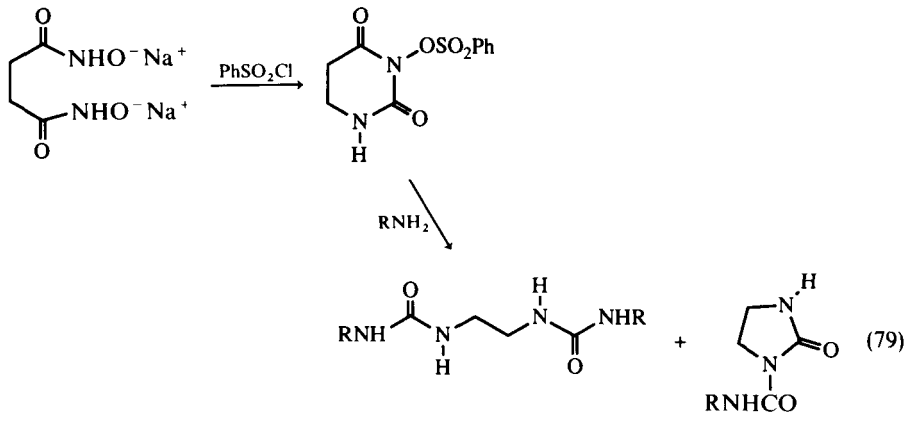
(77)



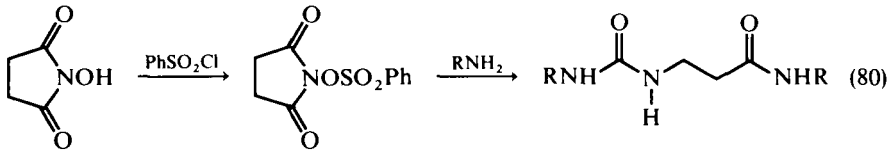
(78)

Alloxacine

Reaction of the disodium salt of succinic acid dihydroxylamide with benzenesulphonyl chloride yields 3-(benzenesulphonyloxy)-5,6-dihydrouracil[198]. This cyclic *O*-sulphonyl carbamate undergoes a second Lossen transposition in the presence of amines, to give the corresponding 1,2-bis(ureido)ethane together with 1-carboxamido-2-imidazolidone. The reaction of *N*-(benzenesulphonyloxy)succinimide to *β*-ureidopropionamide, in the presence of aniline or *t*-butylamine, provides an additional example of a Lossen rearrangement of *N*-sulphonyloxy imides without acidic hydrogens on the nitrogen atom[198] (equations 79 and 80).



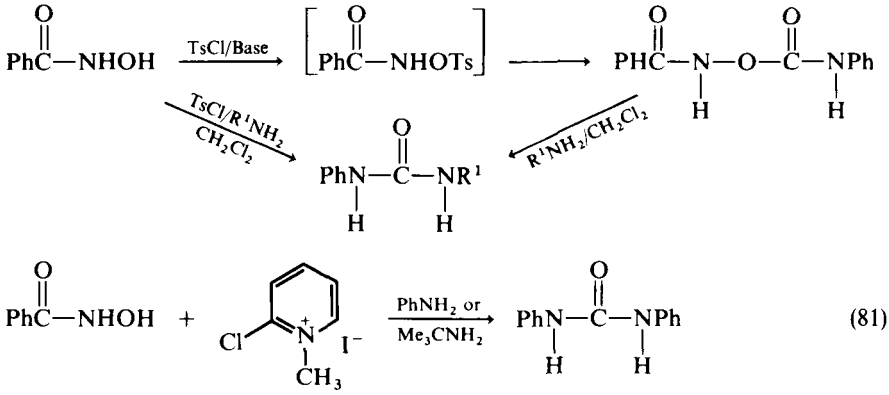
(79)



(80)

N-Phenyl-*N'*-substituted ureas are readily formed from benzohydroxamic acid by treatment with *p*-toluenesulphonyl chloride in dichloromethane in the presence of

three-fold excess of a primary amine[199]. If triethylamine is used, with or without addition of 2-chloro-1-methylpyridinium iodide, the product obtained is *N,N'*-diphenylurea. The above pyridinium salt has been claimed to be a new and efficient reagent to perform Lossen degradations. By contrast, when amines are absent, benzohydroxamic acid reacts with sulphonyl halides in basic media to afford exclusively *O*-carbamyl hydroxamic acids[199]. This product would be formed from the expected non-isolable *O*-sulphonate, which is unstable under the reaction conditions and quickly rearranges to the isocyanate. *O*-Acylation of the starting hydroxamic acid by the isocyanate would produce the observed *O*-(*N*-phenylcarbamyl) hydroxamic acid. Moreover, this compound undergoes a more conventional base-catalysed Lossen rearrangement with primary amines, to furnish *N*-phenyl-*N'*-substituted ureas (equation 81).

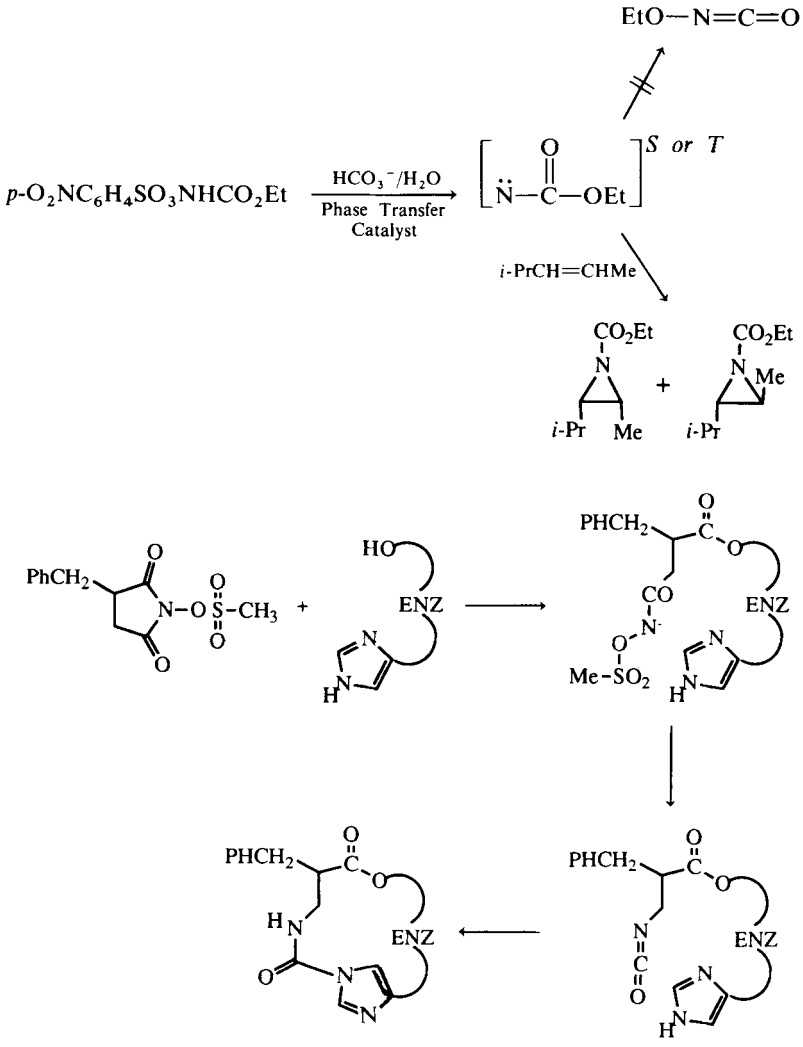


(81)

A much simpler reaction scheme operates in the treatment of aroyl chlorides with hydroxylamine-*O*-sulphonic acid in refluxing toluene, to give the corresponding arylamine[200]. Under the strong acidic conditions imposed by the reagent, it is thought that O-protonation occurs on the hydroxylamine moiety, followed by sulphuric acid elimination and carbon-to-nitrogen aryl migration. This appears to be a quite general method for the synthesis of aromatic and heteroaromatic amines, but it does not work when two strong electron-withdrawing substituents (nitro, trifluoromethyl, etc.) are attached to the migrating aromatic ring.

The reluctance of alkoxy groups to migrate in the Lossen rearrangement has been evidenced during the reaction of ethyl *p*-nitrobenzenesulphonyloxycarbamate with sodium hydrogencarbonate, using a two-phase system consisting of water and an organic solvent, in the presence of tetraalkylammonium or phosphonium halides as phase-transfer catalysts[201,202]. Under these conditions, ethoxycarbonylnitrene is generated, presumably in its singlet excited state, and can be trapped by reaction with olefines to give predominantly *N*-ethoxycarbonylaziridines (equation 82).

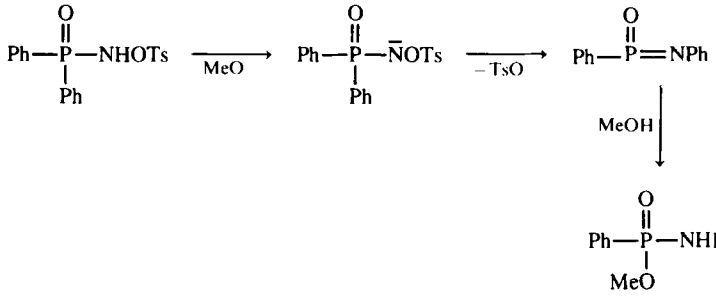
Two interesting applications of the Lossen rearrangement in the field of molecular biochemistry have been recently reported. In the first one, reaction of the labelled residue at the active centre of the bovine lung angiotensin I-converting enzyme with hydroxylamine, followed by rearrangement of the resulting hydroxamic acid, has been used to show that glutamic acid (and not aspartic acid) is the dicarboxylic aminoacid linked at this site of the protein[203]. In the second example[204–206], ^{13}C-NMR evidence has been provided in support of the fact that 3-benzyl-*N*-(methylsulphonyloxy)succinimide, an irreversible inhibitor of α-chymotrypsin and human leukocyte elastase, undergoes an enzyme-induced Lossen rearrangement, which is responsible for its inactivation. These



results are in line with those discussed above for *N*-substituted succinimides, albeit here two isomeric Lossen rearrangement products are possible (equation 83).

Finally, a heteroaromatic version of the Lossen reaction for *O*-sulphonyl derivatives of *N*-phosphinoyl hydroxylamines has been recently developed[207,208]. Thus, *N*-(diphenylphosphinoyl)-*O*-sulphonylhydroxylamines undergo a rapid and quantitative rearrangement with sodium methoxide, *t*-butylamine or aniline-triethylamine, to give *N*,*P*-diphenylphosphoamidates or phosphonic diamides. Substituents have a rather large effect on the migratory aptitude of the aromatic ring, increased by the presence of electron-releasing groups[209]. Alkyl groups are much less prone to intervene in this type of phosphorous-to-nitrogen migration[210], albeit it has been reported[211] that benzyl can migrate in the Lossen-like transposition of phosphinoyl hydroxylamines. Likewise, the *O*-(diphenyl)phosphinoyl analogue undergoes a Lossen-like rearrangement when treated

with *t*-butoxide ion, to afford the phosphonamidic-phosphinic mixed anhydride[212]. Although the mechanism of this transformation has not yet been established, it is thought to proceed *via* monomeric metaphosphonimidates, arising by neutralization of the acidic proton attached to nitrogen, followed by sulphonate or phosphinate elimination and rearrangement in a concerted manner (equation 84).



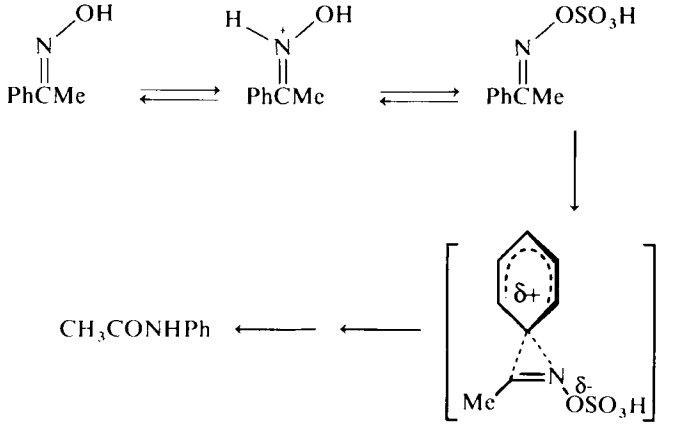
(84)

II. REARRANGEMENTS LEADING TO CARBOXYLIC ACIDS OR THEIR DERIVATIVES

A. Beckmann Rearrangement

A comprehensive review has been published on the acid-promoted Beckmann reactions, with almost 700 references, covering most of the literature up to 1983[213]. Besides the isomerization of oximes to amides, other transformations of oximes such as elimination–addition, fragmentation and rearrangement–cyclization processes are also discussed therein. In the present section we will deal mainly with more recent transpositions of oximes and related compounds to amides, including the photochemical version of the Beckmann rearrangement, not reviewed by Gawley[213].

It has been established in a study on the Beckmann rearrangement of acetophenone oxime in concentrated sulphuric acid, using ^{1}H NMR[214], that the postulated oxime *O*-hydrogensulphate is in fact the reactive intermediate, while hydrolysis of the oxime is not a competing reaction under these conditions. On the other hand, the ^{14}C kinetic isotope effect at the phenyl $C_{(1)}$ reflects bond changes in the rate-determining transition state, giving evidence of the concerted nature of the rearrangement[214]. (Equation 85).



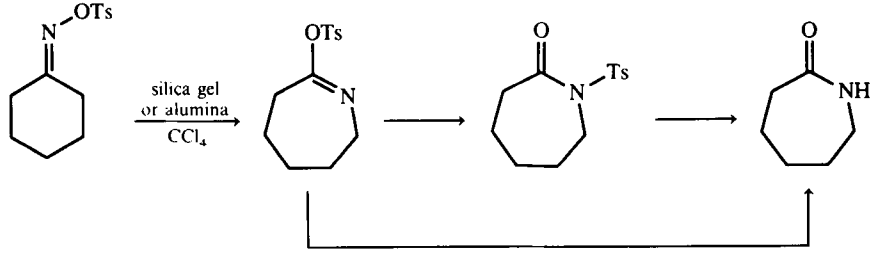
(85)

This conclusion is in agreement with the substituent effects found in the sulphuric acid mediated rearrangement of a series of *meta*- and *para*-substituted acetophenone oximes, which indicates the lack of a resonance-stabilized positive charge in the transition state[215]. However, sulphonation of the aromatic ring under these conditions can be the preferred process in other ketones having aryl substituents, as in the case of 1-phenyl-2-propanone oxime[214].

By contrast, the relative rearrangement rates of substituted aryl[216] and benzyl[217] groups within a series of oxime picrates of methyl ketones show that the migrating moiety possesses a high partial charge as compared to similar aryl and benzyl shifts in the Curtius and Lossen rearrangements. On the other hand, from the determination of migratory aptitudes of *exo* and *endo* 2-norbornyl[217] cycloalkyl, β-, γ- and δ-branched alkyl, as well as polycyclic bridgehead groups, in methylketoxime *O*-picrates, it has been concluded[218] that only small geometrical changes occur at the central carbon atom of the migrating group, thus resembling a pentacoordinated carbonium ion rather than a planar carbenium ion. Due to this non-planar structure around the migrating centre in the rate-determining transition state, a vertical stabilization[219] by positive charge delocalization through the σ-bonds at the β-position is thought to play a significant role. This non-classical kind of stabilization would justify the remarkable increase of the reaction rate with the β-substitution in the migrating group (equation 86 on facing page).

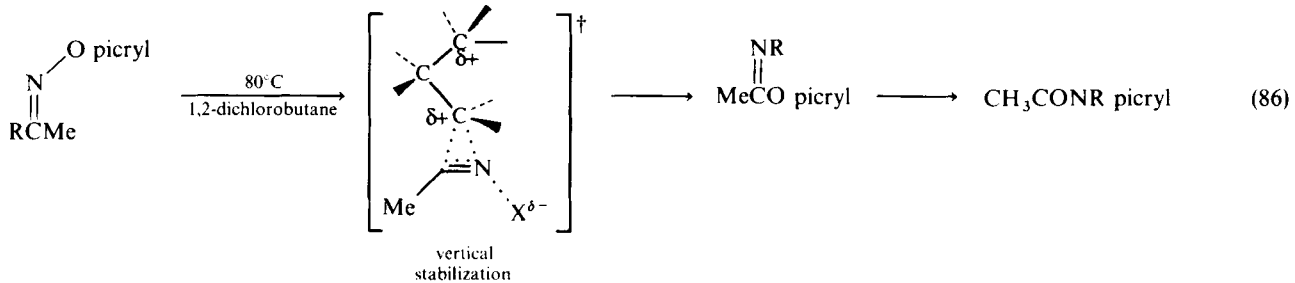
Based on the relationship between reaction rate constants and solvent polarity, the rearrangement of *O*-2,4,6-trinitrophenyl ketoximes has been proposed as a test reaction to build up an empirical solvent polarity scale, where the main factor responsible for the observed effects is the polarizability of the solvent[220]. Aliphatic polycyclic bridgehead groups have been tested as migrating groups to minimize the specific solvent solvation.

The above transformations of oxime picrates[216–220] belong to the Chapman variant of the Beckmann rearrangement. In this class, the mechanism involves an initial rate-determining isomerization of the *O*-substituted oxime to the corresponding imidate, which then undergoes a fast oxygen-to-nitrogen transposition to afford an *N*-substituted amide (Chapman rearrangement), whose hydrolysis occurs during the workup. Alternatively, the imidate itself may be the hydrolysed species[213]. Besides oxime picrates, the Chapman mechanism is also assumed to operate in most of the rearrangements of *O*-sulphonyl oximes. Thus, in the reaction of *O*-tosyl cyclohexanone oxime the *N*-tosyl caprolactam was detected by IR spectroscopy[221] (equation 87).



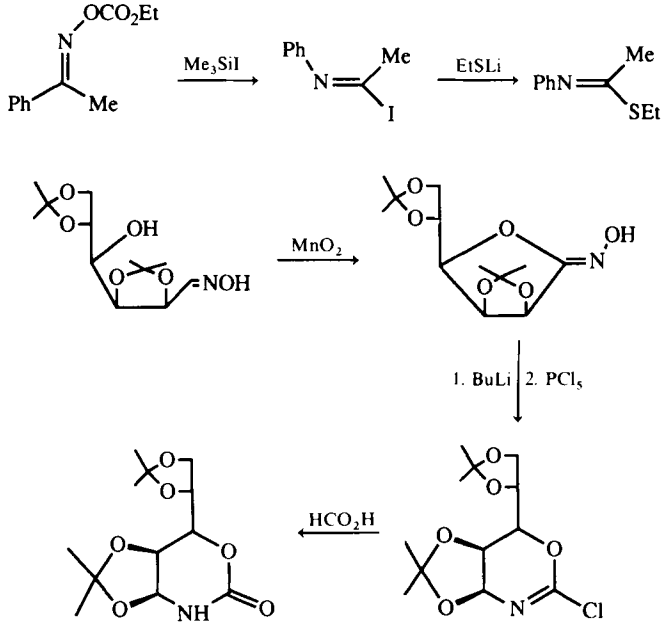
(87)

Rearrangement of oxime sulphonates by trimethylsilyl iodide constitutes an efficient procedure for the preparation of imidoyl iodides, which are versatile synthetic intermediates[222] (equation 88). A similar reaction scheme operates in the transposition of the hydroximinolactone generated by oxidation of diisopropylidenemannose oxime (equation 89). This monosaccharide derivative reacts with butyllithium and phosphorus pentachloride to furnish a chlorodihydrooxazine, which can be hydrolysed by acid to the corresponding carbamate[223].



(86)

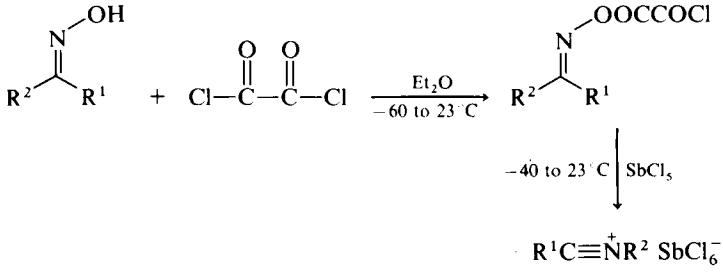
R	n-Pr	n-C_5H_{11}	1-ethylpropyl	1,1,2,2-tetramethylpropyl	1-methyl-1-propylbutyl	1-ethyl-1-propylbutyl
$k \cdot 10^5$ (s^{-1}) 80 °C	0.847	0.672	87.7	888	368	1040



(88)

(89)

Another general mechanism of the Beckman rearrangement involves free nitrilium ions as reaction intermediates. Treatment of *N*-chloroimines[213,224], *O*-chloroformyl[225] and *O*-(trichloromethoxy)formyl[225] ketoximes with antimony pentachloride leads to the formation of nitrilium salts. Furthermore, it has been reported that *O*-chlorooxalyl ketoximes, readily prepared from oximes and oxalyl chloride, react with antimony pentachloride to give pure nitrilium hexachloroantimonates in high yields[225]. In fact, nitrilium salts have been recognized to be a type of reaction intermediate common for the Beckmann, Bischler—Napieralski, von Braun, Ritter and Schmidt reactions[226] (equation 90).



(90)

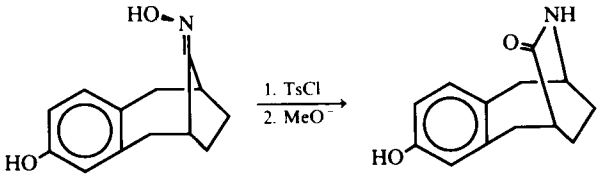
R^1 = Me Me Ph Me
R^2 = Me Ph Ph Tol

It is known that the Beckmann rearrangement of ketoximes proceeds in a stereospecific fashion if the experimental reaction conditions preclude interconversion between the oxime stereoisomers. The key step involves carbon-to-nitrogen migration of the substituent *anti* with respect to the leaving group. Thus, resolution of racemic mixtures

of chiral cyclohexanone oximes by complexation with an optically active host has allowed one for the first time to perform the Beckmann rearrangement of optically active oximes (ee > 79%) to optically active ε-caprolactams (80% ee)[227].

In spite of its stereospecificity, the Beckmann rearrangement has not been extensively used in the synthesis of complex molecules. This is mainly due to the impossibility of controlling the geometry of the oximes, and to the difficulty of isolating both *Z* and *E* isomers and the necessary waste of one of them. In this context, regioselective alkylation of dianions in acetaldehyde oxime[228] can furnish stereochemically pure *Z* aldoximes. Further alkylation of aldoximes with two equivalents of butyllithium and alkyl iodide affords ketoximes. However, this method has only been applied to obtain symmetrically substituted oximes.

On the other hand, separation by means of hplc on silica gel of the *syn* and *anti* 2-hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene allows one to perform the Beckman rearrangement of pure stereoisomers[229,230]. Treatment of the *syn* or *anti* oximes with *p*-toluenesulphonyl chloride in pyridine affords stereoselective 8-hydroxy- or 9-hydroxy-2,5-ethano-3-benzazocine systems, respectively (equations 91 and 92).



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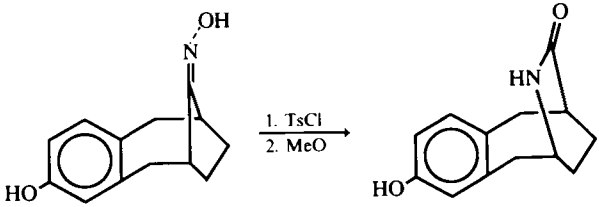
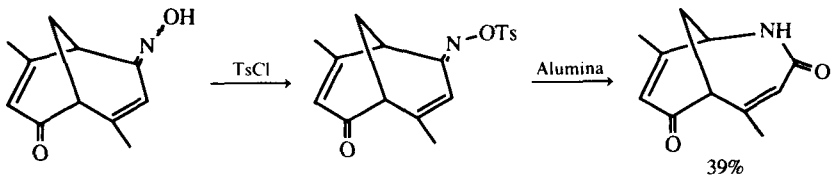


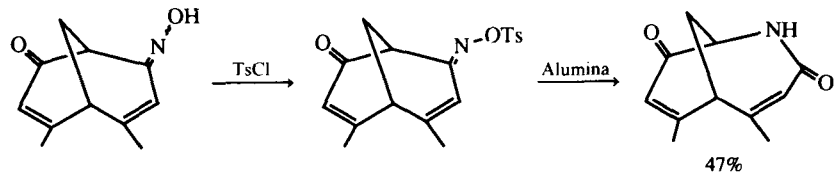
(92)

It has been reported[231] that mixtures of the *syn* and *anti* oximes of symmetrical dimethylbicyclo[3.3.1]nonadiene-2,6 or 2,8-diones, which do not undergo the Beckmann rearrangement with either polyphosphoric acid or phosphorus pentoxide, react with *p*-toluenesulphonyl chloride in pyridine to furnish the *O*-tosyl derivatives. These oxime tosylates rearrange over alumina to afford a single lactam, arising from migration of the bridgehead carbon. This selectivity has been explained by the preferential formation of the *syn* rather than the *anti* *O*-tosyl oxime, due to higher steric hindrance in the latter (equations 93 and 94).

By contrast, the Beckman transposition of the *Z* and *E* oximes of 2,2-dimethyl-2,3-dihydropyran-4-one derivatives in polyphosphoric acid gives rise to the same lactam, irrespective of the configuration of the starting oxime[232]. This result is consistent with the known reluctance of cyclohexenone oximes to undergo stereospecific Beckmann rearrangement[213]. It is generally assumed that the preferential migratory aptitude of the alkyl over the alkenyl group determines that the *Z* oxime reacts faster than its *E* isomer, equilibration between the stereoisomeric oximes taking place prior to the rearrangement. A similar behaviour is observed in the case of the *Z* and *E* oximes of 2-aryl-4,5,6,7-tetrahydro-6,6-dimethyl-2*H*-benzo[*d*]-1,2,3-triazol-4-ones and 4,5,6,7-tetrahydro-6,6-di-

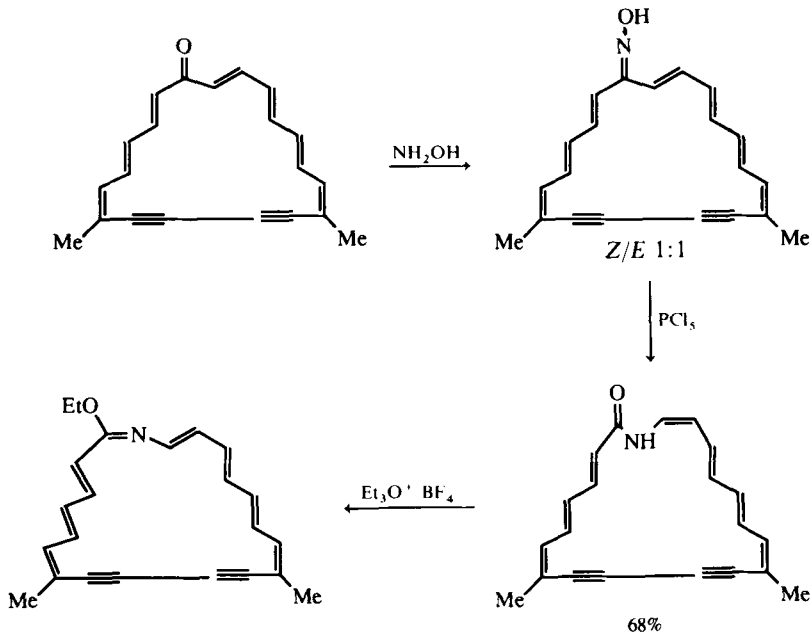


(93)



(94)

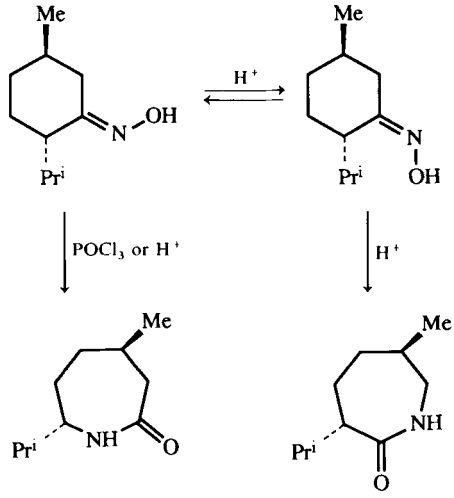
methylbenzo[*c*]-1,2,5-oxadiazol-4-ones[233]. Nevertheless, the ability of trigonal carbon centres to migrate to electron-deficient nitrogen is exemplified in the synthesis of aza[*n*]anulenes (n = 14, 16, 18, 20 or 22) from the appropriate annulenones by nitrogen insertion[234] (equation 95).



(95)

The lack of stereospecificity during the Beckman rearrangement is accepted to be due to thermodynamic equilibration between the stereoisomers prior to the rearrangement. This process results from attack of the catalyst at the nitrogen, while transposition requires interaction of the catalyst with the oxygen of the hydroxylamine moiety. In general, protic acids are much more prone to produce non-stereospecific Beckmann rearrangements.

An interesting example of the role of the catalyst is the rearrangement of (−)-(1*R*,*trans*)-*p*-menthan-3-one (*E*)-oxime[235]. Phosphorus oxychloride effects the rearrangement in a highly stereospecific way, with migration of the group *anti* to the leaving group, while catalysis by protic acids leads to a mixture of the two isomeric lactams. Evidence for the oxime isomerization was obtained by isolating the *Z* isomer from the reaction mixture (equation 96).

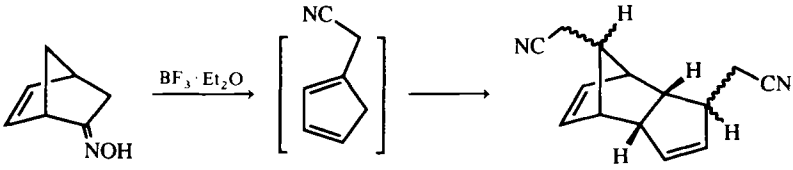


(96)

Of course, there are instances where the rearrangement takes place stereoselectively, even under conditions favourable to interconversion between the oxime stereoisomers. Such is the case of Δ^4-6-hydroxyimino steroids, which have been found to possess an *anti* configuration of the oxime group[236]. A re-investigation[237] has shown that the olefinic group migrates preferentially to the alkyl group using a variety of catalysts, including those that ensure *syn–anti* equilibration.

Another re-examination[238] has shown the inaccuracy of earlier intriguing observations on the totally regioselective bridgehead nitrogen insertion upon rearrangement of the oxime of bicyclo[3.2.1]octan-2-one by using benzenesulphonyl chloride/sodium hydroxide, together with completely regioselective methylene migration upon reaction of the bicyclic ketone with hydroxylamine hydrogen sulphate in sulphuric acid. In fact, mixtures of the two possible isomeric lactams, arising from bridgehead and methylene migration, are formed under both sets of reaction conditions.

Likewise, conflicting reports on the rearrangement of bicyclo[2.2.1]heptan-2-one systems has led to some uncertainty about the conditions of fragmentation versus rearrangement and the actual structure of the resulting lactams. It has been recently reported[239] that a mixture of *syn* and *anti* 5,6-dehydronorcamphor oximes undergoes Beckmann fragmentation and dimerization of the intermediate cyanomethylcyclopenta-1,3-diene isomers. However, this[239] and another complementary study[240] have shown that rearrangement to the bridgehead migration lactam can be successfully achieved, maintaining functionalization at the 5,6 positions, by masking the double bond as *cis–exo* diol acetonide (equations 97 and 98). It appears that the olefinic double bond favours the fragmentation pathway by allylic stabilization of the carbocation intermediate or, alternatively, the dioxolane ring may alter the bicycloheptane conformation, which is thought to play an important role in the course of the reaction. On the other hand, the



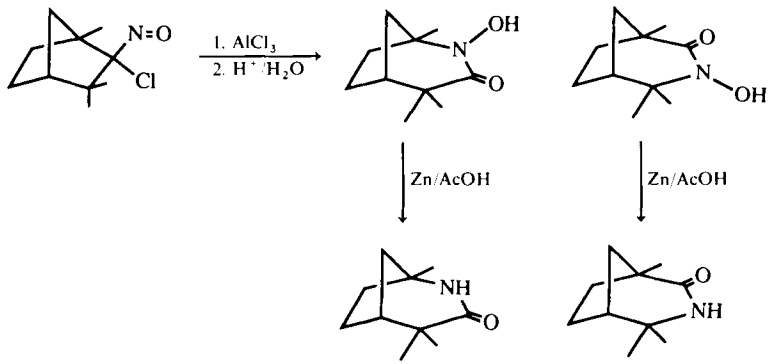
(97)

Mixtures of dimers

(98)

regioselectivity observed has been explained by *syn–anti* equilibration of the oxime. Both the Beckman and Schmidt rearrangements leading to nitrogen insertion in bridged bicyclic ketones have been exhaustively reviewed[241].

Regarding the competition between fragmentation and lactam formation in the terpene series, it has been reported[242] that some α-chloro-α-nitroso derivatives, easily accessible by chlorination of the corresponding oximes, give rise to amides which are not obtainable by direct acid treatment of the oxime. Examples of this variant of the Beckmann rearrangement are the reactions of 2-chloro-2-nitrosofenchane, 2-chloro-2-nitrosocamphane and 2-chloro-2-nitrosothujane with aluminium chloride or dimethylaluminium chloride, followed by hydrolysis with dilute sulphuric acid, which furnish hydroxamic acids. Reduction of the latter with zinc in acetic acid yields the desired lactams. Apparently, there is no relationship between the *endo/exo* ratio of the starting 2-chloro-2-nitroso compound and the regioselectivity of the reaction, quaternary carbon atoms being the only groups capable of migrating. These results point to a stepwise mechanism involving C—C bond rupture to generate stable carbocations (equations 99–101).



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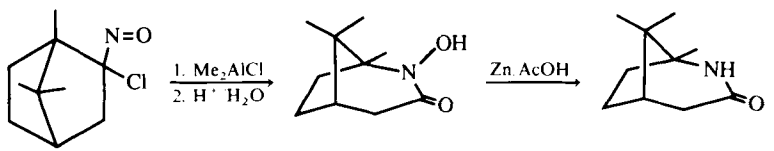

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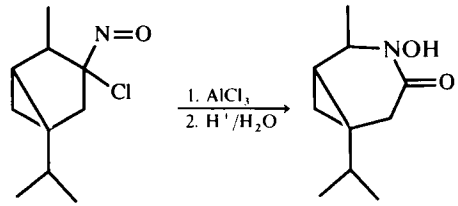
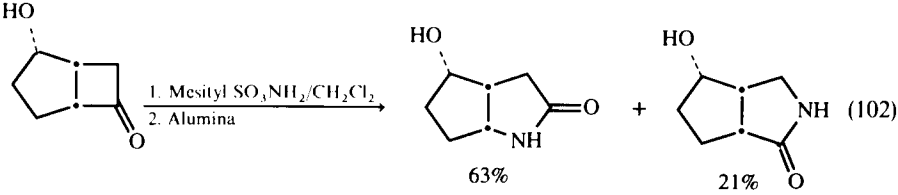


(101)

A large variety of Brönsted and Lewis acids have been employed to effect the Beckmann rearrangement[213]. Among them, phosphorous pentachloride, phophorus pentoxide and polyphosphoric acid are still the most popular. Due to its low viscosity and high solvent power, trimethylsilyl polyphosphate, readily prepared by refluxing phosphorus pentoxide with hexamethyldisiloxane in an inert solvent, has been found to be a more convenient medium than polyphosphoric acid for performing the Beckmann rearrangement at room temperature[243]. Thionyl chloride, methanesulphonyl chloride, benzenesulphonyl chloride and *p*-toluenesulphonyl chloride are also common reagents for the process. In the last case, the reaction can be carried out without isolation of the intermediate O-tosyl oxime, by simple adsorption of the substrates on chromatographic alumina, followed by elution of the reaction mixture[231,237]. Treatment of oximes with arylsulphonyl chlorides is specially convenient when oxime fragmentation or cyclization processes compete with rearrangement[244].

Boron trifluoride in tetrachloroethane has been used for regioselective nitrogen insertion into bicyclic ketoximes[238-240]. More recently, aluminium triiodide in acetonitrile has been found to be an efficient reagent to prepare anilides via Beckmann rearrangement and also for the dehydration of aldoximes to nitriles[245]. Direct treatment of ketones with hydroxylaminesulphonic acid[246-248] or *O*-mesitylenesulphonylhydroxylamine[249] can effect the Beckman rearrangement, without isolation of the corresponding oxime derivatives. In the case of hydroxylaminosulphonic acid, it has been shown that the oxime is not an actual reaction intermediate, since a different product distribution is obtained starting from the sulphonyl oxime under similar conditions. Instead, a mechanism involving rearrangement at the initial tetrahedral carbinolamine with synchronous elimination of sulphuric acid has been proposed.

On the other hand, it has been found that the presence of two chlorine atoms attached at the α-position of the ketone functionality decreases the migratory aptitude of the α-group in the reaction of cyclobutanones with *O*-mesitylenesulphonylhydroxylamine. Taking into account the easy removal of chlorine, this observation provides an example of stereoelectronic control on the regioselectivity of this modified Beckmann rearrangement[249] (equations 102 and 103).



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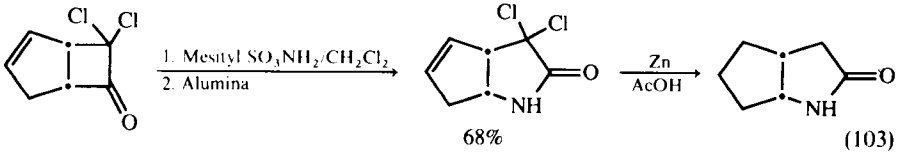
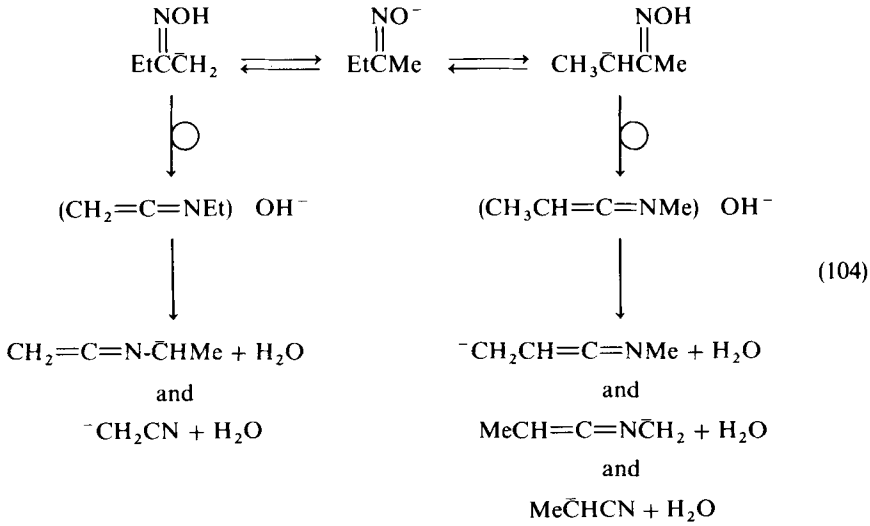


(103)

The Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam, one of the most important fibre precursors, is a multi-ton industrial process of high economic relevance. Since oleum is usually employed to perform this transformation, previous neutralization at the separation stage is required, whereby 2.3 ton of ammonium sulphate per ton of lactam are unavoidably formed as by-product. In order to circumvent this problem, considerable effort has been devoted to introduce solid acids as recoverable heterogeneous catalysts. Synthetic H-ZSM-5 and HY zeolites have been found to be promising materials[250]. In this case, ε-caprolactam is accompanied by minor products arising from hydrolysis and fragmentation of the oxime, together with dehydrogenation products. Studies in vapour[251] and liquid[252] phase have established that the rearrangement occurs exclusively on strongly acidic sites, and that the efficiency of the zeolite increases with the framework silicon-to-aluminium ratio. Similar conclusions about the acidity requirements have been reached employing mixtures of aluminium orthophosphate and γ-alumina as catalyst[253].

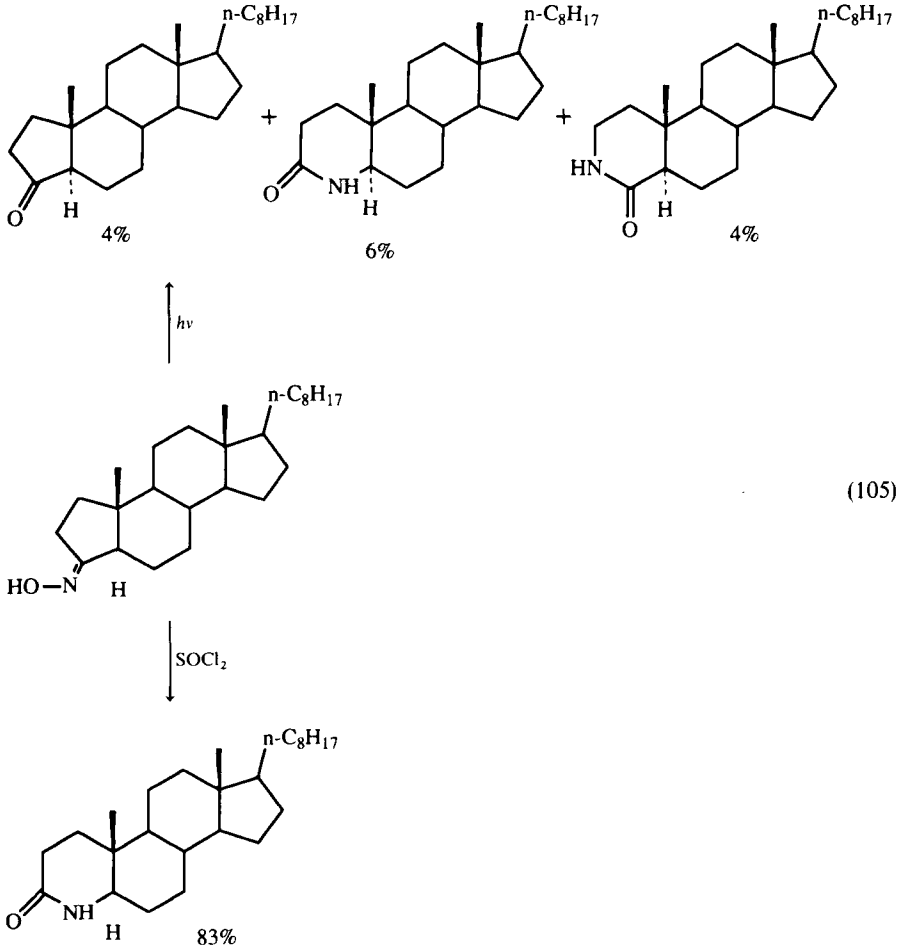
Evidence for a gas-phase thermal Beckmann rearrangement of 2-acetoxy-4-methoxyphenyl 2-thienyl ketone oxime in mass spectrometry at 220 °C prior to ionization has been recently obtained[254]. Ketoximes and aldoximes also rearrange stereospecifically under chemical ionization mass spectrometry conditions[255,256]. Likewise, labelling studies of collisional activation and collisional activation-charge reversal mass spectrometry provide strong support for the fact that deprotonated ketoximes, ketoxime ethers and aldoximes undergo a negative ion Beckmann rearrangement in the gas phase[257] (equation 104).



(104)

A different way of transforming oximes into amides at room temperature and under neutral conditions consists in the irradiation with ultraviolet light. Some general characteristics appear to differentiate the conventional acid-catalysed process and its photochemical version. A series of systematic studies on steroidal substrates showed that photolysis of these cyclic ketone oximes in protic solvents gives nearly equal amounts of the two possible isomeric lactams in low to moderate yields, regardless of the initial configuration of the hydroxyimino group. This lack of regioselectivity is probably due to a competing photochemical *Z*/*E* isomerization of the oxime functional-

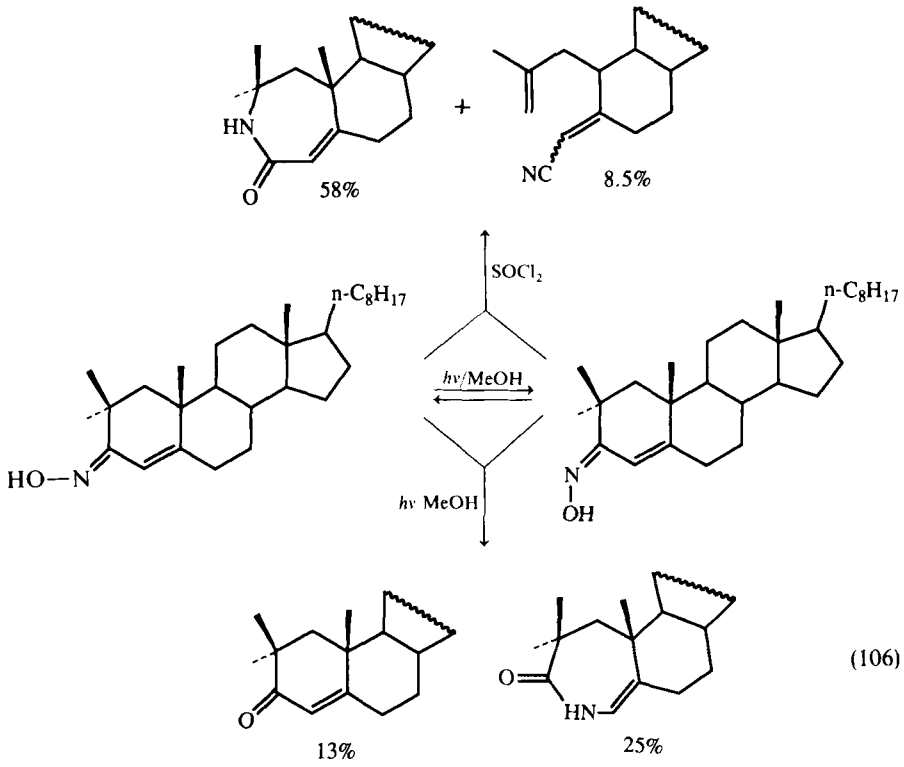
ity. The result obtained in the rearrangement of A-nor-5-α-cholestan-3-one oxime[258] can be considered emblematic (equation 105).



(105)

However, a regioselective photo-Beckmann rearrangement has been reported to occur in the case of α,β-unsaturated cholestenone oximes[259]. Upon irradiation of these compounds, one enamine-type lactam is obtained as the sole product from each substrate, in sharp contrast with the result of treatment with thionyl chloride, which affords the opposite enone-type regioisomer. It is noteworthy that in the photolysis of pure *E*-oxime considerable amounts of the *Z*-oxime are isolated, conclusively establishing that *Z*/*E* isomerization occurs during the photoreaction. It has been suggested that stereoelectronic factors (see oxaziridines below for a discussion) are responsible for the observed photochemical selectivity (equation 106).

The original chirality of the reaction centre in the starting oximes is usually retained in the final lactams, indicating that the transposition takes place as a general rule through a concerted mechanism[258,260,261]. On the other hand, the amounts of fragmentation

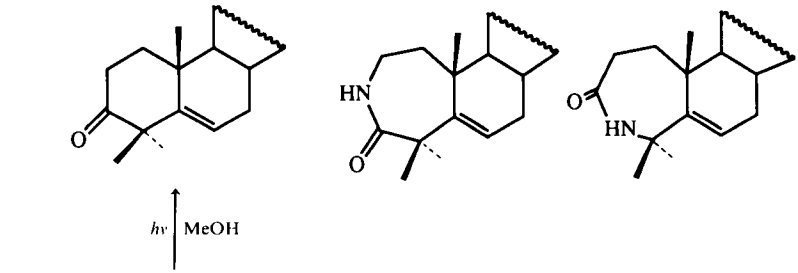


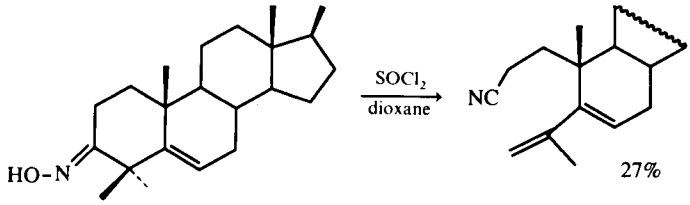
(106)

by-products obtained by treatment of the oximes under acidic conditions are clearly diminished or even suppressed in the photo-Beckmann rearrangement[262–264]. This reluctance to undergo carbon–carbon bond cleavage is best exemplified by the chemical behaviour of the β,γ-unsaturated 4,4-dimethylcholestenone oxime[263]. In this context, it is worthy of mention that α,β-unsaturated oximes can undergo a competitive azadi-π-methane rearrangement leading to the formation of cyclopropyl derivatives, instead of the usual photo-Beckmann rearrangement[265]. Although the nature of the chromophore and the rigidity of the molecular framework must play a significant role, it is not clear as yet how the outcome of the photoreaction can be controlled (equations 107 and 108).

If the cyclic or polycyclic oxime has a considerable strain or steric hindrance to the rearrangement, as in the cases of steroidal α-methylcyclobutanone oxime[266], 2,4,6-tri-*tert*-butyl-2,4-cyclohexadienone oximes[267] and 7,14-dihydrocodeinone oxime[268], it seems that α-scission to give unsaturated nitriles is also photochemically possible, probably through an exceptional mechanism involving biradical or ionic intermediates.

The mechanism generally accepted for the photochemical Beckmann rearrangement is outlined below[259,269,270]. After light absorption, the oxime in its singlet excited state may undergo intersystem crossing to the triplet state, from which *syn–anti* isomerization occurs; alternatively, the singlet state can rearrange to the corresponding oxaziridine. The latter is a labile molecule, which is converted into the parent carbonyl compound, or, alternatively, rearranges to the amide on further photolysis, or also as a consequence of a thermal process. Oxaziridines have also been suggested as intermediates in the formation of lactams by photolysis of steroidal acetylhydrazones in the presence of oxygen[271] (equations 109 and 110).





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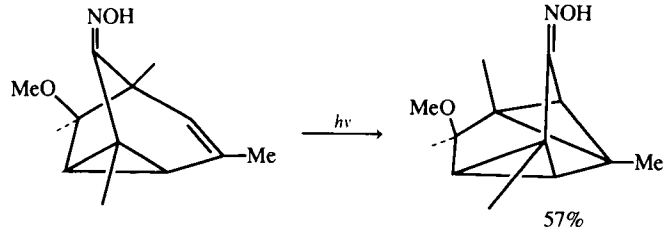

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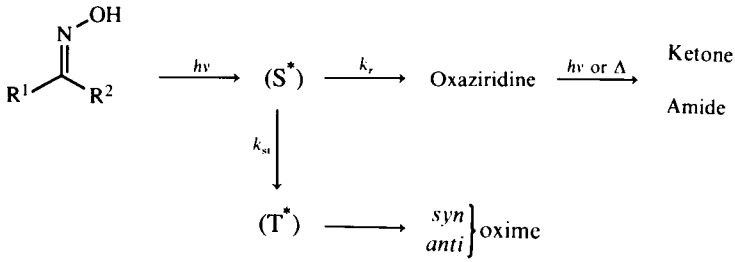

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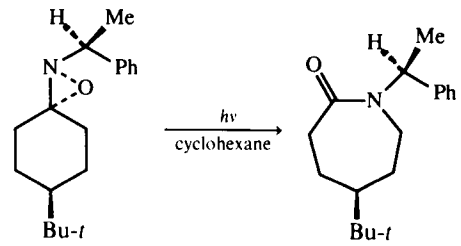


(110)

Studies concerning the effect of guest cations on the photoreactivity of acetophenone oxime derivatives having a crown ether moiety have shown that complexation stimulates *syn–anti* isomerization, while depressing oxaziridine formation[269]. Such behaviour has been interpreted by assuming that formation of the host–guest complex enhances the $n\pi^*$ character of the singlet excited state to the detriment of the $\pi\pi^*$ component, hence favouring intersystem crossing. This effect is also produced by the attachment of electron-withdrawing substituents to the aromatic ring.

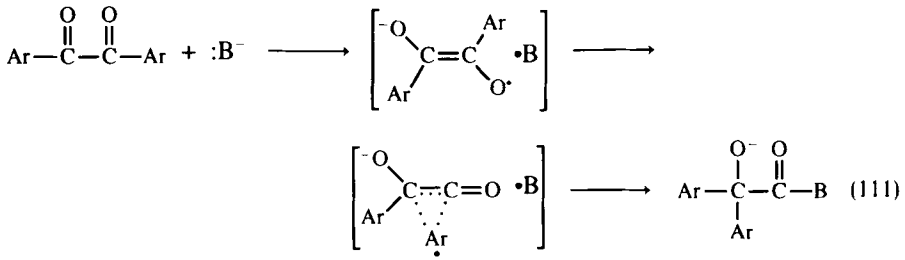
Additional evidence for the intermediacy of oxaziridines in the photochemical Beckman rearrangement is provided by the parallel migratory aptitudes of hydrogen and aryl groups in the photolysis of a series of benzaldoximes and 2-alkyl-3-aryloxaziridines, prepared by oxidation of the corresponding benzaldimines with *m*-chloroperbenzoic acid[270]. On the other hand, the photochemical and thermal rearrangement of oxaziridines to amides has attracted much attention in its own right[272] as the key step for an overall ketone-to-lactam conversion not involving oximes as synthetic intermediates. These transpositions, especially the photochemical isomerizations, are highly regio- and stereoselective. Experimental[273] and theoretical[274] results suggest that the selectivity is governed by stereoelectronic factors, the migrating group being antiperiplanar to the lone pair of the oxaziridine nitrogen atom. Thus, X-ray crystal structure analysis has unambiguously shown that irradiation of enantiomerically pure (2*R*,α*S*)-6-*t*-butyl-2-(α-methylbenzyl)1,2-oxazaspiro[2.5]octane affords after recrystallization (5*S*,α*S*)-5-*t*-butyl-1-(α-methylbenzyl)hexahydro-2-azepinone as the single lactam in 80% yield[273] (equation 110).

Finally, an extension of the above stereospecific transformation of spirocyclic oxaziridines has been developed as a general methodology to achieve asymmetric nitrogen insertion, leading to the formation of chiral, non-racemic caprolactams and valerolactams[275]. The success of the overall process is based on the selectivity of the two consecutive steps involved.

B. Benzil–Benzilic Acid Rearrangement

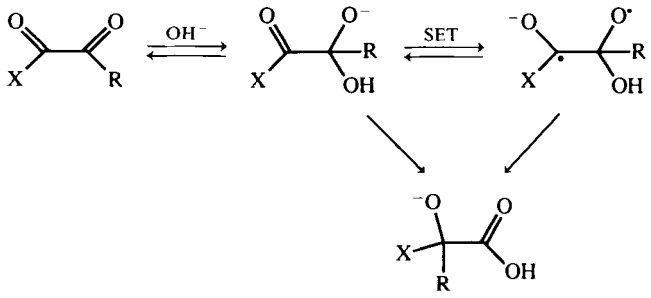
The classical mechanism of the benzil–benzilic acid rearrangement consists basically in the reversible addition of a nucleophile to a carbonyl group, followed by a rate-limiting 1,2-migration of a formally nucleophilic R group to the vicinal carbonyl group[276]. This scheme is, however, under revision after the detection by ESR spectroscopy of semidione-type radicals during the transposition of benzil and other aromatic and heteroaromatic 1,2-ethanediones[277,278].

A reasonable alternative[277] to account for the intermediacy of such species involves an initial single electron transfer (SET) process between the base as donor and the aromatic 1,2-diketone as acceptor. Then, a neophyl-like shift of an aryl radical π-bonded to a ketenic system, rather than to a simple olefinic double bond, which would take place (equation 111).



(111)

The SET pathway in the benzilic acid rearrangement is consistent with other closely related base-catalysed reactions such as the Cannizzaro disproportionation[279,280] and the Meerwein–Ponndorf–Verley reduction[281,282]. In this context, a theoretical study using the MNDO SCF-MO approach on the mechanism of the benzilic acid rearrangement[283] has considered the possibility that, after nucleophilic addition of the hydroxide anion to the *vic*-dicarbonylic substrate, the resulting adduct would undergo an intramolecular SET process prior to the 1,2-migration key step (equation 112).



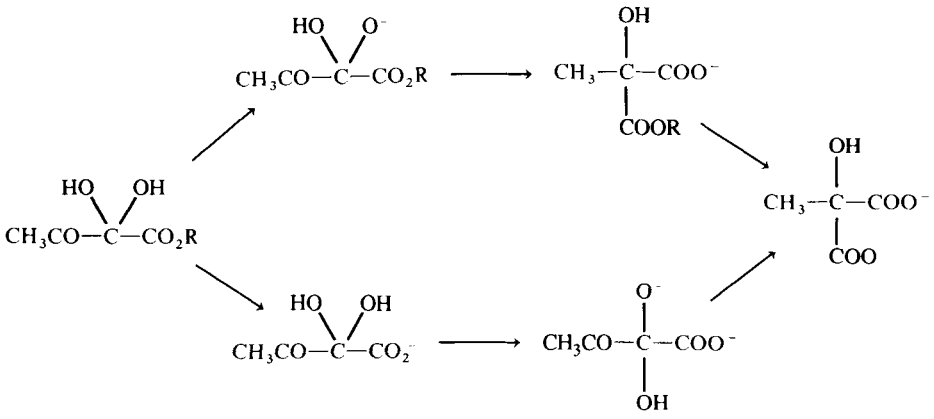
These calculations have shown that such a SET pathway is improbable for the reaction of glyoxal itself, which must rearrange via intramolecular hydride transfer occurring on the closed-shell ground-state singlet surface. However, for the cases of phenylglyoxal, benzil and its derivatives, alternative open-shell pathways involving intramolecular SET from the oxy-anion moiety to the carbonyl group and subsequent radical shift are predicted to be much more favourable than the direct nucleophilic migration. This mechanistic picture is consistent with the experimental migratory preferences (groups such as ester, acid and amide are predicted to have relatively small barriers to migration in contrast with alkyl groups) and also provides an explanation for the fact that the migrating groups appear not to behave as formal nucleophiles in terms of substituent effects.

Accordingly, the 1,2-shift of electron-withdrawing groups towards electron-deficient centres cannot be systematically ruled out in the benzilic acid rearrangement. In fact, for α,β-dioxobutanoic acid derivatives in the stable α-hydrated form it has been found by ^{14}C-labelling that the transposition takes place via shift of the carboxylic moiety, excluding the migration of the alkyl rest to the central α carbonyl group[284–287]. This selectivity has been interpreted by considering the differences between the three carbonyl groups of the dioxoacid: the carbonyl group at $C_{(2)}$, being completely hydrated, is a poor migration terminus for the alkyl group, whereas the unhydrated carbonyl at $C_{(3)}$ is prone to accepting a migrating nucleophile. The third carbonyl group, that of the ester or amide, is not electrophilic enough to be attacked by a migrating nucleophile.

In the case of ethyl and isopropyl dioxobutanoates the course of the reaction depends on the concentration of alkali: for pH values higher than 14 there occurs first a 1,2 shift of the COOR group, followed by ester hydrolysis, while for pH lower than 10 the ester is hydrolysed first and a carboxylate group is subsequently shifted (equation 113).

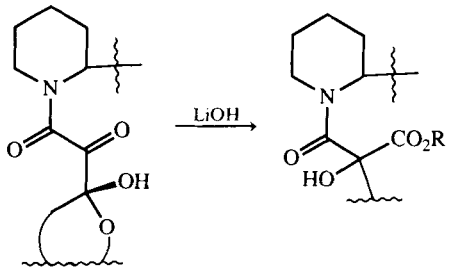
In the cases of *t*-butyl and carboxamide derivatives no hydrolysis of the carboxylic function was observed over the whole range of pH, indicating that the reaction occurs exclusively by migration of the COOBu-t or $CONH_2$ groups, respectively. Kinetic measures showed that rearrangements of ester groups are 10–20 times faster than those of amides and that the rates of the more common rearrangements, involving migration of aryl or alkyl groups, are comparatively much slower.

Another interesting example of a benzilic acid rearrangement comprising a tricarbonyl



(113)

system, again with the result of a selective carboxamide migration, is found in the treatment of the FK-506 antibiotic with lithium hydroxide[288], shown schematically in equation 114.

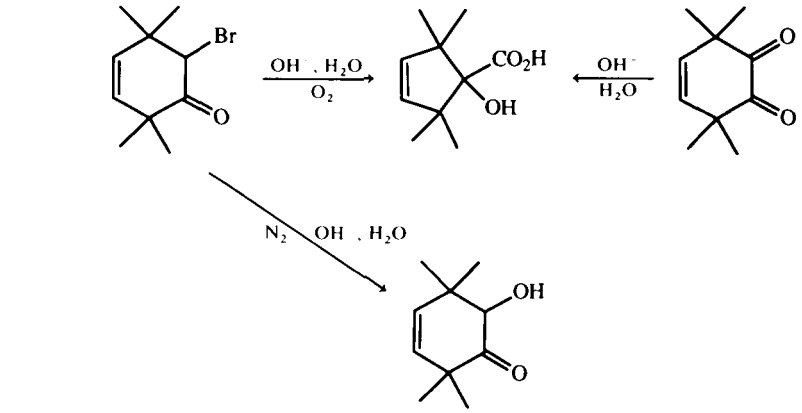


(114)

Certain α-substituted cyclic ketones undergo benzilic acid rearrangement after developing the corresponding α,β-dicarbonyl moiety under basic conditions. In the case of 6-bromo-2,2,5,5-tetramethyl-3-cyclohexenone the presence of oxygen is required, since otherwise substitution of bromine by hydroxy is the only process observed[289] (equation 115).

An analogous ring contraction occurs in the rearrangement of α-acetoxy-α-arylthiocycloalkanones[290]. As these compounds are easily accessible from cyclic ketones by sulphenylation followed by acetoxylation, this transposition coupled with subsequent oxidative cleavage of the resulting α-hydroxyacids has been claimed to be a convenient method to convert a cyclic ketone into its next smaller homologous cycloalkanone (equation 116).

While the benzilic acid rearrangement is usually carried out using hydroxides of alkaline metals, many other bases have been also employed. In recent years the transposition has been effected by means of lithium *t*-butoxide, to yield *t*-butyl α-hydroxyesters[277] (although lithium ethoxide and lithium dialkylamides failed for the same substrates). Sodium hydride has been found to be effective as well[291]. In this context, the reaction of 4,4'-disubstituted benzils with NaH in acetonitrile constitutes a general method for the synthesis of 4-cyano-3,3-diaryl-5-methyl-2-oxo-2,3-dihydropyrroles.



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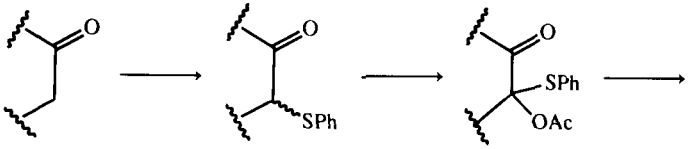
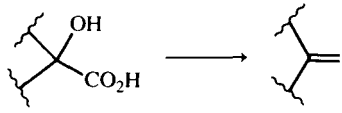
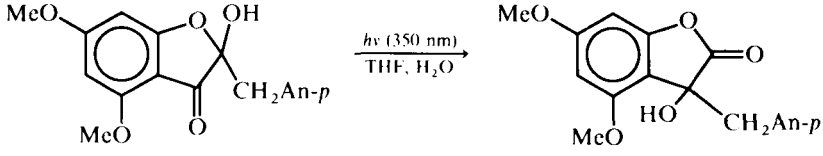




(116)

Rearrangements analogous to that of benzil to benzilic acid have been observed to occur even in the absence of any base. Thus, irradiation of 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-one affords 3-benzyl-3-hydroxybenzo[*b*]furan-2(3*H*)-one in 15% yield[292], which constitutes the first example of a photochemical benzilic acid rearrangement (equation 117).

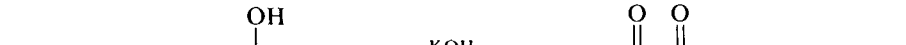


(117)

15%

Although the reaction of 1,2-diketones to give α-hydroxycarboxylic acids is considered to be essentially irreversible, several examples of the inverse transformation, i.e. the 'retro-benzilic acid rearrangement', can be found in the literature. Thus, di-9-anthryl diketone has been successfully prepared from the corresponding acid methyl ester in 33% yield by stirring at 20 °C a dichloromethane solution of this methyl ester in the presence of solid potassium hydroxide and a crown ether as phase-transfer catalyst[293] (equation 118).

Likewise, a 'retro-benzilic acid rearrangement' has also been proposed to occur during



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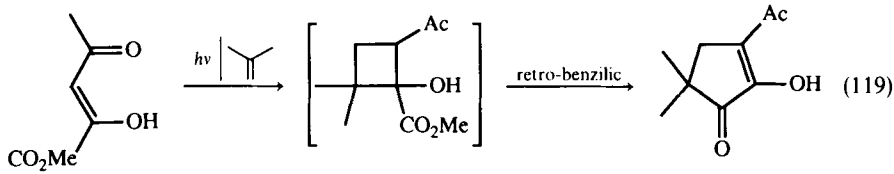
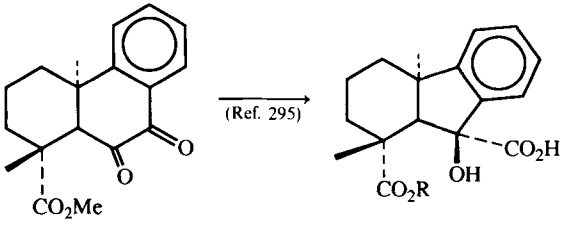


(119)

the pyrolysis at 180 °C of α-methoxycarbonylcyclobutanols, which are thought to be the primary products in the [2 + 2] photocycloaddition of methyl 2,4-dioxopentanoate with olefins[294] (equation 119).

Finally, a number of reports have recently appeared describing approaches based on the benzilic acid rearrangement to accomplish ring contraction from cycles of 6 to 5 members. This strategy has been applied to the synthesis of diterpenoids with a quassinoid skeleton[295–297], pentacyclic triterpenes[298] and the 2-oxo-3-pyrroline dimeric alkalkoid of *Mercurialis Leiocarpa*[299] (equations 120 and 121).



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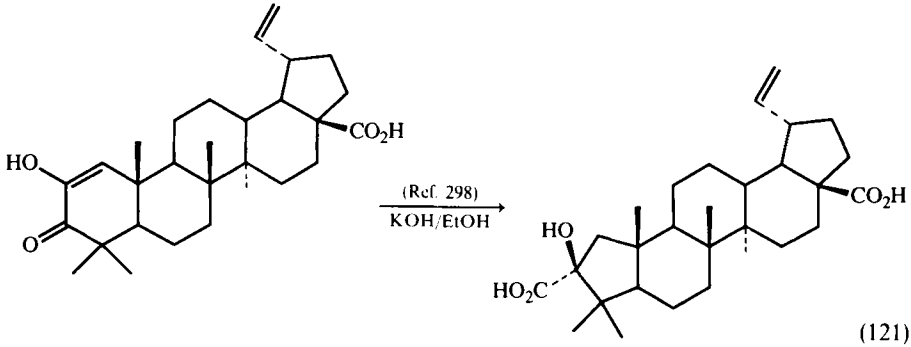
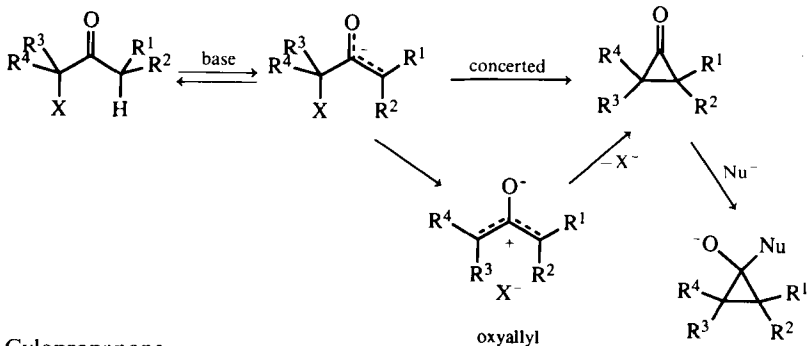


(121)

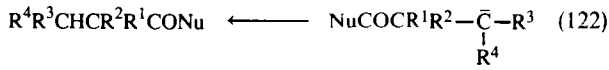
C. Favorskii and Related Rearrangements

The formation of carboxylic acid derivatives from ketones having an α-leaving group by the action of bases is known as the Favorskii rearrangement. There is evidence of the involvement of two different mechanisms, termed the cyclopropanone and semi-benzilic routes. In the more common cyclopropanone mechanism, the base abstracts a proton at the α′-position of the α-substituted ketone to generate an enolate, which then undergoes loss of the leaving group and ring closure to a cyclopropane intermediate.

The latter two processes may occur in a synchronous and stereoselective manner (equivalent to an intramolecular S_N2-like substitution) or, alternatively, in a non-synchronous way, via initial elimination of the leaving group, subsequent generation of a delocalized oxyallyl zwitterion and final disrotatory ring closure, in accordance with the rules of conservation of orbital symmetry. The semi-benzilic pathway applies mainly for substrates lacking hydrogens at the α′-position and involves nucleophilic attack at the carbonyl carbon, followed by an oxyanion-promoted rearrangement, with inversion of configuration at the migrating terminus (equations 122 and 123).

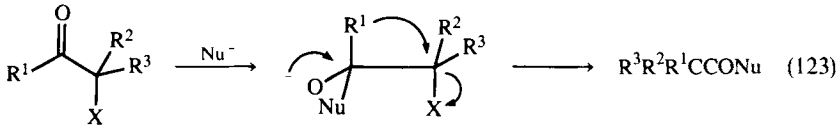


Cylopropanone mechanism



(122)

Semi-benzilic mechanism

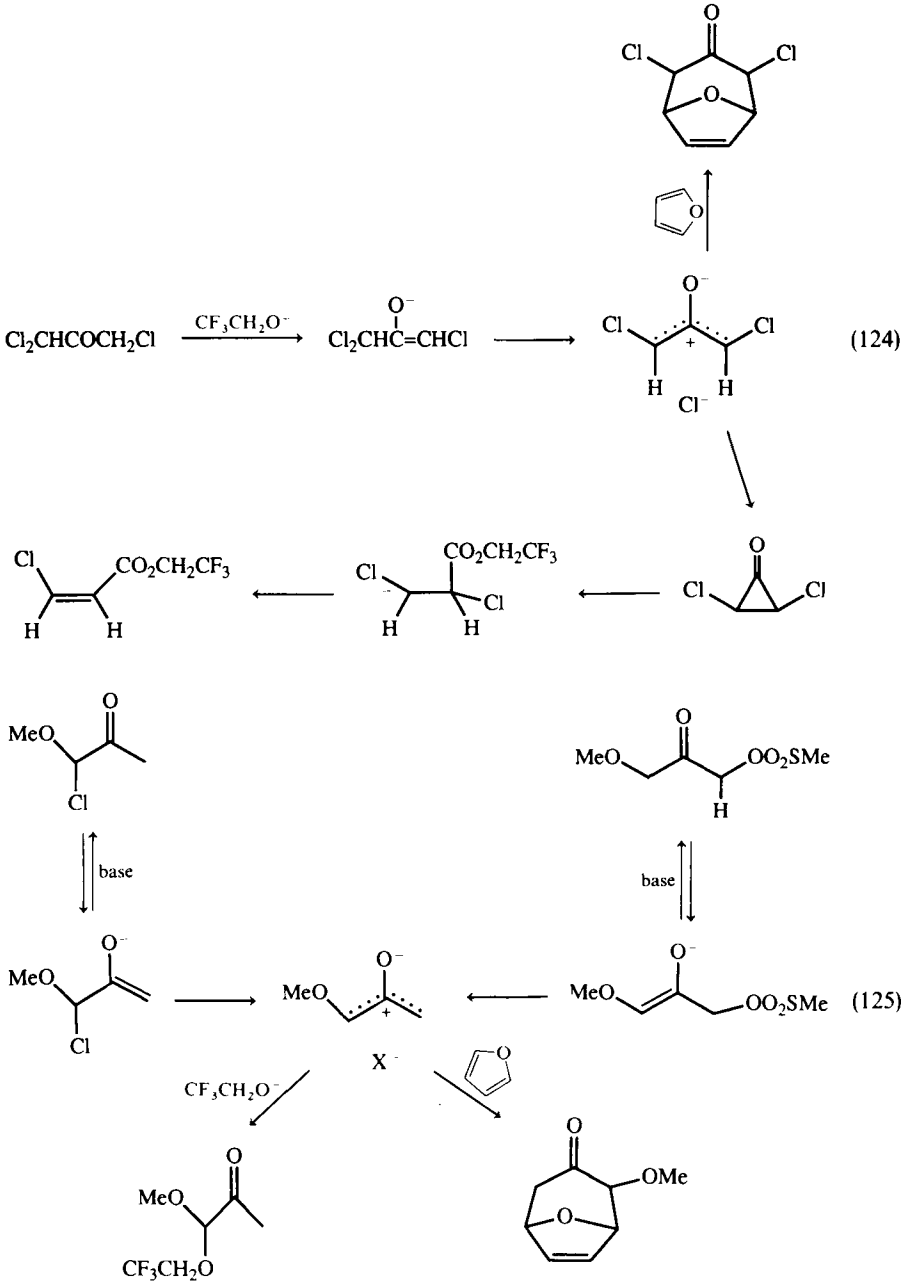


(123)

Concerning the exact timing of the leaving group expulsion and ring closure in the cyclopropanone mechanism, it has been shown that the transposition of 1,1,3-trichloro-2-propanone in basic 2,2,2-trifluoroethanol affords the trifluoroethyl ester of *cis*-3-chloroacrylic acid, through the intermediacy of 1,3-dichloroallylium-2-olate. This zwitterionic oxyallyl species can be trapped by several cyclic dienes, to give stereoisomeric [4 + 3] cycloadducts[300]. In fact, reaction of furan with dipolar oxyallyls, generated by solvolysis of α,α′-dialkyl substituted α-haloketones[301] or α-alkyl-α′-mesyloxyketones[302] in the presence of bases, to form 3-oxo-8-oxabicyclo[3.2.1]oct-6-enes appears to be a general process, even for those α-haloketones which do not undergo the Favorskii rearrangement under these conditions. The use of oxyallyls and cyclopropanones as substrates for cycloadditions has been reviewed[303].

These results, together with the fact that the same substitution product, namely 1-methoxy-1-(2,2,2-trifluoroethoxy)-2-propanone, is obtained in the solvolysis of 1-chloro-1-methoxy-2-propanone and its 'regioisomer equivalent' 1-methanesulphonyl-

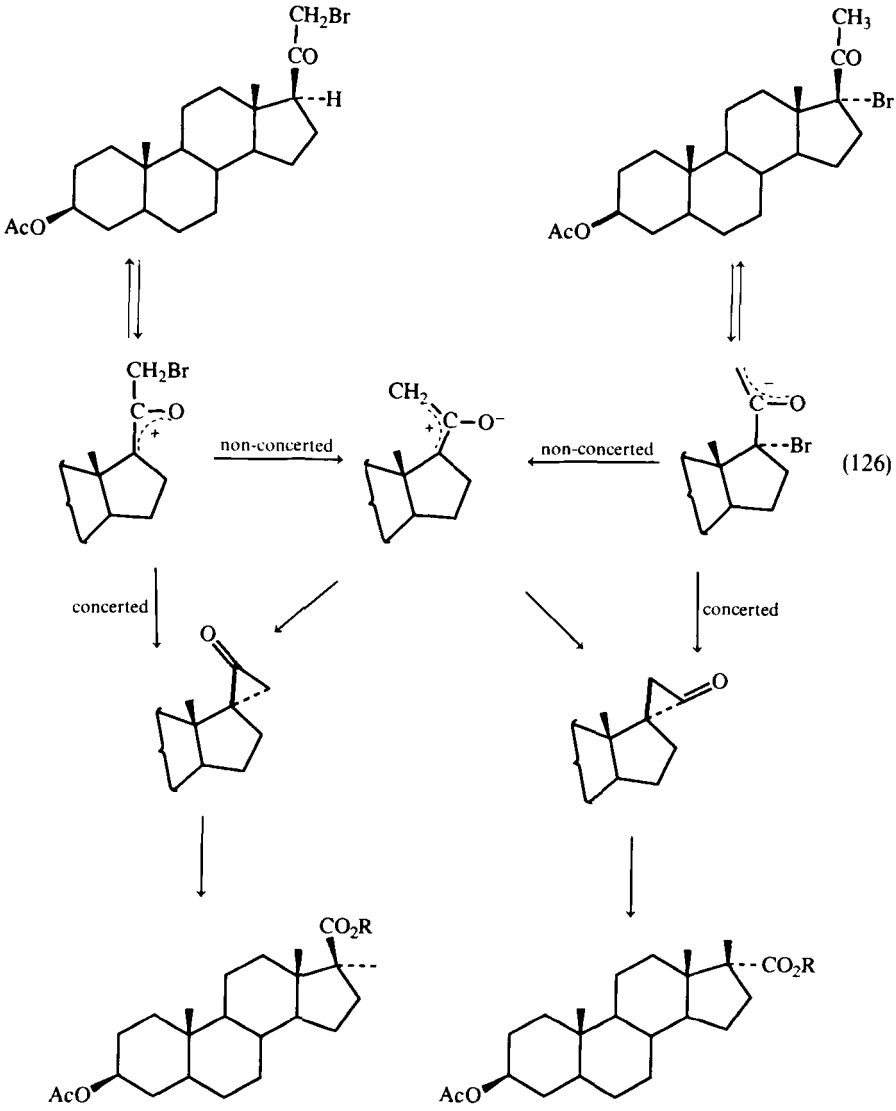
oxy-3-methoxy-2-propanone, through a common oxyallyl intermediate, strongly suggest that the Favorskii rearrangement of these systems takes place through a non-concerted mechanism involving an initial enolization and subsequent elimination of the halide anion (equations 124 and 125).



(124)

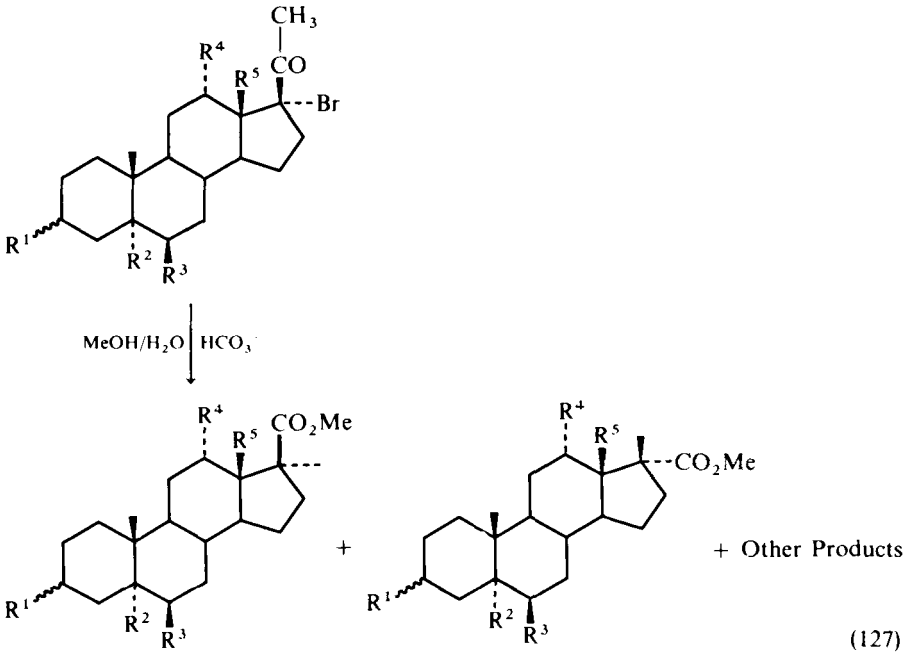
(125)

In this context, the complex stereochemistry of the products arising from the Favorskii rearrangement of α-halogenated 20-ketosteroids can be intrepreted on the basis of competition between a stereospecific concerted cyclopropane formation, favoured in non-polar solvents, and a non-stereospecific non-concerted pathway involving the intermediacy of a dipolar oxyallyl species, favoured in protic and polar media, being assumed that the two mechanisms can be simultaneously operating under intermediate conditions[304–306]. Thus, the different product distributions obtained in the rearrangement of 21-bromopregnanolone acetate and its 17-bromo regioisomer in aprotic medium under identical conditions excludes the possibility that just one common zwitterionic intermediate is involved[305] (equation 126).



(126)

Moreover, although the concerted mechanism should be essentially non-stereoselective, studies on the Favorskii rearrangement in the steroid series have shown that steric factors can influence cyclopropanone formation and ring opening, leading to a high degree of stereoselectivity. Thus, the predominating formation of 17α-methylated etio acid derivatives in the reaction of 17-bromo-5α-pregnan-20-one is due, to an appreciable extent, to the presence of the 18-methyl group and becomes somewhat diminished by a 12α-acetoxy substituent[306]. Likewise, in the Favorskii rearrangement of 16α-bromo-D-homoandrostan-17-one, the steric hindrance of the angular α-methyl group at $C_{(13)}$ (represented by a shaded circle in equation 128) is thought to be responsible for the regioselective ring opening of the cyclopropanone intermediate, leading to an equimolar mixture of 13α-androstan-16α- and 16β-carboxylic acids[307] (equations 127 and 128).

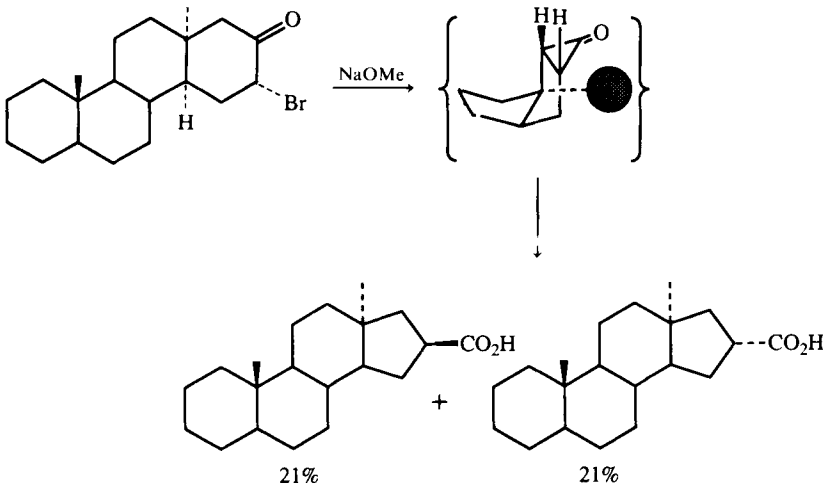


(127)

R¹	R²	R³	R⁴	R⁵	17α-methyl		17β-methyl
β-AcO	double bond		H	Me	23	/	1
α-AcO	H	H	α-AcO	Me	13	/	1
β-AcO	H	H	H	H	4.5	/	1

On the other hand, a rare example has been reported concerning an homologous partial Favorskii rearrangement of a cyclic β-tosyloxyketone in the diterpene series, which leads to the formation of an isolable cyclobutanone[308] (equation 129).

From the preparative point of view, the Favorskii rearrangement is still widely used to perform the ring contraction of α-halocycloalkanones to cycloalkanecarboxylic acids, as for instance the formation of 3,7-cycloundecadienecarboxylic acid by treatment of 2-chloro-5,9-cyclododecadione with potassium hydroxide[309].



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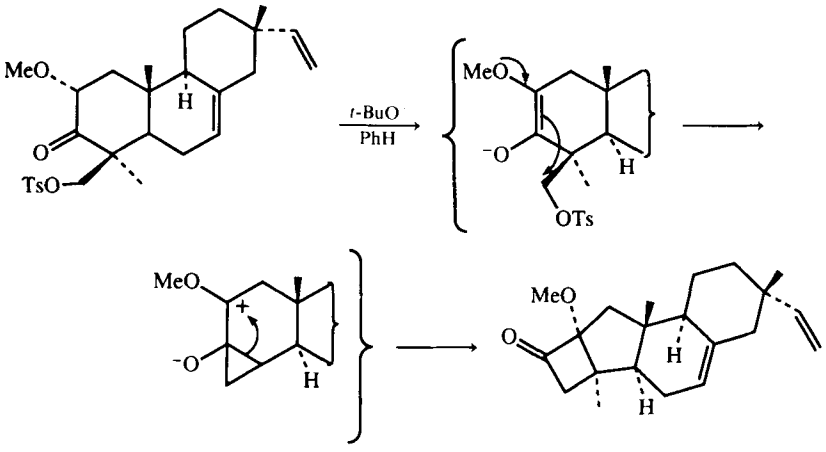
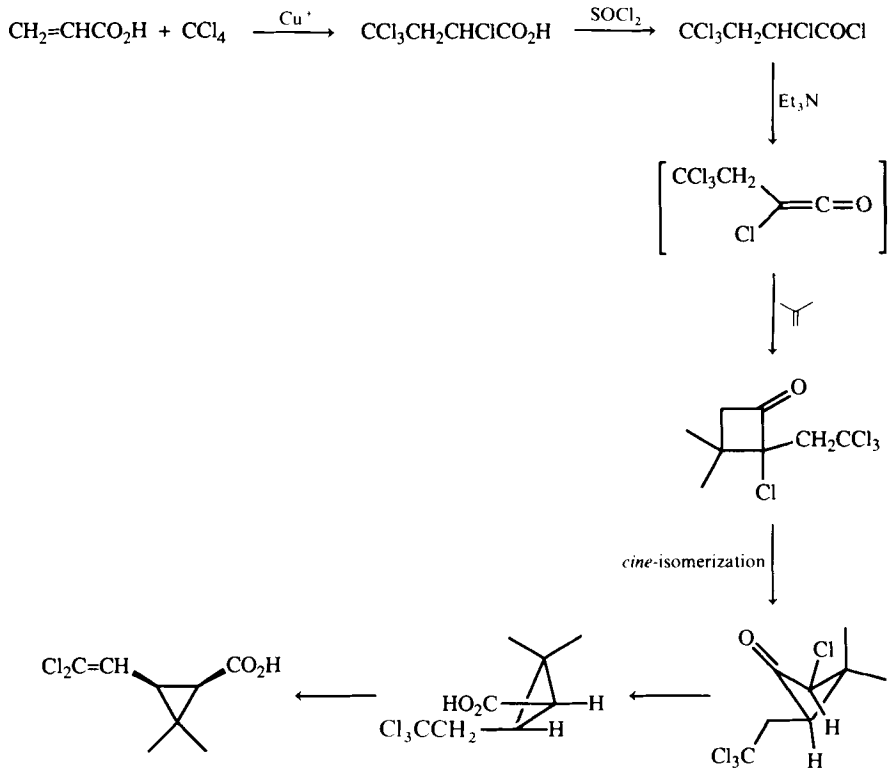


(129)

A versatile, stereoselective preparation of *cis*-cyclopropanecarboxylic acids related to pyrethroid insecticides has been achieved by base-induced rearrangement of 2-chlorocyclobutanones[310]. The overall synthetic route comprises a [2 + 2] cycloaddition of polyhaloketene to an alkene, to give α-halogenated cyclobutanones[311], which are then submitted to *cine-isomerization*[312] and ring contraction (equation 130). A parallel scheme using dienes and dichloroketene, generated *in situ* from trichloroacetyl chloride, has been used for the synthesis of pyrethroid acids[313].

Deuterium exchange experiments on these cyclobutanones have shown[314] that, under the basic conditions required for ring contraction, a rapid *cis/trans* isomerization of the 2,4-disubstituted cyclobutanones takes place prior to the Favorskii rearrangement. Therefore, the stereoselectivity of the process is determined by the *cis/trans* ratio of the equilibrated isomers. Using bulky leaving groups, such as *p*-bromophenylsulphonyloxy, it has been found that only *cis*-cyclopropanecarboxylic acids are formed in the rearrange-

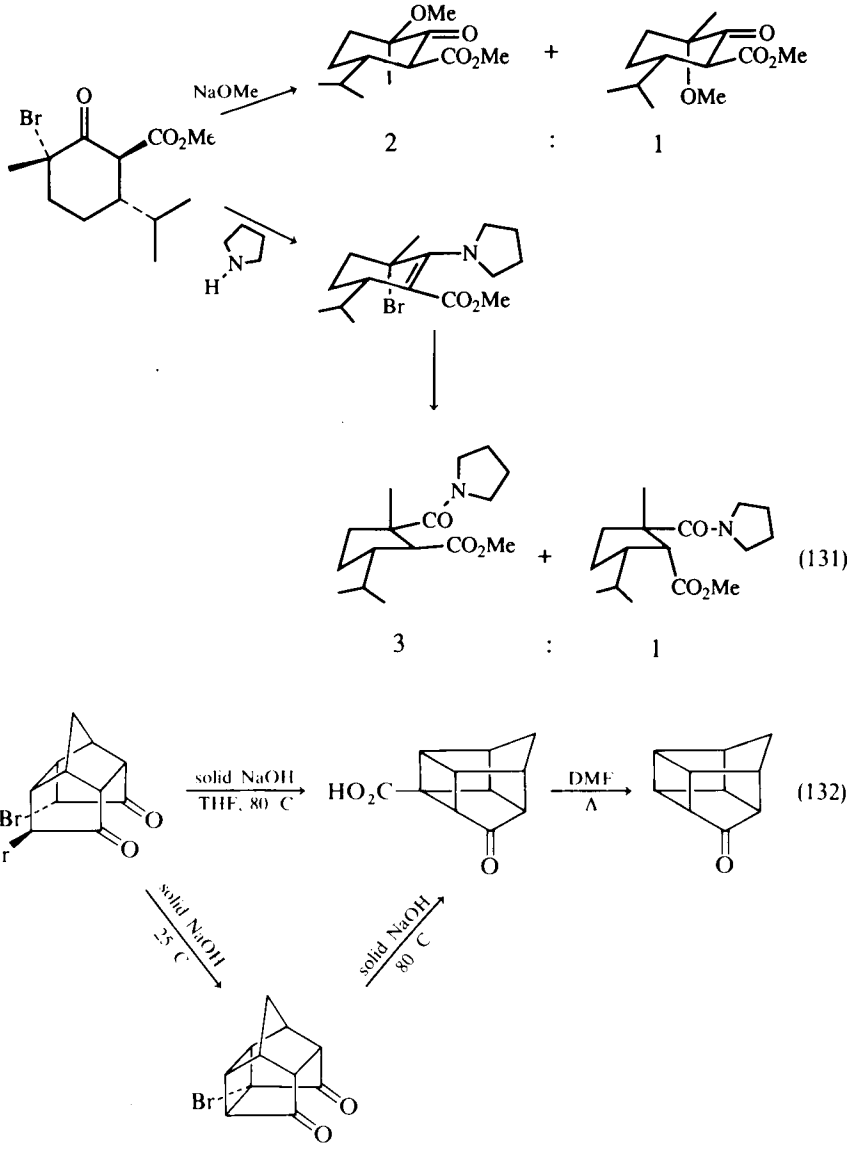


(130)

ment. Low temperatures (−10 °C) and non-homogeneous conditions ($NaOH/H_2O$/toluene) also enhance the stereoselectivity of the process. By contrast, it is noteworthy that the photochemical Favorskii rearrangement of these halocyclobutanones affords the same cyclopropanecarboxylic acids in high yield, but with no stereoselectivity[310].

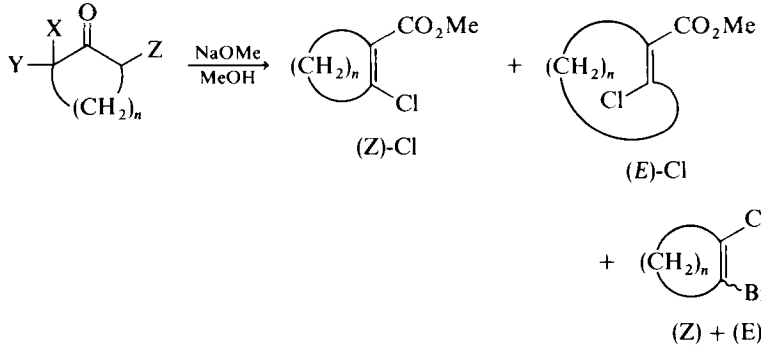
Likewise, the heavily functionalized cyclopentanecarboxylic acid derivative precursor of the "northern" fragment of retigeranic acid A has been prepared with high stereoselectivity by Favorskii rearrangement of methyl 3-bromo-6-isopropyl-3-methyl-2-oxocyclohexanecarboxylate[315]. In this case, treatment of the α-bromocyclohexanone with a methanolic solution of sodium methoxide affords exclusively the α-methoxycyclohexanones, while reaction with pyrrolidine in ether gives rise to the Favorskii products. The stereoisomer ratio has been found to be solvent dependent. This constitutes an additional example of secondary amine-induced transposition of α-halocyclohexanones possessing a group that enables formation of the enamine (equation 131).

Favorskii rearrangement is a useful reaction to obtain highly strained polycyclic compounds. Thus, a tetrahydrofuran solution of the cage 3,6-dibromotetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$] undecane-2,7-dione reacts in the presence of solid sodium hydroxide to furnish the substituted 1,3-bishomocubanone, providing a new entry to these systems from a tetracyclic precursor[316]. The fact that the pentacyclic α-bromodiketone is obtained under these mild conditions suggests that this compound is the involved reaction intermediate (equation 132).



Studies on the sodium methoxide mediated Favorskii rearrangement of a series of α,α,α′-dibromochlorocycloalkanones of medium ring size have established that the reaction occurs selectively with almost complete bromine elimination, to yield the corresponding ring contracted methyl 2-chloro-1-cycloalkenecarboxylate[317,318] (equation 133).

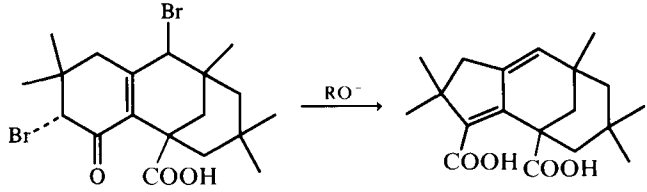
The above transformation fits well in the general reactivity pattern of α,α- and α,α′-dihaloketones, which give rise to α,β-unsaturated esters under Favorskii rearrangement conditions. A related transformation is the ring contraction of a dibromodiisophor-



(133)

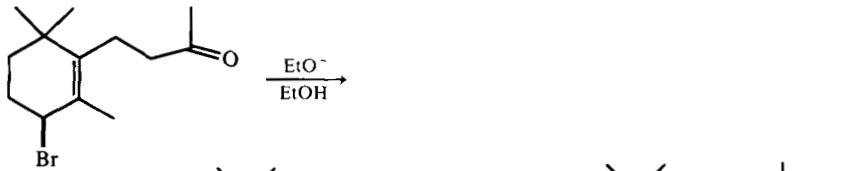
		Preferred loss of Br over Cl (%)	Z-Cl	E-Cl
$n = 2$,	X = Y = Br, Z = Cl	97.7	100	—
	X = Z = Br, Y = Cl	97.6	100	—
$n = 3$	X = Y = Br, Z = Cl	97.4	100	—
	X = Z = Br, Y = Cl	97.2	100	—
$n = 5$	X = Y = Br, Z = Cl	98.3	96.2	3.8
	X = Z = Br, Y = Cl	95.8	51.0	49.0
$n = 7$	X = Y = Br, Z = Cl	99.0	90.7	9.3
	X = Z = Br, Y = Cl	99.0	76.7	23.3

one derivative lacking α′-hydrogens, in the presence of strong alkali, to give 1,3-dicarboxyneodiisophora-2,7-diene[319]. Two interesting reports have appeared on vinylogous Favorskii rearrangement, also in the terpene series. 3-Bromo-β-ionone reacts with sodium ethoxide to afford ethyl 4-(2,6,6-trimethyl-2-cyclohexenylidene) butyrate, via a Favorskii-type rearrangement accompanied by double-bond migration[320]. The use of other bases, such as sodium phenoxide, diethylamine or sodium malonate, leads to the sole formation of a substitution product. Likewise, a Favorskii ring contraction occurs in the reaction of 4-chloroisophorone with sodium methoxide[321] (equations 134–136).



(134)

One of the most relevant synthetic applications of the Favorskii rearrangement reported in recent years is the highly stereoselective preparation of (*Z*)-2,4-pentadienoates from the crude 1,3,4-tribromo-2-alkanones, obtained in turn by bromination of readily available 3-penten-2-ones[322,323]. 1,3,4-Tribromo-2-alkanones with a secondary $C_{(4)}$ fail to yield dienoic esters, giving instead products arising from the 1,3-dibromoenone via initial α,β-dehydrobromination. A disrotatory electrocyclic ring opening with concerted loss of bromide, from the oxyanion resulting from methoxide attack to a *cis*-cyclopropanone, has been suggested as the key step of the rearrangement. The formation of ethyl *trans*-4-methyl-2,4-pentadienoate under similar conditions has been



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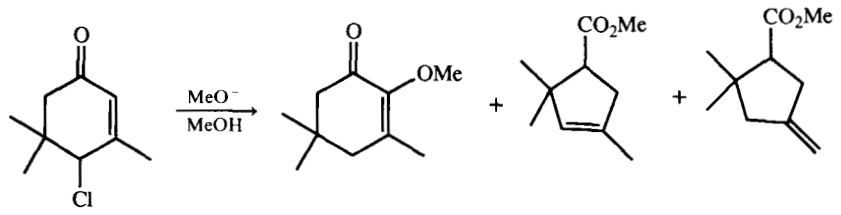
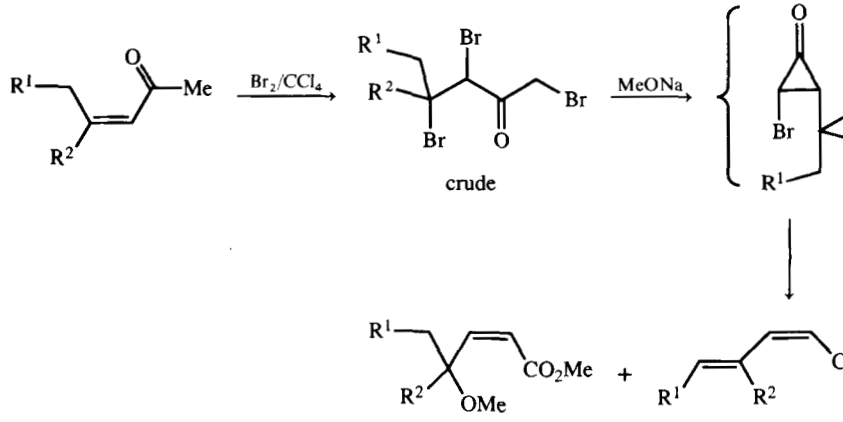


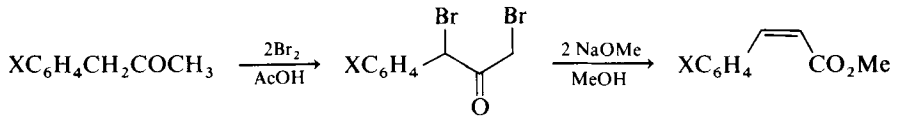
(136)

justified in a previous report[324] through a possible (*Z*) to (*E*) isomerization during the workup or upon isolation of the product. The same method also applies to the preparation of methyl (*Z*)-cinnamates by treatment of 1,3-dibromo-1-phenylacetones with sodium methoxide[325] (equations 137 and 138).



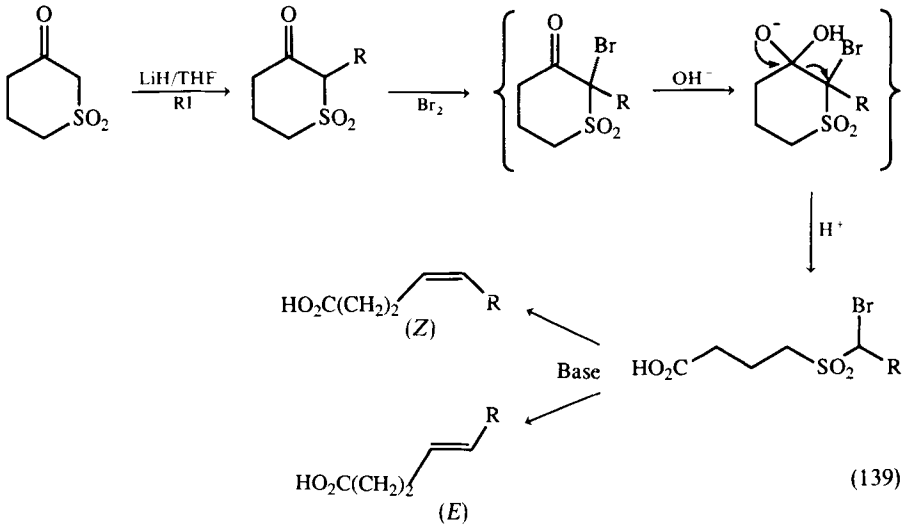
(137)

R^1	R^2	[(*Z*):(*E*)]	Yield (%)
H	Me	66 (97:3)	17
$-(CH_2)_3-$		67 (97:3)	<5
$-(CH_2)_4-$		52 (95:5)	21
H	Ph	46 (>95: <5)	—



(138)

In connection with the stereoselective formation of carbon–carbon double bonds by means of the Favorskii rearrangement, it has been found that tetrahydrothiopyran-3-one 1,1-dioxide is a useful C_4 synthon for the preparation of (*Z*)- or (*E*)-γ,δ-unsaturated carboxylic acids[326]. The overall synthetic method entails base-promoted ring opening of heterocyclic α-bromoketones, generated *in situ* by bromination of the thiopyrone dioxide, through a process analogous to the semi-benzilic Favorskii rearrangement, with formation of a carbanion stabilized by an α-sulphone as the leaving group. The stereochemistry of the process is dependent on the base employed: hydroxide favours formation of the (*Z*) isomer, while *t*-butoxide leads to the (*E*) isomer as major product (equation 139).

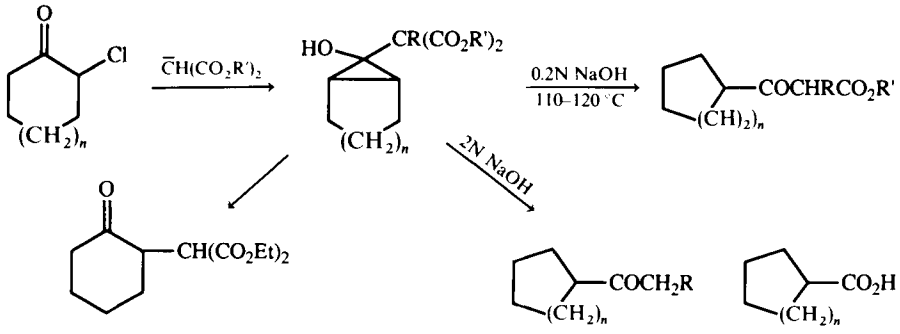


(139)

R	KOH, (*Z*)/(*E*)	*t*-BuO$^-$, (*Z*)/(*E*)
n-Bu	82/18	24/76
n-C_8H_{17}	85/15	22/78

In the Favorskii rearrangement, carbanions may also be used instead of the more conventional hydroxide or alkoxide ions. In this case, the products directly resulting from the transposition obviously cannot be carboxylic acid derivatives. Thus, the reaction of 2-chlorocyclohexanone and 2-chlorocycloheptanone with sodium salts of malonic and methylmalonic acid derivatives in benzene at low temperatures (0–25 °C) does not lead to the C-(2-oxocycloalkyl)malonates, but to the isolation of bicyclic cyclopropanol derivatives, which are the proposed Favorskii reaction intermediates[327].

Interestingly, hydrolysis of bicyclic cyclopropanol malonates with dilute sodium hydroxide gives the ring contracted β-ketoesters. Likewise, 1-chloro-3-halo-2-ketones undergo a Favorskii-type rearrangment with sodiomalonate, sodiomalonodinitrile and sodiocyanoacetate, to form conjugated enones[328]. This reactivity parallels the formation of α,β-unsaturated esters from the same α,α'-dihaloketones in the presence of alkoxides. It is worthy of mention that replacement of the chloro substituent at $C_{(1)}$ by bromine results in a loss of product selectivity and the formation of $C_{(1)}$ substitution products. Similar carbanion-induced Favorskii rearrangements of α,α'-dihaloketones are the reactions with sodium enolates of β-ketoesters, to give dihydro-4-pyrones[329], and with enolates of (diethoxyphosphinyl)acetic esters, to furnish 2-(diethoxyphosphinyl)-3-oxo-4-alkenoates useful for the preparation of α,α'-divinyl ketones[330] (equations 140 and 141).



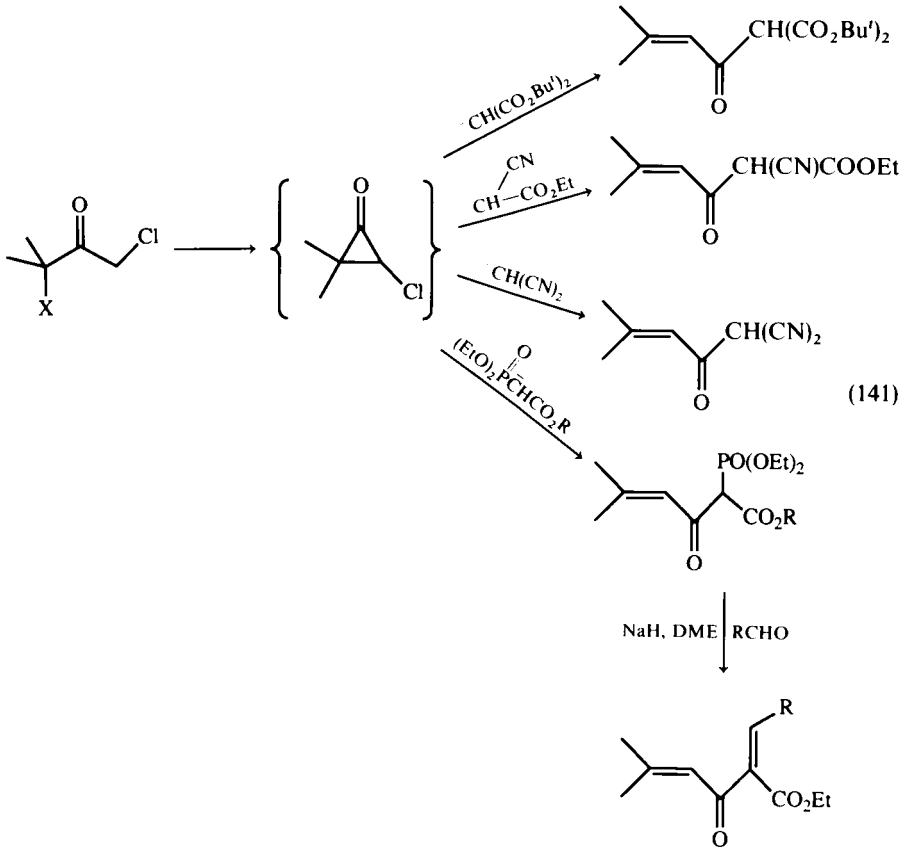
(140)

A new type of Favorskii rearrangement, initiated by Michael addition of alkoxide, has been reported to occur in the reaction of 6-chloro-2-vinylidenecyclohexanone with excess of sodium methoxide[331]. Since no α'-hydrogens are available for proton abstraction, it is proposed that a conjugate addition of methoxide to the C=C bond generates the α'-enolate, which then reacts in the usual way to form a bicyclic cyclopropanone intermediate (equation 142).

Cross aldol reaction can also be followed by a Favorskii rearrangement. Thus, aromatic and heteroaromatic aldehydes react with 3-chloro-3-methyl-2-butanone in ethanolic potassium hydroxide to give 5-aryl-3,3-dimethyltetrahydro-2-furanone and 4-aryl-2,2-dimethyl-3-butenoic acid[332]. The proposed mechanism involves formation of the aldolic oxyanion, 1,3-proton shift to an enolate and subsequent formation of the cyclopropanone intermediate (equation 143).

Recently, considerable attention has been paid to the base-induced transposition of α-haloketimines, as a heteroatomic variant of the Favorskii rearrangement. α-Bromoketimines, when treated with excess potassium *t*-butoxide in tetrahydrofuran, give (*E*)/(*Z*) mixtures of the corresponding cyclopropylidenamines in high yields, via 1,3-elimination of hydrobromic acid[333]. The stability of these imines and the (*E*)/(*Z*) ratio appears to increase with the size of the N-substituent. Alkaline hydrolysis provokes ring opening, to afford the corresponding amides[334].

By contrast, aliphatic α-chloroketimines behave like α-haloketones, reacting with potassium *t*-butoxide to afford the corresponding branched amides without any further treatment[335,336]. Since α-haloimines are less reactive than the corresponding α-haloketones due to the lower electronegativity of nitrogen, strong bases are usually necessary to effect the rearrangement. The less reactive substrates are those having less acidic α'-hydrogens, a fact which explains why secondary α-chloroketimines require milder

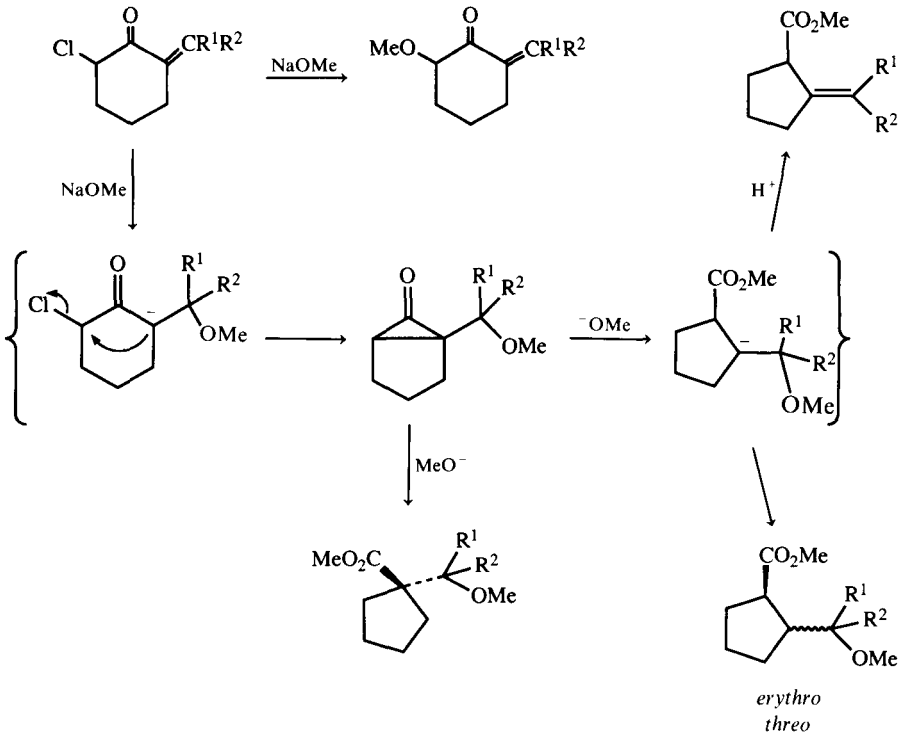


(141)

conditions than their tertiary homologues. Ketimines of α-chloro-α-phenylacetone react with excess of sodium alkoxides to provide non-branched carboxylic imidates in nearly quantitative yields. Depending on the reaction conditions and the substrate, the Favorskii rearrangement of α-chloroketimines can be accompanied by several side reactions, such as nucleophilic substitution, 1,2-dehydrochlorination, rearrangement via α-alkoxyaziridines and self-condensation[336] (equation 144).

The involvement of cyclopropylidenamines as intermediates in the one-step rearrangement of α-chloroketimines has been proven by intramolecular trapping with a suitably functionalized substrate[337], as well as by intermolecular trapping with cyanide[338,339]. In the last case, the reaction has been proposed as a convenient synthesis of 2,2-dialkyl-1-aminocyclopropanecarboxylic acids, provided that the experimental conditions are carefully chosen and a bulky N-substituent is present in the starting α-haloketimine. It is worth mentioning that all attempts to trap the delocalized zwitterionic intermediate with furan or 1,3-diphenylisobenzofuran have been unsuccessful[336] (equations 145 and 146).

A heteroatomic photochemical Favorskii rearrangement leading to N-substituted glycine esters has been reported to occur in the irradiation of chloroacetamides of estrogenic amines and cyclohexylamine in alcohols[340]. Due to the higher polarity of the molecule in its excited state, it has been suggested that the photoreaction proceeds by

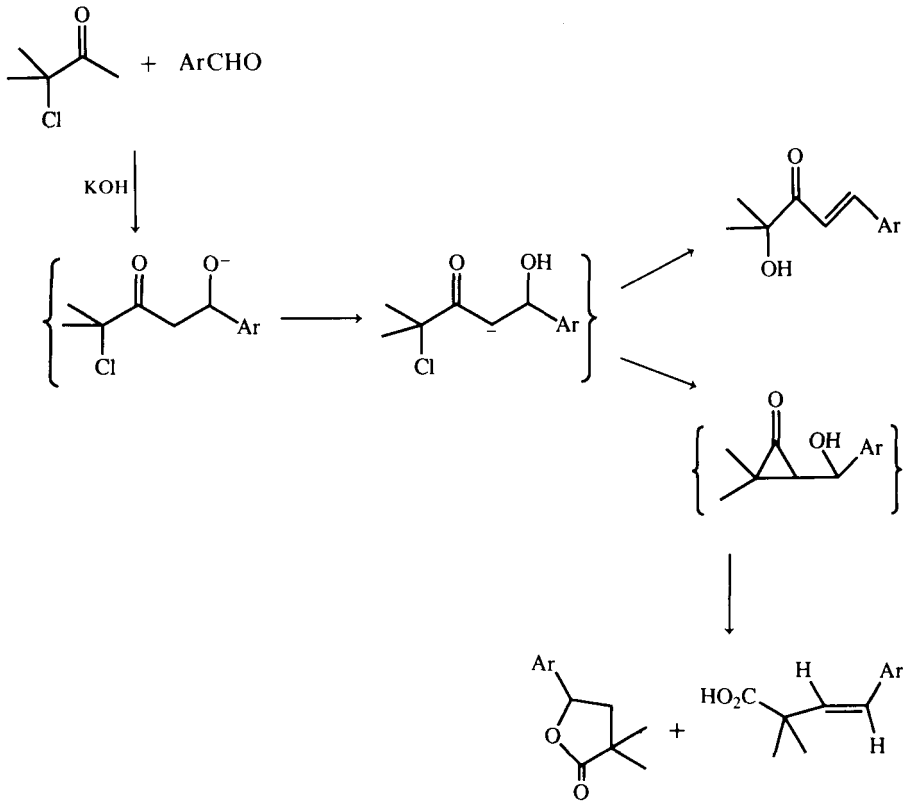


(142)

an intramolecular nucleophilic displacement, through an α-lactam intermediate. Photosolvolysis to the α-alkoxyacetamide is a competing process (equation 147).

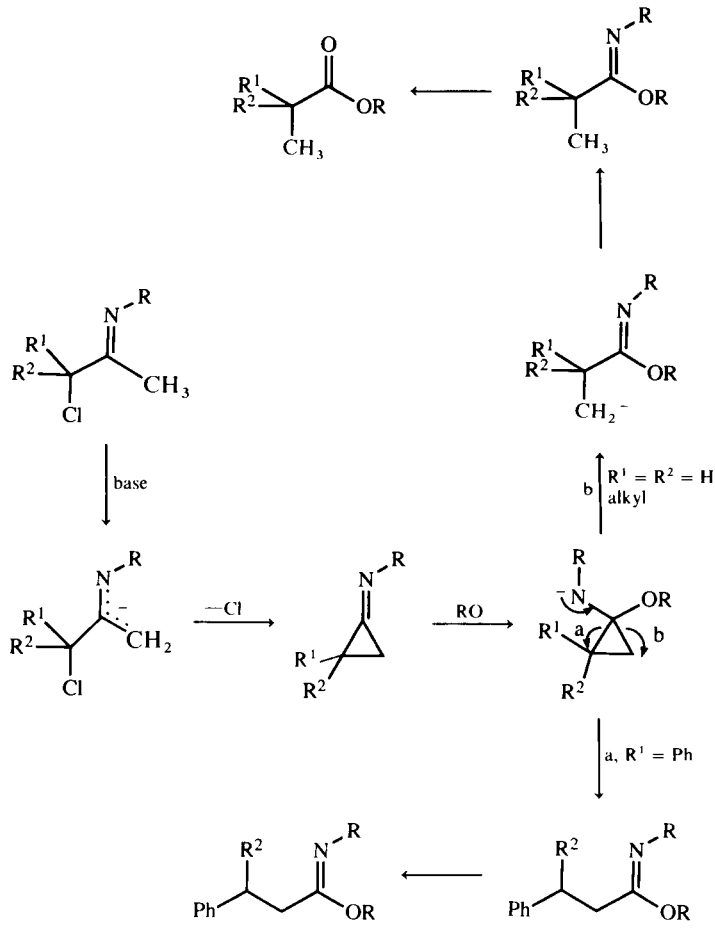
A reaction closely related to the Favorskii rearrangement is the 1,2-aryl shift of α-substituted aryl ketones, which leads to the formation of 2-arylalkanoic acid derivatives. In fact, this and related transformations of aryl ketone derivatives constitute one of the most general synthetic strategies for the preparation of this class of carboxylic acids. In particular, much attention has been devoted to the case of 2-arylpropanoic acids, compounds of high pharmaceutical interest as several of them are marketed as nonsteroidal antiinflammatory drugs. Two reviews have been recently published on this topic[341,342].

α-Halopropiophenones can be transformed into 2-arylpropanoic acid derivatives in the presence of a variety of soft metal ions, such as silver salts, thallium trinitrate and anhydrous zinc dihalides. As the reaction is usually carried out in methanol or trimethyl orthoformate, varying amounts of 2-methoxypropiophenones are sometimes formed as by-products. Better yields of the rearrangement product are obtained with electron-releasing groups attached to the aromatic ring. This reaction when applied to α-bromocycloalkyl aryl ketones affords the ring contracted products in moderate to good yields[343]. The mechanism is believed to involve *in situ* formation of the corresponding acetal or hemiacetal through Lewis acid catalysis by the metal ion. This assumption is supported by the fact that acetals of α-halopropiophenones exhibit the same reactivity pattern under identical experimental conditions, giving selectively propanoic acid derivatives in high yield[343–345] (equations 148 and 149).

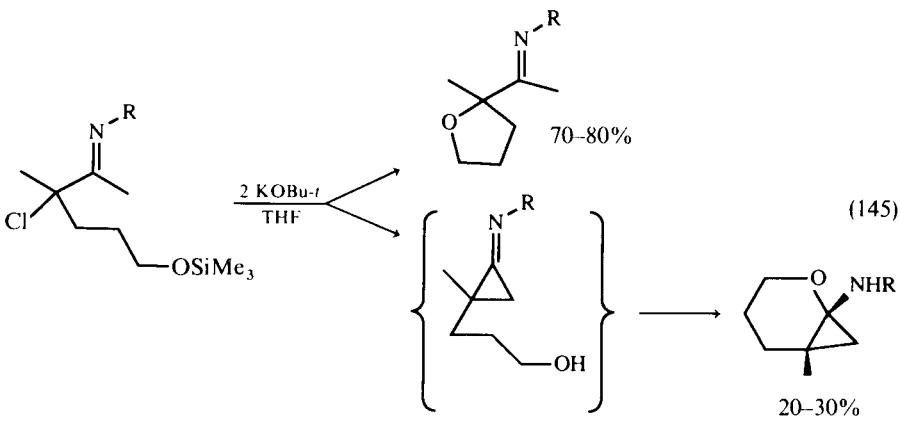


In the case of acetal derivatives, leaving groups other than halides have been used. Thus, *m*-chloroperbenzoic acid (MCPA) oxidation of cyclic ethylene acetals of α-phenylseleno- and α-phenyltelluropropiophenones affords hydroxyethyl 2-arylpropanoates in 56–86% yield, while the corresponding α-phenylseleno aryl ethyl ketones do not rearrange under identical conditions[346]. Dimethyl acetals of α-hydroxypropiophenones react with sulphuryl chloride in basic medium[347] or Ph_3P/CCl_4 in the presence of pyridine, to afford methyl 2-arylpropanoates[348]. In the last case, 1-aryl-1-methoxyacetones are also formed with aromatic rings lacking electron-releasing substituents (equations 150 and 151).

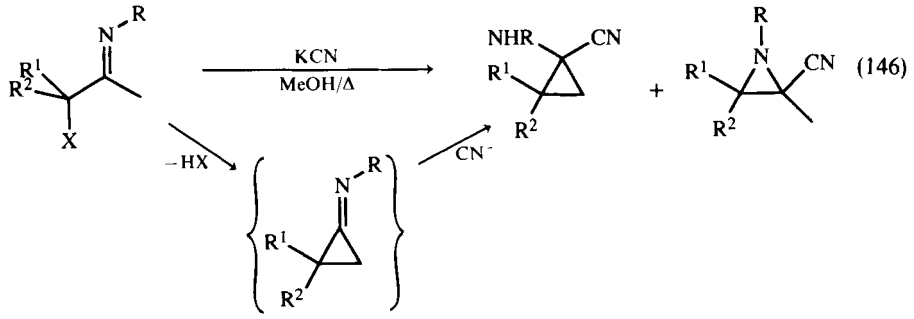
Weak bases have been used to achieve the rearrangement of a series of dimethyl acetals of α-sulphonyloxypropiophenones[349]. When enantiomerically pure 10-camphorosulphonyl is used as leaving group, diastereomerically pure 1-aryl-1,1-dimethoxy-2-(camphorsulphonyloxy) propanes can be isolated and submitted to rearrangement, to afford optically active 2-arylpropanoic acids[350]. The reaction proceeds with 100% inversion of configuration at $C_{(2)}$ of the starting propiophenone. Asymmetric synthesis of these compounds is a very important goal, since one enantiomer usually shows much higher pharmaceutical activity than the other. Another report on the synthesis of enantiomerically pure 2-arylpropanoic acids is the rearrangement of acetals of optically active aryl 1-chloroethyl ketones catalysed by zinc salts[351] (equations 152 and 153).


base
—Cl
RO
b
R¹ = R² = H, alkyl
a, R¹ = Ph
a
b

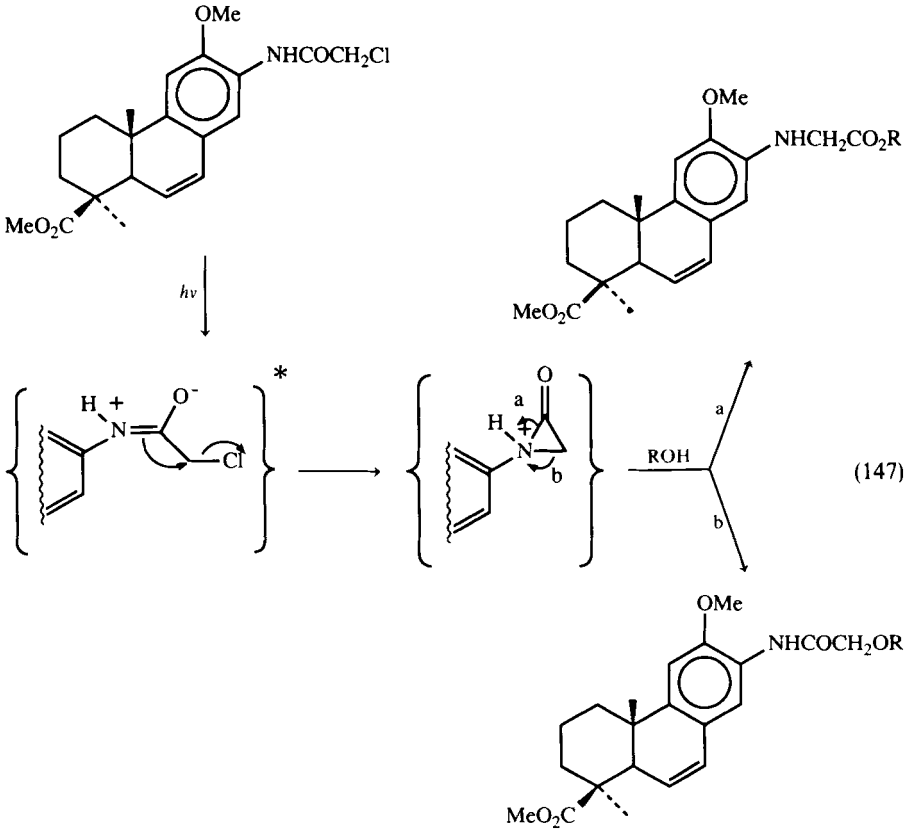
(144)


2 KOBu-t
THF
70–80%
OSiMe3
OH
NHR
20–30%

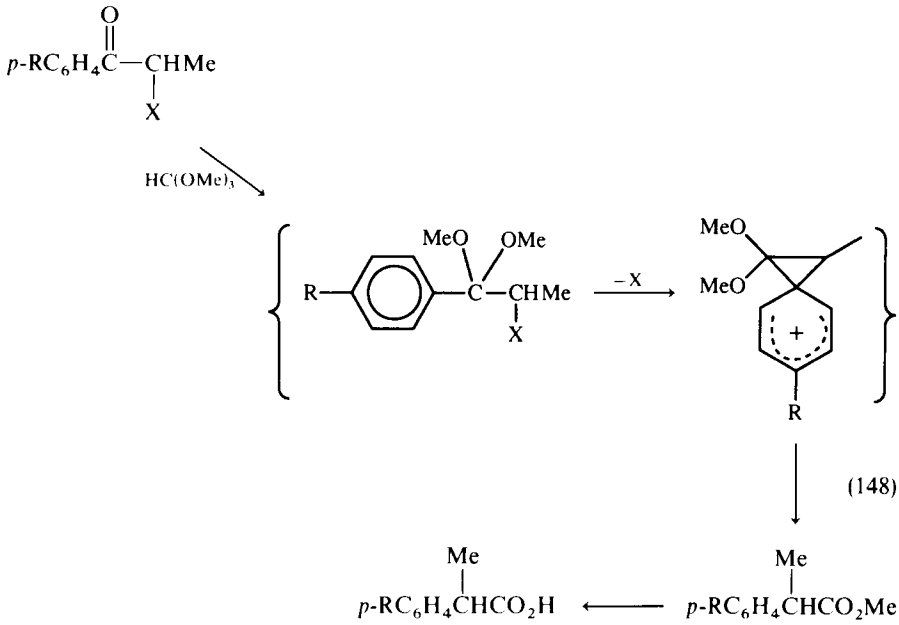
(145)


KCN
MeOH/Δ
−HX
CN⁻
NHR
CN
R¹
R²
X
N
R
+

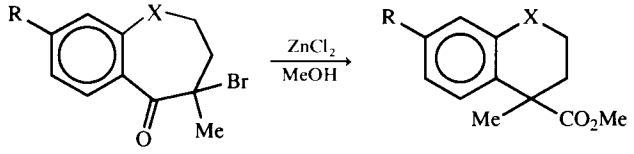
(146)


OMe
NHCOCH₂Cl
MeO₂C
hν
NHCH₂CO₂R
ROH
a
b
NHCOCH₂OR

(147)

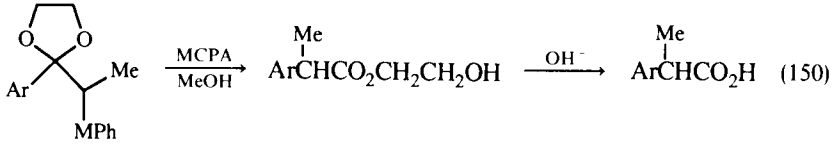


(148)



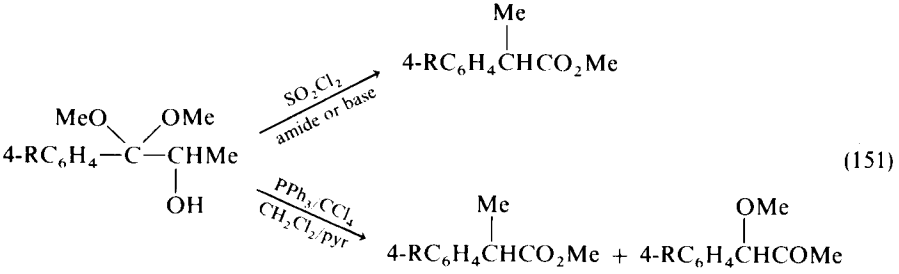
(149)

R = H, MeO; X = O, CH_2

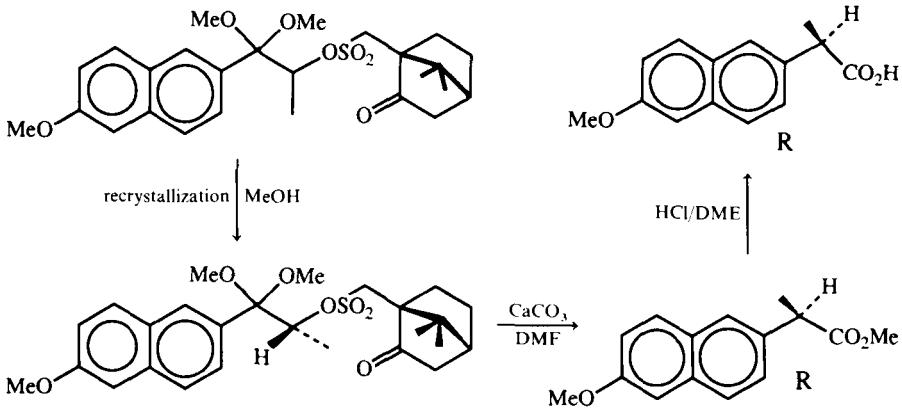


(150)

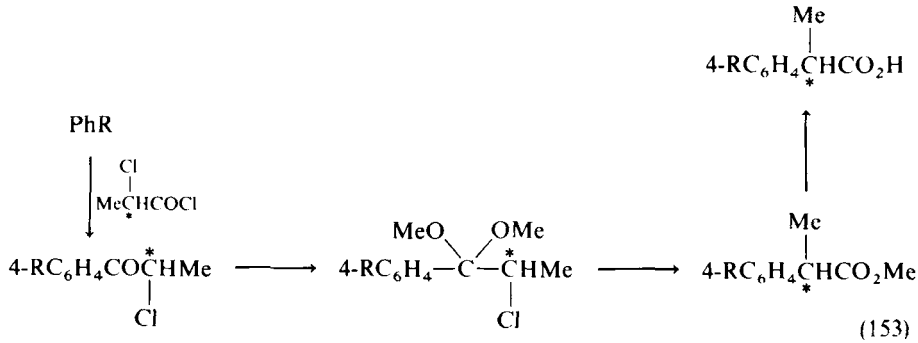
M = Se, Te



(151)

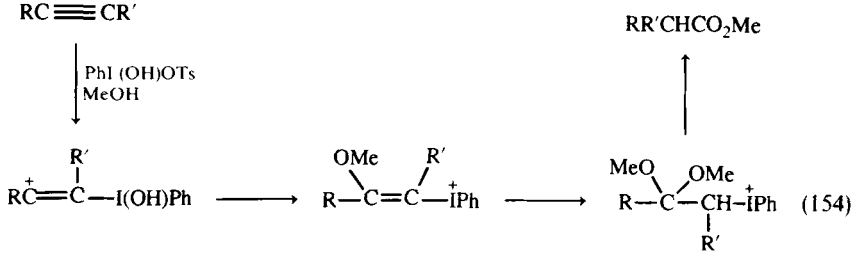


(152)

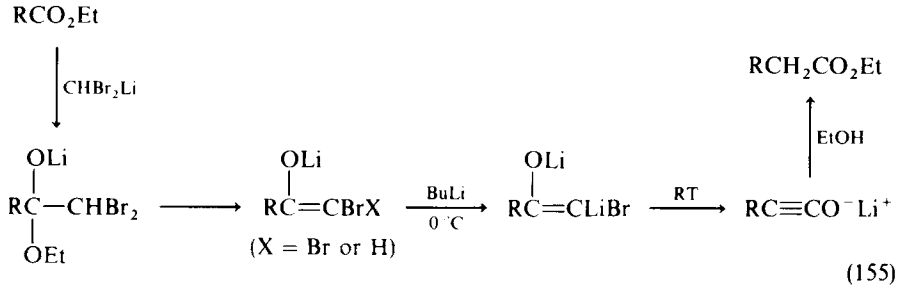


(153)

Aryl alkyl ketones can be directly transformed into 2-arylalkanoic acid derivatives by oxidative rearrangement under more strenuous conditions[341,342]. Thallium trinitrate, lead tetraacetate[352] and hypervalent iodine compounds can be used as oxidants. Similarly, oxidative rearrangement of 1-arylpropynes yields 2-arylpropanoic acids. This method has been extended to the preparation of carboxylic acids from aliphatic, terminal and non-terminal alkynes by reaction with [hydroxy(tosyloxy)iodo] benzene in methanol[353]. Finally, a new methodology for ester homologation, based on the rearrangement of α-bromo-α-keto dianions to alkynolate anions, has been reported[354]. This reaction applies to branched and non-branched alkyl, aryl, alkenyl and alkynyl esters, as well as for lactones (equations 154 and 155).



(154)

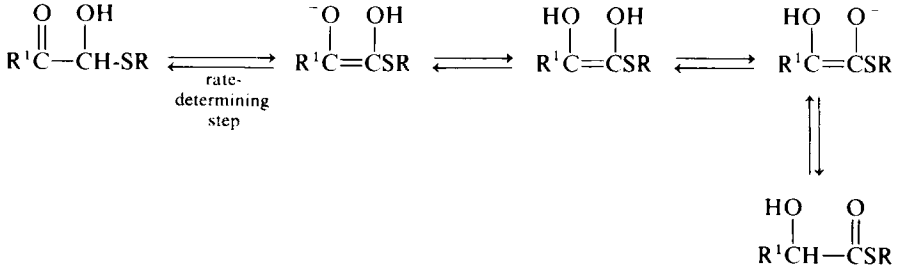


(155)

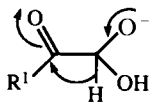
D. Ketol Rearrangement

Under this heading two different types of processes are discussed, having both in common the involvement of two interacting moieties (a carbonyl and a hydroxy group) attached to the same molecular framework. The major difference between the two processes consists in the type of activation required: acid or base catalysis for the α-ketol and related rearrangements, which lead to α-hydroxyacids, or UV-light irradiation for the transformation of ω-hydroxycycloalkenones into lactones.

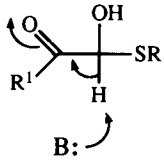
Rearrangements of the hemithioacetals of glyoxal derivatives gives rise to α-hydroxythiocarboxylic *S*-esters through an intramolecular Cannizaro-like reaction (equation 156). This transformation is relevant to the way of action of glutathione, a tripeptide thiol cofactor of the glyoxalase enzymatic system that catalyses the conversion of glyoxals into the corresponding α-hydroxyacids. It is thought that these enzymes play a role in the regulation of cell division and hence their inhibitors may have anticancer activity.



(156)



hydride transfer
benzilic acid rearrangement

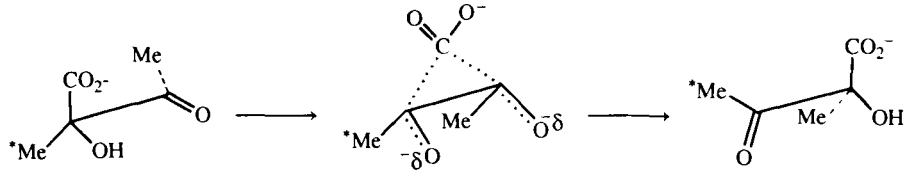


proton transfer

Although this reaction is closely related to the rearrangement of arylglyoxal hydrates in base, it has been shown that the hydride ion transfer mechanism of the benzilic

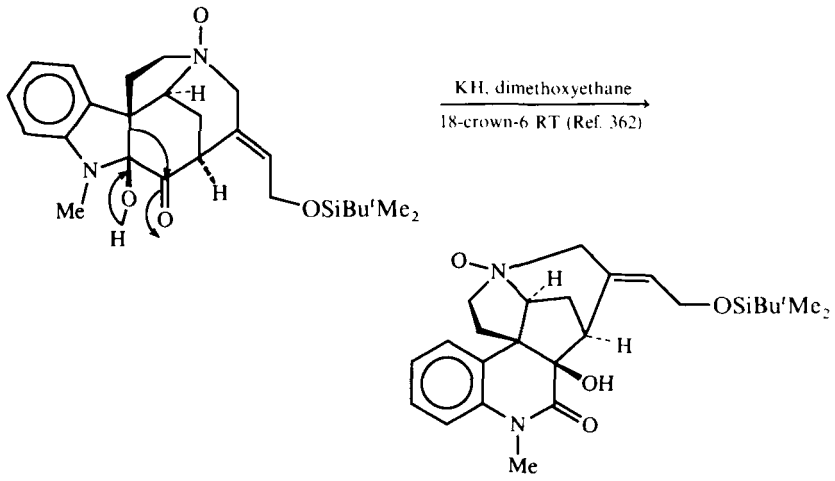
transposition does not apply for the hemithioacetals. Instead, evidence based on flavin-trapping experiments[355], deuterium incorporation into the product[356], effective intramolecular general base catalysis[357], influence of Hammett σ-constants of the substituents[358] and kinetic measurements[356-358] points to the intermediacy of enediol species arising from an initial rate-determining proton transfer. Nevertheless, the involvement of radical intermediates generated by single electron transfer from the alkoxide to the carbonyl group for the Cannizaro reaction has also been suggested[359] (equation 156).

As in the benzilic acid rearrangement, an example of carboxylate ion migration has been reported for the base-catalysed reversible transposition of α-acetolactate and 2-ethyl-2-hydroxy-3-oxobutanoate, which results in the interconversion between the hydroxy and the ketone groups of the molecule[360] (equation 157).

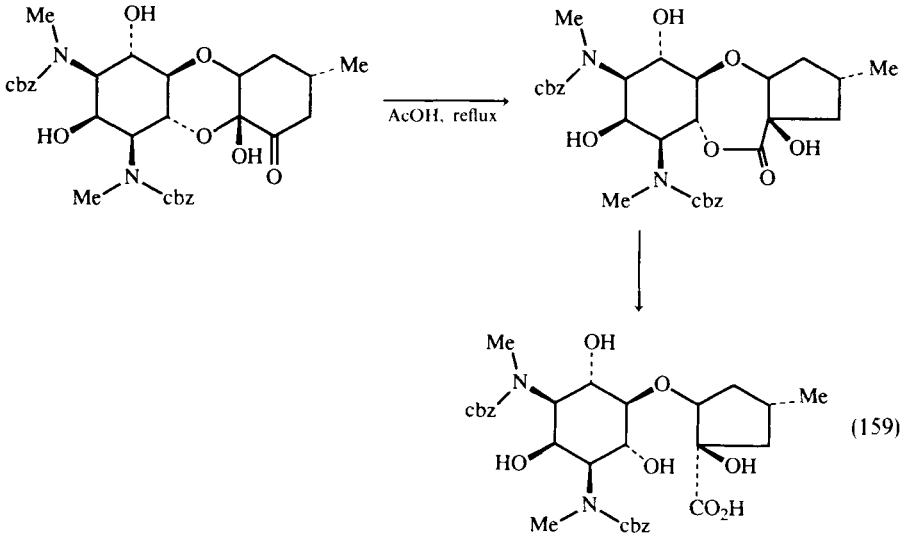


(157)

A variant of the ketol rearrangement has been used as the key step for the conversion of pentacyclic *Aspidosperma* and *Strychnos* indole alkaloids into quinoline derivatives[361,362]. The α-amino-α-hydroxyketone moiety, upon treatment with potassium hydride, undergoes a tandem fragmentation-recyclization with retention of stereochemistry, to give the desired ring junction. An additional example of stereocontrolled modification of the cycle size in polycyclic systems, by way of a ketol rearrangement, has been reported for the acid-catalysed transformation of spectinomycin into spectinoic lactone[363]. A different pathway is followed by a 3-hydroxy-1,4-benzodiazepine derivative, which upon thermal extrusion of CO and ring contraction gives rise to a quinazolinecarbaldehyde[364] (equations 158-161).



(158)



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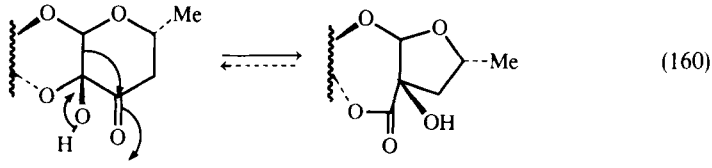
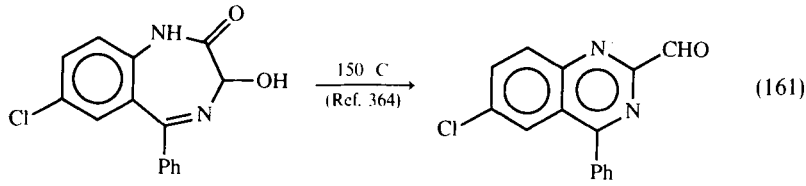


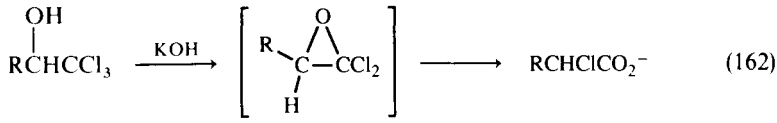
(160)



(161)

A wide variety of substrates without the ketol functionality become involved in reactions with some analogy to the ketol rearrangement. Some selected examples are the potassium hydroxide promoted rearrangement of trichloroethanol and secondary trichloromethylcarbinols to α-chloroacetic acids[365], the acid-catalysed transformation of α-hydroxy-γ-oxoacetals to γ-oxoesters[366] and the photochemical 1,5-methyl migration of *S*-butyl 3-methoxy-2-butenethioate to 4-butylthio-4-methoxy-2-butenone[367] (equations 162–164).

On the other hand, a completely different type of rearrangement involving the α-hydroxyketone moiety is the photochemical conversion of 5-hydroxy-2-cyclopentenones into bicyclic lactones comprising a cyclopropane ring. In fact, this constitutes a particular case of the general photoreactivity found for 2-cyclopentenones. The generally accepted mechanism involves a Norrish Type I homolytic bond cleavage from the excited singlet state, to give a biradical intermediate, followed by cyclization to a hydroxyketene



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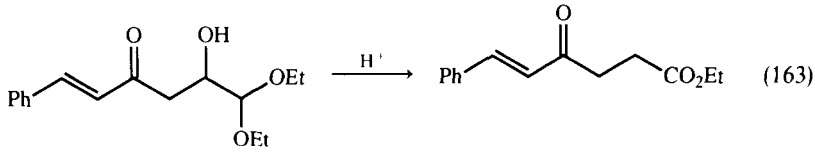
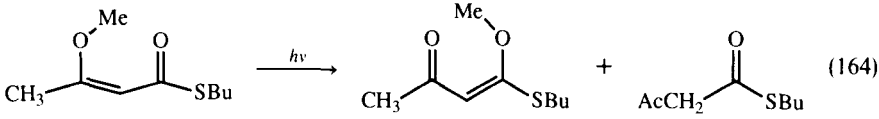
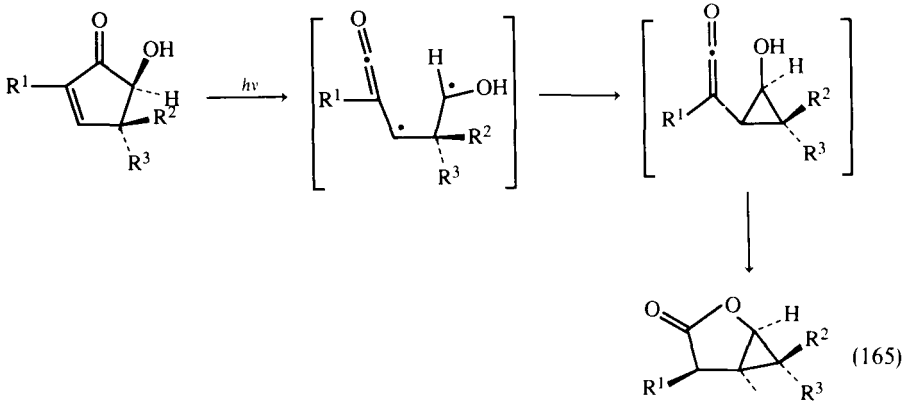


(163)

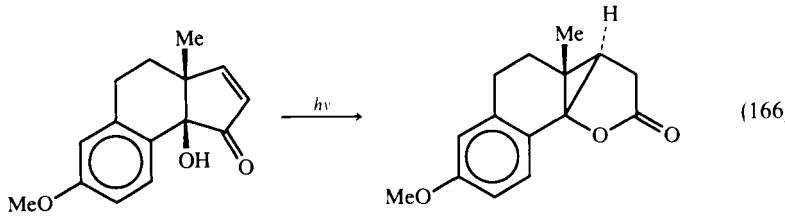


(164)

and final intramolecular trapping, with formation of the lactone ring. The possibility of free rotation in the biradical stage, prior to recombination, would explain the lack of stereospecificity observed for this process[368]. Apparently, hydroxycyclopentenones having a 4-phenyl substituent fail to give the corresponding lactone. Conversely, higher yields are obtained when the hydroxy group is linked to a tertiary carbon, as in the case of a tricyclic ketol steroid with homocyclooestratrienone structure[369]. This has been attributed to the impossibility of deactivation through a competing photoenolization process (equations 165 and 166).

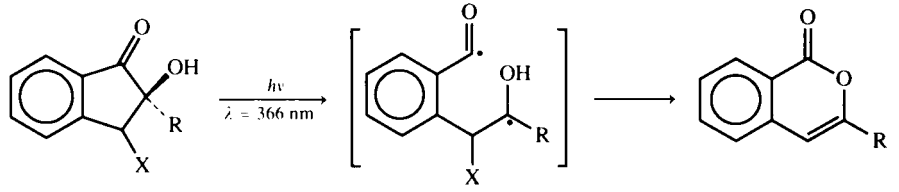


(165)



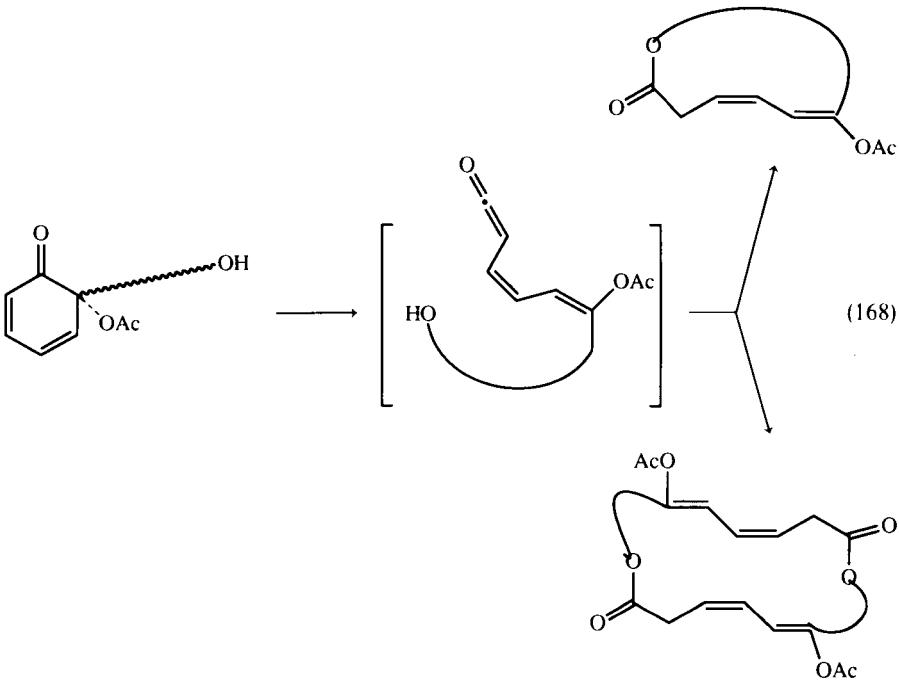
(166)

Likewise, irradiation of 2-hydroxyindanones having a good leaving group (X) at the 3-position gives rise to isocoumarins[370]. The possible involvement of 2,3-epoxyindan-1-ones as intermediates in this rearrangement has been ruled out by stereochemical reasons; however, heterolytic cleavage of the C—X bond must play a role at some stage, since the efficiency of the rearrangement is strongly influenced by the nature of the leaving group. The proposed mechanism is analogous to that described above for simple hydroxycyclopentenones. However, it should be noted that when the 3-substituent is not a good leaving group the photolysis results in ring opening to an *o*-2-oxobenzaldehyde, which is the type of product generally obtained from 2-hydroxyindanones[371] (equation 167).



(167)

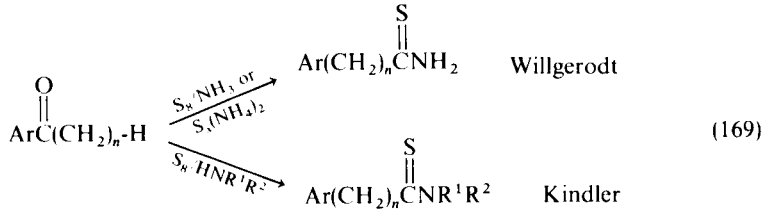
Finally, a comprehensive study of the electrocyclic ring opening of 6-acetoxy-6-alkyl-2,4-cyclohexadienones, to give the corresponding dieneketenes, has been reported[372,373]. These intermediates can be trapped by the nucleophiles present in the reaction medium or intramolecularly, to give unsaturated lactones. The latter process has been claimed to be a convenient route to functionalized macrocycles (equation 168).



(168)

E. Willgerodt–Kindler Rearrangement

This reaction leads to the formation of ω-arylalkanamides and ω-arylalkanoates by oxidation–rearrangement of aryl alkyl ketones in the presence of elementary sulphur and ammonia or ammonium polysulphides. A procedure using primary or secondary amines instead of ammonia, to afford N-substituted or *N,N*-disubstituted ω-arylalkanethioamides, is known as the Kindler modification (equation 169).

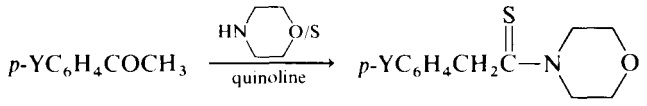


(169)

Although this rearrangement has been studied for many years, a generally accepted reaction mechanism has not yet been established. Therefore, no predictions about the scope and limitations of this reaction can be made based on mechanistic considerations. This fact emphasizes the importance of further exploring this type of rearrangement to obtain more conclusive direct experimental observations. In this context, a series of papers have appeared dealing with optimization of the experimental conditions for the Willgerodt–Kindler reaction of a series of 4-substituted acetophenones[374 378]. It has been found that the yields are strongly influenced by: (a) the nature of the substrate and the amine, (b) the ratios sulphur-to-ketone and amino-to-ketone, and (c) the reaction temperature. Since the variables are not independent and show an appreciable interaction, a multivariate statistic correlation between them is required. The 'response surface' and the 'projection to latent structures' methods have been used to determine the best conditions for each system studied. This methodology also allows one to predict the optimum conditions for other aryl ketones and amines, provided that appropriate descriptors of the reagents and solvents are available. Some predictions made according to this model have been subsequently validated by experimental runs[375 377]. Except for acetophenones with electron-withdrawing substituents, which fail to give the Willgerodt–Kindler product, the optimized yields achieved are in all cases very high (equation 170).

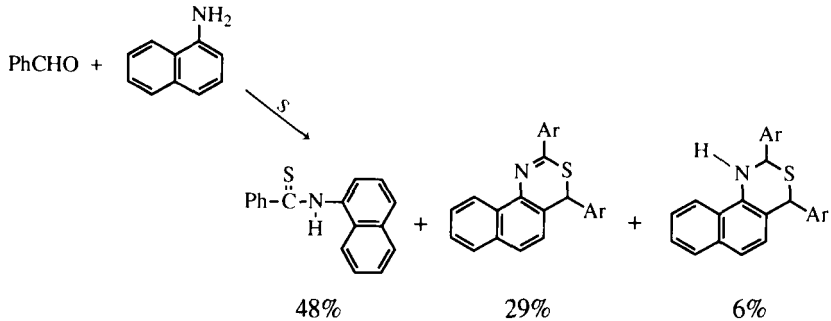
On the other hand, the fact that quite different solvents (polar, non-polar, hydrogen-bond donors and hydrogen-bond acceptors) show a consistent response matrix appears to be against a purely ionic mechanism for this reaction. A wide variety of amines can be used to effect the rearrangement, including branched and unbranched primary amines, as well as secondary amines. Since rather different ratios of sulphur-to-ketone and amine-to-ketone are required in each case to optimize the reaction product, the lack of previous optimization studies explains why morpholine has been considered as the only suitable reagent to perform the Willgerodt–Kindler rearrangement under 'standard conditions'[379].

Polycyclic aromatic amines also react with benzaldehyde and sulphur to give, along with the corresponding Willgerodt–Kindler product, appreciable amounts of condensed 1,3-thiazines[380]. It has been found that the latter arise through Diels–Alder cycloaddition between the imine of benzaldehyde and thiobenzaldehyde, followed by 1,3-hydrogen shift and dehydrogenation by sulphur. At the same time, it has been found that neither the thiazines nor thiobenzaldehyde are reaction intermediates in the formation of *N*-aryl benzothiamides. Analogous reaction of aldehydes with 1,3-diazacycloalkenones in the presence of sulphur fails to give the Willgerodt–Kindler thioamides[381] (equation 171).



(170)

Y	Optimum conditions: Amount of sulphur/ketone (mol/mol)	Optimum conditions: Amount morpholine/ketone (mol/mol)	Optimum conditions: Temperature (°C)	Optimum yields: Predicted (%)	Optimum yields: Found (%)
Me	9.6	8.4	133	96.0	96
MeO	9.3	8.9	130	98.2	100
H	7.5	10.3	123	90.8	94
Cl	9.7	9.9	119	95.0	100
Me_2N	8.8	8.3	127	89.0	89
F	8.3	10.6	116	94.0	93
Br	10.2	9.5	121	95.0	95
MeS	10.4	8.4	129	97.0	95



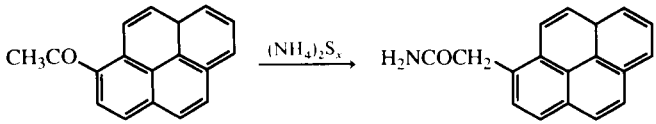
(171)

However, sulphur-containing heterocycles are proposed[382,383] to intervene in the most characteristic feature of the Willgerodt–Kindler reaction, i.e. isomerization of the carbonyl group along a chain. Thus, the first step of the Kindler migration of the carbonyl function would be the reversible formation of an enamine by reaction with a secondary amine. This enamine would be attacked by certain sulphide-amine species to form reactive heterocyclic sulphur intermediates, facilitating the elimination readdition of the amine along the chain. Compounds of the type $R_2NS—SNR_2$ have been shown to be efficient catalysts for this process, while the reverse is true for species of the type $R_2N—S—NR_2$.

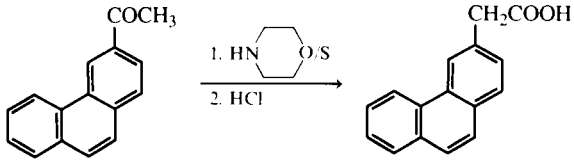
Migration of a carbonyl group around a cycloaliphatic ring containing several connected methylene groups is known to take place under Willgerodt–Kindler conditions. Some additional examples[384,385] describe the isomerization of triterpenoid ketones.

From the preparative point of view, the Willgerodt reaction and its Kindler modification are still widely used to achieve the rearrangement of aryl methyl ketones into arylacetic acids. Starting materials include acetophenones[386–388], 1-acetylpyrenes[389], acetylphenanthrenes[390] and 4-acetylbenzofuran[391]. In the case of acetylpyrene deriva-

tives, the Willgerodt–Kindler reaction was found to be more convenient than the treatment with thallium(III) nitrate[389], while the latter reagent gives higher yields of phenanthrylacetic acids[390] (equations 172 and 173).

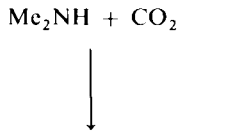


(172)



(173)

Two synthetic procedures have been based on the use of ammonium salts in the Willgerodt–Kindler rearrangement, in order to circumvent the low boiling point of *N*,*N*-dimethylamine. Thus, aromatic aldehydes and ketones react with sulphur, dimethylammonium chloride and anhydrous sodium acetate in DMF, pyridine or DMSO, to afford the *N*,*N*-dimethylthioamides in good yields[392]. The same transformation can be performed using the easily accessible dimethylammonium dimethylcarbamate, which is also effective to afford the thioamide products starting from styrene, phenylacetylene and benzyl cyanide and chlorides[393] (equations 174–178).

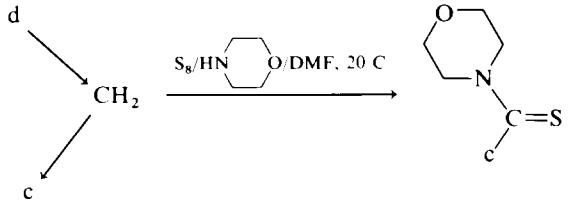


Starting material → Product

Starting material	Product	
PhCHO PhCH$_2$Cl PhCHCl$_2$	PhC(=S)NMe$_2$	(174)
PhCOCH$_3$ PhCH=CH$_2$ PhC≡CH	PhCH$_2$C(=S)NMe$_2$	(175)
PhCOCH$_2$CH$_3$	PhCH$_2$CH$_2$C(=S)NMe$_2$	(176)
3-PyrCOCH$_3$	3-PyrCH$_2$CSNMe$_2$	(177)

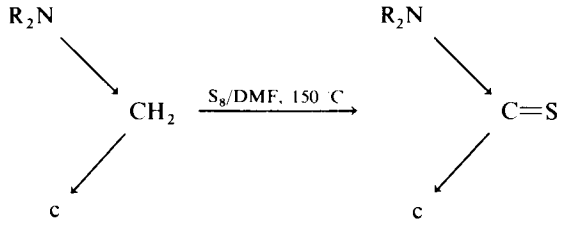
(178)

The reaction of captodative methylene groups (i.e. those simultaneously attached to a donor and an acceptor substituent) under Willgerodt–Kindler conditions, to give morpholides, has been found to be of general applicability[394] (equations 179 and 180). When aminomethylene groups are treated with sulphur, without addition of morpholine, thioamide derivatives are also produced.



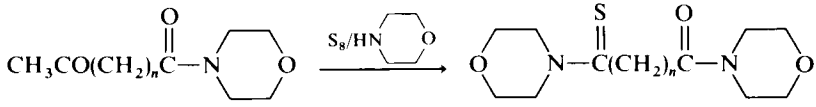
(179)

d = donor group	c = acceptor group	Yield (%)
EtS—	CH_3CO—	26
Cl—	CH_3CO—	73
Cl—	NC—	42
Cl—	*p*-NCC_6H_4—	54



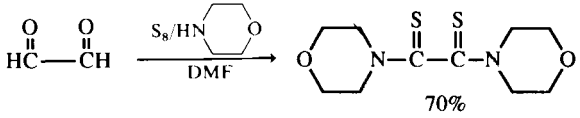
(180)

Finally, the Willgerodt–Kindler rearrangement has been applied to the preparation of monothio diamides of malonic and succinic acids, starting from pyruvic amide and acetoacetamide, respectively[395] (equations 181–183). The same method affords dithio amides of oxalic and malonic acids from glyoxal and acetone.

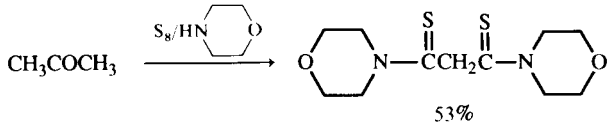


(181)

	Yield (%)
$n = 0$	44
$n = 1$	84



(182)



(183)

F. Wolff Rearrangement and Arndt–Eistert Synthesis

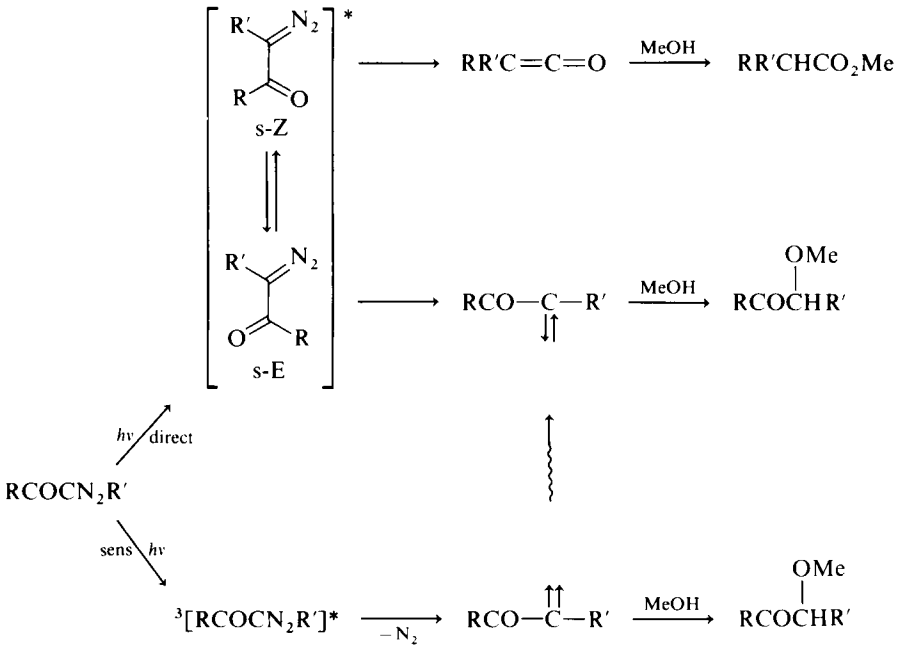
The mechanistic details of the Wolff rearrangement still continue to attract much attention. This is mainly due to the elusiveness of the species involved in the transposition (carbenes, oxirenes and ketenes), which has led to much speculation and controversy in the interpretation of the experimental results.

The photochemical version of this reaction is much more convenient to study than the thermal or catalytic transformation of diazoketones into carboxylic acid derivatives. In this way, variations of the product distribution in the direct and triplet-sensitized photolysis of methyl α-diazoacetate and α-diazocarbonyl compounds at different temperatures has led one to propose[396] that the Wolff rearrangement can take place in some cases in a one-step concerted way, elimination of nitrogen occurring at the same time as migration, from the singlet excited state of the *s-Z* conformer, to afford directly ketene, whereas the excited singlet state of the *s-E* conformer denitrogenates to generate singlet ketocarbene. This intermediate either gives rise to ketene or undergoes characteristic carbene reactions, e.g. insertion or 1,2-hydrogen shift, depending on the migratory aptitude of the substituent. Substantial amounts of singlet carbene can be formed even under sensitized conditions, presumably via efficient intersystem crossing from the initial triplet carbene (equation 184).

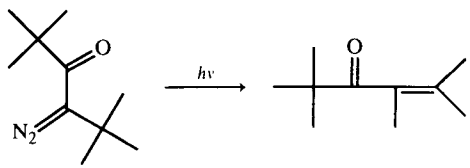
This interpretation fits the initial suggestion of Kaplan and Mitchell concerning the involvement of a concerted mechanism in the Wolff rearrangement[397], and is also in agreement with the CIDNP studies on the decomposition of α-diazoacetone[398]. Moreover, the results obtained in the photochemical and thermal rearrangement in 1-aryl-2-diazo-1,3-alkanediones are in agreement with migration of aryl taking place directly from the excited singlet state of the starting diazo compound, while alkyl migration would occur from the singlet carbene in competition with OH insertion[399].

Several attempts to obtain direct experimental evidence for the nature of the actual intermediates involved in the Wolff rearrangement by means of microsecond flash photolysis of α-diazoketones in argon matrices[400–402], or also during the gas-phase photolysis of 3-diazo-2-butanone monitored by FTIR[403], failed to detect any species other than ketene, although the importance of the conformational control on this rearrangement has been again pointed out[402]. In this context, the preference for a *s-Z* conformation in the Wolff rearrangement has been demonstrated by alternative generation of ketenes through photolysis of cyclic vinylene thioxocarbonates[402,404], which possess a rigid *s-Z* stereochemistry. Comparison of these results with those attained from α-diazoketones (equations 185 and 186) reveals that cyclic precursors are always much more efficient to effect this rearrangement.

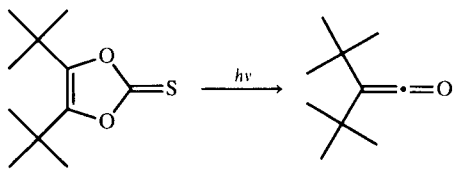
Although there is a significant number of reports about the EPR detection of triplet state ketocarbenes generated by photochemical extrusion of dinitrogen in α-diazoketones at low temperatures[405–411], the first UV-Vis, IR and ESR characterization of α-



(184)

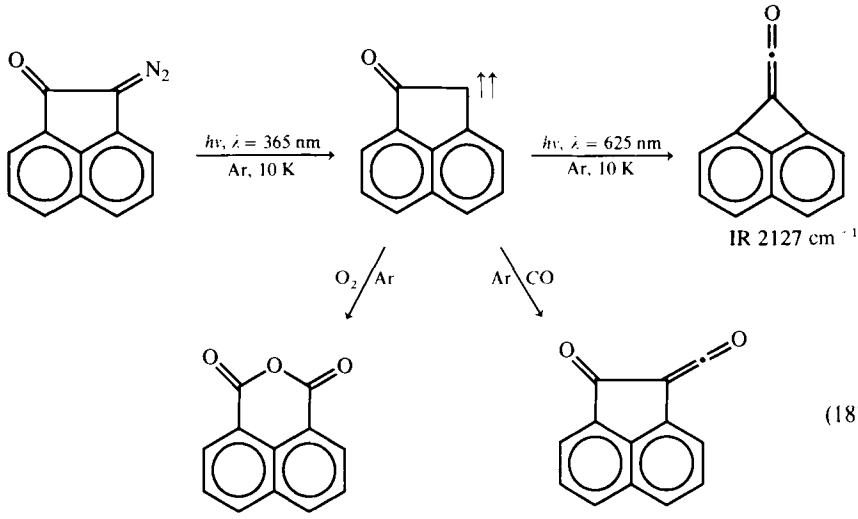


(185)



(186)

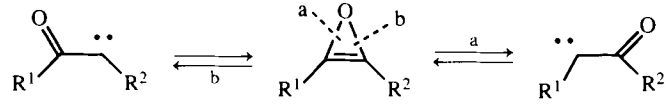
ketocarbenes has been achieved for 2-diazo-1(2*H*)-acenaphthylenones and the 1-diazocyclopent[*c,d*]azulen-2-one in argon matrices at 15 K[412,413]. These compounds are especially adequate substrates to study the spectroscopy and chemistry of the corresponding α-ketocarbenes, since a severe strain in the transition state for ring contraction hinders the Wolff rearrangement[414]. Additional trapping with carbon monoxide and oxygen provides chemical evidence of the spectroscopically characterized α-ketocarbenes (equation 187).



(187)

Spectroscopic monitoring in the photolysis has clearly established that triplet ground state (T_0) ketocarbenes are the primary photoproducts obtained upon irradiation of the diazo ketones, since no ketenes can be initially detected. Photolysis of the triplet ketocarbenes gives rise to the corresponding ketenes, probably through an upper singlet excited state, since the first singlet excited state must be unreactive with respect to the Wolff rearrangement, due to the postulated fast intersystem crossing leading to the more stable T_0 state. This constitutes the first unambiguous example of a fully non-concerted Wolff rearrangement. It is noteworthy that no evidence for oxirene participation has been obtained for these strained diazo ketones.

However, ketocarbene–ketocarbene interconversion has been well established from both thermal and photochemical studies of unsymmetrical substituted diazo ketones and from label scrambling in isotopically marked diazo ketones[402,415 419]. It is widely accepted that these ketocarbene isomerizations occur through oxirene intermediates or oxirene-like transition states[419] (equation 188).



(188)

A kinetic study on the laser flash photolysis of sodium 1-oxo-2-diazonaphthoquinone-5-sulphonate in water solution at 298 K has revealed the existence of one transient species, which appears immediately after the laser pulse and is the precursor of the corresponding ketene[420]. Since this intermediate has been found to be insensitive to the presence of oxygen and does not react with methanol, the possibility that it could correspond to a ketocarbene has been ruled out. Hence, the intermediate is most likely an oxirene.

Evidence for these elusive intermediates has been finally obtained recording the FTIR spectra at different times during the photolysis of 3-diazo-2-butanone isolated in rare gas matrices at temperatures below 25 K[421]. The high wavenumber (2137 cm^{-1}) observed for the C=C vibrational mode of the 2,3-dimethyloxirene has been ascertained by means of SFC calculations, which are in good agreement with that value. Although

the α-ketocarbene cannot be positively observed at the same time, due to the coincidence in the carbonyl region of the absorptions arising from conformers of buten-2-one (one of the reaction products), its intermediacy has been deduced from the discrepancy between the decay of the starting material and the rates of product formation, as well as from trapping with CO to form ketoketene. Moreover, the photoisomerization of oxirene to ketene, presumably through the ketocarbene, has been demonstrated. Finally, these authors argue against the possibility of a concerted component for the Wolff rearrangement in the photolysis of 4-diazo-2,2,5,5-tetramethyl-3-hexanone proposed by Kaplan[397], based on the fact that the product distribution is rather sensitive to the experimental conditions.

With these data at hand, and also with the previously reported results, a theoretical study using the MNDOC-BWEN method has led to a proposed comprehensive energy diagram for the different pathways involved in the photolysis of simple diazo ketones[421] (Figure 1).

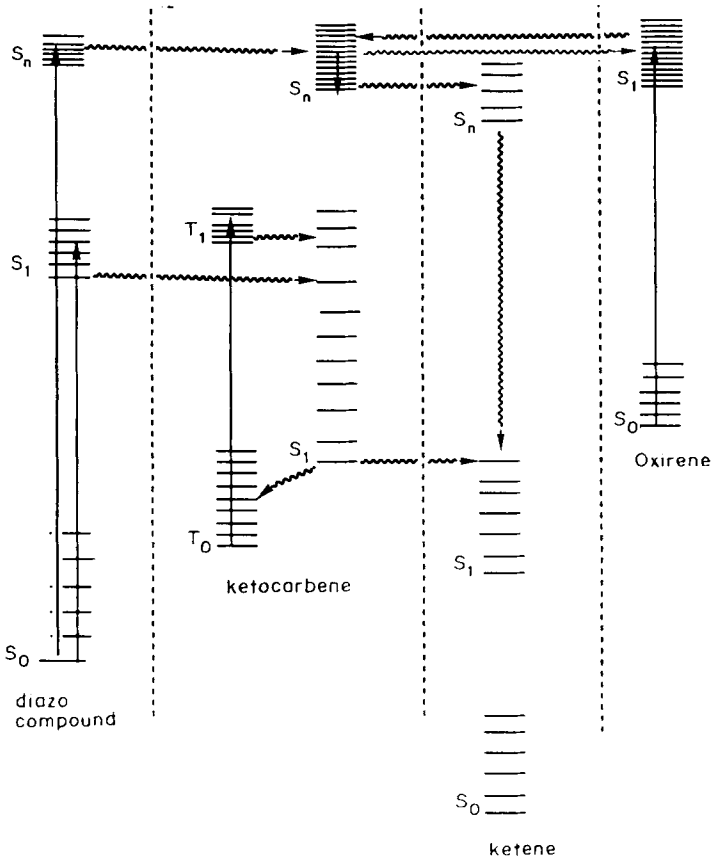
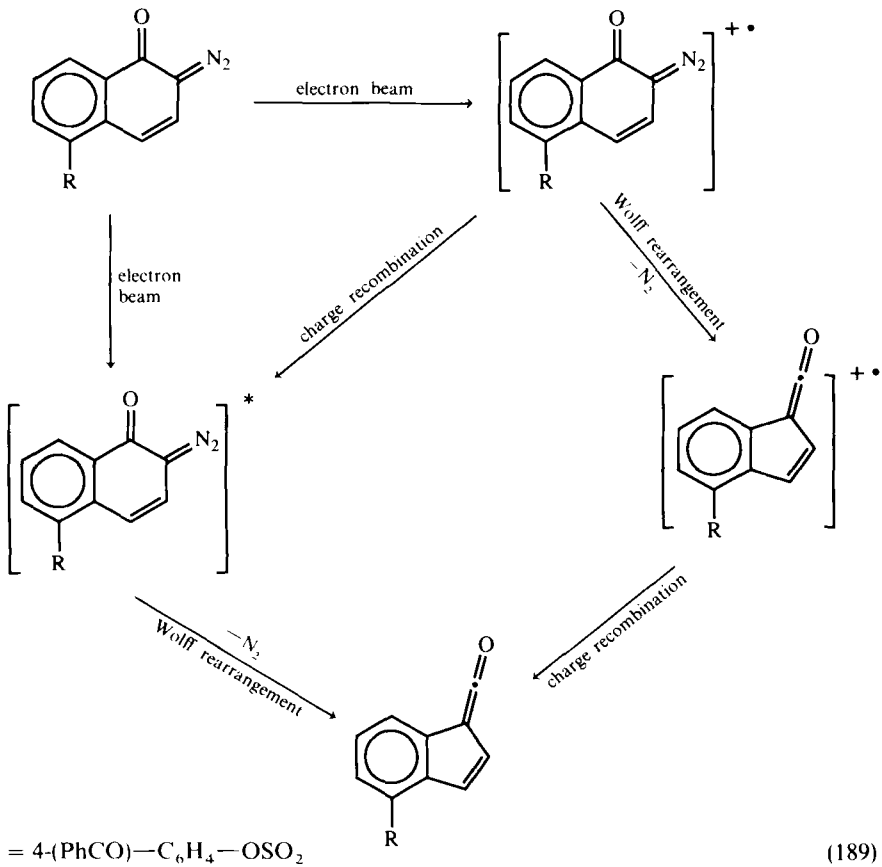


FIGURE 1. Energy correlation diagram for the photolysis of α-diazoketones

These compounds, upon irradiation, give rise to ketocarbenes in the singlet excited states, which after vibrational relaxation rearrange to ketene or alternatively undergo an efficient intersystem crossing to the most stable triplet state. Since all the processes occur in the singlet potential energy surfaces, the triplet ketocarbenes require excitation in order to afford the singlet species, which are the true intermediates. On the other hand, 1,2-hydrogen migration to give α,β-unsaturated ketones must take place from excited vibrational levels of the first singlet state of ketocarbene. This is consistent with the fact that the ratio of the enone increases under conditions in which the vibrational relaxation is disfavoured, such as isolation in krypton matrices or photolysis at low pressure in the gas phase. Similarly, the ketocarbene-oxirene interconversion has an activation barrier and in some cases can compete efficiently with the Wolff rearrangement. Therefore, for some structures such as 4-diazo-2,2,5,5-tetramethyl-3-hexanone, the oxirene appears as a necessary reaction intermediate, which in turn may isomerize thermally or photochemically to the singlet ketocarbene and subsequently to ketene.

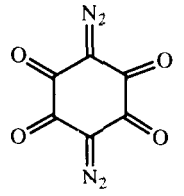
A conceptually new version of the Wolff transposition has been proposed to occur during the electron-beam-induced reaction of 5-substituted 2-diazo-1-oxonaphthalenes[422]. In this case, it has been suggested that the radical cation of the starting



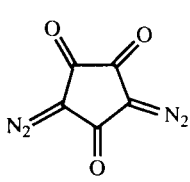
R = 4-(PhCO)—C_6H_4—OSO_2 (189)

diazo ketone can be the actual species undergoing rearrangement to the corresponding ketene radical cation. This interpretation is consistent with electron impact mass spectrometric studies on α-diazo ketones[423,424]. Nevertheless, the possibility that the Wolff rearrangement takes place from the excited states of the diazo ketones, directly reached by electron beam excitation or after initial ionization and subsequent electron capture, cannot be ruled out (equation 189).

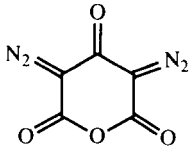
Interesting examples of double and triple Wolff rearrangements, leading to fragmentation with formation of propadienedione, butatrienedione and pentatetraenedione, have been described in the photolysis of cyclic bis(diazo)polycarbonyl compounds[425] and tris(diazo)cyclohexanetrione[426] (equations 190–192).



$$\xrightarrow[-2N_2]{h\nu,\ \Delta} O{=}C{=}C{=}C{=}O \qquad (190)$$



$$\xrightarrow[-2N_2,\ CO]{h\nu} O{=}C{=}C{=}C{=}C{=}O \xleftarrow[-2N_2,\ -CO_2]{h\nu}$$



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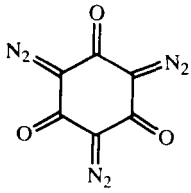
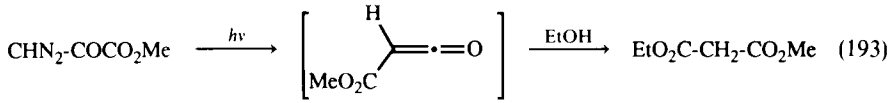


$$\xrightarrow[-3N_2]{h\nu} O{=}C{=}C{=}C{=}C{=}C{=}O \qquad (192)$$

Groups other than alkyl or aryl have been found to be able to migrate. It has been reported that photolysis of methyl 3-diazo-2-oxopropanoate produces shift of the carbomethoxy group, to yield malonic acid derivatives. However, the migratory aptitude of carbomethoxy is lower than that of methyl groups, as shown by the formation of 2-methyl-3-oxosuccinate as the only product in the photolysis of methyl 3-diazo-2,4-dioxopentanoate[427]. It has also been reported that migration of alkylthio substituents occurs in the photolysis of thioester derivatives of α-diazomalonate, affording methyl alkylthioacetate after rearrangement and decarboxylation of the resulting malonic acid[428] (equations 193 and 194). No products arising from the alternative methoxy shift have been observed.

An exampley of 1,2-oxide migration has been reported in the photolysis of salts of α-diazophosphonic acids in methanol, to give α-hydroxyl monomethyl esters[429]. It has been suggested that oxygen migration occurs via an oxaphosphirane intermediate (the



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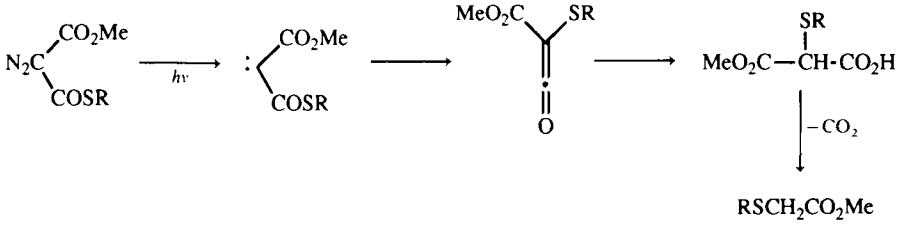
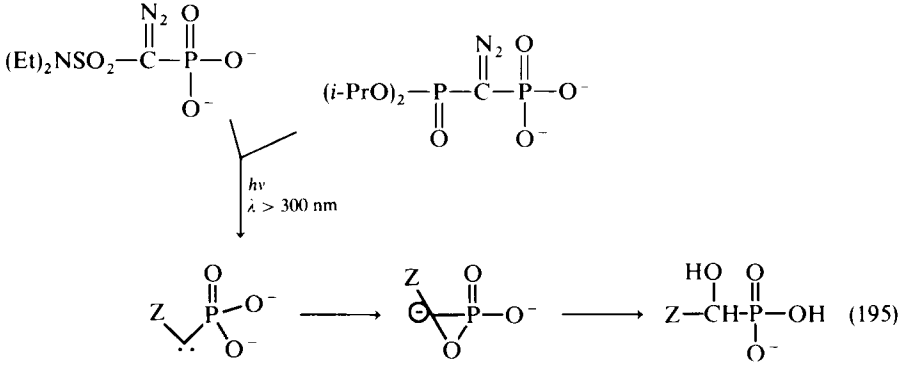


(194)

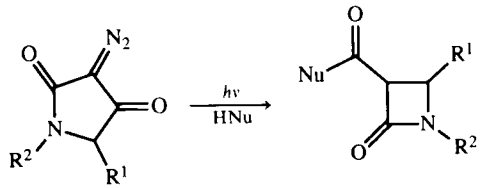
phosphorus analogue of ketene). By contrast, α-phosphonic diesters undergo hydroxyl insertion and photoreduction when alcohols or water are used as solvents[429] (equation 195).



(195)

Z = $Et_2NSO_2^-$ or $(i\text{-}PrO)_2PO^-$

On the other hand, there are several reports indicating that amino groups are not prone to migrate in the Wolff rearrangement. Thus, while (1-diazo-2-oxoalkyl)silanes afford α-silylesters through migration of alkyl group, photolysis of α-diazo-α-silylacetamides gives rise to lactams by carbene insertion into the C—H bonds of the *N*-alkyl substituent[430]. Similar behaviour has been observed in the irradiation of *N*-alkyl-3-diazopyrrolidine-2,4-diones, which affords exclusively β-lactams[431]. However, the same authors have reported a genuine example of amino group migration during the Wolff rearrangement of 4-diazopyrazolidine-3,5-diones to aza-β-lactams[432] (equations 196 and 197).



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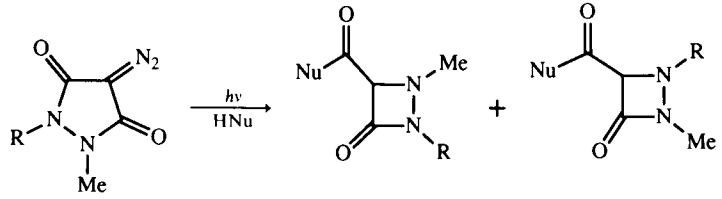
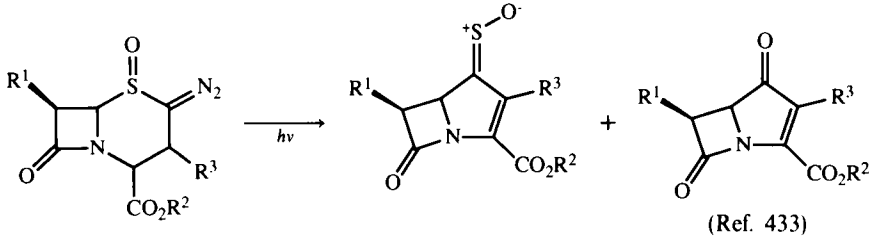


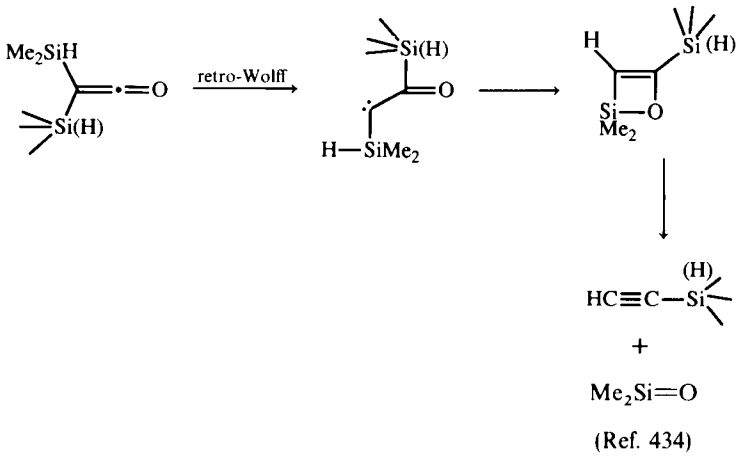
(197)

Two interesting modifications of the α-diazoketone rearrangement involving heteroatoms are relevant in the context of the Wolff reaction, in spite of the fact that no carboxylic acid derivatives are formed. In the first one, cephalosporins comprising an α-diazosulphoxide moiety are converted into carbanopems by means of a Wolff-like transposition[433]. In the second example, a retro-Wolff rearrangement has been claimed to occur, in order to explain extrusion of dimethylsilanone from (hydridosilyl) ketenes[434] (equations 198 and 199). The superb migratory aptitude of silyl groups and the excellent carbene trapping ability of the Si—H bond appear to be responsible for the unprecedented formation of ketocarbenes from ketenes.



(Ref. 433)

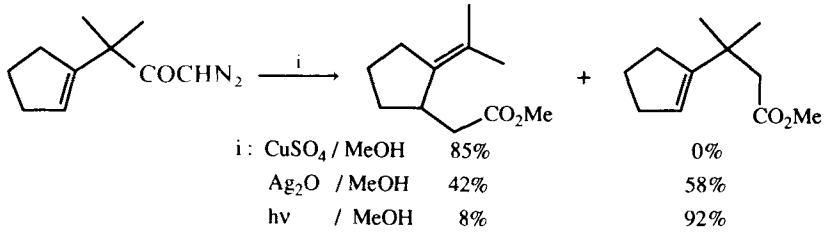
(198)



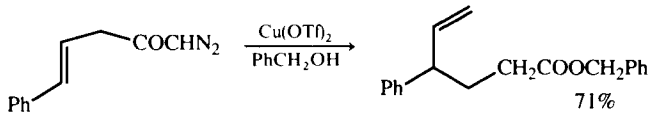
(Ref. 434)

(199)

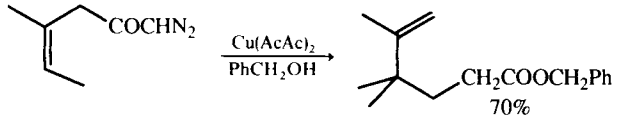
From the preparative point of view, a useful variant of the Arndt-Eistert synthesis consists in the transformation of β,γ-unsaturated diazoketones into γ,δ-unsaturated esters[435 441] (equations 200–204). This reaction, termed as vinylogous Wolff rearrange-



(200)



(201)



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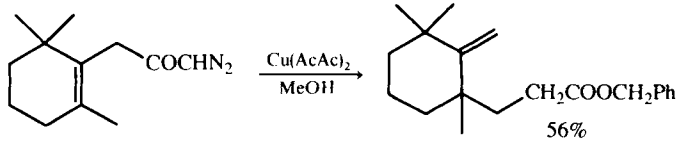
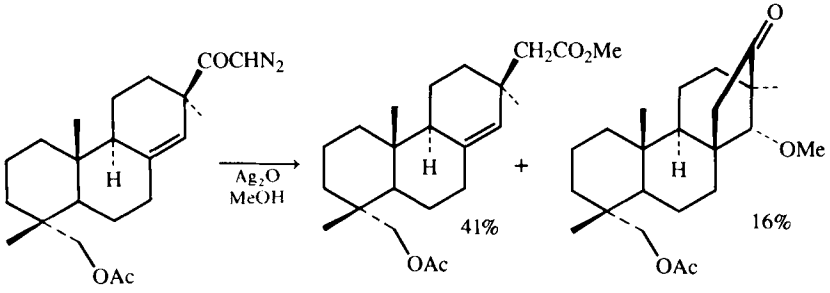


(203)



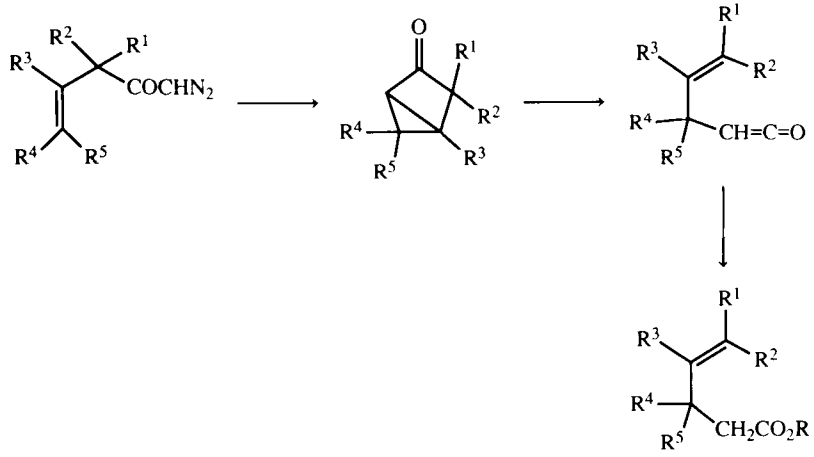
(204)

ment, has been found to be of general applicability, occurring in both acyclic and cyclic substrates.

The best catalysts are based on copper salts [$Cu(AcAc)_2$ and $Cu(OTf)_2$] in alcohols, while photolysis gives rise exclusively to the 'normal' homologated esters and silver oxide affords mixtures of both 'normal' and 'vinylogous' rearranged products[438,441]. The overall reaction yields increase with the degree of substitution at the β,γ-olefinic bond and at the α-position[438]. Although this reaction constitutes a useful alternative to the Ireland–Claisen rearrangement, it must be pointed out that the vinylogous Wolff rearrangement proceeds with little or no stereoselectivity. Concerning the ability of silver

oxide to promote the vinylogous Wolff rearrangement, it has been reported[442] that decomposition of a β,γ-unsaturated diazo ketone with pimarol skeleton leads preferentially to the 'normal' Arndt–Eistert product without implication of the double bond, along with a second isomer with hibaene structure comprising a β-methoxycyclopentanone moiety.

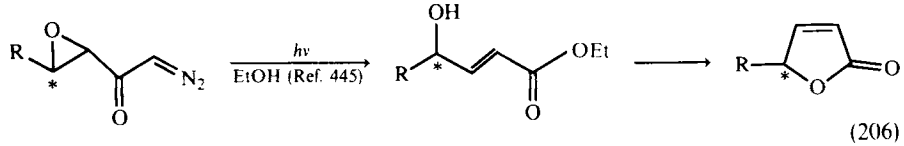
The most likely mechanism for the vinylogous Wolff rearrangement[439] involves formation of an intermediate with bicyclo[2.1.0]pentane skeleton, via insertion into the β,γ-olefin. Fragmentation of this intermediate would then lead to a β,γ-unsaturated ketene. Detection by IR and TLC of this species, together with reactivity studies on bicyclopentanones prepared by alternative syntheses, provide strong support to this proposal (equation 205).



(205)

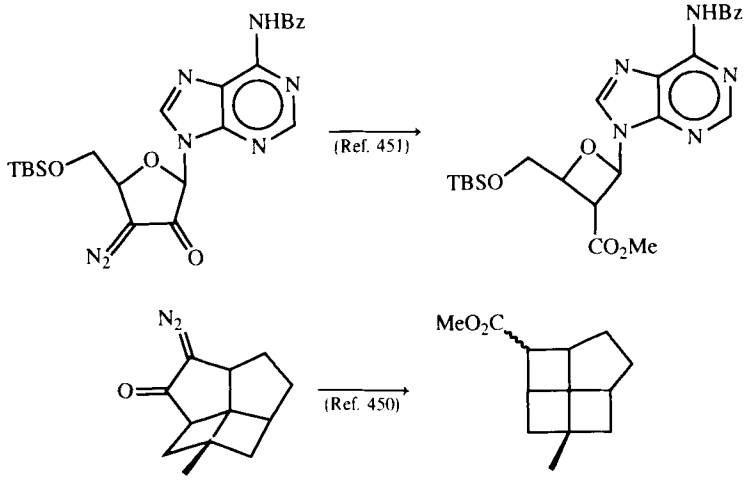
If the location of the double bond is γ,δ relative to the diazoketone no acid derivatives are obtained, but instead carbene insertion occurs leading to the formation of a cyclopropane ring[443,444]. When both processes (γ,δ-cyclopropanation and vinylogous Wolff rearrangement) are structurally possible, it has been shown[438] that the latter pathway predominates in the case of β,γ-olefins equally or favourable substituted as compared to the γ',δ'-double bond. The same trend is observed when a β,γ-olefin competes with a δ',ε'-olefin.

Besides the vinylogous variation of the Arndt–Eistert synthesis, one-carbon homologation of carboxylic acids[445,446] and ring contraction, especially for the construction of four-membered rings[431,432,447–451], still continue to be the most important applications of the Wolff rearrangement. Some selected examples are illustrated in equations 206–208.



(206)

Finally, an application of the Wolff rearrangement in the borderline between chemistry and microelectronics is the use of 2-diazo-1-naphthalenone derivatives as photoresists[452]. In this technique, a semiconductor surface is covered by a multi-component



system containing the photosensitive diazo ketone. Photoprinting produces a change in the solubility of the irradiated regions of the surface from lipophilic naphthalenone, insoluble in aqueous solutions, to the alkali-soluble indenecarboxylic acid. Development of the printed circuit is then easily accomplished by washing with alkali. The same principle is used in a photolithography process[453] (Figure 2).

III. OTHER REARRANGEMENTS

A. Chapman Rearrangement

In the Chapman rearrangement, imidates undergo a thermal oxygen-to-nitrogen aryl or alkyl migration, giving rise to amides. Usually, the three substituents attached to the imino ester functionality are aromatic rings and hence *N,N*-diaryl benzamides are frequently obtained (equation 209).

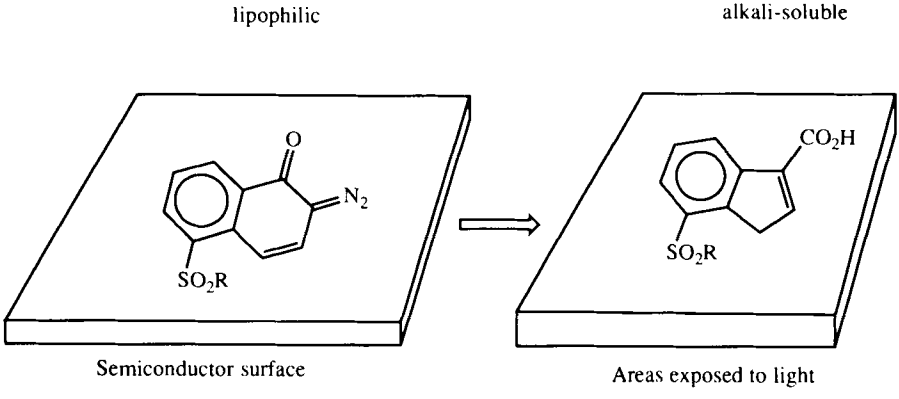
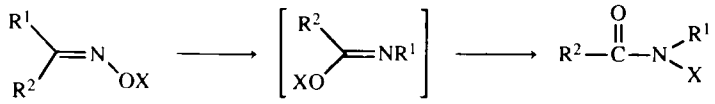


FIGURE 2. Photoprinting process based on solubility changes caused by the Wolff rearrangement

(209)

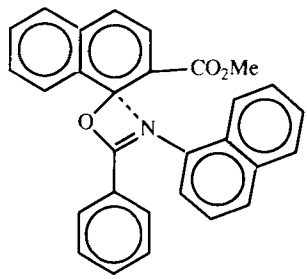
There are a number of Beckmann rearrangements which are thought to involve the transformation of oxime O-derivatives (especially tosyl and 2,4,6-trinitrophenyl) into imidates, followed by transposition of the latter to N-substituted amides. In fact, imidate-like intermediates have been spectroscopically detected, and even isolated, during the course of these reactions. This type of transformation is often referred to in the literature as the Chapman variant of the Beckmann rearrangement and consequently we have dealt with it in the section devoted to the Beckman rearrangement (equation 210).



(210)

X = Tosyl- or 2,4,6(NO_2)C_6H_2

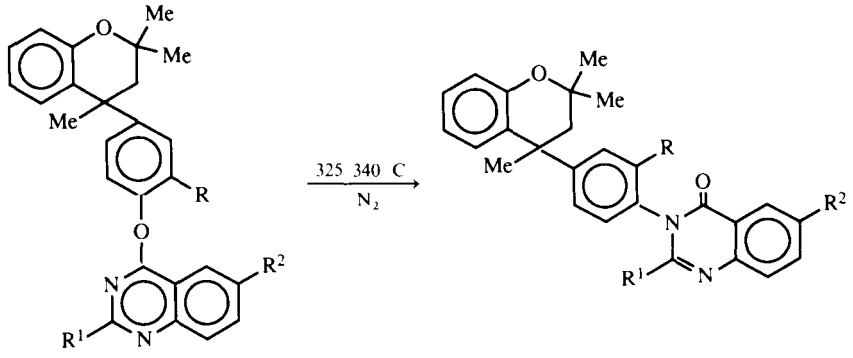
Concerning the more conventional Chapman rearrangement, it is generally assumed that the characteristic 1,3-aryl shift can be considered as an intramolecular nucleophilic aromatic substitution, in which nitrogen is the attacking centre and oxygen is the leaving group. Therefore, the reaction requires formation of a four-membered ring transition state. In this context, determination of the crystal and molecular structure of 2-methoxycarbonyl-1-naphthyl *N*-(1-naphthyl)benzimidate (equation 211) by means of X-ray crystallography has established[454,455] that, although there are no abnormally close intermolecular contacts, the unusual short distance between the nitrogen and the naphthyl carbon attached to oxygen (much shorter than the sum of their van der Waals radii) indicates a non-bonded intramolecular N—C interaction. This finding, together with a bond-angle distortion that directs the nitrogen lone pair towards the migrating naphthyl centre, provides strong support for the accepted 3-oxazetidin mechanism. In fact, this substituted *N*-naphthylbenzimidate rearranges under mild conditions to the corresponding *N*,*N*-dinaphthylbenzamide, which in turn readily undergoes hydrolysis and intramolecular acylation, to give 9-(10*H*)-acridone. A closely related preparation of antiinflammatory *N*-arylanthranilic acids by Chapman rearrangement to *N*,*N*-diarylamides and subsequent hydrolysis has been reported[456].



(211)

The pyridine ring can also undergo this oxygen-to-nitrogen migration, as exemplified by the obtention of *N*-phenyl-*N*-(3-pyridyl)benzamide from 3-pyridyl *N*-phenylbenzimidate[457]. An analogous pyridyl migration occurs during the transposition of 5-picoline

N-phenylbenzimidate, which constitutes the key step in the synthesis of the potentially anthelmintic 6-phenylaminoimidazol[1,2-*a*]pyridine, starting from 5-hydroxy-2-picoline[458]. It appears that the Chapman rearrangement can also take place when the imino C=N double bond is included in a heterocyclic ring. Thus, a series of *N*-(4-chromanylphenyl)quinazolin-4-ones have been obtained by heating the corresponding 4-(4-chromanylphenoxy)quinazolines at about 340 °C[459] (equation 212).



$R = H, NH_2, NO_2$
$R^1 = H, Me, Et, i\text{-}Pr, Ph$
$R^2 = H, MeO$ (212)

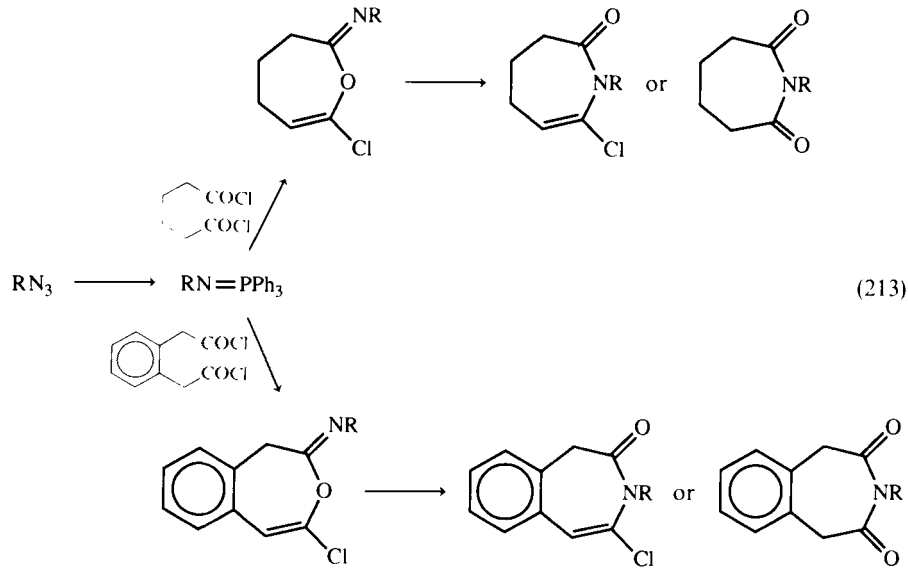
A methyl shift has been reported to occur during the transformation of methyl *N*-(α-phenylalkyl) and *N*-(α-methoxycarbonylalkyl) benzimidates into the corresponding *N*-alkyl-*N*-methylbenzamides[460]. The most relevant feature of this reaction is the catalytic effect of methyl iodide, which suggests that an intermolecular mechanism is operating.

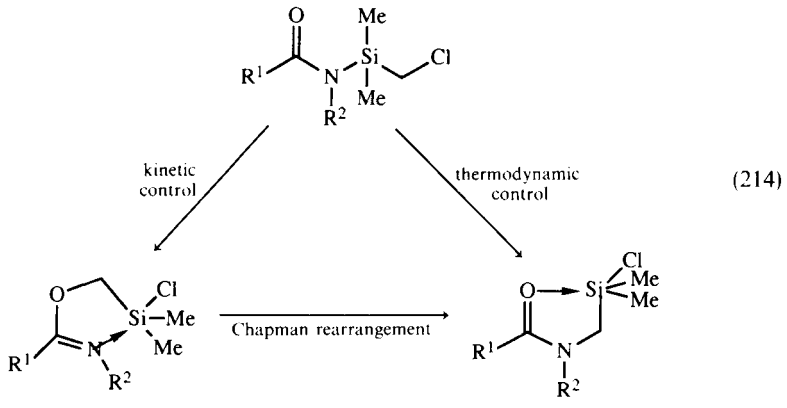
Aliphatic Chapman rearrangement has been assumed to intervene in the condensation of adipoyl chloride or 1,2-benzenediacetyl dichloride with iminophosphoranes[461]. In this case, a 2-imino-2,3,4,5-tetrahydrooxepin, formed from the imidoyl halide resulting after elimination of triphenylphosphine oxide, would undergo oxygen-to-nitrogen transposition of the chloroalkenyl moiety, giving rise to N-substituted 7-chloro-2,3,4,5-tetrahydro-1*H*-azepin-2-ones or their 3-benzazepine analogues. Alternatively, azepine-2,4-diones can be the major final products (equation 213).

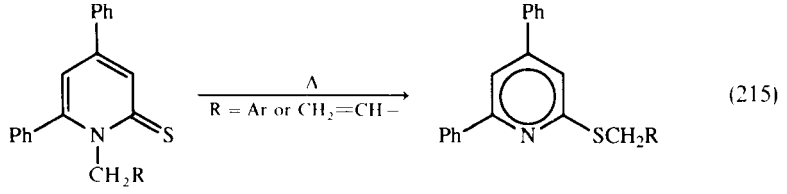
An additional example of the aliphatic variant of this rearrangement is the transformation of *O*-[chlorodimethylsilyl)methyl] imidates into *N*-[(chlorodimethylsilyl)methyl] amides and lactams[462]. Both compounds arise from the intramolecular transposition of *N*-[(chloromethyl)dimethylsilyl] amides and lactams under kinetic or thermodynamic control, respectively. It has been shown that imidates possessing a N--Si chelation are intermediates in the formation of the more stable O--Si chelates (equation 214).

A new nitrogen to sulphur benzyl shift, which can be considered as the S-heteroatomic version of a retro-Chapman rearrangement, has been reported[463]. Thus, *N*-substituted 4,6-diphenyl-1,2-dihydropyridine-2-thiones rearrange upon heating at 170 °C, under nitrogen, to give the corresponding 4,6-diphenyl-2-pyridyl sulphides in excellent yields (equation 215).

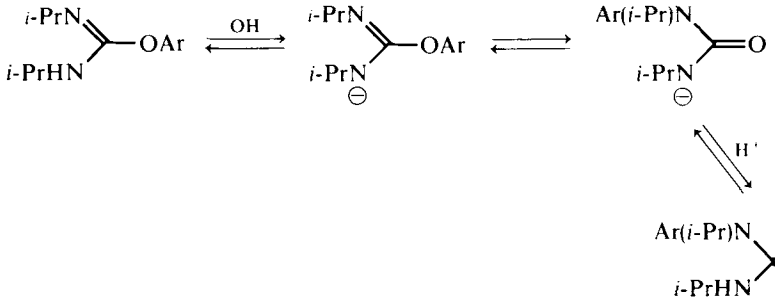
Finally, a facile Chapman isomerization of *O*-arylisoureas to *N*-arylureas, catalysed by hydroxide ions at room temperature, has been reported[464]. This result contrasts with the reluctance of compounds of the same type to rearrange under neutral conditions, where temperatures of about 250 °C are required. The kinetic data of this reaction are


NR
O
Cl
O
NR
Cl
or
O
NR
O
COCl
COCl
RN3
RN=PPh3
(213)
COCl
COCl
NR
O
Cl
O
NR
Cl
or
O
NR
O


O
Me
R1
N
Si
Cl
Me
R2
kinetic control
thermodynamic control
(214)
O
Cl
Si
Me
Me
R1
N
R2
Chapman rearrangement
Cl
Me
O
Si
Me
R1
N
R2


Ph
Ph
N
S
CH2R
Δ
R = Ar or CH2=CH–
(215)
Ph
Ph
N
SCH2R

consistent with a four-membered ring transition state, similar to that depicted above for 1,3-aryl migrations in *N*-arylbenzimidates. Moreover, aryl substituents have a much greater influence on the isourea reactivity in alkali, probably due to the fully negatively charged aromatic ring in the former case, as compared with the zwitterionic character of the transition state in the case of imidates (equation 216).



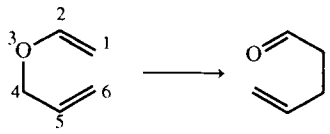
(216)

The above *O*-arylisourea isomerization belongs to the general oxygen-to-nitrogen rearrangements found in isoureas and related compounds. Although these reactions are well known in carbodiimide chemistry[465], they cannot be considered routine transformations, due to the extreme conditions required. By contrast, the related 1,3-acyl shifts of *O*-acyl derivatives occur readily, so that they can represent competing pathways during esterifications and similar dehydration reactions mediated by carbodiimides[466].

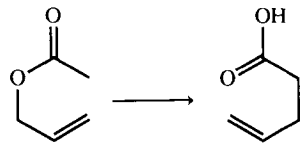
B. Claisen Rearrangement

Since the discovery of the Claisen rearrangement of allyl aryl ethers in 1912[467], a number of variations have been devised and the process has been developed into a powerful and versatile tool for constructing carbon–carbon bonds, that has been found to be extremely valuable in the synthesis of complex molecules of biological interest.

The prototype for the aliphatic Claisen rearrangement is the transformation of allyl vinyl ether into 4-pentenal (equation 217). This reaction has been recently reviewed by Ziegler[468] and therefore we shall concentrate on the most recent contributions dealing with mechanistic aspects or exemplifying the scope of the process.



(217)



(218)

The preparation of γ,δ unsaturated carboxylic acids through rearrangement of allyl esters (equation 218) was reported by Arnold in 1949[469,470]. Much later, Ireland[471,472]

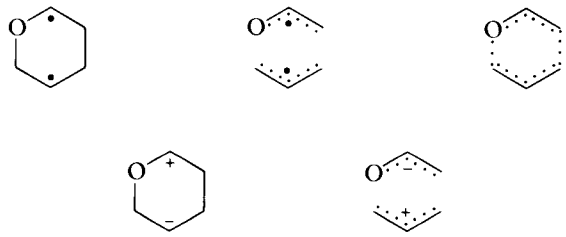


FIGURE 3. Biradical or zwitterionic nature of the different transition states discussed for the Claisen rearrangement

achieved a very important practical improvement by using lithium dialkylamides to generate the ester enolates. This variation (Ireland–Claisen rearrangement) proceeds at room temperature and, at the same time, allows one to control the enolate geometry.

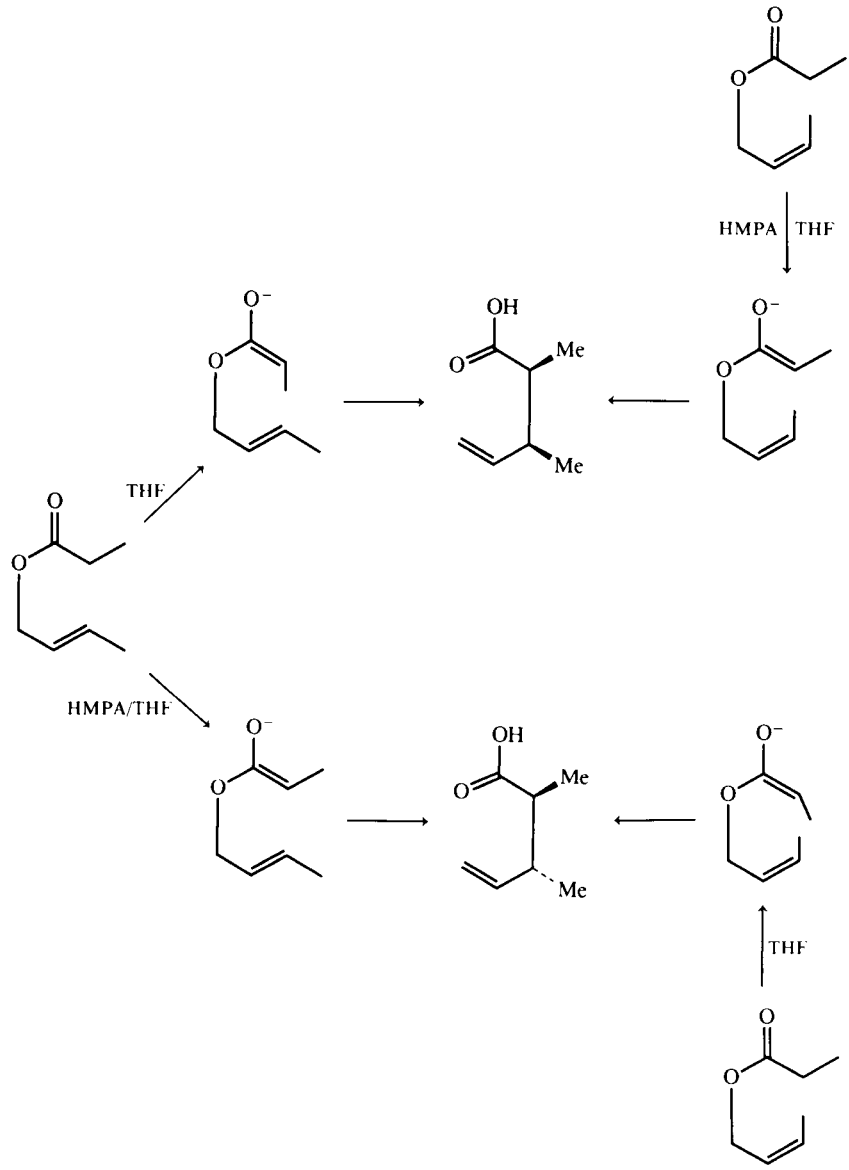
From the mechanistic point of view, the aliphatic Claisen rearrangement belongs to the group of [3,3] sigmatropic migrations and is generally thought to proceed in a concerted manner[468]. However, the extent of bond breaking and bond making in the transition state (Figure 3) has been controversial. Thus, the reaction might occur in a non-synchronous way, through transition states with some biradical or zwitterionic character[473], or, at the other extreme, the possibility also exists that the reaction is synchronous, i.e. there is a greater balance between all changes in bonding and an 'aromatic' transition state is involved[473].

Theoretical calculations[474], substituent effects[475–477], kinetic measurements or secondary isotope effects[478–480] have been interpreted as favouring different transition state structures. However, a picture begins to emerge in which the aliphatic Claisen rearrangement is considered to take place via a single 'merged' mechanism, through a hybrid transition state resulting from the coalescence of the 'biradical' and 'aromatic' extreme situations, with an intermediate geometry.[481].

The rate of the aliphatic Claisen rearrangement becomes strongly affected by the nature and position of the substituents attached to the basic skeleton. In the case of acid derivatives, the presence of electron-donating groups such as RO—, R_3SiO—, R_2N—, etc. at $C_{(2)}$ results in a marked increase of the reaction rate[471,475,476]. The same is true for the enolates of allyl esters[471], since the oxy anion can also be considered as a strong π-donor substituent.

When $C_{(1)}$ and $C_{(6)}$ are substituted in such a way that there are enantiotopic faces at both termini, the rearrangement can in principle afford two racemic diastereomers with new chiral centres at $C_{(3)}$ and $C_{(4)}$. In general, a high stereoselectivity is observed, due to the preferential involvement of chairlike transition states[468]. Thus, kinetic deprotonation of the butenyl propanoates with LDA in THF affords the *Z*-enolates, while thermodynamic deprotonation by means of the same base in HMPA/THF leads to the *E*-isomers[472,482]. Rearrangement of the corresponding silyl ketene acetals produces always a major diastereomer which arises through the respective chairlike transition state[472] (equation 219).

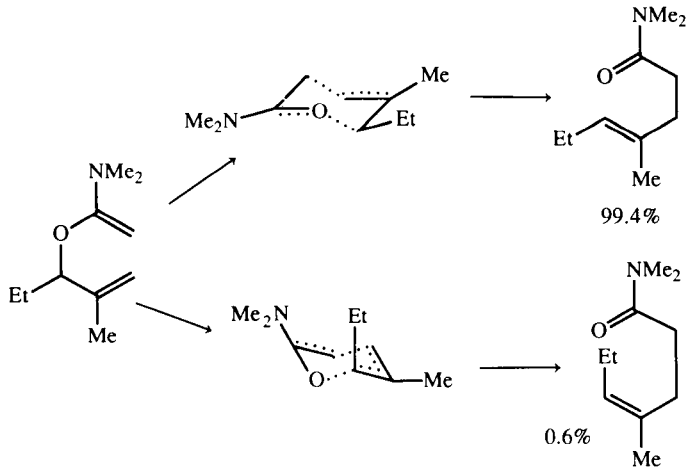
On the other hand, $C_{(4)}$-substituted systems undergo rearrangement with high stereoselectivity, to afford predominantly the (*E*)-γ,δ-unsaturated carboxylic acid derivatives[483,484]. This is exemplified in equation 220 for a ketene *O,N*-acetal and can be explained as resulting from the lack of pseudo-1,3-diaxial interaction in the chairlike transition state that leads to the major product[483].



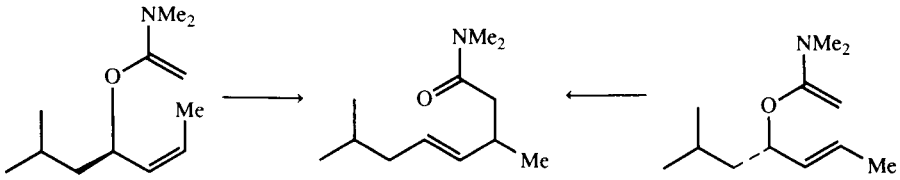
(219)

When the system is $C_{(4)}$,$C_{(6)}$-disubstituted, stereogenicity is transferred in the rearrangement. Thus the (*R*,*Z*)-, as well as the (*S*,*E*)-ketene *O*,*N*-acetals of Equation 221 afford selectively the (*S*,*E*))-γ,δ-unsaturated amides[485].

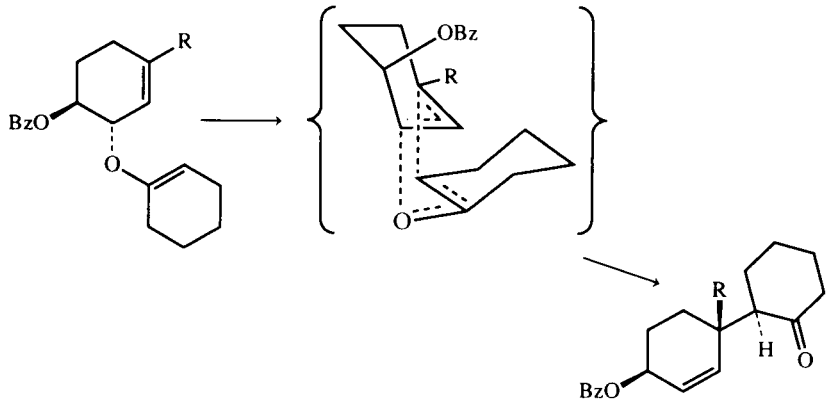
It is noteworthy that, as an exception to the general rule, ring-bearing substrates can undergo the Claisen rearrangement through boatlike transition states. A clear example is the reaction outlined in equation 222, where the chairlike transition state is disfavoured due to steric interactions[486,487].



(220)

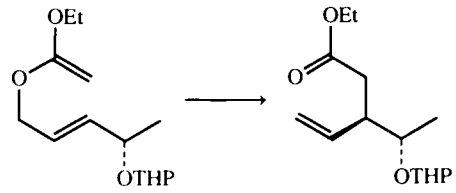


(221)



(222)

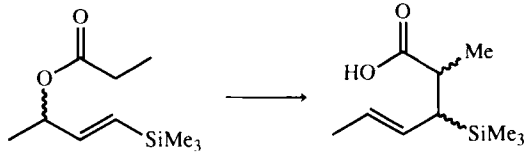
Upon incorporation of a chiral substituent at the olefinic centres (mainly at $C_{(6)}$) it has been possible to achieve a moderate degree of asymmetric induction. This is shown in equation 223 for a chiral ketene acetal, whose *S*-isomer rearranges to afford the corresponding γ,δ-unsaturated ester, the major diastereomer (*S,R*) being obtained with 3:1 diastereoselectivity[488].



(223)

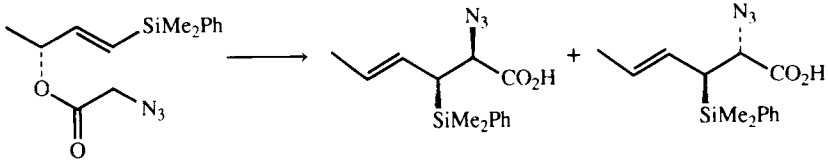
However, the number of experimental studies on asymmetric induction of this type is still rather limited and more work is necessary to confirm the interesting predictions advanced by Kahn and Hehre[489]. According to these authors, the transition state of the Ireland–Claisen rearrangement can be described in terms of a 'nucleophilic' ester enolate allylic component and an 'electrophilic' hydrocarbon allylic component. Stereoselectivity may be then assigned combining the more electron-rich face of the 'nucleophilic' component with the more electron-poor face of the 'electrophilic' component, and assuming that a chairlike transition structure intervenes.

It has been recently reported[490] that variations in the reaction conditions produce a dramatic effect on the stereoselectivity of the Ireland–Claisen rearrangement of a series of acyloxy-(*E*)-vinylsilanes. Thus, the vicinal diastereoselectivity for a racemic propionyloxy derivative (equation 224) can be varied from 1/12 to 16/1 (*syn* to *anti*).



(224)

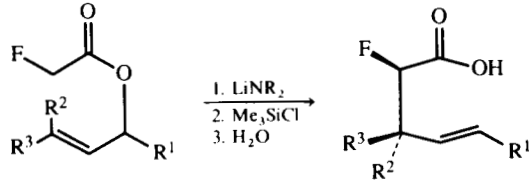
In the same work, the rearrangement of an enantiomerically pure α-azido acetate with (*R*) configuration has been found to occur with modest selectivity (3.3/1) to the *syn* diastereomer, which constitutes the first example of a Claisen rearrangement involving an α-azido ester and provides a new approach toward the asymmetric synthesis of α-amino acids (equation 225).



(225)

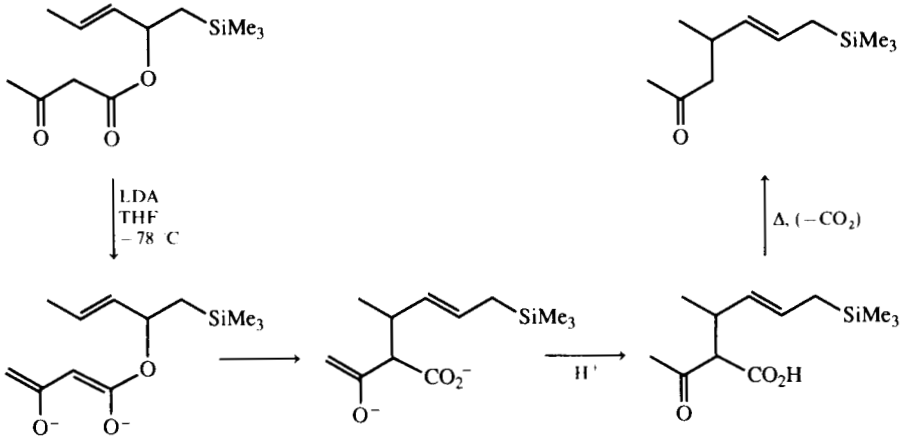
Another recent report[491] has examined the rearrangement of allyl α-fluoroacetates to 2-fluoroalkenoic acids, which proceeds with very good yields and with a considerable degree of internal asymmetric induction (equation 226). The possibility of controlling the stereochemistry of this rearrangement was in principle unexpected, since stereoselective deprotonation of fluoroacetates is usually impossible. However, carbon silylation of the enolates, followed by stereoselective migration of the trimethylsilyl group from carbon to oxygen, leads to the formation of the (*E*) silyl ketene acetal.

Two reactions closely related to those discussed above are the Carroll rearrangement and the Wittig rearrangement. The Carroll rearrangement is a particular type of Claisen rearrangement, in which allylic esters of β-ketoacids are the starting materials. The reaction occurs at low temperatures with generation of dienolates[492], whereby the



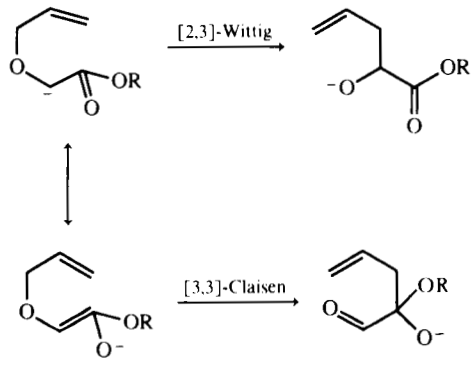
(226)

rearranged β-ketoacids can be isolated, if desired, in good yields. Decarboxylation to unsaturated ketones can be easily achieved (equation 227). This rearrangement has also been conveniently performed by adsorption of the substrates on chromatographic grade alumina[493].



(227)

By contrast, the [2,3] Wittig rearrangement does not belong to the family of Claisen rearrangements, being instead a competing sigmatropic process which can operate for certain substrates (equation 228). This topic has been extensively covered in a recent review[494] and therefore no further details will be given.



(228)

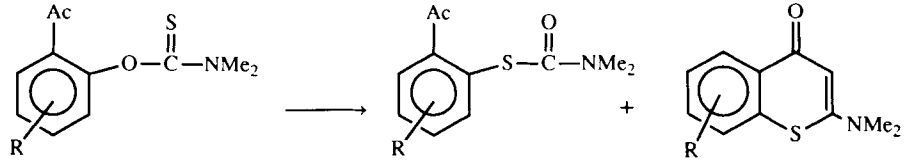
C. Newman–Kwart Rearrangement

One of the most general and convenient procedures for the preparation of thiophenols from the corresponding phenols involves the thermal rearrangement of *O*-aryl dimethylthiocarbamates to *S*-aryl dimethylthiocarbamates[495,496] (equation 229).

$$\mathrm{ArOH} \longrightarrow \mathrm{ArO{-}\overset{\overset{\mathrm{S}}{\|}}{C}{-}NMe_2} \longrightarrow \mathrm{ArS{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}NMe_2} \longrightarrow \mathrm{ArSH} \quad (229)$$

This reaction, which is known as the Newman–Kwart rearrangement, can be effected by pyrolysis at 150–300 °C, in the absence of any solvent. The products are usually obtained in high yield and can be isolated by crystallization or vacuum distillation.

When the aryl group bears electron-withdrawing substituents the reaction is disfavoured and the temperature required is so high that decomposition occurs prior to or during the desired rearrangement[497]. Thus, *o*-acetyl substituted *O*-aryl dimethylthiocarbamates do not yield the corresponding *S*-aryl analogues in the usual experimental conditions. However, recent work[498] has shown that the expected products can be obtained in refluxing *o*-dichlorobenzene when 2-dimethylaminothiochromones are formed as by-products (equation 230).



(230)

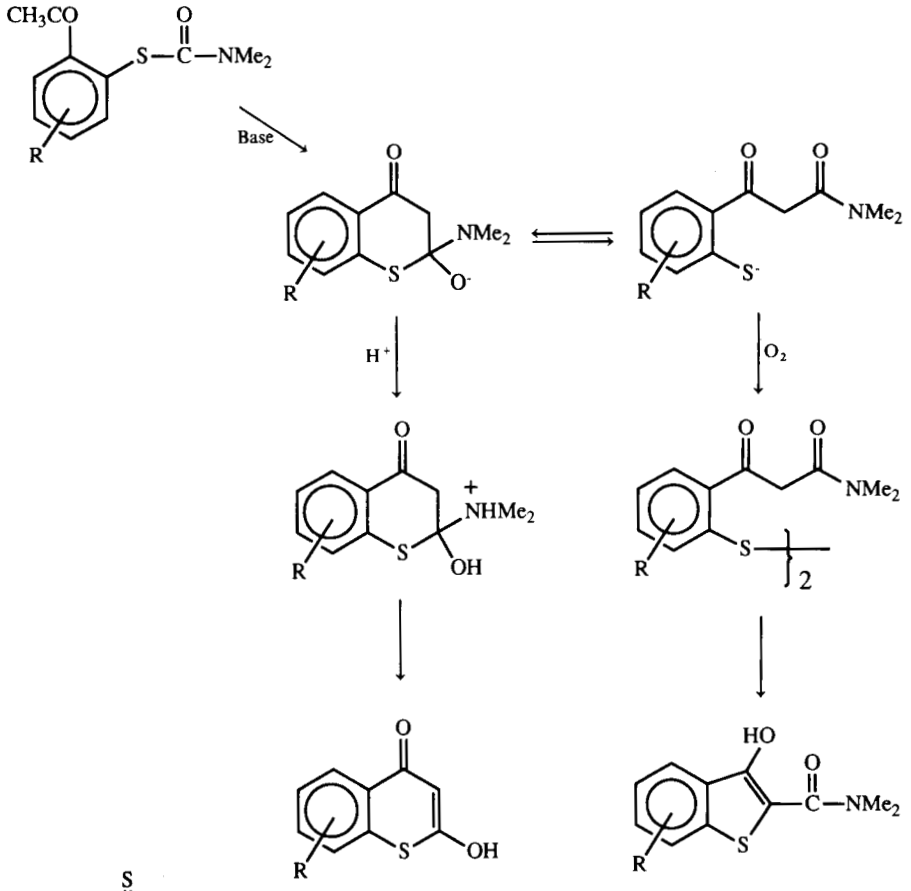
The *S*-aryl dimethylthiocarbamates thus obtained are rather versatile intermediates for the synthesis of heterocycles. Their cyclization with base under inert atmosphere leads to 2-hydroxythiochromones, while in the presence of oxygen *N*,*N*-dimethyl-3-hydroxybenzothiophene-2-carboxamides are the major products[498] (equation 231).

An interesting feature of the Newman–Kwart rearrangement is that it occurs even when one or both positions *ortho* to the phenolic oxygen are substituted by bulky groups, including at the extreme case 2,6-di-*t*-butyl derivatives[497]. This has been exploited in the field of sulphonamide synthesis, since the direct sulphonation or chlorosulphonation of alkylaromatics *ortho* to one or two alkyl groups proceeds with very low yields and, on the other hand, thiophenols can be easily oxidized to benzenesulphonic acids or their chlorides[499] (equation 232).

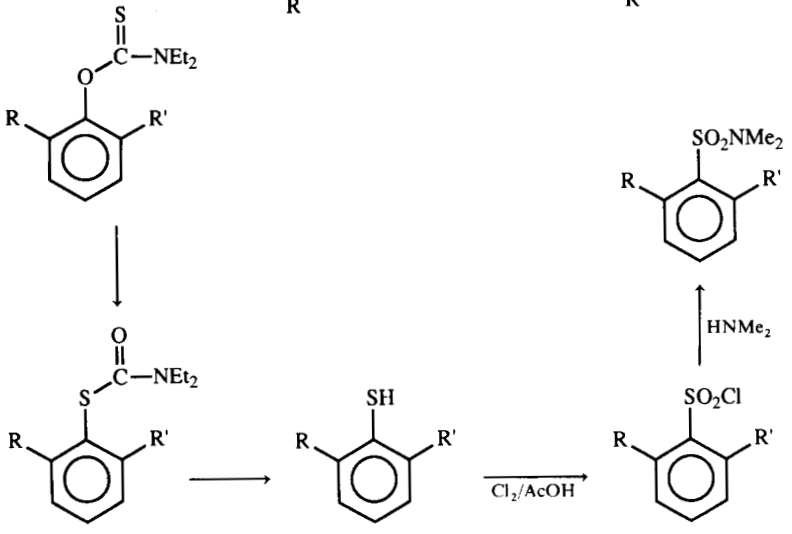
Further applications of the Newman–Kwart rearrangement to the synthesis of pharmacologically interesting compounds include morphine derivatives[500], morphinans[500], benzomorphans[501], isocannabinoids[502] and tetrahydrocannabinols[502] (equation 233).

Finally, there are some reports dealing with similar rearrangements in non-aromatic compounds. For instance, in an attempted thiocarbamoylation of tetrahydro-2*H*-1,3-thiazin-2-one a by-product arising through the Newman–Kwart rearrangement of a thiazinone enol thiocarbamate intermediate, followed by sulphur-to-nitrogen transcarbamoylation, is obtained alongside with the expected product[503] (equation 234).

Likewise, 1,2,4-oxadiazoline-5-thiones are converted into 1,2,4-thiadiazoline-5-ones upon irradiation[504], which constitutes an interesting example of photo-Newman–Kwart rearrangement (equation 235).

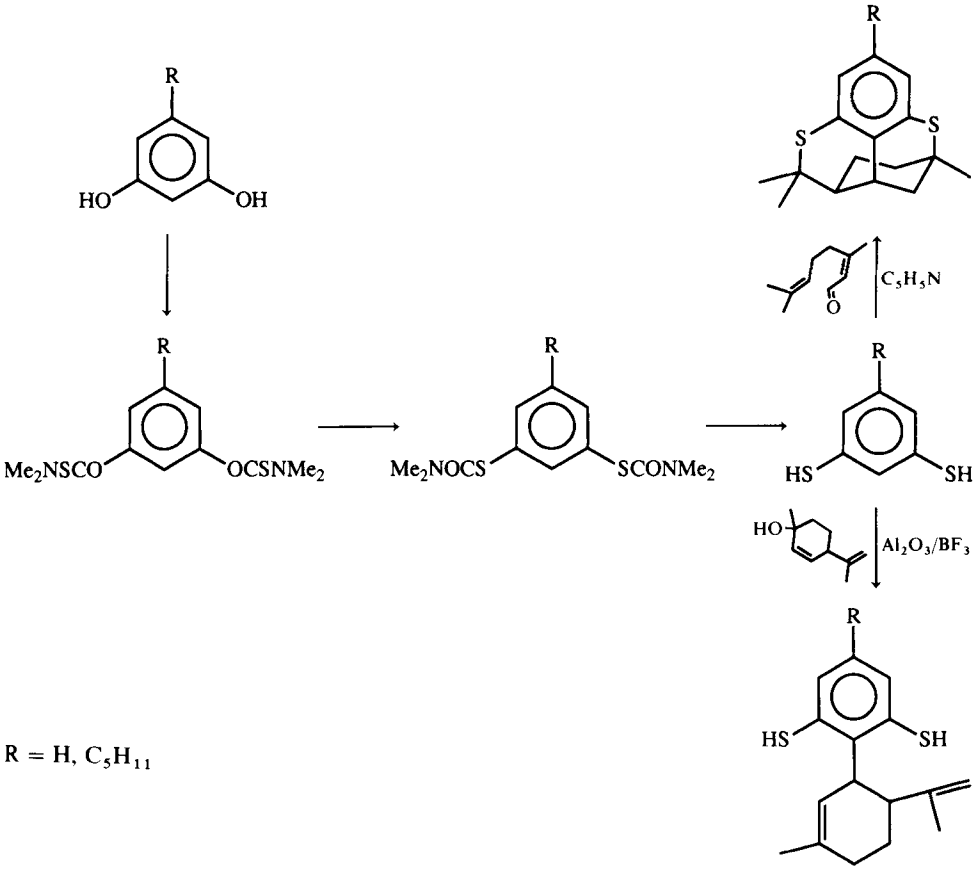


(231)



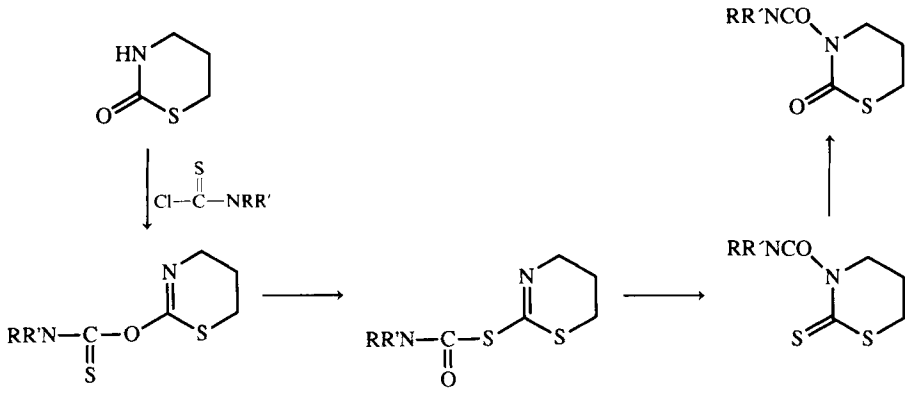
R, R′ = Me, *i*-Pr, *t*-Bu

(232)

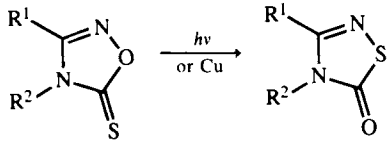


R = H, C_5H_{11}

(233)



(234)



(235)

D. Schmidt Rearrangement

The addition of hydrazoic acids to carboxylic acids, aldehydes or ketones is called Schmidt reaction[19,505,506]. Carboxylic acids rearrange to isocyanates, which are virtually never isolated under the strong acidic conditions usually employed. The actual products are in most cases the corresponding primary amines (equation 236).

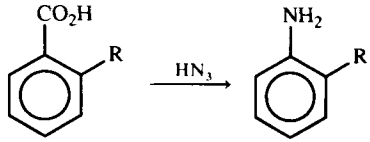
$$RCO_2H \xrightarrow{HN_3} RN{=}C{=}O \longrightarrow RNH_2 \qquad (236)$$

This acid-to-amine conversion is less frequently employed than the Curtius or Hoffman procedures, due to the more drastic conditions, although it has the great advantage of being a one-pot reaction. As a general rule, better results are obtained for aliphatic acids than for aromatic acids[19].

A kinetic study carried out on a series of substituted benzoic acids[507] has shown that the rate of the Schmidt reaction depends on electronic as well as steric effects. Thus, electron-donating substituents increase the rate, while electron-withdrawing substituents produce the opposite effect. On the other hand, the presence of bulky groups at the *ortho* position results in a marked rate acceleration, suggesting steric assistance (equations 237 and 238).

$$p\text{-}RC_6H_4CO_2H \xrightarrow{HN_3} p\text{-}RC_6H_4NH_2 \qquad (237)$$

	K_{rel}
R = H	1
R = Me	1.17
R = Cl	0.43
R = NO_2	0.003



	K_{rel}
R = H	1
R = Me	147
R = Et	272
R = Bu^t	1558

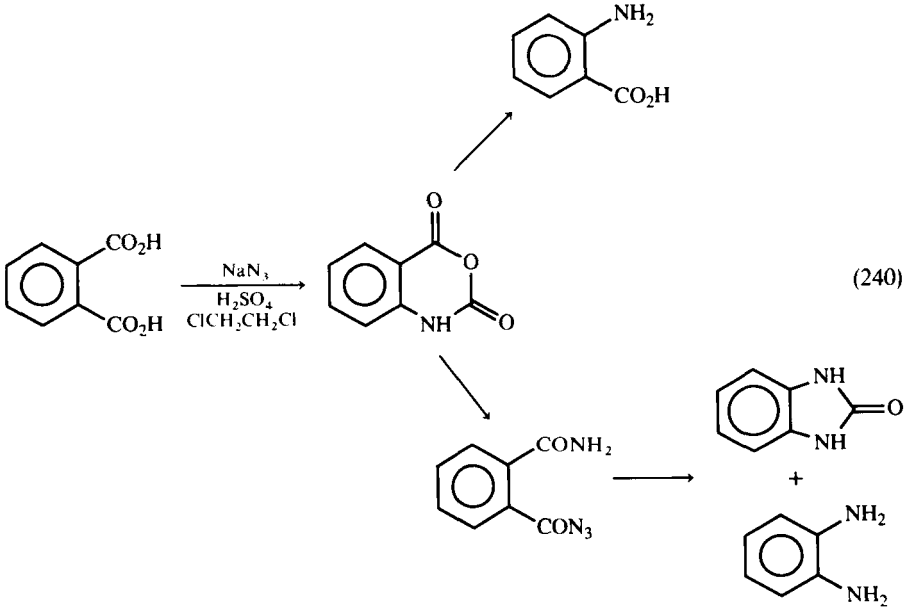
(238)

K_{rel} = relative rate constants

The substituent effects appear to be compatible with the accepted reaction mechanism (equation 239).

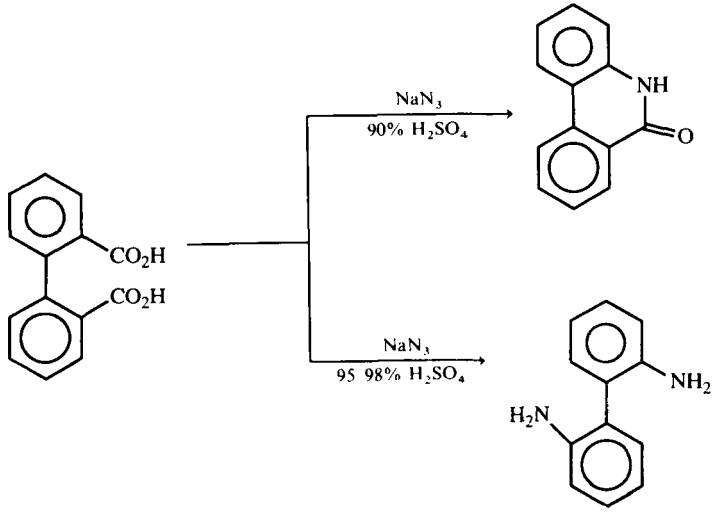
$$RCO_2H \xrightleftharpoons{H^+(-H_2O)} R\overset{+}{C}O \xrightarrow{HN_3} RCONH\text{-}\overset{+}{N}_2 \xrightarrow{-N_2} R\overset{+}{\underset{H}{N}}{=}C{=}O \xrightarrow[-CO_2]{H_2O} R\overset{+}{N}H_3 \qquad (239)$$

Treatment of phthalic acid in 1,2-dichloroethane with sodium azide in concentrated sulphuric acid[508] leads to a mixture of anthranilic acid, anthranilazide, benzimidazol-2-one and *o*-phenylenediamine. Separate experiments have shown that isatoic anhydride is a common intermediate and anthranilazide is the precursor or benzimidazol-2-one (equation 240).

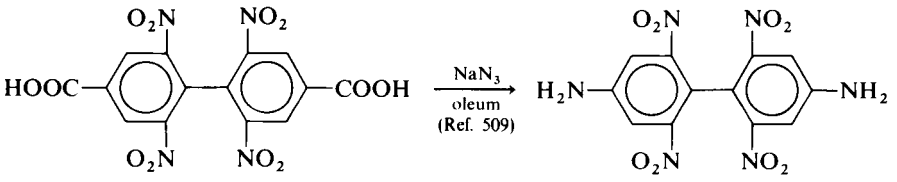


(240)

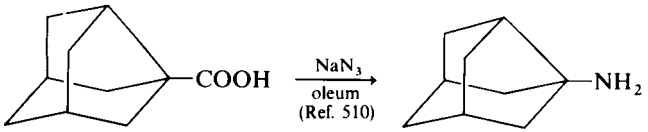
The Schmidt reaction of diphenic acid in 90% sulphuric acid gives phenanthridone as major product; by contrast, when 95–98% sulphuric acid is employed the main product is 2,2'-diaminobiphenyl[508]. This has been explained as resulting from significant protonation of both carbonyl groups, which would undergo rearrangement independently due to repulsion between the positive charges (equation 241).



(241)



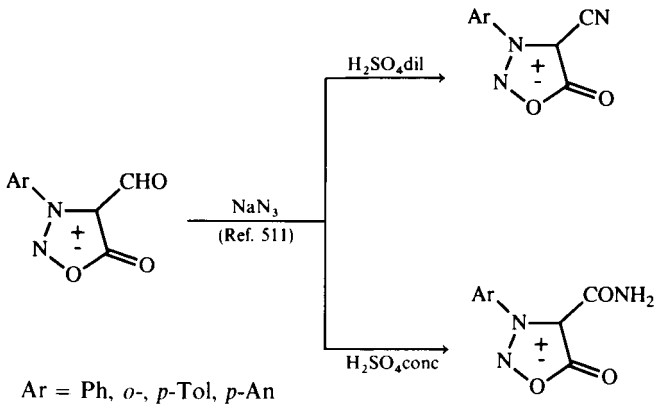
(242)



(243)

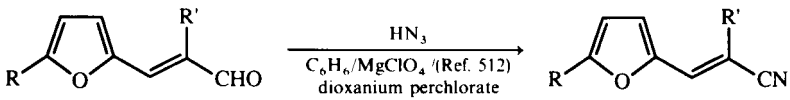
Two more examples of the acid-to-amine conversion under Schmidt conditions are illustrated in equations 242 and 243[509,510].

Compared with the cases of carboxylic acids or ketones, the Schmidt reaction of aldehydes has attracted little attention[511,512]. In general, formation of the corresponding nitriles is the usual result; however, carboxamides can be also obtained if concentrated sulphuric acid is employed (equations 244 and 245).



(244)

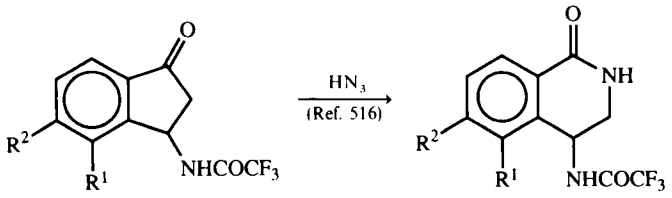
Ar = Ph, *o*-, *p*-Tol, *p*-An



(245)

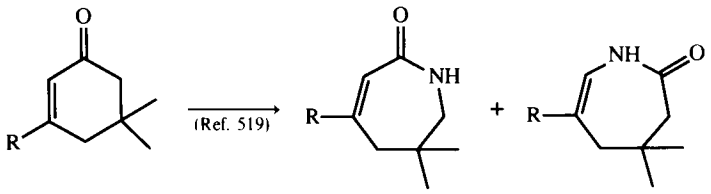
R = H, Me, Ph, NO_2; R′ = H, Me

Ketones have been the compounds most frequently submitted to the Schmidt reaction. This is a good method for insertion of a NH group between the carbonyl moiety and one of the α-carbons, thus obtaining amides from ketones. In the case of cyclic ketones, a ring expansion to lactams is generally observed. This has been found to be the case for cyclopentanone[513–517] as well as cyclohexanone[517–524] derivatives; some examples are given in equations 246–248.



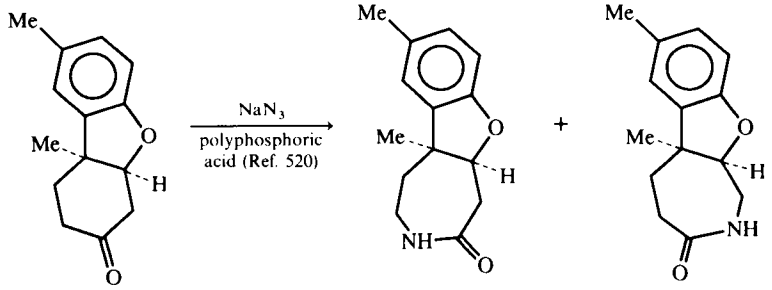
(246)

R^1 = H, Me, Cl, Br; R^2 = H, Cl



(247)

R = H, Me, Et, Me_2CH



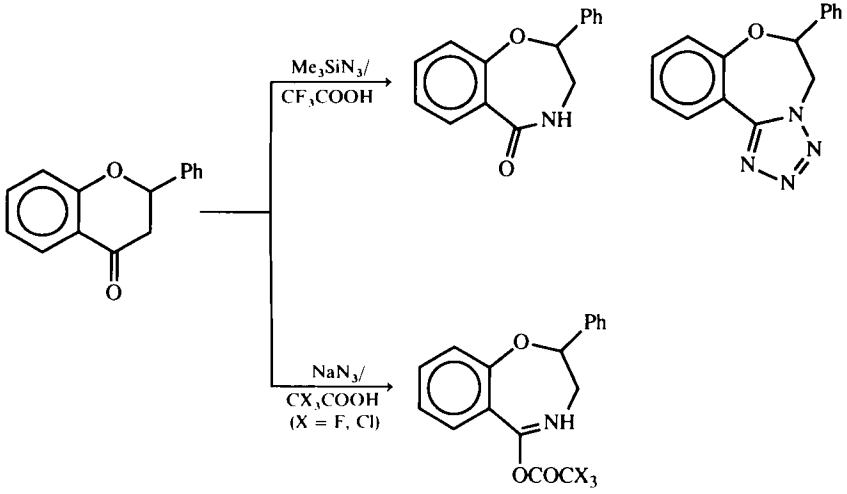
(248)

Heterocyclic six-membered ring ketones such as flavanones[525] and related compounds with sulphur[526,527] or nitrogen[528] behave in a similar way. The product distribution depends upon the reaction conditions as shown in equation 249.

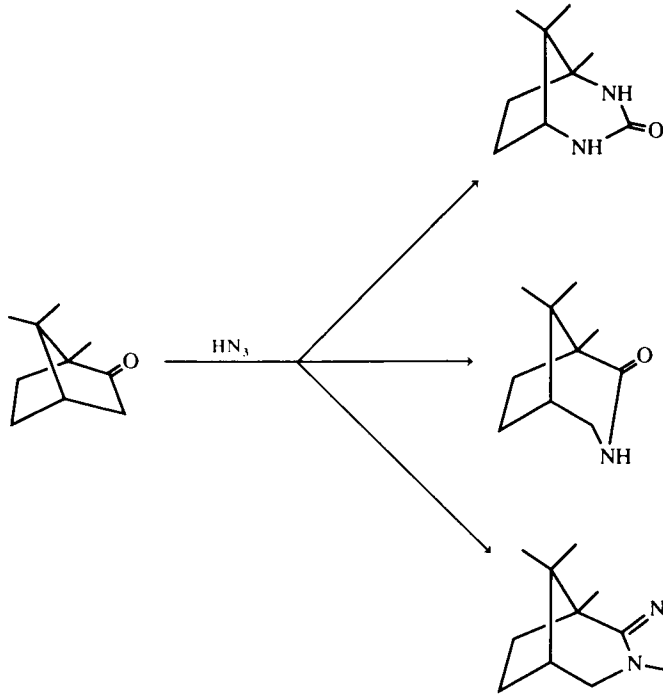
Considerable attention has been paid to the Schmidt reaction of polycyclic ketones[529–534]. These studies have contributed to a better understanding of the reaction mechanism and, in some cases, a revision of the product structures wrongly assigned in the earlier literature has been necessary. Thus, the Schmidt reaction of camphor has been claimed to give a bicyclic urea as major product, together with small amounts of the expected α-camphidone[535]. In the older literature[536], the same reaction has been reported to give a tetrazole (equation 250).

However, more recent work[529] has shown that the structures of the urea and the tetrazole were wrongly assigned and a further minor product with iminonitrile structure has been isolated and identified (equation 251).

On the basis of the above results, a mechanism has been proposed which involves addition of hydrazoic acid to the protonated carbonyl group, followed by dehydration to the iminodiazonium ion and denitrogenation, with rearrangement, to a ring-expanded nitrilium ion (equation 252).

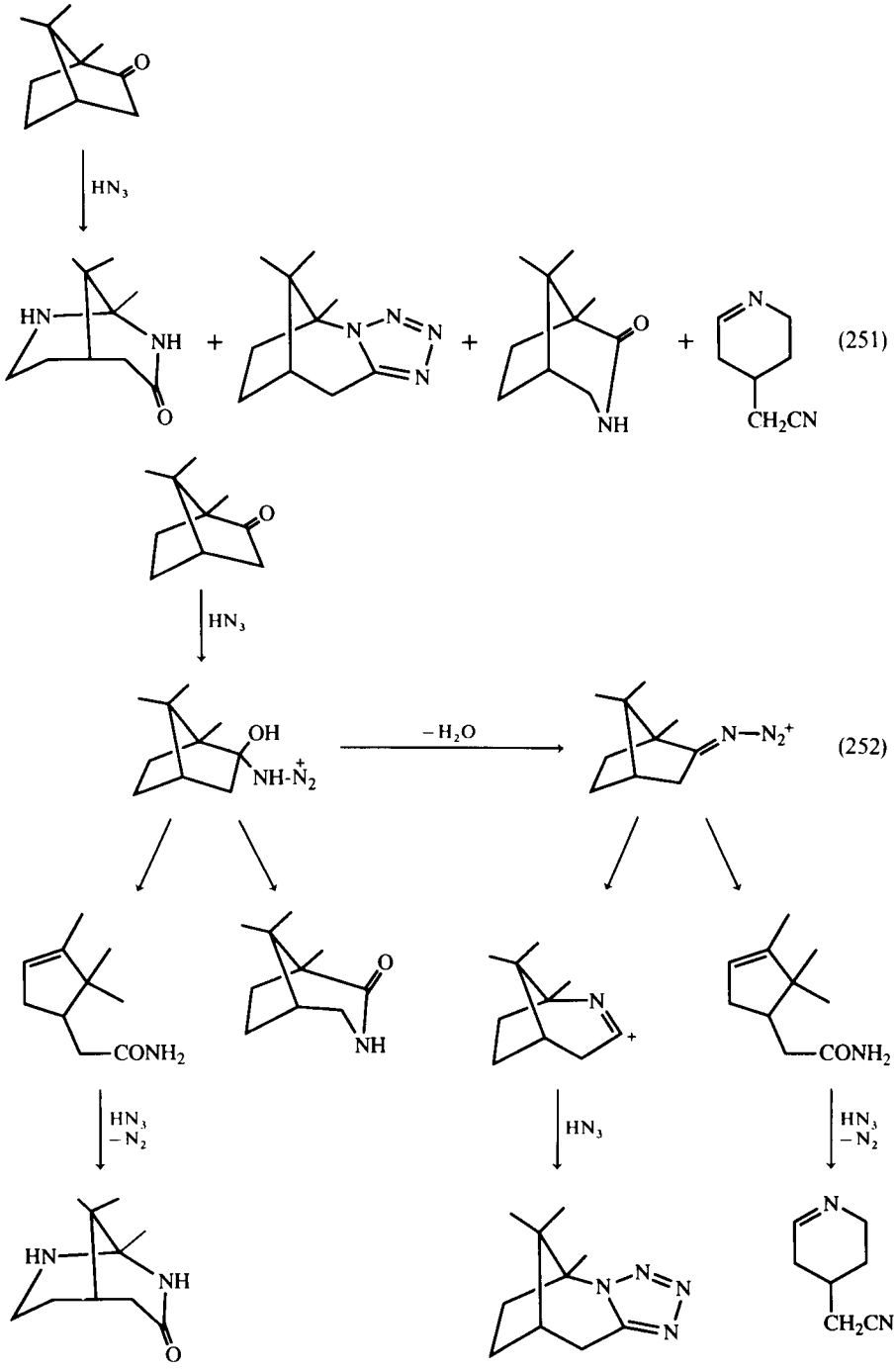


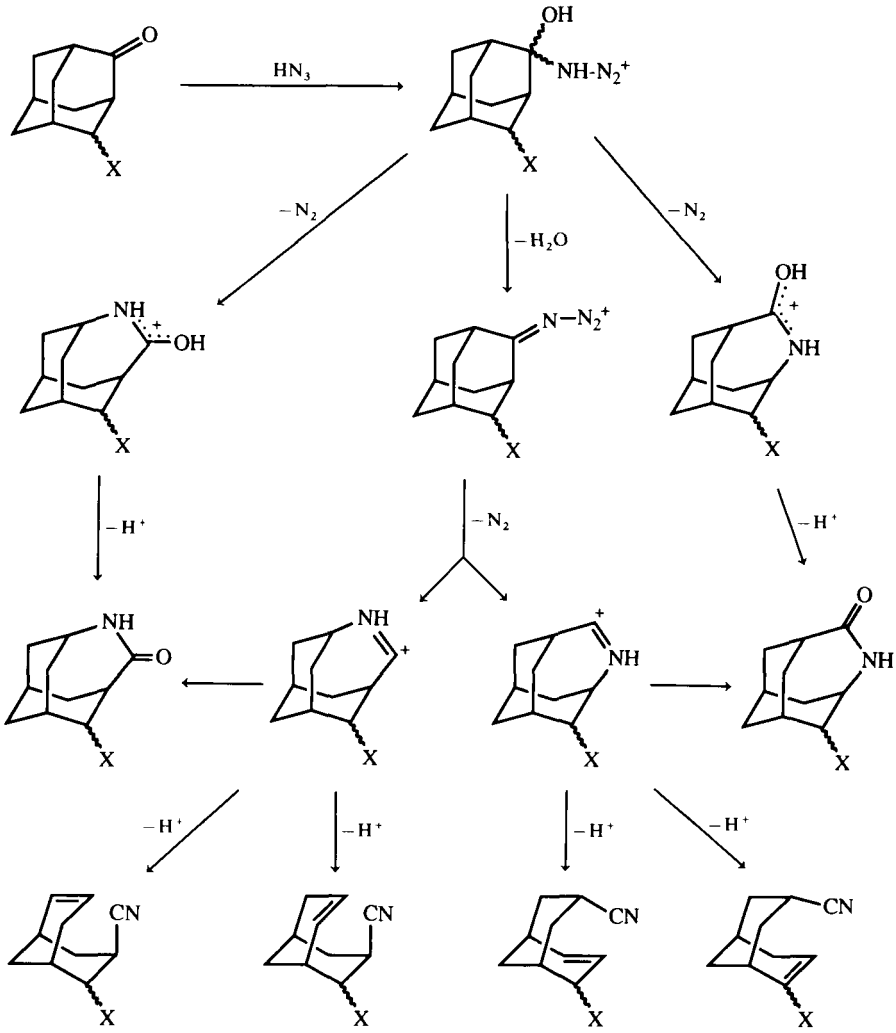
(249)



(250)

A related study with 4-substituted adamantanones[531] has shown that the main reaction pathways involve iminodiazonium ions and nitrilium ions, which then undergo fragmentation to unsaturated nitriles or water addition to ring-expanded amides (equation 253).

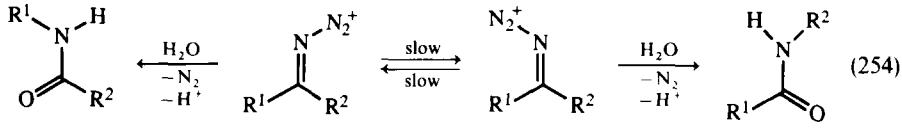

HN3
HN
NH
O
N
N
N
CH2CN
(251)
HN3
OH
NH-N2+
-H2O
N-N2+
(252)
CONH2
NH
HN3
-N2
HN3
HN3
-N2
CH2CN



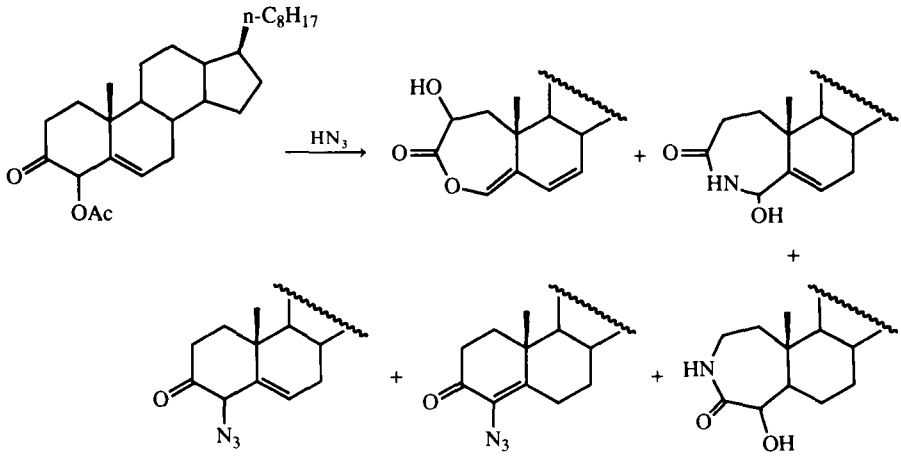
(253)

The latter equation reflects the currently accepted hypotheses on the mechanism of the Schmidt reaction of ketones. It is assumed that iminodiazonium ions[537] and nitrilium ions[506] are the key intermediates from which formation of the different products can be explained. In this context, *ab initio* calculations[537] suggest that the barriers to interconversion, via nitrogen inversion or rotation, of the two possible geometrical isomers of iminodiazonium ions are high enough to preclude rapid equilibration, prior to irreversible migration of the group *trans* to the departing nitrogen. This can be correlated with the regiochemistry of the resulting amides (equation 254).

Steroidal ketones have also been used in the Schmidt reaction[538–543]. For instance, 3-oxocholest-5-en-4α-yl acetate, when treated with hydrazoic acid[539], gives a ring-expanded lactone, two ring-expanded amides and two azides (equation 255).

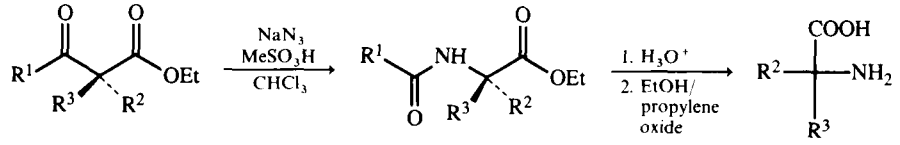


(254)



(255)

All the reactions presented in equations 246–255 correspond to the ring expansion of cyclic ketones under Schmidt reaction conditions. It must be mentioned that, although less intensively, acyclic ketones have also been studied in this connection during the last decade[544–550]. In particular, β-ketoacid derivatives[546–550] are converted into α-acylamino acids and related compounds. Thus, the Schmidt reaction of optically active α,α-bisalkylated β-ketoesters[550] provides a new entry to α-amino acids in high yields and excellent optical purity (equation 256).



(256)

IV. CONCLUDING REMARKS

It is surprising—at the same time exciting—that old name reactions such as those covered in the present chapter continue to be very active areas of research. When reading our textbooks, one has the feeling that everything is known about processes of this type or, at the most, that there is only place for minor, marginal contributions. This is clearly not the case. There are still key mechanistic concepts subjected to discussion, such as the nature of the transition states, the intermediacy of certain short-lived species, the involvement of electron transfer processes or the factors governing stereochemical

control. From the synthetic point of view, the keyword is selectivity. Alternative ways of activation are being introduced, including photochemical and catalytic methods. In this context, the performance of these rearrangements in confined spaces (cyclodextrins, zeolites, etc.) has already attracted some attention and might contribute in the future to achieve preparative importance. In summary, despite their age, the reactions reviewed in this chapter are enjoying a renewed youth and it is probable that they will continue to attract a great deal of interest during the years to come.

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CHAPTER **24**

The application of lipases in organic synthesis

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ABBREVIATIONS

ANL	*Aspergillus niger* lipase
Bn	benzyl
CAL	*Candida antarctica* lipase
CCL	*Candida cylindracea* lipase
CVL	*Chromobacterium viscosum* lipase
GCL	*Geotrichum candidum* lipase
MML	*Mucor miehei* lipase
PFL	*Pseudomonas fluorescens* lipase
PFRL	*Pseudomonas fragi* lipase
PLE	pig liver esterase
PPL	pig (porcine) pancreatic lipase
PSL	*Pseudomonas* sp. lipase
RDL	*Rhizopus delemar* lipase
SPAC	sulphoxide pyridinium and carbonyl

I. INTRODUCTION

This review article focuses on the application of lipases in synthetic organic chemistry, an area which has expanded tremendously during the last few years. The literature search extends to the end of 1990 and the first few months of 1991, and is intended to be fairly comprehensive, but by no means exhaustive. The main emphasis is on the last three years, i.e. 1988, 1989 and 1990, and an attempt is made to put this survey into perspective with earlier work in the field, which has been fairly extensively reviewed[1-3]. The application of lipases in organic media has also been covered recently[3-5].

The first part of this chapter provides some insight into the general aspects of enzymes in organic synthesis, including their main characteristics, scope of application and advantages. The next part provides further insight into the characteristic, properties, availability, application and range of lipase-catalysed reactions, kinetic and mechanistic

aspects and active site studies of lipases and their application in organic solvents. The remaining part deals with reactions and examples of lipases in organic synthesis, and an attempt is made to classify these reactions in a systematic and logical manner. Occasionally, there is some overlap with other reviews, especially in the sections involving the use of lipases in organic media, which has been rather extensively surveyed towards the end of 1989.

It is hoped that this contribution will be of some value to organic chemists, and that they may realize the immense synthetic power and potential offered by the lipases and other enzymes as part of the standard methodology in modern synthetic organic chemistry.

II. ENZYMES IN ORGANIC SYNTHESIS—GENERAL ASPECTS

In the course of the last ten years the application of enzymes in organic synthesis has continued to grow enormously, and enzymes are now widely recognized as practical catalysts for asymmetric synthesis. This field has been extensively reviewed in a number of recent general reviews[1,2,6–17]. The most important feature of enzymes in organic synthesis is their selectivity. Other important characteristic properties of enzymes include their high catalytic efficiency and the mildness under which enzymes exhibit their activity, such as atmospheric pressure, temperature around 20–40°C and pH values near neutrality, under which conditions normal chiral catalysts hardly function at all.

The enzymes distinguish among several substrates competing for their active site. The resulting substrate selectivity is sometimes narrow and sometimes broad. The three-dimensional catalytic site of an enzyme, constituting chiral amino acids aligned in a certain way, binds the substrate in a specific orientation by discriminating between stereogenic centres and enantiotopic groups or faces of the substrate molecule, which leads to enzyme stereoselectivity. Synthetically useful enzymes would accept a wide range of substrates and display high stereoselectivity. Furthermore, enzymes exhibit regioselectivity towards compounds possessing multifunctional groups and chemoselectivity towards different functional groups in a molecule.

The preparation of chiral synthons is the area within organic chemistry in which enzymes have demonstrated highest utility and potential, commonly by kinetic resolutions, but also by enantioselective transformations of *meso* compounds, enantiotopic group differentiation of prochiral compounds, as in asymmetric hydrolysis of diesters, and enantioface discrimination in asymmetric reductions of ketones. The use of chiral synthons is one of the four general approaches that are normally used to obtain enantiomerically pure material in asymmetric organic synthesis. Enzymes have also found applicability in the others, either directly or as a synthetic aid, which include resolution, the application of stoichiometric amount of chiral auxiliary and the use of a chiral catalyst.

The synthetic advantages and opportunities that enzymes offer continue to expand and accelerate and a great number of total syntheses combining enzymatic and chemical methods have emerged. Enzymes have also exhibited utility in the preparation of specialty and fine chemicals, involving sugars, nucleic acids and lipids, as well as a wide variety of substrates used for research in biochemistry, metabolic studies and pharmacology, peptide synthesis and oligosaccharide synthesis. Recently, interest in multi-enzyme syntheses has intensified, which allows parallel or sequential enzyme-catalysed synthetic transformations to be carried out in one-pot reactions and has an enormous synthetic potential[7,9]. Multi-enzyme systems have already been widely applied for coenzyme recycling[12].

Some reluctance has remained among synthetic organic chemists to use biological procedures[1,2,5,12]. The fear of needing to get involved in fermentation, isolation and

purification of enzymes obstructed the use of enzymes, as well as concerns regarding cost, stability and requirements for expensive cofactors. Also, the perceived necessity to work with enzymes in aqueous solvents and their high specificity for their natural substrates precluded their general use in synthesis. This apprehension has faded and enzymes are now being widely accepted as routine reagents. It is important for synthetic organic chemists to realize that many of the methods applied are little different in their execution from conventional chemical reactions.

Based on the reactions they catalyse, enzymes are classified into six groups[1]. The *oxidoreductases* catalyse oxidation–reduction reactions, such as oxygenation of alkanes and elimination or addition of hydrogen atom equivalents from or to alcohols or carbonyl compounds. The *transferases* effect the transfer of groups (acyl, sugar, aldehyde or ketone) between molecules. The *hydrolases* mediate the hydrolysis of a wide variety of functional groups, including esters, acids, peptides and glycosides. The lipases are a subclass of this group, together with the commonly employed esterases and proteases. The *lyases* catalyse addition and elimination reactions involving double bonds. The *isomerases* govern isomerizations such as C=C bond migrations, *cis–trans* isomerizations and racemizations. Finally, the *ligases*, sometimes called synthetases, mediate the formation of carbon–carbon bonds and carbon-heteroatom bonds coupled with pyrophosphate bond cleavage of ATP. Virtually all biochemical transformations *in vivo* are catalysed by these six groups[18], and there is an enzyme-catalysed equivalent for most types of organic reactions[1].

For the enzyme-catalysed biotransformations either isolated enzymes or intact microorganisms can be used. It should be noted that there is a fundamental difference between fermentation and microbial transformations involving whole cells[11]. A microbial transformation is the conversion of one specific substance (substrate) in one or several steps to another (product), catalysed by a particular cellular enzyme or by enzymes originally produced within cells, and the substrate or product does not have to be natural. In fermentation, on the other hand, the product is the result of the complex metabolism of the microorganism. Accordingly, living or growing cells are required for fermentation and the fermentation products are therefore always natural products. In microbial transformations, on the other hand, it is not important whether the cells are alive or not.

For most synthetic organic chemists the simple apparatus and work-up are the main advantages of using isolated enzymes for microbial transformations, compared to the application of whole cells, which often requires sophisticated biochemical equipment[10,11]. Other advantages include fewer side-reactions and better tolerance for co-solvents, and especially monophasic organic solvents. The main disadvantages are the cost of isolated purified enzymes and, for enzymes requiring cofactors, the necessity of such enzyme cofactor recycling. The main advantages of using whole cells is the cheapness and the presence of all the enzyme cofactors required. The disadvantages involved in using whole cells are the bulkiness of the process, the messy work-up, side-reactions, difficulties in using organic solvents, which may disrupt the membrane-bound enzymes, and poor substrate or product permeability through the cell wall.

Immobilization[12,19,20] of enzymes and cells has several advantages. It makes their recovery much easier and allows the re-use of the enzymes, thereby reducing their cost dramatically. Immobilization can also increase the stability of enzymes so they last longer. It makes enzymes susceptible to continuous processes and thus to industrialization. Sometimes, immobilization leads to improvements in the performance of enzymes[21].

For several groups of enzymes cofactors are required, which are normally too expensive to use stoichiometrically, hampering the use of enzymes in synthesis. This problem has been solved quite efficiently for several cofactors, such as ATP, the nicotinamide cofactors and others, by the use of a catalytic amount of the expensive

cofactors in conjunction with continuous regenerating systems, which generate the active form of the cofactor *in situ*[12].

III. LIPASES

A. Lipase Characteristics

Lipases[22,23] (triacylglycerol acylhydrolase EC 3.1.1.3), together with esterases and proteases, belong to the class of hydrolases and occur ubiquitously in nature. The literature distinguishes between esterases and lipases. According to Huang and Dooley[24] an esterase is an enzyme which catalyses the hydrolysis of carboxyl ester bonds, whereas a lipase is an enzyme which catalyses the hydrolysis of a specific type of ester bonds, i.e. triglycerides, to yield free fatty acids, di- and monoglycerides and glycerol. Accordingly, lipases are often termed triacylglycerol hydrolases. Since the reaction is reversible, lipases can also catalyse the formation of acylglycerols from free fatty acids and glycerol. A characteristic property of lipases is the capability of acting on lipids at a lipid–water interface, and they have traditionally been confined to aqueous environments.

Lipases can usually be classified in three groups in terms of their native substrate specificity[20,25,26]. They can be non-regiospecific, which means that they catalyse the complete splitting of triglycerides to free fatty acids and glycerol. They can exhibit specificity and hydrolyse triglycerides to yield free fatty acids, 1,2(2,3)-diglycerides or 2-monoglycerides. Finally, lipases can possess specificity towards particular types of fatty acids.

Since lipases belong to the class of serine hydrolases, they do not require cofactors. They are readily available, inexpensive, highly stable, and exhibit high tolerance for variation in substrate structure, while retaining high stereoselectivity in their action. They do not require water soluble substrates, since they can act at a lipid–water interface. Mechanistically, they are also relatively well understood. Finally, lipases are splendidly suited to retain a high degree of activity in organic media. All this has made lipases among the most widely applied and versatile biocatalysts in organic synthesis[1–5,20,27].

Since no additional cofactors are required, the great majority of cases involves the use of isolated enzymes, either free or immobilized. There are now more than 20 commercially available lipases from animal, plant and microbial sources. Lipases from microbial sources are virtually homogeneous in terms of hydrolytic activity, while mammalian and plant lipase preparations contain several other interfering enzymes, including proteases and esterases. Pig pancreatic lipase (PPL) has been most widely used, but recently the microbial lipases have gained increasing importance, especially the yeast lipase from *Candida cylindracea* and the bacteria lipases from *Pseudomonas fluorescens* and other unclassified *Pseudomonas* species[2]. The *Candida cylindracea* and *Pseudomonas fluorescens* lipases have recently been reclassified to *Candida rugosa* and *Pseudomonas cepecia*. Even though all these enzymes are lipases and catalyse the same type of reactions, their action towards substrates in terms of chemo-, region- and enantioselectivity varies considerably. The optimal operation conditions are greatly different between individual lipases, thus making a general procedure suitable for all lipases difficult or even impossible to develop.

The lipases differ in their actions towards various substrates and conditions. They are very sensitive towards even slight changes in the substrate structure as well as the polarity of the solvent. One problem in enzymatic transformations is the difficulty of predicting the stereochemistry of a reaction. Among lipases, reverse enantiopreference for one substrate, and changeover in stereoselectivity from one substrate to another is not uncommon. A large selection of different lipases is therefore important in finding the right enzyme for a desirable reaction by the traditional biocatalyst screening. But, since

the number of readily available lipases is limited, it is necessary to develop alternative strategies for improving enantioselectivity and extend the usefulness of the already existing commercial lipases. Besides the standard optimization of reaction conditions such as temperature[28] and pH[29,30], approaches used to improve the enantioselectivity of biocatalytic reactions involving lipases[31] include substrate modification[32], solvent screening[4,33–35], product recycling[36], enantioselective inhibition[37], non-covalent enzyme modification[31] and addition of a catalytic amount of an amino alcohol[38].

Another approach is to develop reliable active-site models for the enzyme, that are simple and reliable for use in the prediction of new reactions and in the rationalization of literature results. Several such models have been proposed for lipases[39–46], which usually aim at defining the shape and hydrophobic character of the active site, but in most cases they are only accurate for substrates very similar to those already tested. Very recently, Kazlauskas and coworkers have proposed a rule, similar to the well-known Prelog's rule, for predicting the enantiopreference of the lipases from *Pseudomonas fluorescens* and *Candida cylindracea*, as well as cholesterol esterase, towards secondary alcohol substrates[47].

B. Application of Lipases

Lipases have been used in three main types of asymmetric transformations. These are kinetic resolutions of racemic carboxylic acids or alcohols, enantioselective group differentiations of *meso* dicarboxylic acids or *meso* diols and enantiotopic group differentiation of prochiral dicarboxylic acid and diol derivatives. Although hydrolysis has been the most widely used technique, complementary esterification or transesterification procedures are increasingly coming into use. Lipases are used most frequently in transformations involving chiral alcohols, rather than chiral acids. Since their natural substrates are esters of a chiral alcohol (glycerol) with an achiral acid, lipases would be expected to be most useful in conversions involving esters of chiral alcohols, rather than of chiral acids. However, there are a number of examples of the successful application of lipases involving chiral acids.

Kinetic resolution of racemic compounds[48] is by far the most common transformation catalysed by lipases, in which the enzyme discriminates between the two enantiomer constituents of a racemic mixture, so that one is more readily transferred into a product than the other. This is demonstrated in equations 1 and 2 for two substrates, A and B.

$$S_A \xrightarrow{k_A} P_A \quad (1)$$

$$S_B \xrightarrow{k_B} P_B \quad (2)$$

Kinetic resolution occurs if $k_A \neq k_B$ and the reaction is terminated at some stage between 0 and 100% conversion. The ideal situation is that in which only one enantiomer reacts, A for instance ($k_A \gg k_B$); this enantiomer is completely hydrolysed to the alcohol and acid, while the unreacted enantiomer remains in the ester form. While the maximum yield of a kinetic resolution is restricted to 50% for each enantiomer based on the starting material, this route has the advantage of easy preparation of both enantiomers by using a single enzyme.

In contrast to kinetic resolution, the prochiral route and transformations involving *meso* compounds have the advantage of potentially obtaining a 100% of pure enantiomer. For this type of transformation, no generally applicable method exists in conventional organic chemistry, so the enzymatic 'meso-trick' has been widely applied. The drawback here is the possible formation of the undesired enantiomer, which requires

another enzyme with an opposite stereoselection. However, in the prochiral case, inversion of configuration is normally easily effected by selective functional group manipulation[49–51].

In the hydrolysis of diesters of prochiral and *meso* diols with lipases and esterases, the monoesters generated are normally hydrolysed further to the corresponding diol, unlike dicarboxylic ester substrates, for which the hydrolytic reactions generally terminate at the monoester stage, presumably due to the formation of a carboxylate salt, which is too polar for the hydrolytic binding site of the enzymes. Therefore, the enzymatic reaction can be continued until all the diester is consumed.

Lipases are also gaining increasing importance in solving problems of regioselectivity of various polyol and carbohydrate compounds[2,4,5]. The selective protection and deprotection of polyfunctional molecules is a crucial problem, but in carbohydrate chemistry these problems are intensified due to the presence of multiple hydroxyl functions of very similar reactivity. Lipases have also found application in stereoselective transformations involving lactonization and oligomerization of hydroxy acids and esters[4,5]. Finally, an advantage of the lipases is their mildness. This is particularly important in transformations involving labile compounds that are likely to undergo decomposition, when conventional chemical methods are applied, but they are cleanly and efficiently hydrolysed or esterified by the lipases.

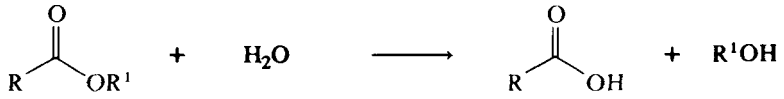
C. Lipase-catalysed Reactions

Conventionally, lipase-catalysed reactions were carried out in emulsion systems, where reactions take place at the interface of oil droplets. Upon the discovery that lipases successfully catalyse reactions under almost anhydrous conditions in organic medium, i.e. in the presence of only an essential thin layer of water needed by the enzyme to maintain its integrity[52,53], the range of possible chemical reactions widened far beyond hydrolysis[4,5]. Thus, lipases can be used for ester synthesis from carboxylic acids and alcohols. In order to shift the equilibrium towards the complete formation of the ester, water must be removed by the aid of molecular sieves or vacuum. Transesterifications (acyl transfer reactions) can similarly be conducted in water-free milieu. They can be divided into alcoholysis, acidolysis and interesterification (ester–ester interchange).

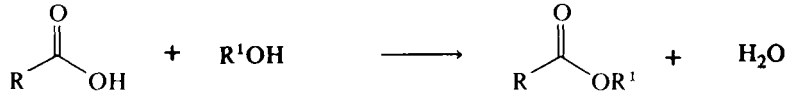
Of these reactions the direct esterification and alcoholysis involving racemic alcohols have been most frequently used in asymmetric transformations involving lipases. It has recently been pointed out that the acidolysis process might be more advantageous in terms of enantioselectivity, since the chiral alcohol must associate with the active site twice during the process, first to undergo deacylation of the ester and then for the subsequent acylation[54]. The same argument should also apply for the interesterification process, although the necessary separation of esters may require difficult chromatography or careful distillation. The whole range of reactions catalysed by lipases involving esters are depicted in Scheme 1.

As would be expected, conditions favouring rapid and irreversible reactions are necessary for the achievement of high enantioselectivity in a kinetic resolution process. The optical purity of the desired product diminishes as the reverse reaction advances, due to the reversible nature of esterification and of interesterification in biocatalytic kinetic resolutions and the same enantioselection of the catalyst in both directions[55]. Thus, the optical purity of both the product and the remaining substrate will decrease progressively, as the extent of the reverse reaction increases. The same situation can be seen in biocatalytic transformations with prochiral and *meso* compounds. There are several strategies available to overcome these problems by suppressing the reversibility or ensuring irreversibility of the processes[4,5], although the slow reaction rate is a more difficult problem to deal with.

Hydrolysis of ester:

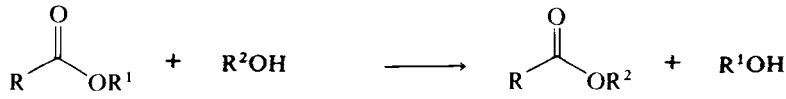


Direct esterification:



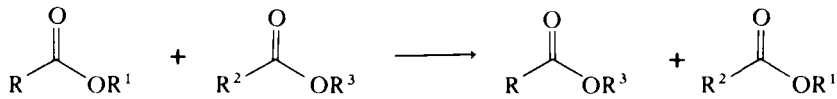
Transesterifications

A. Alcoholysis:



B. Acidolysis:

C. Interesterification:



SCHEME 1

Enol esters, such as vinyl or isopropenyl esters, are most commonly used in the transesterification process[56,57]. Their use minimizes the extent of the reverse reaction by irreversible tautomerization of the enol leaving moiety into volatile acetaldehyde or acetone, which cannot undergo the reverse reaction. The lipase from *Pseudomonas fluorescens* has proved to be particularly effective for transesterifications with enol esters. Anhydrides[58,59] and oximes[60] have also been applied in a similar manner as acyl donors, without the release of nucleophilic alcohols or water, to minimize the reversibility of the process. Active esters such as trifluoroethyl[61] and trichloroethyl[62] esters have similarly been used to speed the acyl-enzyme formation and generate the weakly nucleophilic trifluoro- or trichloroethanol, which do not compete with the substrate alcohol in the acylation.

Primary alcohols have been used as acyl acceptors in transesterifications involving esters of secondary alcohols[63]. The bulkiness of the secondary alcohols renders them less nucleophilic compared to the primary alcohols, and the system thus less susceptible for the reverse reaction. The continuous removal of water or alcohol can be used to shift the equilibrium towards the products by exploiting molecular sieves or vacuum[64]. High vacuum was effectively applied to remove the more volatile ethyl butyrate in the interesterification of long-chain fatty acid ethyl esters with tributyrin to prepare the corresponding triglycerides[65]. Finally, a large excess of acyl acceptor can be used to reduce the relative concentration of the competing alcoholic nucleophile.

D. Lipase—Mechanisms and Kinetics

In the lipase-catalysed cleavage of esters the lipase operates by binding the substrate and cleaving it to release the alcohol with formation of an acyl-enzyme intermediate. This intermediate is formed upon attack by hydroxyl group of the serine residue at the active site. The acyl–enzyme intermediate may be attacked by water, or another nucleophile, to release the product and regenerate the free enzyme. In water the last step is essentially irreversible. In Scheme 2, E is the hydrolytic enzyme, $RCOOR^1$ is the ester substrate, $E \cdot RCOOR^1$ is the enzyme–substrate complex (the Michaelis complex) and $E \cdot COR$ is the covalent acyl–enzyme intermediate[3,5].

$$E + RCO_2R^1 \rightleftharpoons E \cdot RCO_2R^1 \rightleftharpoons E \cdot COR \xrightarrow{H_2O} E + RCO_2H$$
$$+$$
$$R^1\text{—}OH$$

SCHEME 2

A theoretical quantitative analysis of the biocatalytic kinetic resolution of enantiomers, for the irreversible hydrolysis process in aqueous medium, was developed by Sih and collaborators[36,3]. This laid the basis for the application of lipases and allows synthetic chemists to make highly useful predictions. Equation 3 shows the interrelationship between the three key parameters, the extent of conversion of racemic substrate, c, the optical purity, expressed as enantiomeric excess, ee, of the product (ee_P) or the remaining substrate (ee_S), and the enantiomeric ratio, E. The percent enantiomeric excess (ee) vs the percent conversion for various enantiomeric ratios (E) are then plotted. The resulting graphs are extremely useful in predicting when to terminate the reaction to optimize the enantiomeric excess of the product or remaining substrate, once the E value has been determined.

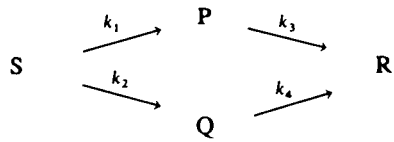
$$E = \frac{\ln[(1 - c)(1 - ee_S)]}{\ln[(1 - c)(1 + ee_S)]} = \frac{\ln[1 - c(1 + ee_P)]}{\ln[1 - c(1 - ee_P)]} \tag{3}$$

As long as the reaction is irreversible the enantiomeric ratio E is a constant that is independent of time, substrate and enzyme concentration, and thus the extent of conversion. It is therefore ideally suited as a measure of comparing the enantioselectivity of different enzymes. The results of these kinetic evaluations reveal that, in such an enzymatic hydrolysis, high chemical and optical yields for both enantiomers can usually only be obtained if their rates of hydrolysis are very different, e.g. by a factor of at least $E > 100$. These results also reveal that the optimum in both chemical and optical yield for the faster hydrolysed enantiomer is to be expected near 40% conversion, and for the remaining slower hydrolysed enantiomer at around 60% conversion. In cases of lower E values, only one enantiomer (the remaining one) can be obtained enantiomeric-

ally pure. Thus, the optical purity depends on the extent of conversion, and in order to get satisfactory enantiomeric excess it is necessary to increase the degree of conversion at the expense of decreased yield. In general, for a satisfactory resolution, E values greater than 10 should be sought. However, if necessary, re-esterification of the product mixture, enriched in one enantiomer, and a second enzymatic hydrolysis by the same enzyme, will give products of higher optical purity.

Sih and coworkers have extended their method for biphasic aqueous-organic and monophasic organic systems, in which the reverse esterification or transesterification reactions are reversible[55,4]. For such systems, a new expression which incorporates the thermodynamic parameter, K, is required for the calculation of the enantiomeric ratio E. The corresponding computer-generated graphs show that a small increase in the value of K has a very pronounced effect on the enantiomeric purity of both the substrate and product fractions, even for systems with very high E values. The results reveal that, due to the reversibility of the reaction, high enantiomeric excess can be expected only for the ester product and not for the unreacted substrate. And, since reversibility can become a significant problem at conversions above 40%, high optical purity of the ester product cannot normally be attained by extending the conversion beyond 50%.

Sih and coworkers have also derived quantitative expressions, which allow the similar prediction of the enantiomeric excess and the optimization of optical and chemical yields of the monoester fraction for the enantioselective hydrolysis and enantiotopic group differentiation of diesters of *meso* and prochiral diols[66,67]. This is illustrated in Scheme 3, where S is the prochiral or *meso* diol diester, P and Q are the fast and slow forming monoesters, respectively, and R the corresponding diol, while k_1, k_2, k_3 and k_4 are the corresponding rate constants.



SCHEME 3

For enantiogroup differentiation it is generally true that, if $k_1 > k_2$, then $k_4 > k_3$, because the stereochemical preference of attack of the two groups is maintained in the successive steps. Also, because $k_1 > k_2$ the enantiomer P is produced faster than Q, but because $k_4 > k_3$ the enantiomer Q is transferred to the product R faster than P. This means that the relative rates of production and reaction of P and Q serve to enhance the concentration of P as the reaction proceeds, which means that P can be obtained to any level of optical purity, provided the overall reaction is taken far enough, even for relatively low ratios of k_1/k_2. The equations of Sih and coworkers can be used to calculate the concentration of all the constituents, S, P, Q and R, for any degree of conversion for the process.

Finally, Sih and coworkers have generated similar useful equations and graphs for predicting the concentration of all six participating constituents at any degree of conversion in the resolution of racemic asymmetric diols, either by enantioselective hydrolysis of the corresponding acetate[68] or the reverse direct esterification of the diol[69]. In such systems two kinetic resolution steps are operating in tandem.

E. Active Site Studies of Lipases

It was not until very recently, when the three-dimensional structure was reported for a lipase, that the long-standing assumption, that lipases were of the serine-hydrolase

type, was eventually confirmed. The X-ray structure of the bacterial lipase from *Mucor miehei* revealed[70] the presence of a trypsin-like Ser···His···Asp catalytic triad[71] with the active serine residue buried under a long loop or flap, covering the hydrolytic site and perhaps serving as a device to regulate the exposure of the active site to substrates, as well as inhibiting the proteolytic activity of the triad. These data indicate that major conformational changes are required before substrates can bind to the active site in lipases. Similar structural features were also observed for the three-dimensional crystal structure of human pancreatic lipase[72]. In analogy with the well-established topography of several serine proteases, these findings should have an enormous impact on research activity in this field in the near future, including mechanistic[73,74] and model studies[75], as well as genetic and protein engineering for modification of these biocatalysts with improved physical and chemical properties[76]. Based on these observations, a mechanism bearing strong resemblance to the charge relay mechanism of Blow[77,78,71] for proteases, is evident for the lipase-catalysed hydrolysis of an ester.

F. Lipases in Organic Media

Klibanov and coworkers recognized the immense synthetic potential of enzymes in organic solvents and their fundamental pioneering studies have generated great interest in these systems[5,34,52,79–82]. Three types of organic systems have been used in biocatalytic conversions involving lipases[4]. These are water-miscible organic cosolvent systems, biphasic systems consisting of water and a water-immiscible organic solvent, and anhydrous monophasic organic solvent (0.01–< 1% water content). The major advantages of anhydrous organic media are: (1) increased solubility of non-polar substrates poorly soluble in water leading to more efficient catalysis (particularly when solid substrates are involved); (2) synthesis of esters favoured over hydrolysis by shifting of thermodynamic equilibria, by which important reactions become possible, including esterification, transesterifications, lactonization, thiotransesterification, aminolysis and oxymolysis[80]; (3) suppression of water-dependent side-reactions; (4) ease of product and enzyme recovery from low-boiling organic solvents; (5) enhanced thermal stability of enzymes in anhydrous organic media; (6) since enzymes are insoluble in organic solvents, immobilization often becomes unnecessary; (7) elimination of microbial contamination; (8) the solvent can be used to regulate substrate specificity of enzymes and enantioselectivity; (9) the possibility of carrying out a reaction solvent-free is another highly valuable advantage[83].

The main disadvantages with organic solvents is lower catalytic activity so that a larger quantity of enzyme is required for the reaction. Another disadvantage is the reversibility of the reactions in organic media with two major consequences: the establishment of equilibrium limits the yield, and the reversibility of the reaction works against the kinetic resolution which lowers the enantioselectivity of such processes.

The parameters that influence enzymatic catalysis in monophasic solvents, such as the role of the enzyme-associated water, the nature of the biocatalyst, including the ionic state of the enzyme and support characteristics, and the properties of the organic solvent, have been intensively studied and discussed in several reviews[4,34,52,79,84]. The results reveal that for maintaining the catalytic function of the enzyme[52] some water is essential which is involved in various types of non-covalent bonding interactions for the maintenance of catalytically active conformations of the enzymes in the organic media. The amount of water required is less clear and appears to be enzyme-dependent. Generally, the least polar and most hydrophobic solvents require the least water for enzyme activity. Klibanov has suggested that the more hydrophilic solvents tend to strip the essential hydration layer from enzymes[52], so that more water must be used in association with such solvents. Also, the enzyme stability has been found to depend on the amount of water in the organic solvent[79], and a balance must be kept between

activity and stability in terms of water concentration. Finally, the presence of even a small quantity of water might be sufficient for a hydrolysis. Hence a compromise must be maintained between activity, stability and reverse hydrolysis in terms of water content.

The pH of the aqueous solution, from which the enzyme was isolated, plays an important role and retains the appropriate ionic state of the enzyme. Similarly, the support material in the case of immobilized enzymes may influence the micro-environment in the vicinity of the enzyme and thus its activity and stability. Therefore, the choice of support may be an effective means to control the local concentrations of substrates and products for catalysis. When the free enzyme is used in organic solvents as a suspension, diffusional limitations must be minimized by agitation and particle-size control.

The type of organic solvent has profound effects on the reaction kinetics and stability of the enzyme. There are three distinct ways for the organic solvent to affect enzymatic catalysis[84]. Direct interaction of the solvent can cause inhibition or inactivation by altering the native conformation of the protein by disrupting hydrogen bonding and hydrophobic interactions. The solvent may also affect enzyme activity by interacting with diffusable substrates or products of the reaction. Finally, the solvent may interact directly with the essential water in the vicinity of the enzyme.

In general, as the polarity of the solvent increases, the catalytic efficiency of the biocatalysts diminishes and more polar, hydrophilic solvents usually denaturate enzymes by stripping off the essential water from the enzyme. Apolar solvents, such as toluene, cyclohexane and isooctane, are most commonly used for the lipase-mediated reactions. Halogenated hydrocarbons, such as trichlorotrifluoroethane, and *tert*-butyl, diisopropyl and *tert*-butyl methyl ethers, have also been successfully employed. Polar solvents, such as DMF, pyridine and butanol, may be used at the expense of enzyme stability when the substrates are more polar. In such cases, immobilization may also be exploited. As was mentioned earlier, both substrate specificity and enantioselectivity can be mediated by the solvent.

G. Esterases and Other Hydrolases

Another class of serine hydrolases that bear close resemblance to lipases is the esterases. They have been often used in asymmetric synthesis and, like lipases, show activity towards a broad range of esters. Unlike lipases, however, they are not readily available, apart from pig liver esterase (PLE) (EC 3.1.1.1), to which their application is almost exclusively confined, and which has been extensively reviewed[1,2,13–15,18,85–87]. Other esterases that have been used include horse liver esterase[88], cholesterol esterase[89,90] and the electric eel acetylcholine esterase[91]. The application of PLE is almost entirely restricted to aqueous solutions and thus to hydrolytic processes, occasionally with an organic water-miscible cosolvent to aid solubility of the substrate. Unlike the lipases, esterases act on water-soluble substrates in a homogeneous milieu, which is a drawback and requires water solubility of the substrate. PLE is one of the most useful hydrolases for discrimination between enantiotopic ester groups in *meso* diester compounds[92]. PLE, like lipases, is cheap, stable, does not require cofactors and hydrolyses a wide variety of esters with high stereoselectivity. Unlike lipases, however, the native substrate of PLE is not known. Although little is known about the topography of the active site, several models for the active site of PLE have emerged for interpreting and predicting the substrate and enantioselectivity properties of the enzyme[93]. In contrast to lipases, PLE has been used relatively infrequently for kinetic resolution of racemates, usually with esters of chiral carboxylic acids and less frequently with esters of chiral alcohols. Esterases have been applied primarily in enantioselective hydrolysis of mono- and diesters with chiral centres on the acid part of the molecule.

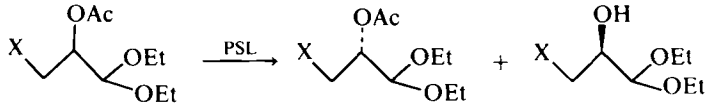
Conversions involving the carboxylic esters are not restricted to lipases and esterases. Just as lipases can catalyse peptide bond formation[2,94–97], proteases such as α-chymotrypsin, trypsin and subtilisin have frequently been used in biocatalytical transformations involving ester hydrolysis and esterification reactions. The different stereoselection of these enzymes often provides a useful complement to the lipases.

IV. KINETIC RESOLUTION BY HYDROLYSIS

A. Chiral Alcohols

1. Acyclic racemic alcohols

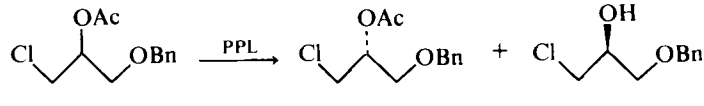
Wong and coworkers[98] used *Pseudomonas* sp. lipase (PSL) to resolve the racemic acetate of 3-azido-2-hydroxypropanal diethyl acetal, (±)-**1** (X = N_3), in excellent chemical and optical yields. At 51% conversion the unreacted acetate (*S*)-**1** was afforded in excellent yield (46%), with excellent optical purity (>98% ee), as well as the corresponding alcohol product (*R*)-**2**, similarly in excellent yield (47%) and almost enantiomerically pure (97% ee). The corresponding α-hydroxy aldehyde derivatives of (*S*)-**1** and (*R*)-**2** were subsequently used as substrates in a high-yield asymmetric synthesis of polyhydroxylated alkaloids, such as 1-deoxynojirimycin and 1-deoxymannojirimycin. This was circumvented on a preparative scale by a combined enzymatic aldol condensation and catalytic intramolecular reductive amination involving a recombinant bacterial fructose-1,6-diphosphate aldolase with minimum protection of functional groups. It is evident that such aldol reactions should become highly valuable synthetic methods in carbohydrate chemistry.



(±)-(**1**) (*S*)-(**1**) (*R*)-(**2**)

Similarly, Wong's team has enantioselectively hydrolysed various related 3-substituted-2-acetoxypropanal diethyl acetals **1**, by using the PSL[99] (X = F, Cl, $C_6H_5CH_2O$). At 50% conversion both the 3-fluoro and the 3-chloro derivatives of **1** were resolved with the lipase to afford the corresponding alcohols and the remaining esters, possessing the same absolute configuration, in excellent optical purities (>98% ee) and yields (>46%). With the benzyloxy adduct, this lipase turned out to be less stereoselective.

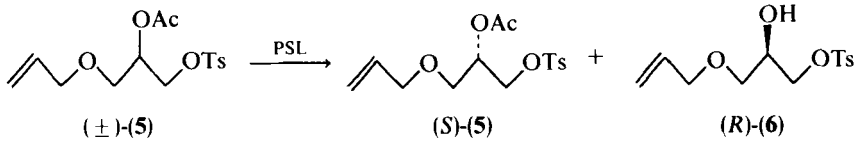
PPL was also employed to resolve the acetate of secondary alcohol **3**. At 25% conversion the alcohol (*S*)-**4** was afforded in 92% ee, and at 60% conversion the unreacted acetate (*R*)-**3** in 98% ee.



(±)-(**3**) (*R*)-(**3**) (*S*)-(**4**)

Similarly, the acetate of the secondary alcohol **5** was resolved with PSL to give (*R*)-**6** and (*S*)-**5** with high enantioselectivity (90 and 94% ee, respectively).

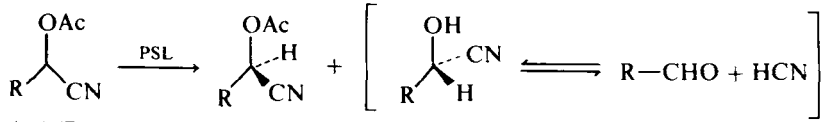
From these derivatives the preparation of the corresponding highly enantiomerically



(±)-(5) (*S*)-(5) (*R*)-(6)

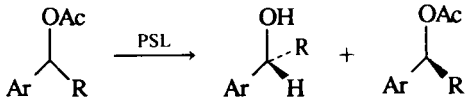
pure epoxy aldehydes and epoxy alcohols was described and the application of these epoxides for the synthesis of other enantiomerically pure compounds including (diethoxymethyl)thiine, (diethoxymethyl)azidine and D-glyceraldehyde 3-phosphate.

Schneider and coworkers[100] have reported the preparation of a wide variety of cyanohydrin acetates by enantioselective hydrolysis of the racemic cyanohydrin acetate substrates **7** by PSL (R-aryl, vinyl, alkyl). The hydrolysis afforded the optically active acetates (*R*)-**7** in good chemical yield and frequently with excellent optical purity (≥98% ee) at approximately 50% conversion. The addition of 20% THF as a cosolvent to the reaction mixture lead to an improved transformation and increases in enantioselectivity. All the products were tentatively assigned to be of the same absolute configuration. The generated cyanohydrins (*S*)-**8** were normally unstable under the conditions employed.



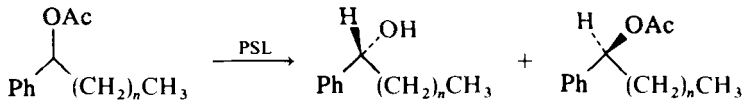
(±)-(7) (*R*)-(7) (*S*)-(8)

They also used PSL to resolve kinetically a wide variety of secondary alcohol substrates of the type **9** with various acyl and alkyl substituents[101]. At approximately 50% conversion both the alcohol product (*R*)-**10** and the unreacted acetate (*S*)-**9** were isolated in excellent yield with very high optical purity (frequently >99% ee). Chloroacetate instead of acetate was successfully used to enhance the rate of the slower transformations without affecting the *E* values.



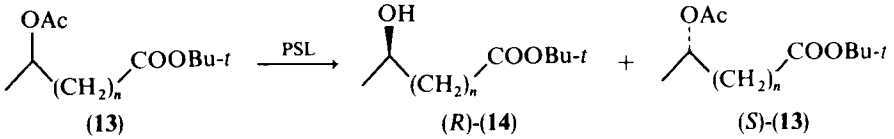
(±)-(9) (*R*)-(10) (*S*)-(9)

Mori and Bernotas[102] have recently reported the kinetic resolution of similar acetates of various 1-phenyl-1-alkanols **11** (n = 5,6,7). Out of several lipases PSL performed best, providing alcohols (*R*)-**12** of high optical purity (92–98% ee), as well as the unreacted acetates (*S*)-**11**, optically pure (100% ee), using 10% acetone as a cosolvent. Extended reaction periods were required (up to 167 h) to reach high extents of conversion (40, 50 or 60%), depending on the *E* values. Attempted esterifications of the corresponding racemic alcohols **12** were unsuccessful due to low reaction rates and low enantioselectivity, unlike several reports in the literature for shorter alkyl chain 1-phenyl-1-alkanols[59,62,103].



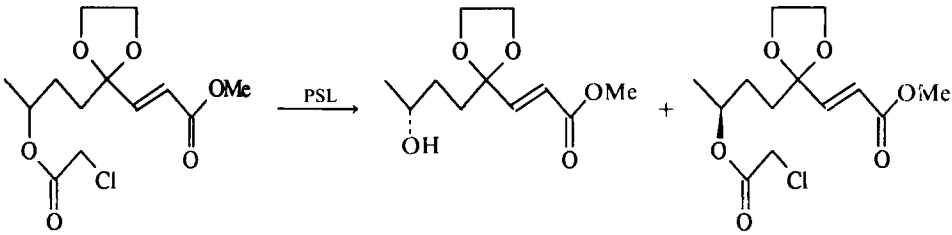
(**11**) (*R*)-(**12**) (*S*)-(**11**)

Sih's team used PSL to resolve a variety of racemic hydroxy alkanoic esters of the type **13** (n = 0,1,5,10)[104]. When the corresponding carboxylic acids of **13** were incubated, the lipase showed *R*-stereochemical preference, but without acceptable enantioselectivity. Also, the methyl esters of **13** were readily cleaved to the carboxylic acid with low enantioselectivity. On the other hand, when the unhydrolysable *t*-butyl esters **13** were subjected to the lipase, the *R*-stereochemical preference was retained, but the enantioselectivity was significantly elevated and the alcohols (*R*)-**14** were afforded optically pure (>99% ee) at 30–40% conversion. More recently, Kazlauskas and coworkers obtained similar results (i.e. elevated enantioselectivities) in going from methyl esters of **13** to the *t*-butyl esters, for lactate ester hydrolysis (n = 0) in substrate model studies for the active site of the *Pseudomonas fluorescens* lipase (PFL)[47].



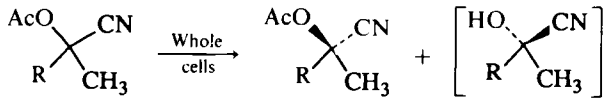
(**13**) (*R*)-(**14**) (*S*)-(**13**)

In their approach towards the synthesis of the natural antifungal macrolide (−)-pyrenophorin, Sih and coworkers[105] exploited PSL for the asymmetric hydrolysis of the racemic methyl 7-(chloroacetoxy)-4,4-ethylenedioxy)oct-2-enoate **15** with very high enantioselectivity in good yields. At 42% conversion the hydroxy product (*R*)-**16** was captured optically pure (>99% ee), and at a conversion of 51%, (*S*)-**15** was also obtained at >99% ee. The synthesis of (−)-pyrenophorin was then completed from (*S*)-**15**.



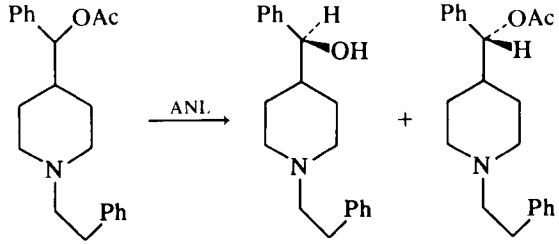
(**15**) (*R*)-(**16**) (*S*)-(**15**)

Ohta and coworkers[106] employed whole cells of the yeast *Pichia miso* for the asymmetric hydrolysis of various racemic 1-cyano-1-methylalkyl- and alkenyl acetates, **17**. The remaining acetate (*S*)-**17** was obtained in good yields and with 95–99% ee, whereas the hydrolysed cyanohydrins (*R*)-**18** were recovered as the corresponding ketones and could be recycled, thus enabling the conversion of all the racemic acetate to a single enantiomer. Employing (*S*)-**17** as a chiral synthon (R = CH_2 = $CH(CH_2)_3$—, 99% ee), they succeeded in the asymmetric synthesis of (*S*)-(−)-frontalin, a beetle pheromone[107]. The same group reported also the microbial asymmetric hydrolysis of racemic α-acetoxyacylophenones, to afford the recovered acetate with 98–99% ee, at 50% conversion, as the *S*-enantiomer[108].



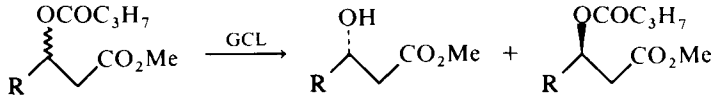
(±)-(**17**) (*S*)-(**17**) (*R*)-(**18**)

Nieduzak and Carr[109] described the enantioselective hydrolysis of acetate **19** utilizing a lipase from *Aspergillus niger* (ANL). Both the alcohol (*S*)-**20** and the remaining acetate (*R*)-**19** were obtained with >97% ee, at approximately 50% conversion. The racemic substrate was made immobilized by adsorption on silica gel. A reaction time of two to three days was required, and in order to achieve the alcohol optically pure, a resubjection of the reacylated alcohol produced from the first run was necessary for one day.



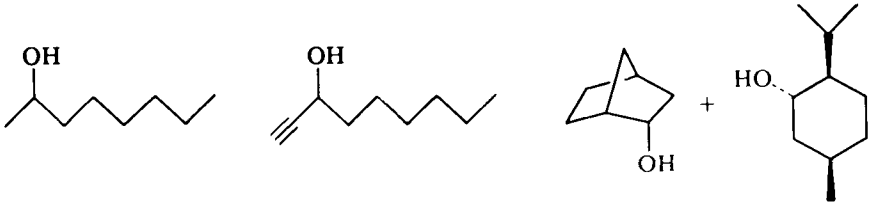
(19) (*S*)-(**20**) (*R*)-(**19**)

Feichter, Faber and Griengl[110] studied the enzymatic resolution of 3-butanoyloxyalkanoates of various chain lengths with *Geotrichum candidum* lipase (GCL) with moderate to good enantioselectivity. The best results were obtained for derivative **21** possessing a branched alkyl group R, and at 40% conversion (*S*)-**22** was obtained with 92% ee. At 60% conversion the remaining ester (*R*)-**21** was obtained at unexpectedly low optical purity (50% ee), and not at all in harmony with Sih's proposal[36]. Undesired cleavage of the methyl ester was observed, which might be the reason for this rather odd behaviour. An attempt to block this side reaction by employing the *t*-butyl ester resulted in non-acceptance by the lipase.



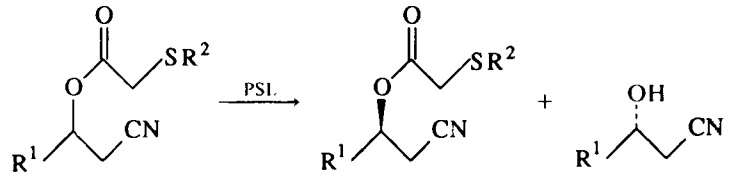
(21) (*S*)-(**22**) (*R*)-(**21**)

The same group has recently reported lipase-catalysed hydrolysis and transesterification of esters in which both the alcoholic and the acidic moieties were chiral[111]. CCL and PSL were used for the hydrolysis and transesterification of (*R*)- and (*S*)-2-chloropropanoates of four racemic alcohols **23**–**26**, and racemic 2-chloropropanoate with the same alcohols optically pure. Unlike in transesterifications the enantioselectivity of the resolution of the racemic alcohol was dependent on a proper choice of configuration in the acid part for the hydrolysis. For the resolution of racemic acids, on the other hand, the reversal of the alcoholic part did not improve the enantioselection significantly for neither the hydrolysis nor the transesterification. It was concluded that both lipases were better able to recognize the chirality of an alcohol moiety rather than that of an acid.



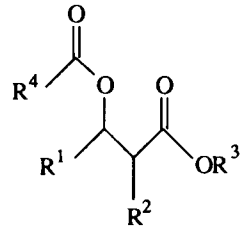
(23) **(24)** **(25)** (±)-(**26**)

In their synthesis of optically active β-hydroxy nitriles, which were expected to be useful chiral building blocks for asymmetric synthesis, Itoh and coworkers discovered that the phenylthio- and methylthioacetoxy groups were efficient in enhancing the enantioselectivity of the PSL[32,112]. The enantioselectivity of the lipase hydrolysis improved dramatically, when 3-methylthioacetoxy- and 3-phenylthioacetoxy nitriles **27** were used. As an example, at 41% conversion, when $R^1 = R^2 = Ph$, the alcohol (*R*)-**28** was afforded with 94% ee, and at 63% conversion the residual ester (*S*)-**27** was obtained with >98% ee, both in good yields.



(±)-(**27**) (*S*)-(**27**) (*R*)-(**28**)

Itoh and coworkers have extended this reaction to various α-alkyl β-hydroxy esters of the type **29**, by using *Aspergillus* sp. lipase, in order to design suitable substrates for this enzyme[46]. They found that the *anti (erythro)* isomer fits this lipase better than does the *syn (threo)* one, and the presence of a sulfur-containing functional group in the acyl residue of the substrate is necessary for obtaining satisfactory results. Some conclusions were drawn about the active site of the lipase and the requirements that substrates of that type must fulfill in order to fit properly into the cavity of the active site.

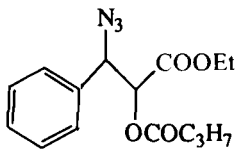


(**29**)

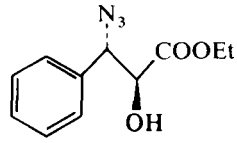
Very recently, Itoh and coworkers have discovered that the amino alcohol L-methioninol was an effective additive for improving the enantioselectivity of the lipase-catalysed hydrolysis of the 3-acetoxybutyronitriles by accelerating the hydrolysis of the *R*-enantiomer, but inhibiting that of the *S*-enantiomer[38]. This is similar to the effect of dextromethrophan reported by Guo and Sih to improve the enantioselectivity of lipase-catalysed hydrolysis[37]. It was evident that a conformational change, as a result of the binding of L-methioninol with a certain part of the enzyme, might alter the affinity towards the substrates, thus providing an increase in the hydrolysis rate of the *R*-enantiomer, while decreasing the rate of hydrolysis of the *S*-enantiomer.

Hönig and coworkers have succeeded in the simultaneous diastereo- and enantioselective hydrolysis by the aid of lipases[113]. As an example, when a 34:66 diastereomeric mixture of racemic *threo/erythro*-3-azido-2-butanoyloxy-3-phenylpropanoate **30** was exposed to PSL, excellent diastereoselectivity (98% de) and enantioselectivity (98% ee) were obtained for the *erythro* alcohol (2*S*, 3*S*)-**31** in good yield at 32% conversion. The remaining ester, as a 50:50 *threo/erythro* mixture, was further hydrolysed to afford the

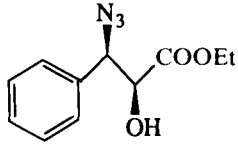
threo alcohol (2*S*,3*R*)-**32** at 20% conversion and good yields were again obtained with 90% de and 94% ee. These results are similar to those obtained by Yamazaki and collaborators for chlorofluoromethylated alcohols[114].



(**30**)

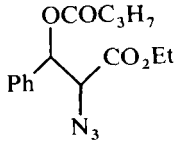


(2*S*,3*S*)-(**31**)

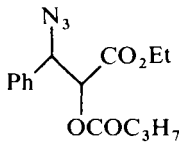


(2*S*,3*R*)-(**32**)

Hönig and coworkers also employed *Pseudomonas fluorescens* and *Candida cylindracea* lipases and subsequent catalytic hydrogenation to generate all stereoisomers of 3-phenylserine and 3-phenylisoserine[115]. They were all obtained in enantiomerically pure form (>98% ee) in good to excellent yields, starting with diasteriomerically pure *threo/erythro* 2-azido-3-butanoyloxy-3-phenylpropionic esters, **33**, and *threo/erythro* 3-azido-2-butanoyloxy-3-phenylpropionic ester, **34**.

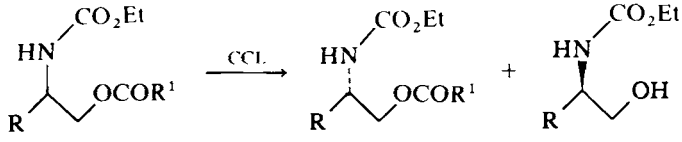


(**33**)



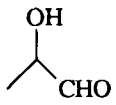
(**34**)

Francalanci and coworkers reported the preparation of optically active 2-aminoalcohols by lipase-catalysed resolution by hydrolysis as well as transesterification[116]. The protection of the amino group was found necessary to accomplish optical resolution of these compounds, using PPL and *Candida cylindracea* lipase (CCL), which both showed strong preference towards the *R*-enantiomers. At low conversion (40%) the *R*-alcohol **36** was afforded with ≥95% ee by hydrolysis ($R^1 = CH_3$ or n-C_3H_7), whereas transesterification in ethylacetate yielded the corresponding *S*-alcohol with ≥95% ee at high conversion (60%) (for $R{=}CH_3$ or C_2H_5).



(**35**) (*S*)-(**35**) (*R*)-(**36**)

Bianchi and collaborators studied the kinetic resolution of α and β-hydroxy aldehydes **37** and **38**, protected as acetic or butyric ester derivatives[117]. When the hydroxythioacetal (1,3-dithiane and 1,3-dithiolane) derivatives of both the acetic and butyric ester derivatives of **37** and **38** were subjected to PSL, both the corresponding *R*-alcohols and the remaining *S*-esters were obtained in good yields with 95–99% ee and 92–95% ee, respectively, at 46–49% conversion. The stereoselectivity dropped dramatically (20–30% ee) when 1,3-dioxan was used as a protective group, although good hydrolytic activity was retained. It was suggested that the enantioselectivity might greatly depend on the lipophilicity of the protective group.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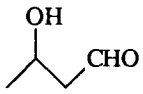
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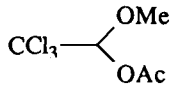
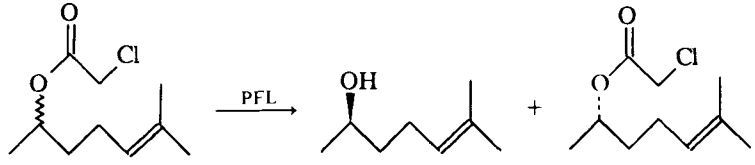

(39)

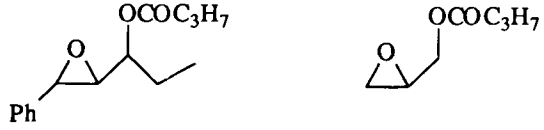
Chenevert's group used various lipases, proteases and esterases to resolve the racemic chloral acetyl methyl acetal **39**[118]. When this was subjected to CCL, PPL or cholesterol esterase at 50% conversion, the remaining acetate (−)-**39** was afforded in good yields with >97% ee, whereas the hydrolysed product decomposed. Subtilisin, on the other hand, exhibited reverse configurational preference and afforded the enantiomer (+)-**39** in good yield and >97% ee.

Liang and Paquette[119] employed the PFL to prepare both sulcatol enantiomers **41** by enantioselective hydrolysis of the corresponding chloroacetate **40**. At 55% conversion, *R*-sulcatol, **41**, was afforded in 89% ee, together with the remaining ester, (*S*)-**40**, virtually optically pure (100% ee) in high yields, which was quantitatively converted to the pure *S*-enantiomer of sulcatol.



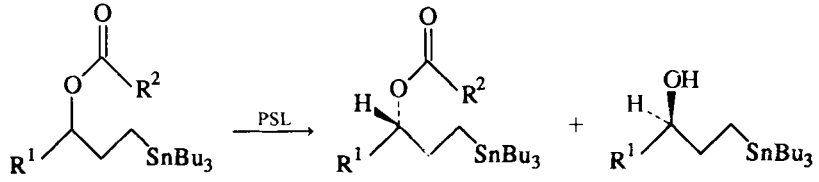
(40) (*R*)-(41) (*S*)-(40)

Marples and Rogers-Evans[120] obtained with PPL the optically active 2,3-epoxy secondary alcohols of the epoxy alcohol ester **42** as an alternative to the Sharpless oxidation[121] of allylic alcohols. At 50% conversion excellent optical purity was obtained (100% ee) and it was found that the *erythro* diastereomer was a far better substrate than the *threo* one. In their asymmetric synthesis of (−)-chorismic acid and (−)-shikimic acid Pawlak and Berchtold found similar preference for the *erythro* isomer when using cholesterol esterase for the resolution of the epoxide (±)-**43** to obtain the desired (1*R*,2*S*,6*R*)-alcohol in good yield and 93% ee at 41% conversion[122]. Ladner and Whitesides had previously reported the application of PPL to resolve epoxy alcohols by lipase-catalysed hydrolysis of the corresponding esters[123].


(42) (±)-(43)

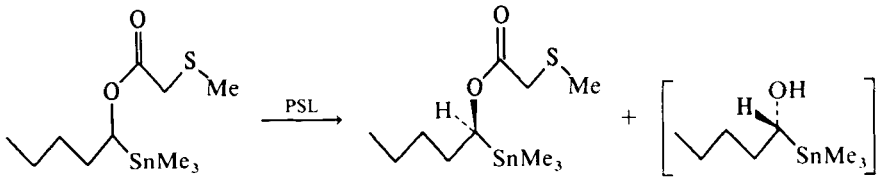
Itoh and coworkers have succeeded in the kinetic resolution of racemic acetates of γ-hydroxystannanes by using PSL[124]. With $R^1 = R^2 = Me$, both(*S*)-**44** and (*R*)-**45** were obtained at 50% conversion with >98% ee. For both $R^1 = n\text{-}C_5H_{11}$ and $n\text{-}C_8H_{17}$ ($R^2 = Me$), results were unsatisfactory, but they could be dramatically improved by replacing the acetate with methylthioacetate (>98% ee) ($R^2 = CH_2—S—Me$). It was anticipated that these compounds might become important in the syntheses of chiral tetrahydrofuranyl compounds and of γ-lactones.

Optically active α-hydroxy stannanes were obtained through hydrolysis with PSL,



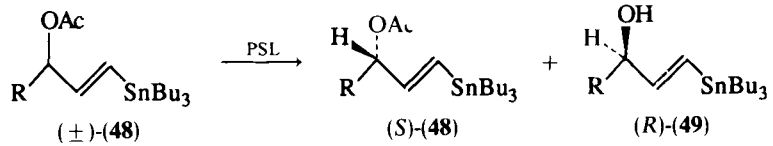
(±)-(**44**) (*S*)-(**44**) (*R*)-(**45**)

although the optical purity was less than with **44**[125]. The best results were accomplished using α-acyloxy trimethylstannane (±)-**46**, with 10% acetone as a cosolvent at 67% conversion, to afford (*R*)-**46** with 86% ee in 33% yield. Methylthioacetate esters were essential in order to reach a sufficient extent of conversion and for achieving reproducible results. The hydrolysed alcohol (*S*)-**47** was found to decompose completely during the reaction.



(±)-(**46**) (*R*)-(**46**) (*S*)-(**47**)

Finally, preparation of optically active γ-hydroxy vinylstannanes by enantioselective hydrolysis of the racemic acetate (±)-**48**, using PSL, has very recently been described by Itoh and Ohta[126]. As an example, when R = n-C_5H_{11}, the γ-hydroxy vinylstannane (*R*)-**49**, a known precursor of the ω-side chain to prostaglandin synthesis, was afforded at 50% conversion with >98% ee in excellent yield, together with the corresponding remaining acetate (*S*)-**48**, also with >98% ee and in high yield. Interestingly, no hydrolysis product was afforded when the *cis*-isomer of **48** was subjected to the lipase.



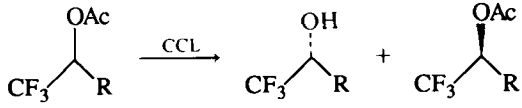
(±)-(**48**) (*S*)-(**48**) (*R*)-(**49**)

2. Fluoroorganic compounds

The preparation of chiral fluoroorganic compounds has recently been reviewed[127] and there are a number of reports on the application of lipases and esterases in that field.

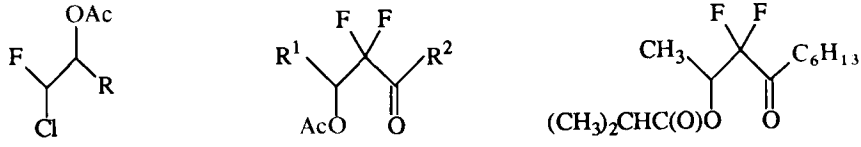
Kitazume and coworkers used CCL for the asymmetric hydrolysis of various 1-substituted 2,2,2-trifluoroethyl acetates **50** to obtain the *R*- and *S*-enantiomers of the corresponding trifluoromethylated secondary alcohols[128]. As an example, the alcohols (*R*)-**51** were afforded with 98% ee for R = $PhCH_2CH_2$ at 44% conversion, and at 55–60% conversion the remaining acetate (*S*)-**50** was also obtained in 99% ee. Several trifluoromethyl substituted β-hydroxy ketone derivatives were also obtained by this method in very high optical purity for both the *S* and *R* enantiomers.

When several chlorofluoromethylated secondary esters of the type **52**, containing two stereogenic centres, were subjected to CCL and PSL, the hydrolysis proceeded efficiently



(±)-(**50**) (*R*)-(**51**) (*S*)-(**50**)

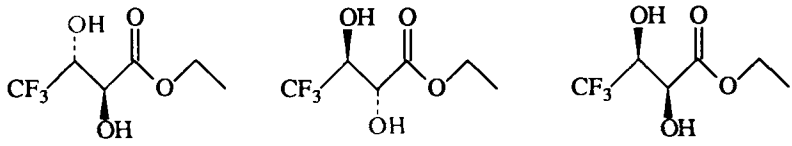
with high to excellent enantio- and diastereoselectivity[114]. The two lipases were found to display opposite configurational preference. Thus, at low conversion (16%) CCL was used to produce the alcohol with moderate diastereoselectivity (60%) and excellent enantioselectivity (98%), whereas for the remaining ester at 71% conversion, high diastereoselectivity was obtained, for R = benzyl (Bn).



(**52**) (**53**) (**54**)

More recently, Kitazume's group employed CCL and PFL to resolve various α,α-difluoro-β-hydroxyketones from the corresponding acetates **53**[129]. Only moderate results were obtained, but when the acyl group was changed from acetyl to isobutyryl, the enantioselectivity was dramatically improved to give both the hydrolysed product and the unreacted substrate with high optical purity (93 and 95% ee) at 52% conversion with PFL for substrate **54**. The absolute configuration was not determined.

Finally, Kitazume and coworkers[130] have described their stereoselective preparation of three out of four possible stereoisomers of 2,3-dihydroxy-4,4,4-trifluorobutyrate, **55**–**57**, with 95–98% ee, by employing in tandem the two lipases, CCL and PFL.



(**55**) (**56**) (**57**)

3. *Monocyclic racemic alcohols*

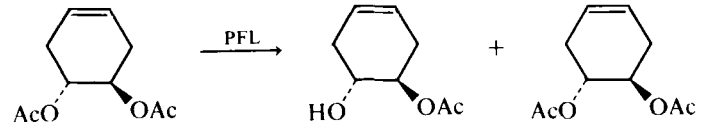
The group of Sakai[131,132] demonstrated that PFL is effective for the enantioselective hydrolysis of various monocyclic five-membered cycloalkane mono- and diacetates (±)-**58**–**60** and the *meso*-diacetate **61**. These five-membered substrates turned out to be inferior substrates to PLE compared to four- and six-membered substrates. In good to very good conversion yield the hydrolysed alcohols of **58**–**60** were afforded in >99% ee, with *R*-preference of the enzyme. In the *meso*-compound **61**, optically pure

(±)-(**58**) (±)-(**59**) (±)-(**60**) (**61**)

product (>99% ee) was also afforded with *pro*-(*S*) preference, but the yields were only 39%.

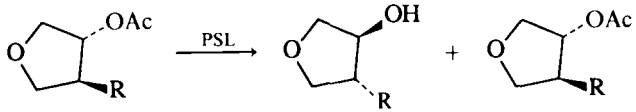
Sakai's group has also studied the hydrolysis of six- and seven-membered ring mono- and diacetates with PFL[43]. Again, optically pure products (>99% ee) were afforded in good to excellent yields, the acetates with the *R*-configuration being preferentially hydrolysed. While the five-membered ring *meso*-diacetate **61** was hydrolysed to the monoacetate with preference for the *S*-configuration, the six- and seven-membered ring *meso*-diacetates were hydrolysed with moderate (70% ee) and very low (2% ee) enantioselectivity, respectively, and with preference for the *R*-configuration.

In their preparation of optically active γ-hydroxyethyl α,β-unsaturated γ-lactones as precursors for eldanolide synthesis, Sakai and coworkers[44] employed the PFL to hydrolyse the racemic *trans*-cyclohexene-4,5-diacetate **62**. The lipase displayed strong preference for the *R*-ester group to afford the monoester (4*R*,5*R*)-**63** in excellent yield (47% and 99% ee), together with the remaining diacetate (4*S*,5*S*)-**62** in excellent yield and with 93% ee.



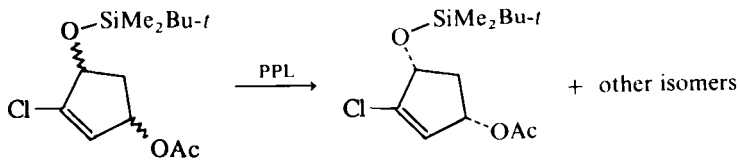
(±)-(**62**) (4*R*, 5*R*)-(**63**) (4*S*, 5*S*)-(**62**)

Seemayer and Schneider[133] have recently used PSL for hydrolysis of various racemic acetates of 3,4-disubstituted tetrahydrofurans **64** in high optical purities. For R = Ph, $PhCH_2$, PhO and $PhCH_2O$, the alcohols **65** were obtained in 80–93% ee, and the unreacted acetates **64** with 93–98% ee, all in very good yields. The corresponding *cis* substrate was also hydrolysed in 92 and 98% ee for the alcohol and acetate, respectively, for R = $PhCH_2O$.



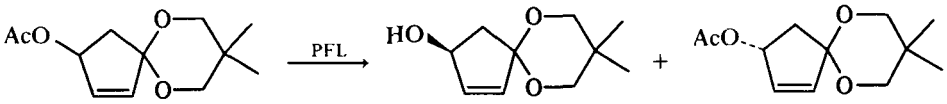
(±)-(**64**) (**65**) (**64**)

Mori and Takeuchi[134] reported the asymmetric convergent synthesis of punaglandin 4, a chlorinated marine prostanoid, utilizing the chlorocyclopentene derivative **67** as a chiral synthon. Adduct **67** was prepared in 100% ee by asymmetric hydrolysis of the corresponding racemic acetate **66** with PPL as the key step. Sugai and Mori had previously described the use of PPL for the preparation of (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentyl acetate, a useful starting material for prostaglandin synthesis, in a similar fashion[135].



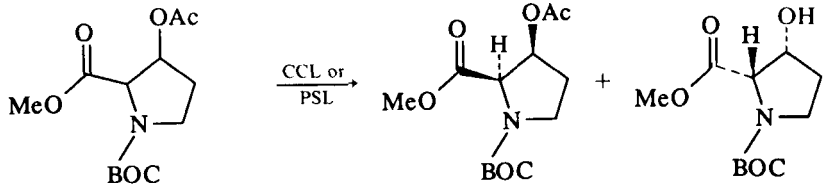
(**66**) (1*S*, 4*R*)-(**67**)

Washausen and coworkers used PFL for the hydrolysis of the racemic acetate of the ketal of 4-hydroxycyclopent-2-en-1-one **68** to prepare both enantiomers of the corresponding alcohol as chiral building blocks for the synthesis of natural cyclopentanoid substances, such as prostaglandins[136]. The alcohol (*S*)-**69** was obtained in 95% ee, and the remaining ester in >95% ee.



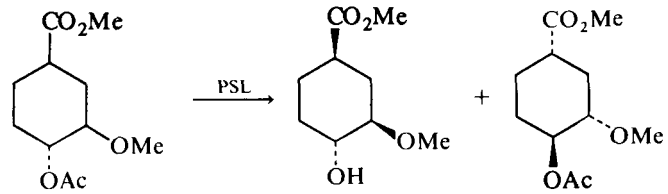
(**68**) (*S*)-(**69**) (*R*)-(**68**)

Sih and coworkers[137] have reported a number of successful resolutions of chiral alcohols by lipase-catalysed enantioselective hydrolysis. They succeeded in a chemoenzymatic synthesis of (+)-castanospermine from the chiral building block (2*R*,3*S*)-**70**, which was obtained via the enantioselective hydrolysis of racemic **70** by employing microbial lipase. Both CCL and PSL showed high chemo- and enantioselectivity towards (±)-**70**, preferentially hydrolysing the 3*R*-acetoxy group, and afforded both the alcohol (2*S*,3*R*)-**71** and the remaining acetate (2*R*,3*S*)-**70** in >99% ee at 50% conversion.



(±)-(**70**) (2*R*, 3*S*)-(**70**) (2*S*, 3*R*)-(**71**)

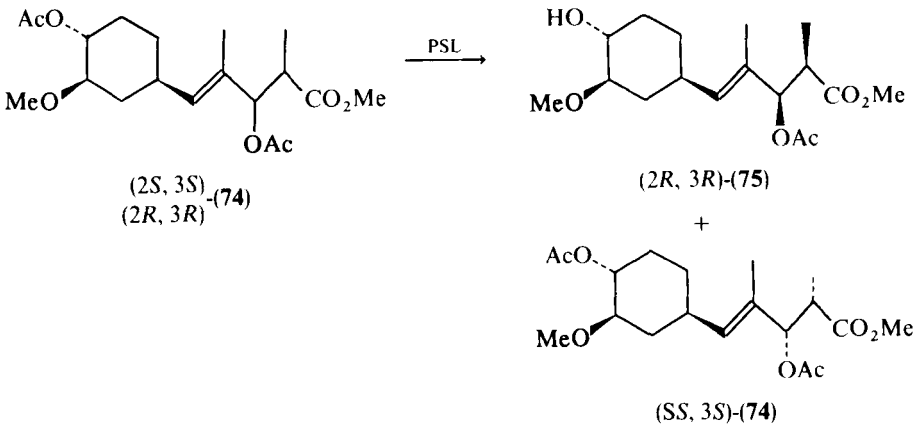
In their synthesis of the 23-membered macrolide immunosuppressant FK 506, Gu and Sih[138,139] exploited several steps based on biotransformations for preparing various chiral synthons for their convergent synthesis of this immensely complicated compound. For the preparation of the C_{20}–C_{34} segment of that molecule, two lipase-catalysed hydrolysis steps were applied and one asymmetric reduction with baker's yeast. PSL was used highly chemo- and enantioselectively to hydrolyse exclusively the *R*-acetoxy ester of (±)-**72** to yield (−)-**73** and (+)-**72** in quantitative yields[139].



(±)-(**72**) (−)-(**73**) (+)-(**72**)

The same lipase was also employed to hydrolyse the (2*R*,3*R*)-isomer of **74** in a highly chemo- and diastereoselective manner (93% de) to yield the monoacetate (2*R*,3*R*)-**75**, which was easily separated from the desired diacetate (2*S*,3*S*)-**74**.

Hoshino and collaborators investigated the lipase catalysed enantioselective hydrolysis of the racemic 4-acetoxytetrahydroisoquinoline **76**[140,141]. The best results were

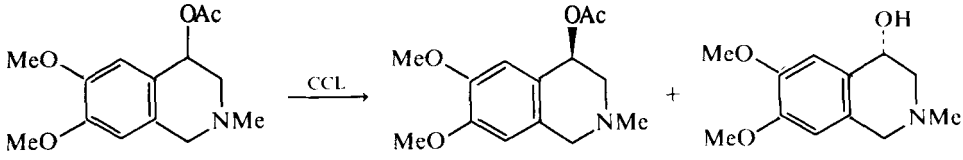


(2*S*, 3*S*)-(**74**)
(2*R*, 3*R*)

(2*R*, 3*R*)-(**75**)

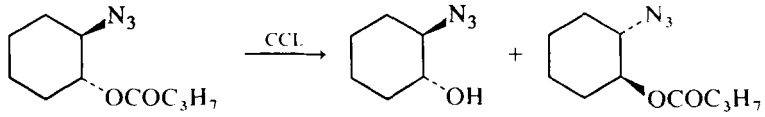
(*SS*, 3*S*)-(**74**)

obtained by using the yeast lipase from *Candida cylindracea*, which was immobilized on celite, in isooctane saturated with water. The hydroxy product (*S*)-**77** and the remaining ester (*R*)-**76** were obtained in very good yields and high optical purity (94 and 93% ee, respectively). It is interesting to note that of several lipases exploited, some were selective towards the *S*-, as the above-mentioned one, and others towards the *R*-configuration of the substrate. The same lipase was then employed in their asymmetric synthesis of related (+)- and (−)-roemercarine, a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid[142].



(±)-(**76**) (*R*)-(**76**) (*S*)-(**77**)

Both enantiomers of *trans*-2-aminocyclohexanol were obtained by Faber and co-workers[143] using CCL with racemic *trans*-2-azidocyclohexanol **78** and subsequent hydrogenation. The alcohol product (1*R*,2*R*)-**79** was afforded in 35% yield and 92% ee at 40% conversion, and the remaining ester (1*S*,2*S*)-**78** similarly in 34% yield and 91% ee at 60% conversion.

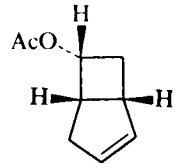


(±)-(**78**) (1*R*, 2*R*)-(**79**) (1*S*, 2*S*)-(**78**)

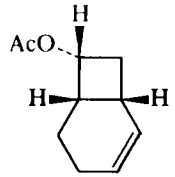
This methodology has more recently been extended to acyclic compounds, using CCL and PFL[144]. PFL was found to be more suitable than CCL for efficient hydrolysis in the acyclic series with the exception of bulky substituted alcohols, which enabled the authors to conclude that the active site of that enzyme possesses a relatively narrow cavity.

4. Bicyclic racemic alcohols

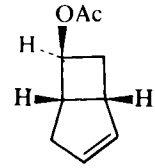
Cotterill and coworkers[145] studied the enantioselective hydrolysis of esters derived from bicyclo[3.2.0]hept-2-en-*endo*-6-ol, **80**, and bicyclo[4.2.0]oct-2-en-*endo*-7-ol, **81** as important chiral synthons in natural product synthesis. They found PPL, CCL and *Mucor miehei* lipases equally effective in catalysing the kinetic resolution of both substrates in high optical purity (≥94% ee and ≥96% ee, respectively, for **80** and **81**) and moderate yields of the *S*-configurated alcohols. The *exo*-acetate adduct of **80**, **82**, was hydrolysed only with low degree of enantioselectivity using these three hydrolases.



(**80**)



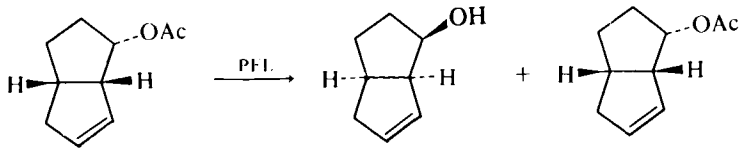
(**81**)



(**82**)

Griengl and coworkers[146,147] have examined various derivatives of bicyclo[3.2.0]-hept-2-en-6-ols, central building blocks for the synthesis of chiral cyclobutane and cyclopentane systems, and found PSL superior to the lipases used by Cotterill's group. Thus optically pure enantiomers were afforded from **80** as a substrate for both the alcohol product (>98% ee) and the unreacted acetate (>99% ee). With this lipase the *R*-alcohol was preferentially formed. In agreement with the work of Cotterill, the *exo*-isomer reacted only with low enantioselectivity with these lipases. Substituents (Cl) at C-7, vicinal to the reaction site, were found to reduce both enantioselectivity and reaction rate, whereas variation of the acid moiety had less influence.

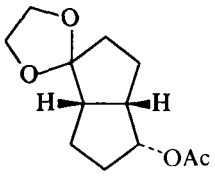
Klempier and collaborators[148] employed several lipases for the enantioselective hydrolysis of the racemic *endo*-bicyclo[3.3.0]oct-7-en-2-ol **83**. PFL was found superior and at 50% conversion both (1*R*,2*R*,5*R*)-**84** and (1*S*,2*S*,5*S*)-**83** were obtained in excellent yields and with >99 and 99% ee, respectively.



(±)-(**83**) (1*R*, 2*R*, 5*R*)-(**84**) (1*S*, 2*S*, 5*S*)-(**83**)

Sakai's group reported that the PFL-catalysed hydrolysis of racemic bicyclo[3.3.0]octane *endo*-acetate derivatives **85**–**87** proceeded with moderate to high yields, to afford the *R*-alcohols with >99% ee[42]. With **85**, the recovered acetate was also afforded with >99% ee in excellent yield (49%). Interestingly, the corresponding *exo*-acetates were very resistant and resulted in complete recovery of substrates. The alcohol product of **85** was found useful as a chiral synthon for the synthesis of isocarbacyclin. These results enabled Sakai and coworkers to propose a model for the catalytic binding site of PFS[42].

A related bicyclo[3.3.0]octane acetate derivative **88**, under the same conditions with PPL, gave the (1*S*,2*R*,3*R*,5*R*)-alcohol **89** in >99% ee, but in low yields (14%)[131,132].



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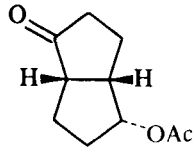

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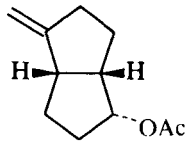

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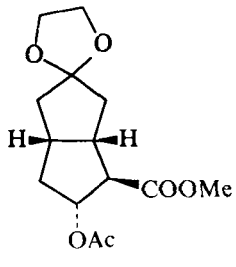
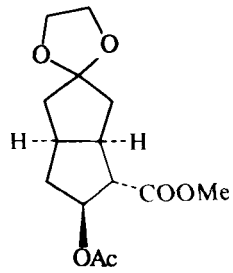
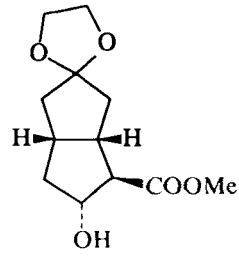


(±)-(88)

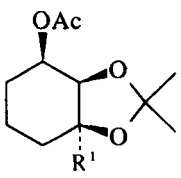


(1*R*, 2*S*, 3*S*, 5*S*)-(88)



(1*S*, 2*R*, 3*R*, 5*R*)-(89)

Finally, Dumortier and coworkers[149] have reported the synthesis of isopropylidene derivatives of 1,2,3-cyclohexanetriols as chiral building blocks with high enantiomeric purity by enzymatic hydrolysis of their racemic acetates or butyrates **90**–**93** (R^1 = H or Me). Both CCL and PSL were effective and at 40–50% conversion gave the alcohol products (95–99% ee) and the residual unreacted esters (>95% ee), all the alcohols having the *R*-configuration for the hydroxy group. The *exo* esters **91** were, however, found to be poor substrates compared to the *endo* esters **90**; this the authors related to the enantioselectivity being highly dependent on the orientation of the acyloxy group in the *cis*-fused substrates **90** and **91**. A similar phenomenon of *endo* vs *exo* has been reported before by Cotterill's group[145].



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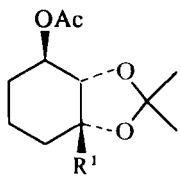

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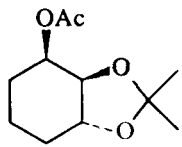

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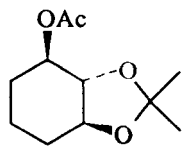
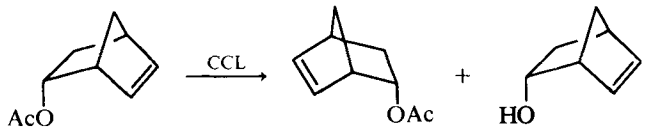


(93)

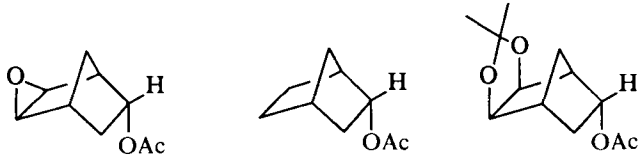
5. *Bicyclic racemic alcohols of the norbornyl type*

Griengl and coworkers[150] prepared both enantiomers of *endo*-norbornenol **95** by resolution of *endo*-norbornenyl acetate (±)-**94** by using CCL. At 40% conversion, (+)-**95** was afforded with 90% ee. The recovered acetate (−)-**94** was further subjected to enzymatic hydrolysis, until 60% conversion was obtained, when the remaining acetate had reached 96% ee. This is in good agreement with the kinetic analysis of Sih and coworkers[36] to optimize the chemical and optical yield for the resolution of substances with moderate enantioselectivity. The *exo*-isomer hydrolysed much more reluctantly, with apparently no enantioselectivity.



(±)-(**94**) (−)-(**94**) (+)-(**95**)

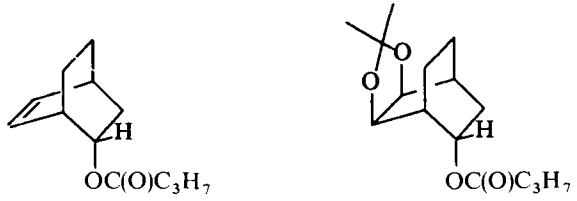
Griengl and his team have investigated various norbornane-type esters, **96**–**98**, as well as **94**, in more detail[151]. While CCL showed good activity towards all the substrates, PFL showed only activity towards substrate **94**, however, excellent enantioselectivity. Thus **94** with PFL gave excellent optical purity at 40% conversion for the alcohol product, considerably better than for CCL. On the other hand, CCL was superior for further hydrolysis to 60% conversion, and the acetate of opposite configuration was obtained with >97% ee. Both lipases showed preference for the *R*-configurated alcoholic centre of these substrates. The *exo*-acetate norbornane substrates were only resolved with CCL in lower enantiomeric excess, and the preference for the cleavage of the *R*-configurated ester groups was lost.



(**96**) (**97**) (**98**)

The corresponding racemic *endo*-7-oxabicyclo[2.2.1]hept-2-yl butyrates of **94** and **98** have also been resolved by CCL[152]. At lower 40% conversion, the alcohols were generated with 93 and >97% ee, respectively, and the remaining butyrates at higher 60% conversion with >97 and 85% ee, respectively. Again, the *R*-configurated esters were preferentially hydrolysed.

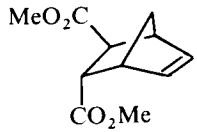
Griengl's group also studied the steric effect of substituents at C-7 on the enantioselection of CCL in *endo*-butyrate norbornene substrates[153]. Substrates possessing bulky substituents in that position were generally only resolved with 30–60% ee, as compared to those with less bulky substituents (70–80% ee). It was shown[151] that bulky *endo*-configurated esters possessing the bicyclo[2.2.1]heptane group, in contrast to their corresponding *exo*-isomers, were resolved by lipases with a high degree of enantioselection. The enantioselectivity of this lipase towards the bicyclo[2.2.2]octane esters, **99** and **100**, was found to be only moderate (60 and 75% ee, respectively) at 40% conversion.



(**99**) (**100**)

Based on these results, Griengl and his collaborators have proposed a model for CCL suited for various esters of secondary alcohols possessing the bicyclo[2.2.1]heptane or bicyclo[2.2.2]octane framework to obtain high enantioselectivity.[39]

Schneider and coworkers[154] used PLE and PSL to hydrolyse the bicyclo[2.2.1]-heptane diester **101** and **102**, with 92–96% ee. Both enzymes showed regioselectivity towards the *exo* group, the esterase being stereoselective towards the *S-exo* group, whereas the lipase was stereoselective towards the *R-exo* group.



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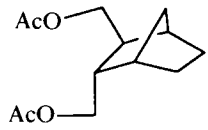
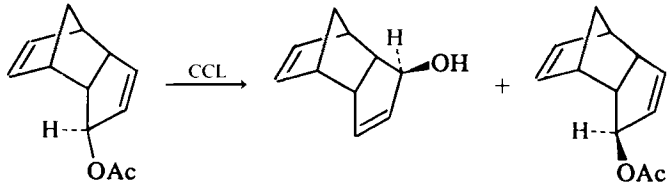


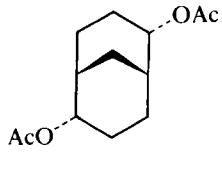
(102)

Takano and collaborators[155] employed lipase hydrolysis as the key step in their synthesis of bicyclic sesquiterpene α-cuparenone. When the acetate **103** was submitted to CCL with 10% acetone as a cosolvent, alcohol (+)-**104** was furnished at 30% conversion, optically pure, albeit after three recrystallizations. The corresponding (*S*)-(−)-**104** could be obtained optically pure after hydrolysis and five successive recrystallizations. The lipase was not very active on this substrate since it took five days to obtain 30% conversion. Also, the performance of the lipase in terms of enantioselectivity and yields is far from clear.

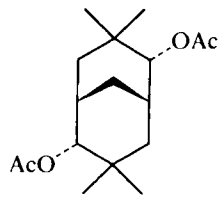


(103) (+)-**(104)** (−)-**(103)**

In their asymmetric synthesis of optically active crown ethers and podands Naemura and coworkers[156] applied asymmetric hydrolysis to prepare the appropriate chiral subunits from racemic 2,6-diacetoxybicyclo[3.3.1]nonanes **105** and **106**, possessing C_2 symmetry. CCL was found highly enantioselective in the hydrolysis of **105** to afford the (1*R*,2*S*,5*R*,6*S*)-monoacetate in excellent yield (46%) and with 95% ee. The remaining (1*S*,2*R*,5*S*,6*R*)-diacetate was obtained in good yield (36%) and 85% ee. PLE was found superior to the lipase for the hydrolysis of racemic **106**, to yield the (1*S*,2*S*,5*R*,6*R*)-diol with very high optical purity as well as the remaining (1*R*,2*S*,5*R*,6*S*)-diacetate with 86% ee, both in very high yield (43 and 46%, respectively).



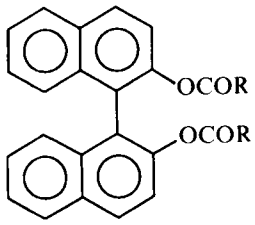
(±)-**(105)**



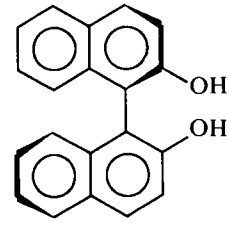
(±)-**(106)**

6. *Substrates possessing axial chirality*

Fujimoto and coworkers[157] were the first to report on the application of enzymatic asymmetric hydrolysis for obtaining axially dissymmetric compounds. When racemic binaphthyl dibutyrate (±)-**107** was subjected to whole cells from bacteria species, the (*R*)-diol, **108**, was afforded in 96% ee as well as the corresponding dibutyrate (*S*)-**107** (94% ee) at 50% conversion. Similar results were obtained by using yeast extract. When the corresponding diacetate was used as a substrate for the bacterial strain, a reverse and drop in selectivity occurred and the *S*-diol was afforded (50% ee).



(±)-(**107**)

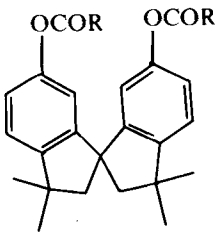


(*R*)-(**108**)

Shortly after this, Sih and coworkers[68] reported the application of whole cells from two fungi species, *Absidia glauca* and *Rhizopus arrhizus* on the corresponding diacetate of **107**. This report contains one of the classical examples of the work of this group in which quantitative definition of the requisite kinetic parameters allowed the prediction of the ee of any chiral species for a given conversion, as well as the optimization of chemical and optical yields. These resolutions involve two enzymatic reactions: hydrolysis of the diester to the monoester, followed by hydrolysis of the monoacetate to the diol. Termination of the reaction with the *Absidia glauca* fungi whole cells at approximately 50% conversion afforded (*S*)-**108** with 90% ee and (*R*)-**107** in 74% ee, in very good yields.

More recently, Miyano and collaborators[158] have reported on the application of PPL to accomplish a similar enantioselective hydrolysis of the diacetate **107**. In an ethanol/hexane/aqueous buffer solution an emulsion of the substrate was hydrolysed to afford the *S*-diol **108** of 95% ee at 46% conversion.

Similarly, kinetic resolution employing isolated enzymes for resolving other types of axially chiral alcohols have been reported. Jones and coworkers[159] reported the enantioselective hydrolysis of racemic allenic esters, using PLE. Cholesterol esterase was also found to catalyse the enantioselective hydrolysis of various binaphthyl and spirobiindanol esters such as **109** in good yield with 90–95% ee[90].



(**109**)

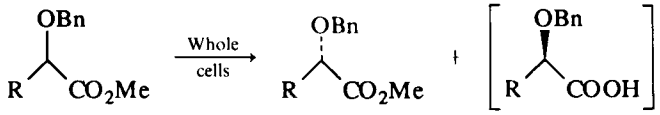
(**110**)

(**111**)

Finally, Naemura and Furutani[160] reported the application of several lipases and of PLE to hydrolyse substrates of the spiro[3.3]heptane type, including prochiral **110** ($R^1 = R^2 = Ac$) and chiral **111** derivatives ($R^1 = R^2 = Ac$). PLE was found to be superior to the lipases for the asymmetric hydrolysis of **110** affording the chiral diacetate ($R^1 = Ac$; $R^2 = H$) in very good yield with 51% ee. On the other hand, the lipases were found to be superior to PLE on the racemic substrate **111**, PPL affording the *R*-monoacetate ($R^1 = Ac$; $R^2 = H$) and the remaining *S*-diacetate in very high yield, but with only low enantioselectivity (44 and 46% ee, respectively) at 50% conversion.

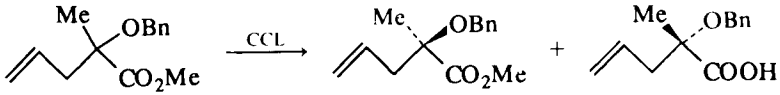
B. Chiral Acids

Ohta and coworkers[161] described the reaction of racemic α-benzyloxycarboxylic esters by incubation with grown cells from the bacterium *Corynebacterium equi* to obtain the chiral esters of high optical purity via asymmetric hydrolysis. For substrates of **112** (R = n-alkyl and allyl) incubated at 30 °C at approximately 60% conversion, the unreacted ester **112** of the *S*-configuration was afforded with >99% ee. The presence of the more bulky isopropyl group lead to reduction in optical purity, although it still remained high (90% ee). The replacement of the alkyl or alkenyl moiety of the substrate by a benzyl (Bn) group resulted in reversal of stereoselectivity and the *R*-enantiomer was afforded in 95% ee. This reversal of absolute configuration was attributed to displacement of the benzyloxy group at the binding site of the enzyme by the similar but more hydrophobic benzyl group. In this reaction, methyl and benzyl esters were observed to be the most suitable ones. The acid product (*R*)-**113** was apparently further degraded in the metabolic system of the microorganism and could not be isolated.



(**112**) (*S*)-(**112**) (*R*)-(**113**)

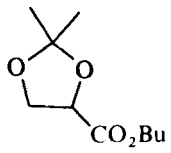
Ohta and coworkers[162] have described the resolution of substrates derived from a tertiary hydroxy moiety with the aid of CCL. For instance, the tertiary α-benzyloxy ester **114** with CCL gave the unreacted ester (*R*)-**114** in >99% ee after 72 h at approximately 60% conversion, together with the *S*-enantiomer enriched acid product **115** (82% ee). Several other tertiary α-benzyloxy acid esters with various straight-chain alkyl groups instead of the allyl group were similarly resolved with high enantioselection. This method provides α-hydroxy acids of opposite configuration to those obtained by Ohta and coworkers[107]. Optically pure (*S*)-**115** was obtained by repeating the hydrolysis on the remethylated acid product, and was used as a chiral synthon for the asymmetric synthesis of (−)-frontalin. Similarly, Ohta and coworkers have recently succeeded in the asymmetric synthesis of (*R*)-(−)-mevalonolactone by using the enantiomer (*R*)-**114** as a chiral carbon source[163].



(**114**) (*R*)-(**114**) (*S*)-(**115**)

Pottie and coworkers[164] used PPL and CCL with n-butyl esters of various 2,2-dimethyl-1,3-dioxolane-4-carboxylic acid derivatives to generate optically active α,β-

dihydroxy carboxylic acid building blocks, including glyceric acid, the parent substance of **116**. The best results were obtained for racemic substrates **116–119**. CCL was found to be superior to PPL, with which **116** was the only one that displayed high enantioselectivity, but only when the lipase was immobilized on celite. For these substrates preference for the *R*-configuration was displayed at C-4 containing the carboxyl function. Substrates **116** and **117** gave the remaining esters at 57 and 69% conversion, with >95 and 95% ee, respectively. **118** yielded the acid product at 45% conversion with 95% ee, while with **119** the acid and the remaining ester were afforded in 93 and 94% ee, respectively, at 50% conversion.



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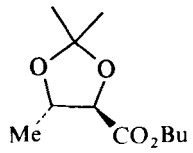
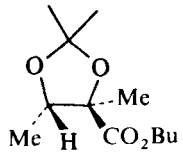
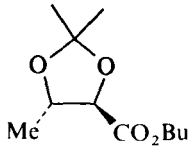


(±)-(**117**)

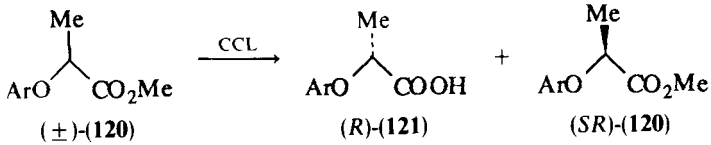


(±)-(**118**)



(±)-(**119**)

Dernoncour and Azerad[165] studied the hydrolysis of 2-(chlorophenoxy)propionic esters **120** by α-chymotrypsin, PLE, CCL and PPL. Only low to moderate enantioselectivity was obtained for the acid product (*R*)-**121** at 20–60% conversion. The most active enzyme was found to be PLE, although low enantioselectivity was displayed. In most cases the *R*-esters were preferentially hydrolysed with all the enzymes.



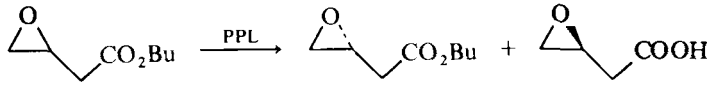
(±)-(**120**) (*R*)-(**121**) (*SR*)-(**120**)

Guo and Sih[37] improved the enantioselectivity of CCL 20-fold by the use of the phenomenon that they call enantioselective inhibition. Thus, when a racemic methyl (or chloromethyl) 2-(2,4-dichlorophenoxy)propionate of type **120** was hydrolysed in the presence of dextromethorphan or levomethorphan, the *E*-values of the lipase were elevated from 1 to 20. As an example, the lipase showed no enantioselectivity towards the substrate in the absence of dextromethorphan, but in its presence it yielded the acid (*R*)-**121** at 30% conversion in 87% ee. Remarkable increase in enantioselectivity was observed for various related derivatives and in some cases optical purity was enhanced from moderate to excellent (>98% ee).

Sih and coworkers[31] have also succeeded in enhancing the enantioselectivity of the CCL with the same type of substrates by non-covalent enzyme modification. The CCL was found to unfold and refold to generate a more stable conformer upon treatment with deoxycholate and organic solvents. This form of lipase was found to be much more effective than the native enzyme in the hydrolysis of esters of the type described above. For example, in the hydrolysis of racemic 2-phenylpropionic ester with a non-covalently modified CCL, the enantioselectivity improved dramatically from being moderate (*E*-value 10) to highly enantioselective ($E > 100$).

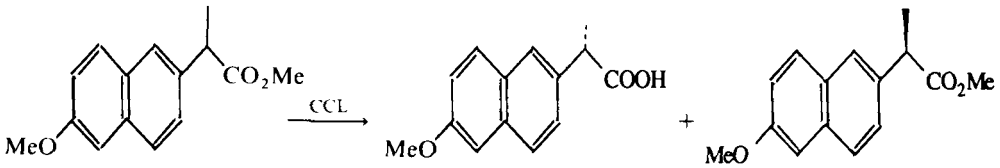
Francalanci and coworkers[166] used PPL with the racemic 3,4-epoxybutyrates **122**. At 60% conversion the remaining ester (*R*)-**122** was obtained in >95% ee. Proteases were found to preferentially hydrolyse the *R*-enantiomer, but with much lower stereoselectivity. Another enzyme, alcalase, was found very useful for hydrolysing the remaining ester (*R*)-**122** under very mild conditions, leaving the oxirane ring unaffected, which

was then exploited as a building block for the asymmetric synthesis of (*R*)-(−)-carnitine chloride.



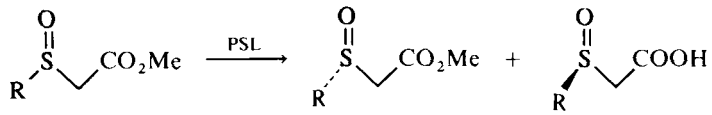
(**122**) (*R*)-(**122**) (*SR*)-(**123**)

Sih and coworkers[167] used CCL to obtain (*S*)-**125** at 39% conversion in >98% ee by hydrolysis of racemic **124**. Several other lipases exhibited high enantioselectivity towards **124**, but yielded the *R*-enantiomer of **125**. More recently, Barton and collaborators[30] have reported the resolution of racemic 2-(4-hydroxyphenoxy)propionic acid methyl ester, with CCL in an aqueous–toluene mixture with >99% ee for the acid at 38% conversion.



(**124**) (*S*)-(**125**) (*R*)-(**124**)

Burgess and Henderson[168] used PSL to prepare homochiral sulphoxides, which were then used for asymmetric synthesis of γ-hydroxy-α,β-unsaturated esters. With various substrates of the methyl sulphinylacetate type **126** (R = aryl and alkyl) in toluene–aqueous media, esters (*R*)-**126** [for R = aryl otherwise (*S*)-] of >98% ee were obtained in good to excellent yield together with the acid product (*S*)-**127** in 88–>98% ee.

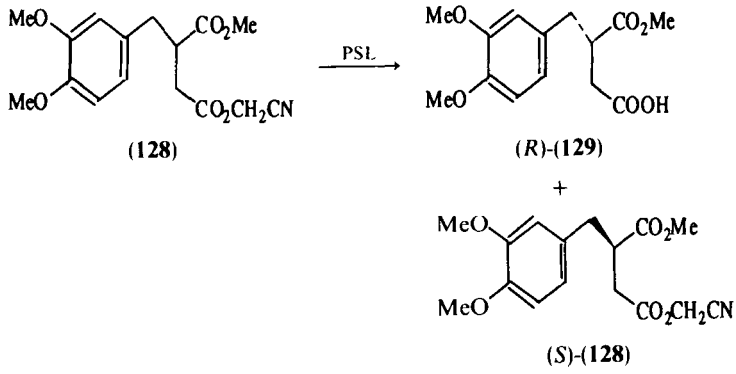


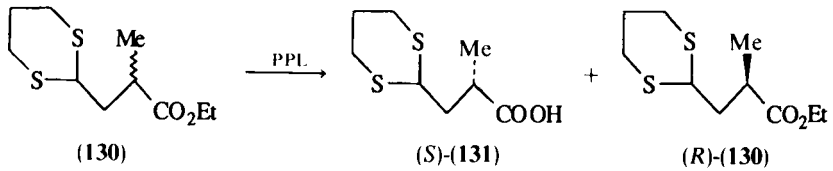
(**126**) (*R*)-(**126**) (*S*)-(**127**)

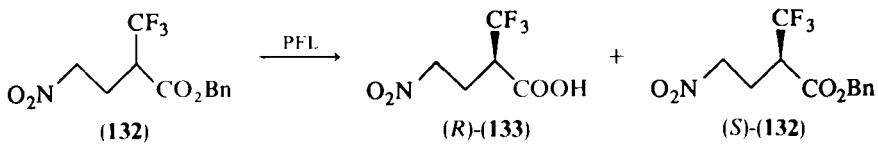
Barnier and coworkers[169] used PSL for the hydrolysis of the racemic succinate **128**. The activated cyanomethyl ester[167] was preferentially cleaved, and at 42% conversion butanoic acid derivative **129** was obtained in >95% ee in very good yields. The remaining ester (*S*)-**128** was obviously afforded in only moderate optical purity at this extent of conversion and further enrichments were apparently not attempted.

For the preparation of the C_{10}—C_{19} segment of the 23-membered macrolide immunosuppressant FK 506, mentioned earlier, Gu and Sih[138,139] employed two lipase-catalysed hydrolyses and one asymmetric reduction with baker's yeast, so this example indeed represents an elegant multi-enzymatic process. PPL was used to resolve the racemic ester **130** to afford the acid (*S*)-**131**, with >99% ee, and the remaining ester (*R*)-**130**, also with >99% ee.

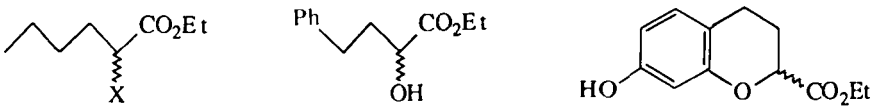
Yamazaki and collaborators[170] described the synthesis of both enantiomers of 2-trifluoromethyl-4-aminobutyric acid by asymmetric hydrolysis with PFL as the key step. At 49% conversion of the racemic benzyl 2-trifluoromethyl-4-nitrobutyrate **132**, both the optically active acid (*R*)-**133** and the remaining ester (*S*)-**132** were obtained, each with >98% ee.





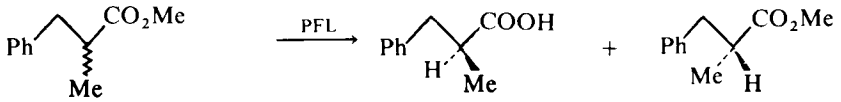


Kalaritis and coworkers[171] used PFL to effect kinetic resolution of various 2-substituted esters. The lipase was found to display very high stereoselectivity in the hydrolysis of several 2-substituted hexanoates of the type **134** (X = F, OH, Br), ethyl 2-hydroxy-4-phenylbutanoate **135** and the chroman **136**. In all cases the lipase preferentially cleaved the *S*-substrate to afford the *S*-acids and the remaining *R*-esters. The esters were usually obtained with 97–99% ee at 50–60% conversion, but in order to prepare an acid of similar purity reesterification and further hydrolysis on the enriched *S*-ester was often required. With solid substrates such as **136**, 10% cosolvent was required for the reaction.



(134) (135) (136)

Finally, Delinck and Margolin[172] hydrolysed racemic 2-benzylpropionic acid **137** in their preparation of chiral building blocks for the synthesis of selective adenosine receptors. From **137** and PFL at room temperature, the acid (*S*)-**138** was afforded in 50% yield and very high optical purity, together with the remaining ester (*R*)-**137** in 44% yield and 98% ee in 3 h. CCL in the mild hydrolysis of (*R*)-**137** afforded the acid (*R*)-**138**, without racemization, in 92% yield.



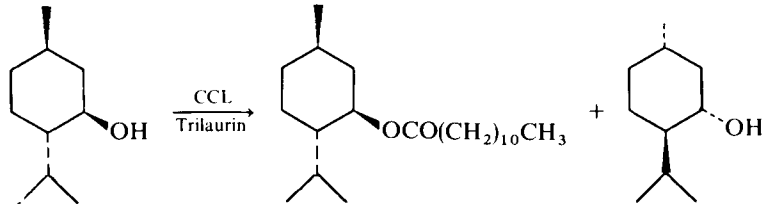
(137) (*S*)-(138) (*R*)-(137)

V. KINETIC RESOLUTION BY TRANSESTERIFICATION

A. Chiral Alcohols

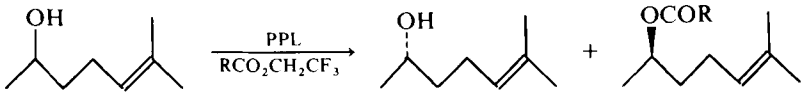
1. Acylation

In one of the first reports of microbial transformations in organic media Triantaphylides and coworkers compared asymmetric hydrolysis, transesterification and esterification reactions for the resolution of menthol using CCL[173]. The highest rate was obtained with the hydrolytic reaction, but only with moderate enantioselectivity (70–85% ee). On the other hand, the enantiomeric excess was much higher (>95% ee) for the reactions in organic solvents at 40% conversion. The transesterification of racemic menthyl laurate **140** with isobutanol (deacylation) in heptane proceeded extremely slowly to reach 45% conversion, at which an equilibrium was attained and (−)-menthol **139** was afforded with 94% ee. The corresponding acylation involving (±)-menthol and trilaurin proceeded even slower to reach an equilibrium at 33% conversion, at which (−)-menthyl laurate **140** was afforded in 95% ee. The direct esterification of (±)-menthol with lauric acid was found to proceed much faster to reach 45% conversion in only 10 h, at which (−)-menthyl laurate was afforded in 95% ee.



(±)-(**139**) (−)-(1*R*, 2*S*, 5*R*)-(**140**) (+)(1*S*, 2*R*, 5*S*)-(**139**)

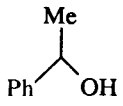
Stokes and Oehlschlager[61] observed a drastic increase in the enantioselectivity for the transesterification of racemic sulcatol **41** by PPL in ether by dehydration of the enzyme and using 2,2,2-trifluoroethyl laurate as the ester. The *R*-sulcatol laurate **40** was afforded at 52% conversion in 75% yield and 90% ee, together with the remaining sulcatol (*S*)-**41** in 86% yield and >97% ee at room temperature in 72 h.



(**41**) (*S*)-(**41**) (*R*)-(**40**)

Similarly, Belan and collaborators resolved sulcatol by PPL using 2,2,2-trichloroethyl butanoate as an acylating agent[174]. At 65% conversion (96 h) the enantiomeric excess of the residual *S*-sulcatol was higher than 99%, but that of the *R*-enantiomer was much lower (80% ee).

Laumen and collaborators[175] studied the enantioselective transesterification of several secondary racemic alcohols, such as **141–143**, with PSL, using as an acyl transfer agent vinyl acetate in *t*-butyl methyl ether at room temperature. Very good results were obtained (>99% ee) either for the R-acetate or the residual S-alcohol, depending on the extent of conversion.



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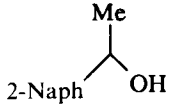

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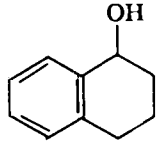
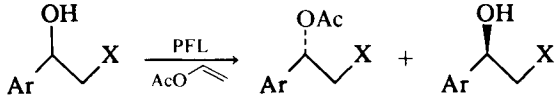


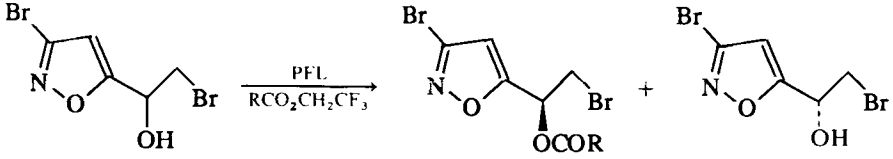
(143)

Hiratake's group[103] resolved several related 2-halo-1-aryl ethanol substrates **144** (X = Cl or Br; Ar = Ph or Naph) in diisopropyl ether with PFL and vinyl acetate as an acyl transfer agent. The reactions proceeded generally in high yield and high optical purity, for both the *S*-ester product **145** (92–97% ee) and the remaining alcohol (*R*)-**144** (80–97% ee), at 50% conversion. Out of several commercial lipases, PFL was the most effective in transesterifications involving enol esters, which were found to be superior to 2,2,2-trichloroethyl acetate as acyl donors.



(144) (*S*)-(**145**) (*R*)-(**144**)

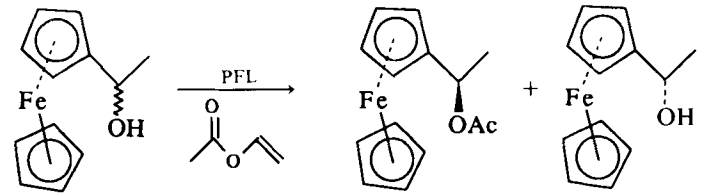
De Amici and coworkers[176] employed different enzymatic routes towards the asymmetric synthesis of each enantiomer of the β-antagonist broxaterol. The *S*-enantiomer was made in <98% ee by reduction with alcohol dehydrogenase, whereas the *R*-enantiomer was obtained in 97% ee through kinetic resolution of the racemic bromohydrin **146** by PFL at 30% conversion in 27% yield in n-hexane/benzene at 45 °C with trifluoroethyl esters as acyl transfer agents. The presence of molecular sieves was essential for obtaining high reaction rates and high ee. The enantioselectivity was also found to be dependent on the chain length of the acyl donor, trifluoroethyl acetate giving the best results.



(146) (*S*)-(**147**) (*R*)-(**146**)

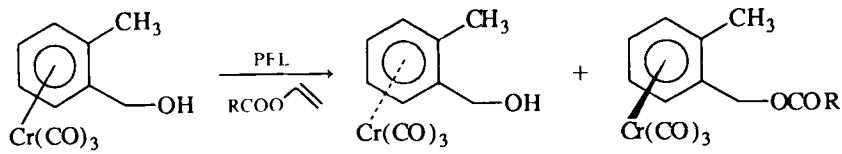
Boaz[45] employed PFL for the reaction of the racemic 1-ferrocenylethanol substrate **148**. The lability of the corresponding acetate substrate to hydrolysis rendered an enzymatic hydrolysis impossible. However, **148** with the lipase at room temperature in *t*-butyl methyl ether with vinyl acetate as an acyl transfer reagent yielded the acetate (*R*)-**149** and the remaining alcohol (*S*)-**148** in 96 and 92% ee, respectively, at 50% conversion in a smooth reaction. This process was extremely slow, taking 12 days, but

at 60 °C, the reaction time for 50% conversion was reduced to 3 days without much reduction in enantioselectivity (92 and 90% ee, respectively).



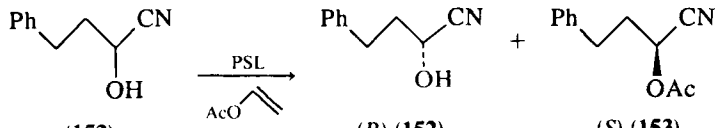
(**148**) (*R*)-(**149**) (*S*)-(**148**)

Yamazaki and Hosono[177] also used irreversible transesterification with vinyl esters to resolve racemic planar chiral organochromium complexes **150**. Again, PFL was the most effective one, and at 30 °C in toluene with vinyl palmitate as an acyl transfer agent, fast reaction (2 h) afforded the ester (*S*)-**151** and the remaining alcohol (*R*)-**150**, both in excellent yields and with >98% ee for each. The enantioselectivity was found to decrease with reducing the size of the acyl donor. The reverse deacylation reaction of the corresponding ester was also found to be catalysed in a highly enantioselective manner by this lipase. At 30 °C in the presence of n-butanol, the acetate of **150** afforded the (*S*)-**150** alcohol product (98% ee) and the (*R*)-**151** (88% ee) remaining acetate in very good yields, in a fast reaction (8 h). Similar work was also reported by Nakamura and coworkers, who also used PSL for the transesterification of **150** with isopropenyl acetate[178]. At 25 °C the *S*-acetate **151** and the *R*-alcohol **150** were afforded in excellent yield (98 and 100% ee, respectively) in 6 h.



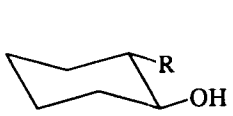
(±)-(**150**) (*R*)-(**150**) (*S*)-(**151**)

Wong and coworkers[179] reported the resolution of several cyanohydrins and the subsequent asymmetric synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutyrate and *S*-propranolol. PSL was used with substrates of the type **152** at 28 °C in dichloromethane with vinyl acetate as an acyl donor. The reaction proceeded very slowly (6–7 days) towards 60% conversion at which the unreacted alcohol (*R*)-**152** was afforded in very high optical purity (98% ee). At lower conversion (22%) the corresponding acetate (*S*)-**153** was afforded in 90% ee. The *S*-alcohols of the corresponding *R* = 1-naphthyloxymethyl and benzyloxymethyl cyanohydrin substrates were similarly afforded at approximately 60% in 96 and 95% ee, respectively, as well as the acetate product of the former (91% ee) at 25% conversion, by this procedure.

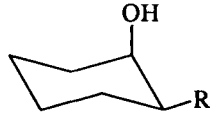


(**152**) (*R*)-(**152**) (*S*)-(**153**)

Schneider and coworkers[180] used the transesterification procedure with PSL in *t*-butyl methyl ether with vinyl acetate as an acyl donor for the kinetic resolution of several 2-substituted *cis*- and *trans*-cyclohexanol derivatives **154** and **155**, respectively (R = phenyl, benzyl, phenyloxy and benzyloxy). At approximately 50% conversion high enantiomeric excess was obtained for both the produced acetate and the residual alcohol (90–>98% ee) in most cases. However, very long reaction times (7–21 days!) were required for reaching 50% extent of conversion. The authors succeeded in reducing the reaction time drastically (3–5-fold) by employing a continuous process, using the immobilized lipase in a column, still obtaining 95–98% ee consistently for all the substrates.

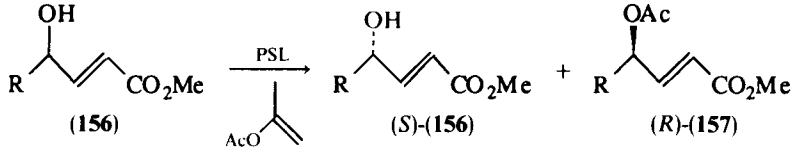


(±)-(**154**)



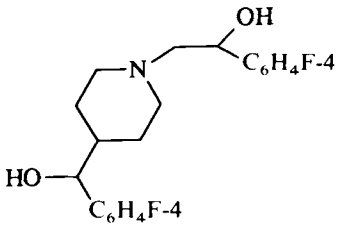
(±)-(**155**)

Burgess and Henderson[181] described the resolution of γ-hydroxy-α,β-unsaturated compounds, such as **156** (R = alkyl), which are products of the SPAC (sulphoxide pyridinium and carbonyl) transformation. When **156** (R = Me) was subjected to PSL in hexane at 25°C with isopropenyl acetate, the reaction proceeded smoothly to afford both the acetate (*R*)-**157** and the remaining alcohols (*S*)-**156** in very high yield and with >95% for both at 50% conversion in 50 h. With more bulky substituents (R = *i*-Pr, *i*-$PrCH_2$, $CyCH_2$), reversed configurational preference was observed. The concept of 'asymmetric amplification' was introduced by the authors for a tandem asymmetric SPAC reaction (moderate optical purity) and subsequent biocatalytic acylation of the aforementioned type (very high optical purity).

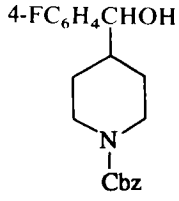


(**156**) (*S*)-(**156**) (*R*)-(**157**)

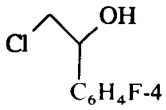
Nieduzak and Margolin[182] described the asymmetric synthesis of each of the four diastereomers of **158**, a non-narcotic analgesic. This was based on the convergent synthesis involving each pair of enantiomers of **159** and **160**, which were prepared by transesterification of the alcohols with PFL. When alcohol **159** was subjected to the lipase in *t*-butyl methyl ether at 45 °C using vinyl acetate as an acyl transfer agent, the reaction gave ≥97% ee for each enantiomer, the *R*-(+)-acetate product and the



(**158**)



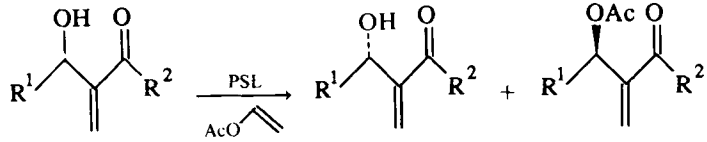
(**159**)



(**160**)

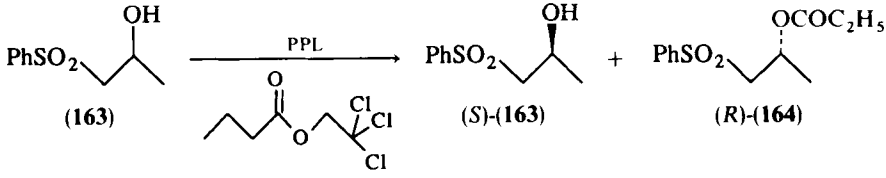
remaining *S*-(−)-alcohol, in high yield (5 days). Similarly, the chloro alcohol **160** was resolved by the same lipase with isoprenyl acetate as an acyl transfer agent in ethyl ether to afford the *R*-(−)-alcohol and the *S*-(+)-acetate at room temperature (2 days) in high yield and with ≥97% ee.

Burgess and Jennings[183] investigated the kinetic resolution of a range of α-methylene-β-hydroxy esters and ketones of the type **161**, but these allylic alcohols cannot be prepared by the asymmetric Sharpless epoxidation due to the electron-withdrawing carbonyl substituent. When allylic alcohol **161** was subjected to PSL at room temperature, acylation with vinyl acetate proceeded smoothly to 50–56% conversion (12–48 h) in hexane, to afford the unreacted alcohol (*S*)-**161** with 95% ee for long-chain R^2 (alkyl or *O*-alkyl) and short-chain R^1 (methyl) substituents. Longer R^1-chains resulted in elongated reaction times, which however could be compensated somewhat for by using longer R^2-chains as well.



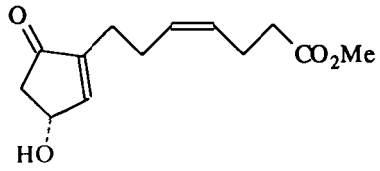
(**161**) (*SR*)-(**161**) (*R*)-(**162**)

Chinchilla and coworkers[184] reported the PPL-catalysed reactions of β-, γ- and δ-hydroxy sulphones with 2,2,2-trichloroethyl butyrate as an acyl donor in ethyl ether in the presence of molecular sieves at room temperature. Best results were afforded for the β-hydroxy sulphone **163**, to afford the unreacted alcohol (*S*)-**163** in moderate yield and 95% ee, together with the butyrate product (*R*)-**164** in 65% ee. The reactions took 7–12 days, but could be speeded up by refluxing the ether. This, however, led to considerable reductions in enantioselection. The enantioselectivity was found to be only moderate for the corresponding γ- and δ-sulphones.



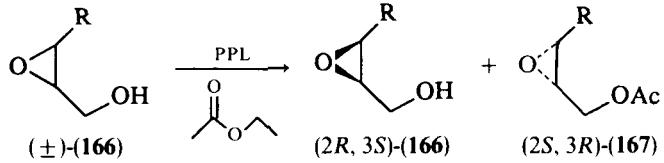
(**163**) (*S*)-(**163**) (*R*)-(**164**)

In an approach towards the asymmetric synthesis of prostaglandins Wong and coworkers[185] investigated the feasibility of the preparation of the chiral intermediate (*R*)-**165** by resolution of the corresponding racemate. In terms of enantioselectivity and efficiency, PSL exhibited superiority over several other lipases and hydrolases in the enantioselective transesterification of the racemate **165** and several other related substrates with neat vinyl acetate. The enzyme exhibited stereoselective preference for the *R*-enantiomer, so the *S*-enantiomer was obtained with >99% ee in 35% yield, together with the desired *R*-acetate of **165**, in 92% ee. This could be enriched ≥98% ee by resubmitting the *R*-enriched product to the lipase. Furthermore, by submitting the optically pure *S*-alcohol to Mitsunobu chemistry[186], inversion of configuration was effected without any loss in optical purity in excellent yield, thus allowing the preparation of either antipode of the optically pure alcohol desired. This is certainly an advantageous alternative to a recycling process involving racemization and allows the theoretical 100% conversion instead of the usual 50% conversion yield normally obtained for the lipase-catalysed kinetic resolution of racemates.



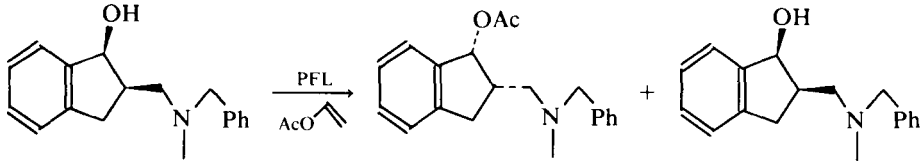
(*R*)-(**165**)

Bianchi and collaborators[187] employed PPL with the racemic 2,3-epoxyalcohols **166** (R = n-$C_{10}H_{21}$, *iso*-C_7H_{15}) to obtain the unreacted epoxyalcohols (2*R*, 3*S*)-**166** with >95% ee and in 31–36% yields at 60–65% conversion with ethyl acetate, serving both as a solvent and an acylating agent. The complimentary epoxyalcohol (2*S*, 3*R*)-**166** was obtained by hydrolysis of the racemic acetate (±)-**167** with >95% ee. The alcohols (2*R*, 3*S*)-**166** were subsequently used as chiral synthons in the synthesis of (+)-disparlure.



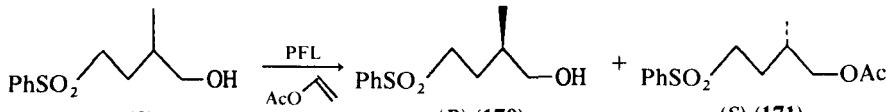
(±)-(**166**) (2*R*, 3*S*)-(**166**) (2*S*, 3*R*)-(**167**)

Margolin and coworkers[188] reported the lipase-catalysed transesterification of the racemic indanamine alcohol **168**. With PFL suspended in a solution of **168** and vinyl acetate in *t*-butyl methyl ether, at room temperature after 4 days both the acetate (−)-**169** and the remaining alcohol (+)-**168**, key intermediates in an asymmetric synthesis of both enantiomers of an indanamine serotonin uptake inhibitor, were afforded in 98% yield and 97% ee. The same process was successfully conducted on a carbon-14 labelled substrate.



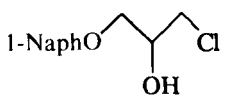
(±)-(**168**) (−)-(**169**) (+)-(**168**)

Ferraboschi and coworkers[189] used lipase-catalysed transesterification of 4-(phenylsulphonyl)-2-methyl-1-butanol, **170**, to obtain valuable C_5 isoprenoid chiral synthons. Thus, **170** gave with PFL and vinyl acetate in chloroform at 30 °C, the unreacted alcohol (*R*)-**170** in 98% ee and in good yield. The acetate (*S*)-**171** was also obtained in 98% ee and good yield. 4-(Phenylthio)-2-methyl-1-butanol under the same enzymatic conditions gave similar results.



(**170**) (*R*)-(**170**) (*S*)-(**171**)

Wong and coworkers[21] employed an immobilized PSL to resolve a whole range of secondary alcohols, such as **172**, **173**, and **174**. All these substrates gave high optical purity for the corresponding acetates at 40% conversion, for both antipodes at 50% conversion, or for the remaining alcohols at 60% conversion. The immobilization was found to render the enzyme up to 200-fold more active. The authors attributed this increase in activity to the homogeneous distribution of the enzyme on the surface of the carrier, as well as the carrier adsorbing the substrate to increase the contact with enzyme.



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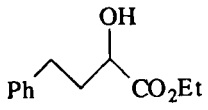

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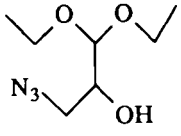
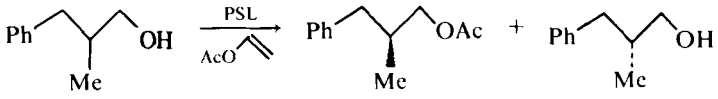


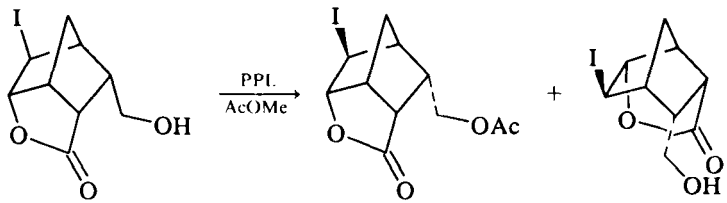
(**174**)

Delinck and Margolin[172] employed PSL to resolve the racemic 2-benzylpropanol **175** via transesterification. In only 2.5 h the unreacted alcohol (*R*)-**175** was obtained in 43% yield and 97% ee, together with the S-enriched acetate **176** (74% ee), which was further enriched by enzymatic hydrolysis with the same lipase to afford (*S*)-**175** in 35% yield and 93% ee.



(**175**) (*S*)-(**176**) (*R*)-(**175**)

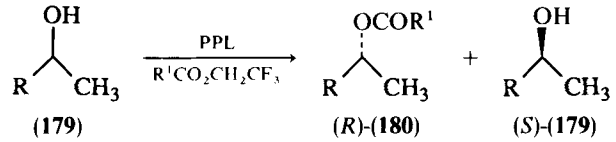
Janssen and coworkers[190] used PPL to resolve the racemic iodolactone **177** by transesterification, with methyl acetate serving both as a solvent and acyl transfer agent. At 40 °C the reaction was extremely slow, but at 40% conversion (8 days) the acetate (+)-**178** was formed in 39% yield and 89% ee. At 60% conversion (another 8 days) the remaining alcohol (−)-**177** was obtained in 42% yield and 89% ee. Their results with various norbornene-type substrates revealed that carboxylic acids or esters, in which the norbornene skeleton forms part of the acyl moiety, were not suitable substrates for lipases, strongly contrasting with the behaviour of the PLE.



(±)-(**177**) (+)-(**178**) (−)-(**177**)

Very recently, Morgan and collaborators[191] reported the resolution of racemic branched and unbranched 2-alkanols of the type **179** by PPL catalysed transesterification. 2,2,2-trifluoroethyl laurate and butyrate were used as acylating agents in ether at room temperature. The enantioselectivity was found to increase for R = ethyl to n-butyl, after which further chain extension had little effect. The *R*-enantiomer was preferentially

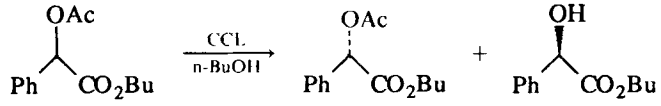
acylated. In most cases (R = alkyl, methyl branched and unbranched, cyclohexyl, phenyl and benzyl), 90–98% ee was achieved for at least the acetate product (*R*)-**180** at 40% conversion and sometimes for both antipodes (50% conversion).



(**179**) (*R*)-(**180**) (*S*)-(**179**)

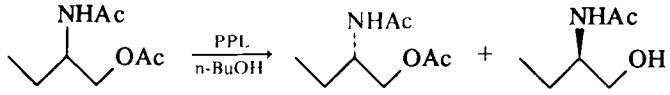
2. Deacylation

Bevinakatti and coworkers[63] employed primary alcohols as acyl acceptors in order to accomplish irreversibility in enantioselective transesterifications involving racemic secondary alcohols. CCL was more suitable than PPL for these conversions. For example, mandelic acid ester **181** in the presence of n-butanol in diisopropyl ether yielded, after 7 days (45% conversion), the hydroxy product (*R*)-**182** in 92% ee, together with the remaining ester (*S*)-**181**.



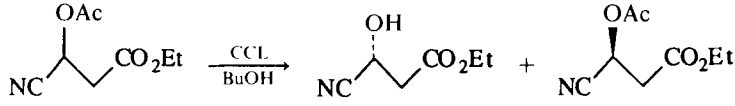
(**181**) (*S*)-(**181**) (*R*)-(**182**)

Bevinakatti and Newadkar[192] also reported the resolution of *N,O*-diacetyl-2-amino-1-butanol **183** in diisopropyl ether, by transesterification with 1-butanol. PPL at 40% conversion (24 h) yielded the alcohol amide **184** only with 62% ee. They assigned the *R*-configuration, thus disputing the results of Gotor's group[193] regarding both the absolute configuration and the enantiomeric purity. At 60% conversion (48 h), 66% ee was obtained for the remaining acetate (S)-**183**. The optical purity could be raised considerably (95% ee) by a single recrystallization of the diacetate product.



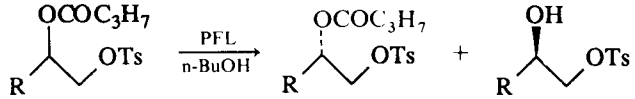
(**183**) (*S*)-(**183**) (*R*)-(**184**)

As key steps in their asymmetric synthesis of both enantiomers of γ-amino-β-hydroxybutanoic acid, Lu and collaborators[194] employed two lipases to resolve the racemic ethyl 3-cyano-3-hydroxypropionate **185**. With CCL in heptane and n-butanol, the alcohol ester (*R*)-**186** was afforded at 40% conversion in good yield. The residual S-enriched *O*-acetyl cyanohydrin was treated with PPL, which preferentially hydrolysed the *S*-enantiomer to afford the alcohol ester (*S*)-**186** in moderate yield at 60% conversion. No experimental details were reported.



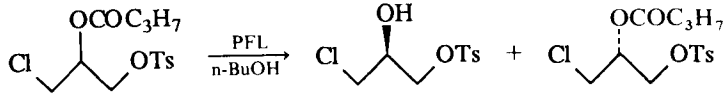
(**185**) (*R*)-(**186**) (*S*)-(**185**)

Chen and Liu[195] prepared various optically active epoxides, by kinetic resolution of tosylate substrates **187** (R = CH_2Cl, alkyl, Ph and CH_2OPh) *via* transesterification. With PFL and isoprenyl acetate as an acyl transfer agent the transesterification of the corresponding alcohols in hexane at 30°C was effected in 66–86% ee. By deacylation of butanoate esters **187** (R = CH_2Cl) in hexane containing n-butyl alcohol as an acyl acceptor, very high optical purity was obtained for the alcohol and the ester (96% ee for both (S)-**188** and (R)-**187**, at 50% conversion).



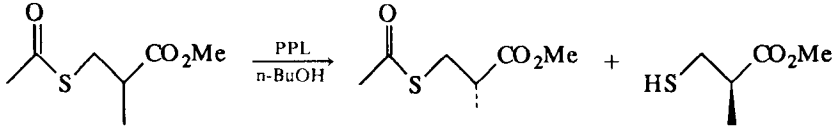
(**187**) (*S*)-(**187**) (*R*)-(**188**)

In their synthesis of an optically active (chloromethyl)oxirane, Chen's group[196] prepared both enantiomers of 1-chloro-3-tosyloxypropan-2-ol **190**. With **189** and PFL the transesterification proceeded with high enantioselection ($E > 100$) in hexane in the presence of 1-butanol at 25 °C. At 49% conversion (72 h) the alcohol (*S*)-**190** was afforded in 97% ee, together with the remaining butyrate (*R*)-**189** (95% ee), both in excellent yields. Transesterification of racemic **190** in water-saturated hexane with isoprenyl acetate at 25 °C, using the same lipase, yielded (*S*)-**189** in 97% ee at 42% conversion (96 h), and (*R*)-**190** in 70% ee. Finally, the butyrate (*R*)-**189** could also be obtained with 98% ee by hydrolysis with PFL at 55% conversion (24 h).



(**189**) (*S*)-(**190**) (*R*)-(**189**)

Finally, Bianchi and Cesti[197] empioyed lipases to facilitate thiotransesterification of mercapto esters for the preparation of optically active thiols. For instance, the racemic mercapto ester **191** with a suspension of PPL in hexane at 25 °C with n-propanol as a nucleophile gave at 51% conversion (72 h) the thiol (*R*)-**192** and the remaining S-enriched thioester (*S*)-**191** in very good yield and with 88 and 95% ee, respectively. PFL also displayed good chemo- and stereoselectivity. The corresponding hydrolysis reaction proceeded efficiently, but with poor stereoselectivity and chemoselectivity, both ester groups being hydrolysed.

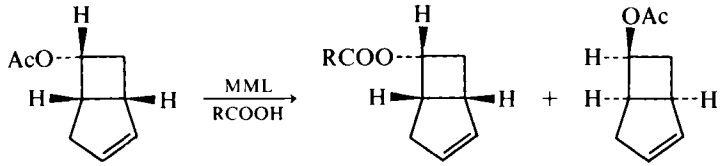


(±)-(**191**) (*S*)-(**191**) (*R*)-(**192**)

3. *Acidolysis*

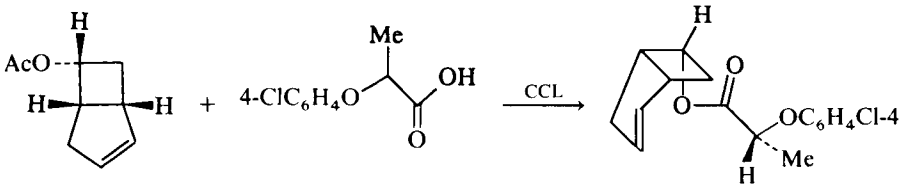
Roberts and coworkers[54] compared the kinetic resolutions of the secondary *endo*-bicyco[3.2.0]hept-2-ene alcohol and its acetate in lipase-catalysed hydrolysis, esterification and transesterification processes, using the immobilized *Mucor miehei* lipase

(MML), Lipozyme. Acidolysis of the acetate **193** with cyclohexanecarboxylic acid exhibited the highest enantioselectivity, producing the ester (−)-**194** in >99% ee after 66 h in moderate yield (27%) in anhydrous hexane. Since no alcohol was present, the chiral alcohol must bind to the enzyme active site twice during the process, first to undergo deacylation and then to combine with the cyclohexanoate moiety at the acylated enzyme. This might indicate that it is more advantageous to employ a chiral alcohol ester and an achiral acid, rather than the more conventional chiral alcohol and achiral ester for the transesterification process, i.e. acidolysis rather than alcoholysis, in order to enhance the enantioselectivity. The esterification of the corresponding alcohol of *endo*-(±)-**193** and cyclohexane carboxylic acid also proceeded smoothly in 48% yield and 94% ee in 29 h to afford (+)-**194**.



(±)-(**193**) (−)-(**194**) (+)-(**193**)

The same group[198] has very recently reported the highly diastereoselective transesterification using two racemic reactants, i.e. the acetate **195** and the carboxylic acid **196**. CCL was found to catalyse the reaction in a highly diastereoselective manner in hexane at 30°C. At 13% conversion after 622 hours the major diastereomer (*R*, *R*)-**197** was formed (92%), together with minor amounts of the others. The enantiomeric excess of the *R*-alcohol and the *R*-acid were found to be 93% and 88%, respectively. As to the

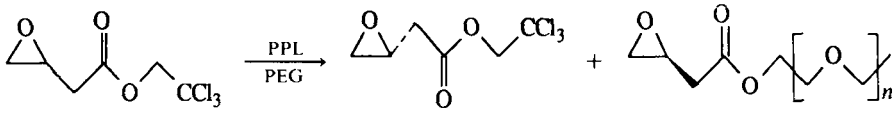


(±)-(**195**) (±)-(**196**) (*R*, *R*)-(**197**)

acidolysis involving the chiral alcohol acetate, the authors believe that the higher enantio- and diastereoselectivity in this process, compared to the esterification of the corresponding alcohol of **195** with acid **196**, which was also conducted with the same lipase, can be attributed to the previously described 'double-sieving' strategy, with the alcohol visiting the active site of the enzyme twice, and thus producing higher enantioselectivity.

B. Chiral Acids

Wallace and coworkers[199,200] used transesterification by PPL to resolve a racemic mixture of 2,2,2-trichloroethyl 3,4-epoxybutanoate, **198**. To ease the separation of the product and the unreacted ester, low molecular weight poly(ethylene glycol) (PEG) was used as an acyl acceptor. In hot diisopropyl ether solvent the polymer formed a molten phase which, upon cooling, solidified and was separated simply by filtration. The reaction required 5 h to reach 50% conversion with the lipase displaying preference for the



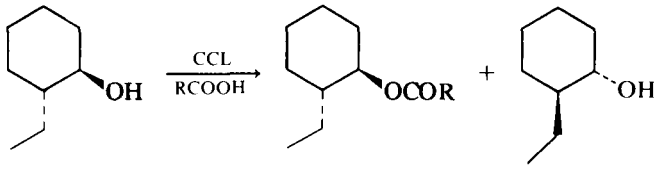
(**198**) (*R*)-(**198**) (*S*)-(**199**)

S-enantiomer of **198**. The remaining ester (*R*)-**198** was obtained in 86% yield and with ≥96% ee. The *S*-enantiomer **199** was cleaved off the polymer, by PPL-catalysed transesterification with methanol, to afford the corresponding methyl ester of **199** with ≥89% ee in 92% yield. The authors could not eliminate the possibility of a second resolution taking place during this latter enzymatic process.

VI. KINETIC RESOLUTION BY DIRECT ESTERIFICATION

A. Racemic Alcohols

Triantaphylides and coworkers[201] were among the first to employ lipases for resolving racemic alcohols by direct enantioselective esterification with carboxylic acids in an organic solvent such as hexane or heptane. Thus (±)-*trans*-2-ethylcyclohexanol **200** was esterified with lauric acid in the presence of CCL in hexane at 40 °C. At 46% conversion the laurate ester (1*R*, 2*R*)-**201** was obtained with 96% ee together with the unreacted alcohol (1*S*, 2*S*)-**200**, in 90% ee. Several related alicyclic alcohols including (±)-menthol



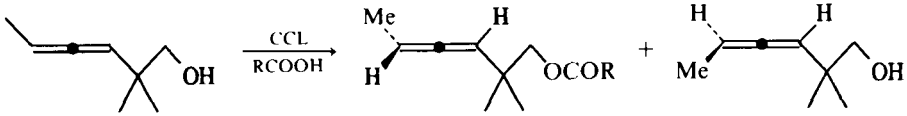
(±)-(**200**) (1*R*, 2*R*)-(**201**) (1*S*, 2*S*)-(**200**)

were similarly resolved with 95–100% ee, at 35–45% conversion. The lipase exhibited preference for the *R*-configurated esters. Fast reaction rates were generally observed for the *trans*-alcohols (5–10 h) (particularly in cases where the alkyl substituent was not too bulky) compared to the *cis*-alcohols, which were slower. Note that the enantioselectivity of the enzyme was much higher under these conditions than in the hydrolyses catalysed by the same lipase.

As mentioned in Section V.A.1, Triantaphylides and coworkers[173] used derivatives of racemic menthol **139** to compare the asymmetric hydrolysis, transesterification and esterification reactions. It is interesting to note that the rate of the esterification reaction was found to be much faster (10 h) than the rates of transesterification reactions of menthyl laurate with isobutanol and also of (±)-menthol with trilaurin (15 days) in heptane as a solvent with CCL. The main reason for this is that the transesterifications are subject to equilibrium, whereas the esterification involves formation of water which was adsorbed by the biocatalyst. However, the enantioselectivities in organic media remained very high and comparable for transesterifications and esterifications (94–95% ee).

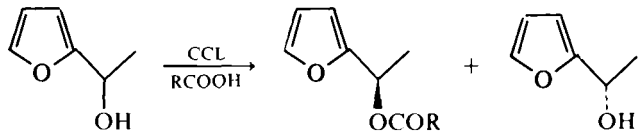
Triantaphylides and coworkers[202] have also used their asymmetric esterification process with CCL to resolve several chiral primary α- and β-allenic alcohols, e.g. the β-substrate **202**. When (±)-**202** was esterified with lauric acid in hexane with the lipase

at 40 °C, the reaction yielded (1 h) the laurate (*R*)-(−)-**203** at approximately 40% conversion or the remaining alcohol (*S*)-(−)-**202** at approximately 80% conversion (5 h). The enantioselection was only 72 and 70% ee, respectively, for the ester and alcohol. With other less hindered substrates poor enantioselectivity was achieved.



(±)-(**202**) (*R*)-(**203**) (*S*)-(**202**)

Wong and coworkers[203] used a double resolution strategy involving esterification and hydrolysis with CCL. The enantioselective esterification of the furylmethylcarbinol **204** with octanoic acid was conducted in water-saturated hexane at room temperature and until 52% of conversion (5 days). The ester **205** of predominantly *R*-configuration was subsequently subjected to hydrolysis, catalysed by the same lipase until 25% conversion, affording the alcohol (*R*)-**204** in 25% yield and 94% ee. The unreacted alcohol (*S*)-**204** had only 52% ee, but the authors reported its preparation by asymmetric reduction with an alcohol dehydrogenase on the corresponding acylfuran substrate.

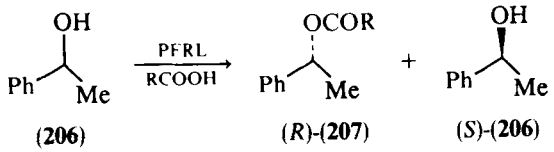


(±)-(**204**) (*R*)-(**205**) (*S*)-(**204**)

Sonnet described the resolution of several aliphatic secondary alcohols by direct esterification with various alkanoic acids in hexane employing immobilized MML[204,205]. Good enantioselectivity was obtained in a few cases ($E > 50$) and the lipase exhibited preference for the *R*-enantiomer. The chain length of the acid was found to influence significantly both the reaction rate and the enantioselectivity. The results also revealed that high enantioselectivity was dependent on the carbinol carbon possessing the chiral centre and that bulky alkyl groups in the close vicinity of that carbon were not tolerated by that lipase.

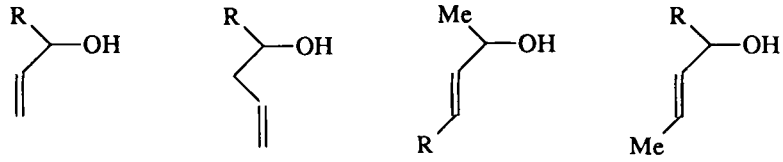
Okahata and coworkers[206] employed a lipid-coated immobilized lipase, soluble in organic solvents, to enantioselectively esterify several secondary alcohols in isooctane as a solvent. A synthetic dialkyl amphiphilic material was used, which formed a lipid monolayer covering the surface of the *Pseudomonas fragi* lipase (PFRL). The reactions proceeded very rapidly (1–2.5 h) in dry organic media at 40 °C in the presence of molecular sieves, and the best results were obtained for the resolution of 1-phenylethanol **206**, for which the lipase displayed very high enantioselectivity ($E = 250$). The lipase exhibited preference for the *R*-alcohol, and the reactivity was found to increase with increasing chain length of the acid. At 51% conversion the remaining alcohol (*S*)-**206** was afforded in excellent yield and optically pure. No data were reported for the ester (*R*)-**207**.

Finally, Lutz and coworkers[207] conducted a systematic survey of the esterification of various unsubstituted and phenyl-substituted racemic alcohols with dodecanoic acid (70 °C, 24 h) in n-hexane with PPL as a catalyst. The substrates can be classified into racemic 1-alken-3-ols **208**, 1-alken-4-ols **209**, (*E*)-3-alken-2-ols **210**, (*E*)-2-alken-4-ols **211**,



(206) (*R*)-(207) (*S*)-(206)

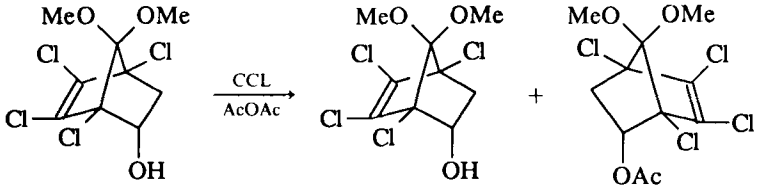
isomeric hexanols, *Z* vs *E* isomeric alkenols and aryl-substituted alkenols. They proposed a model, describing the reactivity and selectivity of the lipase. The substrates **210** gave the best results in terms of efficiency and enantioselectivity. For instance, with (*E*)-3-octen-2-ol (R = C_4H_9), high optical purity was obtained for both the unreacted *S*-alcohol (98% ee) as well as the produced *R*-ester (94% ee) at 43% conversion. Reasonable enantioselectivity was also obtained for the aryl-substituted alcohols, but other classes showed only low or moderate enantioselectivities. The *E*-isomers were found to be substantially better substrates than their *Z*-isomers.



(208) (209) (210) (211)

There are some recent reports on asymmetric esterifications of racemic alcohols with anhydrides. In order to obtain irreversible and rapid esterifications, Bianchi and coworkers used acetic, propionic and butyric anhydrides as acylating agents for the resolution of various primary and secondary alcohols in organic solvents with PFL immobilized on celite[59]. The reaction rates were reported to be considerably higher than those obtained in the equilibrium esterification and transesterification processes. The fastest rates were observed with propionic anhydride as the acylating agent. High enantioselection was obtained for the primary and secondary alcohols, the former reacting considerably faster (0.5–2 h) than the latter (2–30 h) to reach 40–50% conversion. The lipase preferentially acylated the *R*-enantiomer and, e.g., when alcohol **206** was subjected to the lipase in benzene at room temperature with one equivalent of propionic anhydride, the reaction proceeded rapidly (2 h) to reach 48% conversion when the propionate (*R*)-**207** and the remaining alcohol (*S*)-**206** were afforded in 94% yield and >95% ee.

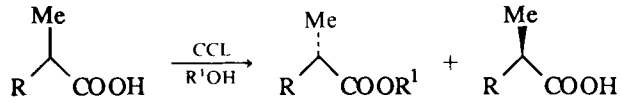
Similar strategy was utilized by Berger and coworkers[208] for the resolution of 7,7-disubstituted 1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-en-2-ols **212**. With acetic anhydride as the acyl donor and with CCL immobilized on celite in toluene at 22 °C, at 45% conversion the ester (+)-**213** was afforded with 98% ee together with the remaining alcohol of 80% ee. In order to employ the anhydride successfully it was found vital to remove the co-produced acid, either directly by adsorption on the celite or by the addition of a weak base. When, alternatively, the transesterification process was performed with vinyl acetate, both serving as a solvent and an acyl transfer agent, at room temperature, excellent enantioselection was accomplished at 50% conversion for both the CCL as well as the *Geotrichum candidum* lipases. As an example, CCL afforded both the ester and the remaining alcohol with >99 and 98% ee, respectively, with *E*-values ~1000.



(±)-(**212**) (−)-(**212**) (+)-(**213**)

B. Racemic Acids

Engel has very recently reported on the application of CCL in heptane to resolve racemic 2-methylalkanoic acids **214** by esterification with various alcohols[209]. The reaction proceeded rapidly at room temperature with primary alcohols (3–22 h), and the lipase showed preference for the *S*-enantiomers with low to moderate enantioselection. The best results were obtained for 2-methylpentanoic acid (R = C_3H_7) with octanol. At 46% conversion (10 h) the ester (*S*)-**215** was obtained with 93% ee, together with the unreacted acid (*R*-**214**) of 80% ee. In contrary to Klibanov and coworkers[62], these



(**214**) (*S*)-(**215**) (*R*)-(**214**)

results, as well as results described earlier by Lazar[210] and by Kodera's group[211], demonstrate that the acceptance of α-substituted acids as substrates by this enzyme does not necessarily require an electron-withdrawing group in the α-position. However, a methyl substituent in the same position caused a sharp decrease of the esterification rate as compared to the unsubstituted acid. A similar effect has also been observed for esterification reactions involving a variety of saturated, unsaturated and branched carboxylic acids catalysed by immobilized MML[212].

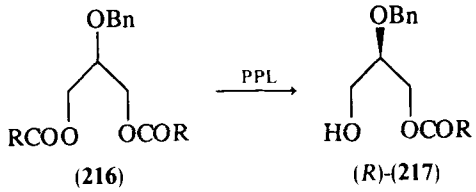
VII. PROCHIRAL COMPOUNDS

A. Asymmetric Hydrolysis

1. Prochiral diol esters

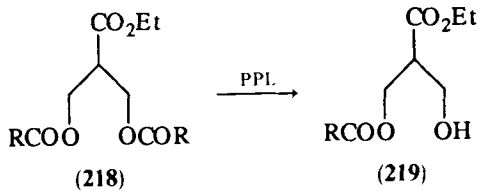
In their approach towards the asymmetric synthesis of the platelet activating factor, Suemune and coworkers[213] employed PPL for the hydrolysis of prochiral 1,3-di-*O*-acetyl-2-*O*-benzylglycerol **216** to afford the desired 3-*O*-acetyl-2-*O*-benzyl-*sn*-glycerol (*R*)-**217** in good chemical, but rather low optical purity (41% ee), at 30 °C, with acetone as a co-solvent. PLE gave the opposite enantiomer (*S*)-**217** of similar optical purity, but in low yields.

Schneider and coworkers[214] similarly reported the asymmetric hydrolysis of **216** with PPL to afford (*R*)-**217** in 40% yield at 50% conversion, with 80% ee. Using lipoprotein lipase, the yield was improved (75%) as well as the optical purity of (*R*)-**217** (91% ee). Kerscher and Kreiser[215] obtained 50% yield with >95% ee by reacting the dipalmitate ester with PPL.



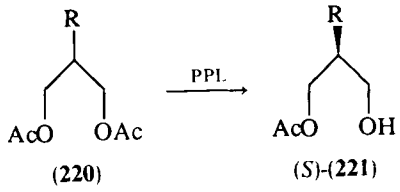
(216) (*R*)-(217)

Ehrler and Seebach[216] used PPL for the asymmetric partial hydrolysis of the prochiral triester substrate **218**, and obtained **219** in 57% yield and 87% ee, but unfortunately they could not assign the absolute configuration of the product.



(218) (219)

Several groups studied the asymmetric hydrolysis of 2-substituted 1,3-propanediols. Ramos Tombo and collaborators[217] used PPL for the synthesis of chiral 2-substituted 1,3-propanediol monoacetates with high enantiomeric purity. As an example, when the prochiral 2-phenyl-1,3-propanediol diacetate **220** was subjected to hydrolysis catalysed by immobilized PPL, the monoacetate (*S*)-**221** was afforded in 91% yield and >95% ee. Excellent results were also obtained for the corresponding 2-(3-butyl) substrate, but only moderate optical purity was obtained with several alkyl groups such as benzyl or cyclohexyl. Transesterification of the diol of **220** with methyl acetate in the presence of immobilized lipase yielded the other enantiomer (*R*)-**221**, similarly in excellent chemical (98%) and high optical (92% ee) yield.

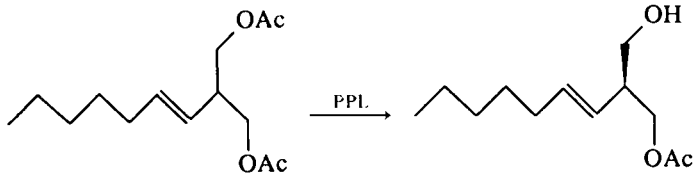


(220) (*S*)-(221)

Mori and Chiba[218] also used PPL and CCL for the asymmetric hydrolysis of similar compounds with 30% acetone as a cosolvent. Thus PPL with **220** (R = benzyl) yielded the monoacetate (*R*)-**221** in 83% ee and 56% yield. CCL gave the antipode (*S*)-**221**, but with only 38% ee. For R = allyl, CCL afforded (*S*)-**221** in 89% ee, but in low yield. Employing PFL, Sakai's group[219] prepared optically pure (>99% ee) (*R*)-**221** (R = Me) in 33% yield from **220**. The product was used as a chiral synthon for the synthesis of (−)-muscone.

Guanti and coworkers[49] used PPL to hydrolyse the 2-substituted 1,3-diol prochiral diacetate ester **222** in their approach towards the synthesis of a tris(hydroxymethyl)-methane derivative as a chiral building block. At 50% conversion the monoester (*S*)-**223** was afforded in 63% yield and 96% ee.

The same group[220] recently demonstrated the importance of the 2-substituent in 2-substituted 1,3-diacetoxy propanes to possess an *E*-alkenyl or an alkynyl moiety for



(222) (*S*)-(223)

improvement of both the yield and enantioselectivity in the asymmetric hydrolysis of such prochiral substrates with PPL. These results also confirm the preference of this enzyme for the *S*-enantiomer of such substrates. The change of configuration from (*E*) to (*Z*) caused a reversal of enantioselection together with considerable reduction in optical purity of the products. The effect of added cosolvent, such as diisopropyl ether or *t*-butyl alcohol, on the yield and enantioselectivity also became apparent.

In addition, to exploit further the influence of electronic effects on the yield and enantioselectivity of lipase-catalysed asymmetric hydrolysis of 2-aryl substituted 1,3-propanediol diacetates, Guanti and coworkers[221] studied a whole range of related compounds with PPL, CCL and PLE in aqueous medium at 50% conversion. PPL was the best for such transformations, while with PLE and CCL substantial amounts of the diol were usually formed together with lower enantioselectivity. PPL, on the other hand, exhibited on many occasions high enantioselectivity (92–96% ee) and good yields with consistent preference for the *S*-configuration, and these hydrolyses were found to cease almost spontaneously at the monoacetate stage, unlike with the other enzymes. These results revealed no electronic effects to be responsible for the enzyme enantioselectivity.

2. Prochiral diacid esters

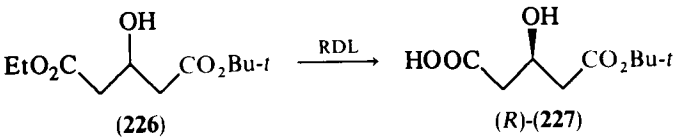
Kitazume and collaborators[222] used CCL to prepare optically active 2-fluoro-2-alkyl-substituted malonic acid monoesters by asymmetric hydrolysis of the corresponding prochiral malonates. Thus dimethyl 2-fluoro-2-ethyl malonate gave the (−)-2-fluoro-2-ethylmalonic acid monoester in 87% yield and 99% ee. The absolute configuration was not reported.

Monteiro and coworkers[223] employed a commercial bacterial lipase, 'Esterase 30000', for the selective synthesis of (*R*)- and (*S*)-3-hydroxyglutaric acid ethyl and *t*-butyl monoesters from the prochiral diethyl 3-hydroxyglutarate **224**. In three hours the enzyme with *pro-S* preference hydrolysed the diester to the monoester (*S*)-**225** in 94% yield and 100% ee in a cyclohexane/water system.

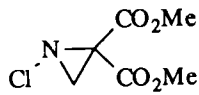
(224) (*S*)-(225)

The ethyl *t*-butyl 3-hydroxyglutarate **226** was quantitatively prepared from **225** and submitted to the hydrolysis conditions described above. Due to the bulkiness of the *t*-butyl group, the lipase exclusively hydrolysed the ethyl ester moiety to the (*R*)-*t*-butyl monoester **227** in 90% yield and >95% ee, but required a considerably longer reaction time.

Bucciarelli and coworkers[224] used *Rhizopus delemar* lipase for the enantioselective hydrolysis of the racemic *N*-chloro-2,2-bismethoxycarbonylaziridine **228**, with the asym-



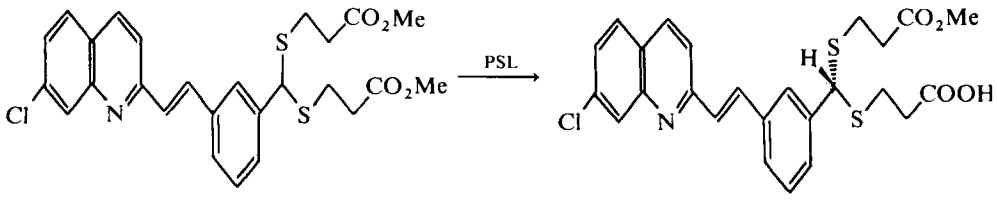
(226) (*R*)-(227)



(228)

metry centred on the trivalent nitrogen atom, to afford the unreacted (−)-*N*-chloro-2,2-bismethoxycarbonylaziridine at 70% conversion with 76% ee. The absolute configuration of the diastereomer afforded was not assigned.

Hughes and collaborators[50,51] employed PSL for the asymmetric hydrolysis of the prochiral diester **229**, an important chiral precursor for the synthesis of LTD_4 antagonist. The lipase displayed strong preference for the *pro-S* group hydrolysis and the resulting acid ester (*S*)-**230** was afforded in excellent yield and in 99% ee. The presence of a non-ionic surfactant was essential for the reaction to proceed at a sufficient rate. The effect of the distance between the prochiral centre and the reacting carbonyl group on chemical yields and on the enantioselectivity was studied. The results revealed that selectivity does not necessarily diminish as the distance between the chiral centre and the reaction site increases, since the substrate with four bonds between the prochiral centre and the ester carbonyl group was a considerably better substrate than the three-bond and the five-bond analogues. An interesting dual enzyme experiment involving PSL and CCL was conducted in order to increase the optical purity of the monoester product for the five-bond analogue mentioned above. CCL was employed to resolve the monoester which was formed in the PSL catalysed reaction after 62 h in 88% yield and 80% ee, to increase its optical purity to 95% ee after 46 additional hours with CCL, but the chemical yield dropped to 55%.

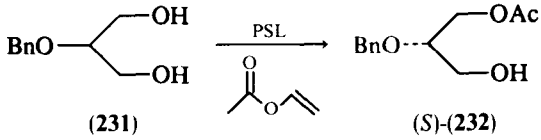


(229) (*S*)-(230)

B. Asymmetric Transesterifications

Wang and Wong[56] used PSL for the enantioselective transesterification of 2-*O*-benzyl glycerol **231**, with the irreversible vinyl acetate acyl transfer agent in chloroform at 25 °C. After 24 hours the monoacetate (*S*)-**232** was obtained in 53% yield and with 96% ee. The (*R*)-**232** antipode was obtained with the same lipase in the asymmetric hydrolysis of the diacetate of **231** in similar yield (52%), but only moderate optical purity (71% ee).

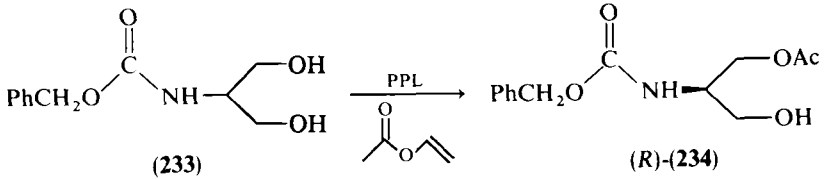
Achiwa and coworkers[225,226] employed PFL for the asymmetric transesterification of the prochiral 2-*O*-benzyl glycerol **231** with various acetates at 25 °C, using the acetates



(231) (*S*)-(232)

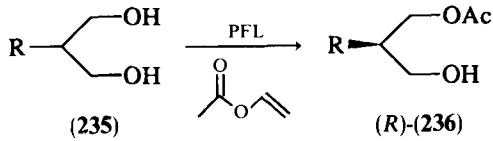
as a solvent. The lipase exhibited preference for the *pro-S* hydroxy group, and the reaction proceeded smoothly in 3 hours to afford the (*S*)-2-*O*-benzylglycerol-1 acetate **232** in 92% yield and 94% ee with vinyl acetate at 50% conversion. The utility of **232** as a chiral building block was demonstrated by the synthesis of (*S*)-propranolol, an aryloxypropylamine-type *β*-blocker. Similar results were also obtained with the corresponding 2-*O*-methyl- and ethyl-substituted glycerol substrates.

2-*N*-(benzyloxycarbonyl)serinol **233** was esterified with PPL at 28 °C with vinyl acetate as an acyl transfer agent by Wong and collaborators[57]. This time the *pro-R* hydroxy group of **233** was preferentially acylated and the monoacetate (*R*)-**234** was afforded in 77% yield with 97% ee at 60% conversion.



(233) (*R*)-(234)

Achiwa and coworkers[227] have also demonstrated the preparation of chiral 1,3-propanediols as chiral synthons by employing PFL. With the prochiral 2-substituted 1,3-propanediol **235** (R = Bn) at 25 °C in vinyl acetate, the transesterification reaction proceeded very efficiently to afford the monoacetate (*R*)-**236** in excellent yield with 97% ee in 1.5 hours. Similar results were obtained for the 1-naphthyl substituted substrate of the **235** type with that lipase. The configuration of **236** was rather surprising, since the transesterification of the corresponding 2-*O*-benzylglycerol **231** with the same lipase gave the *S*-monoester **232**.



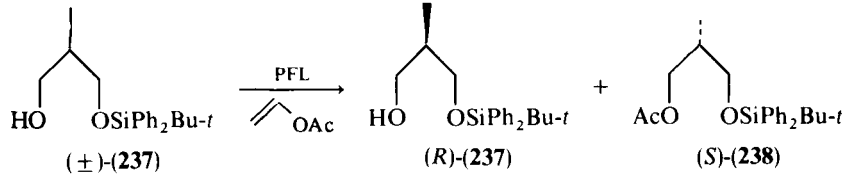
(235) (*R*)-(236)

Atsuumi and collaborators[228] used PFL for the asymmetric transesterification of 2-benzyl-1,3-propanediol **235** in vinyl acetate. The reaction yielded the 2-substituted monoacetate (*R*)-**236** in quantitative yield and with >94% ee. The 1-naphthyl substituted analogue also gave an excellent yield (93%), but with lower enantiomeric excess (86% ee). The 2-substituted 1,3-propanediol product could be converted into the corresponding chiral 2-substituted-3-hydroxypropionic acid, a key intermediate in the asymmetric synthesis of potent rennin inhibitors.

Achiwa and coworkers had reported that the asymmetric transesterification of the prochiral 2-methyl-1,3-propanediol **235** with PFL in ethyl acetate gave the monoacetate (*R*)-**236** in 70% yield, but only 60% ee[227]. Santaniello and coworkers[229] reported results with the same enzyme in chloroform containing vinyl acetate at 30 °C. When all the initial diol had reacted and 60% of the corresponding diacetate had formed at 80%

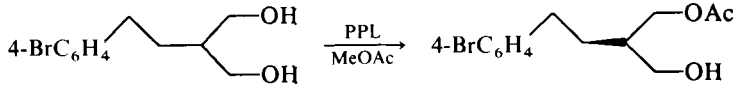
conversion, the desired monoacetate was afforded in 40% yield, with >98% ee. Furthermore, the configuration was assigned as *S*, based on solid evidence, opposite to the former report.

The (*S*)-**236** product was converted into the synthetically useful 3-(diphenyl-*t*-butylsilyloxy)-2-methylpropane-1-ol, (*R*)-**237**. The authors could also prepare the antipode of that compound by enantioselective transesterification of the racemic substrate **237** under the same conditions. The (*S*)-acetate **238** was afforded in 39% yield with >98% ee, and the remaining alcohol (*R*)-**237**, similarly in 38% yield and >98% ee.



(±)-(**237**) (*R*)-(**237**) (*S*)-(**238**)

Barnett and Wilson[230] used lipase-catalysed enantiodifferentiation of the prochiral 1,3-diol **239** to prepare the monoacetate (*R*)-**240**, which in turn was utilized in the asymmetric synthesis and consequent configurational assignment of some folate antimetabolites. In the presence of immobilized PPL, **239** underwent an asymmetric transesterification with methyl acetate to produce the monoacetate (*R*)-**240** in 90% yield and 88% ee. The hydrolysis with the same lipase of the corresponding diacetate proceeded with less enantioselection to afford (*S*)-**240**.

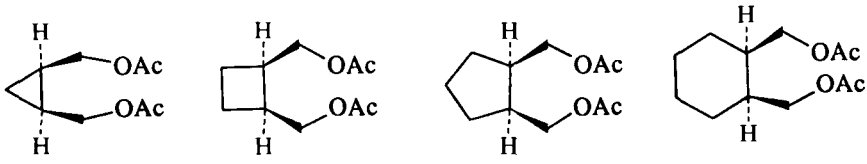


(**239**) (*R*)-(**240**)

VIII. *Meso* COMPOUNDS

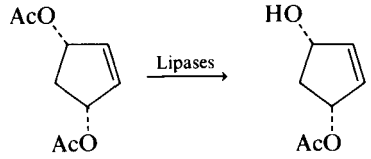
A. Asymmetric Hydrolysis

Laumen and Schneider[231] studied and compared the asymmetric hydrolysis of various monocyclic *meso*-diacetates, such as **241**–**244**, with PLE and PPL. Unlike the corresponding *meso*-diacid esters these substrates were found to be poor for PLE, but with PPL they obtained good to excellent yields and moderate to fairly high optical purities (72–88% ee), although the absolute configuration was not assigned. The best results were obtained with *cis*-1,2-diacetoxy-3,5-cyclohexadiene (90% yield and 98% ee). With PPL, in contrast to PLE, the hydrolysis was found to cease at 50% conversion with these diacetates, and cyclopentane substrates also yielded with PPL high optical purities. Schneider and coworkers[232] improved these results considerably for substrates **241**–**244** by employing PSL, when at 50% conversion they obtained 90–>95% ee and assigned the (1*R*, 2*S*)-configuration for all substrates. Jones and coworkers[233] reported similar studies with PPL on the same *meso*-diacetates and the corresponding dipropionates **241**–**244**. In contrast to PLE, the PPL exhibited consistent selectivity for the *S*-configurated ester, thus affording the corresponding (1*R*, 2*S*)-monoesters in high yield and with 93 and 96% ee, respectively, for substrates **241** and **242**, with much lower yields for **243** and **244**, but with 89 and 87% ee, respectively.



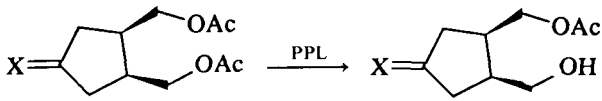
(241) (242) (243) (244)

The same group[234] reported also the asymmetric hydrolysis of *meso*-1,4-diacetoxycyclopent-2-ene **245** with several lipases (PPL, PSL, MML and *Chromobacterium viscosum* lipase) to obtain the monoacetate (1*R*, 4*S*)-**246** in 80–90% yield and 91–97% ee for all the lipases at 50% conversion. Thus, in contrast to PLE, all lipases selectively hydrolysed the (*S*)-ester group and very little was transformed into the *meso*-diol. The product **246** is an important chiral building block for the synthesis of cyclopentanoid natural products, such as prostaglandins, prostacyclins and thromboxans.



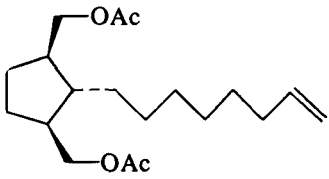
(**245**) (1*R*, 4*S*)-(**246**)

Hemmerle and Gais[235] also studied a number of 4-substituted cyclopentanoid *meso*-diacetates **247** with PPL. (X may represent a carbonyl oxygen, various carbonyl protection groups or several other substituents.) Where the absolute configuration could be assigned, the ester **248** with the *S*-configuration was preferentially hydrolysed in good yields (60–81%) with the enantioselectivity ranging from 26–96% ee. High enantioselection was obtained for substrates with the 4-substituent in *anti*-position to the acetate functions, and when that substituent constituted a third acetate group regioselective hydrolysis occurred, favouring the primary alcoholic functions. It was clearly demonstrated that transesterification of the corresponding *meso*-diols yielded complementary stereoisomers, (1*S*, 4*R*)-**248** when carried out in methyl acetate. Good yields were obtained for the transesterification, but the enantioselection was found to depend greatly on the water content of the catalyst.



(**247**) (1*R*, 4*S*)-(**248**)

Suemune and collaborators[236] investigated the ability of several enzymes to discriminate between enantiotopic groups of the symmetric *meso*-substrates **249**, including PLE, PPL, CCL and *Rhizopus delemar* (RDL) lipase. The latter was found to be the most suitable one to hydrolyse **249** in a buffer containing 10% acetone at 30 °C to afford the chiral monoacetate (1*R*, 2*R*, 3*S*)-**250**, a chiral synthon for their approach towards the asymmetric synthesis of 11-deoxyprostaglandin, in 69% yield and with >99% ee. Porcine pancreatic lipase afforded the same enantiomer, whereas the CCL and PLE afforded the antipode, but in much lower enantiomeric excess.



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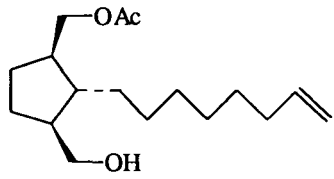
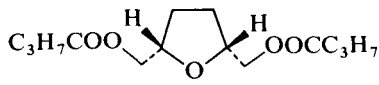


(1*R*, 2*R*, 3*S*)-(250)

Estermann and coworkers[237] employed several lipases, as well as PLE, to asymmetrically hydrolyse the *meso*-dibutyrate tetrahydrofurans **251** and **252**. The lipase from *Mucor javanicus* displayed superiority over PLE, PPL and CCL to produce (2*S*, 5*R*)-monoesters for both substrates in good yields and >99% ee. Previously, Naemura's group[238] had employed PLE, PPL and CCL for the hydrolysis of the corresponding *meso*-diesters **251**, constituting various RCO groups with [R = CH_3, CH_2CH_3, $CH(CH_3)_2$ and $C(CH_3)_3$]. PLE was found to be the most efficient and gave 86% yield and 96% ee for the diacetate. The stereogenic centre constituting *S*-configuration was predominantly hydrolysed to afford the (2*S*, 5*R*)-monoester for both PLE and PPL. CCL, on the other hand, displayed stereoselection towards the (2*R*, 5*S*) antipode with moderate enantioselectivity. The rates of hydrolysis were influenced by the nature of the acyl groups to a considerable extent.



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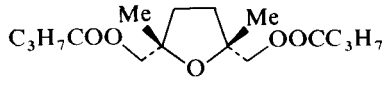
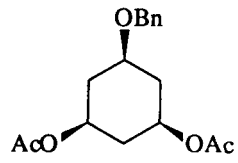


(252)

Finally, PLE was found superior to several lipases for the hydrolysis of **253** and **254**[239,240]. With **253** the lipases consistently showed preference for the *S*-configurated ester function, whereas PLE had the opposite preference[240]. PFL showed dramatic improvement in the presence of added DMSO.



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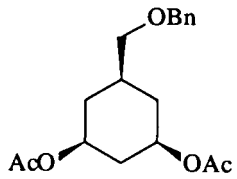


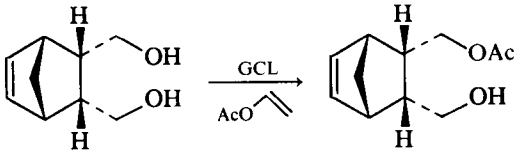
(254)

B. Asymmetric Transesterification

Schneider and coworkers[232] employed PSL to study the asymmetric acylation of the parent diols of **241–244** with vinyl acetate in *t*-butyl methyl ether or, alternatively, in neat vinyl acetate. With vinyl acetate the transesterification was complete within only a few hours (5–7 h), as compared to several days (2–6 days) with ethyl acetate. 88–>95% ee was obtained under these conditions in very good yields. Interestingly, however, this lipase did not tolerate the six-membered ring analogues very well as substrates.

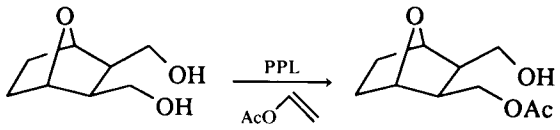
Wong and coworkers[21] employed immobilized PSL similarly in the asymmetric transesterification process of *meso*-1,4-dihydroxycyclopent-2-ene, the parent diol of **245** with vinyl acetate in *t*-butyl methyl ether or dichloromethane at 25 °C. The lipase exhibited stereochemical preference for the *S*-configurated hydroxyl group to afford the monoacetate (1*S*, 4*R*)-**246** with 98% ee at 68% conversion in less than one hour.

Achiwa and coworkers[241] used GCL for asymmetric transesterification of the *endo*-norbornene *meso*-diol **255** in diethyl ether at room temperature with vinyl acetate. The (2*S*, 3*R*)-monoacetate **256** was obtained in 72% yield, with 95% ee, accompanied by the corresponding diacetate (25%). Adduct **256** was subsequently used as a chiral building block in the asymmetric synthesis of TXA_2 antagonist. Since previously asymmetric hydrolysis of the dicarboxylic acid dimethyl ester of **255** with PLE had failed[242], this was quite an important achievement.



(**255**) (2*S*, 3*R*)-(**256**)

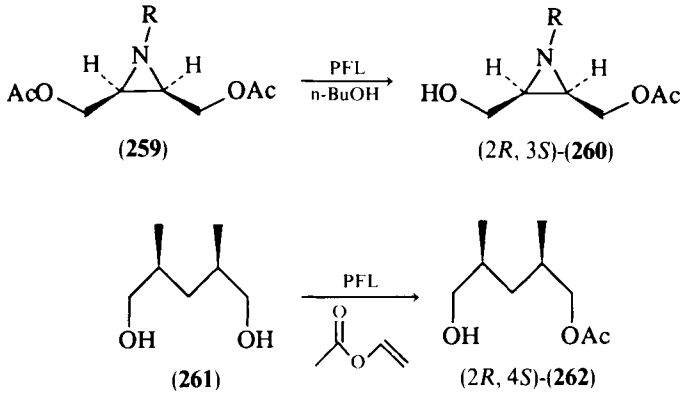
Andreu and coworkers[243] employed lipases for the asymmetric monoacylation of the *meso*-diol substrate *exo*-**257** by transesterification using ethyl, vinyl or isopropenyl acetates both as a solvent and as an acyl transfer agent. PPL yielded (2*S*, 3*R*)-**258** in 92% and >99% ee in vinyl acetate. Ethyl acetate gave the same product in >99% ee but with lower yield. In isopropenyl acetate, no reaction took place. However, CCL behaved quite differently. With isopropenyl acetate the monoacetate was afforded in good yield and 97% ee while much lower enantioselectivity was displayed with vinyl acetate, and in ethyl acetate no reaction took place. What is even more interesting and really demonstrates the variety and diversity among lipases, was that the (2*R*, 3*S*)-antipode was formed with the *Candida* lipase, i.e. a reverse stereogroup differentiation between these two lipases. The corresponding *endo*-diol substrate turned out to be less suitable, especially for PPL. Interestingly, with the *endo*-diol substrates both lipases generated the same enantiomeric product.



(**257**) (2*S*, 3*R*)-(**258**)

Fuji and collaborators[244] prepared chiral *cis*-disubstituted aziridines from *meso*-bis(acetoxymethyl)aziridine **259**. Several lipases were investigated using n-butanol as an acyl acceptor and diisopropyl ether as a solvent. The best results were obtained with PFL, when (2*R*, 3*S*)-**260** was afforded in good yield with 95% ee and 98% ee for R = p-toluenesulfonyl (3 days) and R = benzyloxycarbonyl (6 days), respectively. All lipases yielded the same enantiomer and PLE failed to catalyse these reactions.

Achiwa and coworkers[227] described the lipase-catalysed transesterification of the acyclic *meso*-2,4-dimethyl-1,5-pentanediol **261** in neat vinyl acetate. With PFL, the (2*R*, 4*S*)-monoacetate **262** was afforded in 82% yield and with 98% ee.

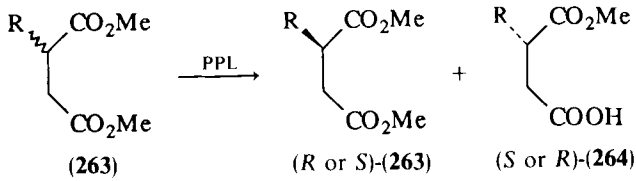


IX. REGIOSELECTIVE BIOTRANSFORMATIONS

A. Non-carbohydrates

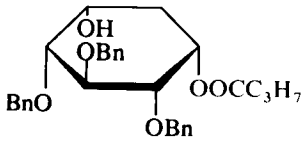
1. Regioselective hydrolysis

Guibé-Jampel and coworkers[245] reported on the regio- and enantioselective hydrolysis of diesters **263** with PPL. In the case of alkyl-substituted dimethyl succinates the β-ester underwent regioselective hydrolysis (90:10), and at 50–55% conversion the *R*-diester (*R*)-**263** (R = methyl) or the *S*-diester (*S*)-**263** (R = benzyl) were hydrolysed in high yield with 95% and 98% ee, respectively. The L-N-protected aspartic (R = NHZ or NHAc) and L-glutamic (N-Ac protected) esters were also excellent substrates for the lipase, but with these the α-ester was hydrolysed, also in very high yield and with 100% ee. Similar regioselectivity was obtained when dimethyl methylsuccinate **263** (R = methyl) was transesterified by immobilized PPL with n-propanol as a nucleophile, but the reaction was very slow (7 days)[246]. Under the same conditions CCL showed reverse regioselectivity, preferentially reacting at the α-ester group.



PPL was employed for the highly regioselective hydrolysis of several similar diesters by De Jeso and coworkers[247], as well as the chemoselective cleavage of a certain type of ester in a mixture of esters[248, 249]. Substitution in either the acid or alcoholic moiety of the ester leads to dramatic reduction in hydrolysis rate for this lipase.

Hönig and coworkers[250] used CCL for the regio- and enantioselective hydrolysis of diacyl-substituted benzyl-protected deoxyinositols. Thus, from the appropriate diacylated inositol substrates, compounds (+)-**265** and (−)-**266** were prepared in good yields and in 98 and 95% ee, respectively, with the lipase exhibiting strong preference for the *R*-configurated ester function. Similar work was also reported on the regio- and enantioselective hydrolysis of protected diacetates of inositol with cholesterol esterase[251].



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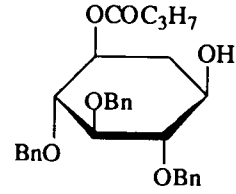
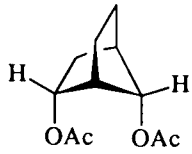


(266)

Naemura's group[252] examined the enantioselective and regioselective hydrolysis of racemic bicyclic diacetates **267** and **268** with several lipases and PLE. In phosphate buffer at 25–30 °C the hydrolysis was terminated at 50% conversion. It was clearly demonstrated that the acetoxy group located on the methano bridge was preferentially hydrolysed for all enzymes. In terms of regioselectivity the best results were obtained with PLE on substrate **268**, in which case the hydrolysis of the acetyl group located on the methano bridge occurred exclusively. In most cases moderate to high optical purities were obtained for the various products of the rather complicated mixture of enantiomers and diastereomers obtained.



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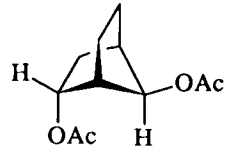
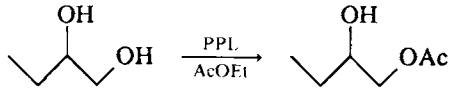


(268)

2. Regioselective transesterifications

Klibanov and coworkers[253] employed PPL to regioselectively acylate various 1,2- and 1,3-diols in organic media using ethyl carboxylates, such as ethyl acetate, both as an acyl transfer agent and a solvent. Very high regioselectivity was obtained for most cases and the primary hydroxyl group in the diols was exclusively acylated. For example, when 1,2-butanediol **269** was reacted with ethyl acetate at 30 °C, 97% of the glycol was acetylated after 23 h, and the monoester **270** was isolated in a pure state in 83% yield.

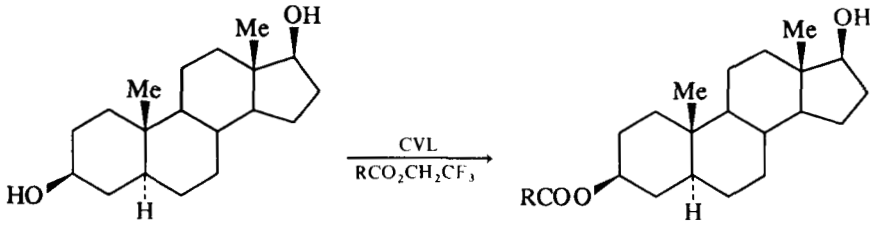


(269) (270)

Njar and Caspi[254] investigated the regioselectivity in the conversion of steroid acetates into the corresponding alcohols. CCL was used with n-octanol as a nucleophile in either isopropyl ether or acetonitrile containing 5% water as a solvent. In the numerous steroid ester derivatives investigated it became evident that 3α-acetoxy, 17β-acetoxy and 19-acetoxy groups resisted cleavage.

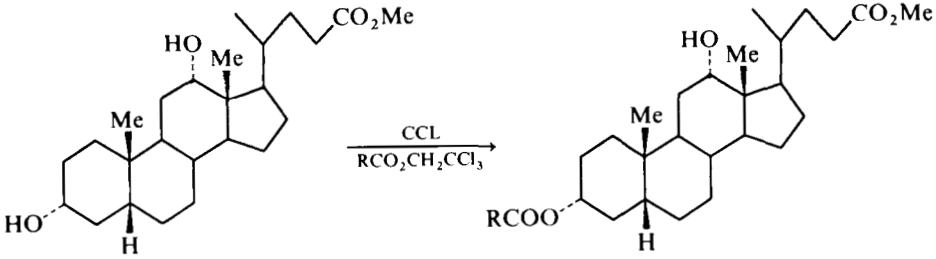
Riva and Klibanov[255] investigated the regioselective acylation of various hydroxy steroids. Thus, when the dihydroxy steroid 5α-androstane-3β-17β-diol **271** was butyrated with *Chromobacterium viscosum* lipase (CVL) in anhydrous acetone with 2,2,2-trifluoro-

ethyl butyrate as an acylating agent at 45 °C, acylation took place exclusively at the 3β-hydroxy group at 98% conversion in 23 h. The monobutyrate **272** was isolated in 83% yield. Another hydrolase, subtilisin, was observed to exhibit opposite regioselectivity towards the 17β-hydroxyl group, which was exclusively acylated under the same conditions, although not as efficiently (7 days, 79% conversion). A number of analogues of **271** were investigated to ascertain the structural requirements of the lipase in the acylation process. The results revealed the necessity of the C-3 hydroxyl group to remain in the equatorial (β) position and the A/B ring junction to possess the *trans*-configuration.



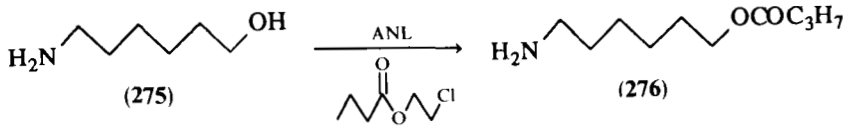
(271) **(272)**

More recently, Carrea and coworkers[256] carried out similar investigations of various steroid substrates using CCL in anhydrous benzene at 45 °C with trichloroethyl butanoate as an acyl transfer agent. Their results revealed that the stereochemical requirements were broader than those for CVL and in some cases the 17β as well as the 3α hydroxyl groups were acylated. These investigations were then successfully extended towards regioselective acylation of various bile acid derivatives. For instance, deoxycholic acid methyl ester **273** with CCL, under the conditions described above, gave the 3α-*O*-butanoyldeoxycholic acid methyl ester **274** at 96% conversion after 48 h in 85% yield.



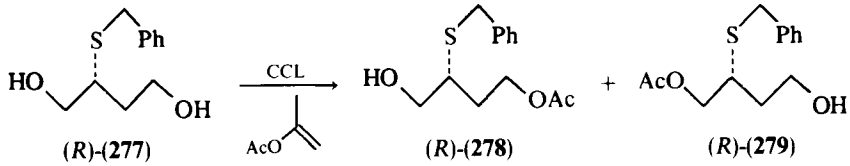
(273) **(274)**

Klibanov and coworkers[257] have also demonstrated the discrimination of enzymes between different groups in heterofunctional compounds. Thus, ANL catalysed the chemoselective transesterification of 6-amino-1-hexanol **275** in *t*-amyl alcohol as a solvent at 45 °C with 2-chloroethyl butyrate as an acyl transfer agent. The amino ester **276** was afforded, but in low yield (47%). The protease subtilisin could be used to selectively acylate the amino function in good yields.



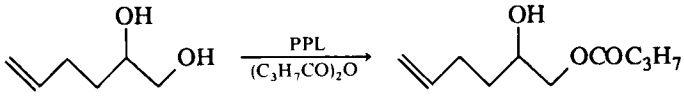
(275) **(276)**

Fuganti and coworkers[258] were interested in the regioselective protection of one of the two primary hydroxyl groups in the optically pure thiobenzyl diol (*R*)-**277**. This was accomplished by lipase-catalysed transesterification of the diol, which was found to be superior to hydrolysis of the corresponding diacetate. When isopropenyl acetate was used as an acyl transfer agent in hexane at 0 °C with CCL the monoacetate (*R*)-**278** was afforded at 70% conversion (2 h), contaminated with less than 10% of the monoacetate **279**. At a higher conversion the corresponding diacetate started forming. When racemic **277** was used as a substrate, racemic **278** was afforded as the main product, suggesting that the recognition of the enzyme was a result of steric rather than stereochemical factors.



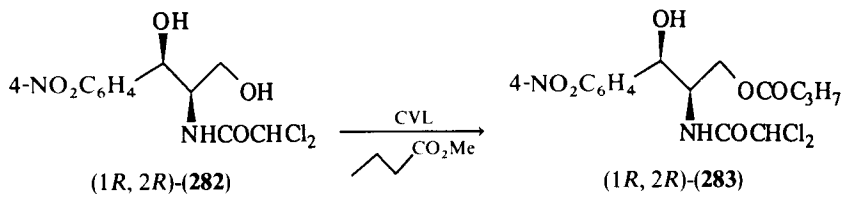
(*R*)-(**277**) (*R*)-(**278**) (*R*)-(**279**)

Ramaswamy and collaborators[259] employed PPL for the regioselective acylation of various aliphatic diols possessing primary and secondary hydroxyl groups at 0 °C in diethyl ether with acetic or butyric anhydride as an acylating agent. Excellent regioselectivity was obtained with the primary hydroxyl groups exclusively acylated and the products containing only traces of diester. The reactions were much faster with butyric anhydride than with acetic anhydride (3–15 h, compared to 18–48 h). For example, diol **280** with the lipase gave with butyric anhydride the monobutyrate **281** in 95% yield with the monoester/diester ratio of 99:1 in only 3 h.



(**280**) (**281**)

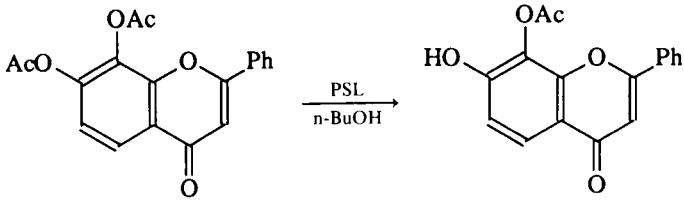
Carrea and coworkers[260] used lipases for the regioselective acylation of *threo*-(1*R*, 2*R*)-chloramphenicol, a natural antibiotic, **282**, in organic media. Out of several lipases with methyl butanoate serving both as a solvent and an acyl transfer agent the CVL was found to be the most effective one. At 99% conversion (7 h) the monoacylated product **283** was obtained in 95% yield at 45 °C. The presence of molecular sieves was found to improve the performance of the lipase dramatically. Long-chain fatty acyl groups could similarly be introduced to **282** using the corresponding trifluoroethyl ester in acetone with lipase from *Penicillium cyclopium* as a catalyst.



(1*R*, 2*R*)-(**282**) (1*R*, 2*R*)-(**283**)

Finally, Nicolosi and coworkers[261] have recently reported on the regioselective lipase-catalysed transesterification of polyhydric phenols. When flavone acetate **284** was subjected to PSL in THF at 45°C with n-butanol as an acyl acceptor, the 8-acetoxy-7-

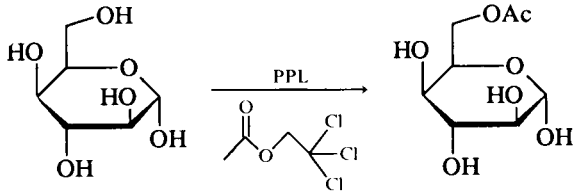
hydroxyflavone **285** was afforded in a highly regioselective fashion in 95% yield. Very high regioselectivity was also achieved for several other analogous di- and triacetoxyflavones.



(284) (285)

B. Carbohydrates

In one of the first reports on the regioselective transesterifications of carbohydrates with lipase Therisod and Klibanov[262] described the regioselective acylation of several monosaccharides. At 45 °C with various trichloroethyl carboxylates as acylating agents in pyridine (one of very few organic solvents that dissolve sugars), PPL was used to obtain very high regioselectivity. The primary alcohol moiety was preferentially acylated, up to 100% at lower conversion (40%) in some cases, consequently with relatively low yields. For instance, with D-mannose **286** and trichloroethyl octanoate, 95% regioselectivity was obtained and the monoacylated sugar **287** was isolated in good yield at 100% conversion (2 days). Under similar conditions fructose was exclusively acylated at the primary position to afford the 1-*O*-acetyl (71%) and 6-*O*-acetyl (25%) derivatives.

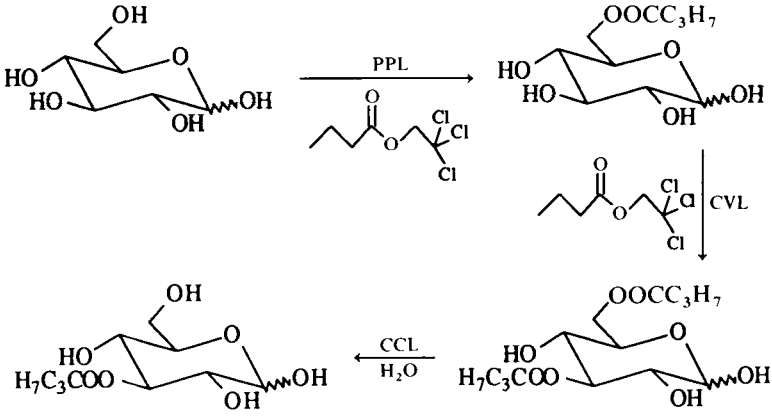


(286) (287)

Therisod and Klibanov[263] used enzymatically formed 6-*O*-acylated and related 6-*O*-protected monosaccharides to investigate the regioselective transesterification of the four unblocked secondary hydroxyl groups in glucose, galactose and mannose. In dichloromethane or THF at 45 °C with 2,2,2-trichloroethylbutyrate the CVL and ANL exclusively acylated the hydroxyl group at the C-3 position of glucose. Conversely, PPL exhibited an overwhelming preference towards the C-2 position. Similar regioselectivity (>90%) of lipases in the acylation of sugars, including numerous furanose and pyranose substrates, has also been confirmed by Wong and coworkers[57].

The diacetylated derivatives thus made could then be selectively deblocked by hydrolysis with CCL to afford 3-*O*- or 2-*O*-acylated monosaccharides, as demonstrated for the preparation of 3-*O*-butyrylglucose from 3,6-di-*O*-butyrylglucose in 85% yield[263]. The overall process is illustrated in Scheme 4 for glucose.

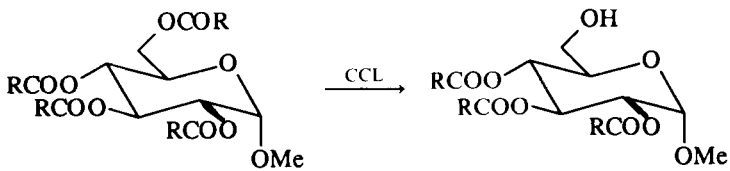
Klibanov's group[264] has also demonstrated the application of the subtilisin protease to catalysing regioselective esterification of sugars and related compounds, such as di- and oligosaccharides and nucleotides, in anhydrous DMF with trichloroethyl



SCHEME 4

butyrate as an acylating agent. In all cases the enzyme exhibited an overwhelming preference for the primary hydroxyl group in these molecules, but the yields were rather low.

Sweers and Wong[265] reported the selective hydrolysis of peracylated methyl hexopyranosides to occur at the primary position with 60–100% regioselectivity, in high yields. When α-D-glucoside **288** (R = C_4H_9), for instance, was subjected to CCL in aqueous buffer with 10% acetone as a cosolvent, the reaction gave exclusive hydrolysis at the primary position to afford the 6-hydroxy derivative **289** in 90% yield. Other corresponding sugars including D-galactose and D-mannose derivatives and the β-derivatives were good substrates for this enzyme and were hydrolysed selectively at the primary position. Similar results were obtained by Kloosterman and coworkers[266] for the regioselective deprotection of various acylated carbohydrates by PPL and CCL.

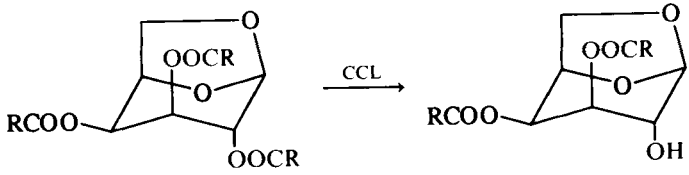


(288) **(289)**

Wong and coworkers[267] have described the selective acylation and deacylation of a number of furanose and pyranose derivatives in lipase-catalysed transesterifications. The primary hydroxyl functions of several methyl furanosides were selectively acylated by PPL in THF by employing trifluoroethyl acetate as an acyl donor. Good to excellent regioselectivity was achieved, as well as high yield, on several occasions. Highly selective cleavage of the primary hydroxyl functions in several peracylated methyl furanosides was efficiently accomplished with CCL in 10% DMF as a cosolvent and good to excellent yields. This lipase was also found to be the most suitable one for selective deacylation at the primary position for peracylated methyl pyranosides. On the other hand, PPL was the most suitable one for selective hydrolysis of the 1-*O*-acetyl groups of several pyranose pentaacetates, which occurred exclusively and in good yield. More

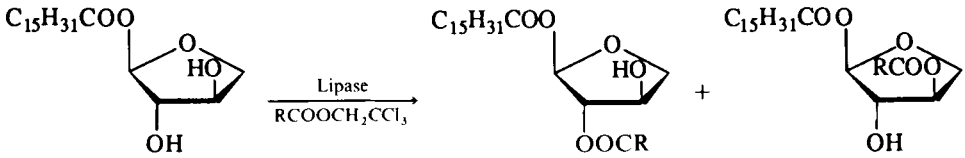
recently, Wong and coworkers[76] have described the application of a genetically engineered subtilisin mutant in the regioselective acylation of nucleosides in anhydrous dimethylformamide with high regioselectivity at the 5′-position.

Ballesteros and coworkers[268] employed CCL to carry out regioselective hydrolysis of the conformationally rigid β-D-galactopyranose derivative **290**. High regioselectivity was apparently obtained for the axially oriented *O*-butanoyl group in the C-2 position to afford the 3,4-di-*O*-butanoyl derivative **291**, apparently in high yield. Extended reaction times resulted in cleavage of the esters at C-3 and C-4, the equatorially oriented group at C-4 being preferentially cleaved to the axially oriented C-3 acyl ester.



(290) **(291)**

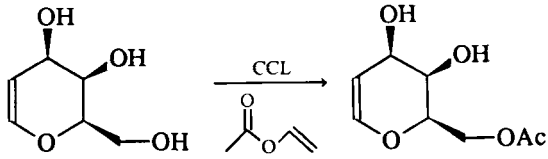
Nicotra and coworkers[269] described the regioselective acylation of secondary hydroxyl groups in 1,4-anhydro-5-*O*-hexadecyl-D-arabinitol **292** in dry benzene at 45 °C, employing trichloroethyl butyrate as an acylating agent. Complementary results were obtained from *Rhizopus japonicus* and *Humicula lanuginosa* lipases. The former one afforded the 3-*O*-acylated product **293** with good regioselectivity (86:14 for **293:294**) and 79% yield at 96% conversion, whereas the latter one afforded the 2-*O*-acylated product **294** with very high regioselectivity (3:97 for **293:294**) in 66% yield at 71% conversion, within 24 h. More recently, CCL was used to introduce regioselectively various ω-substituted acyl groups into the 3-*O*-position of **292** in moderate or low yields[270].



(292) **(293)** **(294)**

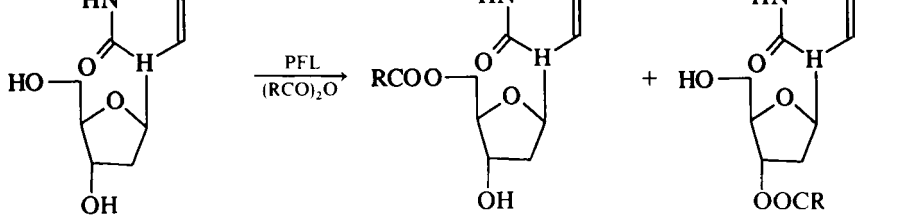
Björkling and coworkers[271,272] used an immobilized thermostable lipase from *Candida antarctica* to catalyse the highly efficient direct esterification of various alkyl-D-glucopyranosides with C_8–C_{18} fatty acids. The reaction took place at 70°C under reduced pressure to remove the water being generated in the absence of any solvent, and the products were obtained in 85–95% yields at 96% conversion (24 h). Interestingly, this non-specific lipase in terms of triglyceride hydrolysis was found superior to several 1,3-specific lipases in esterifying the primary alcoholic function of the substrate in a highly regioselective fashion.

The highly regioselective acetylations of D-glucal and D-galactal were described by Holla[273]. For instance, when D-galactal **295** was exposed to CCL in the presence of vinyl acetate, highly regioselective acetylation took place to afford the 6-*O*-acetyl-D-galactal **296** in 93% isolated yield in less than 1 h. Similar results were also obtained with PFL and for D-glucal, although the reactions were slower. The hydrolysis of the corresponding tri-*O*-acetyl glucal with PFL lead to the formation of the 4,6-di-*O*-acetyl-D-glucal, similarly in a highly regioselective fashion and excellent yield (90%).



(295) (296)

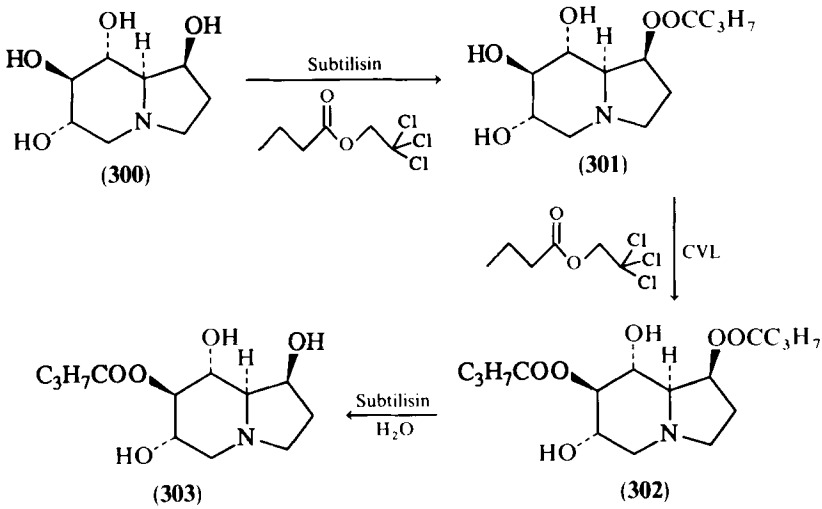
Uemura and coworkers[274] reported moderately regioselective acylation of 2′-deoxypyrimidine nucleoside **297** by PFL in anhydrous DMSO with hexanoic anhydride as an acyl donor at room temperature. Thus, the 5′-*O*-hexanoyluridine **298** (X = H, CH_3, Br, CF_3) was afforded in 75% yield together with the corresponding 3′-hexanoyluridine **299** in 22% yield at 96% conversion (24 h). The lipase was similarly employed to hydrolyse regioselectively the 3′-*O*-ester in 2′-deoxy-3′,5′-di-*O*-hexanoyl pyrimidine nucleoside to afford the monoester **298** with similar degree of regioselectivity at very high conversion (93–100%) (18 h), and in similar yield[275]. This appears to be the only report of a lipase not to act preferentially on the primary alcoholic function in a polyhydroxy substrate. Subtilisin was found to afford the complementary 3′-*O*-hexanoyluridine product **299**, however, in a far less regioselective fashion.



(297) (298) (299)

Margolin and coworkers[276] described a combinative enzymatic approach to regioselective esterification of castanospermine **300**, a potent plant alkaloid. Subtilisin was found to act highly regioselectively on **300** in anhydrous pyridine at 45°C with trichloroethyl butyrate as an acyl transfer agent to afford the monobutyrylated 1-*O*-acylcastanospermine **301** in 82% yield in 92 h. Even better results were afforded with vinyl acetate (91% yield) (84 h). CVL then exhibited high regioselectivity in the acylation of **301** to afford the corresponding 1,7-di-*O*-butyrylcastanospermine **302** in good yield (72%) and high regioselectivity (90:10), the 1,6-adduct being formed in low yield. This reaction took place in anhydrous THF with trichloroethyl butyrate as an acylating agent. Finally, subtilisin was employed in the regioselective hydrolysis of **302** to yield the 1-*O*-butyrylcastanospermine product **303** in an aqueous buffer containing 10% ethanol as cosolvent at 20 °C in 7 h in 64% yield with high regioselectivity (>25:1). The overall process is depicted in Scheme 5 and obviously represents a viable methodology towards the synthesis of individual esters of castanospermine as well as other amino sugars[277], which normally require multistep protection and deprotection processes.

Ronchetti and coworkers[278,279] were interested in the selective acylation of the unreactive 4-hydroxyl group in the naturally occurring 6-deoxy sugars L-rhamnose and L-fucose as their methyl α-pyranosides, **304**, and **305**, respectively, as well as their enantiomers D-rhamnose and D-fucose methyl α-pyranosides. PPL, CCL and PFL were

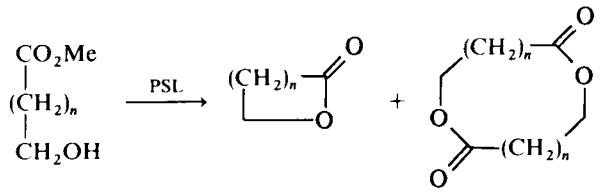


SCHEME 5

employed to regioselectively acylate these sugars in THF, THF/pyridine (4:1) and methylene chloride/acetone (4:1), respectively, with trifluoroethyl butyrate as an acyl transfer agent. The D-sugars were observed to afford the 2-butyrate as the main constituent in all cases, whereas the L-enantiomers exhibited different regioselectivity. Although extended reaction time was required (12 days) both PFL and PPL were able to acylate the 4-hydroxyl group of the L-series in a highly regioselective manner, especially the former enzyme.

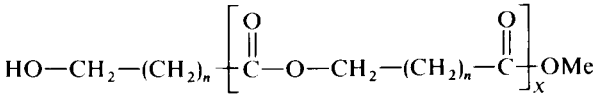
X. LACTONIZATION AND POLYCONDENSATION

Yamada and coworkers[280] described the preparation of macrocyclic lactones from several ω-hydroxyacid methyl esters **306** (n = 11,12,13,14) via lipase-catalysed intramolecular transesterification in organic solvents under high-dilution conditions. In benzene at 40 °C with PSL, the lactonization was observed to be dependent on the chain length of the substrate. For 16-hydroxyhexadecanoate (n = 14) and 15-hydroxypentadecanoate (n = 13) **307** was obtained in 80% yield (72 h) with very little of the diolide **308** being formed. Methyl 13-hydroxytridecanoate (n = 11), on the other hand, yielded only 38% of the lactone **307** and 25% of the diolide **308**. When the racemic methyl 10-hydroxyundecanoate was used as a substrate, the lipase was found to exhibit preference for the *R*-enantiomer.



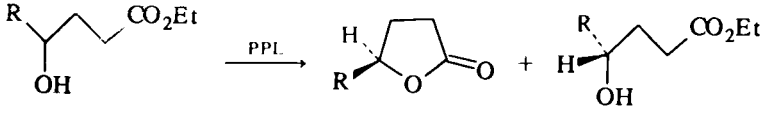
(306) (307) (308)

Gutman and coworkers[281] similarly examined the lipase-catalysed intramolecular transesterification of shorter-chain ω-hydroxyesters. They showed that PPL can act as a highly stereoselective catalyst for intramolecular transesterification of γ-hydroxesters in dry ether and prepared optically pure substituted γ-lactones in high yields. When unsubstituted β-, δ- and ε-hydroxyacid methyl esters were submitted to PPL, they almost exclusively underwent intermolecular transesterification to afford the corresponding oligomers **309**[282]. In contrast, the racemic secondary alcohol δ-methyl δ-hydroxyester underwent lactonization, and, as with γ-hydroxyesters, the reaction slowed down considerably near 50% conversion, indicating that an enantioselective process was taking place.



(309)

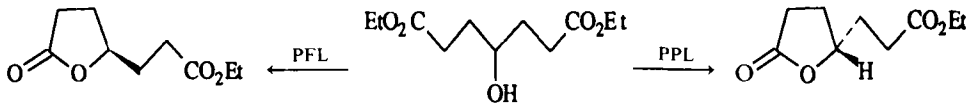
Gutman and coworkers[283] have very recently extended this work to the synthesis of optically pure γ-butyrolactones **311** from esters of racemic γ-hydroxy esters **310** (R = various alkyl and aryl groups) with PPL in dry hexane. The γ-alkyl substituted substrates reacted much faster than the γ-aryl substituted ones, but even so the rates of the latter were acceptable. At lower conversion (30–40%) high enantioselectivity was obtained for the lactones (*S*)-**311** (R-alkyl) and (*R*)-**311** (R-aryl) 82–>98% ee). At higher conversion (60%) the corresponding enantiomeric hydroxy esters **312** were obtained in, e.g., ee > 95% for R = methyl and were converted to the corresponding opposite enantiomeric lactone. In both reaction rates and stereoselectivity, the α-substituted γ-hydroxyesters were very poor substrates for the lipase.



(310) (311) (312)

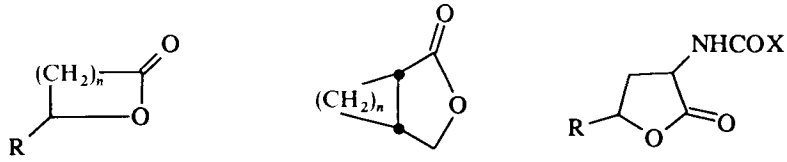
Gutman and coworkers[283,284] described the enantioselective lactonization of prochiral γ-hydroxy diesters. Thus, when the prochiral γ-hydroxypimelate ester **313** was submitted to PPL in hexane at 40 °C, the γ-lactone (*S*)-**314** was afforded in >98% ee at 100% conversion. However, when PPL was replaced by PFL, reverse enantiotopic group preference was observed and the antipode (*R*)-**314** was afforded, but in only 32% ee at 100% conversion.

It is also possible to obtain optically active lactones by lipase-catalysed enantioselec-



(*R*)-(**314**) (**313**) (*S*)-(**314**)

tive hydrolysis of racemic lactones. Blanco and coworkers[285] employed PPL, horse liver esterase and PLE to hydrolyse alkyl substituted γ-, δ- and ε-lactones of the type **315** (n = 2,3,4, respectively) (R = C_2H_5, C_3H_7, C_5H_{11} or C_7H_{15}). For γ-butyrolactone the best results were obtained with the lipase, which displayed preference for the *S*-enantiomers. At 55% conversion the *R*-enantiomers were isolated in 60–76% ee. For δ-valerolactone (n = 3) the horse liver esterase gave the best results and reverse preference for the *R*-enantiomers, and the *S*-lactones were afforded with 92% ee. With ε-caprolactones moderate enantioselectivity (72% ee) was obtained with the esterases, which displayed opposite configurational preference. In the case of the γ- and δ-lactones the initial hydroxyacids (40–50% ee) were relactonized chemically and resubjected to the enzymes to afford the hydroxy acids of high optical purity at approximately 40% conversion.



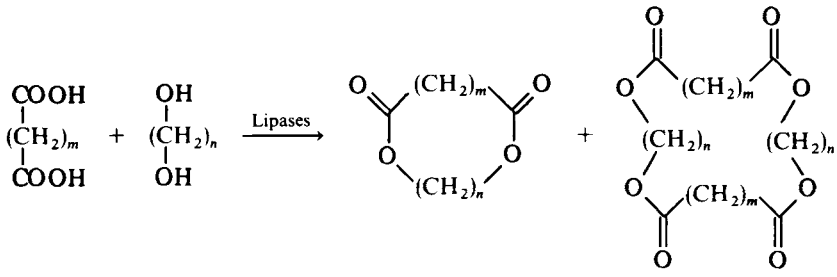
(**315**) (**316**) (**317**)

The same group has also reported on the preparation of optically active *cis*-fused bicyclic γ-lactones by enantioselective hydrolysis of substrates **316** (n = 1,2,3) catalysed with horse liver esterase[286]. High yields and very high optical purity was obtained for the smallest carbocyclic ring lactone (n = 1) (98% ee) at 55% conversion. Finally, the group of Gutman recently reported the hydrolysis of γ-substituted N-protected α-aminobutyrolactone of the type **317**[287] in which PPL yielded both the unreacted and the relactonized product in moderate to high optical purity at 27–50% conversion.

Klibanov and coworkers[288] used several lipases to catalyse stereoselectively polycondensation reactions between racemic diesters and achiral diols, or achiral diesters and racemic diols, in organic solvents to prepare optically active oligomers, the products mainly composed of trimers and pentamers. Wallace and Morrow[289] further developed this process to accomplish high molecular weight optically active polymers.

Guo and Sih[290] reported lipases to catalyse the formation of macrocyclic lactones by the condensation of diacids **318** and diols **319** in anhydrous nonpolar organic solvents such as the isooctane. Di- and tetralactones, **320** and **321**, were the main products of this reaction, accompanied by linear oligomeric esters, with yields depending upon the type of substrates as well as on the reaction conditions. Higher temperature (55–75 °C) favoured lactonization, whereas at lower temperature ($\leq$45 °C) oligomeric esters became the predominant products. The lipases could accommodate acyclic diacids (m = 2–12) and diols (n = 5–16) of various sizes, but the optimum yield of lactones was achieved for ring sizes in the range of 24–28. The most suitable lipases for these transformations were CCL, PSL and PPL.

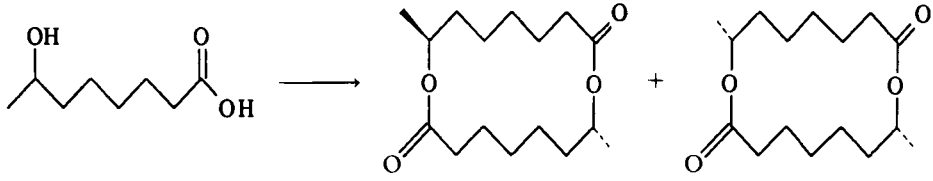
Sih and coworkers[291] investigated the lactonization of medium-size hydroxy acids with several lipases. The product constitution was considerably more complex than anticipated and was dependent on the length of the hydroxy acid, the lipase and the



(318) (319) (320) (321)

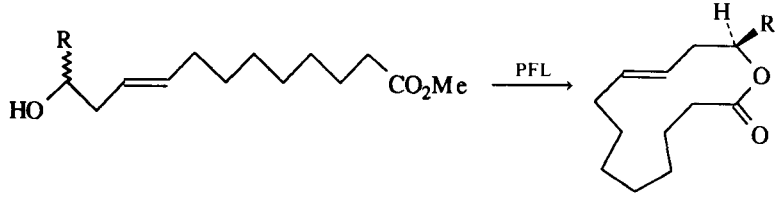
reaction conditions. With 10-hydroxydecanoic acid and several lipases in isooctane, no decanolide was detected. Instead, a complex mixture of di-, tri-, tetra- and pentalactones were formed in different ratios, depending on the lipase used. For example, PSL and PPL afforded di- and trilactones as the major products, whereas the lipases CCL and MML gave mostly tri- and tetralactones. On the other hand, hexadecanolide was found to be the dominant product on exposure of 16-hydroxyhexadecanoic acid to the lipases, confirming previous reports.

Lipase-catalysed lactonization of chiral hydroxy acids to form diolides was also investigated by Sih and coworkers[291]. Thus 7-hydroxyoctanoic acid **322** with PSL in isooctane at 25 °C for 144 hours gave the dilactone in only 17% yield, together with tri- (7%) and tetralactone (2%). Analysis of the dilactone fraction revealed the formation of two diastereomeric dilactones (*R*, *S*)-**323** and (*R*, *R*)-**324** in the ratio of 1:2.4. The enantioselectivity in the formation of **324** was very high, the ratio of (*R*, *R*) to (*S*, *S*) being 96:4 (92% ee)[105].



(322) (*R*, *S*)-(323) (*R*, *R*)-(324)

Finally, Ohta and coworkers[292] studied the lipase-catalysed macrolactonization of hydroxyacid esters in organic solvents. With PFL in isooctane in the presence of molecular sieves under high-dilution conditions at 65 °C, the racemic long-chain hydroxy acid methyl ester **325** (R = C_6H_{13}) underwent lactonization in a highly enantioselective fashion to afford the 13-membered lactone (*R*)-**326**, optically pure, at 87% conversion



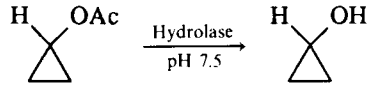
(±)-(325) (*R*)-(326)

in 18% yield. The presence of a double bond in the acyl part was found to favour the formation of the monomeric product. The yields were dependent on the chain length of R.

XI. MILDNESS AND MISCELLANEOUS REACTIONS CATALYSED BY LIPASES

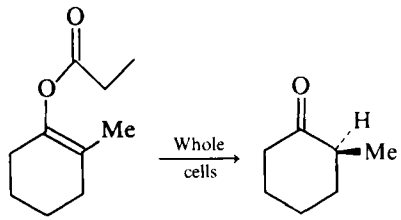
In earlier work, yeast lipase[293] and PPL[294,295] were used for the hydrolysis of the methyl ester function of highly labile prostaglandin precursor derivatives to the corresponding acids to avoid undesired side reactions in high to excellent yield.

Jongejan and Duine[296] employed several lipases and PLE for hydrolysis of cyclopropanol acetate **327** at pH 7.5 to avoid complications accompanying conventional chemical methods. The resulting cyclopropanol **328** was isolated in 95% yield and PLE was found to exhibit the highest activity towards this substrate.



(327) **(328)**

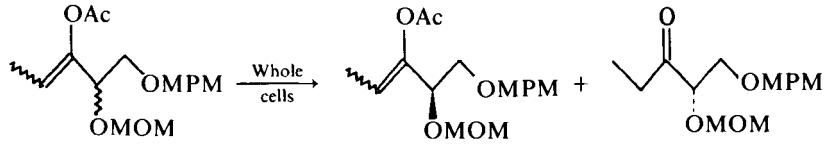
Quite remarkably, Ohta and coworkers[297] have succeeded in what they call enantioface-differentiating enzyme hydrolysis of enol esters. This means that simultaneously with the hydrolysis of the acyl group, protonation occurs from one specified side of the double bond of the enol ester without formation of an enol intermediate. If the double bond of the enol ester is appropriately substituted, the resulting ketone will be optically active. Such a reaction requires an enzyme with the ability to differentiate enantiotopic faces. When several α-substituted cyclohexanone enol esters were incubated at 30 °C with microbial cells from *Pichia mico*, very good results were obtained, with the propionyl ester **329** as a substrate. The chiral product **330** was obtained in 98% yield with 94% ee, in the *S*-configuration. Ohta and coworkers[298] have also reported the highly successful application of this methodology to a whole variety of α-substituted cycloalkanone enol esters, including medium-ring cyclic ketones, i.e. eight-, ten- and twelve-membered rings.



(329) **(*S*)-(330)**

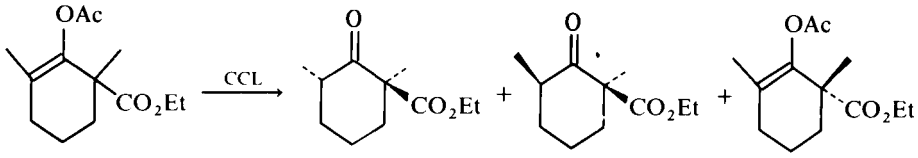
Matsumoto and Ohta[299] have modified this procedure for obtaining optically active α-substituted ketones by kinetic resolution of enol esters already possessing a chiral centre. When, e.g., substrate **331** was exposed to whole cells from the bacterium *Bacillus coagulans* and the reaction allowed to proceed well beyond 50% conversion, the optically active enol acetate (*R*)-**332** and the ketone (*S*)-**333** were obtained in 33 and 64% yield, respectively. As expected, the enantiomeric excess of the ketone was rather low (42% ee), but the enol acetate was afforded in 95% ee. In order to generate the chiral ketone

corresponding to (*R*)-**332**, CCL was employed to afford the ketone in excellent yield (96%), without any racemization.



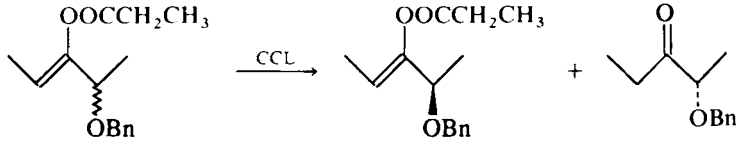
(**331**) (*R*)-(**332**) (*S*)-(**333**)

In their attempt to synthesize both enantiomers of deoxypodocarpic acid methyl ester, useful intermediates for the synthesis of various diterpenes, Ohta and coworkers[300] tried whole cells from both *Pichia miso* and *Bacillus coagulans* for hydrolysis of (±)-**334**. No satisfactory results were obtained, but when they applied CCL, good diastereoselectivity was obtained in that the ratio of the ketones **335** and **336** was 1:45 at 45% conversion, although only with moderate enantioselectivity (55% ee). On the other hand, the enol acetate (*R*)-(+)-**334** was obtained in good yield and with >99% ee, with the *S*-enantiomer of enol acetate **334** preferentially hydrolysed.



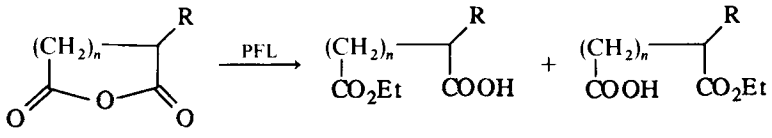
(±)-(**334**) (+)-(**335**) (−)-(**336**) (*R*)-(**334**)

Ohta and his collaborators[301] have similarly used CCL to prepare several optically active protected α-hydroxy ketone derivatives. For instance, when the racemic substrate **337** was incubated, optically pure *R*-enol propionate **338** was afforded (99% ee), but in low yields (12%) at a high conversion, together with the *S*-ketone **339**, in low optical purity. The latter could be racemized and the enzymatic hydrolysis repeated to increase the efficiency of the process. This methodology has been applied in the stereoselective synthesis of (+)-*endo* and (+)-*exo* brevicomins by Ohta and coworkers[302].



(**337**) (*R*)-(**338**) (*S*)-(**339**)

Hiratake and collaborators[303] reported the highly regioselective irreversible ring opening of α-substituted cyclic acid anhydrides **340** (R = Me, *i*-Pr, Ph, OBu; n = 1,2) by PFL in diisopropyl ether in the presence of ethanol. The reaction preferentially occurred at the less hindered carbonyl group to afford the corresponding racemic monoesters **341** and **342** in excellent yields. The regioselectivity was found to improve by increasing the size of the substituent R and was almost complete for R = *i*-Bu and Ph. For R = OBu, electronic and steric factors were found to compensate each other and an approximately 1:1 mixture of **341** and **342** was obtained.



(340) (341) (342)

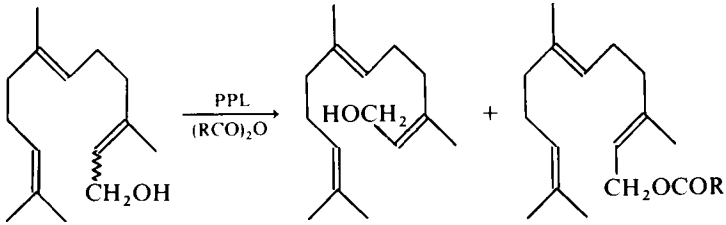
Gotor and coworkers[304] used CCL to catalyse the formation of propargylamides **343**, usually in high yields (80–85%), when reacting ethyl propionate and aromatic amines in tetrachloromethane at 25 °C. Under these conditions, the competing Michael addition, leading to adduct **344**, was apparently impeded due to the mild reaction conditions.

$$HC{\equiv}C{-}CONHAr \qquad ArNHCH{=}CH{-}CO_2Et$$

(343) (344)

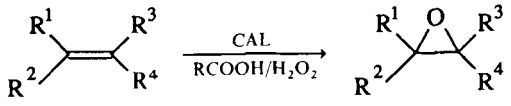
This group also reported highly diastereoselective preparation of diamides by the enzymatic aminolysis of racemic ethyl 2-chloropropionate with diamines[305]. 100% diastereoselectivity was obtained with CCL, which also showed high enantioselectivity (88% ee) and opposite configurational preference to both PFL and subtilisin. They also reported the enantioselective aminolysis of racemic ethyl 2-chloropropionate with racemic amines using CCL and subtilisin[306]. In most cases high enantioselectivity was obtained and moderate to good diastereoselectivity.

Fourneron and coworkers[307] used anhydrides as acyl donors with PPL for the diastereoselective acylation of several terpenic allylic alcohols containing a mixture of geometrical isomers. The lipase preferentially catalysed the acylation of the *E*-isomer. As an example, when 2*E*/*Z*,6*E* farnesol **345**, as a 67:33 *E*/*Z* mixture, was subjected to the lipase in ether with hexanoic anhydride, the unreacted alcohol was obtained as the pure *Z*-isomer (99%) (2*Z*, 6*E*)-**345** in 40–45% yield after 6–12 h. The *E*-enriched ester product was hydrolysed and resubmitted to the lipase to afford the *E*-isomer (2*E*, 6*E*)-**346** in a pure (98%) state in 50–60% yield.



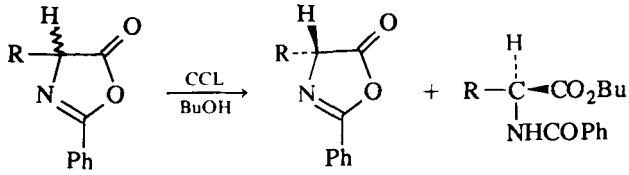
(2*Z*/*E*, (6*E*)-(**345**) (2*Z*, 6*E*)-(**345**) (2*E*, 6*E*)-(**346**)

Björkling and coworkers[308] used lipases to catalyse the epoxidation of alkenes under very mild conditions. In the presence of a catalytic amount of a medium-chain (C_4–C_{10}) carboxylic acid, hydrogen peroxide and an olefin, in hexane at room temperature, several lipases were able to generate the corresponding peroxycarboxylic acid, which concurrently epoxidized the olefin. The best results were obtained with the immobilized yeast lipase from *Candida antarctica* (CAL). For example, a quantitative yield was obtained with tetramethylethylene **347** to afford epoxide **348** in 4 h. This method provides a very mild alternative to the highly acidic conditions usually applied for the *in situ* generation of peroxycarboxylic acids.



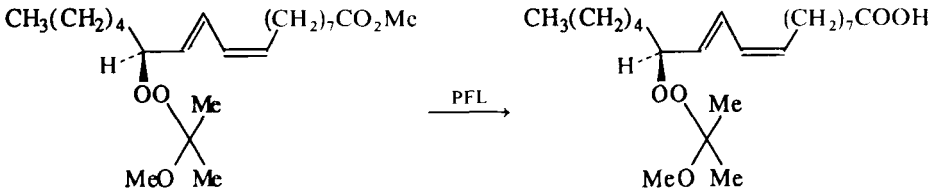
(347) (348)

Bevinakatti and coworkers[309] used MML for the ring opening of azlactone **349** with butanol to produce the amide ester (*S*)-**350**. The enantioselection was only 57% ee at 45% conversion, but optically pure product could be obtained by recrystallization. The remaining azlactone was isolated as a racemate, indicating that an *in situ* racemization was taking place. This was confirmed by allowing the reaction to attain 100% conversion at which the isolated S-enriched product had 34% ee. In the presence of water, azlactones undergo spontaneous hydrolysis.



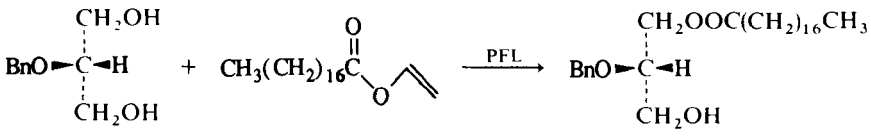
(±)-(**349**) (*R*)-(**349**) (*S*)-(**350**)

Matsuo and coworkers[310] have described a remarkable asymmetric synthesis of a diacylglycerophosphocholine hydroperoxide involving both lipoxygenase and lipase. The lipoxygenase was used to introduce a hydroperoxy function into γ-linolenic acid. PFL was then employed to hydrolyse in 99% yield the resulting methyl ester derivative, protected as a perketal, **351**, under mild conditions, without affecting the perketal protection moiety of the molecule, to afford the corresponding acid **352**.



(**351**) (**352**)

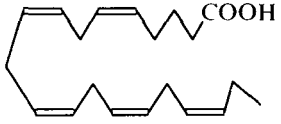
In the same synthesis PFL was again used to enantioselectively acylate the prochiral adduct **353** at the *sn*-1 position by vinyl stearate to afford 1-stearoyl-2-O-benzyl-*sn*-glycerol **354** with high 92% ee and 50% yield. (*sn* = stereochemical numbering).



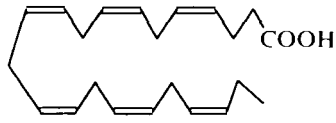
(**353**) (**354**)

Lipases have been exploited to a considerable extent in the field of fats and oils[20,311–313]. In enzymatic fat hydrolysis the mildness offered by lipases is of high advantage, particularly when more unstable oils containing conjugated or highly unsaturated fatty acid residues are involved. The discovery that lipases are active under anhydrous conditions is of great benefit for the fats and oils industry and has had an enormous impact on research activity in that field. Transesterification (acidolysis and interesterification) processes have been developed for modification of fats and oils, e.g., in the production of fats mimicking the properties of the highly valuable cocoa-butter. Direct esterification has also been used either to produce monoglycerides or triglycerides. In the latter case Ergan and coworkers[64,314] esterified glycerol with oleic acid in the absence of any solvent to produce over 90% pure triglycerides. The water generated during the process was removed by the presence of molecular sieves. Okahata and Ijiro[315] have applied their lipid-coated *Pseudomonas fragi* lipase as a soluble catalyst to effect the synthesis of di- and triglycerides from monoglycerides and aliphatic acids in organic solvents, such as benzene and n-hexane, in the presence of molecular sieves. Similar procedures have been employed to prepare wax esters directly from fatty acids and fatty alcohols[316,317].

The mildness of the lipases is especially useful for transformations involving long-chain polyunsaturated ω-3 type fatty acids, such as eicosapentaenoic acid **355** and docosahexaenoic acid **356**, which are characteristic of marine oils. These fatty acids are highly labile, and procedures that involve extremes of pH or high temperature may partially destroy their natural all-*cis* framework by oxidation or by *cis–trans* isomerization.



(355)



(356)

Haraldsson and coworkers[83,318–320] have employed the immobilized bacterial MML to prepare triglycerides highly enriched with these fatty acids. This was accomplished either by interesterification or acidolysis of cod liver oil with ethyl ester and free fatty acid concentrates, respectively, without a solvent. The lipase was observed to exhibit a strong preference for **355** as compared to **356**[318], a feature that has been utilized for fractionation of these fatty acids by selective esterification[321,322] by this lipase and selective hydrolysis[323] by several other lipases as well. Very recently, Haraldsson and coworkers[65,324] have succeeded in preparing homogeneous triglycerides of both **355** and **356** by a lipase-catalysed interesterification. In the presence of an immobilized *Candida antarctica* lipase, tributyrin was reacted with stoichiometric amount of ethyl esters of 99% pure eicosapentaenoic acid or docosahexaenoic acid to produce pure triglycerides of either fatty acid. High vacuum was applied under solvent-free conditions to remove the ethyl butyrate generated during the reaction to shift the equilibrium towards completion.

XII. ACKNOWLEDGEMENT

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CHAPTER **25**

Diazoacetic acids and derivatives

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ABBREVIATIONS

ACC	alkoxycarbonylcarbene
ADA	alkyl diazoacetate
BSA	*N*-benzylsalicylaldiminato
DMAD	dimethyl acetylenedicarboxylate
DBU	1,4-diazabicyclo[2.2.2]undecene
DCCD	dicyclohexylcarbodiimide
EDA	ethyl diazoacetate
MDA	methyl diazoacetate
MDM	dimethyl diazomalonate
TBDMS	*t*-butyl(dimethyl)silyl
TEBA	triethylbenzylammonium halogenide

I. INTRODUCTION

The beginning of the diazoacetic acid chemistry dates back to 1883, when Curtius synthesized ethyl diazoacetate N_2CHCO_2Et (EDA)[1]. Since then this branch of organic chemistry has been developing steadily, revealing many new fields for the application of these molecules. The tremendous synthetic potential of diazoesters stems from the presence of three reaction centers in the molecule which can react independently of each other: a diazo group, a mobile hydrogen atom in the α-position and an alkoxycarbonyl group.

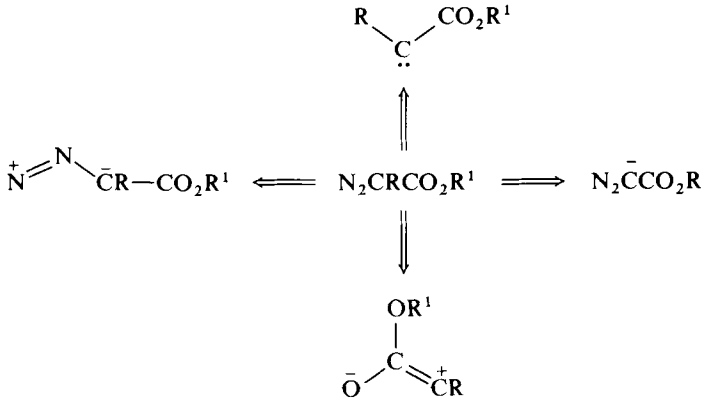
All transformations of diazoacetic acid derivatives may be subdivided into two large groups: reactions with diazo group preservation and reactions with nitrogen elimination. A number of transformations, connected with each of the three reaction centers, can be distinguished in each of these groups.

Reactions, proceeding with nitrogen elimination and generation of carbenes or of their complexes with transition metals, are very diverse. These transformations of diazoesters are the best known and have been widely used practically since the discovery of EDA, for the production of carbofunctional cylopropane and cyclopropene derivatives. In recent years, due to the development of new, highly effective catalysts based on rhodium(II) compounds, carbene reactions of diazoesters could also be used for carboxymethylenation of compounds with saturated bonds. Examples are also known when the carbene generated by the dediazotation of a diazoester behaves in cycloadditions to multiple bonds as a 1,3-dipole.

An active hydrogen atom at the diazo group is capable of being rather easily substituted by metal atoms with the formation of α-metallated diazoesters. Chemical transformations of these derivatives, in their turn, made it possible to synthesize functionally substituted diazoesters, the intramolecular transformations of which were used in the synthesis of analogs of important natural polycyclic compounds.

The diazoester molecules were also functionalized through transformations of the carboxyl and alkoxyl moieties. Finally, the molecules of diazoacetates can react as 1,3-dipoles in cycloadditions to compounds containing multiple bonds. This group of transformations enables the synthesis of diverse nitrogen-containing heterocycles.

The large body of accumulated data permits one to regard diazoacetic acid and its derivatives as important reagents of organic synthesis. Actually, these molecules may be regarded as synthetic equivalents of the various synthons shown in Scheme 1.



SCHEME 1

This circumstance accounts for the continued interest of synthetic chemists in this class of compounds. During the past 20 years several voluminous reviews have been published, devoted to different aspects of diazo chemistry[2—14]. However, the latest review[4], devoted specifically to diazoester chemistry, dates back to 1974, and the diazoesters are treated in it only as precursors of alkoxycarbonylcarbenes (ACC), whereas reactions with diazo group preservation as well as methods of diazoester synthesis are not discussed in the review.

In the present review we tried to give a systematic survey of all aspects of diazoester chemistry in organic synthesis. The material discussed is mainly restricted to publications in the last decade. Nevertheless, in some cases earlier studies are also considered, if the logic of exposition demands it or if the studies in question are only little known to the scientific community.

In order to enable a more complete review of the synthetic potentialities of diazoester reactions, our treatment of the mechanistic aspects of the given transformations is intentionally brief; in some cases we did not even consider them at all, restricting ourselves to references dealing specifically with such questions. Many interesting publications devoted to the physicochemical investigation of the structure and properties of diazoesters do not enter into the scope of the present review as well. In this connection it should be noted that, for example, the behavior of diazoesters under conditions of electrolysis and EI, as well as their thermodynamic and thermochemical characteristics were recently reviewed by McDonald[15]; FTMS investigations of EDA were carried out by Wilkins' group[16] and a NMR ^{15}N study was published by Volpin and coworkers[17].

In accordance with the above-stated classification the main contents of this review are divided into three sections, devoted to the methods of creating the diazo group, to reactions with diazo group preservation and to transformations proceeding with nitrogen elimination.

II. METHODS OF DIAZO GROUP FORMATION

The present-day arsenal of methods used to produce diazoacetic acid derivatives may be subdivided into two large groups. The first group comprises reactions which generate the diazo group in the precursor molecule; the second group comprises processes in which the molecules of diazo compounds undergo transformations with diazo group retention. Only the first group of reactions is considered in this section. The methods involving transformations of diazo compounds are discussed in Section III.A

A. Diazotation of Amino Acid Esters

Diazotation of the hydrochloride of glycine ethyl ester was proposed by Curtius, as a method of EDA production, as long ago as the turn of the last century[1,18]. Since then different updated versions of the classical Curtius scheme have been widely used in research and, since the late 1940s, in chemical manufacturing as well[19]. Though this method consists of two reactions, namely the synthesis of amino acid esters followed by their diazotation, in practice both reactions are often carried out without isolation of the amino acid esters. Nevertheless, in view of the decisive importance of the synthesis of the amino acid esters for the entire process as a whole, these reactions are considered by us separately in Section II.A.2.

1. Diazotation

Diazotation of amino acid esters is the simplest method of diazoester production. The diazotizing agent is usually nitrous acid obtained from sodium nitrite[20] (see equation 1).

$$HX \cdot H_2NCH_2CO_2R + NaNO_2 \xrightarrow[-H_2O,\ -NaX]{H_3O^+} N_2CHCO_2R \qquad (1)$$

The diazotation reaction is usually accompanied by the decomposition of the alkyl diazoacetates (ADA) under the action of the acid. In the case of hydrochlorides this process leads to monochloroacetic acid esters. To inhibit this side reaction, a number of procedures are resorted to, aimed at optimizing the pH and reducing the time of contact of ADA with the acid. As a rule, the reaction is carried out in a two-phase water–organic solvent system; in this case the resulting ADA passes into the organic

phase and has only short contact with the acid. It is most preferable to use as solvents halogenated hydrocarbons, which stabilize the ADA[21,22]. Periodic extraction of the ADA with fresh portions of the solvent[23–25] or carrying out the process in a continuous mode[26,27] contribute to the contact time reduction.

The diazotation is sensitive to the value of the pH of the medium. At pH < 3 the acid decomposition of the ADA is intensified, at pH > 5 the diazotation reaction is decelerated strongly. The optimal pH value of 3–5 is maintained by adding periodically 4–8 M sulfuric[24,25,28] or 2.8% hydrochloric acid[29] or by using buffer solutions. In practice an acetate buffer with a pH of 3.0–3.5 is commonly used, when the formation of monochloroacetic acid esters is reduced from 10 down to 1.5%[23,25,30–33]. The use of a borate buffer with pH 4.5–5.0 makes it possible to work without an organic solvent and to obtain pure EDA directly in the aqueous solution of $NaNO_2$ at 20 °C with the yield of 97%[34]. To purify the ADA from by-products, it is distilled with steam in the presence of $Ba(OH)_2$[35].

Systematic studies of the effect of substituents in the alcoholic part of the molecule on the yield of the diazoesters have not been carried out. Nevertheless, the application of this method to glycine gave a number of functionally substituted diazoesters, described in Section II.A.2.

Diazotation with sodium nitrite is usually limited to the production of diazoacetic and diazopropionic acids esters. Other α-substituted diazoacetates are usually produced by using alkyl nitrites as the diazotizing agent, the yield in the case of α-phenyldiazoacetate reaching 86%[29,36,37] (see equation 2).

$$\mathrm{PhCH_2CHCO_2Et} \xrightarrow[\mathrm{AcOH,\ CHCl_3}]{i\text{-}\mathrm{C_5H_{11}NO_2}} \mathrm{PhCH_2CCO_2Et} \quad (2)$$
$$\mathrm{NH_2} \qquad\qquad \mathrm{N_2}$$
$$86\%$$

2. Synthesis of amino acid esters

The synthesis of amino acid esters is a traditional task of the peptide chemistry and can be realized in different modifications[38,39]. Often one of the simplest methods of esterification is employed, based on the use of the corresponding alcohol in the presence of anhydrous hydrogen chloride[40] (see Scheme 2).

$$\mathrm{H_2NCH_2CO_2H + ROH + HCl} \xrightarrow[-\mathrm{H_2O}]{\text{reflux}}$$

$$\mathrm{HCl \cdot H_2NCH_2CO_2R} \xrightarrow[\mathrm{H_2SO_4}]{\mathrm{NaNO_2}} \mathrm{N_2CHCO_2R}$$

SCHEME 2

In this reaction hydrogen chloride behaves both as an esterification catalyst, and as a protective agent precluding the formation of 2,5-diketopiperazines as by-products[41]. To shift the equilibrium in the esterification, a large excess of alcohol is usually used. In this way C_1–C_{10}-alkyl esters can be obtained, and also some functionally substituted glycine esters in yields of 60–90%, e.g.

$$\mathrm{HCl \cdot H_2NCH_2CO_2CH_2CH_2Cl}^{42},\ \mathrm{HCl \cdot H_2NCH_2CO_2CH_2CH_2OH}^{43}$$

and

$$\mathrm{HCl \cdot H_2NCH_2CO_2CH_2CH_2OCOCH_2NH_2 \cdot HCl}^{43}.$$

Concentrated hydrobromic acid may also be used for the esterification. Thus, the hydrobromide of glycine 2-bromoethyl ester is obtained by esterification by ethylene bromohydrin, generated *in situ* by the action of hydrobromic acid on ethylene glycol; excess water is removed by azeotropic distillation with benzene, and the resulting glycine ester is diazotated without isolation[44] (see Scheme 3).

$$H_2NCH_2CO_2H + HOCH_2CH_2OH \xrightarrow[-H_2O]{48\%\ HBr,\ C_6H_6} HBr \cdot H_2NCH_2CO_2CH_2CH_2Br$$

$$\xrightarrow[AcONa/AcOH]{NaNO_2} N_2CHCO_2CH_2CH_2Br \text{ (total yield 55\%)}$$

SCHEME 3

In another frequently used version of this process esterification is carried out in the presence of $SOCl_2$, which, reacting with the alcohol, gives hydrogen chloride, that protects the amino group, and alkyl sulfites, that bring about esterification of the amino acid[45,46]. As a result, the reaction proceeds faster and with a smaller excess of the alcohol (see equation 3).

$$H_2NCH_2CO_2H + ROH + SOCl_2 \xrightarrow[-SO_2]{} HCl \cdot H_2NCH_2CO_2R \qquad (3)$$

R = alkyl, $PhCH_2$

For the esterification of alcohols with low reactivity TosOH is employed, as in the synthesis of glycine butylthioethyl ester and of the corresponding diazoacetate (see Scheme 4).

$$H_2NCH_2CO_2H + HOCH_2CH_2SBu + TosOH \xrightarrow[-H_2O]{\text{toluene, reflux}}$$

$$TosOH \cdot H_2NCH_2CO_2CH_2CH_2SBu \xrightarrow[AcONa/AcOH]{NaNO_2}$$

$$N_2CHCO_2CH_2CH_2SBu \text{ (total yield 20\%)}$$

SCHEME 4

It has been found recently that concentrated H_2SO_4 has advantages for the production of ADA[48]. In this case stoichiometric quantities of the reagents are used and the reaction mixture for the preparation of glycine esters is subjected directly to diazotation. This substantially simplifies the process and makes it promising commercially (see equation 4).

$$H_2NCH_2CO_2H + ROH + H_2SO_4 \xrightarrow[2.\ NaNO_2]{1.\ 70\ ^\circ C} N_2CHCO_2R \qquad (4)$$

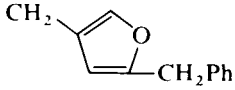
R = alkyl C_1–C_7 50–85%

If the direct esterification produces esters not stable to the action of acids of $SOCl_2$, milder methods have to be used in which stable precursors of amino acids rather than amino acids themselves are subjected to esterification. Thus, arylmethyl and hetarylmethyl diazoacetic acid esters are synthesized from monochloroacetic acid esters in several stages[49], as shown in Scheme 5.

According to another method, glycine esters are synthesized by esterification of a K-salt of an N-protected amino acid with a halogen derivative, followed by removal of the protective group by treatment with HCl, CF_3CO_2H or TosOH[50]. A modification of this method made it possible to extend it to the synthesis of allyl, propargyl, cyano-, acyl-, alkylthio- and imidoalkyl esters of diazoacetic acid[48,51] (see Scheme 6).

$$ClCH_2CO_2R \xrightarrow{NaN_3} N_3CH_2CO_2R \xrightarrow[2.\ HCl]{1.\ H_2/Raney\text{-}Ni} HCl\cdot H_2NCH_2CO_2R$$

$$HCl\cdot H_2NCH_2CO_2R \xrightarrow[pH\ 4,9]{NaNO_2} N_2CHCO_2R$$

R = $CH_2C_6H_{5-m-n}Cl_mF_n$ (*m*, *n* = 0–5), $CH_2C_6H_4OPh$-3, CHC_6H_4OPh-3 (CN), 

SCHEME 5

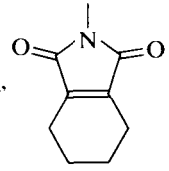
$$H_2NCH_2CO_2H \xrightarrow[60\ ^\circ C,\ MeOH,\ 2\text{–}4h]{EtO_2CCH_2Ac,\ KOH} EtO_2CCH{=}CMeNHCH_2CO_2K \xrightarrow[DMF,\ 18\text{-}C\text{-}6]{RCH_2X,\ 65\ ^\circ C}$$

$$EtO_2CCH{=}CMeNHCH_2CO_2CH_2R \xrightarrow[ether]{HA,\ 30\ ^\circ C}$$

$$HA\cdot H_2NCH_2CO_2CH_2R \xrightarrow[AcOH,\ AcONa]{NaNO_2} N_2CHCO_2CH_2R$$

total yields 40–80%

HA = HCl, TosOH

R = H, alkyl C_1–C_9, $CH{=}CMe_2$, $C{\equiv}CH$, $C{\equiv}N$, MeCO, PhCO, CH_2SR^1, 4-ClC_6H_4, 3-$PhOC_6H_4$, 

SCHEME 6

B. Diazo Transfer Reactions

The method of diazo transfer is based on the base-catalyzed reaction between sulfonyl azides and compounds containing a methylene fragment activated by a carbonyl group (see Scheme 7). The yields of diazoesters range from 60 to 80%, depending on the activity of the methylene group and on the type of the azide and base used.

$$RCH_2CO_2R^1 \xrightarrow[-HB^+]{B} RCH^-CO_2R^1 \xrightarrow{N_3Tos}$$

$$TosN^-N{=}NCHCRCO_2R^1 \xrightarrow[-HNTos]{} N_2CRCO_2R^1$$

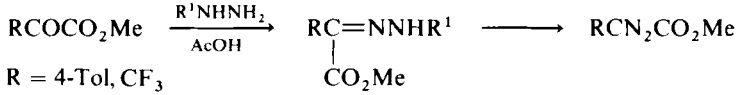
SCHEME 7

This method is usually employed for the production of diazomalonates $N_2C(CO_2R)_2$[52–59] and α-acyldiazoacetates $N_2C(COR^1)CO_2R$[55,56,60–63]. The following substances were synthesized with the help of this method: α-substituted diazoacetates, e.g. $N_2CAlkCO_2R$[59], aryldiazoacetates N_2CArCO_2R[64], diazoamidoacetates $N_2C(CONR^1R^2)CO_2R$[65–67], α-thiocarbonyldiazoacetates $N_2C(COSR^1)CO_2R$[57], α-sulfonylcarbonyldiazoacetates $N_2C(SO_2R^1)CO_2R$[68], α-nitrodiazoacetates $N_2C(NO_2)CO_2R$[69], phosphorus derivatives of diazoacetates $N_2C[PO(OR^1)_2]CO_2R$[70–72] and α-vinyldiazoacetates $MeO_2CCH{=}CHCN_2CO_2R$[73].

Besides tosyl azide, it is possible to use mesyl[74,75], *p*-carboxybenzenesulfonyl, *p*-chlorobenzenesulfonyl[76], trifluoromethanesulfonyl[76,77], *p*-nitrophenylsulfonyl azides[76], (azidochloromethylene)dimethylammonium chloride[78], *p*-(dodecyl)benzenesulfonyl and naphthalene-2-sulfonyl azide[79] as donors of the diazo group. NEt_3 and $NHEt_2$ are the bases usually used. Successful examples of carrying out the reaction under interphase conditions with solid bases, for instance K_2CO_3[80], NaOH[81] and potassium fluoride on alumina[82], can be cited.

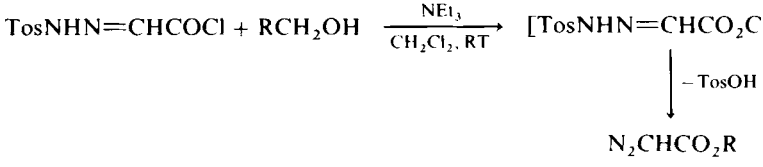
C. Hydrazone Transformations

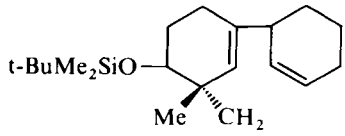
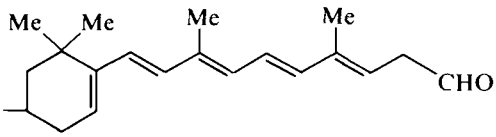
Splitting of hydrazones of aldehydes or ketones with lead(IV) acetate[64] or $POCl_3$ in pyridine[87] is also used for the preparation of some diazo compounds (see Scheme 8).



SCHEME 8

Alkaline splitting of tosylhydrazones formed *in situ* by the interaction of glyoxilic acid tosylhydrazone chloride is widely used for the production of highly labile diazoacetic acid esters (see Scheme 9).

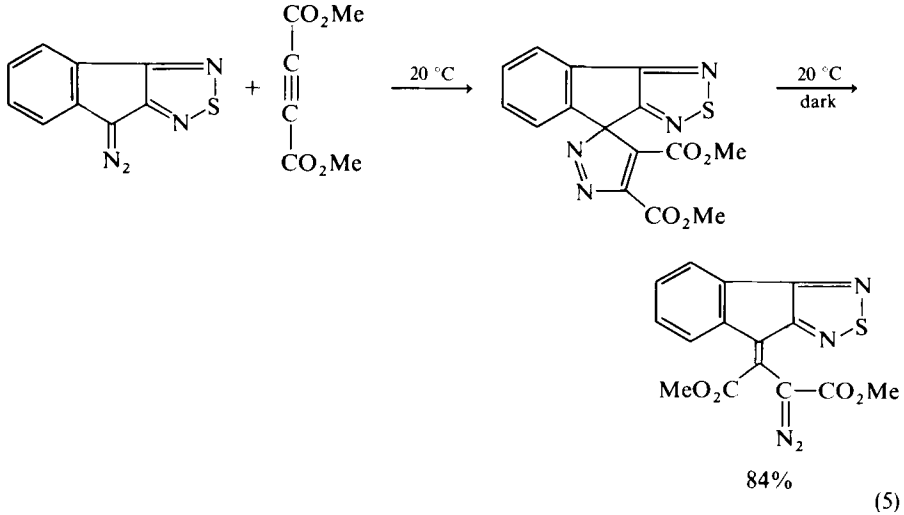


R	Yield (%)	References
$Me_2C{=}CHCHCCl_3$	92	83
$Me_2C{=}CHCH_2$	90	83
$RCOCH_2$	—	84
	—	85
	10	86

SCHEME 9

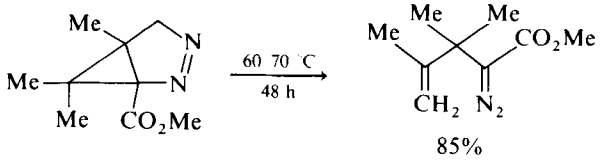
D. Isomerization of Azaheterocycles

Thermal isomerization of certain diazaheterocycles may be in some cases a convenient method for the production of diazoacetic acid derivatives (see equations 5[88] and 6[89]).

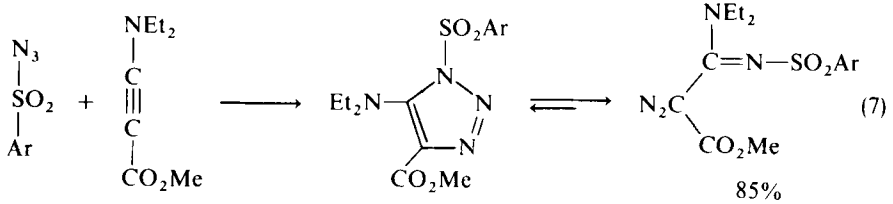


(5)

Some 1,2,3-triazoles isomerize into the corresponding diazoacetates spontaneously[90] (see equation 7).



(6)



(7)

III. REACTIONS WITHOUT NITROGEN ELIMINATION

Reactions in which the diazo group is not involved (Section III.A) and reactions of 1,3-cycloaddition to unsaturated dipolarophiles (Section III.B) belong to the transformations of this type.

A. Reactions with Retention of the Diazo Group

The diazoacetate molecule has two positions which can be transformed with retention of the diazo group: the H atom of the diazo group and the alcoholic moiety. Since these transformations can be carried out selectively, they are discussed separately.

1. Electrophilic substitution in the acid moiety

In the presence of strong bases different electrophiles are capable of substituting the H atom of the diazo group, giving α-substituted diazoesters. Transformations of this type comprise metallation, transmetallation, nitration, halogenation, alkylation and acylation. The latest review, devoted to electrophilic substitution in diazoalkanes, including diazoacetates, was published in 1985[91]. The present section contains data borrowed from this review, and also results of investigations published after 1985.

a. Metallation and transmetallation. Compounds of some metals, acting on ADA form stable α-metallated derivatives. Thus, HgO and Ag_2O interact with EDA already at 0 °C, giving the corresponding organometallic diazoesters with yields up to 75%[92–96] (see equation 8).

$$2N_2CHCO_2R + M_xO \xrightarrow[0\ ^\circ C]{\text{abs. ether}} M(CN_2CO_2R)_x \qquad (8)$$

M = Hg, Ag; $x = 1, 2$
R = Et, Bu-*t*

Alkoxyl derivatives of Hg(II)[97] and Sn(IV)[98] also enter into the metallation reaction. Asymmetric Hg–diazoacetates can be obtained in this way (see equations 9 and 10).

$$RHgOEt + N_2CHCO_2Et \xrightarrow{-EtOH} RHgCN_2CO_2Et\ (80\text{–}99\%) \qquad (9)$$

$$R_3SnOMe + N_2CHCO_2Me \xrightarrow{-MeOH} R_3SnCN_2CO_2Me\ (\text{up to } 80\%) \qquad (10)$$

R = Et, Bu

The most universal method for the production of α-metallated diazoacetates, suggested and developed by Lorberth[99–102], is based on the interaction of ADA with amides of metals. In this way it is possible to produce practically all derivatives of transition metals with yields up to 100% (see Table 1).

With the help of this method[103] or by the action of BuLi at low temperatures[104] α-lithiodiazoacetate can be obtained, which is unstable under normal conditions and is usually employed in subsequent transformations (see equation 11).

$$N_2CHCO_2Et + BuLi \xrightarrow{THF,\ -110\ ^\circ C} N_2CLiCO_2Et \qquad (11)$$

The action of MeMgI on EDA in THF at −70 °C gives unstable α-halogenomagnesiumdiazoacetate, which is in equilibrium with the corresponding magnesium bisdiazoacetate[105]. At 0 °C the Grignard reagent reacts with the diazo group of EDA (see equation 12)[106].

$$N_2CHCO_2Et + MeMgI \xrightarrow[-70\ ^\circ C]{THF\text{–}ether} IMgCN_2CO_2Et \rightleftharpoons Mg(CN_2CO_2Et)_2 + MgI_2 \qquad (12)$$

TABLE 1. Metallation of ethyl diazoacetate with metal amides

$$A(NRR^1)_n + N_2CHCO_2Et \xrightarrow[-NHRR^1]{\text{ether, } -20 \text{ to } 35\,^\circ C} \frac{1}{n} M(CN_2CO_2Et)n$$

R	R^1	A	n	Yields (%)	References
Me	Me	$SnMe_3$	1	~100	99
Me	Me	$SnEt_3$	1	85	99
Me	Me	$SnBu_3$	1	80	99
Me	Me	$SnPh_3$	1	~100	99
Me	Me	$SnMe_2$	2	70	99
Me	Me	$SnEt_2$	2	60	99
Me	Me	$Sn(Bu^t)_2$	2	35	99
Me_3Si	Me_3Si	$PbMe_3$	1	—	100
Me	Me	$GeMe_3$	1	50	100
Me_3Si	Me_3Si	Hg	2	~100	100
Me_3Si	Me_3Si	Zn	2	—	100
Me_3Si	Me_3Si	Cd	2	—	100
Me	Me	$AsMeCN_2CO_2Et$	1	55	101
Me	Me	$As(NMe_2)_2$	1	47	101
Me	Me	$AsMe(NMe_2)$	1	60	101
Me	Me	AsMe	2	60	101
Me_3Si	Me	$BiMe_2$	1	~100	102
Me	Me	$SbMe_2$	1	71	102

Some α-metallated diazoacetates are capable of reacting with organoelement compounds, when an exchange of metals atoms (transmetallation reaction) takes place. The reactions of α-lithiodiazoacetate, generated *in situ*, with metal chlorides are used particularly often[94,105,107,108]. Examples of transmetallations with the participation of Hg- and Sn-containing diazoacetates are known (see Table 2). Even Pd-derivatives of diazoacetates could be obtained in this way (see entries 7 and 8), though some compounds of this metal are powerful catalysts of dediazotation of the diazo compounds (see Section IV.A).

Sulfides of the IV Main Group metals are also capable of causing transmetallation of ethyl Hg-diazoacetate[109–111] (see Eequation 13).

$$Hg(CN_2CO_2Et)_2 + (Me_3M)_2S \xrightarrow[-HgS]{} 2Me_3MCN_2CO_2Et \qquad (13)$$

M = Si (75%)
Ge (57%)
Sn (30%)

b. Nitration and halogenation. Examples of such reactions are few, owing mainly to the low stability of the formed α-halogeno-, and α-nitrodiazoacetates, liable to spontaneous explosion[112] (see equation 14).

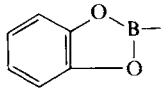
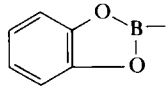
$$N_2CHCO_2Et + N_2O_5 \xrightarrow[-30\,^\circ C]{CCl_4} \left[\begin{array}{c} N_2CHCO_2Et \\ | \\ NO_2 \end{array}\right] \xrightarrow[-N_2+CH_2CO_2Et]{N_2CHCO_2Et} \begin{array}{c} N_2CCO_2Et \\ | \\ NO_2 \end{array}$$

60%

(14)

TABLE 2. Synthesis of α-metallated diazoacetates by transmetallation reactions

$$M^1(CN_2CO_2Et)_n + M^2Cl_n \longrightarrow M^2(CN_2CO_2Et)_n + M^1Cl$$

Entry	M^1	M^2	n	Yield (%)	References
1	Hg		1	90	94
2	Li		1		94
3	Et_3Sn	Me_3Si	1	--	98
4	Li	Me_3Si	1	52	105
5	Li	Me_3Sn	1	50	105
6	Li	Me_3Pb	1	< 10	109
7	Hg	$ClPd(PPh_3)_2$	1	39	106
8	Li	$Pd(PEt_3)_2$	2	73	108

Dinitrogen pentoxide is capable of nitrating ADA or their Hg-derivative at a low temperature, giving alkyl α-nitrodiazoacetates with a yield of 60%[113–115] (see equation 15).

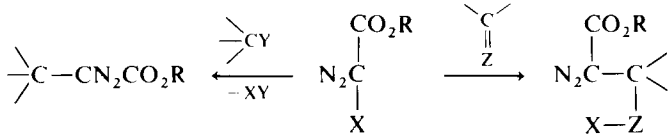
$$Hg(CN_2CO_2Bu\text{-}t)_2 \xrightarrow{N_2O_5} \underset{\displaystyle NO_2}{\overset{\displaystyle |}{N_2CCO_2Bu\text{-}t}} + Hg(NO_3)_2 \qquad (15)$$

Direct halogenation of ADA is not known. However, metallated diazoacetates react with I_2[96,112,116], Br_2[112], BrCN[96] and SO_2Cl_2[112], forming the corresponding α-halogenodiazoacetates with high yields (see equations 16 and 17).

$$AgCN_2CO_2Et \xrightarrow[THF]{I_2(BrCN)} HalCN_2CO_2Et \qquad (16)$$
$$Hal = I, Br; 80\%$$

$$Hg(CN_2CO_2Et)_2 \xrightarrow[-HgX_2]{SO_2Cl_2;\ Br_2;\ I_2} 2XCN_2CO_2Et \qquad (17)$$
$$X = Cl, Br, I; 70\text{–}90\%$$

c. Alkylation. Alkylation of diazoacetates can be effected by the substitution of a hydrogen or metal atom in α-position of diazoesters or by addition of a diazoester to the multiple bond of certain olefins of carbonyl compounds (see Scheme 10).



SCHEME 10

Alkylation of ADA by activated halogen derivatives, stabilized and aromatic cations proceeds by the first pathway; reactions of ADA with enamines, Schiff bases and carbonyl compounds proceed by the second one.

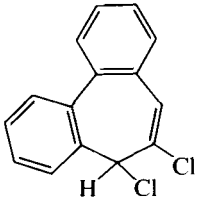
It is possible to produce α-alkenyl[96]- and α-arylmethyldiazoacetates[110,117] by the reaction of α-metallated diazoesters with active halogen derivatives (see equations 18–20).

$$H_2C{=}CHCH_2I + AgCN_2CO_2Et \xrightarrow[-AgI]{\text{ether, } 0\ ^\circ C} H_2C{=}CHCH_2CN_2CO_2Et \quad (18)$$

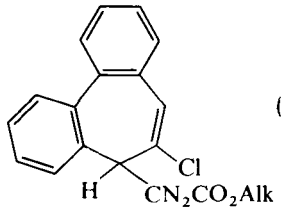
66%

$$2BrCPh_3 + Hg(CN_2CO_2Et)_2 \xrightarrow[-HgBr_2]{CH_2Cl_2,\ 0\ ^\circ C} 2Ph_3CCN_2CO_2Et \quad (19)$$

55%



$$+ Hg(CN_2CO_2Alk)_2 \xrightarrow[-HgBr_2]{CH_2Cl_2,\ 0\ ^\circ C}$$



(20)

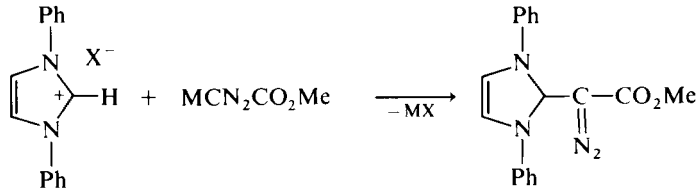
Stabilized cations are capable of reacting not only with α-metallated diazoesters but also directly with ADA. For instance, *in situ* generated triethylsilyl perchlorate easily alkylates EDA with the formation of ethyl α-triethylsilyl diazoacetate (see equation 21).

$$N_2CHCO_2Et \xrightarrow[CH_2Cl_2,\ -78\ ^\circ C \rightarrow 0\ ^\circ C]{Ph_3C^+ClO_4^-,\ Et_3SiH} \left[\begin{array}{cc} H & CO_2Et \\ Et_3Si & N_2^+\ ClO_4^- \end{array}\right] \longrightarrow Et_3SiCN_2CO_2Et$$

~100%

(21)

At the same time, the interaction of salts of 1,3-diphenyl-imidazolidinium with α-metallated diazoesters leads to alkylation products with low yields[119] (see equation 22), while ethyl α-(benzoselenazolidinyl)diazoacetate, which is definitely formed in the



(22)

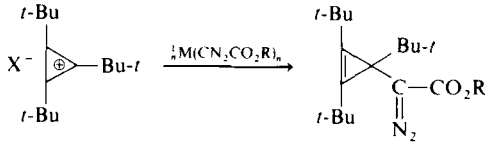
6–44%

X = Cl, Br; M = Ag, ½Hg, Me_3Si

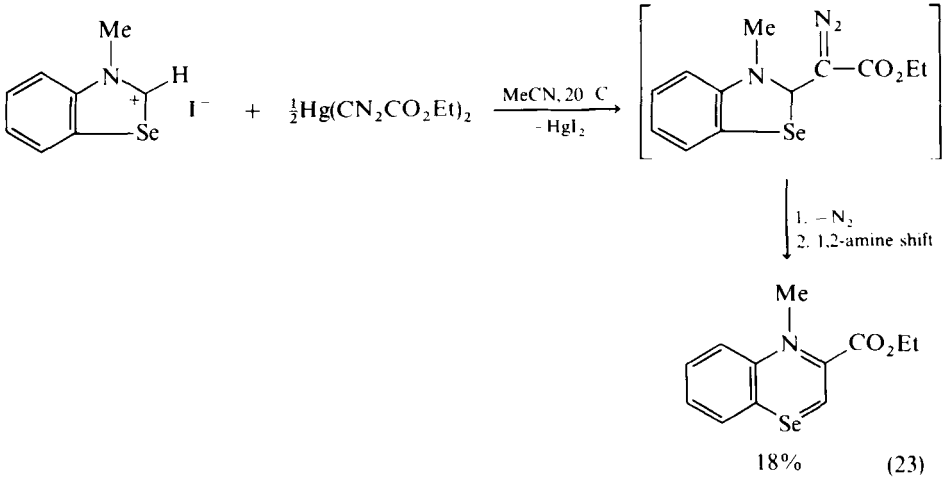
reaction of the corresponding selenoindolinium salt with a Hg-derivative of EDA, in the course of the reaction undergoes dediazotation with ring expansion, giving the corresponding selenoquinoline[120] (see equation 23).

Among the known examples of substitution of the metal atom in α-metallated diazoesters by aromatic cations, the reaction with cyclopropenyl cations, leading to

TABLE 3. Alkylation of cyclopropenylium cations by α-metalated diazoacetates

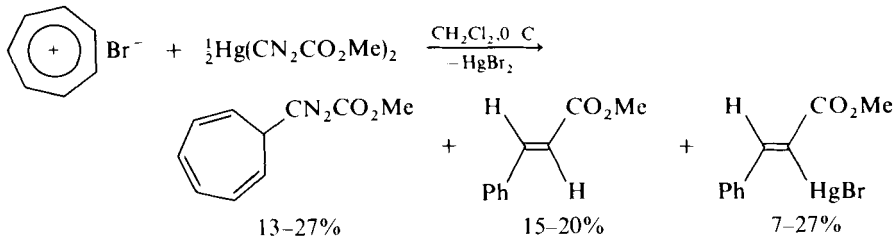


X	M	n	R	Yield (%)	References
BF_4	Li	1	Me	88	126
Br	Hg	2	Me	50	127
Br	Hg	2	Bu-*t*	60	95



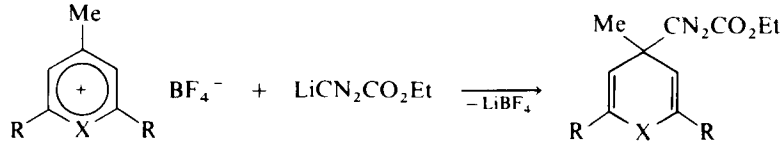
(23)

α-cyclopropenyl diazoacetates with high yields, is of preparative importance (see Table 3). Tropylium bromide with mercury bis(methyl diazoacetate) forms methyl α-cycloheptatrienyl diazoacetate together with its dediazotation products[121] (see equation 24).



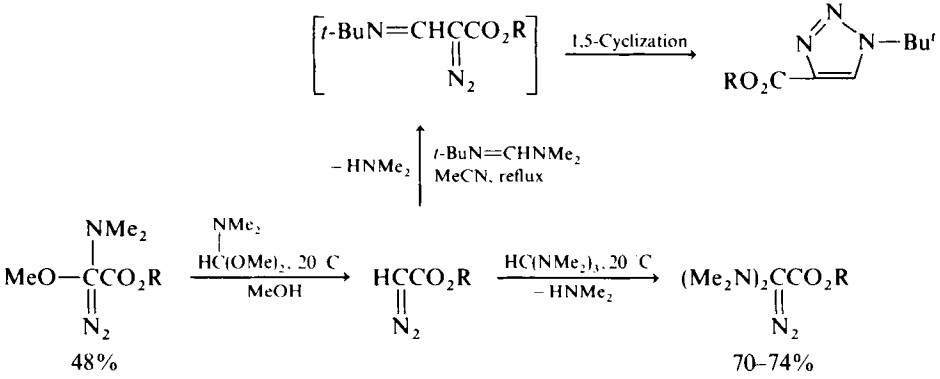
(24)

Reactions of Hg- and Li-diazoacetates with thiapyrilium and pyrilium cations lead to stable α-(4*H*-pyranyl)- and α-(4*H*-thiapyranyl)-diazoacetates with low yields[122-125] (see equation 25).



R = Me, Ph, Bu = *t*; X = O,S (25)

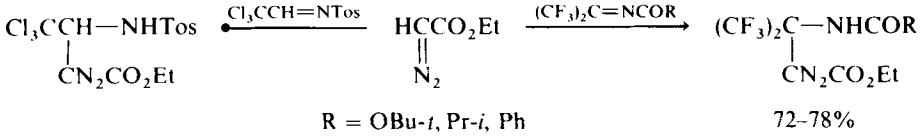
Dimethylformamide diacetal, its Schiff base with *t*-butylamine, and tris(dimethylamino)methane can be used as alkylating reagents. The unstable Schiff base of α-formyldiazoacetate formed in the second base undegoes 1,5-cyclization into the corresponding triazole[128] (see Scheme 11).



R = Me,Et,*t*-Bu

SCHEME 11

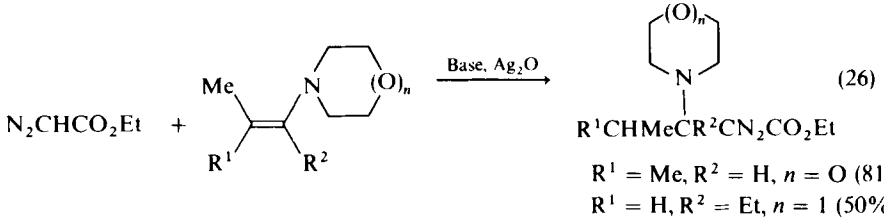
At the same time, alkylation of ADA by Schiff bases with acceptor substituents proceeds via addition to the C=N bond[129] (see Scheme 12).



R = OBu-*t*, Pr-*i*, Ph 72–78%

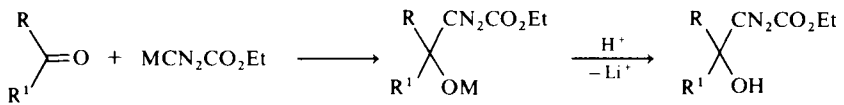
SCHEME 12

Some enamines react with EDA in a similar manner, giving in the presence of a base and Ag_2O as a catalyst α-aminoalkyl diazoacetates with the yield up to 81%[130] (see equation 26).

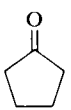
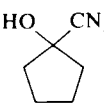
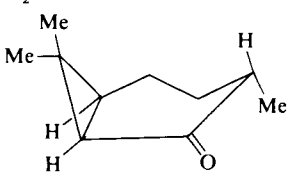
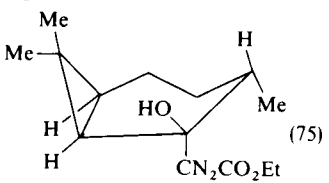


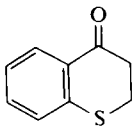
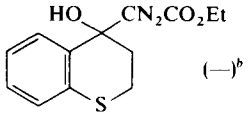
$R^1 = Me, R^2 = H, n = O$ (81%)
$R^1 = H, R^2 = Et, n = 1$ (50%)

TABLE 4. Synthesis of α-(Hydroxymethyl)diazoacetates by reaction of α-metallated ADA with carbonyl compounds



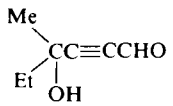
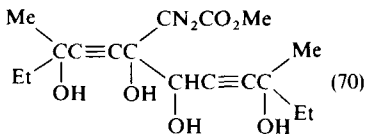
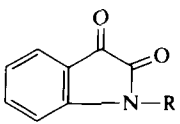
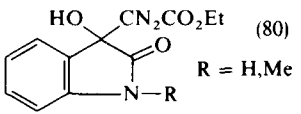
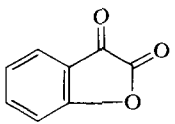
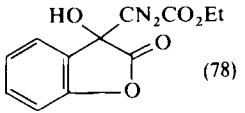
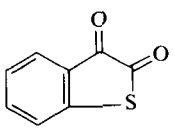
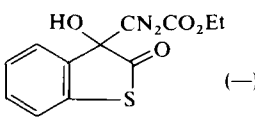
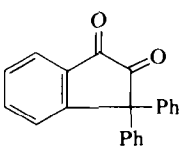
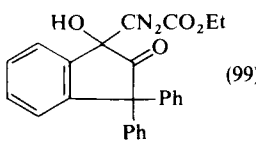
M = H, Li, $SiMe_3$

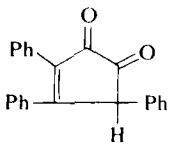
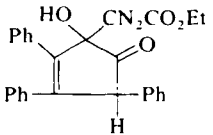
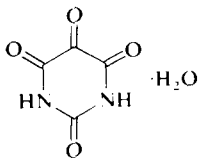
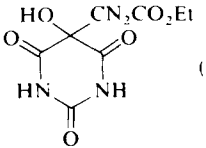
Entry	Substrate	Reagent[a]	Product (yield, %)	References
1	MeCHO	LDA	$MeCHOHCN_2CO_2Et$ (68)	131, 132
2	*i*-PrCHO	LDA	*i*-$PrCHOHCN_2CO_2Et$ (62)	131
3	$C_7H_{15}CHO$	LDA	$C_7H_{15}CHOHCN_2CO_2Et$ (45)	131
4	PhCHO	LDA	$PhCHOHCN_2CO_2Et$ (67)	131
5	$H_2C{=}CMeCH_2CH_2CHO$	LDA	$H_2C{=}CMeCH_2CH_2CHOHCN_2CO_2Et$ (30)	133
6	Me_2CO	LDA	$Me_2CHOHCN_2CO_2Et$ (—)[b]	133
7		LDA	 (85)	133
8	PhCOMe	LDA	$PhCHOHMeCN_2CO_2Et$ (67)	133
9	$H_2C{=}CHCHO$	LDA	$H_2C{=}CHCHOHCN_2CO_2Et$ (87)	133
10		LDA	 (75)	134

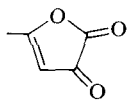
11		LDA	 (—)[b]	135
12	$C_5H_{11}CHO$	EDA/18-C-6	$C_5H_{11}CHOHCN_2CO_2Et$ (68)	136
13	*i*-PrCHO	EDA/18-C-6	*i*-$PrCHOHCN_2CO_2Et$ (89)	136
14	PhCHO	EDA/18-C-6	$PhCHOHCN_2CO_2Et$ (69)	136
15	4-ClC_6H_4	EDA/18-C-6	4-$ClC_6H_4CHOHCN_2CO_2Et$ (25)	136
16	*i*-PrCHO	SDA/18-C-6	*i*-$PRCHCN_2CO_2Et$ (93) | $OSiMe_3$	136
17	PhCHO	SDA/18-C-6	$PhCHCN_2CO_2Et$ (86) | $OSiMe_3$	136
18	4-ClC_6H_4CHO	SDA/18-C-6	4-$ClC_6H_4CHCN_2CO_2Et$ (93) | $OSiMe_3$	136
19	4-$MeOC_6H_4CHO$	SDA/18-C-6	4-$MeOC_6H_4CHCN_2CO_2Et$ (83) | $OSiMe_3$	136
20	MeCH=CMeCHO	SDA/18-C-6	$MeCH{=}CMeCHCN_2CO_2Et$ (44) | $OSiMe_3$	136
21	$PhCOCO_2Et$	EDA/EtONa	$EtO_2CCPhOHCN_2Et$ (52)	130
22	*t*-BuC≡CCHO	MDA	*t*-BuC≡$CCCHOHCN_2CO_2Me$ (87)	137
23	$Et_3SiC{\equiv}CCHO$	MDA	$Et_3SiC{\equiv}CCHOHCN_2CO_2Me$ (54)	138
24	$Et_3GeC{\equiv}CCHO$	MDA	$Et_3GeC{\equiv}CCHOHCN_2CO_2Me$ (27)	138
25	BuC≡CCHO	MDA	BuC≡$CCHOHCN_2CO_2Me$ (33)	138
26	PhC≡CCHO	MDA	PhC≡$CCHOHCN_2CO_2Me$ (64)	138

(*continued*)

TABLE 4. (*continued*)

Entry	Substrate	Reagent[a]	Product (yield, %)	References
27		MDA	 (70)	138
28	4-$MeOC_6H_4COCH{=}C{=}O$[c]	EDA	4-$MeOC_6H_4COCH_2COCN_2CO_2Et$ (96)	139
29		EDA/Et_2NH	 (80) R = H,Me	140
30		$EDA/ZnCl_2$	 (78)	141
31		$EDA/ZnCl_2$	 (—)[b]	141
32		EDA/Et_2NH	 (99)	142

33		EDA		(—)[b]	141
34		EDA		(90–95)	143

[a] LDA = $LiCN_2CO_2Et$, MDA = N_2CHCO_2Me, EDA = N_2CHCO_2Et, SDA = $Me_3SiCN_2CO_2Et$.
[b] Product is not isolated.
[c] This ketene was generated *in situ* by pyrolysis (80 C) of 4-$MeOC_6H_4$- 
(continued)

ADA and its α-metallated derivatives react readily with different carbonyl compounds, giving α-(hydroxymethyl)diazoacetates (see Table 4). High yields of the products make this reaction very attractive from the preparative standpoint.

d. Acylation and deacylation. Carboxylic acid halides[144–150] and some anhydrides[151] interact with EDA yielding ethyl α-acyldiazoacetates with high yields (see equations 27 and 28).

$$N_2CHCO_2Et + RCOCl \xrightarrow{-HCl} RCOCN_2CO_2Et\ (19\text{–}91\%) \qquad (27)$$

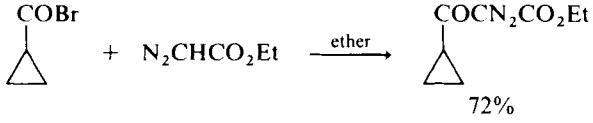
R = alkyl C_1–C_{15}, CCl_3, CF_3, polyhalogenalkenyl, aryl, hetaryl

$MeOC_2CN_2CO(CH_2)_n$ (n = 4–7), $PhC{\equiv}C$

$$N_2CHCO_2Et + CF_3CO_2COCF_3 \xrightarrow{-CF_3CO_2H} CF_3COCN_2CO_2Et\ (84\%) \qquad (28)$$

In the not distant past these reactions were the main methods for the synthesis of diazoacetates, but at present they are almost completely supplanted by the method of diazotransfer (see Section II.B).

Acid chlorides usually react with ADA at 20 °C slowly, and higher temperatures are required to accelerate the process. In some cases acid chlorides must be replaced by the more active acid bromides[25] (see equation 29).

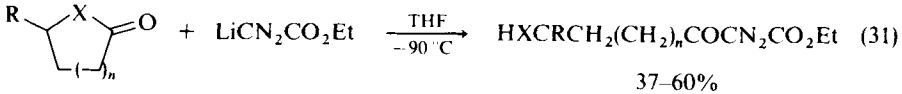


(29)

With some acid chlorides, however, e.g. with oxalyl chloride, phosgene and EtOCOCl, the reaction proceeds so vigorously that it is necessary to cool and dilute the reaction mixture with a solvent[152a] (see equation 30).

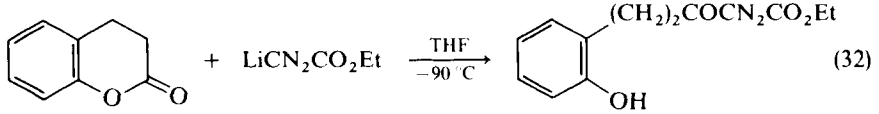
$$(COCl_2)_2 + N_2CHCO_2Me \xrightarrow{\text{ether, } 0\,^\circ C} (COCN_2CO_2Me)_2 \qquad (30)$$

In recent years lactones, thiolactones and lactams have been found capable of acylating lithiumdiazoacetate, with the formation of the corresponding α-hydroxy-, α-thio- or α-amino substituted acyldiazoacetates with preparative yields[152b,153,154] (see equations 31–34).

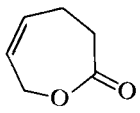


(31)

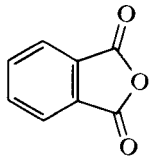
R = alkyl, alkenyl, acyl, benzyl; X = O, S or NR^1; n = 1–2



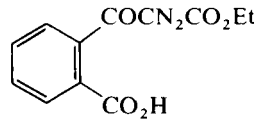
(32)



$$+ \ LiCN_2CO_2Et \xrightarrow[-90\ ^\circ C]{THF} HOCH_2CH{=}CH(CH_2)_2COCN_2CO_2Et \quad (33)$$

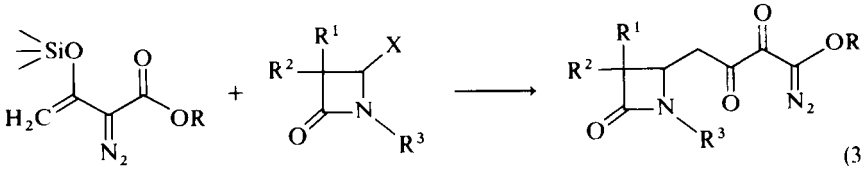


$$+ \ LiCN_2CO_2Et \xrightarrow[-90\ ^\circ C]{THF}$$



(34)

Trimethylsilyl enols of α-acyldiazoacetates may be used for the synthesis of other α-carbonyldiazoacetates, for instance, by interaction with 3-lactams[155–160] (see equation 35).



(35)

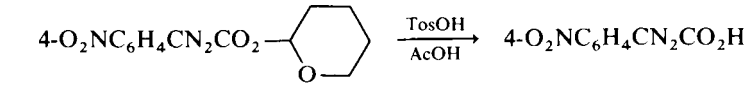
α-Acyldiazoacetates can be converted into diazoacetates by treatment with $LiOH \cdot H_2O$ in THF[161] (see equation 36).

$$AcCN_2CO_2R + LiOH \cdot H_2O \xrightarrow[0\ ^\circ C]{H_2O/THF} \underset{>50\%}{N_2CHCO_2R} \quad (36)$$

These deacylations are used for synthesis of complex diazoacetic acid esters, which by other methods are difficult to prepare.

2. *Transformations of the carboxyl group*

Only a few examples of reactions with the participation of the alcohol moiety of the ADA molecule have been described. Thus, only one example of a diazoacetate hydrolysis is known[162]: treatment of 2-pyranyl-α-(*p*-nitrophenyl)diazoacetate with acetic acid in the presence of TosOH yields the diazoacid (see equation 37).



(37)

In a modified procedure, such acids were also obtained by alkaline (pH > 10) splitting of α-diazoacetoxyethyldimethylsulfonium iodide[163].

Syntheses of some other diazoacetic acid derivatives: anhydrides, chlorides and amides, are also described in the literature. Thus α-aryldiazoacetic acids with benzoyl chloride yielded α-diazoacetic benzoic anhydride[163] (see equation 38).

$$4\text{—}X\text{—}C_6H_4CN_2CO_2H + ClCOC_6H_4\text{—}Y\text{—}4 \xrightarrow{NEt_3} 4\text{—}X\text{—}C_6H_4CN_2CO_2COC_6H_4\text{—}Y\text{—}4 \quad (38)$$

X = Y = Cl; X = NO_2, Y = N

Diazoacetic acid chloride, synthesized from diazomethane with phosgene, upon esterification with phenol gives phenyl diazoacetate[164]. In a similar reaction of a secondary amine with a malonic acid chloride derivative, diazomalonic acid monoamide was synthesized[165] (see equations 39 and 40).

$$CH_2N_2 \xrightarrow{COCl_2} N_2CHCOCl \xrightarrow[-HCl\cdot NEt_3]{PhOH/NEt_3} N_2CHCO_2Ph\ (90\%) \quad (39)$$

$$EtO_2CCN_2COCl + MeNHCH_2CH{=}CH_2 \xrightarrow[CH_2Cl_2]{NEt_3,\ 0\ ^\circ C}$$

$$EtO_2CCN_2CONMeCH_2CH{=}CH_2\ (87\%) \quad (40)$$

With aliphatic amines in aqueous solutions, diazoacetates undergo ammonolysis with the formation of *N*-alkyldiazoacetamides[166] (see equation 41).

$$N_2CHCO_2C_6H_4NO_2{-}4 + MeNH_2 \xrightarrow{H_2O}$$

$$N_2CHCONHMe + HOC_6H_4NO_2{-}4\ (\sim 100\%) \quad (41)$$

The reaction of 2-bromoethyl diazoacetate with primary amines in the presence of K_2CO_3[167] yields [2-(alkylamino)-ethyl] diazoacetates, as well as *N*-(2-hydroxyethyl)-diazoacetamides, their rearrangement products (see equation 42).

$$N_2CHCO_2CH_2CH_2Br + H_2NR \xrightarrow[MeCN]{K_2CO_3,\ 20\ ^\circ C}$$

$$N_2CHCONRCH_2CH_2OH\ (50\text{–}70\%) + N_2CHCO_2CH_2CH_2NHR\ (5\text{–}35\%) \quad (42)$$

On the other hand, 2-alkylaminoethyl[167] and 2-iminoethyl[168] diazoacetates are the only products of the reactions of 2-bromoethyl diazoacetate with hydrochlorides of primary amines or with secondary amines or with imides of phthalic acid derivatives (see equations 43–45).

$$N_2CHCO_2CH_2CH_2Br + H_2NR\cdot HCl \xrightarrow[MeCN]{K_2CO_3,\ 20\ ^\circ C}$$

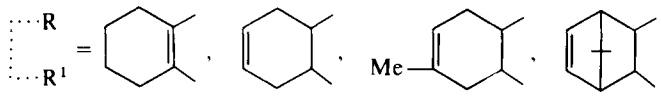
$$N_2CHCO_2CH_2CH_2NHR\ (60\text{–}70\%) \quad (43)$$

$$N_2CHCO_2CH_2CH_2Br + HNRR^1 \xrightarrow[MeCN]{K_2CO_3,\ 20\ ^\circ C} N_2CHCO_2CH_2CH_2NRR^1 \quad (70\text{–}80\%)$$

R, R^1 = alkyl (44)

$$N_2CHCO_2CH_2CH_2Br + \begin{array}{l} \cdots R \\ \cdots R^1 \end{array}\!\!>\!N{-}H \xrightarrow[MeCN]{KOH,\ TEBA,\ 25\ ^\circ C} \quad (45)$$

$$\begin{array}{l} \cdots R \\ \cdots R^1 \end{array}\!\!>\!N{-}CH_2CH_2OCOCHN_2 \quad (40\text{–}70\%)$$



The mobile Br atom in 2-bromoethyl diazoacetate is also easily substituted by iodine[169] (see equation 46).

$$N_2CHCO_2CH_2CH_2Br + NaI \xrightarrow[-NaBr]{\text{acetone, } 20\,^\circ C} N_2CHCO_2CH_2CH_2I\ (75\%) \quad (46)$$

Some diazoesters, such as diazomalonates, preserve their diazo function upon reduction of the carboxylate group[170] (see equation 47).

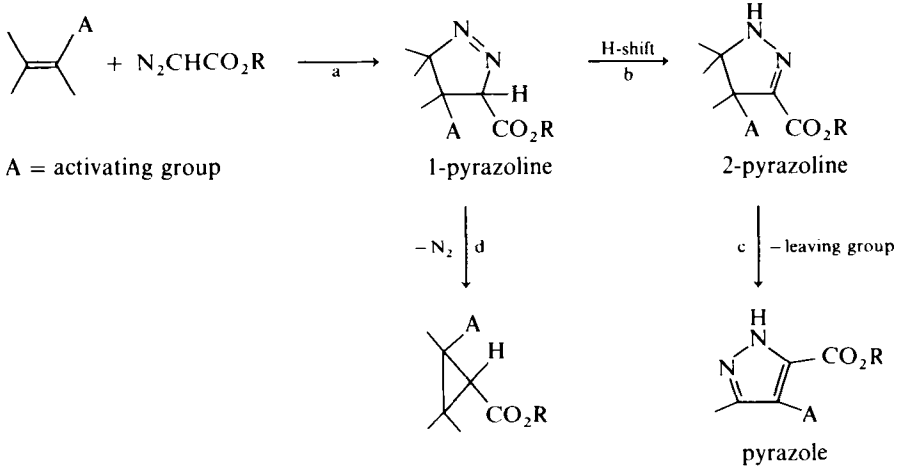
$$N_2C(CO_2R)_2 \xrightarrow{LiAlBu^t_2} HOCH_2CN_2CO_2R \quad (47)$$

C. 1,3-Dipolar Cycloaddition

Esters of diazoacetic acid are capable of behaving as 1,3-dipoles in cycloadditions to unsaturated compounds, containing carbon–carbon, carbon–heteroatom and heteroatom–heteroatom multiple bonds. The brilliant review of Regitz and Heydt[7], published in 1984, gives a comprehensive consideration of the preparative potentialities of 1,3-cycloaddition reactions of aliphatic diazo compounds, including diazoacetic acid esters. In the present section the data of this review on the reactions with the participation of ADA are supplemented with the results of investigations carried out during the period from 1983 to 1990 inclusive, as well as with some little known data obtained earlier.

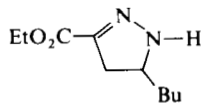
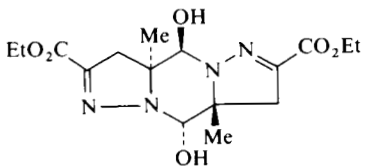
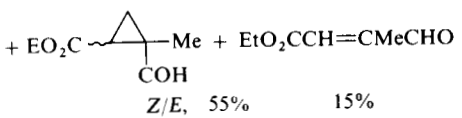
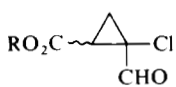
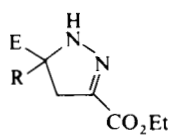
1. C=C bonds

Publications dealing with the cycloaddition of diazoacetates to double bonds are listed in Table 5. The general scheme of the interaction with olefins is presented in Scheme 13.

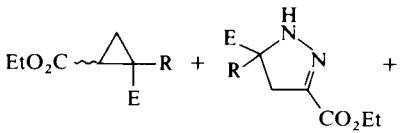
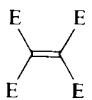
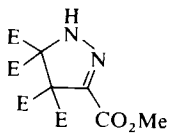
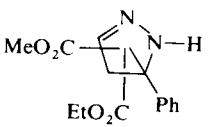
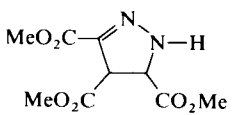


SCHEME 13

TABLE 5. Diazoacetates 1,3-dipolar cycloaddition to compounds with C=C bonds

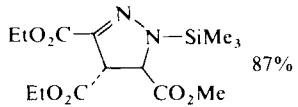
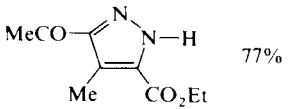
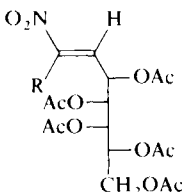
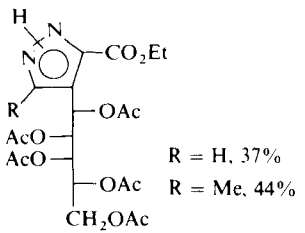
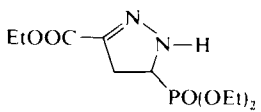
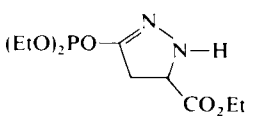
Entry	Olefin	Diazoacetates[a]	Product and yields	References
1	$BuCH{=}CH_2$	EDA	 56%	173
2	$H_2C{=}CMeCHO$	EDA	 10%	173, 174
			 Z/E, 55% 15%	
3	$H_2C{=}CClCHO$	EDA	 90% E/Z	174, 175
4	$H_2C{=}CRE$	EDA pyridine		172

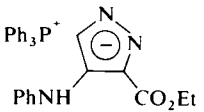
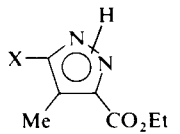
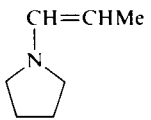
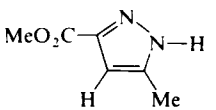
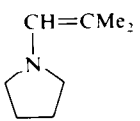
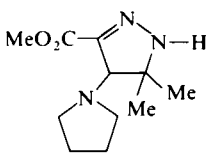
E = CO_2Et, R = H, 99%
E = CO_2Et, R = Me, 99%
E = CN, R = H, 100%
E = CN, R = Me, 90%

5	$H_2C{=}CRE$ R = H, Me E = CO_2Alk Ac, CN	EDA/$Mo(CO)_5$	 *E*, *Z*, total 32–80% 0–50% + $EtO_2CCH_2CH{=}CRE$ 4–13%		
6		MDA		E = CN, 97% E = CO_2Me, 98%	175, 176
7	*trans*-$PhCH{=}CHCO_2Et$	MDA	 mixture of isomers, total 90–95%		177
8	*trans*-$MeO_2CCH{=}CHCO_2Me$	MDA		94%	178

(*continued*)

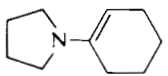
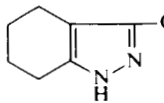
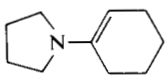
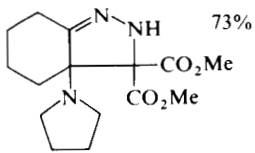
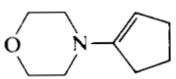
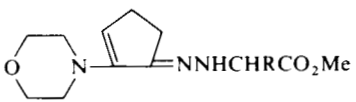
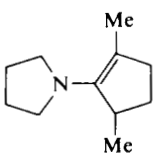
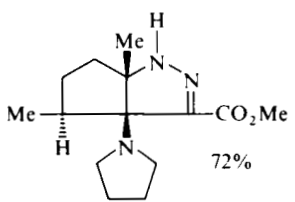
TABLE 5. (*continued*)

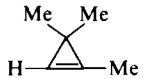
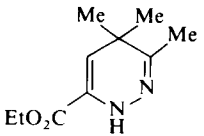
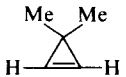
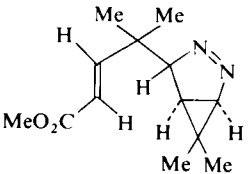
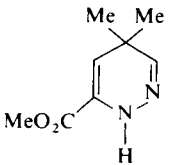
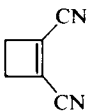
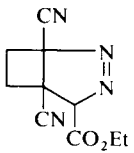
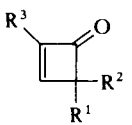
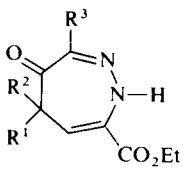
Entry	Olefin	Diazoacetates[a]	Product and yields	References
9	*trans*-$EtO_2CCH{=}CHCO_2Et$	N_2CCO_2Me | $SiMe_3$	 87%	179
10	$MeCOCH_2COMe$[b]	EDA + KOH	 77%	180
11		EDA	 R = H, 37% R = Me, 44%	181
12	$H_2C{=}CHPO(OEt)_2$	EDA	 + 	182 mixture of isomers, total 99%

13	$Ph_3P^+ {}^-C{=}C{=}NPh \leftrightarrow Ph_3P{=}C{=}C{=}NPh$	EDA		69%	183
14	$H_2C{=}C{=}CHX$	EDA			184
			X = MeCO, 7% X = PrCo, 56% X = CO_2Me, 39% X = Ph_2CHO_2C, 72%		
15		MDA		85%	185
16		MDA		73%	185

(*continued*)

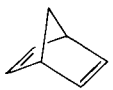
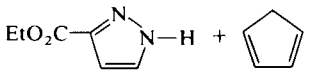
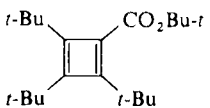
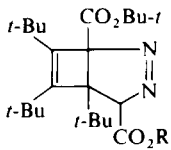
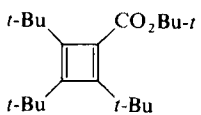
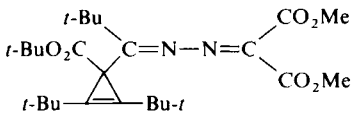
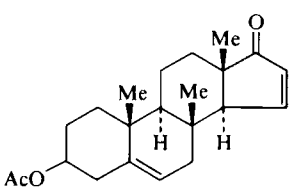
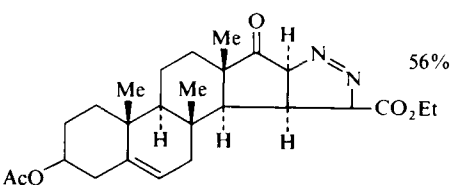
TABLE 5. (*continued*)

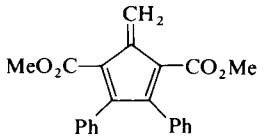
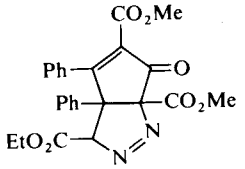
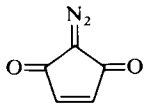
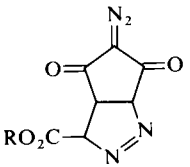
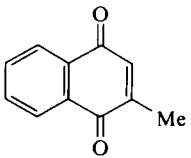
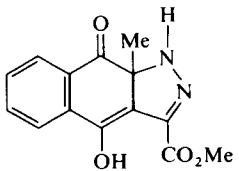
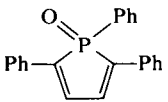
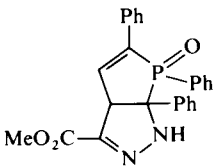
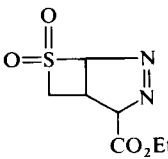
Entry	Olefin	Diazoacetates[a]	Product and yields	References
17		N_2CHCO_2R	 R = Me, 82% R = Et, 55%	185 186
18		MDM	 73%	187
19		N_2CRCO_2Me	 R = H, 51% R = CO_2Me, 66%	188
20		MDA	 72%	189

21		EDA		59%	190
22		MDA	 or  (in presence of NEt_3)		191, 192
23		EDA		53%	193
24		EDA		4 examples 8-54%	194

(continued)

TABLE 5. (*continued*)

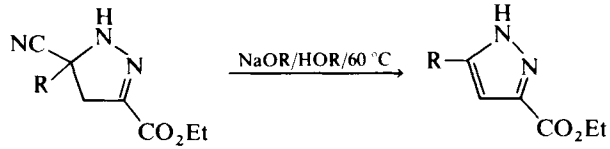
Entry	Olefin	Diazoacetates[a]	Product and yields	References
25		EDA	 total 95%	195
26		N_2CHCO_2R	 R = Et, 31% R = *t*-Bu, 25%	196
27		MDM	 45–60%	196
28		EDA	 56%	197

29		EDA		72%	198
30		$N_2CRCO_2R^1$		R = H, R^1 = Et, 90% R = H, R^1 = Me, 83% R = D, R^1 = Et, 93%	199
31		MDA		41%	200
32		MDA		34%	201
33		EDA		64%	202

[a] EDA = ethyl diazoacetate, MDA = methyl diazoacetate, MDM = dimethyl diazomalonate.
[b] Reacts with EDA in enol form, MeCOCH=CMeOK.

Concerted cycloaddition of ADA to olefins leads to 1-pyrazolines as primary products (step a), which usually, as a result of H-shift, become transformed into the thermodynamically more stable 2-pyrazolines (step b). Bases promote this process whereas $Mo(CO)_6$ and $Mo_2(OAc)_4$ inhibit it[171]. The presence of easily migrating trialkylsilyl, hydroxy, nitro or amino groups in 2-pyrazolines may bring about their further transformation into pyrazoles (step c) (see Table 5 entries 10, 11, 15 and 17).

For exmple, Na alcoholates readily convert 2-pyrazolines derived from α,β-unsaturated nitriles to the corresponding pyrazoles through HCN elimination[172] (see equation 48).



70–85% (48)

Pyrazoles are also formed in the reaction of ADA with allenes as a result of migration of the exocyclic double bond in the initially formed methylene-1-pyrazolines (entry 14). 1-Pyrazolines may undergo dediazotation with the formation of cyclopropane compounds (step d), which in the case of some α,β-unsaturated carbonyl compounds and nitriles are the main isolated products (entries 2, 3 and 5). It should be pointed out that dediazotation of 1-pyrazolines derived from acrylic and methacrylic acids or nitriles proceeds only in the presence of Mo-inhibitors of isomerization of 1-pyrazolines to 2-pyrazolines[171].

The reactions of cycloaddition of ADA to olefins usually proceed regioselectively by an attack of the most electron-deficient atom of the double bond at the end nitrogen atom of the diazo group. This leads to pyrazolines, in which the CO_2R group of the diazoester and the activating substituent at the double bond are in neighboring positions. However, steric effects or secondary orbital interaction between the substituent and the CO_2R group of the diazoester may exert an essential effect on both the regio- and stereoselectivity of the process. For example, secondary orbital interaction between the phenyl substituent in ethyl *trans*-cinnamate and the CO_2Me group in MDA leads to the formation of a mixture of pyrazolines as a result of different orientation of MDA in the attack of the double bond (entry 7). In some cases the substituents may cause a change of the concerted cycloaddition mechanism to a zwitterionic one, which leads to the formation of acyclic azo compounds rather than diazaheterocycles (entries 19 and 27). Such a course of the process is characteristic for the MDM reactions.

The facility of the ADA cycloaddition to double bonds is determined, first of all, by the degree of the double bond activation. Cyclopropenes, cyclobutadienes, cyclobutenones and norbornadiene, in which the exocyclic multiple bond is strongly activated because of angular strain, undergo the reaction very easily (entries 21, 22 and 24–27). In this case cyclopropenes and cyclobutenones also give strained bicyclic pyrazolines, which isomerize into more stable dihydropyridazines and tropadienones, respectively. Tricyclic 1-pyrazolines formed from norbornadiene undergo Diels–Alder retro-reaction in the course of the reaction process, with the formation of pyrazolylcarboxylic ester (entry 25).

Less strained cyclobutenes, cyclopentenes and cyclohexenes react with ADA only in the presence of activating substituents, such as C=O, CN or CO_2R groups, and give stable pyrazolines (entries 23 and 28–31). Thus, diethyl 3,4-diphenylcyclopenta-2,4-diene-2,5-dicarboxylate adds EDA at room temperature (entry 29), whereas the reaction of EDA with Δ^{15}-17-ketoandrostane proceeds only under a pressure of 14 kbar (entry 28).

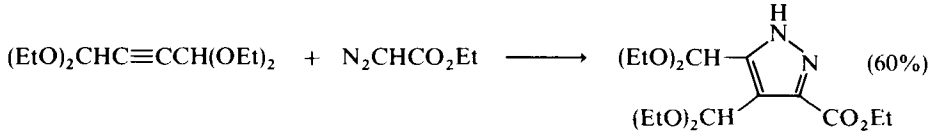
Strongly activated double bonds in phosphols (entry 32) and sulfenes (entry 33) add ADA, giving the corresponding bicyclic pyrazolines.

Only one example of cycloaddition of ADA to a nonactivated bond is known in the series of acyclic olefins: the reaction of EDA with 1-hexene (entry 1). In the overwhelming majority of cases, for the reaction to proceed the presence of activating electron-acceptor substituents of C=O, CN, NO_2, $PO(OR)_3$ or CO_2R type is necessary (entries 2–12). The double bond in enamines is activated as well (entries 15–20).

2. C≡C bonds

Cycloaddition of diazoacetates to acetylenes is a direct method of producing 1*H*-pyrazole-3-carboxylic acids. However, the number of syntheses based on it is not large because of the relatively low electrophilicity of the isolated triple bond that limits the range of the acetylenes capable of reacting with diazoesters in the given manner. Furthermore, in some cases the cycloaddition is complicated by isomerization of the primary reaction products, 3*H*-pyrazoles, into aromatic 1*H*-pyrazoles and by their dediazotation with the formation of esters of cyclopropenecarboxylic and acyclic unsaturated acids.

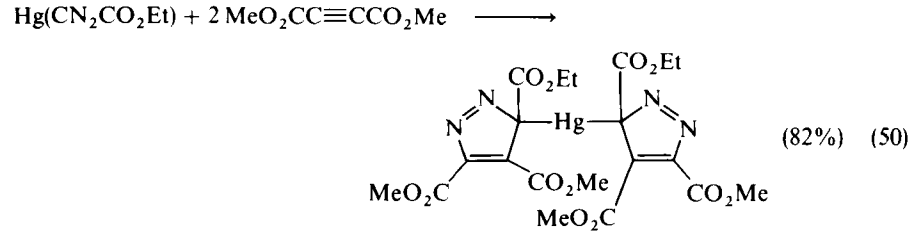
In particular, internal acetylenes react with ADA only in the presence of activating substituents. For example, 1,1,4,4-tetraethoxybut-2-yne reacts with EDA, giving 1*H*-pyrazole (see equation 49).



(49)

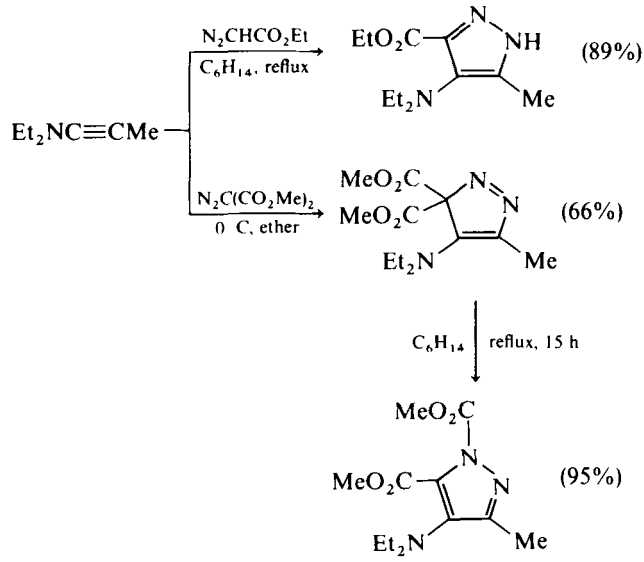
EDA also easily reacts with *N*,*N*-diethlyaminoprop-1-yne, giving the corresponding 1*H*-pyrazole. In the reaction of the same ynamine with MDM it was possible to isolate the primary reaction product, 3*H*-pyrazole, which upon heating isomerizes into 1*H*-pyrazole, involving [1,5]-migration of the CO_2Me group[204] (see Scheme 14).

There are several examples of cycloaddition of organoelement diazoesters to dimethyl acetylenedicarboxylate[205,206,206a] (see equations 50 and 51).

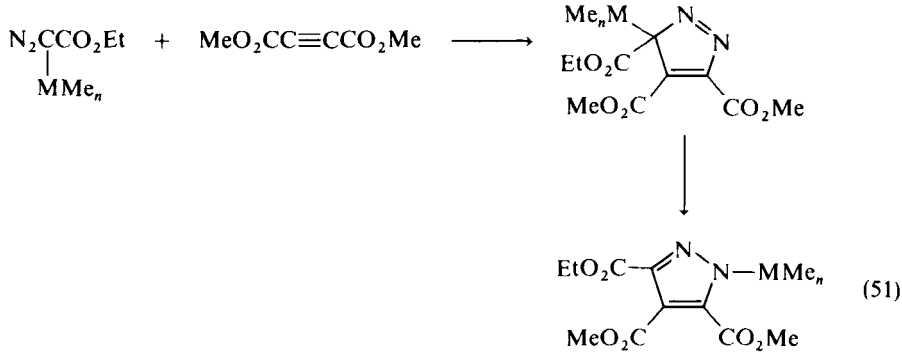


(50)

The lowered electrophilicity of the triple bond in bis(trimethylsilyl)acetylene contributes to the formation of pyrazoles even in the presence of carbene decomposition of ADA (see Scheme 15). Heating of EDA and the silylated acetylene leads to 1*H*-pyrazole as the sole reaction product. The corresponding pyrazole is also formed in the presence



SCHEME 14

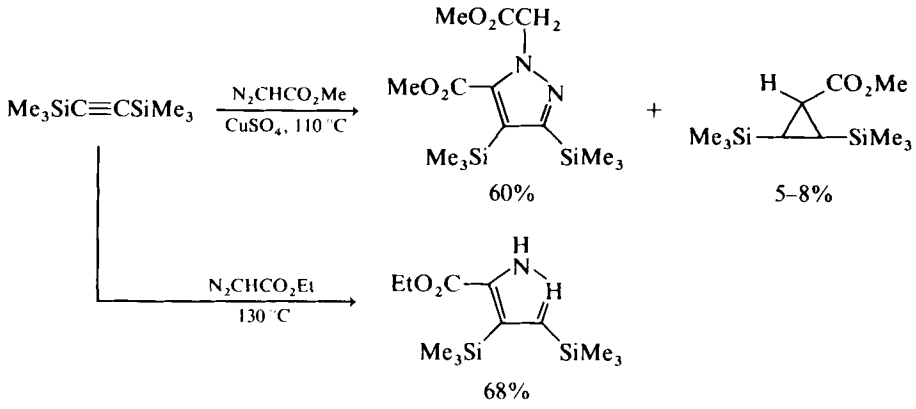


M = Si, Sn(84%), Pb(87%), Sb(43%), Bi(93%); n = 2–3

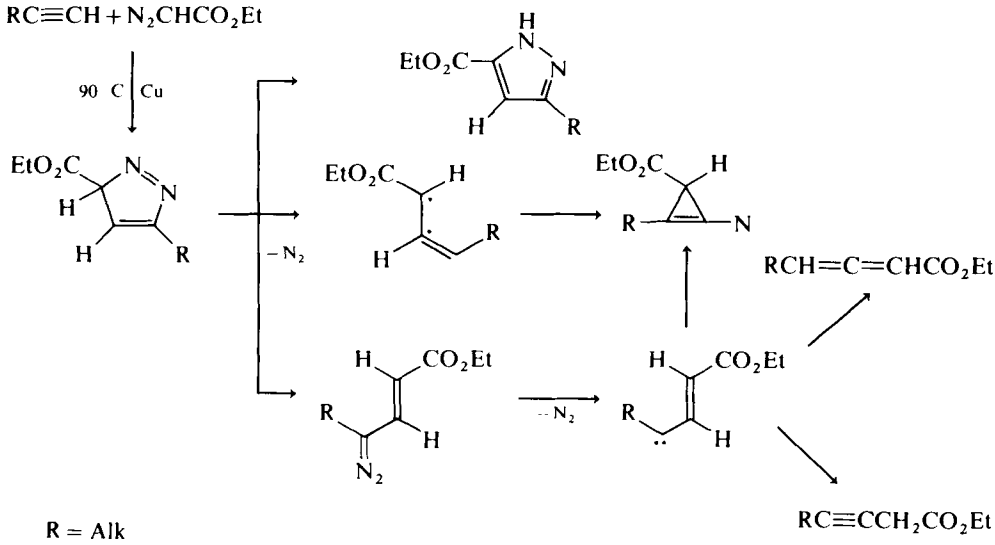
of anhydrous $CuSO_4$ that causes MDA dediazotation. However, methoxycarbonylcarbene originating under these conditions is reluctant to add to the multiple bond of acetylene and to give cyclopropene (the yield being 5–8%); it predominantly inserts into the N—H bond of 1*H*-pyrazole with the formation of an *N*-alkylated pyrazole[207].

Terminal acetylenes, whose triple bond is more electrophilic than that of internal ones, react by cycloaddition with ADA more readily. Scheme 16 shows the pathway suggested by Vidal and coworkers[208], which explains the appearance in the products of catalytic reaction of EDA with 1-alkynes of the corresponding 3-alkynoates and 2,3-alkadienoates alongside of 3-cyclopropenecarboxylate as a result of dediazotation of pyrazoles formed as by-products.

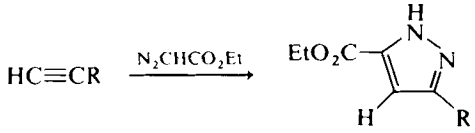
For the reaction of acetylene (R = H; see equation 52) with EDA to proceed in the



SCHEME 15



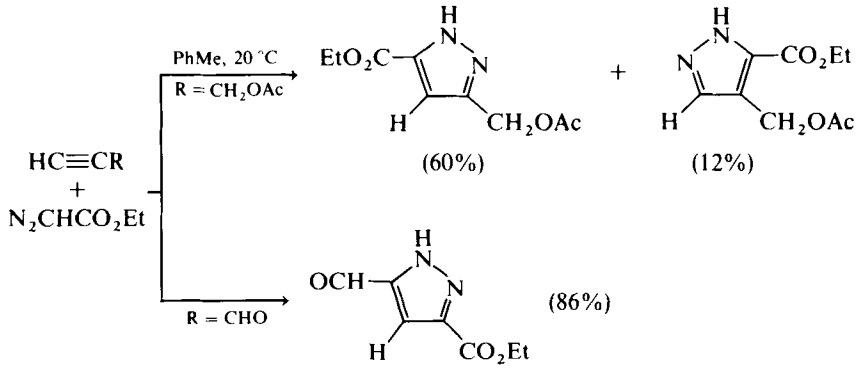
SCHEME 16



(52)

absence of a catalyst, a pressure of 36 atm and temperature of 100 °C are required; in this case ethyl 1*H*-pyrazole-3-carboxylate is formed in 72% yield[209]. Phenylacetylene (R = Ph) adds EDA already at 20 °C, giving the corresponding pyrazole in 45% yield[210], while trimethylsilylacetylene (R = $SiMe_3$) under the same conditions readily reacts with MDA, giving pyrazole in almost quantitative yield[211].

Reactions of EDA with propargyl acetate[212] and propynal[213] are of preparative importance for the synthesis of bifunctional pyrazoles (see Scheme 17).

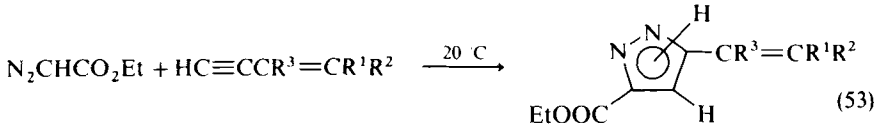


SCHEME 17

The formation of cycloadducts together with products of α-alkylation of diazoesters (see Section III.A.1.c) is also observed in the interaction of MDA with silyl- or germyl-substituted acetylene aldehydes or propiolic acid chloride[138,146,214]. In a number of cases this reaction proceeds selectively and may be of preparative importance for the synthesis of carbofunctionally substituted pyrazoles (see Scheme 18).

Recently propargyl diazoacetate has been found to oligomerize spontaneously as a result of [1,3]-cycloaddition of the $CH{=}N_2$ fragment of one molecule to the terminal triple bond of another molecule[215]. According to PMR and ^{13}C NMR spectra, the crystalline product thus formed is a mixture of oligo-3*H*-pyrazoles and oligo-1*H*-pyrazoles. This transformation of propargyl diazoacetate is the first example of the synthesis of polyheterocyclenes from functionally substituted diazoesters (see Scheme 19).

There are several examples of the formation of 1*H* pyrazoles from EDA and terminal enynes, in which the triple bond is still more electrophilic than in terminal alkynes[216] (see equation 53).

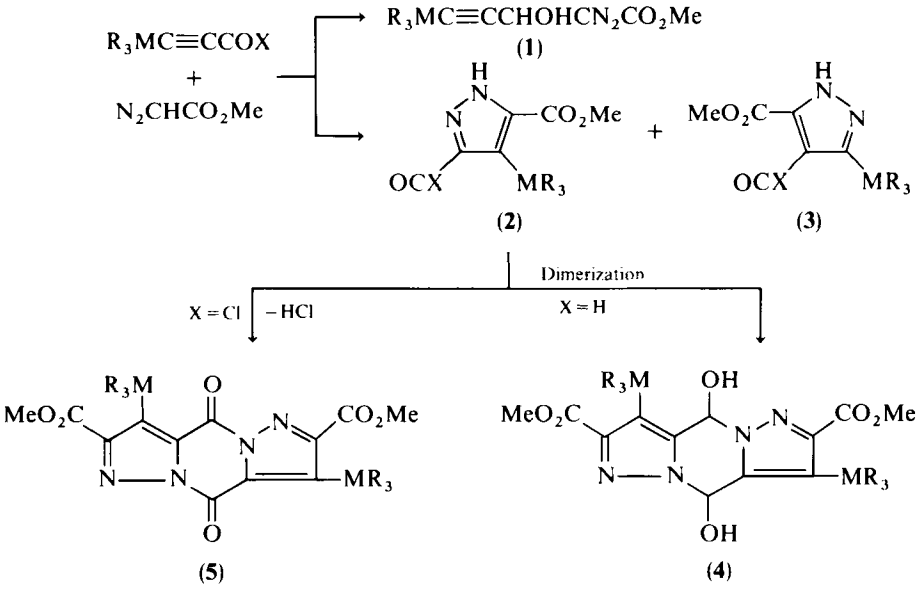


(53)

$R^1 + R^2 = H$, $R^3 = Me$, 49%
$R^1 + R^3 = (CH_2)_3$, $R^2 = H$, 25%
$R^1 + R^2 = (CH_2)_4$, $R^3 = H$, 36%

3. *Multiple C—X and X—Y bonds*

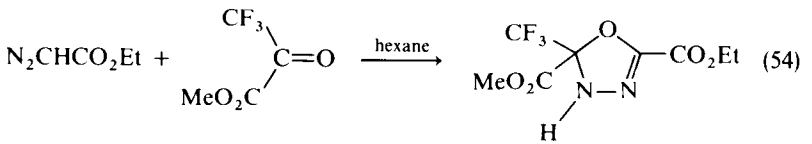
By now, examples of ADA cycloaddition to the C=O, C=S, C=N, C≡N, C=P, C≡P and N=N bonds are known.



			Products (yield, %)				
R	X	M	1	2	3	4	5
Me	H	Si	—	42	—	—	—
Et	H	Si	54	—	25	—	—
Et	H	Ge	27	23	20	—	—
Ph	H	Ge	—	—	6	42	—
Me	Cl	Si	—	—	—	—	17

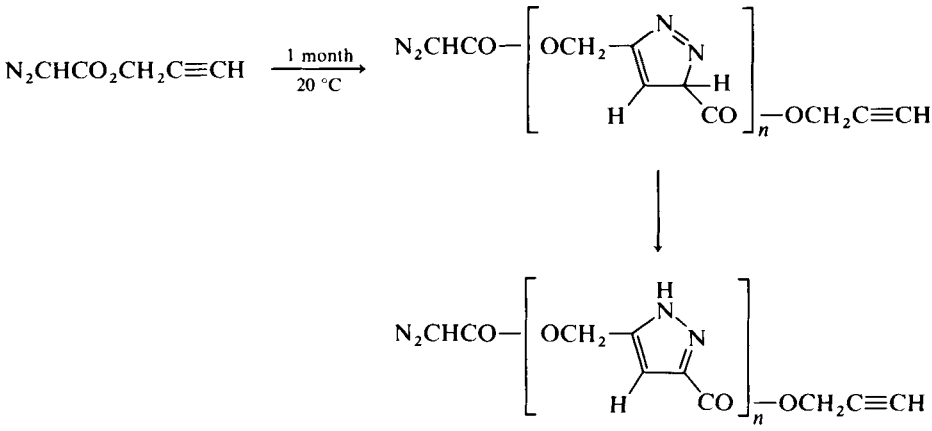
SCHEME 18

Cycloaddition of EDA to the carbonyl group of methyl 3,3,3-trifluoropyruvate gave the corresponding 1,3,4-oxadiazole in 84% yield[217] (see equation 54).

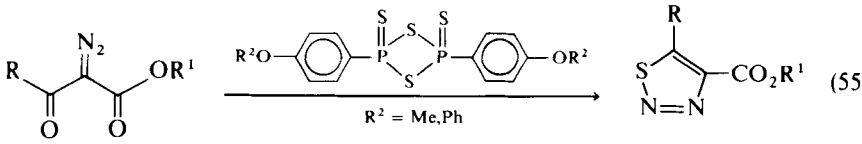


(54)

Diazoesters react similarly with thioketones. Thus, 1,2,3-thiadiazoles were produced in yields up to 95% as a result of intramolecular cycloaddition of the CH=N_2 group to the C=S bond of the derivatives of thioacetoacetic ester, which is formed *in situ* under the action of Lawesson's reagent on the corresponding α-acyldiazoacetates[218] (see equation 55).

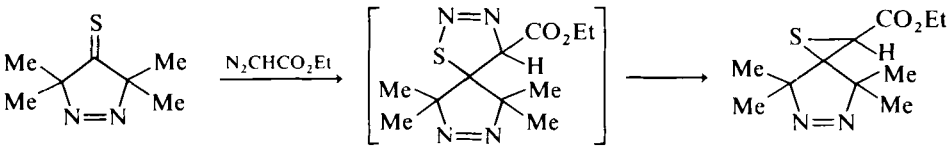


SCHEME 19



(55)

However, the spiro-1,2,3,7,8-thiatetrazole, which is considered to originate in the reaction of EDA with 3,3,5,5-tetramethyl-4-thiopyrazoline, is dediazotized in the course of the reaction, with the formation of thiiranes in 74–99% yields[219] (see equation 56).

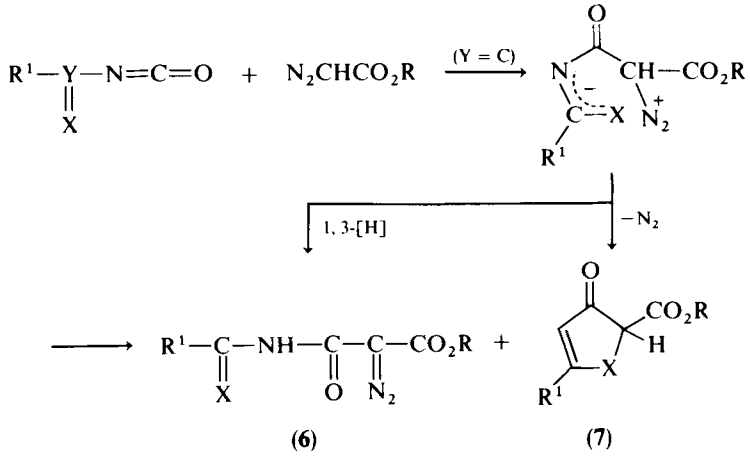


(56)

Cycloaddition of ADA to C=N bonds usually proceeds through zwitterionic intermediates rather than by a concerted mechanism; further transformations of these intermediates may go in several directions: hydrogen migration with the formation of acyclic diazo compounds, cyclization with nitrogen elimination or with diazo group participation. As a result the preparative importance of this reaction is thus not high. For example, reactions of ADA with acylcarbamates in most cases lead to mixtures of diazoesters and furanones or thienones, formed as a result of transformations of the stabilized zwitterion, as shown in Scheme 20[219–221]. Diazoester is the only reaction product in the reaction of EDA with *N*-chlorosulfonylcarbamate at low temperatures[222].

In contrast, reactions of EDA with thiocyanates proceed more selectively and lead to 5-amino-1,2,3-thiadiazoles, often in good yields[217,222] (see equation 57).

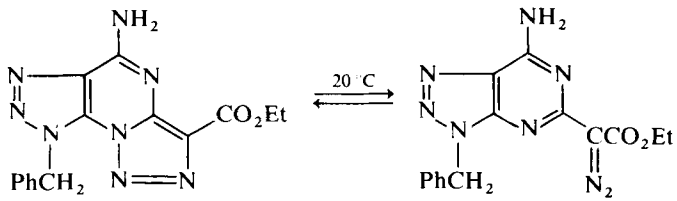
Cycloaddition to C=N bonds may be reversible. The high stability of α-(2-triazolpyrimidinyl)diazoacetate (**9**) leads to an equilibrium with the cyclic form (**8**) as the intramolecular [3 + 2]-cycloadduct to the C=N bond. In solid state the cyclic form is predominant, whereas in solutions the diazoester dominates[223] (see Scheme 21).



(6) (7)

R	X	R^1	Y	Product yields (%) 6	7	References
Et	O	Ph	C	60	—	220
Et	O	MeS	C	14	31	221
Bu^t	S	Ph	C	23	17	222
Et	O_2	Cl	S	40	—	222

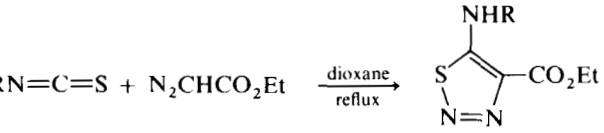
SCHEME 20



(8) (9)

Product ratio (%) 8	9	Solvent
65	35	KBr
20	80	CDCN
7	93	$(CD_3)_2CO$
0	~100	$CDCl_3$

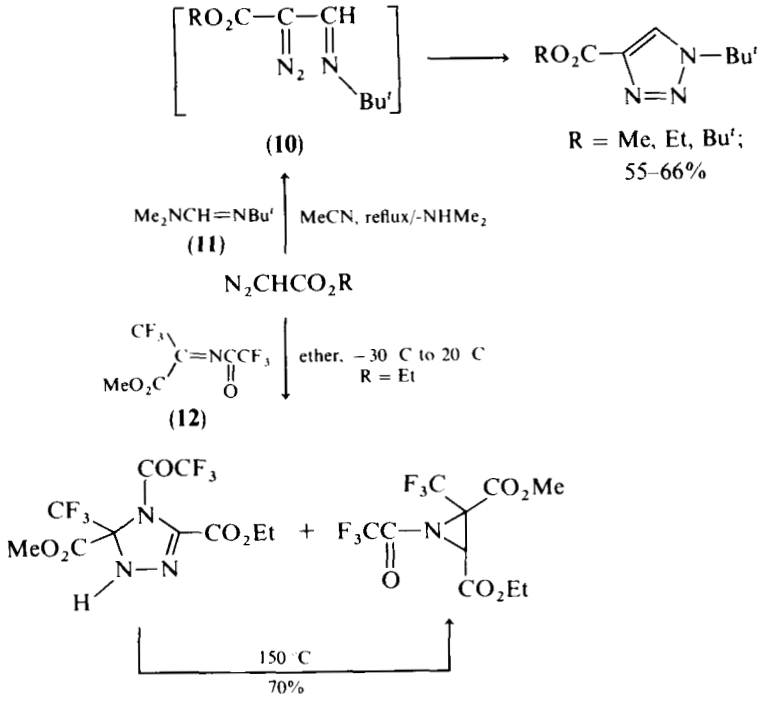
SCHEME 21



(57)

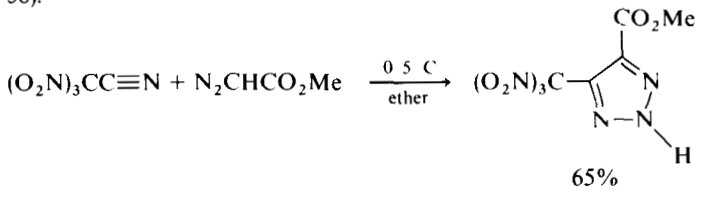
R = allyl, aryl, CO_2Et, PhCO 10 examples, 3–82%

The formation of triazolines, [3 + 2]-cycloadducts of ADA to C=N bonds, has been noted in two cases only: in the course of the reaction of ADA with Schiff base (**11**) as a result of the cyclization of the intermediate unstable ester (**10**)[128] and in the reaction of EDA with the iminoketone (**12**)[224], that leads to a 1,2,4-triazoline together with an aziridine (see Scheme 22).



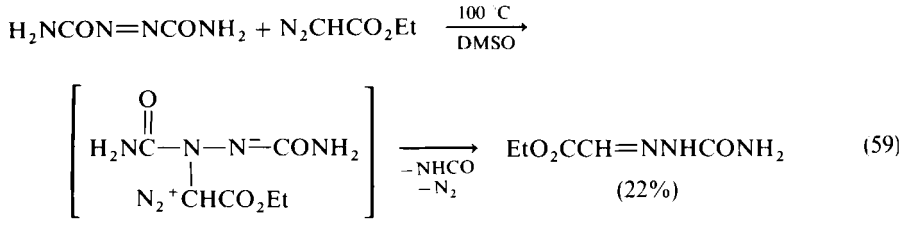
SCHEME 22

Recently, it has been found that cycloaddition of MDA to the C≡N bond in trinitroacetonitrile with formation of a stable 2*H*-1,2,3-triazole takes place[225] (see equation 58).

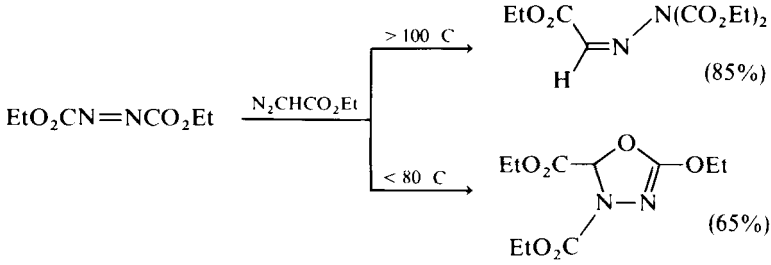


(58)

The interaction of ADA with azo compounds activated by acceptor groups proceeds as a nucleophilic attack of the carbon atom of the diazoester on the electrophilic azo group with the formation of a zwitterionic intermediate. The latter may be transformed into hydrazones or 1,3,4-oxadiazolidines with N_2 and HNCO elimination (see equation 59[226] and Scheme 23[227]). In this case, tetrazolines, i.e. products of [3 + 2]-cycloaddition, are not formed.

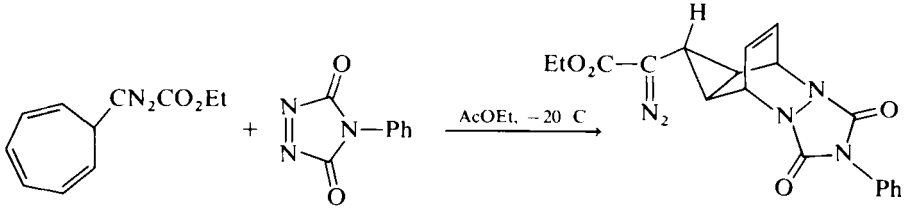


(59)



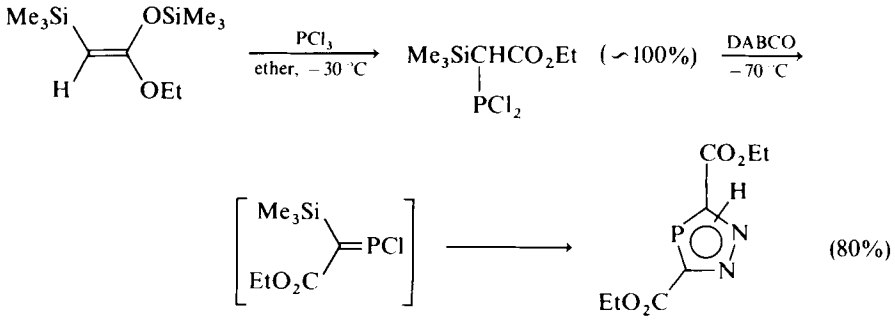
SCHEME 23

If a diene fragment is present in α-substituted diazoesters, e.g. α-(cyclohepta-2,4,6-trienyl)-diazoesters, the reaction with azocarbonyl compounds proceeds as a [4 + 2]-cycloaddition to the N=N bond with formation of the corresponding Diels–Alder adduct[228] (see equation 60).

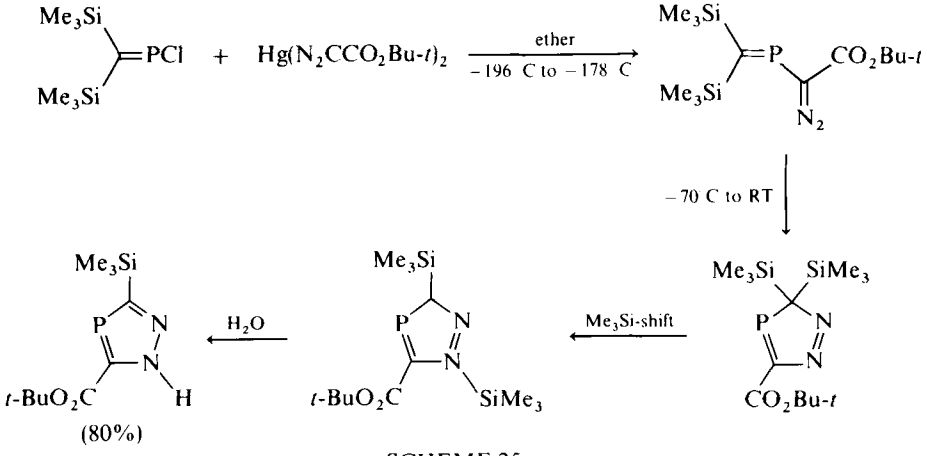


(60)

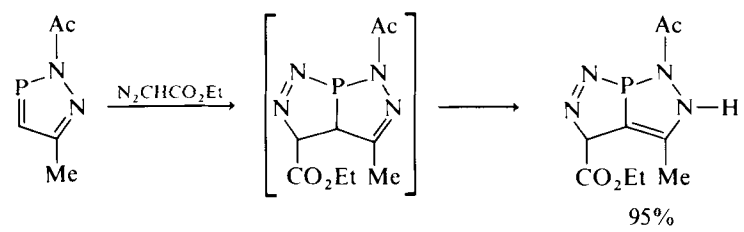
The ability of ADA to add to C=P and C≡P bonds was used for the synthesis of diazophosphols (see Schemes 24[229], 25[230] and 26[233] and equation 61[231,232,234]). In this case activation of the C=P bond by trimethylsilyl substituents ensures effective reaction even at low temperatures.



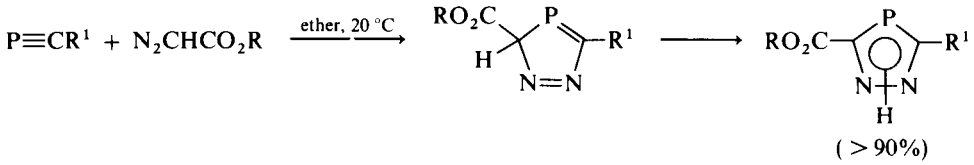
SCHEME 24



SCHEME 25



SCHEME 26



(61)

IV. REACTIONS WITH NITROGEN ELIMINATION

Diazoester dediazotations are accompanied by generation of highly reactive intermediates: first of all, of carbenes and their complexes with transition metals, and also of cationoid reagents and biradicals. Further transformations of these molecules are very diverse and may be accompanied by cleavage of saturated bonds in the substrate and insertion of the $CRCO_2R^1$ fragment into the aliphatic bond (insertion reactions), by its addition to multiple bonds with the formation of three-membered cycles (cyclopropanation or cyclopropenation reactions), by the formation of ylides and products of their transformations, etc. In this connection the problem of increasing the selectivity of reactions with the participation of ACC is a significant challenge.

One of the main methods of solving this problem is to use the catalytic method of dediazotation of diazoesters which makes it possible to carry out reactions under mild conditions and to regulate the activity of carbenes through their complexation with transition metals, usually employed as catalysts. In view of the importance of this subject the review of the dediazotation reactions is preceded by a section in which the present state of the problem of dediazotation catalysts is considered.

A. Catalysts for the Dediazotation Process

The mechanism of catalytic action of different metals and their compounds in the processes of dediazotation is treated in a large number of studies, which are considered critically in an excellent review by Maas[9]. However, in spite of a number of attempts[8,235], the creation of a general theory of catalysis by transition-metal compounds of the reactions of carbene decomposition of diazo compounds has proved to be unsuccessful so far. Nevertheless, the vast experimental data accumulated by now allow one to formulate some empirical rules, helpful in the *a priori* choice of the catalyst.

A large number of transition metal compounds are known, which are capable of causing carbene decomposition of diazoesters. It is traditional to use copper, its salts and complexes. In this case copper powder, copper bronze, $CuSO_4$ and copper(I) halides are usually used as heterogeneous catalysts, whereas $CuCl{\cdot}P(OPh)_3$, copper(II) acetylacetonate [$Cu(acac)_2$] and copper(II) trifluoromethanesulfonate [$Cu(OTf)_2$] are used as homogeneous ones.

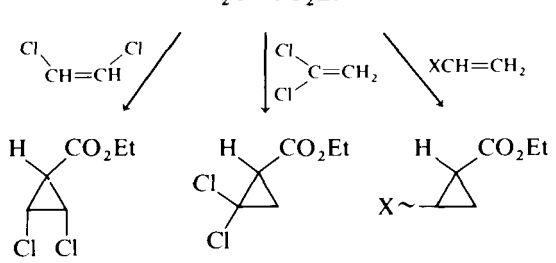
Heterogeneous copper catalysts are advantageous, first of all because they are inexpensive, inert to the starting reagents and easy to isolate from the reaction products, this being of special importance in industrial realization of carbene processes. However, both copper and its salts possess a comparatively low activity, so that in many cases it is necessary to use elevated temperatures (to 100 °C in the case of copper powder), as well as insufficient regio- and stereoselectivity. At the same time, the reported possibility of inducing optical activity in cyclopropane carboxylates with the help of a copper–(L-amino acid) complex, containing x-type zeolites[236], makes further investigations devoted to developing selective heterogeneous catalysts promising.

The advantages of homogeneous copper catalysts are primarily due to their higher activity and selectivity. Thus, $Cu(OTf)_2$ often promotes the process already at 20 °C while homogeneous chiral copper(II) complexes enable enantioselective synthesis of cyclopropanecarboxylates (see Section IV.C.1.a).

The main disadvantage of the homogeneous catalysts is that they are difficult to regenerate from the reaction products. One of the successful attempts to overcome this difficulty is the development of copper cation-exchanged perfluorinated sulfonic acid and carboxylic acid polymers (mol. weight ≥ 5000)[237]. This catalyst, which is a heteroanalogue of $Cu(OTf)_2$, effectively catalyzes cyclopropanation of different olefins already at 20 °C and solves in many respects the problem of recuperation.

Thus, copper catalysts continue to be recommended for extensive application in both laboratory practice and industry.

The catalysts which have received in recent years the most extensive acceptance are rhodium(II) carboxylates and, in particular, $Rh_2(OAc)_4$. These most effective catalysts can be used for cyclopropanation of terminal and nonterminal olefins, strained olefins and some conjugated olefins with excellent yields of cyclopropanes. Thus, rhodium(II) pivalate promotes cyclopropanation with acceptable yields of even such low activity olefins as vinyl halides[238] (see Scheme 27). Copper catalysts are less effective in these reactions[238,239].



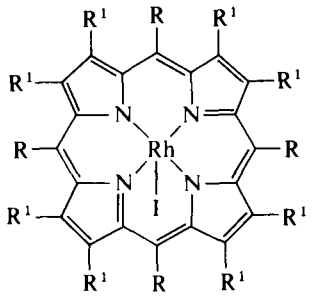
$Rh_2(OCOBu^t)_4$, 25 °C	32%	76%	62% (X = Br)
Cu powder, 80–100 °C	1.4%	20%	9% (X = Br)
CuO, 150 °C, flow reactor	—	—	20% (X = Cl)

SCHEME 27

The influence of the counterion on the reactivity of rhodium(II) carboxylates and on the stereochemistry of the reaction products is studied in a number of investigations[240–242].

Rh(II) compounds are unique catalysts for carrying out cyclopropenation of terminal acetylenes (see Section IV.C.2), insertion reactions (see Section IV.B) as well as ylide formation (see Sections IV.B.4 and IV.C.4). Chiral rhodium(II) carboxylates and rhodium(II) carboxamides make it possible to effect enantioselective synthesis of cyclopropanecarboxylates (see Section IV.C.1.a) and cyclopropenecarboxylates (see Section IV.C.2.a).

Iodorhodium(III) porphyrins[243,244] possess the ability to enhance *syn:anti* selectivity in cyclopropanation of olefins, unapproached by any other transition-metal catalyst. However, the high cost of rhodium compounds necessitates developing methods of their regeneration, as well as searching novel rhodium catalysts, capable of ensuring work at minimal concentrations. Among the latest achievements along these lines we would like to mention the development of an air-stable rhodium carbonyl cluster $Rh_6(CO)_{16}$, which



R = Ph, R^1 = H
R = H, R^1 = Et

in some cases exhibits activity comparable with that of $Rh_2(OAc)_4$ and, for example, allows ethyl chrysanthemate to be synthesized in 90% yield at catalyst concentrations as low as 0.05 mol%[245a]. Performing this reaction in a CO atmosphere provides a possibility to recover the catalyst quantitatively and to use it repeatedly (see equation 62).

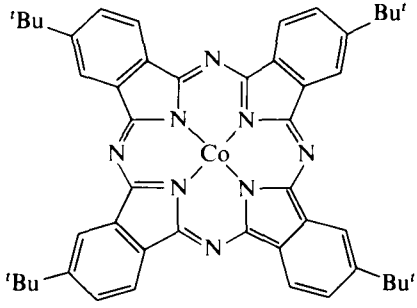
$$N_2CHCO_2Et + Me_2C{=}CHCH{=}CMe_2 \xrightarrow[-N_2]{Rh_6(CO)_{16}} Me_2C{=}CH\text{—}C(Me)(Me)\text{—}CO_2Et \quad (90\%) \qquad (62)$$

The activity of this catalyst in the cyclopropanation of olefins depends on its solubility. This imposes certain limitations on the versatility of $Rh_6(CO)_{16}$.

When planning carbene syntheses with the participation of rhodium catalysts, it is necessary to take into account also their ability to bring about polymerization of the initial olefins and of the reaction products.

The popular catalyst for the dediazotation of diazoalkanes, $Pd(OAc)_2$, is employed much more rarely in reactions of diazoesters and, in the main, in those cases when copper and rhodium compounds do not give the desirable result, for instance, for cyclopropanation of electrophilic olefins[245b].

Among compounds of other transition metals, capable of bringing about carbene decomposition of diazoesters, one should point to complexes of Co(II), Ni(II), Fe(II), Mn(III), Ru(II) and W(0). Thus, Fe(II)·Py_2, Ni(II), Rh(III)Cl and especially Co(II) tetra-4-*t*-butylphthalocyanine complexes (**13**) are effective catalysts for cyclopropanation of conjugated olefins (styrenes, methacrylates, methacrylonitriles, dienes and enynes) with EDA[246].

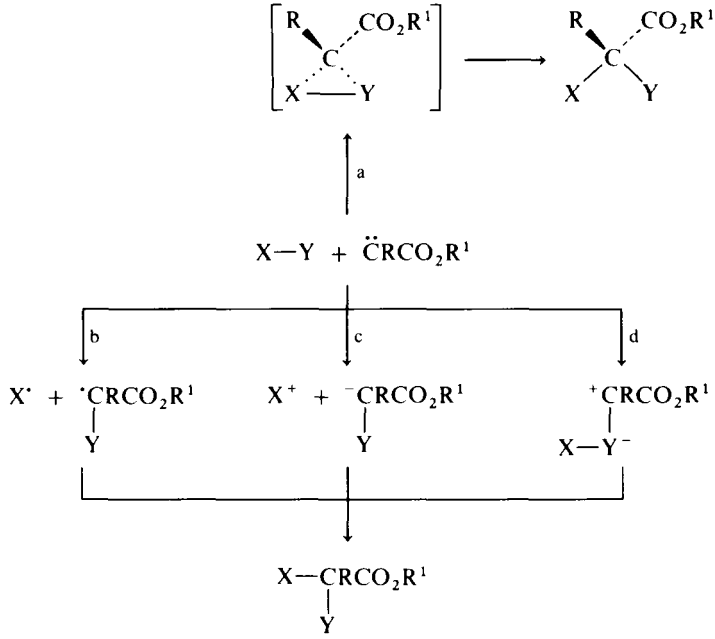


(**13**)

Chiral cobalt(II) camphor dioxamate complex makes it possible to carry out enantioselective cyclopropanation of styrene with a high enantioselective excess[247]. Unfortunately, in reactions with other olefins the effectiveness of this catalyst is not high. There are examples of using $Ru_3(CO)_{12}$ for intramolecular cyclopropanation[248]. However, $Ru_2(OAc)_4$-promoted interaction of norbornene and styrene with EDA is accompanied by competitive selective cross-metathesis of alkenes and leads to the corresponding cyclopropane adducts with low yields[249]. In the presence of the Fischer carbene complex $(CO)_5W{=}C(OMe)Ph$ reactions of EDA with alkenes at 35 °C lead to the corresponding cyclopropanes in 25–70% yields[250].

B. Reactions with Single Bonds

The ability of ACC, generated by dediazotation of diazoesters, to react with saturated σ-bonds with the formation of insertion products provides extensive opportunities for carbofunctionalization of compounds containing no multiple bonds. This reaction is presented in a general form in Scheme 28.



SCHEME 28

Cleavage of the X—Y bond and formation of C—X and C—Y bonds occur in the course of the process. This transformation may be realized either in a concerted manner through a three-center transition state (path a) or stepwise by the abstraction–recombination type with the participation of radical moieties (path b), of dipolar intermediates (path c) or of ylide structures (path d). When X or Y are chiral atoms, concerted insertion (path a) proceeds with preservation of configuration, while abstraction–recombination types of insertion lead to racemization.

The true mechanism depends not only on the structure of the substrate but also on the method of carbene generation, and it is not quite clear in many cases. In particular the application of a catalyst, capable of giving electrophilic complexes with carbene, will complicate the mechanism of insertion reactions, though it does not change it essentially.

Mechanistic aspects of these reactions are covered adequately in the literature[2,4–6,8,9,14]. In the present review studies of the last decade are mainly discussed, considering the synthetic potentialities of insertion reactions into ordinary C—H, heteroatom–hydrogen, carbon–heteroatom or heteroatom–heteroatom bonds.

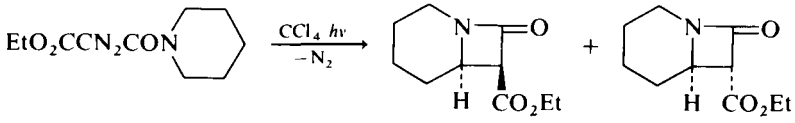
1. C—H bonds

The known reactions of insertion of ACC into the C—H bonds of alkanes, alkenes and alkynes may be represented in a general form by the following equation:

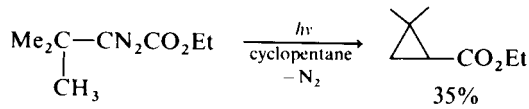
$$\geq C{-}H + N_2CRCO_2R^1 \xrightarrow[-N_2]{h\nu,\ \Delta,\ Cat} \geq C{-}CHRCO_2R^1 \qquad (63)$$

The synthetic applicability of the reaction with alkanes is limited, since because of a high reactivity of ACC is proceeds with low selectivity to primary, secondary and tertiary C—H bonds, as well as being accompanied by oligomerization of carbenes and hence leading usually to mixtures of products. However, with the use of rhodium(II) carboxylate catalysts a high total products yield (up to 90%) can be reached[251]. The regularities of the catalytic action of these catalysts, depending on the structure of the substrate, diazoester, counterion and on the catalyst concentration, are considered in a number of publications[252,253]. High yields of the products of insertion into C—H bonds of alkanes can also be obtained with the use of a traditional copper catalyst (CuCl) in combination with diazoacetates having a complicated alcoholic component, e.g. prenyl diazoacetate[254]. The intermolecular reaction of C—H insertion found practical application for the modification of ethylene–propylene rubber by copyrolysis with EDA at 210 °C (the degree of functionalization is 5–10%)[255].

Intramolecular reactions of C—H insertion are of considerably greater importance for organic synthesis. Thus, selective transformations of diazomalonohexanimide (equation 64[256]) and some diazoesters (equations 65[179], 66[257] and 67[258]) into esters of cyclic carboxylic acids were carried out successfully using copper catalysts or by dediazotation due to irradiation or pyrolysis.



(64)



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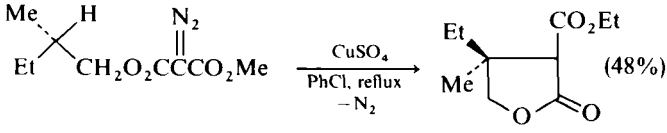
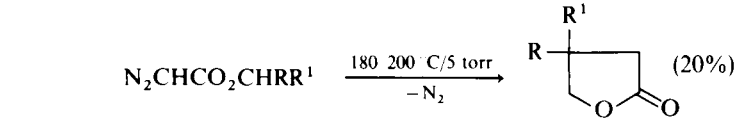
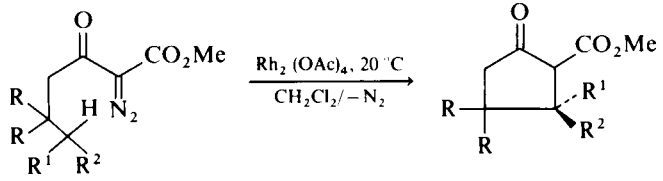


(66)



(67)

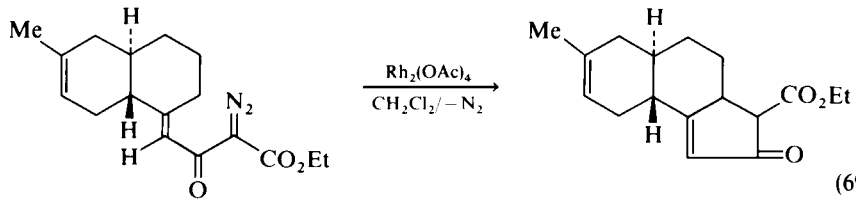
The application of rhodium(II) carboxylate catalysts allows one to use milder conditions for carrying out these reactions, attaining higher yields and selectivity[259,260] (see equation 68).



(55–77%) (68)

R = Me, *i*-Pr, C_8H_{17}, $CH{=}CH_2$, $CH_2CH{=}CMe_2$
R^1, R^2 = H, Me

The activity of the C—H bonds in this reaction decreases in the series tertiary > secondary > primary, all of them being more active than the protons of benzyl and allyl types[264,265]. However, steric factors can essentially change this order of bond activity. For instance, Rh-promoted cyclization of a carbene may proceed with the participation of the secondary C atom, not of the tertiary one (see equation 69)[263].



(69)

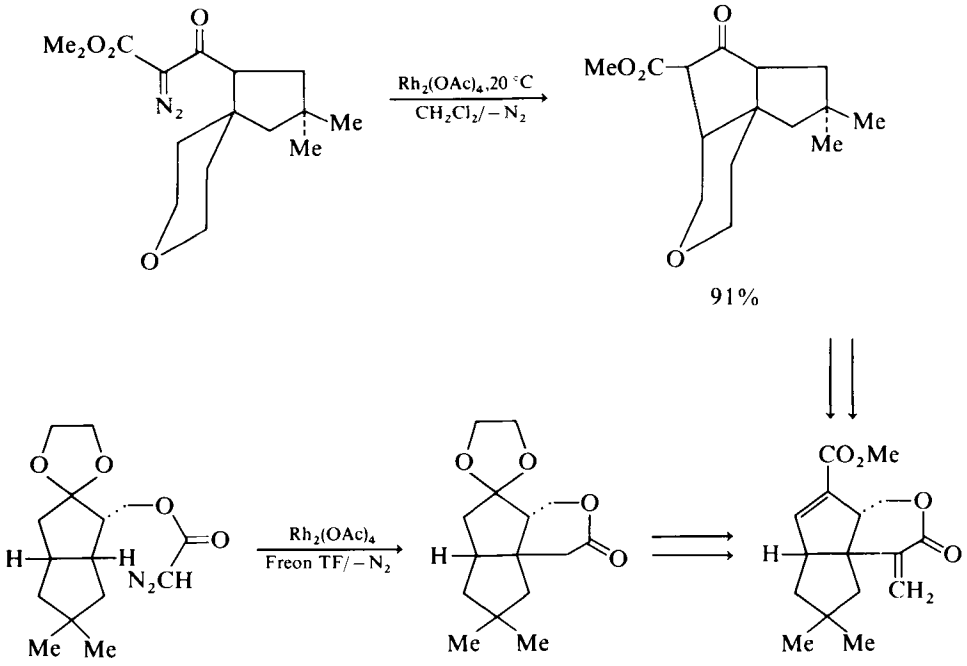
This case also demonstrates the ability of Rh(II) catalysts, unlike Cu catalysts, to promote C—H insertion even in the presence of a double bond.

Sensitivity of intramolecular insertion reactions to steric factors should be taken into account when choosing the strategy of the synthesis. Thus, two schemes, proposed by Taber[261] and Cane[262] for the synthesis of pentalenolactone (see Scheme 29), are based on the preference of an attack by the carbene on the sterically most accessible bond, although in Cane's scheme this leads to the formation of a six-rather than a five-membered cycle.

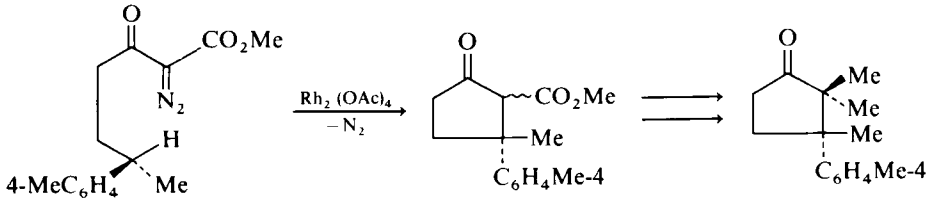
The Rh(II)-induced insertion reactions in the case of α-acyldiazoacetates are noted for a high degree of stereoselectivity and proceed with retention of the configuration of the attacked carbon atom, which was used, for example, by Taber's group for the synthesis of α-cuparenone[265] (see Scheme 30).

The same group established the *trans*-selectivity of 3,4-dialkyl cyclopentanone substituents[266] (see equation 70) and the enantioselectivity of cyclization of the rhodium-carbene complex from the chiral diazoketoester precursor[267] (see equation 71).

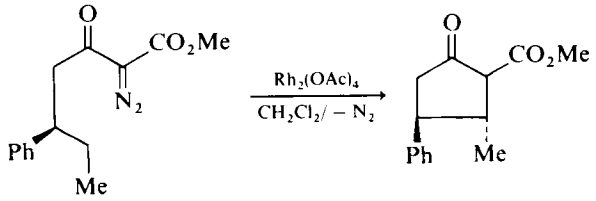
The bulky naphthalene moiety of the (+)-camphor diazoester derivative effectively shielded one face of the pendant chain of the substrate and favored the insertion of the carbene center into the $C—H_R$ bond. This scheme makes it possible to realize en-



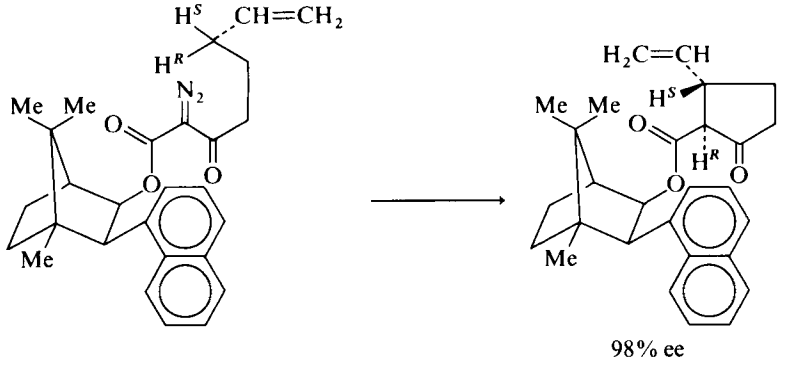
SCHEME 29



SCHEME 30



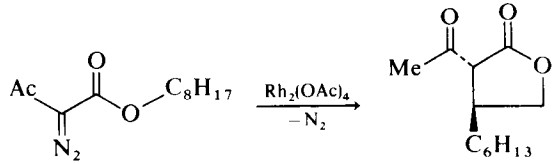
(66% *trans* only) (70)



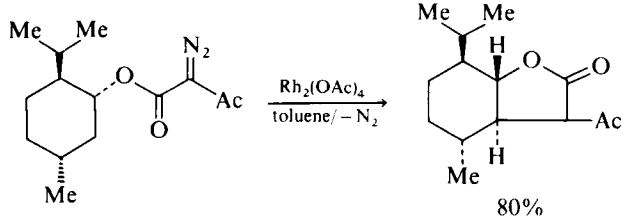
(71)

antioselective syntheses of cyclopentanones, in which the ester can be easily transformed by hydrolysis and decarboxylation.

The reactions of C—H insertion involving the alcohol moiety of α-acyldiazoacetates under the effect of rhodium(II) acetate and rhodium(II) acetamide catalysts proceed with an equally high selectivity. In such a way it is possible to produce γ-lactones with a high yield and with high regio- and diastereoselectivity[268] (see equations 72 and 73).

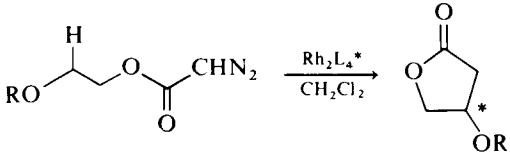


(72)



(73)

In recent years data have been published on asymmetric synthesis of lactones with a high enantioselectivity (50–85% ee) by intramolecular C—H insertions of some alkoxyethyl diazoacetates in the presence of chiral rhodium(II) carboxamides, in particular, dirhodium(II) tetrakis[methyl-2-pyrrolidone-(*S* or *R*) carboxylate] $[Rh_2(MEPY)_4]$[269] (see equation 74).

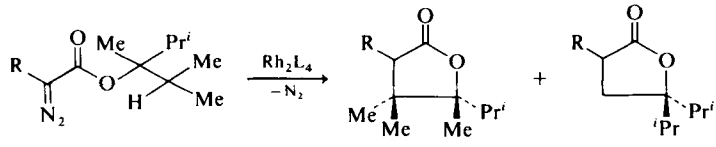


(74)

R = Me, Et, $PhCH_2$; 42–56%

$Rh_2L_4^*$ = *R*- or *S*-$[Rh_2(MEPY)_4]$ 77–85%

TABLE 6. Regioselectivity of intramolecular C—H insertion reactions with the participation of the alcohol moiety of diazoacetates



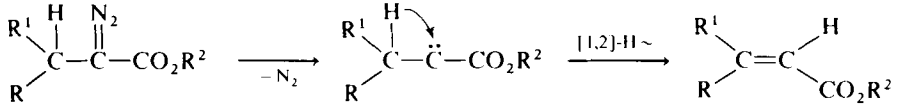
(14) (15)

Rh_2L_4[a]	R = H total yield (%)	R = H 14:15 ratio	R = Ac total yield (%)	R = Ac 14:15 ratio
$Rh_2(pfb)_4$	56	32:68	45	45:55
$Rh_2(OAc)_4$	81	53:47	97	90:10
$Rh_2(acam)_4$	96	>99:1	89	>99:1

[a] $Rh_2(Pfb)_4$ = rhodium(II) perfluorobutyrate, $Rh_2(acam)_4$ = rhodium(II) acetamide.

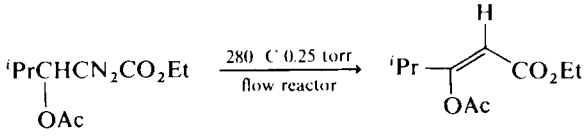
Intramolecular C—H insertion reactions with the participation of the alcohol moiety or diazoacetates are very sensitive to the structure of the diazoester and of the catalyst counterion. Thus, both diazoacetates and α-acyldiazoacetates in the presence of rhodium(II) perfluorobutyrate are cyclized with the predominant formation of the products of C—H insertion into the bond formed by the primary carbon atom, the process selectivity in the case of diazoacetates being somewhat higher[268] (see Table 6). On the other hand, under the action of rhodium(II) acetate and rhodium(II) acetamide the reaction proceeds practically only with respect to tertiary C—H bonds.

An interesting case of intramolecular transformations of diazoesters with the participation of C—H bonds is the [1,2]-hydride shift of the hydrogen atom toward the neighboring carbene center with the formation of acrylic acid derivatives (see Scheme 31).



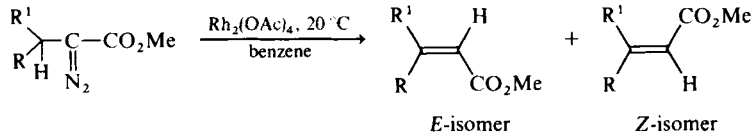
SCHEME 31

In the absence of active carbene acceptors this rearrangement is the main process in the thermal dediazotation of the esters of α-substituted diazoacetic acid (see equation 75), and also under the action of transition-metal catalysts (see Scheme 32[170] and Scheme 33[271], path a) or Lewis acids[272] (see Scheme 34, path a).



(75)

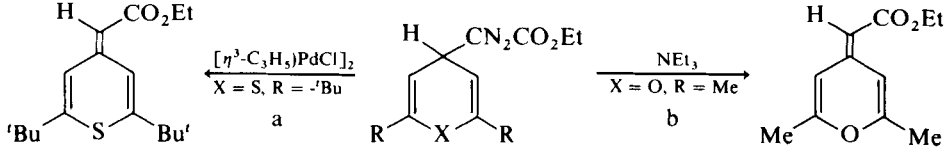
Under these conditions acrylic acid derivatives are produced with high yields (to 98%) and predominantly in the form of Z-isomer; in the case of H-shift of the hydrogen



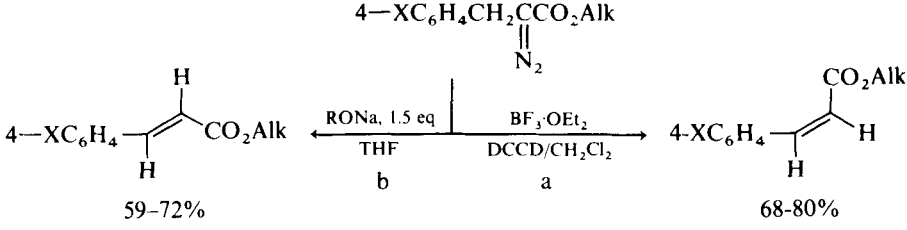
R	R^1	Share of *Z*-isomer (%)	Total yield (%)
^{i}Pr	H	~100	99
Ph	H	~100	~100
$PhCH_2O$	H	~100	90
Me	Et	57	95
$H_2C{=}CH$	H	~100	39[a]

[a] Another product is methyl bicyclo[1.1.0]butanoate (51% yield).

SCHEME 32



SCHEME 33



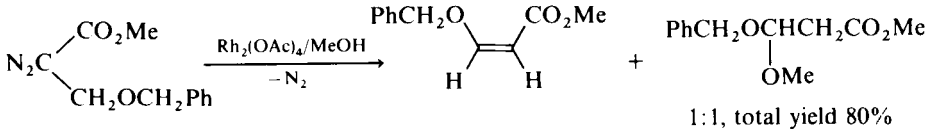
X = H, NO_2, MeO

SCHEME 34

atom of the methylene fragment the reaction leads only to the *Z*-isomer. Similar transformations of diazoesters may be initiated by bases (see Scheme 33, path b[273], and Scheme 34, path b[272]). In the last case, however, the reaction leads to the *E*-isomer.

Migration of hydrogen to a substantial extent proceeds in the case of rhodium(II)-catalyzed dediazotation of some diazoesters with an active methylene group even in the presence of methanol[170], which under these conditions is an active carbene acceptor (see Section IV.B.2.b); see equation 76.

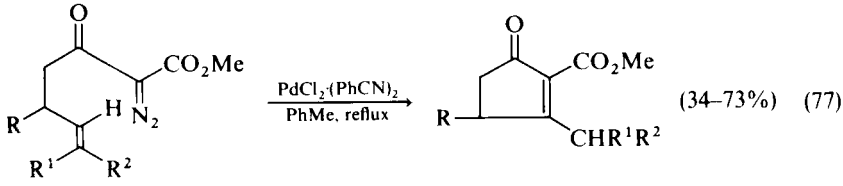
The known examples of C—H insertion reactions of carbenes into vinyl C—H bonds of alkenes are few in number. Thus, though ACC, generated by ADA photolysis



1:1, total yield 80%

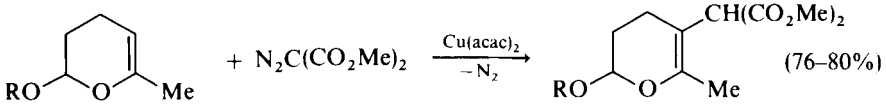
(76)

or pyrolysis, in the reaction with olefins give predominantly cyclopropane adducts, products of insertion into the vinyl C—H bonds are also formed in small quantities (3–5%)[274]. On the contrary, catalytic dediazotation of ADA allows one to obtain the corresponding C—H insertion products with a high selectivity. Thus, intramolecular transformation of α-acyldiazoacetates under the effect of palladium(II) catalysts leads to 3-alkyl-2-carbomethoxycyclopentenones[275] (see equation 77).



(34–73%) (77)

The formation of vinyl insertion products also occurred in the reaction of MDM with vinyl esters in the presence of copper catalysts[276]. However, the reaction with EDA under these conditions leads only to the cyclopropane adduct[277] (see equation 78).



(76–80%)

(78)

The products of formal insertion of carbenes into aromatic C—H bonds are formed in reactions of ADA with arenes and heteroarenes as well. Taking into account the preparative importance of these reactions, they are discussed separately in Sections IV.C.3. and IV.C.4.

The examples of ACC insertion into the C—H bonds at the sp-hybridized carbon atom of alkynes are still fewer in number. As with alkenes, direct insertion of carbenes into these bonds with the formation of 3-alkynoates is unlikely. Indeed, ADA photolysis in the presence of terminal alkynes leads, along with cyclopropenes, to C—H insertion products in the alkyl substituents[208].

The formation of formal products of insertion into the acetylene C—H bond of terminal acetylenes was observed in catalytic dediazotation of ADA[278]. However, in this reaction they are obviously obtained from the initially formed 1-pyrazoles[208] (see Section III.B.2); see equation 79.

$$^{t}BuC{\equiv}CH + N_2CHCO_2Et \xrightarrow{Cu,\ 100\ ^{\circ}C} {}^{t}BuC{\equiv}CCH_2CO_2Et + {}^{t}BuCH{=}C{=}CHCO_2Et \qquad (79)$$

The only example of a preparative reaction of this type is copyrolysis of acetylene

with EDA over a copper contact in a through-flow reactor, which led to butynoic acid ester (see equation 80).

$$HC{\equiv}CH + N_2CHCO_2Et \xrightarrow[\text{flow reactor, } -N_2]{\text{CuO/pumice, 50–180 °C}} HC{\equiv}CCH_2CO_2Et\ (36\text{–}50\%) \quad (80)$$

In a similar reaction with methylacetylene the yield of the corresponding ester did not exceed 16%. However, the synthesis of 3-alkynoates from lithium derivatives of terminal acetylenes with the use of ADA can be carried out in three steps (see Scheme 35): borylation of 1-alkynes, interaction of the obtained trialkynylboranes with EDA in THF under −20 °C and final hydrolysis[281].

$$RC{\equiv}CH \longrightarrow RC{\equiv}CLi \xrightarrow[THF]{BF_3\cdot OEt_2,\ -20\ °C}$$

$$(RC{\equiv}C)_3B \xrightarrow[2.\ H_2O]{1.\ N_2CHCO_2Et/THF/-20\ °C/-N_2} RC{\equiv}CCH_2CO_2Et\ (63\text{–}92\%)$$

R = Bu, *t*-Bu, Ph, allyl

SCHEME 35

2. X—H bonds

ADA and other diazoesters, upon irradiation, heating and under the effect of catalysts, react with compounds containing heteroatom–hydrogen bonds, with the formation of the insertion products of the corresponding carbenes (see equation 81). Insertion into

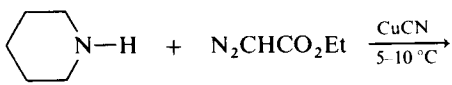
$$RXH + N_2CRCO_2R^1 \xrightarrow[-N_2]{h\nu,\ \Delta,\ Cat} RXCHRCO_2R^1 \quad (81)$$

N—H, O—H, S—H, Si—H and Ge—H bonds are known which, as a rule, proceed with high yields and selectivity.

a. N—H bonds. Both aliphatic (see equations 82[282] and 83[283]) and aromatic primary and secondary amines (see equation 84[284] and 85[285]) enter into the reaction with ADA irrespective of the method of its dediazotation, giving *N*-alkylated glycine esters with high yields.

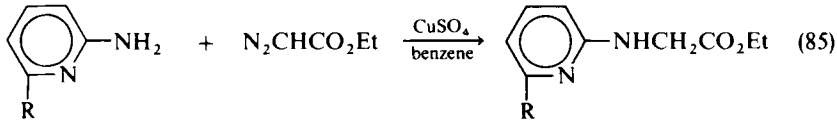
$$Et_2NH + N_2CHCO_2Et \xrightarrow{Cat} Et_2NCH_2CO_2Et \quad (82)$$

Cat = CuCN (72%), CuCl (33%)



$$+ N_2CHCO_2Et \xrightarrow[5\text{–}10\ °C]{CuCN} \quad (72\%) \quad (83)$$

$$PhNH_2 + 2\,N_2CHCO_2Me \xrightarrow[45\text{–}50\ °C]{Rh_2(OAc)_4} PhN(CHCO_2Me)_2 \quad (61\%) \quad (84)$$

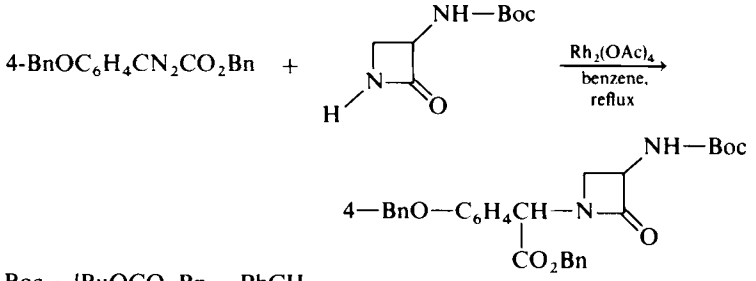


(85)

R = H or Me

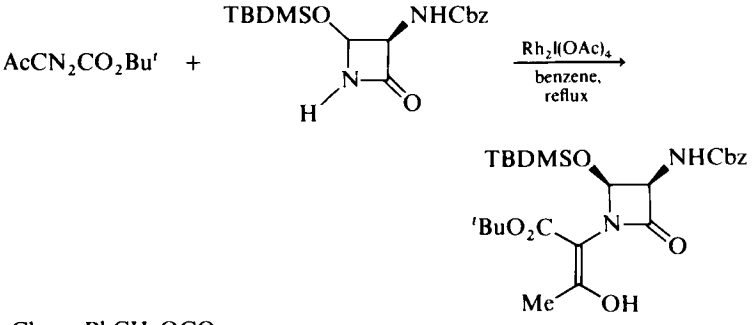
Intermolecular catalytic N—H insertion proceeds so easily, that dediazotation of 2-alkylaminoethyl diazoacetates even in the presence of olefins leads not to cyclopropane adducts but exclusively to oligomers, as a result of carbene center insertion into the N—H bond of another molecule[167].

The use of the rhodium(II) acetate catalyst allows the intermolecular N—H insertion reactions to be effected with such labile products as azetidinones. In the case of 3-aminoazetidinones this reaction proceeds extremely selectively, only at the nitrogen atom in the cycle, and leads to *N*-alkylated azetidinones—building blocks for producing β-lactam antibiotics (see equations 86[286] and 87[287]).



(67%) (86)

Boc = ^{t}BuOCO, Bn = $PhCH_2$

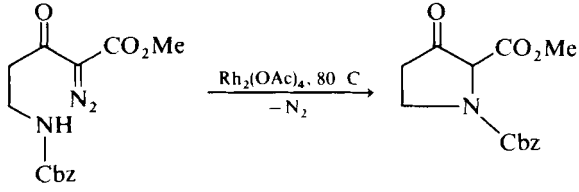


(54%) (87)

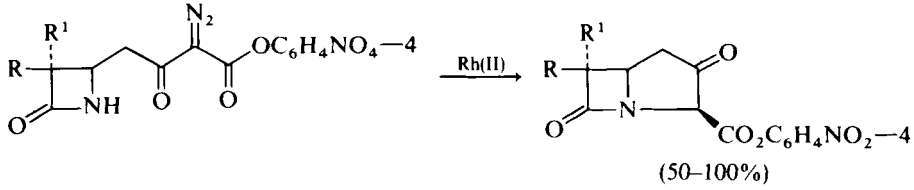
Cbz = $PhCH_2OCO$

Examples of intramolecular N—H insertion of diazoesters under dediazotation conditions under the effect of Rh(II) compounds are also known. However, these reactions proceed effectively only in the case of compounds containing the N—H bond at the C atom in the δ-position. Thus, cyclization of methyl 5-(substituted amino)-3-oxo-2-diazopentanoate leads to 3-oxopyrrolidine-2-carboxylate[288] (see equation 88).

The N—H insertion of rhodium(II)-promoted metal carbenes from α-acyldiazoacetates containing an azetidinone fragment is extensively used for the synthesis of β-lactam antibiotics[289] (see equation 89).



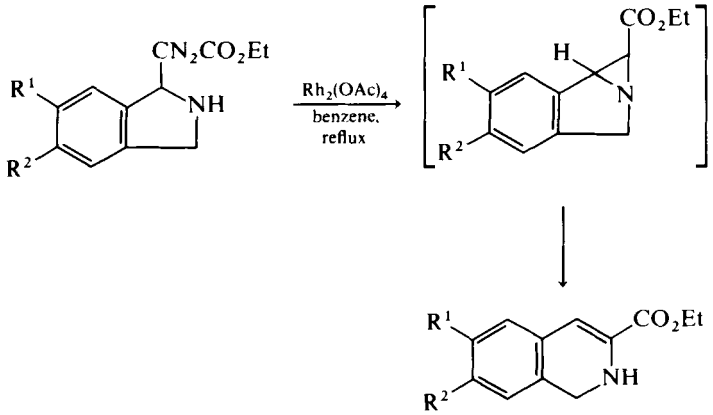
(90%) (88)



(50–100%)

(89)

Examples of intramolecular diazoester cyclizations with the participation of a more or less remote amino group are extremely scarce. Thus, cyclization of α-aminodiazoesters with the formation of unstable aziridines which isomerize into isoquinolinecarboxylates (involving the opening of the three-membered ring) has recently been found to occur[291] (see equation 90).

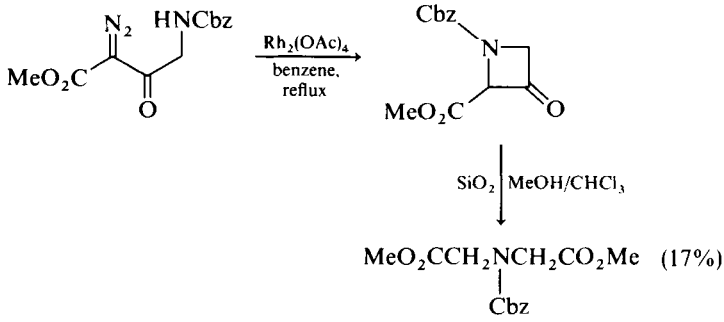


(56–66%) (90)

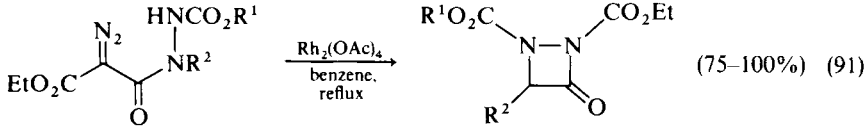
Reactions of intramolecular N—H insertion with the participation of a γ-amino group are also known. For instance, rhodium(II)-catalyzed decomposition of methyl 4-(N-protected amino)-3-oxo-2-diazobutanoate leads, though in poor yield, to 2-oxoazetidine-2-carboxylates, which easily isomerize upon isolation into glycine derivatives[290] (see Scheme 36).

Cyclization of monocarbazides of diazomalonates under these conditions proceeds substantially more easily, leading to 1,2-diazetidinones with high yields[292] (see equation 91).

The reaction of intramolecular N—H insertion in diazoesters with a δ-amino group is complicated by the formation of side products of C—H insertion into the

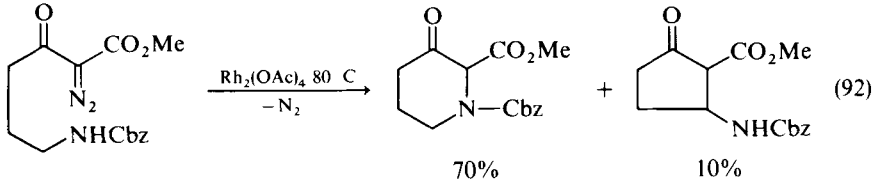


SCHEME 36

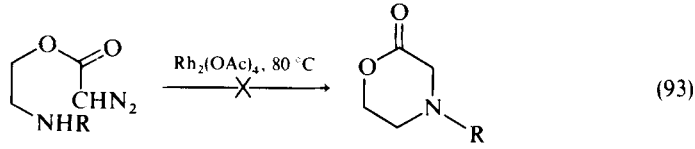


(75–100%) (91)

γ-position[290] or does not proceed at all, as has been noted in the transformations of 2-aminoethyl diazoacetates[167] (see equations 92 and 93).

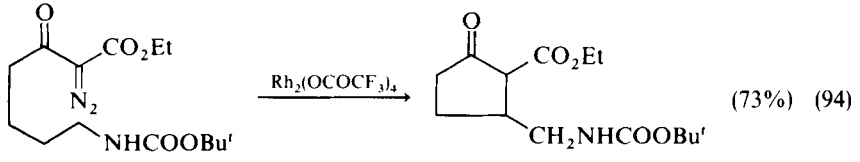


(92)



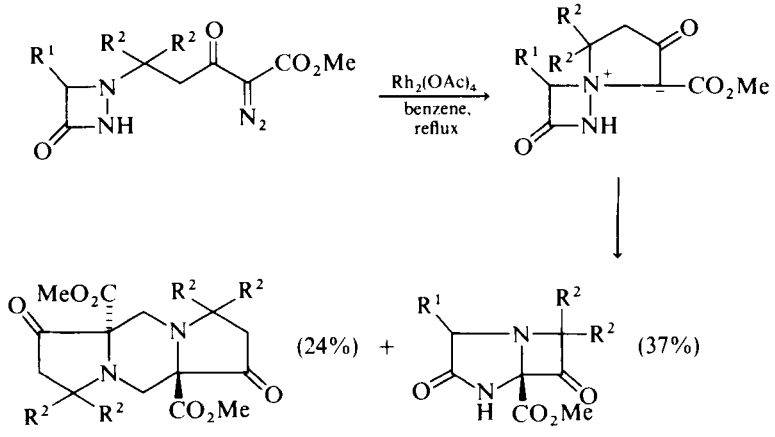
(93)

The data regarding N—H insertions with the participation of more remote amino groups are contradictory. Thus, cyclization in the case of *t*-butyl ethyl-7-amino-3-oxo-2-diazocaproate leads exclusively to the products of C—H insertion at the δ-atom of carbon[152b] (see equation 94).

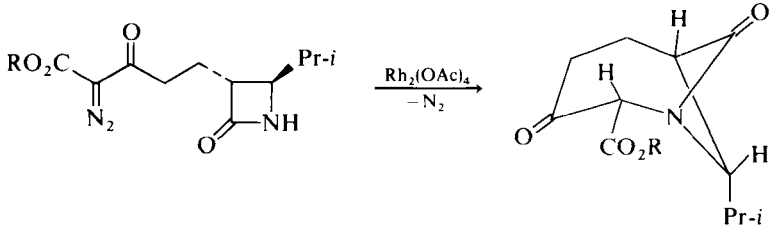


(73%) (94)

In the absence of C—H bonds at the δ-atom, as in the case of methyl 5-(1,2-diazetedinyl)-3-oxo-2-diazopentanoate, products of insertion into the cyclic C—N bond of azetidine are formed, apparently, through intermediate formation of ylides[293] (see Scheme 37). Recently, however, a carbene center has been found to insert intramolecularly into the N—H bond, separated by a chain of 5 C atoms[294] (see equation 95).



SCHEME 37



(95)

b. O—H bonds. Reactions of ADA with hydroxy compounds, leading to the formation of the products of insertion of the corresponding carbenes into O—H bonds, are rather diverse. Thus, some organic acids, for example, trifluoromethanesulfonic acid, are capable of reacting with EDA in liquid SO_2 at −78 °C with the formation of the corresponding glycolic acid sulfonate [295] (see equation 96).

$$CF_3SO_2OH + N_2CHCO_2Et \xrightarrow[-78\ ^\circ C]{\text{liquid } SO_2} CF_3SO_2OCH_2CO_2Et\ (73\%) \quad (96)$$

However, other hydroxy compounds (water, alcohols, carboxylic acids) give O—H insertion products only in photolysis, pyrolysis or in catalyst-initiated dediazotation of ADA[283,296] or of their α-metallated derivatives[97] (see equation 97).

$$ROH + N_2CR^1CO_2R^2 \xrightarrow{h\nu,\ \Delta,\ Cat} ROCHR^1CO_2R^2 \quad (97)$$

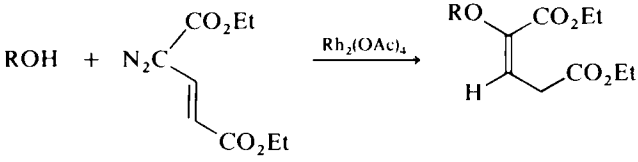
R = H, alkyl, Ac
R^1 = H, MeHg

This reaction became of preparative importance only after the discovery of catalysts based on rhodium compounds, ensuring high yields (>80%) with different diazoesters and with a wide range of hydroxy compounds[240].

The effectiveness of these catalysts allows one to realise reactions even with diazoacetates having complicated structures, such as reaction of propargyl diazoacetate with water[215] (see equation 98).

$$H_2O + N_2CHCO_2CH_2C{\equiv}CH \xrightarrow[CH_2Cl_2]{Rh_2(OAc)_4,\ 20\ ^\circ C} HOCH_2CO_2CH_2C{\equiv}CH\ (15\%) + O(CH_2CO_2CH_2C{\equiv}CH)_2\ (20\%) \quad (98)$$

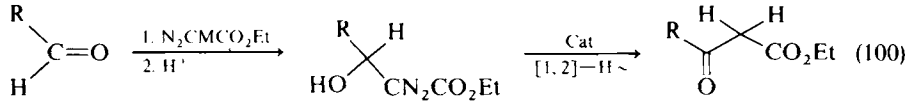
In the case of carbenes containing an allyl moiety, for instance, with a $Rh_2(OAc)_4$-promoted carbene from ethyl α-(2-ethoxycarbonylvinyl)diazoacetate, the insertion is accompanied by a [2,3]-sigmatropic rearrangement[297] (see equation 99).



$$ROH + N_2C(CO_2Et)CH{=}CHCO_2Et \xrightarrow{Rh_2(OAc)_4} RO(CO_2Et)C{=}CH(CO_2Et)H \quad (72\text{–}91\%) \quad (99)$$

R = Me, Et, i-Pr, t-Bu

Examples of intramolecular transformations of diazoesters with the participation of O—H bonds have a number of specific features, compared with similar reactions of N—H insertion. Thus, rhodium(II)-induced dediazotation of β-hydroxy-α-diazopropionate leads not to three-membered heterocycles as in reactions with the participation of β-amino-α-diazoacetates (equation 90), but to acylacetates as a result of [1,2]-H-shift[170,298–301] (see equation 100).



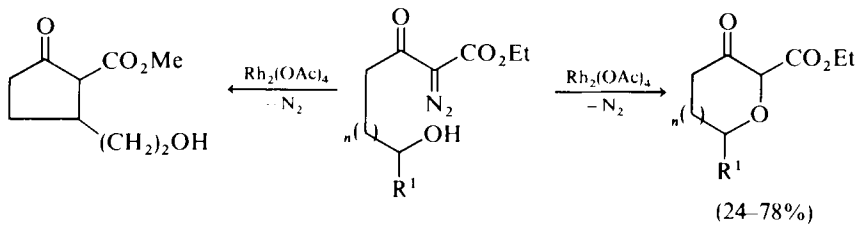
$$R(H)C{=}O \xrightarrow[2.\ H^+]{1.\ N_2CMCO_2Et} R(H)C(OH)CH(N_2CO_2Et) \xrightarrow[[1,2]-H\ shift]{Cat} R(H)C(H)CH(CO_2Et)C(=O) \quad (100)$$

(71–100%)

Cat = Rh_2L_4, Sn(II)

R = H, alkyl, Ph, $H_2C{=}CH$, trans-PhCH=CH etc.

Furthermore, with the help of N—H insertion reactions, as a rule, one cannot obtain rings with more than six atoms; attempts to obtain larger rings led to the



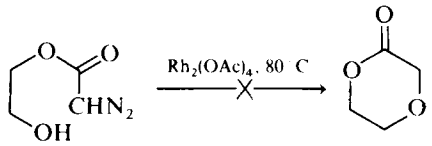
$n = 5$, $R^1 = H$ $n = 1\text{–}3$

(24–78%)

SCHEME 38

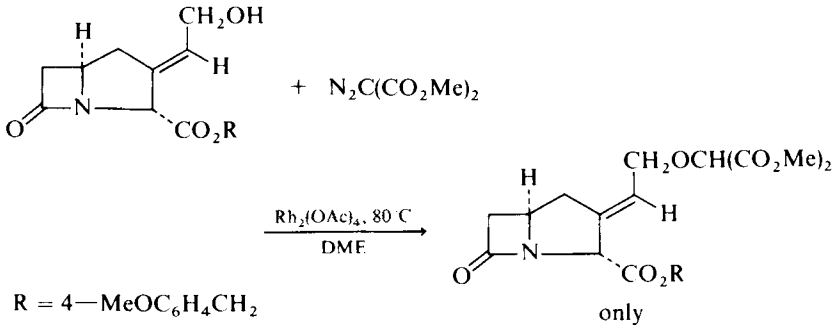
formation of cyclopentanones, i.e. products of competitive C—H insertion, whereas similar cyclizations with the participation of hydroxyl-containing diazoesters lead easily to 6-, 7- and 8-membered cyclic esters with high yields[153,302] (see Scheme 38).

The preparation of 1,4-dioxanone-2 by $Rh_2(OAc)_4$-promoted cyclization of 2-hydroxyethyl diazoacetate also failed. The dediazotation of this diazoester resulted in oligomer formation probably by intermolecular O—H insertion[43] (see equation 101).

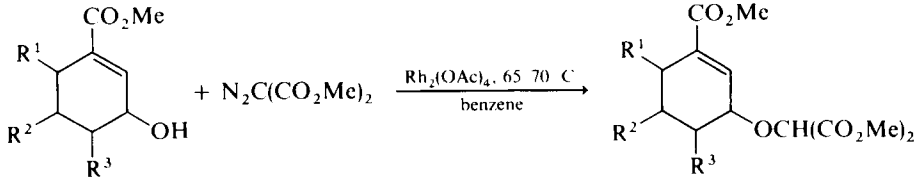


(101)

The insertion reactions with the participation of allyl and propargyl alcohols are a specific case, since the carbenes formed are capable of adding to the multiple bond and yield also cyclopropane and cyclopropene adducts, so that the synthetic value of the reaction is lowered[303,304]. Nevertheless, in the case of MDM (see equation 102[305] and Scheme 39) the interaction with allyl alcohols proceeds in high yields and with high selectivity.



(102)



R^1	R^2	R^3	Yield (%)	References
H	H	OCH_2CH_2OMe	75	306
H	H	$NHCO_2Bu^t$	94	307
H		O	82	308

SCHEME 39

c. S—H and other X—H bonds. Reactions of diazoesters with compounds containing S—H bonds, which lead to thioglycolic acid derivatives, are also known, though in a fewer number of examples. In reactions with thiols both $CuCl$[283] and $Rh_2(OAc)_4$[309] are used as ADA dediazotation catalysts (see equation 103). However, Rh(II) compounds are usually employed for the intramolecular transformations of diazoesters containing S—H groups[152b,288] (see equation 104).

$$RSH + N_2CHCO_2R^1 \xrightarrow[-N_2]{Cat} RSCH_2CO_2R^1 \text{ (60–90\%)} \qquad (103)$$

$$Cat = CuCl,\ Rh_2(OAc)_4$$

$$HS{-}(CH_2)_n{-}COCN_2CO_2Et \xrightarrow[-N_2]{Rh_2(OAc)_4} \text{(cyclic thioester, } CO_2Et,\ (\ )_n,\ S\text{)} \quad n = 3\ (73\%),\ n = 4\ (35\%) \qquad (104)$$

Reactions of diazoesters with mono-, di- and trisubstituted hydrosylanes, leading to esters of silyl-substituted acetic acids, are of preparative importance. The reactions proceed with high yields, involving either thermal or catalytic decomposition of ADA (see equations 105[310,311] and 106[312]).

$$RR^1R^2SiH + N_2CHCO_2R^3 \xrightarrow[-N_2]{Cat} RR^1R^2SiCH_2CO_2R^3 \qquad (105)$$

Cu, 94 °C (<90%)
$Rh_2(OAc)_4/CH_2Cl_2$ (90–94%)

$$PhMe_nSiH_{3-n} + N_2CHCO_2Et \xrightarrow[-N_2]{130\text{–}140\ ^\circ C} PhMe_nSiH_{2-n}CH_2CO_2Et \qquad (106)$$

$$n = 0\ (59\%),\ n = 1\ (92\%),\ n = 2\ (94\%)$$

In the case of alkynylhydrosilane, Si—H insertion competes successfully with cyclopropenation of the triple bond[313] (see equation 107).

$$BuC{\equiv}CSiMe_2H + N_2CHCO_2Et \xrightarrow[-N_2]{150\ ^\circ C \text{ (or CuCl, 80 °C)}} BuC{\equiv}CSiMe_2CH_2CO_2Et \text{ (50–60\%)} + \text{(Bu, H, } CO_2Et,\ SiMe_2H\text{)} \text{ (5–15\%)} \qquad (107)$$

Data are available on the possibility of carbene insertion into the Ge—H bond of triethylgermane[314] (see equation 108) and into the Sn—H bond of (neo-

$C_5H_{11})SnH^{314}$ SnH^{314} (see equation 109). In the case of stannanes this reaction proceeds in the absence of catalysts.

$$Et_3GeCN_2CO_2Et + Et_3GeH \xrightarrow{Cu/benzene,\ 100\,^{\circ}C} (Et_3Ge)_2CHCO_2Et\ (66\%) \quad (108)$$

$$(neo\text{-}C_5H_{11})_3SnCN_2CO_2Et + (neo\text{-}C_5H_{11})_3Sn \xrightarrow{benzene,\ 100\,^{\circ}C} [(neo\text{-}C_5H_{11})_3Sn]_2CHCO_2Et\ (65) \quad (109)$$

3. C—C bonds

Dediazotation of some α-diazocarboxylates may be accompanied not only by a [1,2]-H-shift (see Section IV.B.1) but also by a [1,2]-shift of the carbon atom toward the developing carbene center with the formation of products of formal carbene insertion into the C—C bond. Most often rearrangements of this type are encountered in transition-metal-catalyzed and photolytic decomposition of diazoacetates having a cyclic substituent in the α-position. Dediazotation of such diazoesters leads to ring enlargement by one carbon atom and may furnish a convenient method for homologization of alicycles. The publications devoted to the [1,2]-carbon shift in the series of α-cyclyldiazoacetates are listed in Table 7.

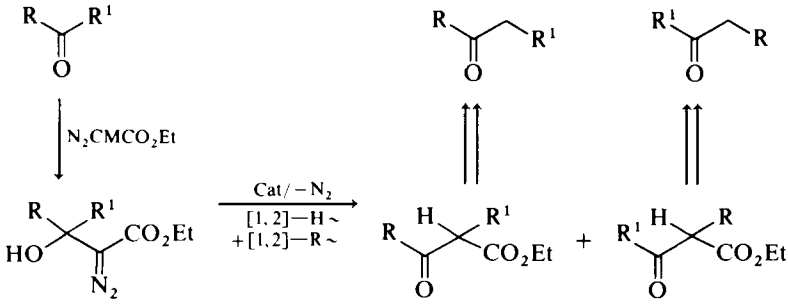
[1,2]-Carbon shifts are often accompanied by other reactions, for instance, by [1,2]-hydride shift (see Table 7, entry 1). Both [1,2]-H and [1,2]-C shifts are of great synthetic importance for homologization of ketones. As pictured in Scheme 40, the ketones are first transformed to β-hydroxy-α-diazocarboxylates, which have no hydrogen atom in the α-position, by action of α-metallated diazoacetates (see Section III.A.1.a). Transition-metal dediazotation of such diazoesters leads to a mixture of α-alkyl-α-acylacetates, which can be transformed to homologs of the starting ketones easily.

In the case of cyclic β-hydroxy-α-diazocarboxylates, similar transformations lead to ring enlargement with the formation of 2-oxocyclocarboxylates. This reaction is the first example of a migration of the less substituted carbon atom in alicyclic unsymmetrical ketones.

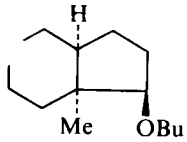
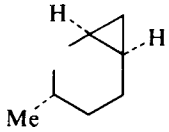
4. C—X bonds

Dediazotation of diazoesters in the presence of compounds containing carbon–heteroatom and heteroatom–heteroatom bonds is accompanied by carbene attack on the unshared pair of the heteroatom with ylide formation as a primary product. Further transformations of these ylides which depend on the substrate structure and are rather diverse. The [1,2]-shift of the carbene moiety from the heteroatom to the neighboring C atom (Stevens rearrangement) with the formation of a product of formal carbene insertion into the C—X bond (path A, Scheme 41) is the most frequently encountered mechanism; sometimes it is complicated by the elimination of an H atom from the β-carbon atom with transfer of a HX moiety from the substrate to the carbene (path b). In case of allyl derivatives [2,3]-sigmatropic rearrangement of the ylide proceeds effectively, leading to a rearranged product of insertion (path c).

All these processes, bringing about appreciable changes in the carbon skeleton of the initial molecule, in many cases proceed selectively and offer an effective way for functionalization of acyclic heteroatomic compounds and for the building of carbofunctional heterocycles. Numerous publications, dealing with the mechanistic aspects of the



Cat = $Rh_2(OAc)_4$ (RH); $RhCl(PPh_3)_3$ (RC), $PdCl_2$ (PD) or $CoCl_2$

R	R^1	Catalyst	Yield (%) (16:17 Ratio)	References
Et	Me	RH	87 (6:5)	299
Bu	Me	PD	86 (7:5)	299
Bu^t	Me	PD	59 (1:0)	299
$PhCH_2$	Me	RH	73 (5:8)	299
Ph	Ph	RH	70	299
$(CH_2)_4CHMe$		PD	82 (1:0)	299
		RC	~100 (1:0)	299
$(CH_2)_4$		RH	~100	133
		RH	55	134

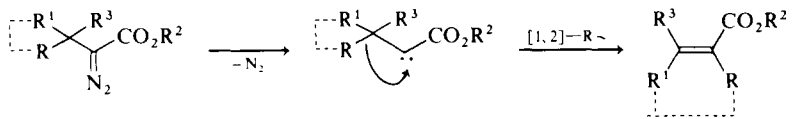
SCHEME 40

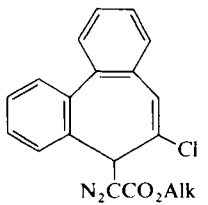
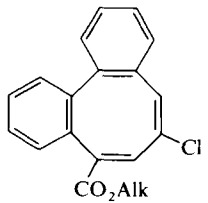
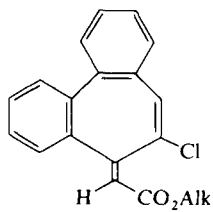
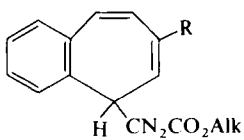
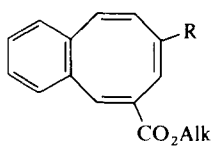
insertion reactions of the given type, are discussed in detail in a number of reviews[4,9,318,319]. We shall consider the synthetic potentialities of these reactions.

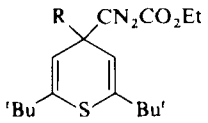
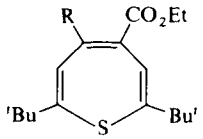
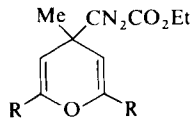
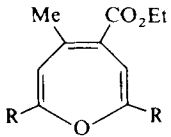
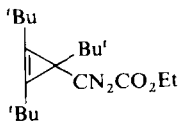
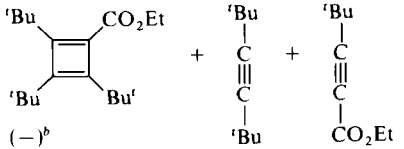
Diazoesters are capable of reacting with C—Hal, C—N, C—O and C—S bonds; some reactions with the participation of C—B and C—Se bonds are discussed in section IV.B.1 and Section IV.B.4.d, respectively.

a. C—Hal bonds. Reactions with monohaloalkanes proceed usually nonselectively and lead to esters of monochloroacetic and ω-haloaliphatic acids as a result of β-elimination and C—H insertion reactions, respectively, and are of no preparative

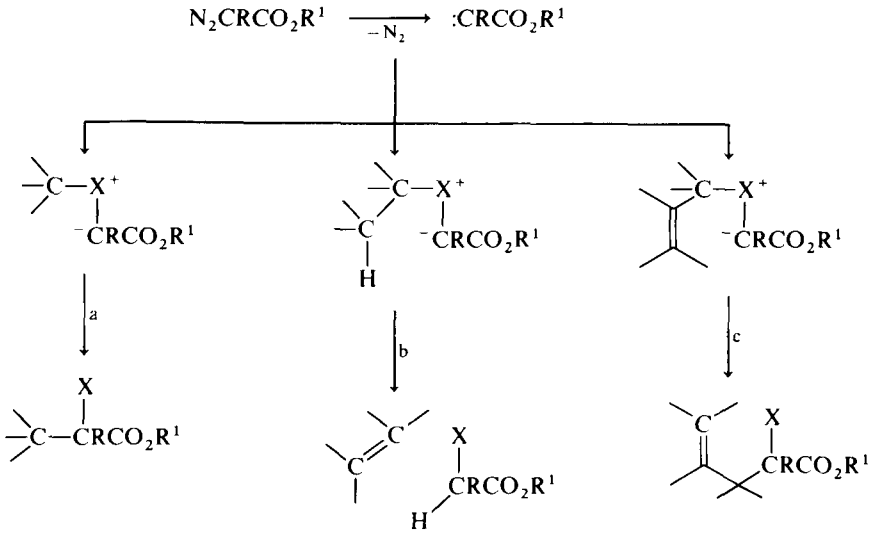
TABLE 7. Homologization of cyclic compounds by way of [1,2]-C-shift in ACC



Entry	Diazoester	Conditions	Product(s) (yields)	References
1	 Alk = Me, Et	$Cu(acac)_2$ toluene reflux	 (25%) + N_2  (10%)	117
2		$Cu(acac)_2$ toluene reflux	 R = Br, Alk = Me, Bu^t (70–86%) R = Cl, Alk = Me (64%)	315, 316

3		$[\eta^3\text{-}C_3H_5)PdCl]_2$ $CHCl_3$, 0 °C	 R = CO_2Et (—)[a] R = Me; (99%)	124, 317
4		Benzene, 20 °C $[(\eta^3\text{—}C_3H_5)PdCl]_2$	 R = 'Bu (92%) R = Me, Ph; (97–98%)	123, 125
5		*hv* pentane, 20 °C	 (—)[b]	

[a] Yield is not determined.
[b] Products ratio is 54:23:23.



SCHEME 41

importance. The reaction of EDA with trinitrobromomethane, leading to the C—Br insertion product in 67% yield, is an exception[320] (see equation 110).

$$N_2CHCO_2Et + (O_2N)_3CBr \xrightarrow[-N_2]{\text{ether, } 20\,^\circ C} (O_2N)_3CCHBrCO_2Et \qquad (110)$$

The reactions of diazoesters with allyl halides containing two reaction centers: a double bond and a C—Hal bond, were studied rather intensively. It was found that carbenes in the singlet state add to the same extent to the double bond, giving cyclopropane adducts, and also react with the C-Hal bond, giving ylides that undergo [2,3]-rearrangement into products of C-Hal insertion; triplet carbenes, on the contrary, add mainly to the multiple bond[4]. This enabled Ando to propose allyl halides as test reagents of the spin state of the carbenes[319].

With the advent of catalysts based on Rh(II) carboxylates, which allow an essential increase in the selectivity of the insertion processes of carbenes into the C—X bond, this reaction became of some preparative significance. The use of $Rh_2(OAc)_4$ as a catalyst of EDA dediazotation in the reaction with allyl iodide makes it possible to obtain ethyl 2-iodo-3-butenoate practically with a quantitative yield[321] (see equation 111).

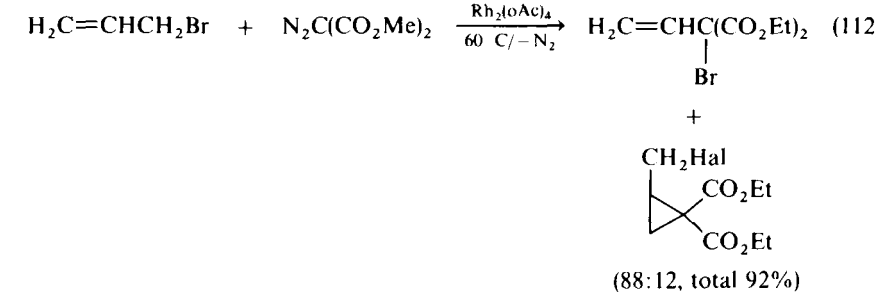
$$H_2C{=}CHCH_2Hal + N_2CHCO_2Et \xrightarrow[-N_2]{\text{Cat, } 60\,^\circ C} H_2C{=}CHCHCO_2Et + \text{cyclopropane adduct}$$

(Hal on the CHCO$_2$Et; cyclopropane: CH$_2$Hal and CO$_2$Et)

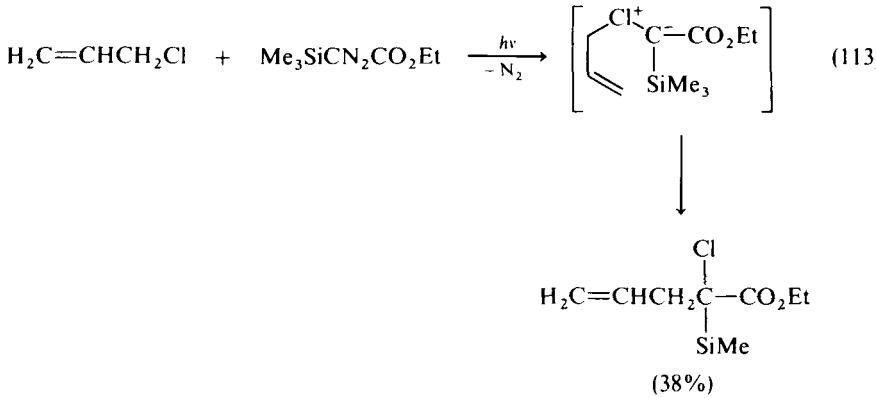
Cat = $Rh_2(OAc)_4$,	Hal = I	98%	----
Cat = $Rh_2(OAc)_4$,	Hal = Cl	<2%	93%
Cat = $Rh_2(OAc)_4$,	Hal = Br	30%	46%
Cat = Cu–bronze.	Hal = Br	50%	6%

However, in the case of allyl bromide and allyl chloride cyclopropanation dominates; the lowering of the share of the C—Hal insertion products in favor of cyclopropane adducts parallels the decrease of nucleophilicity in the I—Br—Cl series, this being a confirmation of the ylide mechanism of the reaction. Thus, allyl chloride with EDA in the presence of $Rh_2(OAc)_4$ gives ethyl 2-chloromethylcyclopropanecarboxylate with a yield exceeding 95%. Nevertheless, in the reaction with allyl bromide the same catalyst conducts the process nonselectively: almost equal quantities of cyclopropane adducts and α-bromobutenoates are formed, although the use of copper–bronze makes it possible to increase to some extent the process selectivity with respect to the insertion product.

An Rh(II)-promoted metal–carbene complex from MDM[321] (see equation 112) and a carbene generated by photolysis of ethyl α-trimethylsilyldiazoacetate[322] (see equation 113) are still more liable to form ylides with allyl halides. In the first case the product of insertion into the C—Br bond of allyl bromide is predominant even with the use of $Rh_2(OAc)_4$; in the second case the corresponding cyclopropane adduct is not formed at all.



(88:12, total 92%)



(38%)

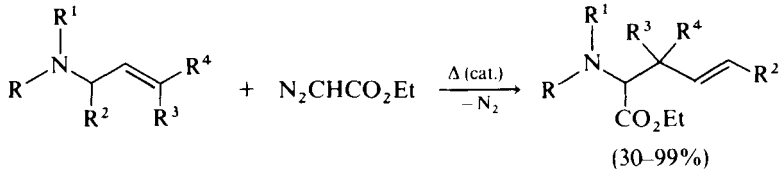
Reactions of diazoesters with alkane polyhalogenides[4] have not found preparative application because of the low selectivity of carbenes generated by photolytic decomposition of the diazoesters. The synthetic possibilities of catalytic processes are as yet hardly explored, though recent examples give promising results. Thus, propargyl diazoacetate in the presence of $Rh_2(OAc)_4$ can give an insertion product into the C—Cl bond of

methylene chloride[215] (see equation 114).

$$CH_2Cl_2 + N_2CHCO_2CH_2C{\equiv}CH \xrightarrow{Rh_2(OAc)_4} CH_2ClCHClCO_2CH_2C{\equiv}CH\ (15\%) \quad (114)$$

A similar reaction with MDA does not take place.

b. C—N bonds. The number of syntheses based on ADA reactions with amines, leading to products of insertion into the C—N bond, is limited. The interaction of EDA with tertiary allyl amines on heating to 144–175 °C or in the presence of catalysts based on Rh(II), Cu(II), Ni(II) or Zr(IV) compounds at 60 °C, as a result of [2,3]-rearrangement leads to esters of unsaturated *N,N*-dialkylamino acids with high yields[323] (see equation 115).

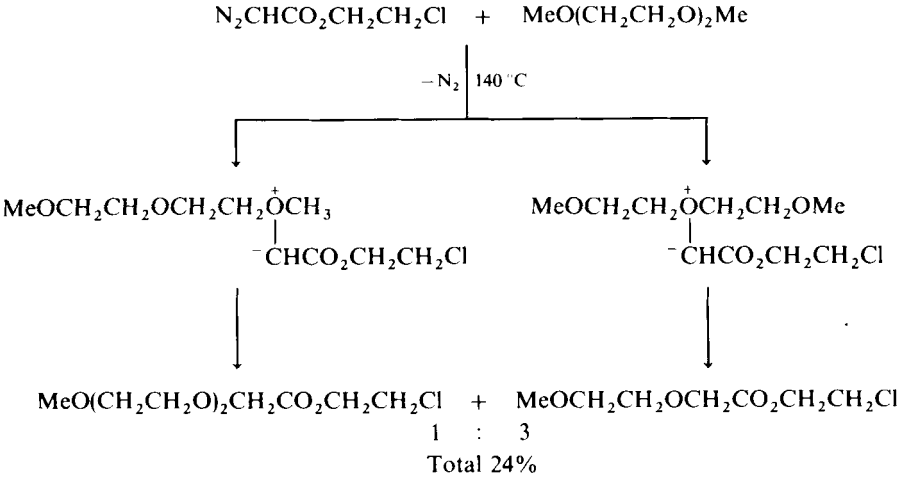


(115)

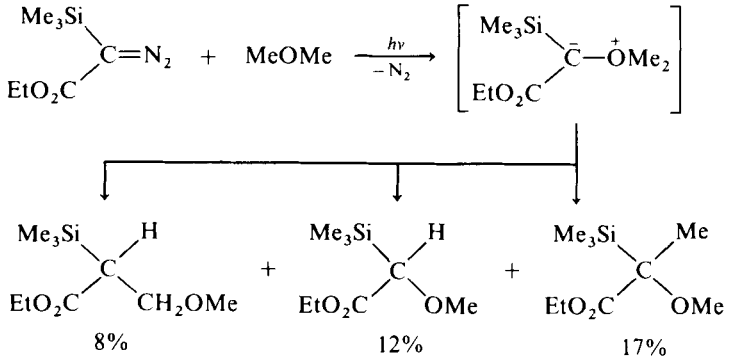
(30–99%)

R, R^1 = alkyl or R + R^1 = $(CH_2)_n$ (n = 5–6) or $CH_2CH_2OCH_2CH_2$;
R^2 = alkyl;
R^3, R^4 = alkyl or ω-alkenyl

The reaction is very sensitive to the catalyst concentration. The highest yields are attained when the catalyst:amine molar ratio equals 1:800; as the catalyst concentration increases, the proportion of competitive addition of carbene to the double bond grows appreciably[324].

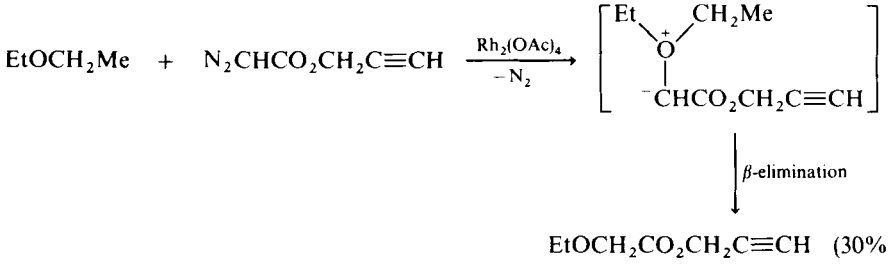


SCHEME 42



(116)

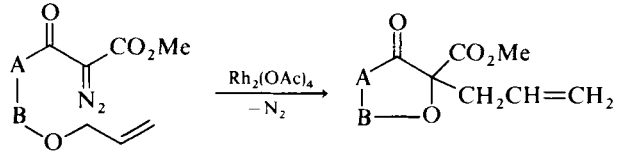
c. C—O bonds. Diazoester reactions with acyclic ethers, initiated by heating[42] (see Scheme 42), irradiation[322] (see equation 116) and $Rh_2(OAc)_4$[215] (see equation 117), usually proceed nonselectively, leading to esters of alkoxyacetic acids as a result of β-elimination from the initially formed *O*-ylides. Formation of C—O insertion products usually does not occur (as an exception see equation 116).



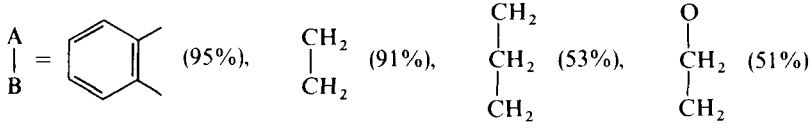
(117)

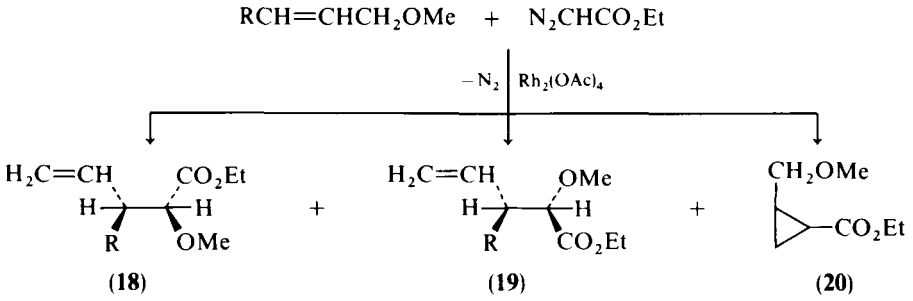
The reactions of EDA with allyl methyl ethers in the presence of $Rh_2(OAc)_4$, though they lead to the C—O insertion products as a result of [2,3]-rearrangement of an ylide, also proceed nonselectively and are complicated by the competitive formation of cyclopropane adducts, whose share may reach 30%[325] (Scheme 43).

The $Rh_2(OAc)_4$-induced reactons of intramolecular cyclization of allyl and propargyl diazoacetates find a much more extensive synthetic application[326] (see equations 118–120). In this case the reactions are characterized by high selectivity and lead to 5- and 6-membered oxacyclonones as a result of C—O insertion and [2,3]-rearrangement.



(118)

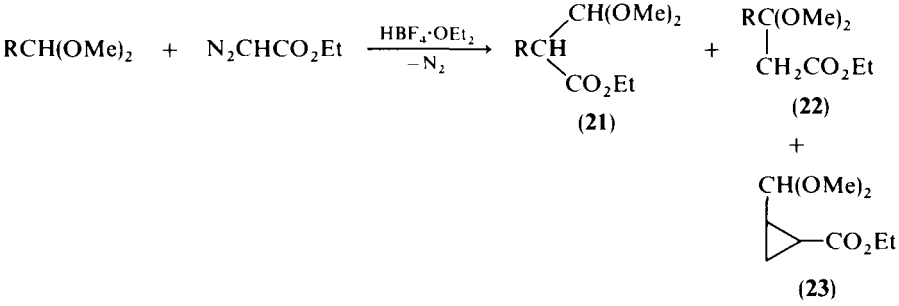




(18) (19) (20)

R	Configuration of double bond	Total yield (%)	Products ratio (%)		
			18	**19**	**20**
Ph	*E*	95	83	17	27
Ph	*Z*	95	6	94	26
Me	*E*	86	79	21	8
Me_3Si	*E*	68	97	3	6

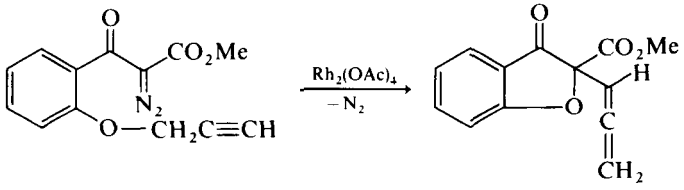
SCHEME 43



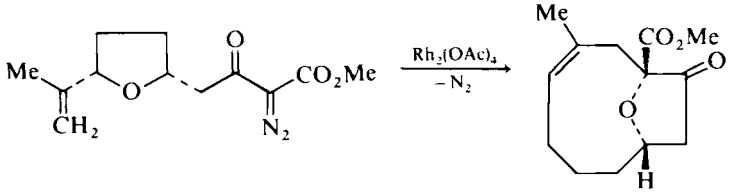
(21) (22) (23)

R	*T* (°C)	Total yield (%)	Products ratio		
			21	**22**	**23**
H_2C=CH	−15	70	75	10	10
E-PhCH=CH	0	70	~100	<1	<1
Ph	25	85	97	3	<1
PhC≡C	25	22	~100	<1	<1

SCHEME 44

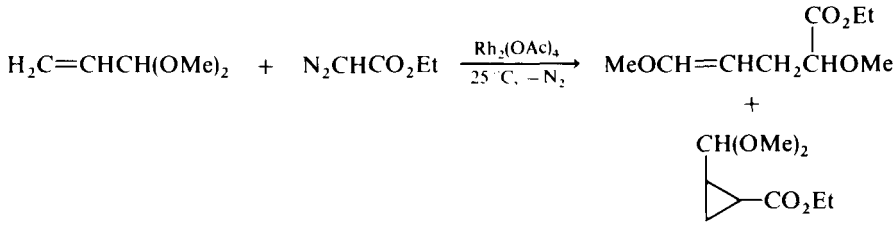


(92%) (119)



(67%) (120)

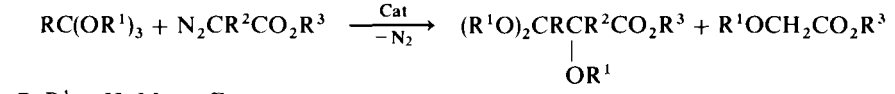
The formation of C—O insertion products was also noted in EDA reactions with acetals and *ortho*-esters. In the presence of $Rh_2(OAc)_4$, EDA reacts with acrolein dimethylacetal, giving the product of *O*-ylide [2,3]-rearrangement together with the cyclopropane adduct[327] (see equation 121). However, when this reaction is initiated by BF_3 etherate, the main and sometimes the only products are those of C—C insertion: diacetals of formylacetic acid derivatives alongside small quantities of cyclopropane adduct products (see Scheme 44)[328].



76:24, total yield 47%

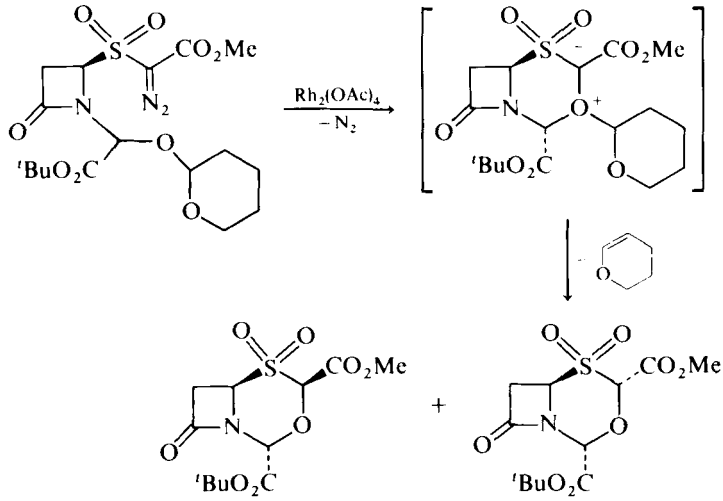
(121)

On the contrary, reactions of diazoesters with *ortho*-ethers in the presence of BF_3 etherate lead exclusively to C—O insertion products. Metal-promoted processes are less selective and are accompanied by β-elimination[329] (see equation 122).



R, R^1 = H, Me or Et
R^2 = H or Co_2Me
R^3 = Me or Et

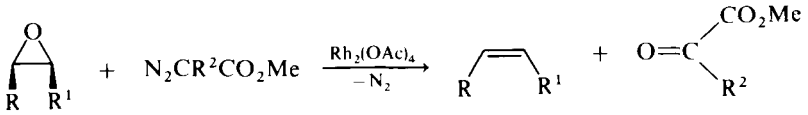
Cat = $BF_3 \cdot OEt_2$, 25 °C	45–85%	<5%
$Rh_2(OAc)_4$, 60 °C	3–20%	11–27%
$Cu(OTf)_2$, 25 °C	38–46%	6–20%



SCHEME 45

Recently, the process of *O*-ylide β-elimination has been used for the synthesis of 3-oxacepham type antibiotics[330] (see Scheme 45).

The reaction of diazoesters with cyclic oxa-compounds has a number of specific features, the size of the ring being the decisive factor. $Rh_2(OAc)_4$-initiated dediazotation of MDM and methyl α-trimethylsilyldiazoacetate causes deoxygenation of oxiranes, which gives high yields of the corresponding olefins, with preservation of the configuration of the initial oxirane in the resulting olefin[331] (see equation 123).

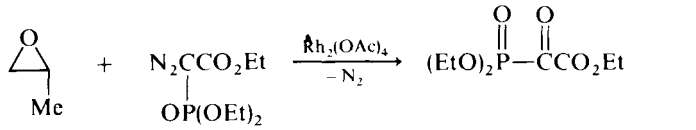


(123)

60–85%

$R^2 = CO_2Me$ or Me_3Si

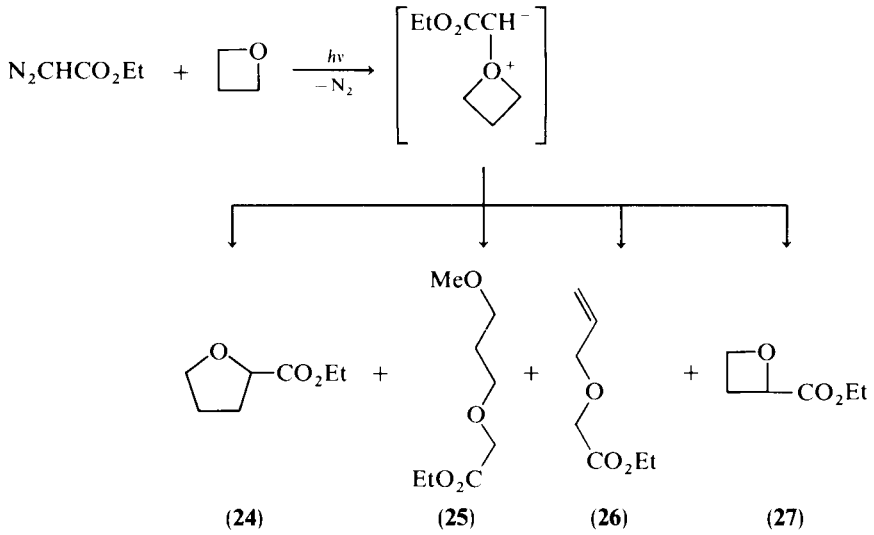
A similar reaction of ethyl α-phosphoryldiazoacetate with methyl oxirane was used for the production of oxophosphonates[72] (see equation 124).



(124)

Photolysis of EDA in an oxetane medium leads to the corresponding *O*-ylide, while Stevens rearrangement results in tetrahydrofurane-2-carboxylate as the main product[332] (see Scheme 46). However, in the medium of methanol the major process is β-elimination, leading to the cycle opening and to the alkoxyacetate formation.

The interaction of EDA with 1,3-dioxolanes leads to the products of formal C—O insertion, 1,4-dioxanecarboxylates, apparently as a result of Stevens rearrangement of



Solvent	Total yield (%)	Product ratio (%)			
		24	**25**	**26**	**27**
Oxetane	54	70.3	—	12.2	17.5
MeOH	54	23.6	51.9	6.3	18.2

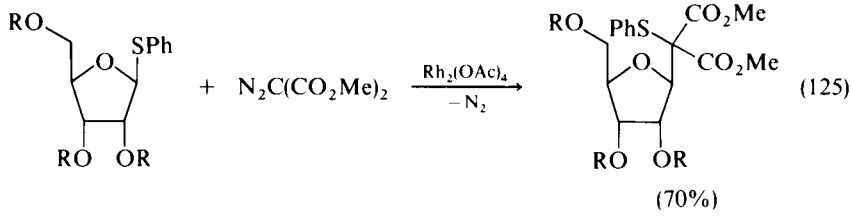
SCHEME 46

the oxygen–carbon ylide[333]. Low yields of the resulting products (<50%) are caused by the rather severe reaction conditions (140 °C); data on milder conditions, for instance with the use of rhodium(II) catalysts, are not found in the literature.

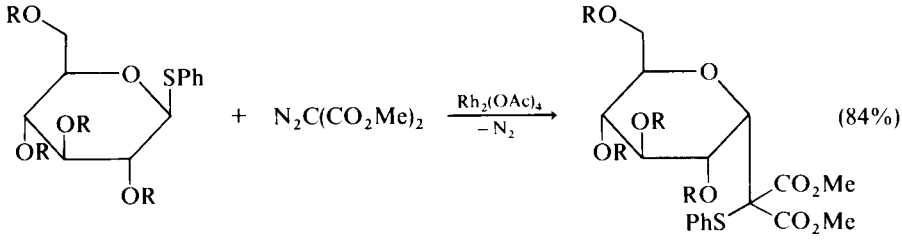
d. C—S bonds. The enhanced nucleophilicity of the S atom compared with that of the N or O atoms causes a higher reactivity of sulfur-containing compounds and is thus responsible for more diverse synthetic possibilities of their reactions with carbenes. This accounts for the interest in studying diazoester reactions with compounds containing C—S bonds and for the considerable number of investigations carried out in this field. Moreover, in the reactions of diazoesters with S-containing compounds stable *S*-ylides were isolated, transformations of the latter were studied and thereby direct proofs of their intermediacy in the formation of the final esters were obtained (see also Section IV.C.3.b)

Diazoesters react practically with any acyclic sulfide, giving products of C—S insertion as a result of [1,2]-shift of the carbene fragment in the initially formed *S*-ylide[334] (see equations 125 and 126), *S*-ylides from allyl sulfides having undergone the [2,3]-rearrangement (see equations 127[335] and 128[336]).

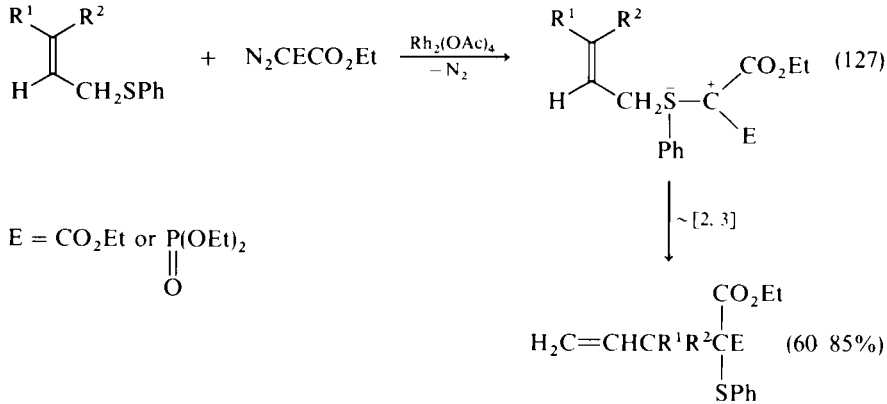
Attack of the carbene generated from the diazoesters on the S atom is preferred even if other heteroatoms, such as O (see equations 125 and 126) and N (see equation 129[337] and Schemes 47[339] and 48[338]), are present in the substrate molecule. However,



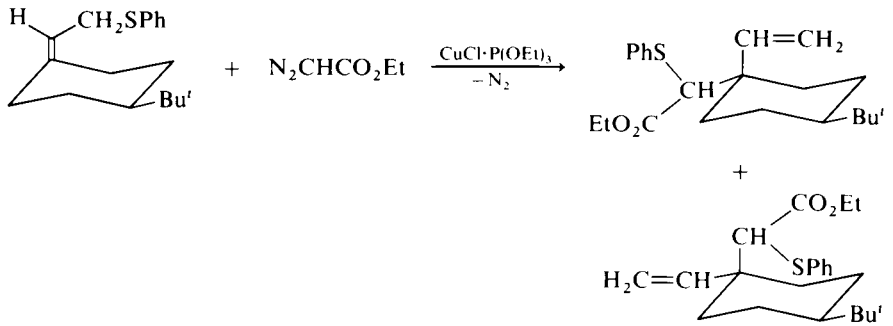
(70%) (125)



(84%) (126)

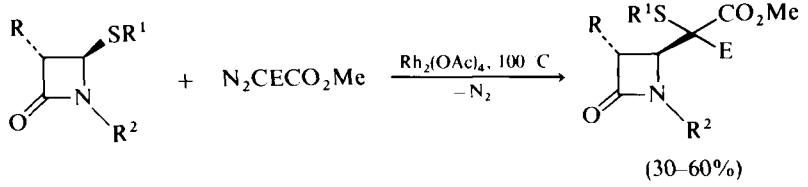


(60–85%) (127)



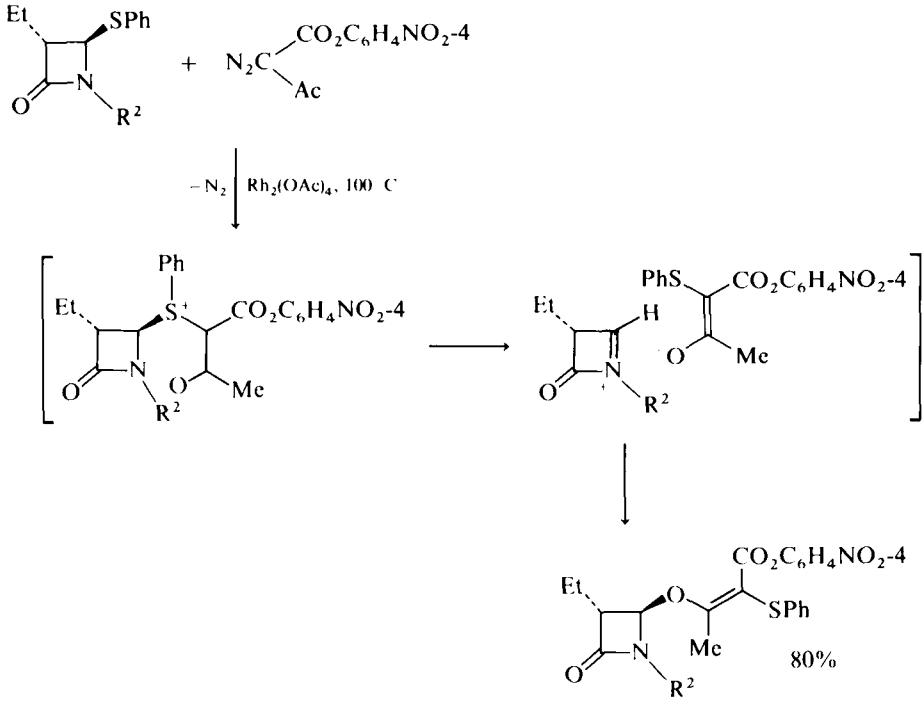
91:9, total yield 59%

(128)



(129)

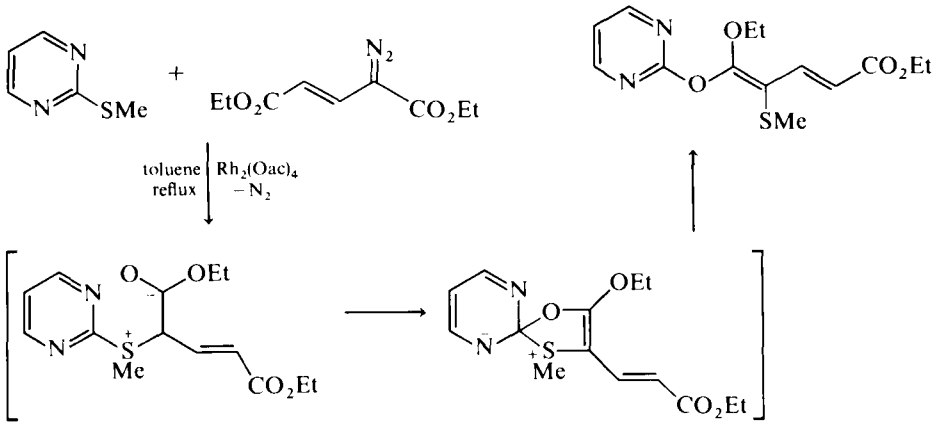
R and R^1 = alkyl, Ph or CH_2Ph
R^2 = H, $CH_2CO_2R^3$ or $SiMe_2Bu^t$
E = CO_2R^4 or P(O) $(OEt)_2$



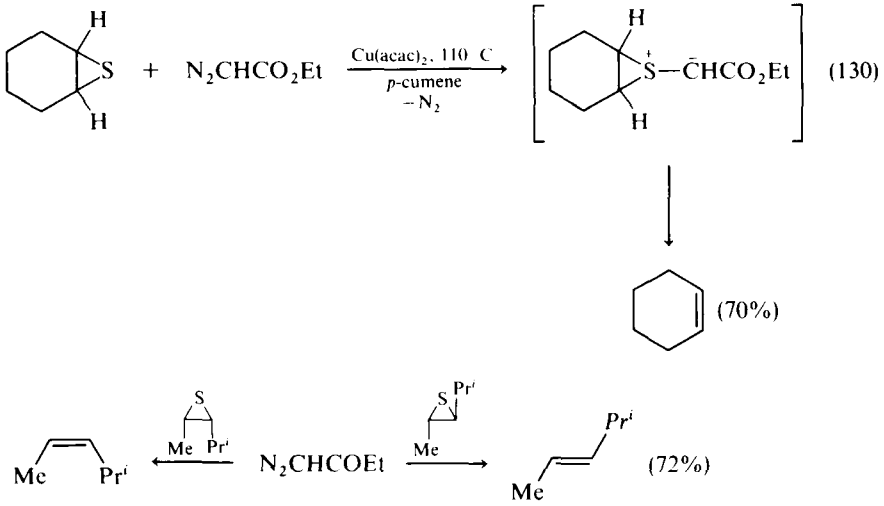
SCHEME 47

in the reaction of such polyheteroatomic molecules with some diazoesters, e.g. with *p*-nitrophenyl α-acetyldiazoacetates (see Scheme 44) or ethyl α-(ethoxycarbonylvinyl)diazoacetates (see Scheme 48), possibilities are provided for additional stabilization of the cation and anion centers in the originating *S*-ylide, which contributes to its [1,4]-rearrangement with the formation of the *O*-alkylated product.

Carbene decomposition of ADA in the presence of cyclic thio ethers is also accompanied by *S*-ylide formation, when further transformations are usually accompanied by a change of the ring size. For example, as in the case of reactions with oxiranes, the interaction of EDA with thiiranes is accompanied by selective desulfuration and leads to olefins preserving the initial configuration of the three-membered heterocycle[340] (see equation 130 and Scheme 49).



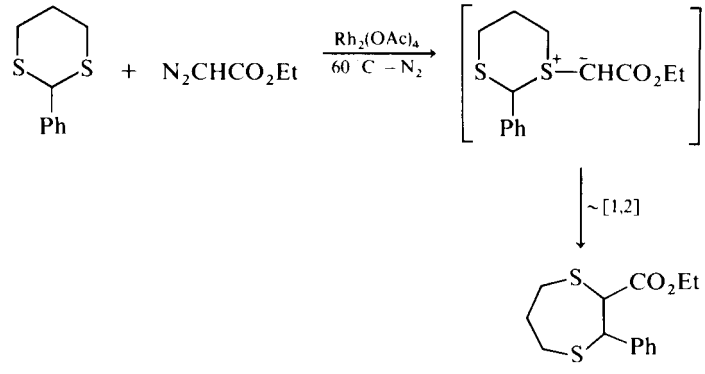
SCHEME 48



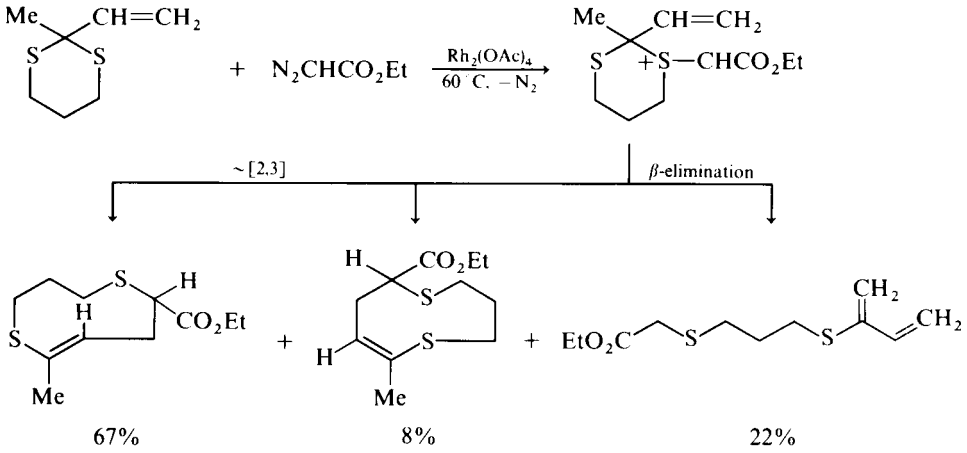
SCHEME 49

In the reaction with thiacyclanes having a larger number of carbon atoms, ring-enlargement occurs. For example, the interaction of EDA with 2-phenyl-1,3-dithiane, catalyzed by $Rh_2(OAc)_4$, leads to the corresponding 1,4-dithiepane as a result of Stevens rearrangement of the initially forming *S*-ylide[327] (see equation 131).

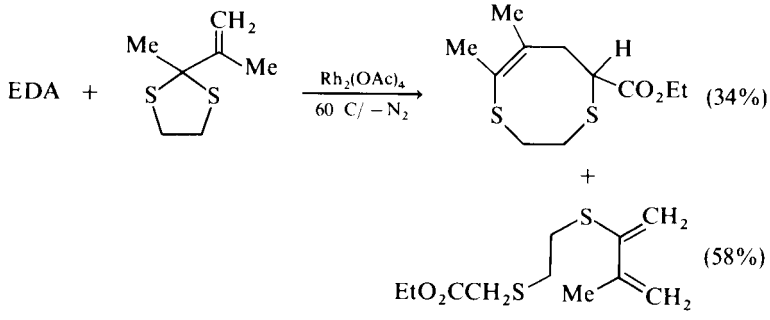
In the reactions of ADA with thiacyclanes containing an allyl fragment, the composition of the reaction products depends on the position of this fragment outside or inside the cycle and may be accompanied by an expansion or contraction of the substrate ring. Thus, $Rh_2(OAc)_4$-catalyzed interaction of diazoesters with vinylthiacyclanes, e.g. 2-methyl-2-vinyl-1,3-dithiane[327] (see Scheme 50), and 2-methyl-2-isopropenyl-1,3-dithiolane[327] (see equation 132) and 2-vinyltetrahydrothiophene[341] (see equation 133) leads, as a result of [2,3]-sigmatropic rearrangement of *S*-ylides, to 9- and 8-membered thiacyclanes, respectively, together with acyclic products of β-elimination.



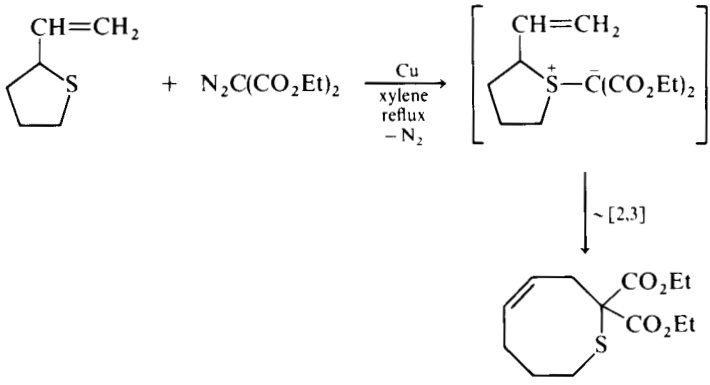
(131)



SCHEME 50

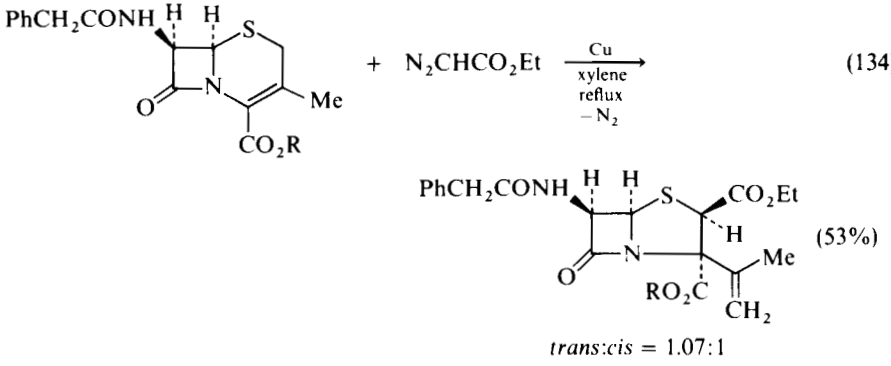


(132)



(133)

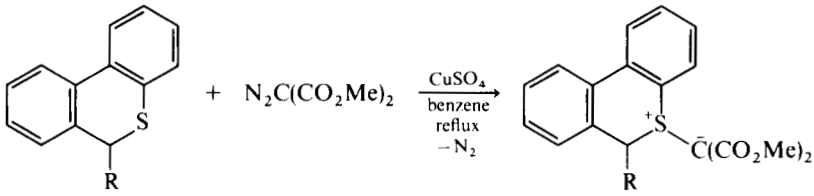
At the same time, the reaction of cephalosporanic acid esters with EDA is accompanied by ring contraction with the formation of 3-(2-propenyl)penicillanic acid esters[342] (see equation 134).



(134)

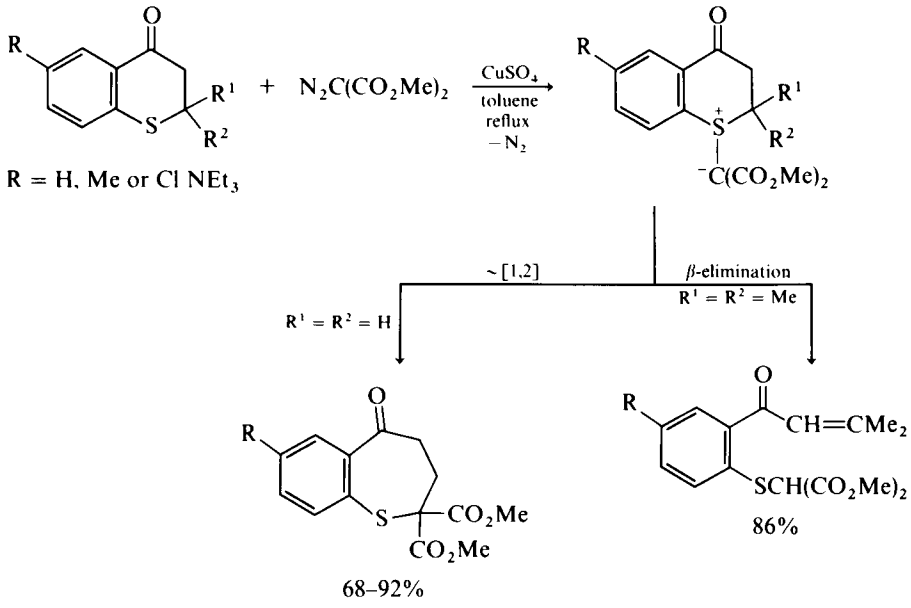
trans:*cis* = 1.07:1

Unlike ADA, diazomalonates or diazomalononitriles in reactions with thiacyclanes form sufficiently stable S-ylides which can be isolated as the main or the only reaction products, so that their subsequent transformations can be studied (see also Section IV.C.3.b). For example, $Rh_2(OAc)_4$-promoted decomposition of MDM in the presence of thiachromones leads to stable *S*-ylides, and decomposition of the latter under the action of triethylamine leads to homothiachromones or thiobenzophenones as a result of either a [1,2]-shift or a β-elimination[343] (see Scheme 51).



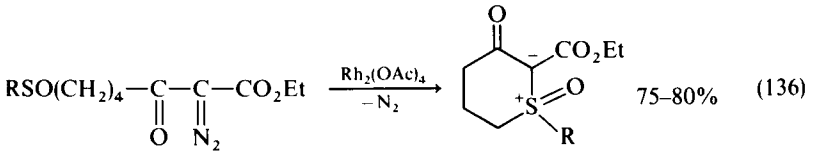
(135)

R = H (85%), R = Ph (90%)

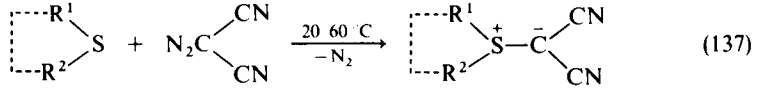


SCHEME 51

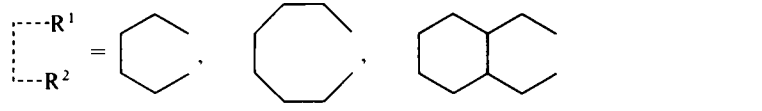
Sometimes the *S*-ylides formed (see equations 135[344], 136[346] and 137[345]) are so stable that they do not undergo rearrangements even on melting.



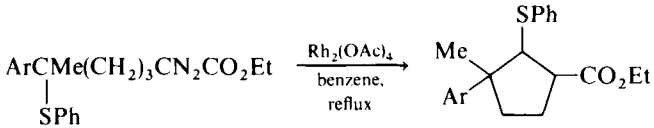
R = Et, $PhCH_2$, $H_2C{=}CCH_2$, *trans*-$PhCH{=}CHCH_2$



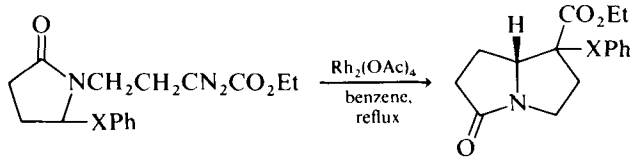
R^1, R^2 = alkyl or aryl



Intramolecular reactions of sulphur- and selenium-containing diazoesters, proceeding in a similar manner, offer a synthetic method of constructing cyclic and condensed systems. For example, cyclization of Rh(II)-promoted metal carbenes from 6-thiodia-



(138)



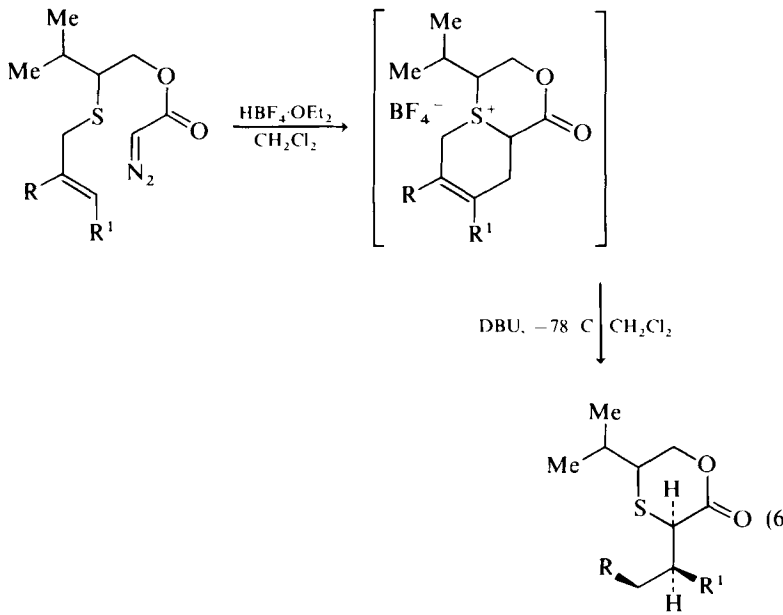
(139)

X = S (55%), Se (36%)

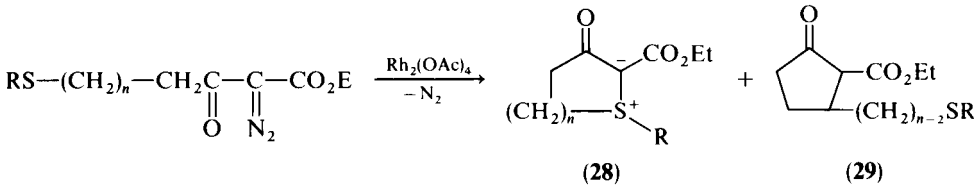
zoalkanoates into 5-membered rings occurs rather easily (see equations 138[347] and 139[348]).

Unfortunately, six and more membered rings cannot be produced in such a manner, because of the competition of C—H insertion. In a number of cases the reaction ceases at the formation stage of stable *S*-ylides, whose decomposition occurs only in more severe conditions and does not always lead to the expected products of C—S insertion[349] (see Scheme 52).

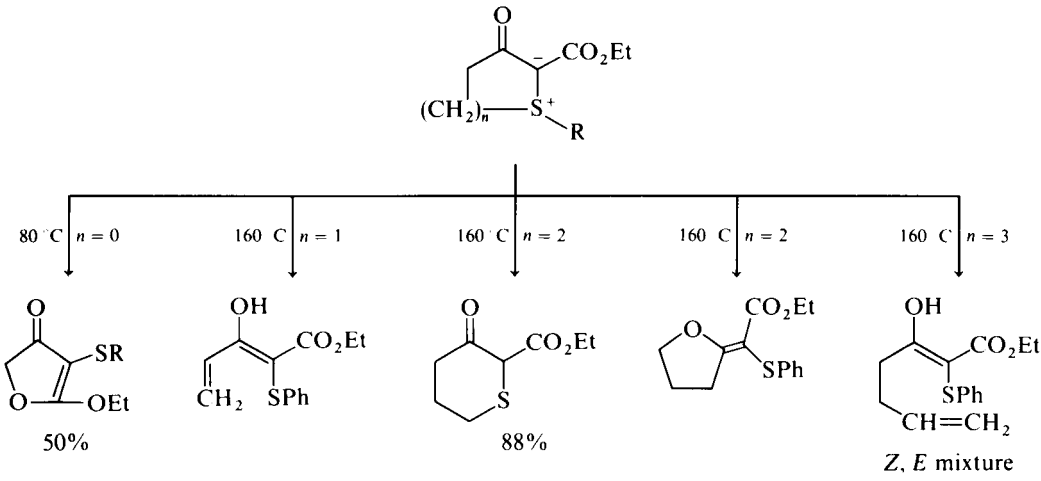
Heterocycles with more than five atoms in the ring can be obtained in intramolecular reactions of diazoesters containing an allyl fragment. Thus, $Rh_2(OAc)_4$-catalyzed dediazotation of 6-(2-alkenyl)thio-3-oxo-2-diazohexanoates (see Scheme 53) and ethyl 7-(2-alkenyl)thio-3-oxo-2-diazoheptanoates (see Scheme 54), thianones-3 and thiepanones-3 are formed with fair yields; formation of C—H insertion products is not observed in this case[346].



(64%) (140)



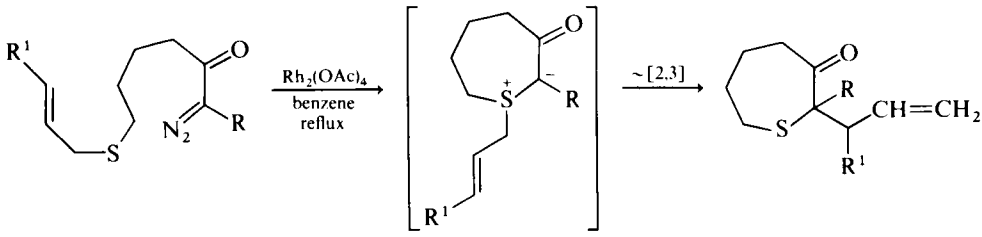
		Products yield (%)	
n	R	**28**	**29**
0	Ph	53	—
1	Et	69	—
2	Ph	67	—
3	Ph	45	16
4	Ph	—	64
6	Ph	—	71



SCHEME 52

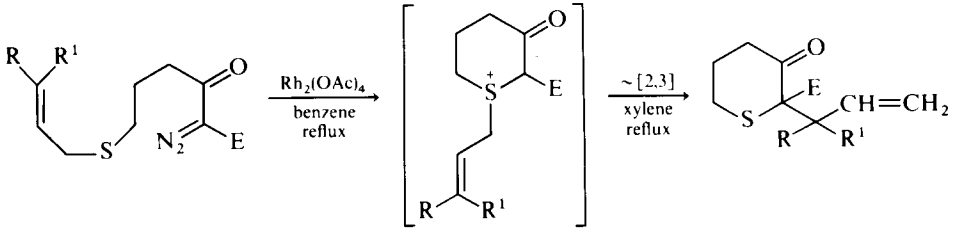
The presence of an allyl fragment in the alcohol part of the monoethyl diazomalonate molecule allows one to synthesize also vinyl-substituted 5- and 6-membered cyclic lactones as a result of stereoselective [2,3]-rearrangement of the *S*-ylide originating in cyclization of rhodium-promoted metal–carbene complex[346,350] (see Scheme 55).

The diastereoselectivity of this reaction can be essentially increased by using $HBF_4 \cdot Et_2O$-promoted heterocyclization of diazoesters followed by DBU treatment of the intermediately forming thioxonium salt. In this way from allylthioalkyl diazoacetate thioxanones were obtained from allylthioalkyl in good yield and with excellent diastereoselectivity (>93%)[351] (see equation 140).



R	R^1	Yield (%)
CO_2Et	Ph	29
H	H	42
H	Ph	64

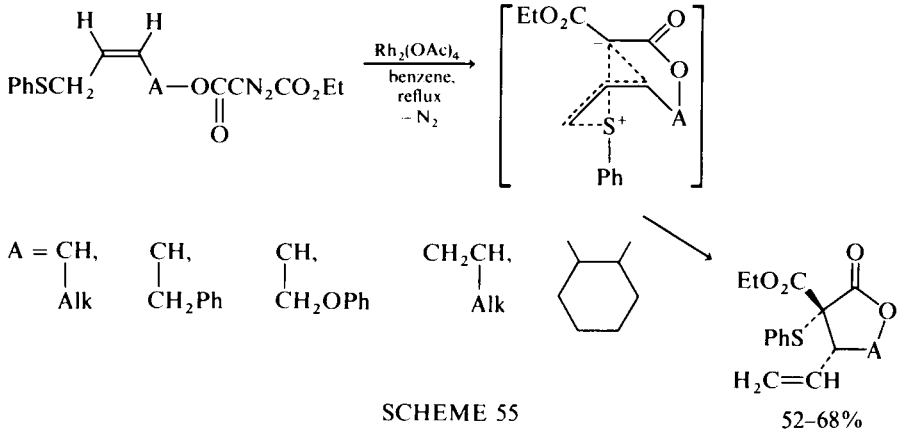
SCHEME 53



55–85%

R	R^1	Yield (%)
Me	Me	66
H	H	59
Ph	H	78
Me	H	71

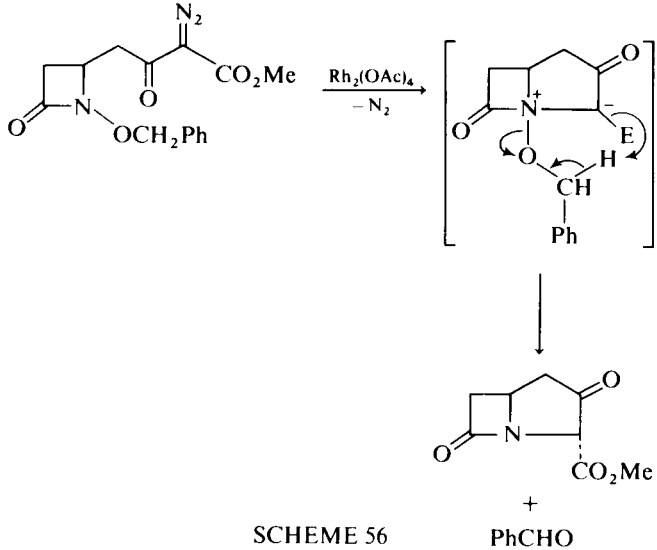
SCHEME 54



SCHEME 55

5. X—Y bonds

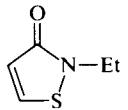
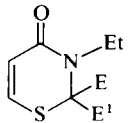
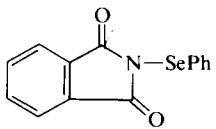
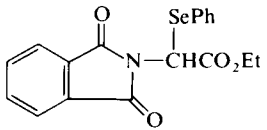
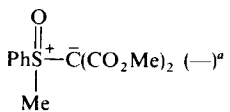
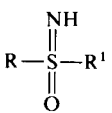
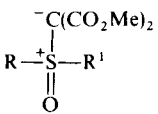
Reactions of diazoesters, involving carbene insertion into heteroatom–heteroatom bonds, are presented in Table 8. These reactions also proceed with intermediate formation of ylides. For example, the interaction of MDM with sulfoxides leads to stable *S*-ylides (see entries 10 and 11) which can be isolated; the optical activity of the initial sulfoxide is preserved in the ylide. In carbene reactions of diazoesters with organosilicon compounds (see entries 5–7) in the forming ylides, various side reactions of [1,2]-shifts, β-eliminations and C—H insertions occur; this lowers the preparative significance of these transformations. Nor do the transformations of ylides always lead to the products of carbene insertion into the attacked bond. Thus, intramolecular attack of the carbene center at the N—O bond in a diazolactam leads to an *N*-ylide, which rearranges involving the breakage of the N—O bond and formation of an N—C bond[364b] (see Scheme 56).



SCHEME 56

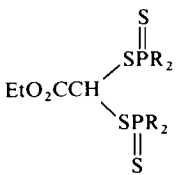
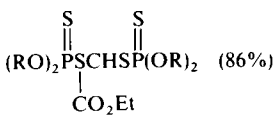
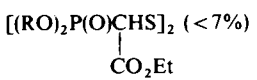
TABLE 8. Reactions of diazoesters with element-element bonds

Entry	Bond	Substrate	Diazoester	Conditions	Product(s) (yield)	Reference
1	O—Cl	*t*-BuOCl	EDA	−10 °C, CH_2Cl_2	*t*-BuOCHCO$_2$Et (Cl) (36%)	352
2	O—Cl	*t*-BuOCl	EDA	−10 °C CH_2Cl_2/ROH	$(RO)_2CHCO_2Et$ R = *t*Bu(36%), Et(57%)	352
3	O—Cl	ROR^1/SO_2Cl_2	EDA	0 °C, dark CH_2Cl_2	ROCHCO$_2$Et (Cl) R = R^1 = Et (75%) R = Me, R^1 = $CH(OMe)_2$ (64%) R = Me, R^1 = CH_2CH_2OMe (76%)	353
4	O—Cl	$H_2C—(CH_2)_n$ (O) SO_2Cl_2	EDA	0 °C, dark CH_2Cl_2	Cl(CH$_2$)$_n$CHCO$_2$Et (Cl) *n* = 2–5 (63–85%)	353
5	Si—O	Me_3SiOEt	EDA	*hv*, MeCN	$Me_3SiCHOEt$ (31%) (CO_2Et) $EtOCH_2CO_2Et$ (14%) Me_2SiOEt (14%) ($CH_2CH_2CO_2Et$)	354a
6	Si—S	Me_3SiSEt	EDA	*hv*, MeCN	$Me_3SiCHSEt$ (28%) (CO_2Et) $EtSCH_2CO_2Et$ (8%)	354
7	Si—Cl	Me_3SiCl	EDA	Cu/NEt_3 80 °C	$Me_3SiCHCl$ (20%) (CO_2Et) $ClCH_2CO_2Et$ (25%)	354b

8	N—S			$Rh_2(OAc)_4$ benzene reflux	 $E = E^1 = CO_2Et$ (70%) $E = Ac$, $E^1 = CO_2Et$ (74%) $E + E^1 = COCMe_2OC$ (74%)	355
9	N—Se		EDA		 (58%)	356
10	S—O	PhS(O)Me	MDM	$CuSO_4$ benzene reflux	 (—)[a]	357
11	S—N		MDM	$CuSO_4$ benzene reflux	 (16–60%)	357

(*continued*)

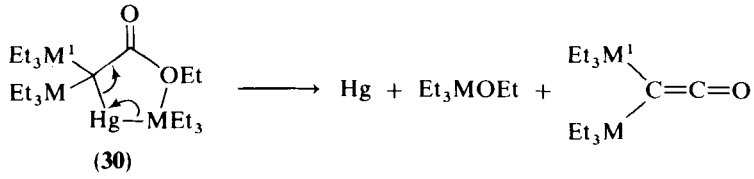
TABLE 8. (*continued*)

Entry	Bond	Substrate	Diazoester	Conditions	Product(s) (yield)	Reference
12	S—Se	PhSeSCN	EDA	CH_2Cl_2 20 °C	PhSeCHNCS (82%) CO_2Et PhSeCHSCN (18%) CO_2Et	358
13	Se—Se	PhSeSePh	EDA	Cu–bronze xylene 100 °C	$(PhSe)_2CHCO_2Et$ (46%)	358
14	Se—Se	PhSeSePh	MDM	100 °C	$(PhSe)_2C(CO_2Me)_2$ (32%) $PhSeCH(CO_2Me)_2$ (12%)	358
15	S—S	$[R_2P(S)S]_2$	EDA	Cu, 80 °C	 R = OAlk, Ph (73–97%)	359
16	S—S	$S[(RO)_2P(S)]_2S_n$	EDA	Cu, 80 °C		360
17	S—S	$[(RO)_2P(O)S]_2$	EDA	Cu, 80 °C	 + 	362

18	S—P	$[(RO)_2P(O)S]_2$	EDA	80 °C benzene	$[(RO)_2P(O)CHS]_2$ CO_2Et R = Alk (11%)	263
19	S – P	$[(RO)_2P(O)S]_2$	EDA	120 °C	$(RO)_2POCHSP(OR)_2$ O, S, CO_2Et (63%)	362
20	S—P	$[(RO)_2P(O)]_2S_n$	EDA	70–100 °C	$(RO)_2PCHS_nP(OR)_2$ O, O, CO_2Et (>80%)	360
21	Hg—Si Hg—Ge	$Hg(MEt_3)_2$	N_2CCO_2Et $SiEt_3$	Cu, 100 °C hexane	Et_3Si, Et_3M, C=C=O M = Si (58%), Ge (92%)	363
22	Hg—Ge	$Hg(GeEt_3)_2$	N_2CCO_2Et $SnEt_3$	Cu, 100 °C hexane	Et_3Sn, Et_3Ge, C=C=O (73%)	363
23	Hg—Ge	$Hg(GeEt_3)_2$	N_2CCO_2Et $GeEt_3$	Cu, 100 °C hexane	Et_3Ge, Et_3Ge, C=C=O (72%)	364a

[a] Yield is not shown.

It is believed that the formation of organoelement ketenes as a result of interaction of α-metallated diazoesters with bis(trimethylsilyl or trimethylgermyl)mercury (see entries 21–23) also takes place by decomposition of the initially formed unstable product (**30**) or carbene insertion into the Hg—Si or Hg—Ge bond (see Scheme 57).



(**30**)

SCHEME 57

A number of transformations of diazoesters proceed along a pathway other than a carbene one, though they lead to the formation of formal insertion products. Thus, though the interaction of EDA with *t*-Bu hypochlorite does lead to the product of insertion of the carbene fragment $CHCO_2Et$ into the O—Cl bond (see entries 1 and 2), attempts to intercept the carbene by an olefin were not successful. The formation of O—Cl insertion products was observed in the reaction of EDA with ether and ethylene oxide in the presence of SO_2Cl_2 (see entries 3 and 4).

C. Reactions with Multiple Bonds

Carbenes from diazoesters are capable of reacting with a variety of multiple bonds. The character of the bonds is decisive for the character of the products formed. Therefore, the reactions of diazoesters with each type of multiple bond are considered separately.

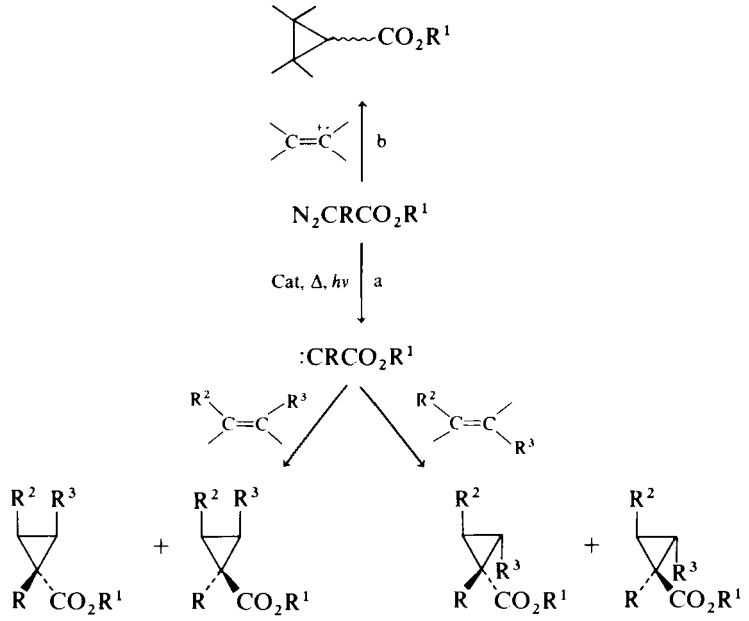
1. C=C bonds

The synthetic importance of carbenic diazoester reactions with C=C bonds in aliphatic compounds is mainly due to the possibility of direct syntheses of cyclopropanecarboxylic esters, the latter being valuable building blocks for the preparation of many important products, such as pesticides, drugs and natural compounds.

Cyclopropanation is commonly carried out by photolytic, thermal or catalytic decomposition of diazoesters in the presence of olefins. The ACC or its complexes which are considered to be the intermediates in these processes easily add to double bonds of various unsaturated compounds (see Scheme 58, path a). Recently an alternative method of olefin cyclopropanation with EDA, based on cation radical chain reactions, has been developed (path b).

The high activity of diazo compounds in carbene reactions enables cyclopropanation of practically any double bond with acceptable yields, the configuration of the initial olefin being preserved (see Scheme 58). However, in the case of unsymmetrical diazoesters and olefins the reaction leads to a mixture of diastereomers. The high activity of carbenes is also responsible for side processes of insertion into saturated bonds (see Section IV.B), for reactions with other multiple bonds and, in the case of electron-deficient olefins, for competitive 1,3-dipolar cycloadditions of diazoesters (see Section III.B.1). Finally, carbene reactions of diazoacetates, as a rule, are accompanied by dimerization and oligomerization of ACC.

As has already been mentioned in Section IV.A, one of the ways for solving the problem of regio- and stereoselective cyclopropanation is to use the catalytic method of dediazotation of diazoesters, which makes it possible to regulate the reactivity of



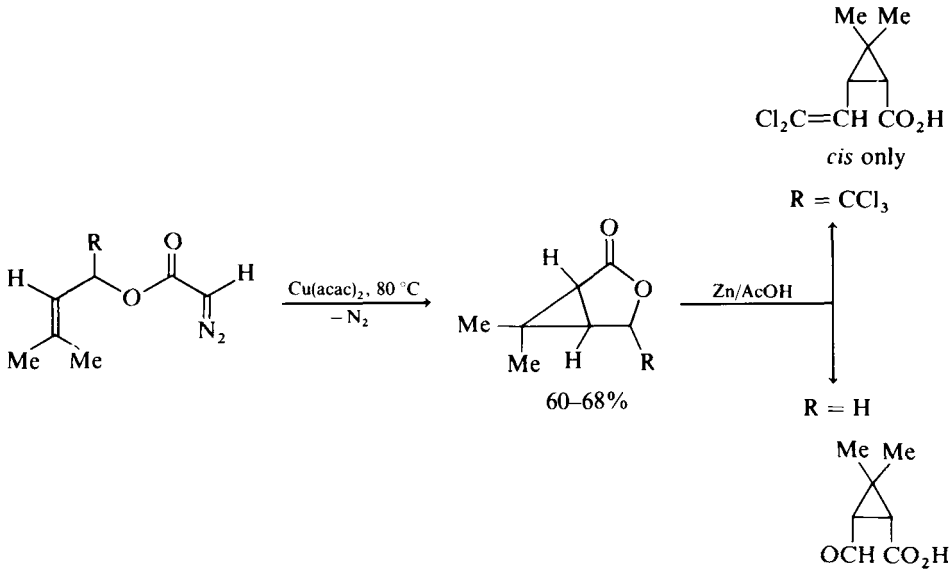
SCHEME 58

carbenes through complexation with transition metals. Therefore, at present cyclopropanations of olefins with the participation of diazoesters are carried out almost exclusively in the catalytic version.

a. Stereoselectivity of olefin cyclopropanation. Carbene addition to the C=C bond, as a rule, leads to mixtures of geometrical and optical isomers of the corresponding cyclopropanecarboxylates; depending on the predominance of the first or second kind of the isomers, the process is said to be diastereoselective or enantioselective. In many synthetic procedures the use of mixtures of enantiomers or of diastereomers is permissible. However, in the synthesis of biologically active compounds, whose properties are radically dependent on the configuration of substituents at the three-membered ring, the development of diastereoselective and enantioselective methods of olefin cyclopropanation is an urgent necessity and is decisive for further progress in this field.

The reactions of intramolecular cyclopropanation involving carbenes proceed stereoselectively and lead to only one of possible geometrical isomers. This feature has been widely used in the synthesis of natural and synthetic biologically active substances, and the approach has been discussed in detail in reviews[5,9,365].

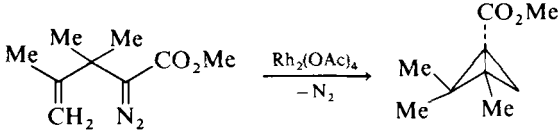
For example, dediazotation of prenyl diazoacetates[51], R = H, and of 1,1,1-trichloromethyl-3-methyl-2-butenyl diazoacetate[366], R = CCl_3, in the presence of $Cu(acac)_2$ leads to bicyclic lactones, which on hydrolysis and dehydrochlorination yield *cis* permethrinic acid and *cis* caronaldehyde, respectively (see Scheme 59). The intramolecular cyclopropanation of the optically active diazoester, R = CCl_3, proceeds enantioselectively.



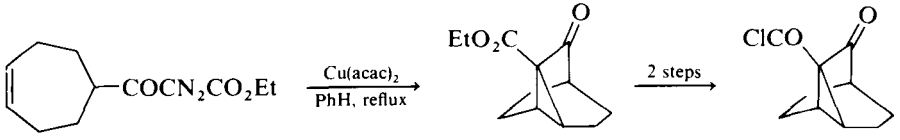
SCHEME 59

Other examples of stereoselective intramolecular reactions of polyunsaturated diazoesters are presented in Section IV.C.1.b, where they are discussed in connection with the problems of regioselectivity of cyclopropanation.

Stereoselective intramolecular cyclopropanation is also used in the synthesis of highly stressed structures, e.g. bicyclo[1.1.0]butane[89] (see equation 141) and tricyclo[3.3.1.$0^{2,8}$]nonane derivatives[367] (see equation 142).



(>90%) (141)

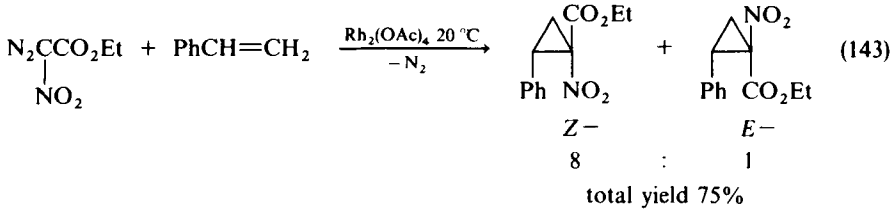


(31%)

(142)

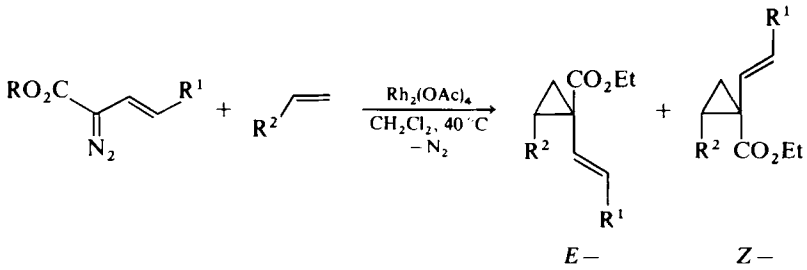
As distinct from intramolecular processes, control over the diastereoselectivity of intermolecular cyclopropanation by diazoesters involves appreciable difficulties due to the absence of conformational factors, which determine the direction of carbene attack. For regulating the stereoselectivity of such a process, one must resort to the secondary effects of steric and electronic interaction between the substituents in the olefin and diazoester by choosing the corresponding ligand environment in the catalyst.

Such interactions cause high diastereoselectivity in the reaction of some α-substituted diazoesters. Thus, the stabilizing effect exerted by the oxygen atoms of the nitro group on the transition state of $Rh_2(OAc)_4$-catalyzed cyclopropanation of different olefins with ethyl α-nitrodiazoacetates favors the formation of the *Z*-isomer of the cyclopropane[368]. In the reaction of the same diazoester with styrene, the proportion of the *Z*-isomer reaches 90% (see equation 143).



(143)

The electronic effects determine, apparently, the high *trans* stereoselectivity of the reaction of olefin cyclopropanation by ethyl α-vinyldiazoacetate[369] (see Scheme 60).



R	R^1	R^2	Yield (%)	Ratio *E*/*Z*
Me	Ph	Ph	94	>20:1
Et	CH=CHPh	Ph	94	>20:1
Et	CO_2Et	4-An	80	18:1
Et	CO_2Et	AcO	79	>20:1
Et	CO_2Et	$PhCH_2$	68	8.1:1

SCHEME 60

Diastereoselectivity of olefin cyclopropanation is also influenced noticeably by the substituents in the alcohol moiety of the diazoester. Exceptionally high *trans*(*anti*) stereoselectivity is obtained in rhodium(II) carboxylate and especially dirhodium(II) tetrakis(acetamide)–catalyzed alkene cyclopropanations with 2,6-di(*tert*-butyl)-4-methylphenyl diazoacetate[370] (see equation 144). Even in the case of 2,5-dimethyl-2,4-hexadiene, the selectivity of cyclopropanation of which is sensitive only a little to the structure of the diazoester and catalyst, the proportion of the *trans* isomer reaches 94%, while in the reaction of this diene with EDA in the presence of the same catalyst the *trans*/*cis* ratio is only 62:38.

$$N_2CHCO_2R + MeC{=}CHCH{=}CMe_2 \xrightarrow[RT/-N_2]{Rh_2(NHAc)_4} Me_2C{=}CH\text{—}\overset{Me\ Me}{\underset{}{\triangle}}\text{—}CO_2R$$

trans: *cis* = 94:6

R = 2,6—^{t}Bu$_2$—4—Me—C$_6$H$_2$ (144)

The *trans/cis* ratio in the cyclopropanecarboxylates can be varied within narrow limits by using porphyrin[244] and phthalocyanine[246] complexes of Rh(III), Fe(III) and Co(II) (see Section IV.A), which are capable of increasing the proportion of *trans* cyclopropanation products.

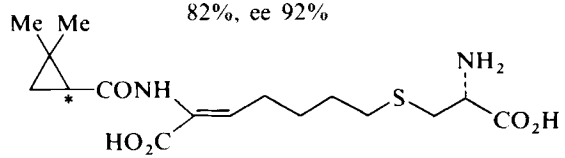
Enantioselective catalysts based on chiral copper(II) chelate complexes and chiral rhodium(II) acetates and acetamides proved, however, to be much more promising. In recent reviews exhaustive information is given on the mechanism of optical induction in the course of transition-metal-catalyzed reactions of diazo compounds, on the design of chiral catalysts and also on their application in directed synthesis of optically active cyclopropanes[371–373].

One of the most successful chiral copper catalysts is Aratani's salicylaldimine complex (AC)[376]. This catalyst ensures highly selective processes with a wide range of olefins, and is the basis of two industrial enantioselective processes involving the diazo method[374,375]. The first is the production of methyl 2,2-dimethylcyclopropanecarboxylate which is an important starting material in the synthesis of cilastatin, an enzyme inhibitor, used in combination with the β-lactam antibiotic, imipenem (see Scheme 61). The second

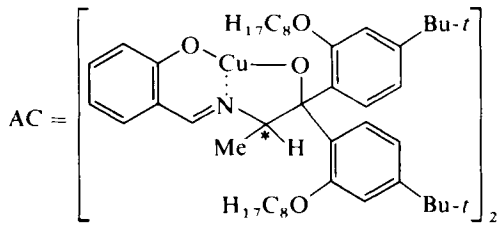
$$N_2CHCO_2Me + Me_2C{=}CH_2 \xrightarrow[-N_2]{R\text{—AC, 40 °C}} \overset{Me\ Me}{\underset{}{\triangle}}\text{—}\underset{*}{C}O_2Et \longrightarrow\!\!\!\!\longrightarrow$$

S-isomer

82%, ee 92%



cilastatin



SCHEME 61

$$N_2CHCO_2Et + Me_2CH{=}CHCH_2CCl_3 \xrightarrow[-N_2]{S-AC,\ 30\,^{\circ}C} Cl_3CCH_2\text{-}\overset{Me\ Me}{\underset{\diagdown\diagup}{\triangle}}\text{-}\sim CO_2Et$$

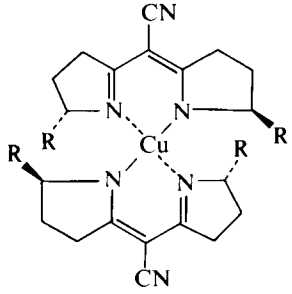
cis:*trans* = 85:15
ee (+) *cis* isomer 91%
total yield 59%

(145)

is the production of pyrethroid acids, e.g. chrysanthemic and permethrinic acids (equation 145).

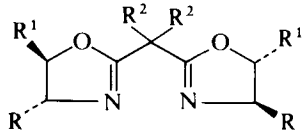
In some cases the use of AC makes it possible to realize not only enantioselective but also highly diastereoselective cyclopropanation. For instance, the reaction of MDA with 1,1,1-trichloro-4-methyl-4-pentene proceeds with high *cis* selectivity (*cis*/*trans* ratio 85:15) in 91% ee of the (+) *cis* isomer[376].

An intensive search for new enantioselective copper catalysts is in progress involving both modifications of ligands in the series of Schiff bases[377,378] and designing ligands of other types. The best results are obtained with the use of N-containing heterocycles as ligands. For example, semicorrin copper complexes (**31**) as catalysts for styrene cyclopropanation with *l*-menthyl diazoacetate lead to a considerable predominance of the *trans* isomer (*trans*/*cis* ratio 85:15) with enantiomeric excess of 90% for 1*S*,2*R*-enantiomer[379]. Derivatives of bis(oxazolines) (**32**) are also a promising type of ligand[380]. Copper(II) complexes of **32** promote the cyclopropanation of styrene with 2,6-di-*t*-butyl-4-methylphenyl diazoacetate, when the enantiomeric excess of 1*R*,2*R*-enantiomer attained is up to 99% with a *trans*/*cis* ratio 94:6[381–384].



(**31**)

R = CMe_2OH



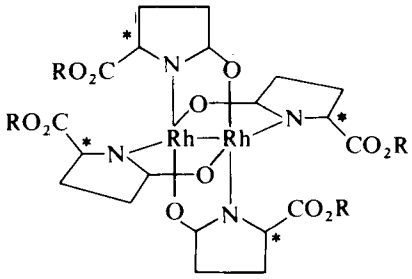
(**32**)

R = Ph, CH_2Ph, Pr^i, Bu^t; $R^1 = R^3 = H$
R = Me, Et, CH_2OH; R^1 = H, Ph; R^2 = H
R = Pr^i, Bu^t; R^1 = H; R^2 = Me

The use of oxazoline derivatives as asymmetric catalysts has been reviewed[385]. Unfortunately, cyclopropanation of other olefins in the presence of both semicorrin and chiral oxazoline copper catalysts proceeds with much poorer diastereoselectivity.

Among other optically active catalysts having preparative importance we should mention chiral rhodium(II) carboxamide (**33**) catalysts, proposed by Doyle and co-workers[386].

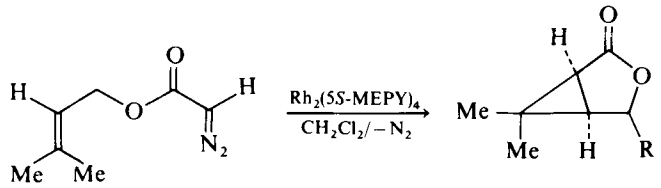
Due to the closeness of the chiral center to the carbene center, this type of catalyst provides high selectivities in intermolecular cyclopropanation reactions. For example, the use of Rh_2(5*S*-MEPY)$_4$ instead of Cu(acac)$_2$ in intramolecular cyclopropanation of



(33)

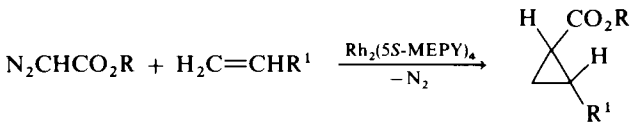
$Rh_2(5S\text{-MEPY})_4$, R = Me
$Rh_2(5S\text{-IPPY})_4$, R = Pr^i
$Rh_2(5S\text{-NEPY})_4$, R = neoPent

prenyl diazoacetates yields the corresponding bicyclic lactone with 82% yield and in 92% enantiomeric excess[387] (see equation 146).



(146)

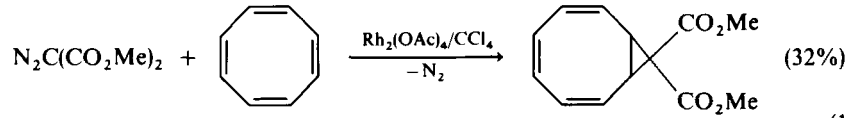
High ee can also be attained in reactions of intermolecular cyclopropanation of alkenes, catalyzed by these complexes, for instance, of 3,3-dimethyl-1-butene and styrene, by sterically bulky esters of diazoacetic acid[373]. Thus, in $Rh_2(5S\text{-MEPY})_4$-promoted dediazotation of *l*-menthyl or 2,3,4-trimethyl-3-pentyl diazoacetates in the presence of these olefins the ee of the *cis* isomers of the cyclopropane carboxylates can reach 91%[373]. Unfortunately, the predominance of the *trans* isomer and its ee are not sufficiently high in these reactions (see Scheme 62).



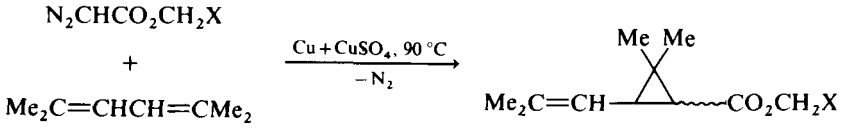
R	R^1	*trans/cis*	ee (%)	
			trans	*cis*
l-menthyl	Pr^i	71/29	65	91
$^iPr_2CH$	Ph	73/27	67	83

SCHEME 62

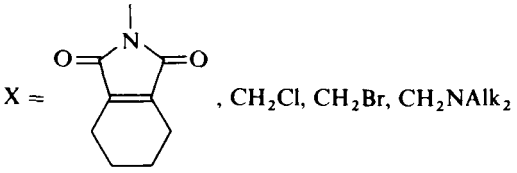
b. Regioselectivity of olefin cyclopropanation. The presence of several double bonds or other reaction centers in the olefin molecule and the presence of functional groups in the diazoester enable the occurrence of reactions competitive with the desired cyclopropanation. In this connection the problem of regioselectivity in many cases is decisive in carbene cyclopropanation of olefins.



(147)

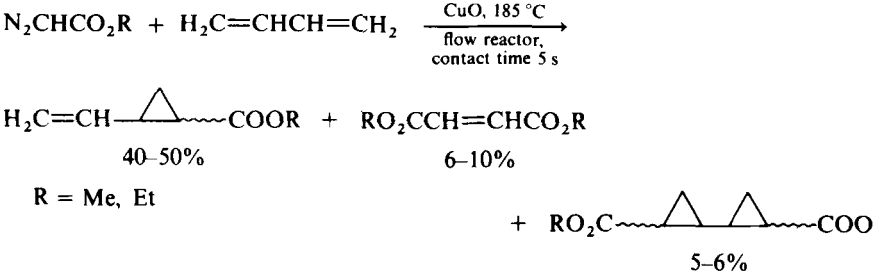


cis/trans = 45:55
Total yield 40–55% (148)

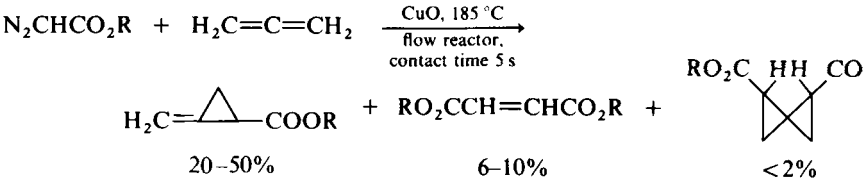


Catalytic reactions of diazoesters of various structures with excess of 1,3-dienes lead to cyclopropane monoadducts (see equations 147[389] and 148[42,44,388]).

The formation of diadducts in noticeable quantities occurs only in reactions of diazoesters with equimolar amounts of dienes or under specific conditions. For example, when the flow technique was used for CuO-catalyzed reactions of gaseous 1,3-butadiene and 1,2-propadiene with EDA, the corresponding diadducts of carbene were found in the reaction products even in the case of 90–100-fold excess of olefins and contact time of 5 *s*[390] (see equations 149 and 150).

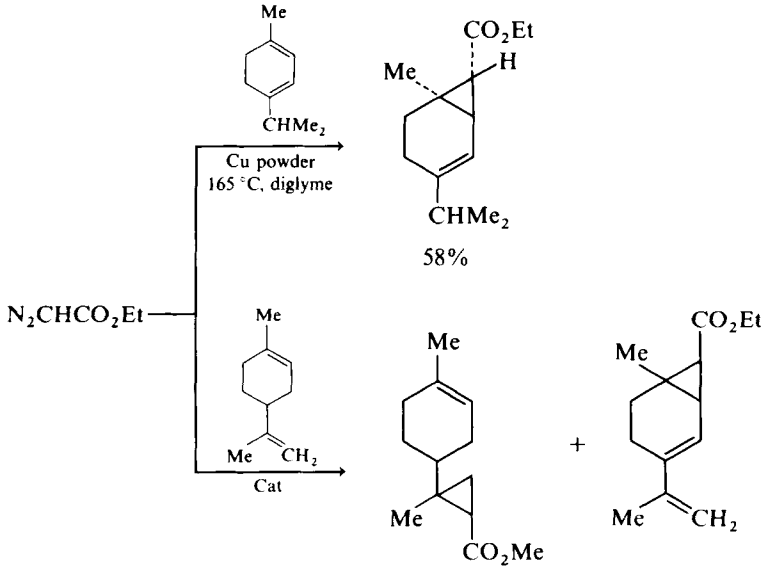


(149)



(150)

Regioselectivity of the reactions of diazoesters with substituted dienes or polyenes depends, in the main, on a fine balance of electronic and steric factors and is hardly dependent on the catalyst. In intermolecular cyclopropanation of alkyl-substituted dienes, e.g. α-terpinene[391] and limonene[392] (see Scheme 63), and 2-(3-methyl-2-butenylidene)-adamantane[393] (see Scheme 64), the attack proceeds, as a rule, at the least hindered double bond, irrespective of the catalyst. Cyclopropanation of the hindered double bond in the latter case can be effected only with the use of a ninefold excess of EDA under rigid conditions.

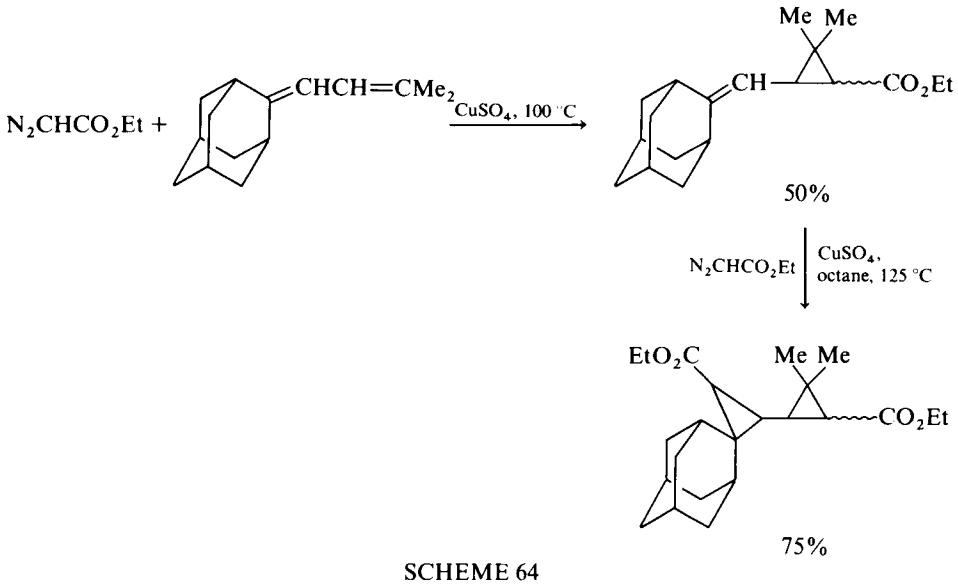


$Rh_2(OAc)_4$	76%	22%
$Cu(OTf)_2$	47%	12%
$PdCl_2 \cdot 2PhCN$	25%	7%

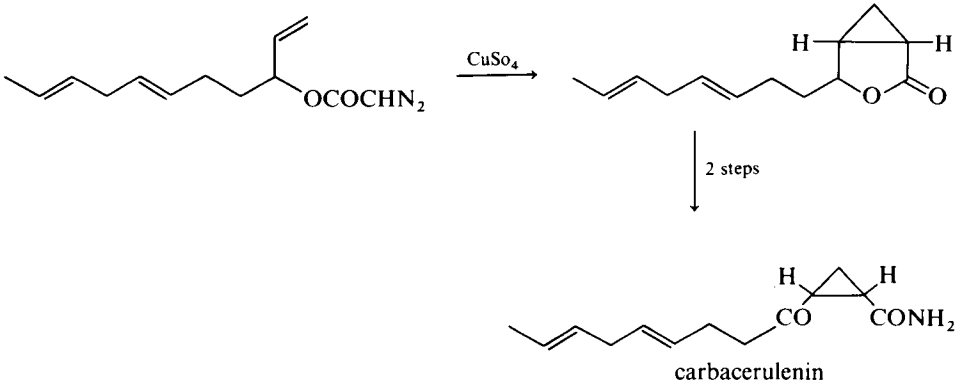
SCHEME 63

This regularity is true also for intramolecular cyclopropanation, and enables one to use these reactions in the syntheses of natural polycyclic compounds. Thus, $CuSO_4$-promoted dediazotation of the nonconjugated undeca-1,5,8-trien-2-yl ester of diazoacetic acid leads to cyclopropanation of the terminal double bond with the formation of a bicyclic lactone, from wich carbacerulenin, an inhibitor of the biosynthesis of lipids in fungal cells, is obtained in two steps[394] (see Scheme 65).

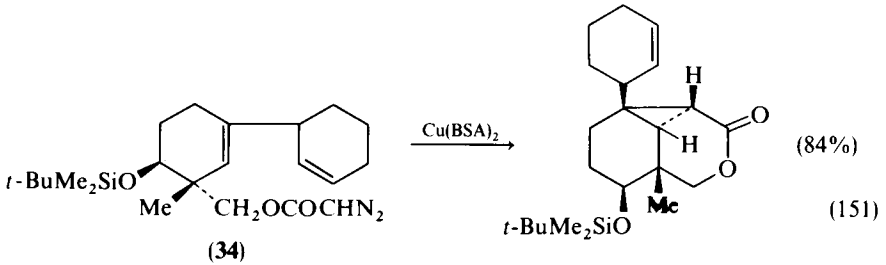
However, in the case of intramolecular processes the direction of carbene attack is substantially dependent also on the distance of the double bond from the carbene center. As a rule, the nearest double bond is subjected to cyclopropanation, even if it is sterically more hindered. For instance, cyclization of cyclic diene esters of diazoacetic acid (**34** and **35**), used in the synthesis of the antheridiogens of *Anemia phyllitidis*, proceeds under the effect of bis(*N*-benzylsalicylaldiminato)copper(II) [Cu(BSA)$_2$] as described above[85] (see equations 151 and 152).



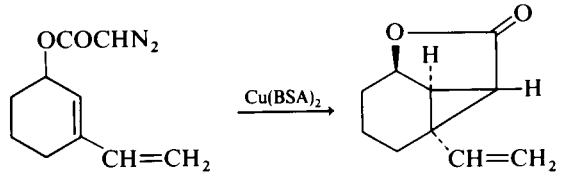
SCHEME 64



SCHEME 65



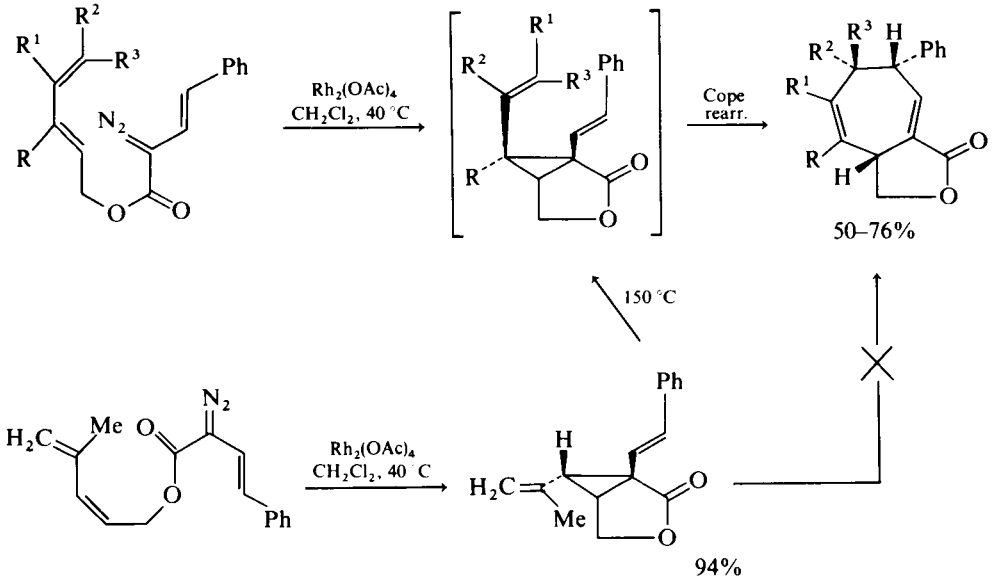
(34) (151)



(92%) (152)

(35)

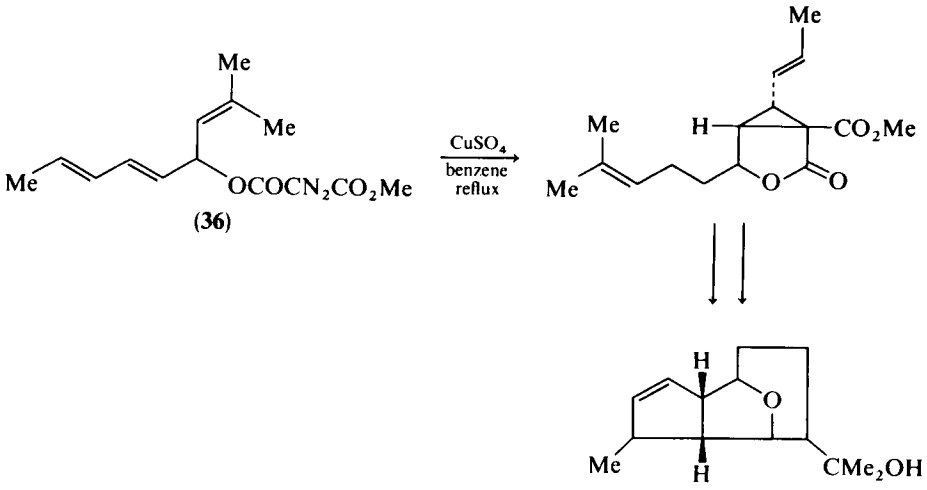
The same feature in the behavior of diene esters of diazoacetic acid was used advantageously for the synthesis of some natural products containing seven-membered rings by an intramolecular tandem cyclopropanation/Cope rearrangement sequence [395,396]. A necessary condition for this reaction to be successful is an *E*-configuration of the nearest double bond, because the resulting *cis* divinylcyclopropane undergoes Cope rearrangement spontaneously. In the case of *Z*-configuration, the product is the *trans* divinylcyclopropane, which can be transformed into the corresponding cycloheptadiene only through initial rearrangement into the *cis* isomer under stringent conditions (see Scheme 66).



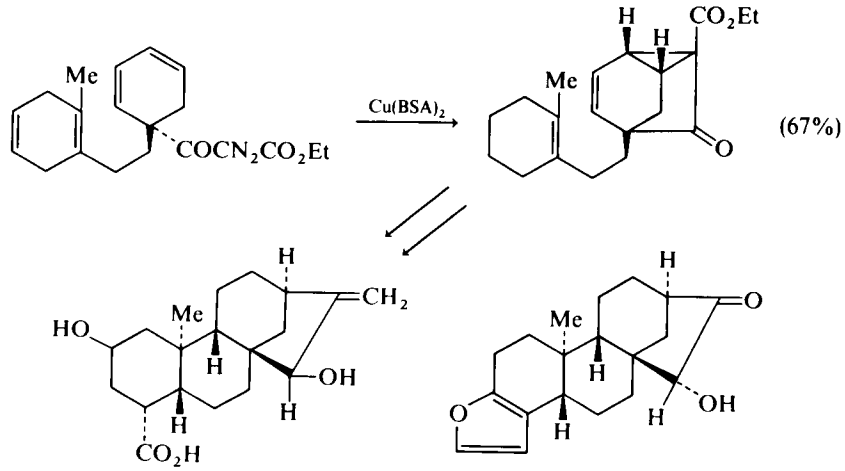
SCHEME 66

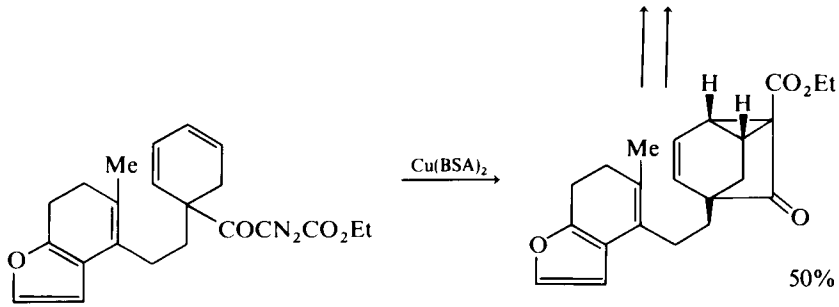
In triene esters of monoalkyl diazomalonates (**36**) containing a 1,3-diene unit and isolated double bond(s), the nearest conjugated double bond is subjected to the attack exclusively[394] (see Scheme 67).

This circumstance was used to advantage for the synthesis of the guaiane ring system[397], the known natural toxin (±)-atractyligenin[398] and antiinflammatory agent cafestol[399] (see Scheme 68). Similar regularities were established earlier in intermolecular cyclopropanation of mercene and related trienes[400].

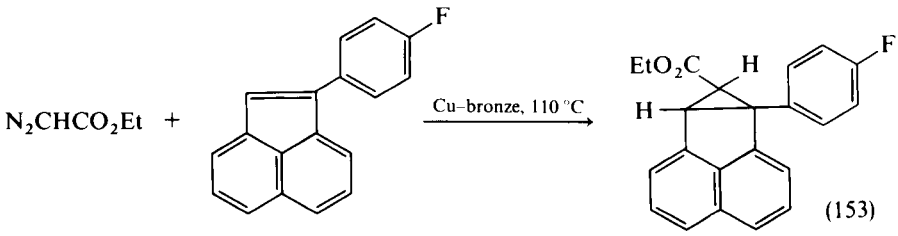


SCHEME 67



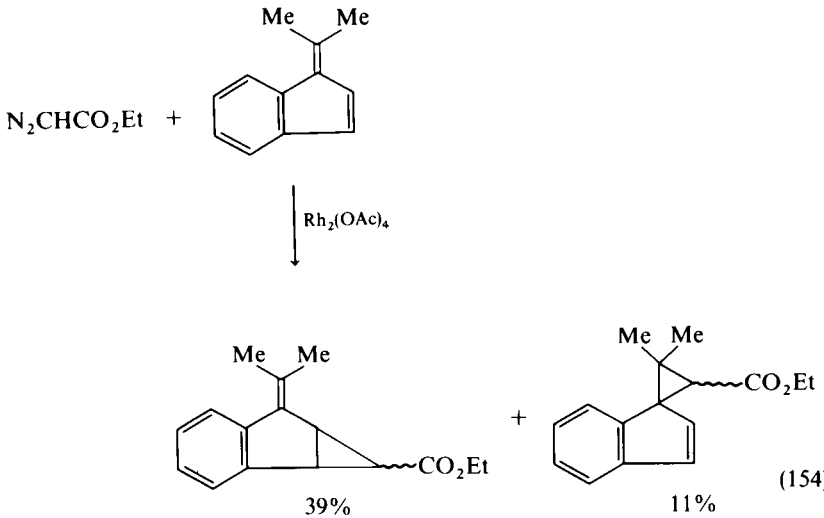


SCHEME 68



(153)

anti 34%, *syn* 15%



(154)

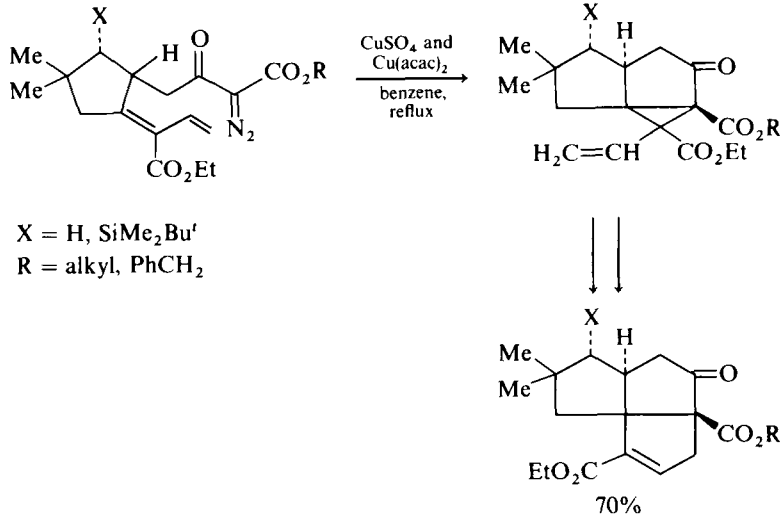
39% 11%

In the case of double bonds, conjugated with the aromatic system, e.g. in acenaphthylene[401] (see equation 153) or 2-isopropylidenindene[402] (see equation 154), aliphatic bonds are exclusively cyclopropanated, preferably the less substituted ones.

The influence of a phenyl substituent on the activity of conjugated bonds in 1,3-dienes depends on its position. If the substituent is in the terminal position, the carbene attacks mainly the unsubstituted bond; in the case of internal position of the substituent the attack proceeds predominantly with the adjacent bond[403]. Other substituents F[404], Cl, OMe, Me, *t*-Bu[405] influence the regioselectivity of reactions of 1,3-dienes in a similar manner. The activating effect of internal alkoxycarbonyl group on the adjacent double bond of the 1,3-diene system was used in stereocontrolled synthesis of nonlinear triquinanes[405] (see Scheme 69).

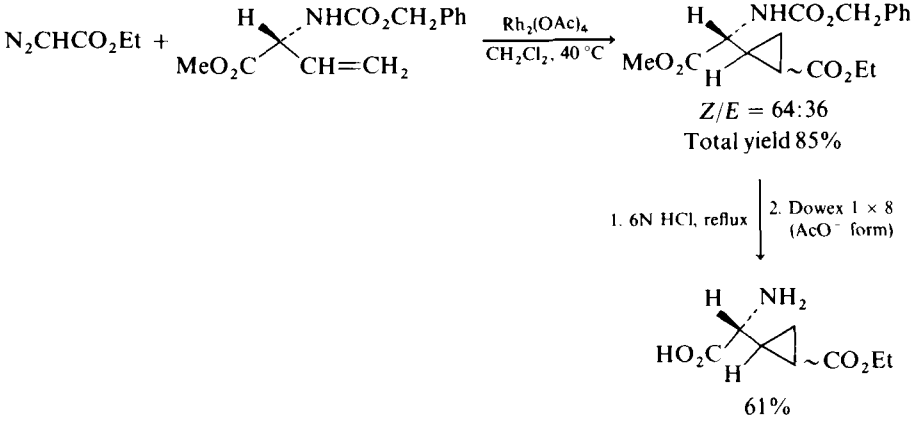
Another aspect of the regioselectivity in the reactions of diazoesters with unsaturated compounds is connected with the possibility of competitive reactions of carbenes with active bonds (C—H, N—H, O—H, C=O etc.) and ylid formation. In most cases these competitions can be minimized by using of appropriate catalyst or protective groups. For example, the use of $Pd(OAc)_2$ as the catalyst makes it possible to cyclopropanate even electron-deficient double bonds in α,β-unsaturated carbonyl compounds with satisfactory yields[245b,406].

The use of acyl protection enables cyclopropanation of allyl- and even vinylamines.



SCHEME 69

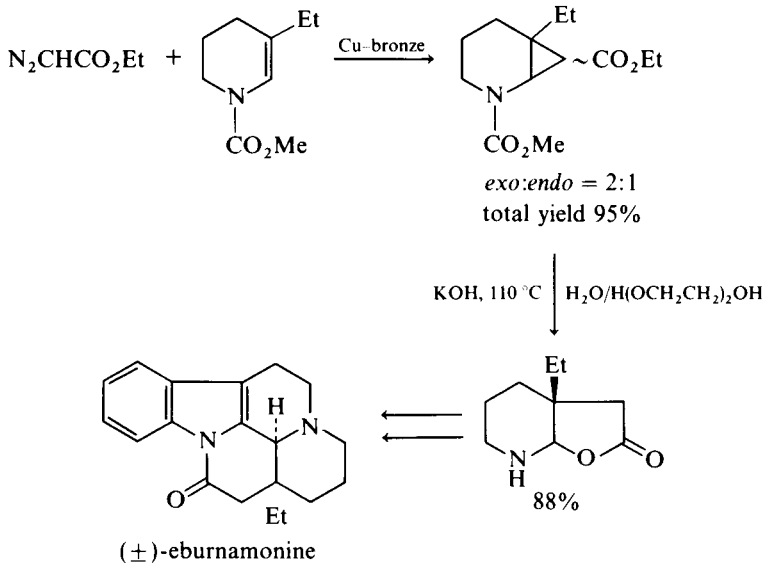
The corresponding cyclopropylmethylamines and cyclopropylamines were used further in the synthesis of amino acids[407] (see Scheme 70) and alkaloids[408] (see Scheme 71).



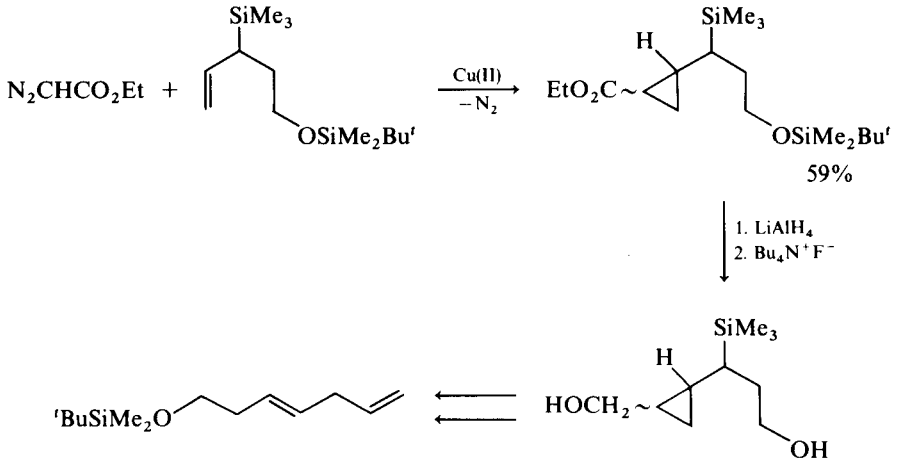
SCHEME 70

Acyl or silyl protection of hydroxy groups, and also acetal protection of carbonyl groups precludes completely the formation of *O*-ylides; this makes it possible to carry out cyclopropanation of unsaturated alcohols (see Scheme 72[409] and equation 155[410]) and carbonyl compounds[411] (see Scheme 73) and to use the resulting cyclopropanes in the synthesis of important building blocks, e.g. 1,4-dienes and bicyclo[3.3.0]octanes.

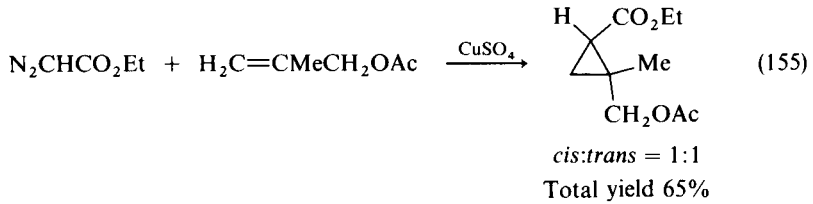
Reactions of diazoesters with silyl enol ethers are of special importance. They furnish β-silyloxycyclopropane carboxylates with high yields even with the use of copper catalysts[412–414] (see equation 156).



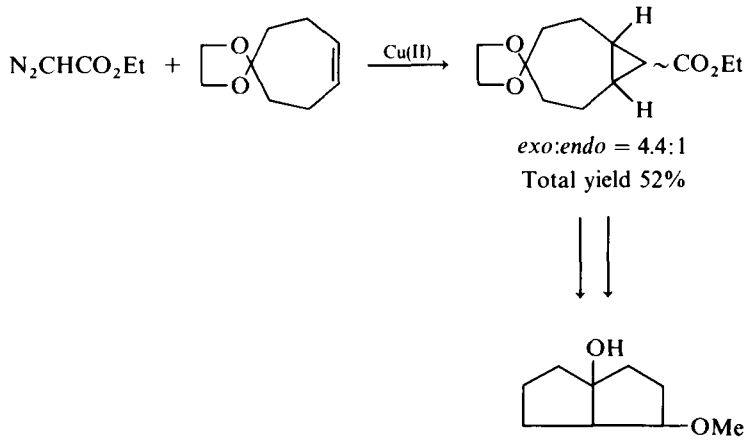
SCHEME 71



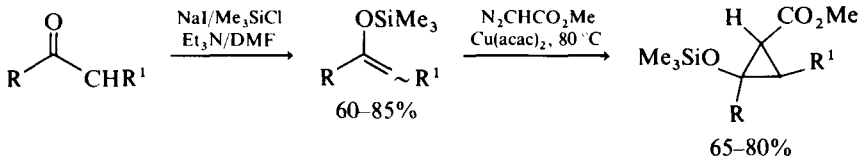
SCHEME 72



(155)



SCHEME 73

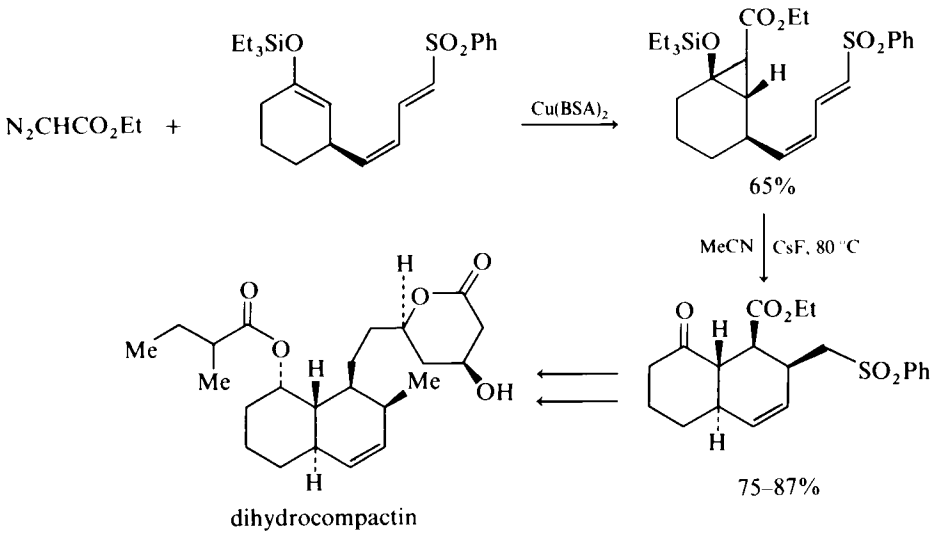


(156)

High reactivity of these donor–acceptor-substituted cyclopropanes makes them extremely valuable starting materials for many synthetic purposes, e.g. for production of 1,4-dicarbonyl and β,γ-unsaturated carbonyl compounds, 4-oxocarboxylic acids and esters, butanolides etc.[415–417]. For example, fluoride-promoted scission of a three-membered ring in the bicyclic adduct obtained through addition of ACC to the most electron-rich double bond of 3-(buta-1,3-dienyl)cyclohexanone is accompanied by annelation of the cyclohexane ring with the formation of octahydronaphthalene, which is used further in the synthesis of dihydrocompactin[418] (see Scheme 74).

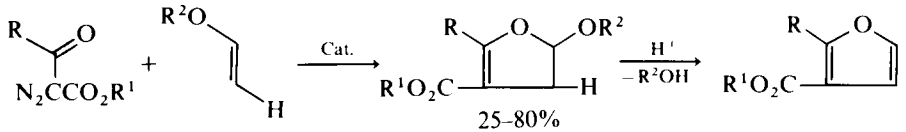
Finally, the third aspect of regioselectivity stems from possible participation of α-substituents in reactions of the corresponding α-substituted diazoesters with olefins. Thus, in the case of α-acyldiazoacetates, dihydrofurans rather than cyclopropanes are formed[419,420]. Actually, in these reactions the corresponding carbenes function as 1,3-dipoles. The reaction proceeds regio- and stereospecifically, i.e. the configuration of the double bond in the initial enol ether is preserved in the dihydrofuran, whereas the carbene center attacks the carbon atom of the double bond, remote from the alkoxyl substituent. This reaction is of definite synthetic importance, since dihydrofurans thus produced can be transformed into furoic esters and furanones, as well as into a number of natural products containing a furan ring[415] (see Scheme 75).

Another example of competitive processes with the participation of an α-substituent in the diazoester are $Rh_2(OAc)_4$-promoted reactions of ethyl α-nitrodiazoacetate with unsaturated acceptors (see Scheme 76). Metal–carbene complexes originating in dediazotation of this diazoester are capable of rearranging into acyl nitroso compounds, which can react as eneophiles with olefins. As a result, depending on the olefin, the reaction can lead to both cyclopropanes and the corresponding ene adducts[368].



dihydrocompactin

SCHEME 74

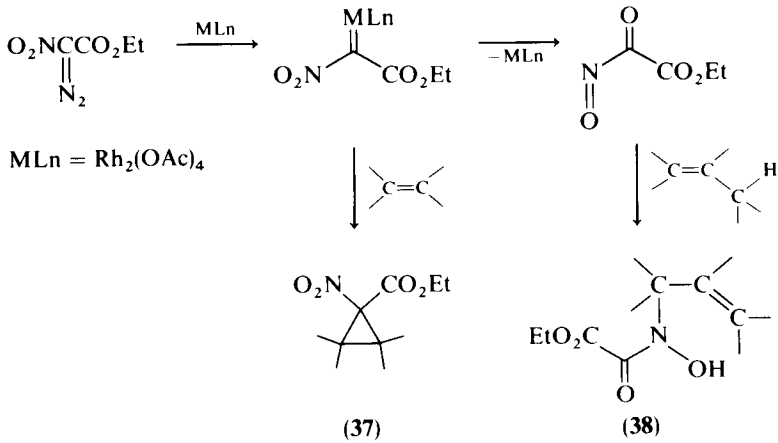


R = H, Me, CO_2Et

Cat. = $Cu(hfacac)_2$, $Rh_2(OAc)_4$

hfacac = hexafluoro acetyl acetonate

SCHEME 75

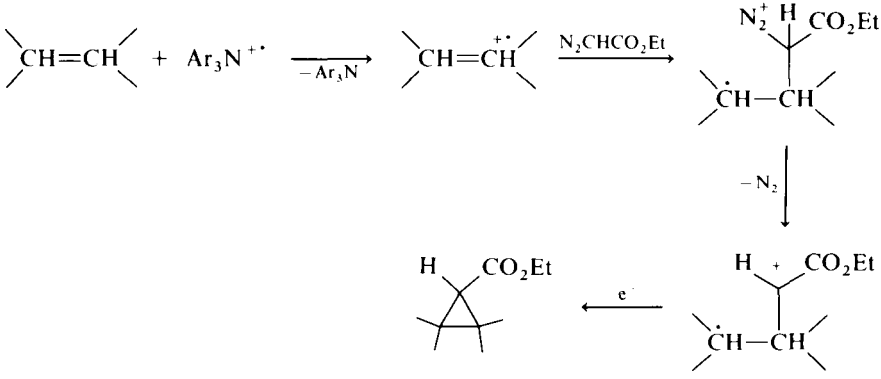


(37) (38)

R	Yield	
	37 (*cis*/*trans*)	**38**
$PhCH{=}CH_2$	75 (8:1)	0
$AcOCH{=}CH_2$	55 (3:1)	0
trans-$MeCH{=}CHMe$	0	86
$Me_2C{=}CMe_2$	0	81

SCHEME 76

c. Ionic cyclopropanation with diazoesters. Though at present the overwhelming majority of reactions of olefin cyclopropanation with diazoesters are transition-metal-promoted carbene processes, recently the ability of aminium salts, such as $Ar_3N^+SbCl_6^-$, has been revealed to catalyze the cyclopropanation of a range of olefins with EDA in high yields[421] (see Table 9). The reaction proceeds through the formation of cation radical intermediates, originating in the interaction of an aminium salt with an olefin (see Scheme 77). An attack of this intermediate at the diazo group of EDA with subsequent elimination of nitrogen leads to the formation of a three-membered ring.



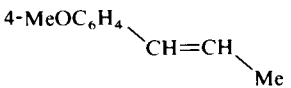
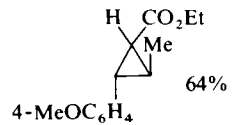
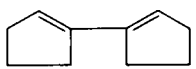
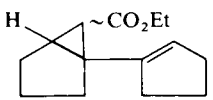
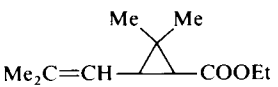
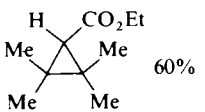
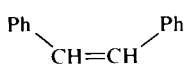
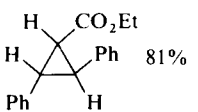
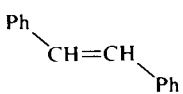
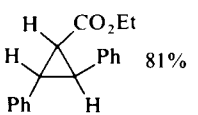
SCHEME 77

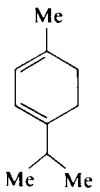
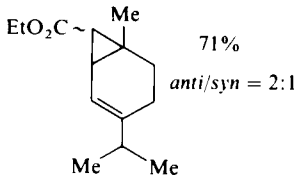
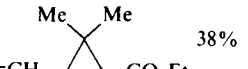
The conditions of these reactions differ from the carbenic ones. The process is effected at a lowered temperature (from 0 to −78 °C) by adding the catalyst to a mixture of an olefin with an excess of EDA. The reactions proceed with high yields of cyclopropanecarboxylates; by-products here are usually the products of transformation of alkenes and final products; no traces of ACC dimers are registered. The stereoselectivity of cation-radical processes is not high, due to the possibility of changes in the configuration of carbon atoms of the olefin in the cation-radical intermediate.

2. *C≡C and C≡N bonds*

Carbenic reactions of diazoesters with acetylene compounds, nitriles, and also with conjugated double and triple bonds in enynes and acrylonitriles are described in the literature.

TABLE 9. Cation-radical cyclopropanation of olefins with ethyl diazoacetate

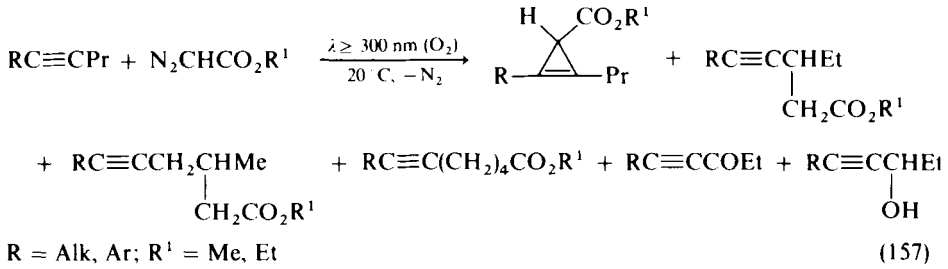
Olefin	Catalyst[a]	Temperature (°C)	Product, yield
	A	0	 64%
	A	0	 67%
$Me_2C{=}CHCH{=}CMe_2$	A	0	 60%, *trans*:*cis* = 1.15:1.00
$Me_2C{=}CMe_2$	B	−78	 60%
	A	0	 81%
	A	0	 81%

	B	−78	 71% *anti*/*syn* = 2:1
$Br_2C{=}CHCH{=}CMe_2$	B	−78	 38% + $Br_2C{=}CHCH{=}CMeCHMeCO_2Et$ 38%

[a] A = $(p\text{-}BrC_6H_4)_3N^+SbCl_6^-$, B = $(2,4\text{-}Br_2C_6H_3)_3N^+SbCl_6^-$.

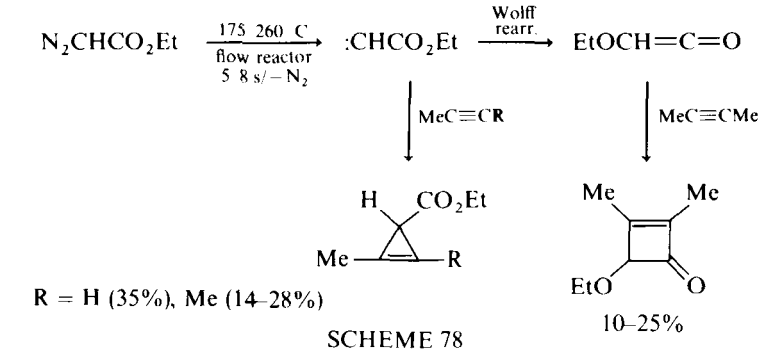
a. Alkynes. Interest in reactions of this type was aroused by the possibility of synthesizing 3-cyclopropenecarboxylates, promising reagents for organic synthesis[422], directly from alkynes. Different aspects of these reactions have been considered in early reviews[6,9].

Carbenic diazoester–acetylene reactions are complicated by side processes because of the relatively low nucleophilicity of the triple bond. Thus, photolysis of diazoesters in the medium of acetylenes is accompanied by the formation of carbene insertion products into the C—H bonds of alkyl substituents, yielding esters of acetylenic acids, and in the presence of air producing acetylenic ketones and alcohols as well[208] (see equation 157). As a result, the yield of cyclopropenes from internal acetylenes usually does not exceed 40%[208, 423], and from terminal acetylenes, in which the nucleophilicity of the triple bond is still lower, the yields are only 17–20%[208].



R = Alk, Ar; R^1 = Me, Et (157)

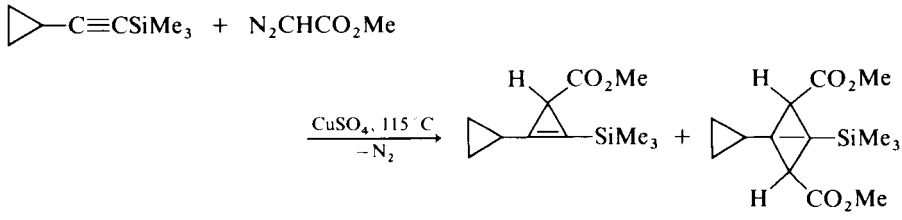
In the absence of catalysts in the liquid phase at temperatures below 150 °C, 1,3-dipolar cycloadditions take place instead of cyclopropenation (see Section III.B.2). At higher temperatures, C—H insertion and destruction of the reaction products occurs[424]. If the reactions are carried out in the vapor phase and at elevated temperatures, even thermally unstable esters, 1-*H*-cyclopropene-3-carboxylates, can be obtained[425a]. However, under the same conditions Wolff rearrangement of ACC into alkoxy ketenes proceeds easily, this being followed by their [2 + 2]-cycloaddition to acetylenes with the formation of 4-alkoxycyclobutene-2-ones, so that the yields of cyclopropenes do not exceed 35%[425a] (see Scheme 78).



R = H (35%), Me (14–28%) 10–25%

SCHEME 78

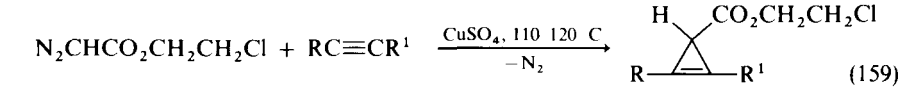
Copper-catalyzed dediazotation of diazoesters also proceeds under rather severe conditions (90–140 °C) and gives satisfactory yields of cyclopropene esters only in the case of internal acetylenes, usually taken in excess so as to preclude the formation of bicyclobutane derivatives[425b] (see equation 158).



Alkyne/MDA = 3:1	25%	1%
Alkyne/MDA = 1:1.5	37%	4%

(158)

Cupric sulfate can be used for the synthesis of more complicated esters from functionalized diazoesters, e.g. 2-chloroethyl diazoacetate[42] (see equation 159).



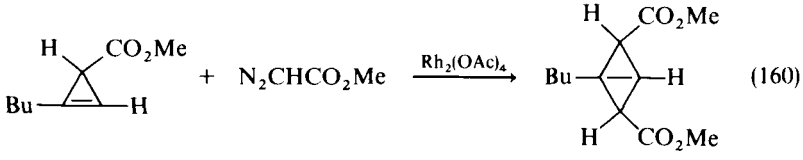
(159)

R = Pr, R^1 = Pr, $SiMe_3$;
R = cyclo—C_3H_5, R^1 = $SiMe_3$

Labile 1-*H*-3-cyclopropenecarboxylates under these conditions are easily isomerized into furane derivatives or oligomerized even at contact times of 3–5 s, when the reaction is carried out in a flow reactor[425a]. Besides, with terminal acetylenes formal carbene insertion products into the acetylene C—H bonds are obtained (see Section IV.B.1) so that the yields of cyclopropenes are not higher than 16%. Special methods of synthesizing 1-*H*-3-cyclopropenecarboxylates with the use of 'silylic protection' of the C—H bonds allowed an increase in the selectivity of Cu-catalyzed reactions by suppressing the formation of insertion products into the acetylene C—H bonds[426]. However, the multistage character of this scheme and low (5–10%) total yields hold little promise for extensive application.

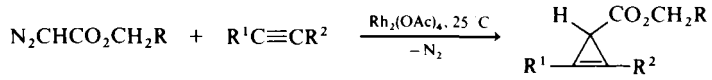
Cardinal changes in the preparative significance of these reactions occurred in the late '70s, with the introduction of catalysis by rhodium compounds. Catalysts of this class in the presence of internal and terminal alkynes bring about dediazotation of a wide range of diazoesters with the formation of the corresponding 3-cyclopropene-carboxylates with fair yields. These reactions with the use of $Rh_2(OAc)_4$ up to August 1985 have been reviewed by Maas[9], while Table 10 presents new data for the period 1985–1990, and also some unpublished studies of the present authors.

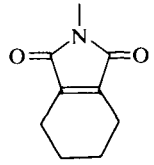
Rh-catalyzed reactions proceed under very mild conditions with high selectivity, and with practically no side processes. For example, bicyclobutane dicarboxylates are not formed from ADA in the presence of $Rh_2(OAc)_4$, although they can be formed from the corresponding cyclopropenes[429] (see equation 160).



(160)

TABLE 10. Cyclopropenation of alkynes with diazoacetates



Entry	R	R^1	R^2	Yield (%)	References
1	H	H	H	45[a]	433
2	H	Me	Me	75	433
3	CH_2NEt_2	n-C_5H_{11}	H	16	434
4	Me	Et	Et	78	435
5	Me	Bu	H	86	435
6	Me	*t*-Bu	H	59	435
7	Me	$(CH_2)_3Cl$	H	97	435
8	Me	Ph	Me	93	435
9	Me	Me	$SiMe_3$	71	435
10	C≡CH	Pr	H	80	215
11		Me	H	45	436
12	3-$PhOC_6H_4$	Pr	H	80	236
13	$CH{=}CMe_2$	Pr	H	85	236
14	CN	Pr	H	85	437
15	CN	C_5H_{11}	H	80	437

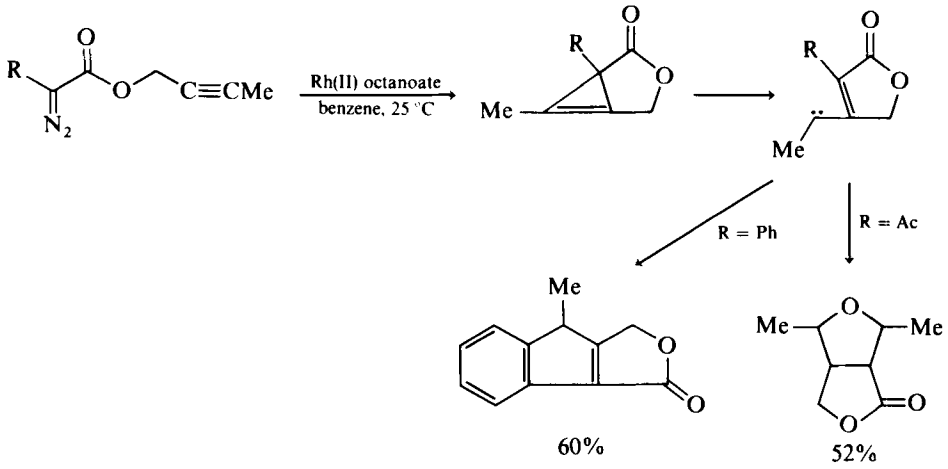
[a] Neat product is polymerized under normal conditions.

Cyclopropenation of neat acetylene and methylacetylene was carried out successfully in the presence of $Rh_2(OAc)_4$ at 15 °C in the liquid phase, and the simplest 3-cyclopropenecarboxylates were obtained with good yields (see entries 1 and 2 in Table 10).

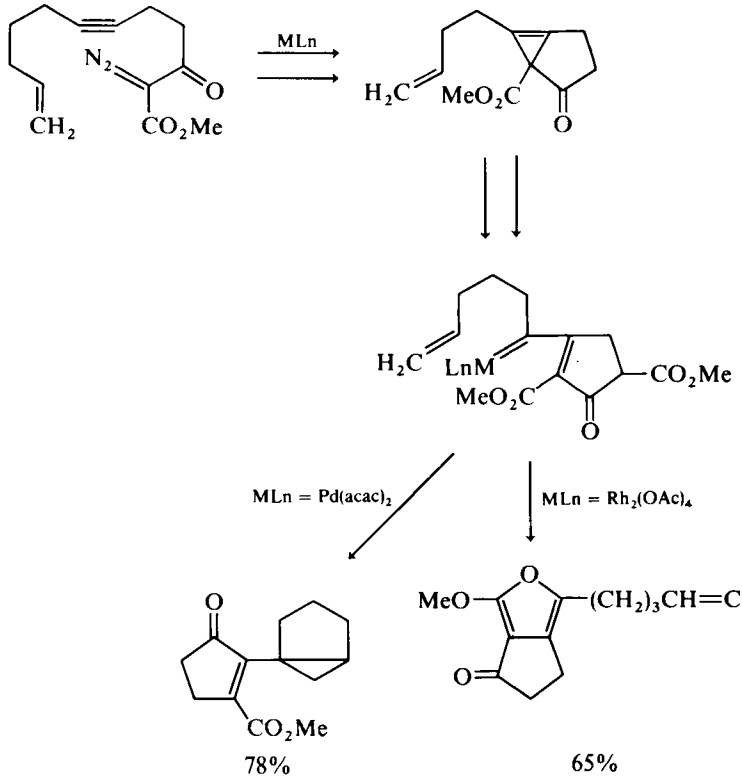
These reactions also proceed smoothly when the diazoacetic esters are carrying active functional substituents (see entries 3, 11–15).

Some diazoesters, containing a triple bond in the alcohol part of the molecule, are capable of intramolecular transformations, giving, as is believed, extremely unstable bicyclic butanolides containing a cyclopropene fragment. The isomerization of such a cyclopropene, obtained by cyclization of 2-butynyl substituted diazoacetates, is believed to proceed with generation of isoelectronic vinylcarbenes, which in turn yield complicated bicyclic butanolides[430] (see Scheme 79).

A similar transformation is the isomerization of a bicyclic cyclopropene, formed in the intramolecular interception of a metal-promoted carbene obtained from a diazoester containing both a triple bond and a double bond[431]. The direction of the isomerization depends on the catalyst. It is supposed that under the effect of $Pd(acac)_2$, isomerization of the cyclopropene into metal–vinylcarbene takes place, with subsequent interception of it by the terminal double bond to yield a cyclopropyl-substituted 2-oxo-4-cyclopentenecarboxylate. In the presence of $Rh_2(OAc)_4$, the vinylcarbene is



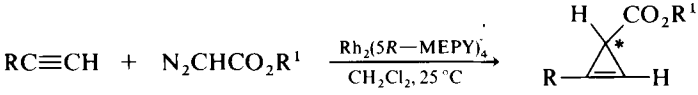
SCHEME 79



SCHEME 80

cyclized with the participation of the carbonyl group of the ester yielding a bicyclic furane (see Scheme 80).

The latest achievement in the use of rhodium catalysis is enantioselective synthesis of the esters of 1-*H*-3-cyclopropenecarboxylates by the interaction of alkynes or methyl propargyl ether with diazoacetates in the presence of a chiral catalyst, dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*R*)-carboxylate][Rh_2(5*R*-MEPY)$_4$][432] (see equation 161).



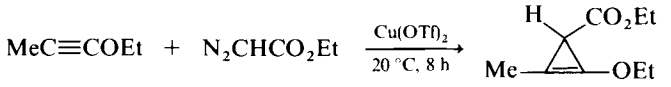
$$RC{\equiv}CH + N_2CHCO_2R^1 \xrightarrow[CH_2Cl_2,\ 25\ ^\circ C]{Rh_2(5R\text{—}MEPY)_4}$$

43–85%, ee 53–98% (161)

R = n—Bu, *t*—Bu, $MeOCH_2$

R^1 = Et, *t*—Bu, d-menthyl

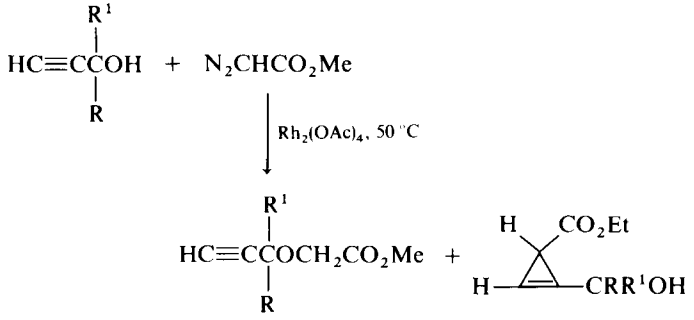
The limitations in these Rh-promoted reactions are not many, and are connected either with the polymerization of the initial alkynes or of the products under the effect of rhodium compounds, or with side reactions of carbene insertion into saturated bonds. Thus, both ethoxyacetylene and phenylacetylene are polymerized by $Rh_2(OAc)_4$[428]. However, the use of $Cu(OTf)_2$ as a catalyst enabled one to carry out a direct synthesis of 1-ethoxy-2-methyl-3-cyclopropenecarboxylate from 1-ethoxy-1-propyne[438] (see equation 162).



$$MeC{\equiv}COEt + N_2CHCO_2Et \xrightarrow[20\ ^\circ C,\ 8\ h]{Cu(OTf)_2}$$

(162)

Cyclopropenation of acetylenic alcohols is successful only in the case of hindered ones. Insertion into the O—H bond with the formation of propargylic ethers is predominant in the reactions of diazoesters with propargyl alcohol[303,427] (see equation 163).



$$HC{\equiv}CC(R^1)(R)OH + N_2CHCO_2Me \xrightarrow{Rh_2(OAc)_4,\ 50\ ^\circ C}$$

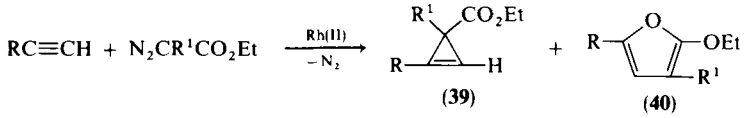
$$HC{\equiv}CC(R^1)(R)OCH_2CO_2Me + \text{cyclopropene}$$

(163)

R = R^1 = H	60%	12%
R = Me, R^1 = Et	37%	36%

Diazoesters with an acceptor substituent in the α-position (diethyl diazomalonate and ethyl α-(2-ethoxycarbonylvinyl)diazoacetate are also capable of cyclopropenating alkynes in the presence of $Rh_2(OAc)_4$[439] (see Table 11). Only a small amount (3–12%) of cyclopropene derivatives was detected in the MDM reactions with decyne-5 and

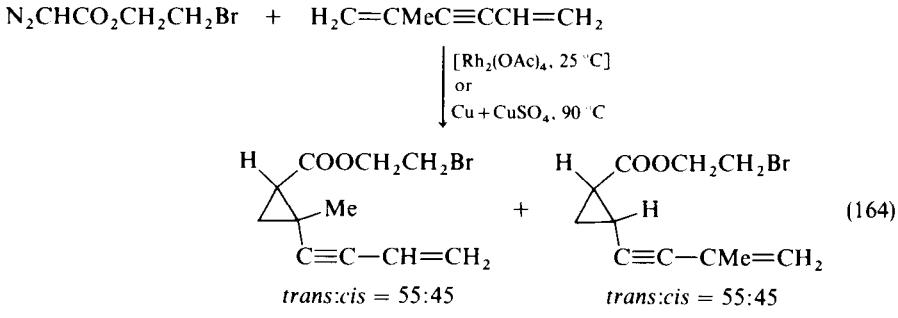
TABLE 11. Alkoxyfurane formation in the reaction of diazoesters with 1-alkyne



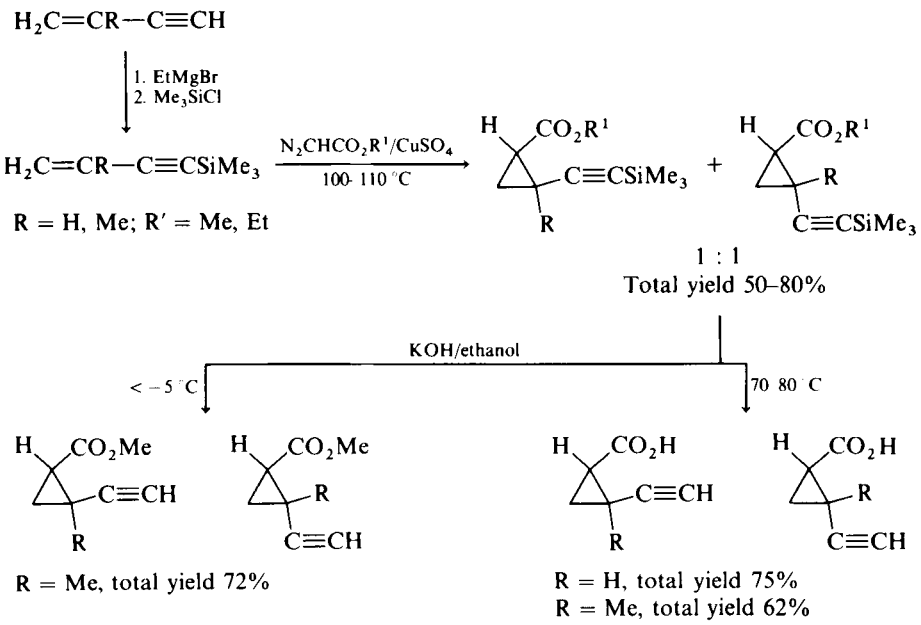
R	R^1	Yields (%) 39	40
Bu	CO_2Et	54	—
Bu	$CH{=}CCHCO_2Et$	61	—
Ph	$CH{=}CHCO_2Et$	85	6
Ph	Ac	—	45
4-$MeOC_6H_4$	CO_2Et	—	53
3,4-$(MeO)_2C_6H_3$	Ac	—	69
2,4-$(MeO)_2C_6H_3$	CO_2Et	—	72

1-trimethylsilyl-1-hexyne[440], while in ethyl α-acetyldiazoacetate and diethyl diazomalonate reactions with arylacetylenes they were absent altogether[439]. The main processes in the first case are carbene dimerization and C—H insertion; in the second case the main process is alkoxyfurane formation (see Table 11).

b. Enynes and diynes. Though conjugation lowers to a considerable extent the reactivity of the triple bond in carbene reactions of 1,3-enynes with diazoesters, only in the case of a few internal enynes with strongly deactivated triple bonds, e.g. 2-methyl-1,5-hexadiene-3-yne[44] (see equation 164) or 4-trimethylsilyl-3-buten-1-yne[441] (see Scheme 81), is it possible to avoid the formation of adducts with the triple bond and to effect syntheses of 2-alkynylcyclopropane carboxylates with acceptable yields.



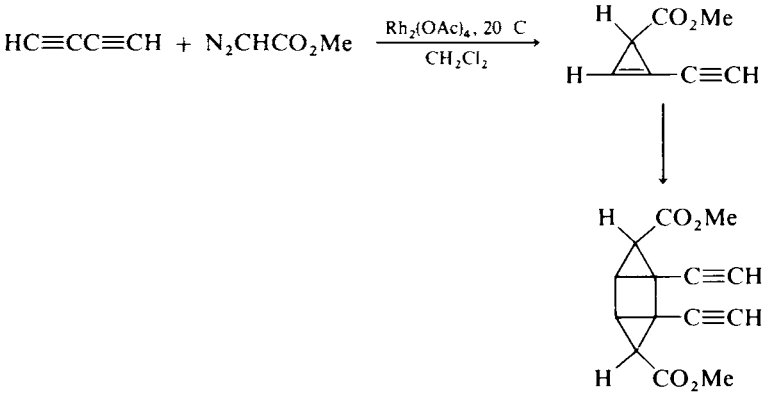
1,3-Enynes with a terminal triple bond add Rh-promoted metal–carbenes predominantly to the triple bond with the formation of 1,6-dialkenyl-tricyclo[3.1.0.$0^{2,4}$]hexanedicarboxylates (**41**)[442], which are [2 + 2]-cycloadducts of 2-alkenyl-3-cyclopropenecarboxylate (**42**) (see Scheme 82). The formation of a carbene adduct (**43**) to the double



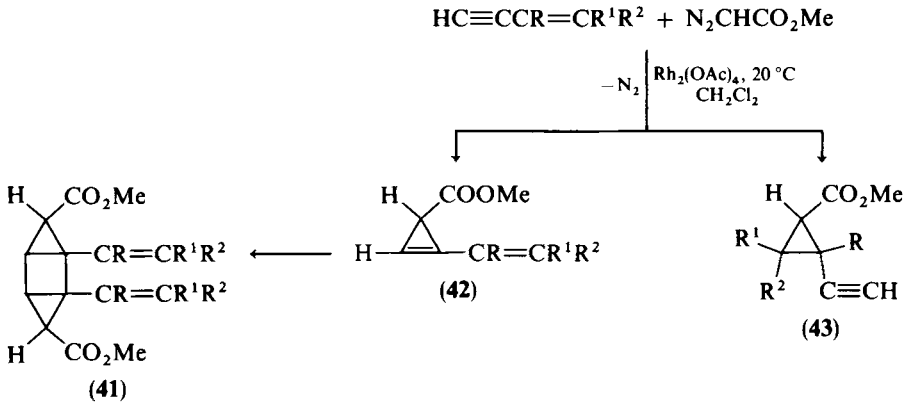
SCHEME 81

bond could be proven only in the case of 2-methyl-3-buten-1-yne, in which the double bond is activated by the methyl substituent.

ADA interaction with diyne compounds remaines practically unstudied. Recently we have carried out the addition of Rh(II)-promoted carbene to the triple bond of diacetylene with the formation of extremely unstable 2-ethynyl-3-cyclopropene carboxylates, which cyclodimerize *in situ* into 1,6-diethynyltricyclo[3.1.0.0^{2,4}]-hexanedicarboxylates[442] (see equation 165).



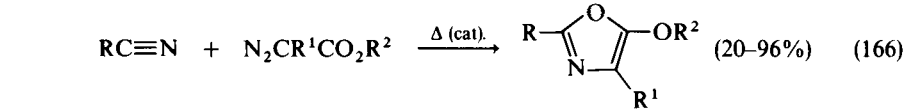
(165)



			Yields (%)	
R	R^1	R^2	**41**	**43**
Me	H	H	48	20
H	H	H	70	—
H	Me	Me	67	—
H	Me ($Z:E = 1:1$)	H	73	—

SCHEME 82

c. Nitriles. The interaction of diazoesters with nitriles leads to 1,3-oxazoles with moderate to high yields[443–446a] (see equation 166).

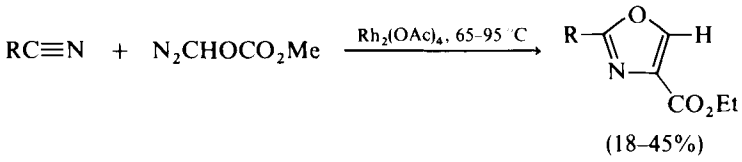


Cat. = $Cu(C_{17}H_{35}CO_2)_2$, 80 °C; $Rh_2(OAc)_4$, 70 °C
R = alkyl, aryl, $PhCH_2$, PhCH=CH, MeCH=CH, H_2CMe
R^1 = H, CF_3, CO_2Alk

This reaction is of general character and proceeds with diazoesters of different types and with various nitriles both in the absence of catalyst at 150 °C and under the effect of traditional ADA dediazotation catalysts [copper compounds, $Rh_2(OAc)_4$, $Pd(OAc)_2$]. The reaction is also catalyzed by Lewis acids, e.g. $BF_3 \cdot OEt_2$ or $AlCl_3$[447].

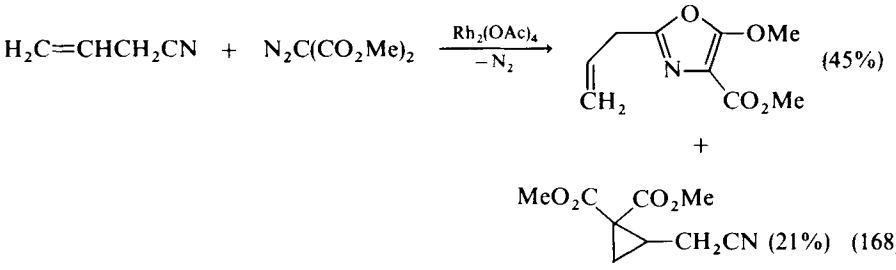
In the case of α-formyldiazoacetate the formation of the corresponding 1,3-oxazole occurs with the participation of the more nucleophilic formyl rather than of the alkoxycarbonyl group[448] (see equation 167).

The reaction is best applied to unsaturated conjugated nitriles, but in the case of allyl cyanide[445] (see equation 168) and α-cyanfurane[446b] (see equation 169) a considerable quantity of cyclopropane adducts of carbene to the double bonds is observed.



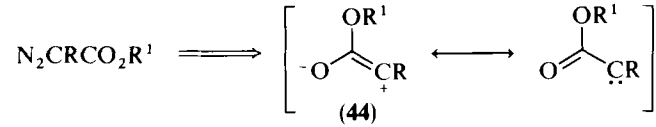
(18–45%)

R = Me, Ph, 4—MeC_6H_4, *E*—MeCH=CH, *E*—EtO_2CH=CH, *E*—PhCH=CH



(169)

Thus, in the reactions with nitriles the diazoesters behave as synthons (**44**) of the 1,3-dipole type, isoelectronic to the corresponding carbenes.

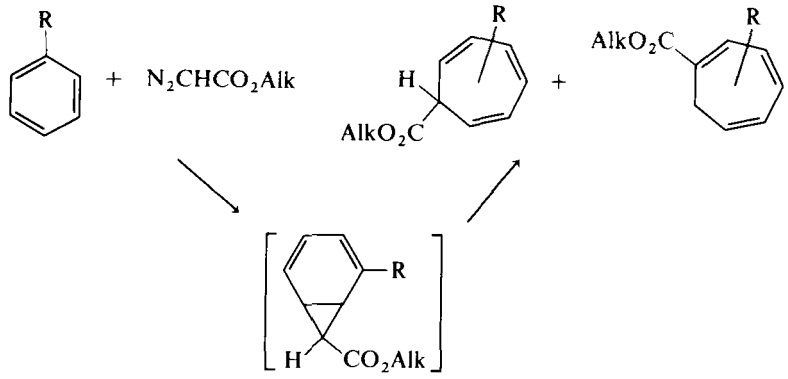


(**44**)

It is believed[444], however, that 1,3-dipolar cycloaddition of carbenes is unlikely and that the reaction proceeds by way of the C≡N bond being attacked by triplet carbene, this being followed by an intercombination conversion and intramolecular recombination of the biradical. Here, the nitrile behaves as a sensitizer of the singlet–triplet transition. Probable reaction mechanisms in the catalysis by Lewis acids were suggested by Doyle and coworkers[447].

3. Reactions with homoaromatics

Carbenes generated by dediazotation of diazoesters, in the absence of more active acceptors, are capable of adding to multiple bonds of homoaromatic compounds. However, the bicyclo[4.1.0]heptadienes forming in this case are practically never identified in the products, because they easily isomerize into 1-*H*-cycloheptatriencarboxylates and their thermodynamically stable conjugated isomers (see Scheme 83). Conversion and selectivity of this reaction depends on the carbene generation mode and on the



SCHEME 83

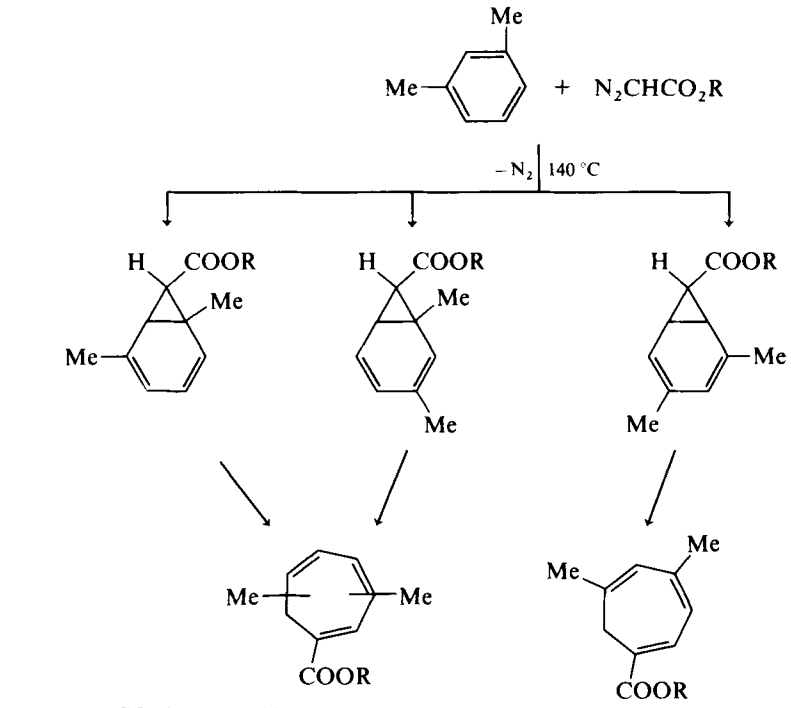
structure of the substrate. Electrophilic ACC resulting in thermolysis of EDA reacts predominantly with benzene derivatives carrying electron-donating substituents, e.g. alkyl or alkoxyl, and also with condensed aromatic hydrocarbons with lowered delocalization energy[449]. Thus, the activity of benzenoid aromatic compounds in reactions with ethoxycarbonyl carbene increases in the series benzene $\ll$ naphthalene $<$ phenanthrene.

ACC, having a more complicated structure, are also sufficiently active in addition reactions to aromatic multiple bonds. Thus, 2-chloroethoxycarbonyl carbene, generated by thermolysis of the corresponding diazoacetates, react with *m*-xylene, giving a mixture of the thermodynamically stable 2-chloroethyl-7*H*-cyclohepta-1,3,5-triene carboxylates[42] (see Scheme 84). In this mixture the 2,6-dimethyl isomer is predominant, and is formed in the carbenic attack of the unsubstituted 5,6-bond of *m*-xylene, this being consistent with the data reported by Huisgen's group[450] for the EDA reactions with dimethylnaphthalene.

A conjugated vinylcarbene of complicated structure generated by thermolysis of methyl α-indenylidenediazoacetate, also adds to the multiple bonds of benzene[451] (see Scheme 85). For the resulting vinylcyclopropane, however, an *exo*-cyclic [1,3]-rearrangement with the formation of an indene rather than a cycloheptatriene structure proves to be preferable.

Unlike thermally generated carbenes, rhodium(II)-promoted metal–carbenes react with homoaromatics resulting in both products of addition to multiple bonds and of C—H bond insertions, broadening synthetic potentialities of the ADA reactions with aromatic compounds.

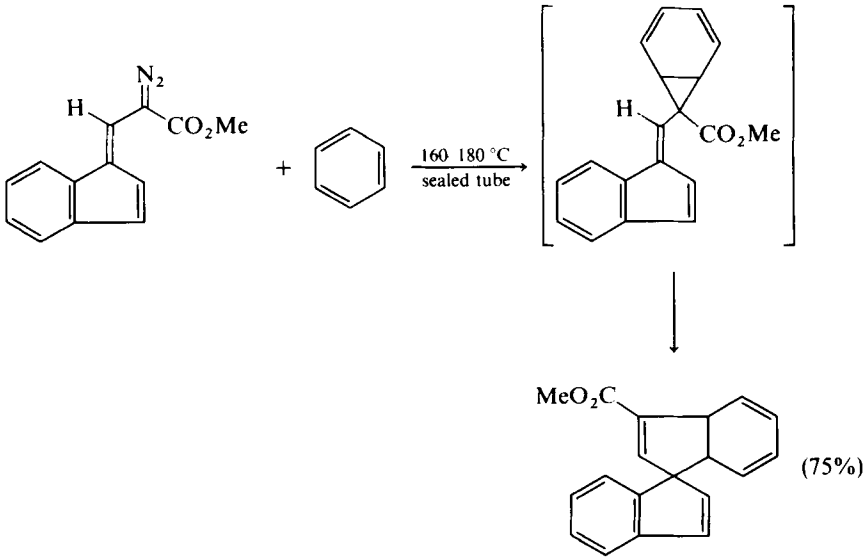
The use of tetrakis(carboxylato)dirhodium(II) complexes of very strong organic acids, such as trifluoroacetic and perfluorobenzoic acids, increasing the electrophilicity of metal–carbene species, allows one to prepare 1-*H*-carbalkoxy-2,4,6-cycloheptatrienes



R = $CO_2CH_2CH_2Cl$ 45 : 55

Total yield 37%

SCHEME 84



SCHEME 85

TABLE 12. Formation of 1-methoxycarbonyl-2,4,6-cycloheptatrienes from substituted benzenes and methyl diazoacetate (molar ratio benzenes:diazoacetate = 20:1; rhodium(II) trifluoroacetate, 0.4% mol; 22 °C)

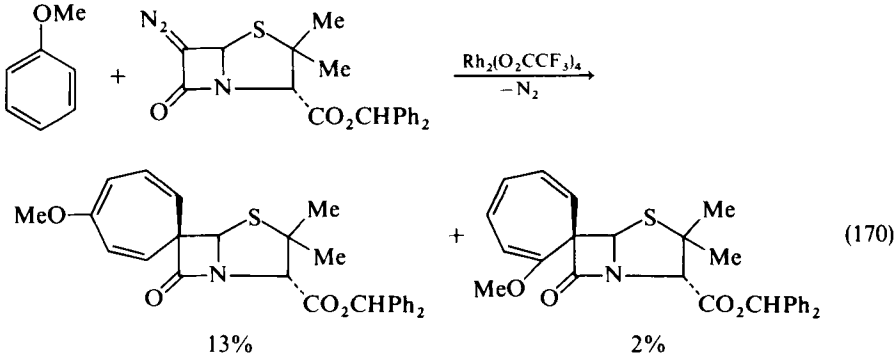
Substrate	Yield (%) (isomeric distribution[a])
Benzene	100 (—)
Toluene	95 (*p*:*m*:*o* = 56:23:14)
o-Xylene	80 (2,3:3,4:4,5 = 18:39:43)
m-Xylene	90 (2,4:2,6:3,5 = 12:43:43)
p-Xylene	90 (2,5:3,6:others = 85:10:5)
Anisole	73 (*p*:*m*:others = 56:8:36)
Chlorobenzene	72 (*p*:*m*:*o* = 80:15:5)
Fluorobenzene	46 (*p*:*m*:*o* = 80:12:8)

[a] 'Others' means conjugated isomers of cycloheptatrienes.

from a wide range of aromatic compounds in very good yields and with reasonable selectivity at room temperature[452] (see Table 12). The attack of metal–carbene species is directed to the bond most remote from the substituents.

This method can be used for direct and controlled functionalization of some polymers. For example, polystyrene was converted into a polymer containing up to 10% incorporated ACC units[452].

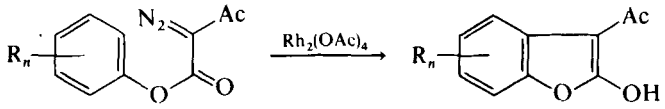
The application of the rhodium(II) catalyst makes it possible to carry out reactions with the participation of strained and labile diazoesters, e.g. 6-diazopenicillanic acid ester. As a result, spiro derivatives of this acid were obtained, containing a cycloheptatriene fragment[452] (see equation 170).



(170)

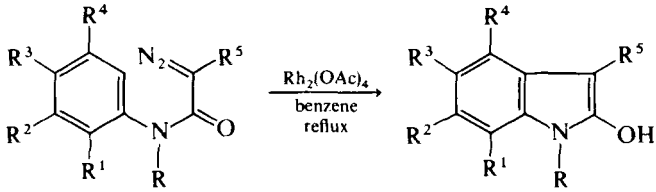
In recent years much attention has been paid to the investigation of intramolecular reactions of cyclization of ACC-containing aromatic substituents. These reactions yield carbene insertion products into C—H aromatic bonds rather than cycloheptatriene

derivatives. Though it is still unclear whether this reaction is the result of concerted insertion of carbene into the C—H bond or the result of isomerization of the initially formed cyclopropane adduct, it is a convenient method for the synthesis of polycyclic systems. For instance, Rh(II)-promoted dediazotation of phenyl α-acetyldiazoacetate[454] (see equation 171) or *N*-phenyl diazoamide[455] (see equation 172) is accompanied by intramolecular cyclization of the corresponding metal–carbenes with the formation of substituted enols of benz[*b*]furanone or benzindanone, respectively, with good yields.



(92–98%) (171)

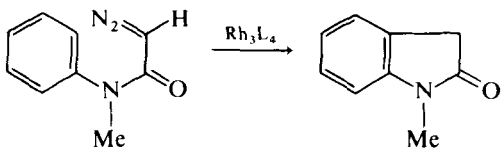
R = H, 2—Me, 2—Br, 3,4—OCH_2O



(77–97%) (172)

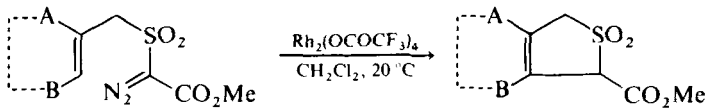
R = alkyl or CH_2Ph, R^5 = H or Ac
R^1–R^4 = alkyl or $R^2 + R^3$ = CH=CHCH=CH

This cyclization takes place only in the case of substituted phenyl derivatives of α-acetyldiazoamide (R^1–$R^3 \neq$ H), though under similar conditions unsubstituted *N*-phenyl-*N*-methyldiazoacetamide becomes transformed into benzindanone[456] (see equation 173).

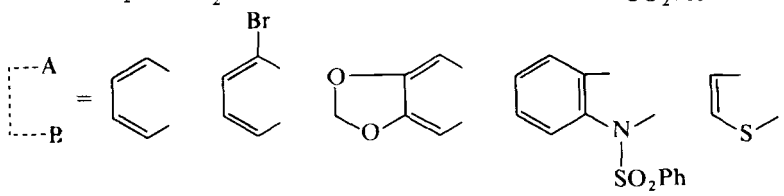


(86%) (173)

L = OAc, $OCOCF_3$, $OCOC_3F_7$ or NHAc



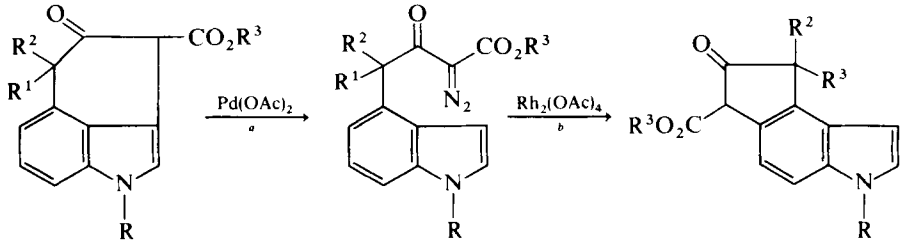
(174)



(46%) (48%) (47%) (24%) (50%)

Under similar conditions intramolecular cyclization with the participation of α-[aryl (or hetaryl)sulfonyl]diazoacetates, leading to the corresponding 1,1-dioxyl benz[*c*]thiophenes with moderate yields, proceeds easily[68] (see equation 174).

Dediazotation catalysts influence essentially the regioselectivity of aromatic C—H insertion reactions. Thus, cyclization of metal–carbenes, generated by catalytic dediazotation of α-[(4-indolyl)acetyl]diazoacetate, proceeds, depending on whether palladium(II) or rhodium(II) acetate is used as a catalyst, with the participation of either the indole ring (see path a in Scheme 86) or of the benzene ring (see path b in Scheme 86)[457].

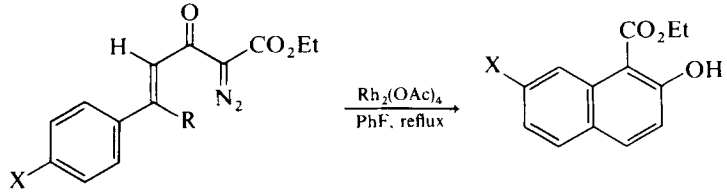


51–76% R = H, Tos, CH_2Ph; R^1, R^2 = H, Alk; R^3 = Me, Et 61–89%

SCHEME 86

This is caused, apparently, by different mechanisms of the catalytic action of Pd and Rh compounds in carbene reactions of diazoesters; in the case of Pd compounds the authors suggest the participation of carbocation rather than carbene intermediates.

In some cases intramolecular C—H insertion into the aromatic nucleus is preferred, even if there is a multiple bond in the molecule, as in the case of α-[(2-arylvinyl)acetyl]diazoacetate, in which the double bond is deactivated by conjugation with the carbonyl group. As a result, the reaction leads to derivatives of β-naphthols with high yields[63] (see equation 175).



(175)

R = Ph, X = H (90%)
R = *p*—MeC_6H_4, X = Me (76%)
R = *p*—ClC_6H_4, X = Cl (97%)

4. Reactions with heteroaromatics

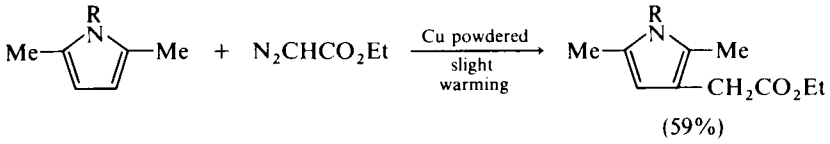
The multiple-bond character in heteroaromatic compounds, which occupies an intermediate position between benzenoid aromatic bonds and dienic conjugated bonds, and also the presence of the nucleophilic heteroatom, determine the broad diversity of

the reactions of this class of compounds with carbenes or their transition-metal complexes. Carbene reactions usually proceed in parallel via several reaction sites of the heterocycle; this makes systematization of these processes difficult. Hence in this secton data are presented on carbene reactions of diazoesters with heteroaromatic multiple bonds together with transformations involving the heteroatom as well as C—H bonds.

A number of reviews[2,4,9,458] are devoted to the preparative potentialities of carbene reactions with five-membered aromatic heterocycles, such as pyrrole, thiophene, furane and their derivatives. These data are supplemented with the results of the latest investigations, as well as with some little-known studies carried out earlier, broadening the overall pattern of the behavior of heterocycles.

a. Pyrroles and related compounds. Reactions of diazoesters with pyrrole itself and with *N*-alkylpyrroles lead only to the products of formal insertion into C—H bonds of the pyrrole ring, among which the products of α-insertion predominate; in these cases products of N—H insertion are never formed (see Table 13). The regioselectivity of this reaction depends on the catalyst, diazo compound, and substituent at the N atom. Maximal yields (to 92%) and reaction selectivity (>90%) for the insertion into the α-C—H bonds are attained in reactions with the participation of MDM and homogeneous Cu(II) catalysts or $Rh_2(OAc)_4$. The reactions of EDA and other diazoesters with pyrroles generally proceed with lower yields and selectivity: rhodium compounds in EDA dediazotation quickly lose their reactivity and yield complex mixtures with traces of C—H insertion products.

Substituents in the pyrrole nucleus, irrespective of their character, do not produce any substantial effect on the regioselectivity of the reaction, except in the cases when they occupy positions 2 and 5 in the ring. EDA reaction with such pyrroles leads to products of insertion into the β-C—H bonds[462] (see equation 176).

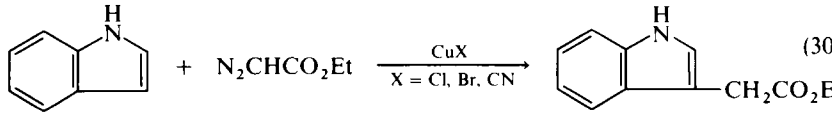


(59%) (176)

The influence of *N*-alkyl substituents causes an increase in the proportion of the β-isomer with the growth of the size of the group in the series H < Me < *i*-Pr < *t*-Bu, reaching exclusive formation of the β-isomer in the *t*-Bu case.

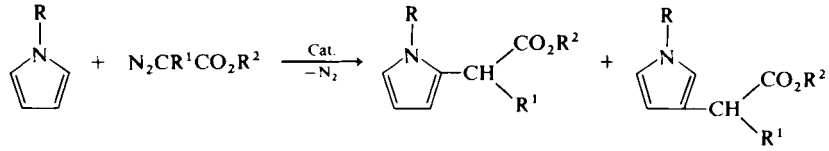
In the case of 1-methyl-2-alkenylpyrroles a possibility for competition of the carbene attack between the pyrrole nucleus and the alkenyl group arises, as a result of which, together with the products of C—H insertion, cyclopropane adducts to the *exo*-cyclic double bond are also formed[463,464]. The relation between these directions of the reaction depends on the structure of the diazoester and to a smaller extent on the substituents at the double bond (see Scheme 87). In reactions with MDM, alkylation of the pyrrole nucleus at the α-position dominates, whereas in the case of MDA this occurs only in the presence of substituents at the double bond.

Some other N-heteroaromatic compounds also behave similarly to pyrroles in reactions with diazoesters. Esters of the corresponding heteroarylacetic acids are the



(30–45%) (177)

TABLE 13. Regioselectivity of ACC insertion into C—H bonds of pyrroles

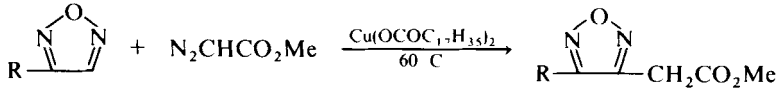


(45) (46)

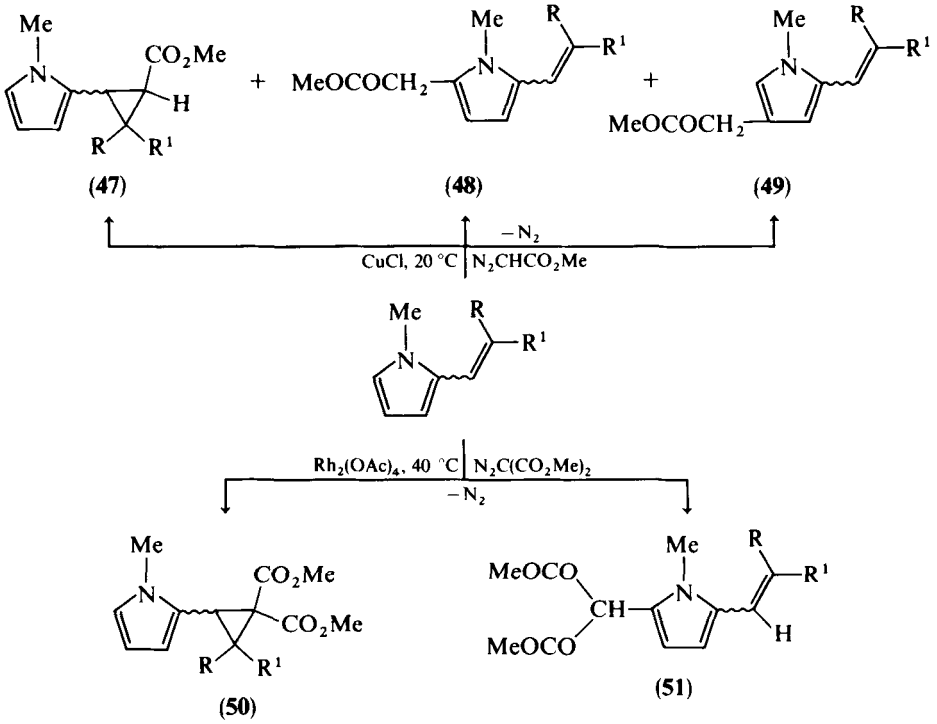
R	R^1	R^2	Catalyst	Total yield 45 + 46 %	Ratio 45/46	References
H	H	Et	Cu-bronze	42	11	459
			$Cu(OTf)_2$	52	2.7	459
Me	H	Et	Cu-bronze	40	5.2	459
			$Cu(hfacac)_2$[a]	57	3.5	459
			$Cu(ipsal)_2$[b]	50	16.9	459
			$Cu(OTf)_2$	63	1.4	459
			$Rh_2(OAc)_4$	[c]	[c]	459
Me	CO_2Me	Me	Cu-bronze	~30	6.5	460
			$Cu(hfacac)_2$[a]	83	7.3	460
			$Cu(ipsal)_2$[b]	76	12.0	460
			$Cu(OTf)_2$	70	5.0	460
			$Rh_2(OAc)_4$	92	9.8	460
Me	Ac	Me	$Cu(hfacac)_2$[a]	68	—[d]	460
			$Cu(ipsal)_2$[b]	62	—[d]	460
			$Rh_2(OAc)_4$	72	—[d]	460
H	$EtO_2CCH{=}CH\text{-}(E)$	Et	$Rh_2(OAc)_4$	71	—[d]	461
Me	$EtO_2CCH{=}CH\text{-}(E)$	Et	$Rh_2(OAc)_4$	86	9.8	461

[a] hfacac = hexafluoroacetylacetonate.
[b] ipsal = *N*-isopropylsalicylaldiminate.
[c] Mixture of products with little **45** and **46**.
[d] Only **45** is formed.

main products of EDA reactions with indoles[465] (see equation 177) and furazans[466] (see equation 178). In the reaction with indole the β-isomer is predominant.



R = H, Ph, 2—thienyl (9–12%) (178)



		Product yields (%)				
R	R^1	**47**	**48**	**49**	**50**	**51**
H	H	43	14	3.5	60	16
H	Me	29	38	6	74	7
Me	Me	20.4	41	7	68	4

SCHEME 87

Several examples of intramolecular C—H insertions with the participation of a pyrrole nucleus are known. Thus carbenes, generated by dediazotation of ethyl α-(2-pyrrolylethyl)diazoacetate[467] (see equation 179) or methyl α-[(3-indolyl)sulfonyl]diazo-

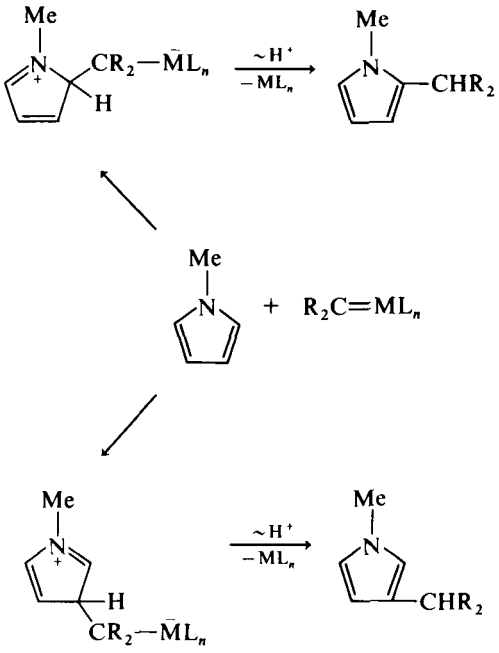
(179)

Z, E
total yield <35%

acetates[68] (see equation 174), become transformed into the corresponding polyheterocycles with low yields.

At the same time, metal–carbene from 4-(4-indolyl)-3-oxo-2-diazobutanoates cyclizes with the participation of C—H bonds of the indole ring, in 76% yield (see Section IV.C.3, Scheme 86, path a)[457].

The tendency of pyrrole and related heteroatomic compounds to form products of C—H insertion with diazoesters is attributed to the absence of unshared pairs at the N atom and to the strong aromatic character of the pyrrole nucleus[459]. As a result, the formation of the insertion products proceeds as an electrophilic substitution by the metal–carbene in the heteroaromatic nucleus through a metastable σ-complex (see Scheme 88).

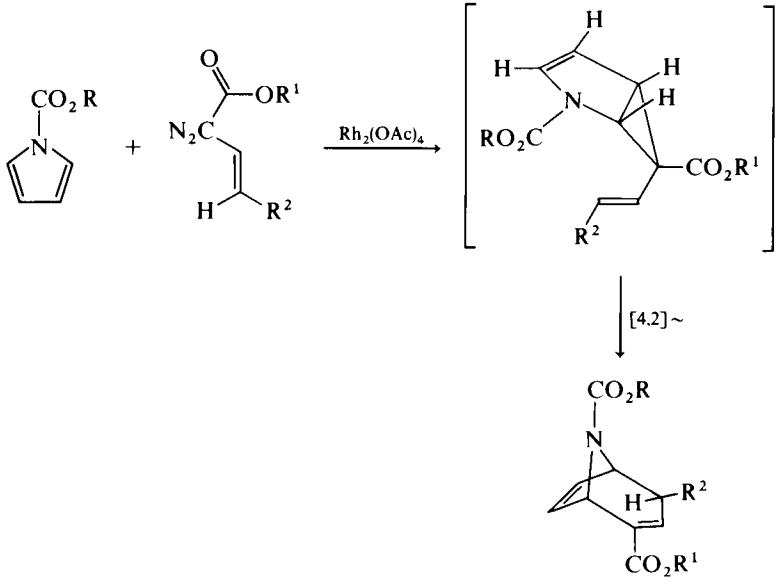


SCHEME 88

This mechanism provides a good explanation also for the difference in the regioselectivity of the reactions of diazoesters with pyrroles and indoles. It is known that electrophilic substitutions in indoles, in contrast to pyrroles, occur predominantly in position 3 of the indole ring and this is also the case in the reactions with diazoesters.

The introduction of acceptor substituents at the N atom radically dearomatizes the pyrrole ring, so that it can react as a diene. Thus, $Rh_2(OAc)_4$-promoted dediazotation of ethyl α-vinyldiazoacetates in the presence of *N*-(alkoxycarbonyl)pyrroles leads to 8-azatricyclo[3.2.1]octa-2,6-dienes, which are templates for obtaining natural tropane alkaloids[461] (see Scheme 89).

The formation of these azatricycles is unlikely to proceed by way of [3,4]-cycloaddition of carbenes to pyrroles. Direct cyclopropanation of the multiple bond of the pyrrole



R	R^1	R^2	Yield (%)
Me	Et	CO_2Et	62
Et	Et	CO_2Et	54
$CH_2CH_2SiMe_3$	Et	CO_2Et	71
Me	Et	SO_2Ph	61
Me	Me	Ph	53
Me	Et	CH=CHPh	18
Me	Me	H	21

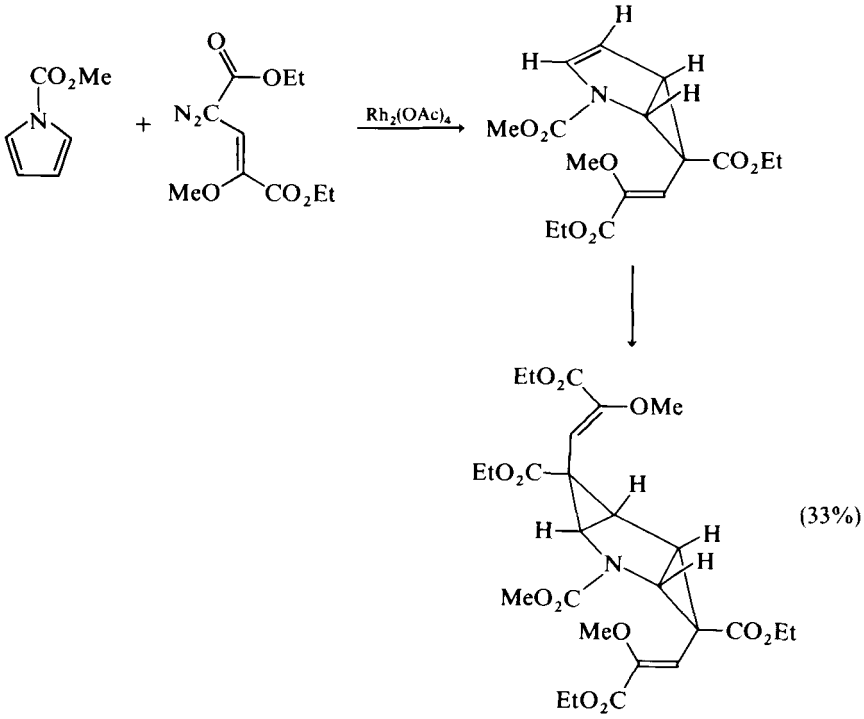
SCHEME 89

nucleus with subsequent Cope rearrangement of the originating bicyclic cycloadduct seems to be more probable.

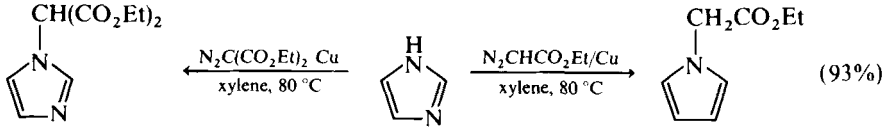
The proof for this mechanism is furnished by the isolation of stable cycloadducts of methoxy derivatives of vinylcarbenes with *N*-methoxycarbonylpyrrole, which are unable to undergo Cope rearrangement because of steric hindrances[461] (see Scheme 90).

Electrophilic substitution in the heteroaromatic nucleus does not occur in reactions with imidazole either. Instead, in the case of copper-catalyzed decomposition of EDA or diethyl diazomalonate in imidazole medium, *N*-alkylation of these heterocycles occurs with the formation of esters (imidazol-1-yl)acetates or (imidazol-1-yl)malonates with excellent yields (78–93%)[468] (see Scheme 91). The reaction in the case of benzimidazole proceeds in a similar manner[469].

This behavior of imidazoles is thought to be caused by easy formation of *N*-ylides with the N-3 atom. Subsequent migration of the hydrogen atom at the N-1 atom in the ylide leads to the products of formal N—H insertion[468].



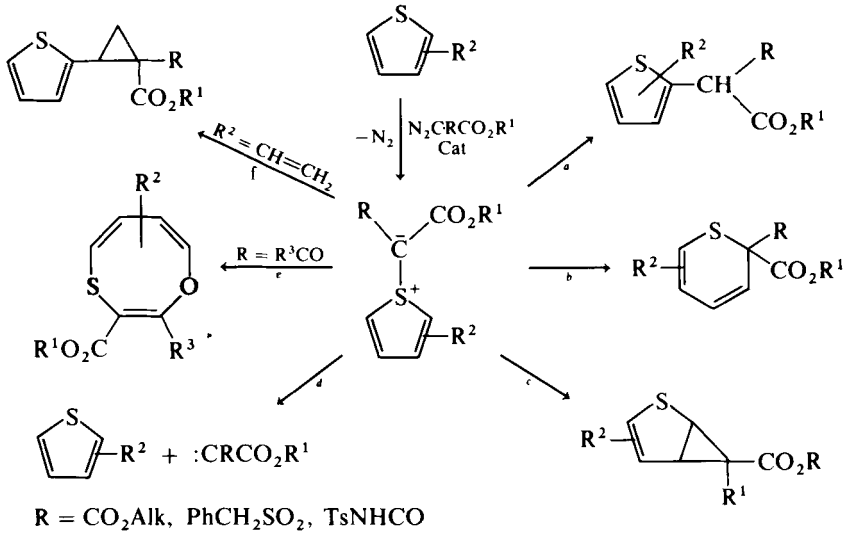
SCHEME 90



SCHEME 91

b. Thiophenes. The unshared pair on the S atom and the smaller aromaticity of thiophene compared to pyrrole bring about a greater reactivity of the former in reactions with diazoesters. At present it is universally accepted that the reaction of singlet carbenes or of their electrophilic transition-metal complexes derived from diazoesters proceeds by way of carbene attack at the sulphur atom of the thiophene ring with the formation of *S*-ylides. In some cases these ylides are stable and can be isolated, but more often they undergo further transformations. Generally, four major reaction pathways are possible (see Scheme 92): (a) formation of formal products of carbene insertion into the α-C—H bonds of thiophene, (b) 2*H*-thiopyrane formation, (c) formation of bicyclic cyclopropane adducts and (d) carbene fragmentation of ylides.

Besides these major pathways, other reactions with the participation of ylides are possible. Thus, some ylides can be transformed into oxathiocins (path e), while in the

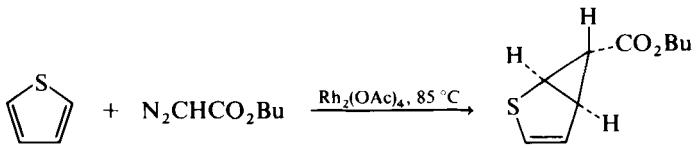


SCHEME 92

presence of an unsaturated substituent in the side chain a transfer of the $CRCO_2R^1$ fragment to the double bond with the formation of 2-thienylcyclopropanecarboxylates is possible (path f).

The relationship between these pathways is strongly dependent on the diazoester, catalyst, the structure of the substrate and the character of substituents in it, and also on the conditions under which the process is conducted; often, several pathways are realized simultaneously. However, by now methods have been developed for selective performance of each reaction which increases their preparative importance.

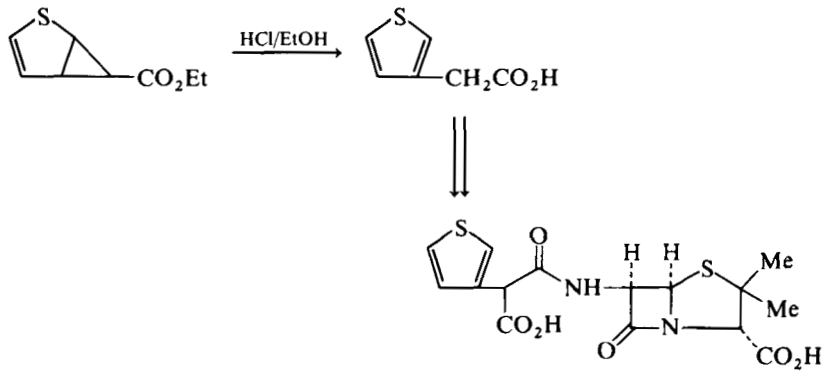
In the presence of the Rh(II) catalyst ADA react with thiophene, giving only products of addition of carbenes to the multiple bond of the thiophene nucleus. Thus, the main product of the reaction of n-butyl diazoacetate with thiophene, catalyzed by $Rh_2(OAc)_4$, is n-butyl 6-*exo*-2-thiabicyclo[3.1.0]hex-3-ene-6-carboxylate[286] (see equation 180). Cu(I) compounds as catalysts under these conditions are less effective: the yield of the cyclopropane adduct does not exceed 20%.



(180)

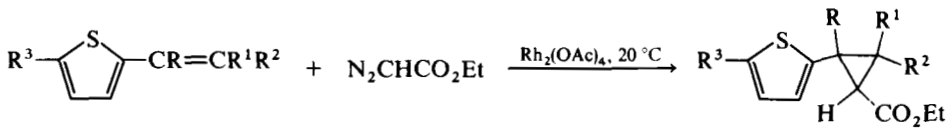
This reaction is of great preparative importance, because acid isomerization of thiabicyclohexene leads to (3-thienyl)acetic acid, the key intermediate in the production of the semisynthetic β-lactam antibiotic ticarcillin[286,470] (see Scheme 93).

In the case of 2-alkenylthiophenes the alkoxycarbonyl attack is directed exclusively to the exocyclic double bond and the reaction leads to the corresponding 2-thienyl cyclopropane carboxylates with fair to excelleny yields[471] (see equation 181).



ticarcillin

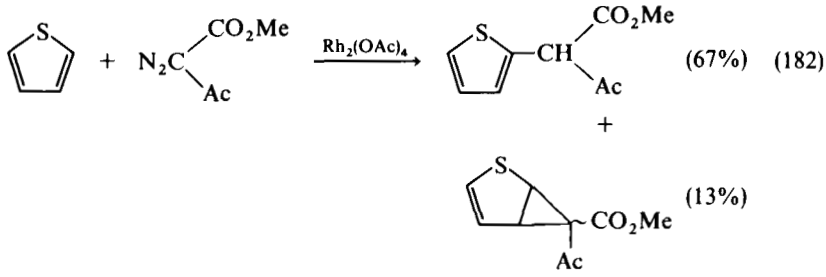
SCHEME 93



(181)

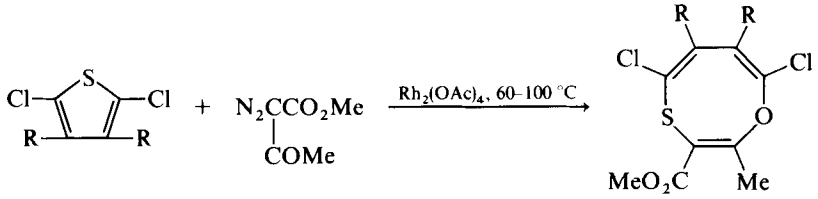
R	R^1	R^2	R^3	Yield (%)
H	H	H	H	94
H	Me	H	H	98
H	H	Me	Me	41
H	H	Me	H	90
Et	H	H	H	86
Et	H	Me	H	58

As distinct from ADA, the reaction of methyl α-acetyldiazoacetate with thiophene under similar conditions leads as a rule to the formal product of carbene insertion into the α-C—H bond of thiophene, methyl 2-(2′-thienyl)-3-oxobutanoate, together with the corresponding 6,6-disubstituted 2-thiabicyclo[3.1.0]hex-3-ene as the minor product[286] (see equation 182).



(67%) (182)

(13%)



(183)

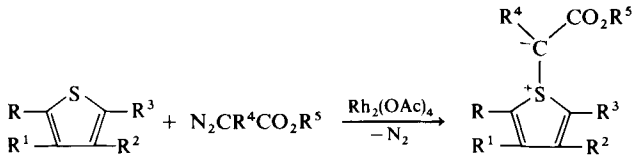
The interaction of methyl α-acetyldiazoacetate with 2,5-dichlorosubstituted thiophenes in the presence of $Rh_2(OAc)_4$ leads to oxathiocin formation[472] (see equation 183).

Unlike ADA and methyl α-acetyldiazoacetate, the interaction of diazomalonates with thiophenes, catalyzed by $Rh_2(OAc)_4$ at 20 °C, furnishes stable *S*-ylides (see Table 14).

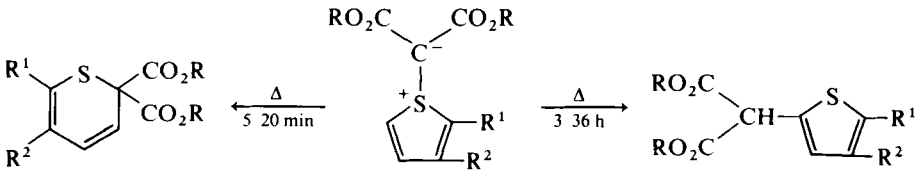
Thermal rearrangement of these ylides leads to 2*H*-thiopyrans as thermally unstable kinetic products and 2-thienylmalonates as major rearrangement products with acceptable yields[473,474]. Since the latter are of great practical importance as intermediates of the synthesis of semisynthetic β-lactam antibiotics, e.g. cephalothin, these reactions were studied in detail.

In particular, it was established that the final composition of the products of thermal isomerization of *S*-ylides is determined by the character of substituents, the temperature and duration of heating (see Scheme 94). Thus, short heating (< 20 min) of thiophenium or substituted thiophenium bis(*t*-butoxycarbonyl) methylides leads to the corresponding 2*H*-thiopyrans with yields up to 98%, while longer heating leads to 2-substituted thiophenes.

TABLE 14. Ylide formation in the reaction of diazoesters with thiophenes



R	R^1	R^2	R^3	R^4	R^5	Ylide yield (%)	References
H	H	H	H	CO_2Me	Me	95	476
Cl	H	H	Cl	CO_2Me	Me	100	477
$HOCH_2$	H	H	H	CO_2Me	Me	92	477
Br	Me	H	H	CO_2Me	Me	86	477
Me	H	H	H	CO_2	Me	90	477
Br	H	H	H	CO_2Me	Me	95	477
Cl	Cl	Cl	Cl	$PhCH_2SO_2$	Et	53	477
Cl	Cl	Cl	Cl	TosNHCO	Et	88	286
CH=CHCH=CH		H	H	CO_2Me	Me	97	286
$CH=CMe_2$	H	H	H	CO_2Me	M	40	478



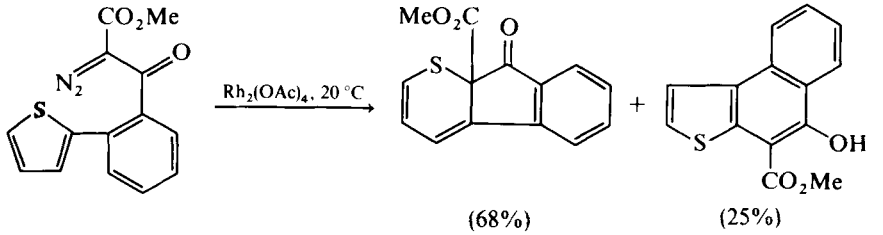
R	R^1	R^2	Yield (%)
Me	H	H	30
Me	Br	H	89
'Bu	H	H	84
'Bu	Me	H	98
'Bu	I	H	60
'Bu	$PhOCH_2$	H	97
'Bu	Br	H	75
'Bu	H	Br	22

R	R^1	R^2	Yield (%)
Me	H	H	82
Me	Me	H	94

SCHEME 94

The ease of rearrangement of *S*-ylides into 2*H*-thiopyrans depends on the substituents. Thus, 2-phenoxymethyl ylide becomes transformed into the corresponding 2*H*-thiopyrane during recrystallization from methylcyclohexane, whereas the 3-bromoylide is transformed *in situ* in the course of reaction of di(*t*-butyl) diazomalonate with 2-bromothiophene.

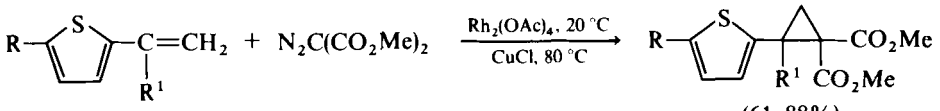
The formation of 2*H*-thiopyrans together with products of 2-substitution was also observed in isomerization of cyclic *S*-ylides, formed in the course of Rh-promoted dediazotation of thienyl-substituted α-acyldiazoester[475] (see equation 184).



(184)

The similar intramolecular transformation of α-[(2-thienyl)methylsulfonyl]diazoacetate leads exclusively to the product of α-substitution in the thiophene nucleus (see Section IV.C.3, equation 174).

The pathway of MDM reaction with alkenylthiophenes depends on the character of substitution at the exocyclic double bond and in the thiophene ring. MDM reacts with 2-alkenylthiophenes having an unsubstituted end-group in the same manner as EDA, giving exclusively a cyclopropane adduct to the exocyclic double bond both in the presence of CuCl and of $Rh_2(OAc)_4$[479] (see equation 185).

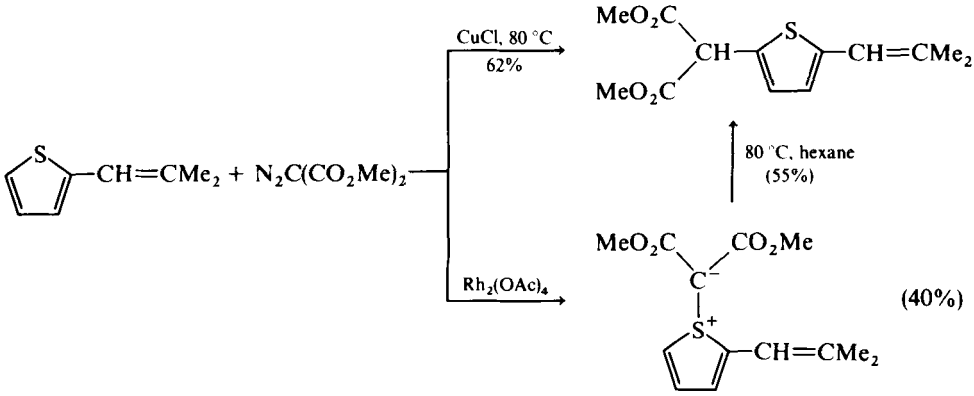


(61–88%)

R, R^1 = H, Me or Et

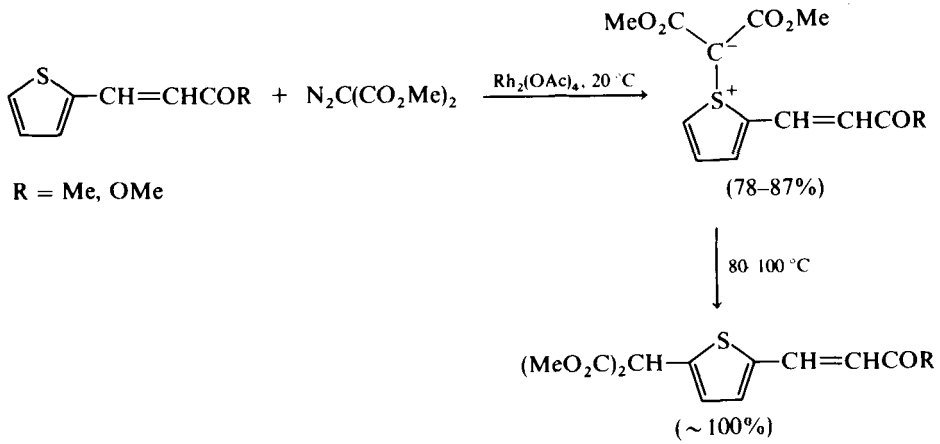
(185)

The presence of substituents in the β-position of the exocyclic double bond favors the formation of stable *S*-ylides. Thus 2-(2-methylprop-2-enyl)thiophene with $Rh_2(OAc)_4$ yields the corresponding ylide, which on heating (hexane, 80 °C) is transformed into 5-substituted 2-alkenylthiophene. In the presence of CuCl at 80 °C this α-substituted thiophene is formed directly[479] (see Scheme 95).



(40%)

SCHEME 95



R = Me, OMe

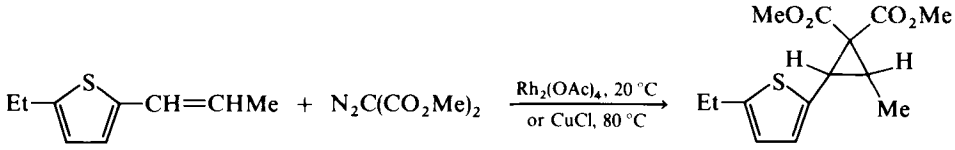
(78–87%)

(~100%)

SCHEME 96

Vinylthiophenes with acceptor substituents at the exocyclic multiple bond, in $Rh_2(OAc)_4$-catalyzed reactions with MDM, also give stable ylides as the only products, which on heating are transformed quantitatively into thienylmalonates[12] (see Scheme 96).

However, in thiophenes with the same type of substitution at the exocyclic multiple bond, but containing also a substituent in position 5, transformation of the initially formed ylides into α-substituted thiophenes is impossible. Therefore, ylide thermolysis proceeds by way of transfer of the $C(CO_2Me)_2$ fragment from the S atom to the exocyclic double bond with the formation of the corresponding cyclopropane products. In this case reaction is very sensitive to the structure of alkenylthiophene. Thus *Z*-isomer of 2-(1-propenyl)-5-ethylthiophene reacts with MDM and the *cis* isomer of the cyclopropane dicarboxylate both in the presence of CuCl and in the presence of $Rh_2(OAc)_4$[479] (see equation 186). The *E*-isomer of this alkenylthiophene is inert in the reaction with MDM.



Z-isomer 75%, *cis*

(186)

The transfer of the carbene fragment can proceed intermolecularly as well, this being confirmed by its interception by different acceptors. Thus, 2,5-dichlorothiophenium bis(alkoxycarbonyl)-methylides[480] under the effect of $Rh_2(OAc)_4$ or $Cu(acac)_2$, and also 2-alkenylthiphenium bis(methoxycarbonyl)-methylides[479] upon heating in the absence of catalyst, generate bis(alkoxycarbonyl)carbenes, which are intercepted by olefins with the formation of cyclopropane adducts (see Scheme 97).

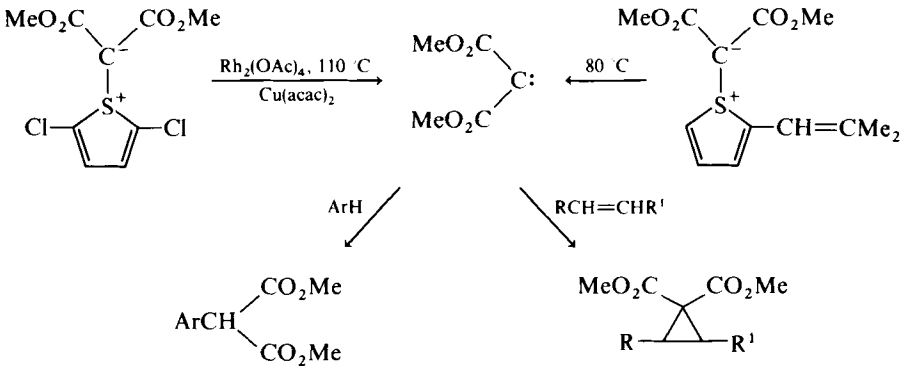
The same reaction was used for a direct one-pot synthesis of dimethyl 2-aryl (or hetaryl) substituted malonates[479,481] in fair to excellent yields and by deoxygenation of epoxides[482] (for the latter, see Sections IV.B.4.c and IV.B.4.d).

Thus, these ylides, which are stable crystalline products, may be regarded as convenient sources of bis(alkoxycarbonyl)carbenes.

c. Furans. Furans in catalytic reactions with diazoesters behave as cyclic analogs of dienol esters, giving bicyclic adducts of the carbene to the double bond of the furane nucleus and also 1,4-diacyl-1,3-dienes. This is consistent with the low aromaticity of the furan nucleus, compared with other heteroaromatic systems. The mechanism of this reaction still remains unclear. Nevertheless, there are convincing proofs of the formation of the cyclopropane adducts and the oxodienes from common precursors, namely *O*-ylides[12] (see Scheme 98, path a) or four-membered metallocycles[483] (path b).

The selectivity of these reactions is materially dependent on the structure of both the furans and the diazoesters[483]. However, regularities exist which are characteristic for all reactions with participation of furan and its derivatives. Thus, irrespective of the catalyst [$Rh_2(OAc)_4$ or Cu(I) compound], in the resulting bicycloadducts the alkoxycarbonyl group is in the *endo* position to the three-membered cycle, while in 1,4-diacyl-1,3-dienes the double bond, adjacent to the carbonyl group, always has the *Z*-configuration.

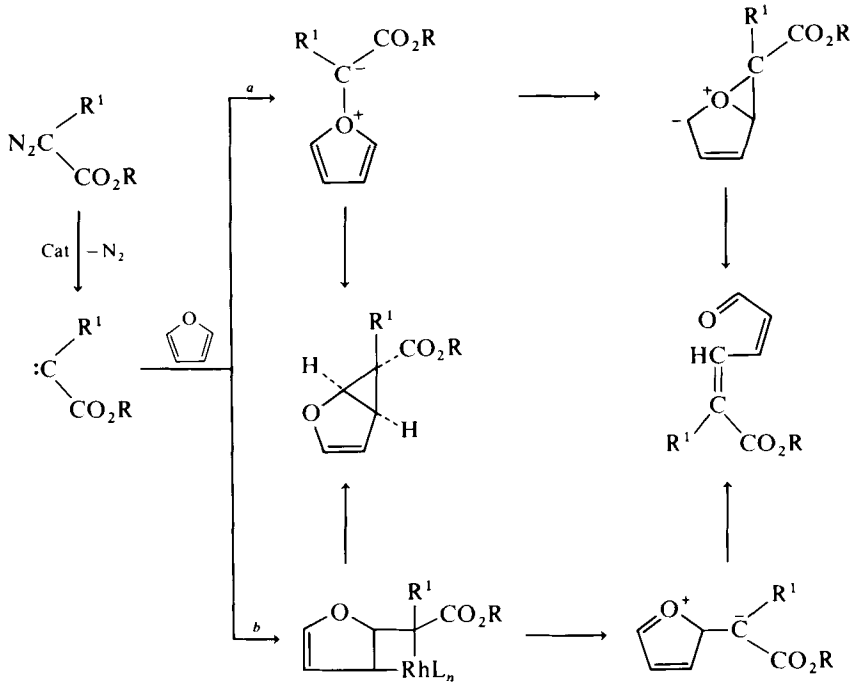
In Rh(II)-promoted ADA reactions the substituents in the furan nucleus exert little influence on the reactivity of the heterocycle, but they determine the selectivity to a large



Aryl	Yield (%)
$(3,4\text{-}OCH_2O)C_6H_3$	20
$p\text{-}MeOC_6H_4$	48
2-Pyrrolyl	79
2-Thienyl	98
2-Indolyl	85

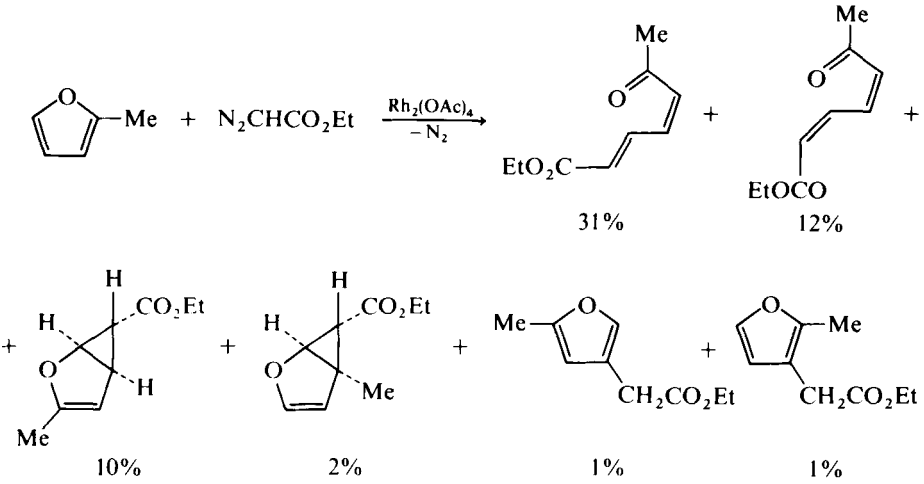
R	R^1	Yield (%)
	$(CH_2)_4$	66
	$(CH_2)_6$	86
H	$(CH_2)_4CH=CH_2$	83
H	OAc	81

SCHEME 97



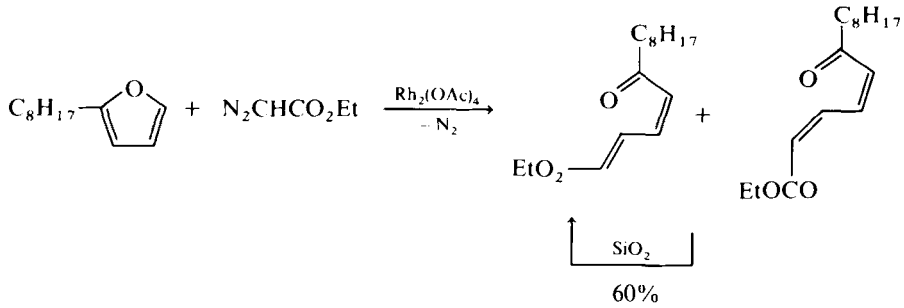
SCHEME 98

measure[483]. Thus, formation of the three-membered ring proceeds predominantly with the participation of the least substituted bond of the furan. Alkyl substituents favor the formation of acyclic products. In 2-methylfuran, for example, the ratio of cycloadducts to the unsubstituted and substituted bonds is 1:5, while the ratio of the overall amounts of acyclic products and cycloadducts is 3.6:1[483] (see equation 187).



(187)

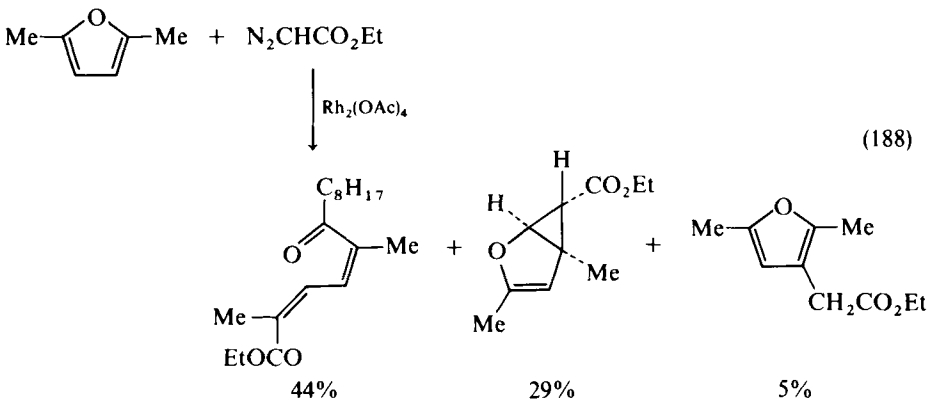
An increase in the steric bulk of the substituents leads to an increase in the proportion of the acyclic product. Thus, rhodium-catalyzed dediazotation of EDA in 2-n-octylfuran yields a *ca* 1.5:1 mixture of *Z,E*-1,4-diacyl-1,3-diene and its highly metastable *Z,Z*-isomer. The mixture on silica chromatography affords as sole product the *Z,E*-isomer in 60% yield[483] (see Scheme 99).



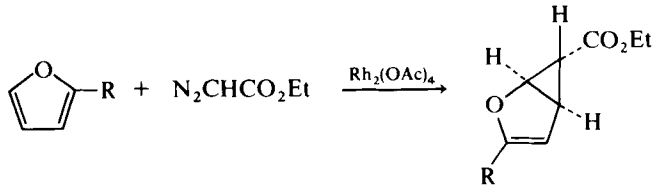
SCHEME 99

In the case of substituents being present in positions 2 and/or 5, as, for example, in 2,5-methylfuran, besides cycloadducts and acyldienes, small quantitites of 3-furylacetates are also formed[483], this showing the possibility of direct electrophilic substitution in the furan nucleus[484] (see equation 188).

Electron acceptors in the furan nucleus, in contrast to the donors, contribute to the formation of bicyclic adducts[483] (see equation 189).



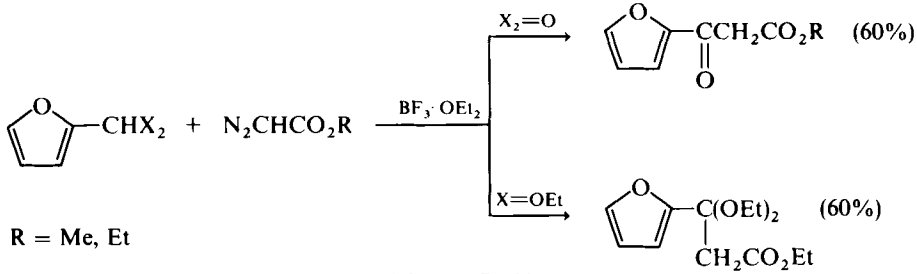
(188)



(189)

R = CO_2Me (55%)
R = *E*-CH=$CHCO_2Me$ (51%)

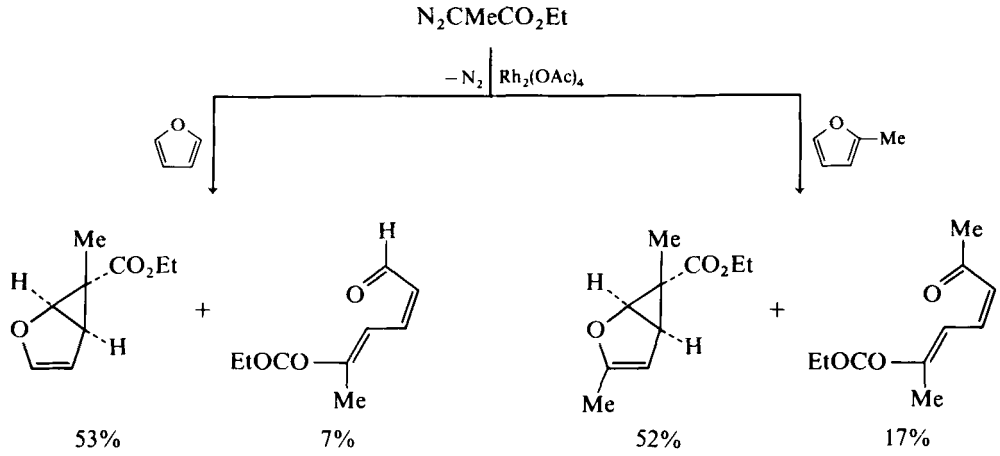
Unlike transition-metal catalysis, $BF_3 \cdot OEt_2$-catalyzed ADA reaction with furfural or its diethylacetal leads exclusively to the products of formal insertion of carbene into the C—H bonds of the formyl group[485] (see Scheme 100).



SCHEME 100

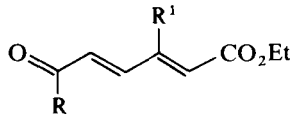
Similar regularities are observed in the reactions of furans with ethyl α-diazopropionate, which yield mixtures of *endo*-cyclopropanecarboxylates and oxoesters with predominance of the former in total yields up to 70%[483] (see Scheme 101). In this case the reaction proceeds also via the least saturated bond of the furan ring.

In spite of the low selectivity of the reactions of ADA and diazopropionates with furans, their use together with the isomerization of 6-oxodieneoates and with minor bicyclic adducts, e.g. by the action of iodine in CH_2Cl_2[483], made available a high-yielding two-step, 'one-pot' reaction scheme for preparation of 6-oxo-*E*,*E*-dienoate as a single

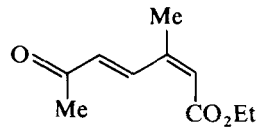


SCHEME 101

product per reaction sequence. For instance, such treatment of the products of EDA reactions with furan, 2-methyl-2-octyl, 2,5-dimethyl- and 2-(2-methoxycarbonylvinyl)-furans leads to oxoester (**52a**), a 1.5:1 oxoester **52b**–(**53**) mixture, oxoester **52c**, **52d** and **52e** in 68, 70, 85, 65 and 77% yields, respectively[483]. Products from ethyl α-diazopropionate and furan or 2-methylfuran have been transformed to oxoesters **54** and **55** in 63% and 72% yields, respectively. Cyclopropanecarboxylate derived from methyl furoate is inert to iodine and can be converted to the useful oxoester **52f** by treatment with boron trifluoride in 80% yield[483].

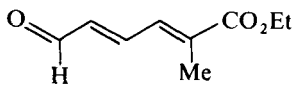


(**52a–f**)

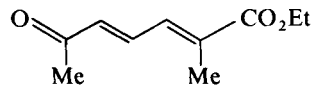


(**53**)

(**a**) R = R¹ = H
(**b**) R = Me, R¹ = H
(**c**) R = $(CH_2)_7Me$, R¹ = H
(**d**) R = R¹ = Me
(**e**) R = CO_2Me, R¹ = H
(**f**) R = CH = $CHCO_2Me$, R¹ = H



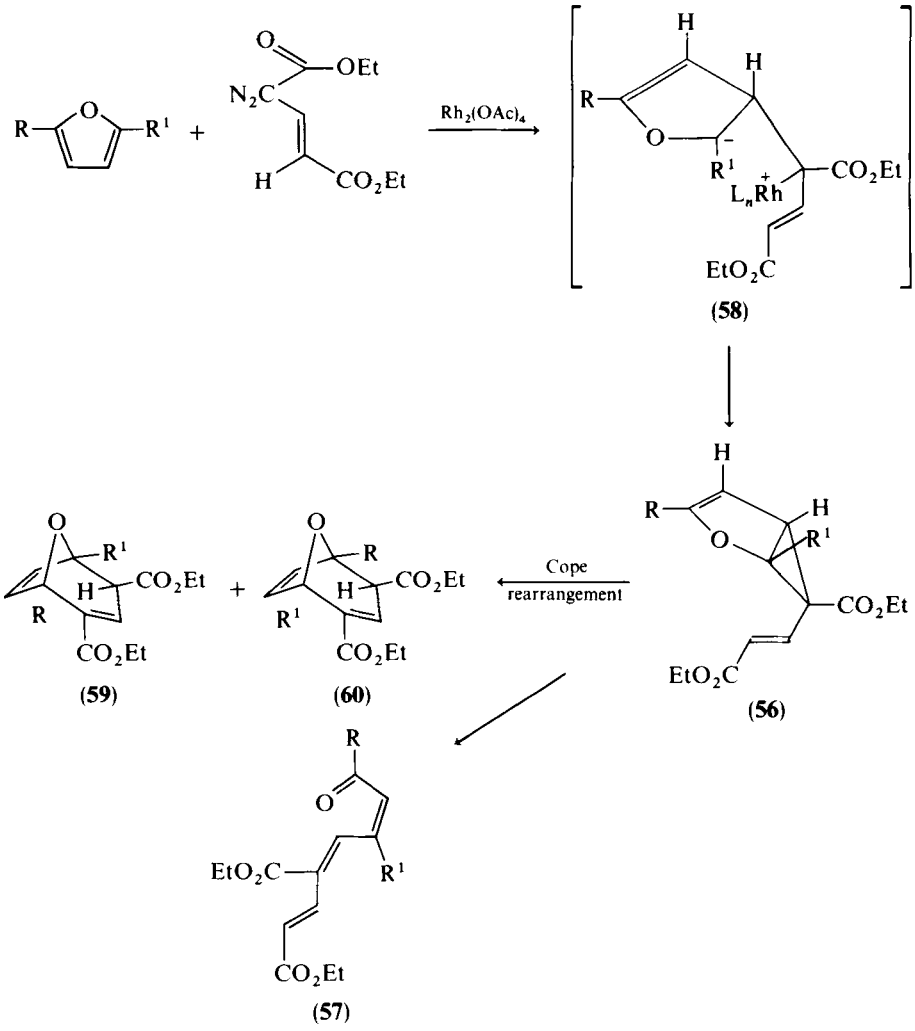
(**54**)



(**55**)

In their turn, oxoesters **52** and **53** serve as starting materials in the total synthesis of some retinol–carotene fragments, LTB_3 and other leukotrienes, etc.

As in the case of ACC, the interaction of α-vinylalkoxycarbonylcarbenes, derived from $Rh_2(OAc)_4$-promoted decomposition of α-vinyldiazoacetates, with a range of furans leads to the bicyclic carbene adduct (**56**) and to oxotrienoates (**57**), presumably through a dipolar intermediate (**58**)[73] (see Scheme 102).

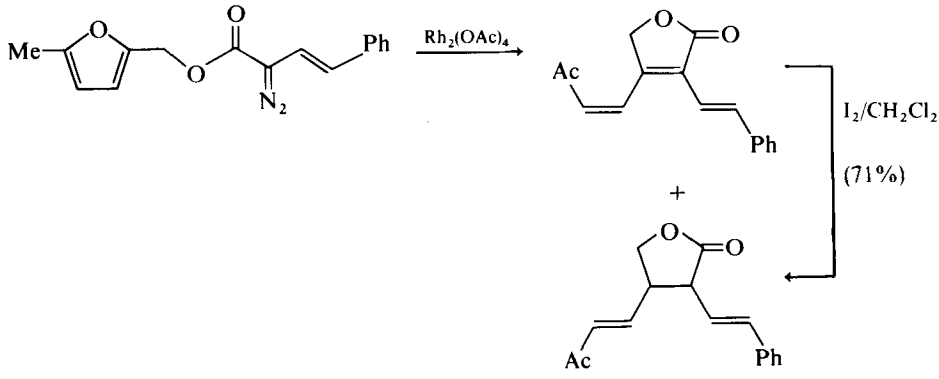


		Products, yield (%)	
R	R^1	**59 + 60**	**57**
H	H	62	26
Me	H	8	74
MeO	Me	—	92
Me	Me	70	—
Me	$SiMe_3$	61	—
MeO	Me	54	—

SCHEME 102

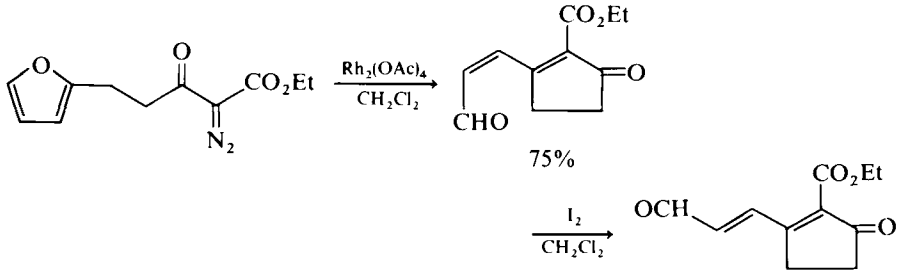
In addition, as a result of a Cope rearrangement the bicyclic adduct **56** in the course of the reaction transforms into diethyl 8-oxabicyclo[3.2.1]octa-2,6-diene-2,4-dicarboxylates **59** and **60**.

Similar intramolecular transformations of α-vinyl diazoesters containing a furan fragment in the molecule lead to high yields of a mixture of products consisting of *E,E*- and *Z,E*-divinylbutenolides that slowly equilibrate to the more stable *E,E*-isomer on treatment with iodine in CH_2Cl_2[486] (see Scheme 103).



SCHEME 103

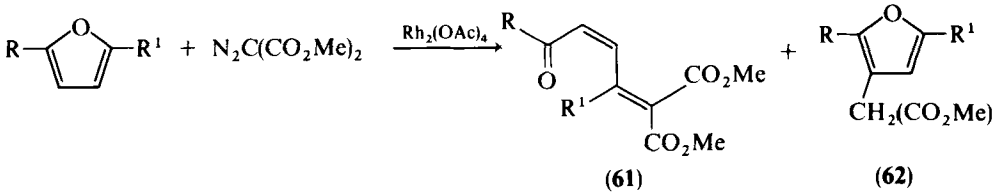
The intramolecular transformation of ethyl 2-diazo-3-oxo-5-(2-furyl)-pentanoate under these conditions leads to the corresponding 2-cyclopentenones in 75% yield[487] (see Scheme 104).



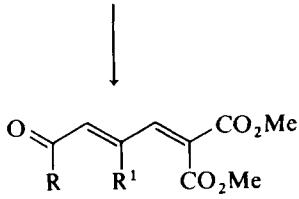
SCHEME 104

Oxodienes are also the main products in the reactions of furans with MDM in the presence of $Rh_2(OAc)_4$[484] (see Scheme 105). The initially formed acyclic oxodiene compounds with *Z*-configuration of the double bond are thermally easy to rearrange into the corresponding *E*-isomers. (3-Furyl)malonates are formed as alternative products in the reactions of this diazoester with 2,5-disubstituted furans.

In the reaction of MDM with vinylfuran having an exocyclic double bond as one more active site, the main product is 2-(2-furyl)-cyclopropyldicarboxylate[12] (see Scheme



(61) (62)

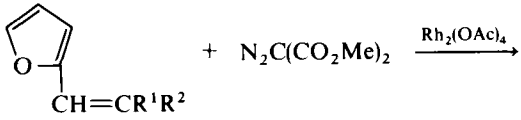


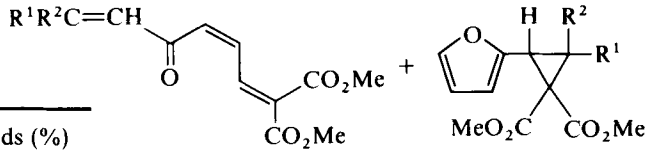
92–98%

R	R^1	Product yields (%)	
		61	**62**
H	H	~100	—
Me	H	~100	—
Et	Et	70	10
Me	$CH{=}CMe_2$	6	80[a]
$CH(OEt)_2$	H	63	—

[a] The mixture (1:1) of (furyl-3 and -4)malonates is formed

SCHEME 105





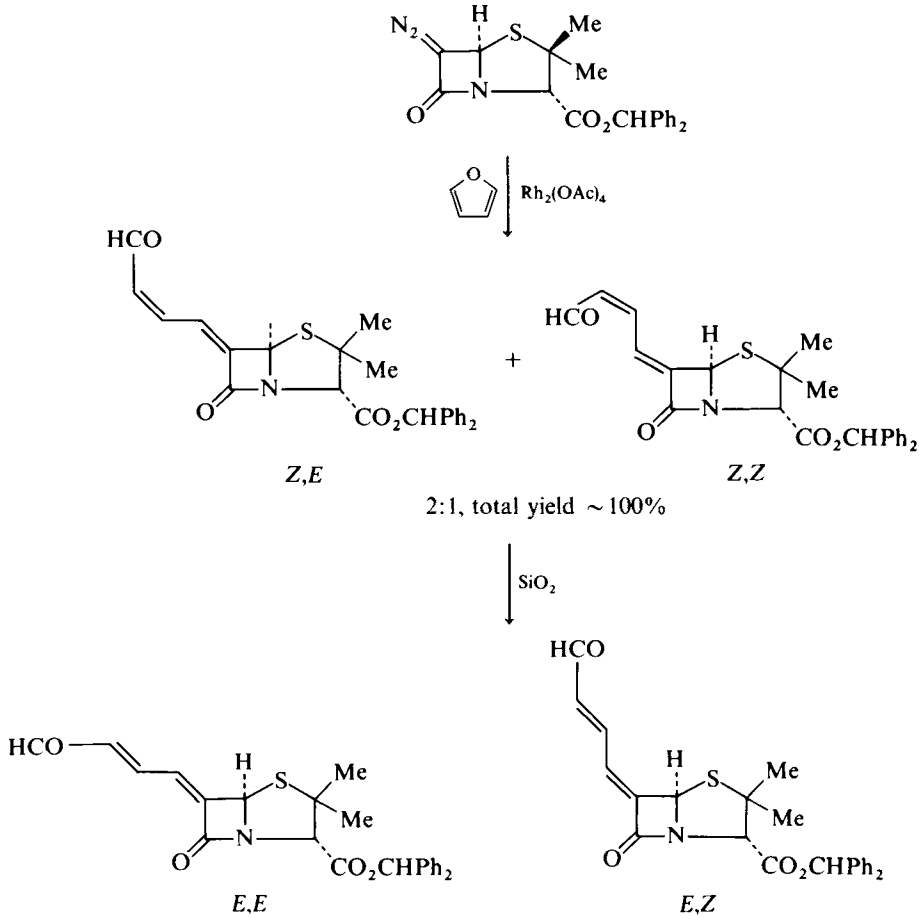
(62) (63)

		Yields (%)	
R^1	R^2	**62**	**63**
H	H	11	75
Me	H	74	14
Me	Me	~100	—

SCHEME 106

106). However, as the substitution of the exocyclic bond grows, the proportion of the acyclic product, 5-oxohepta-1,3,6-triene-1,1-dicarboxylate, increases, up to exclusive formation of the latter in the isobutenyl case. In the reaction of 2-methyl-5-(2-methylpropen-1-yl)furan the main product are (3-furyl)malonates, as in the case of 2,5-dialkylfuran (see Scheme 105).

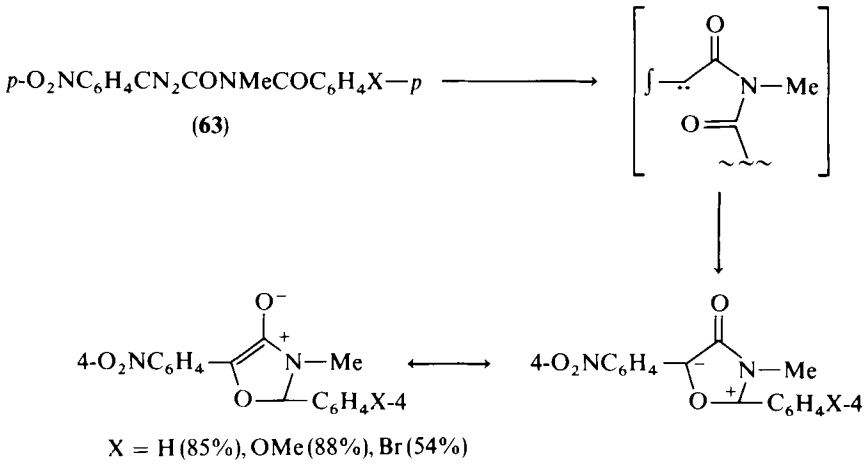
In the reactions with furans cyclic diazoamides behave similarly to diazomalonates. The reaction leads to a mixture of *Z,E*- and *Z,Z*-isomers of 6-(4′-oxobut-2′-enylidene) penicillanates, which under the isolation procedure are transformed into a mixture of the more stable *E,E*- and *E,Z*-isomers[488] (see Scheme 107).



SCHEME 107

5. *C=X and X=Y bonds*

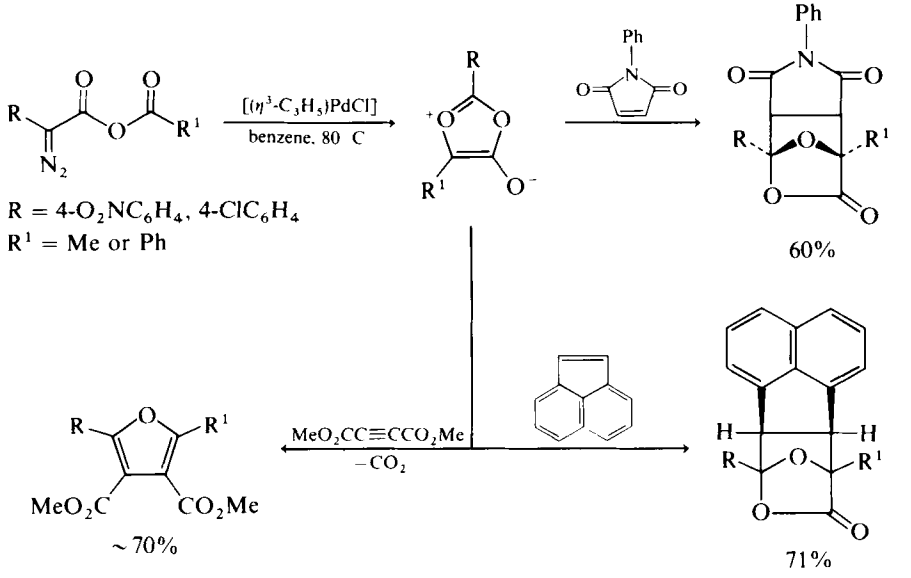
Strong polarization of the bonds of this type and the presence of unshared pairs at the heteroatom enable carbenic attack at the heteroatom with the formation of an ylide,



SCHEME 108

the subsequent transformations of which are decisive for the ultimate composition of the reaction products. At present this hypothesis is generally accepted. Direct proofs of the existence of such ylides in reactions of the diazoamide (**63**) with carbonyl compounds were obtained[489] by synthesizing stable *O*-ylides in the form of oxazole-type mesoionic compounds (see Scheme 108).

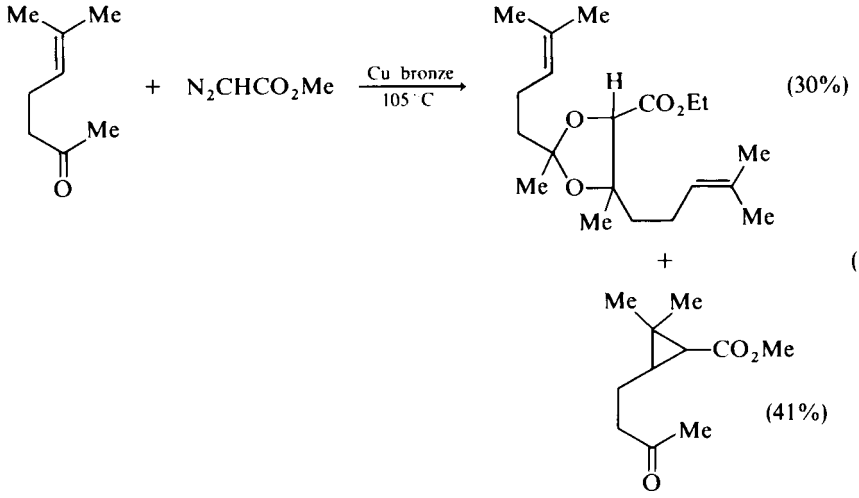
O-ylides in the form of mesoionic compounds with three oxygen atoms were also obtained in dediazotation of diazoacetic acid anhydrides in the presence of allyl complexes of Pd(II) or $Cu(acac)_2$[490]. Unlike N-containing analogs, betaines of this type



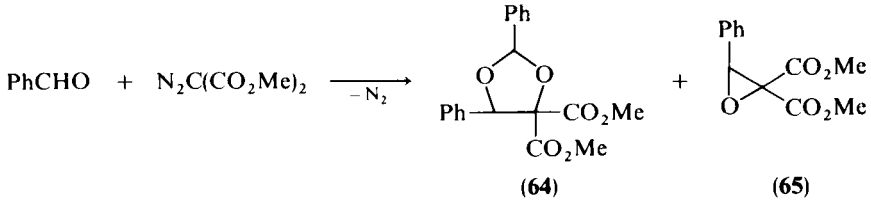
SCHEME 109

proved to be unstable but reacted easily with different dipolarophiles, giving [3,2]-cycloadducts (see Scheme 109).

The formation of ylides occurs to an appreciable measure even when an active double bond is present in the molecule, as, for example, in 2-methylheptanone-6, and competes actively with cycloaddition of the carbene to the double bond; thus an ylide in excess ketone reacts with the carbonyl groups of two ketone molecules, yielding a dioxolane[491] (see equation 190).



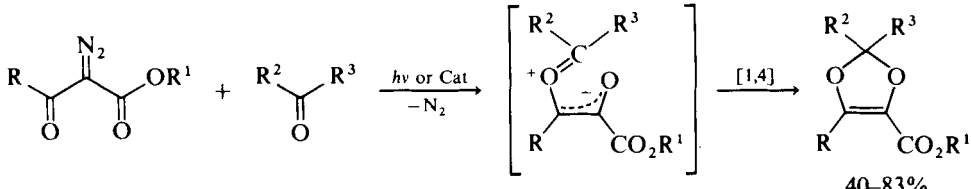
The reaction of MDM with benzaldehyde proceeds in a similar manner[492] (see Scheme 110). The thermolysis MDM or its $Cu(acac)_2$-induced dediazotation is accompanied by formation of small quantities of oxirane. This oxirane is a formal adduct of the carbene to the C=O bond, and it becomes the sole product when equimolar amounts



Cat	T (°C)	Solvent	**64** (*cis*:*trans*)	**65**
none	125	PhCHO	56 (58:42)	10
Cu $(acac)_2$	125	PhCHO	83 (55:45)	7
Rh_2 $(OAc)_4$	75	PhCHO	72 (55:45)	0
CuOTf	25	PhCHO	87 (71:29)	0
Cu[a]	reflux	PhCl	0	72

[a] Equimolar quantity of reagents.

SCHEME 110



Cat = Cu, $Cu(OTf)_2$ etc.
R = CF_3 or Me; R^1 = Alk;
R^2 = H, R^3 = alkyl, Ph, 2-furyl or *trans*-CH=CHMe;
R^2 or R^3 = alkyl or $R^2 + R^3$ = alkylene

SCHEME 111

of the reagents and of copper powder as the catalyst are used. In all likelihood, however, the formation of oxiranes also proceeds as a result of ylide isomerization.

In contrast, reactions of α-acetyldiazoacetates with aldehydes and ketones lead exclusively to 1,3-dioxoles, which are formed with high yields in the cases of both photolytic[493] and catalytic[494,495] initiations of carbene decompositions of diazoesters (see Scheme 111).

Formation of oxiranes or 1,3-dioxoles was not noted. This is caused, apparently, by [1,4]-rearrangement of the ylide, which proceeds effectively in reactions with the participation of diazoesters of this type (see, e.g., Section IV.B.4.c).

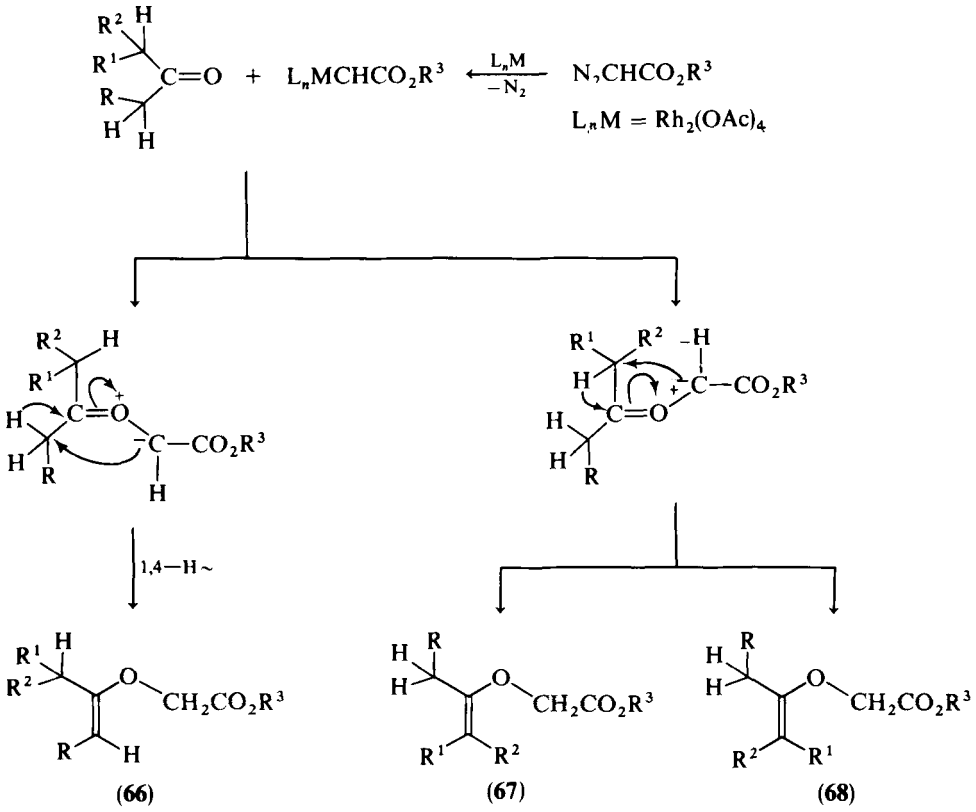
Another rearrangement of an *O*-ylide, formed in the transition metal catalyzed reaction of ADA with ketones, which is of preparative importance, is the [1,4]-hydride shift leading to *O*-alkylated enols of ketones[496,497] (see Scheme 112). In the case of aliphatic ketones, with the use both of CuCl (75 °C) and of $Rh_2(OAc)_4$ (20–25 °C), the total yield of isomeric enol ethers is in the range of 25–65%.

This process is noted for high regio- and diastereoselectivity and has an intermolecular concerted character. Steric hindrances, arising upon changes of the molecule conformation in the course of H-migration, as well as stoichiometric factors, favor, and in some cases make exclusive, the formation of isomers of enol ethers with *E*-configuration of the double bond and predominantly of a less substituted isomer. The case with benzylketones is an exception: here the formation of a more substituted isomer is comparable or predominant, apparently because of strong conjugation with the aromatic ring[497].

In the reaction of EDA with β-ketoesters, together with enol ethers, products of formal insertion of the $CHCO_2Et$ fragment into the α-C—H bond of the ketone are also formed. Their share in the reaction products is much greater when CuCl is used as the dediazotation catalyst (up to 65%) than with the use of $Rh_2(OAc)_4$ (<11%), though the latter catalyst, as has been noted in Section IV.B.1, favors the formation of insertion products in reactions with the participation of diazoesters (see Scheme 113). This gave grounds to Landgrebe and coworkers[497] to explain the formation of these products not by C—H insertion of carbene, but by isomerization of the initially formed cyclopropane adduct to the double bond of the enol.

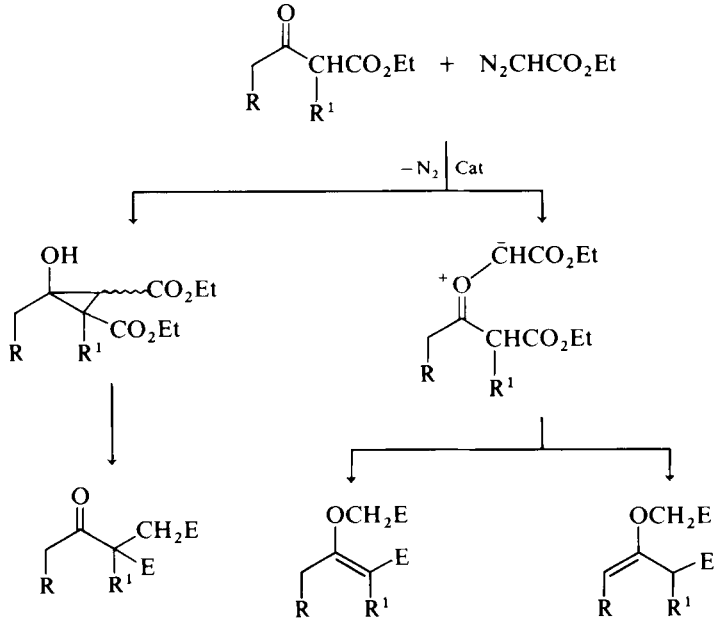
An intramolecular [1,4]-H shift in the course of methyl β-benzoyloxy-α-diazopropionate dediazotation under the effect of $Rh_2(OAc)_4$ leads to the enol ester of methyl pyruvate[170] (see equation 191).

The ADA reaction with ketones can also be induced by Lewis acids. In the case of dimedone and its homologs, for example, the corresponding enol ethers are the only reaction products[498] (see equation 192).



			Ratio of isomers (%)			
R	R^1	R^2	**66**	**67**	**68**	References
H	H	Me	75	4	23	497
H	H	Pr^i	77	0	23	497
H	Me	Me	~100	0	0	497
Me	Me	Me	~100	0	0	497
H	H	Ph	45	0	55	497
H	Me	Ph	85	0	15	497
(CH$_2$)$_3$		H	~100	—	0	496, 497
(CH$_2$)$_3$		Me	88	—	12	496, 497
(CH$_2$)$_3$		Ph	44	—	56	497
(CH$_2$)$_4$		Ph	40	—	60	497

SCHEME 112



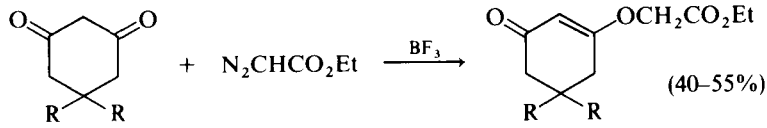
Total yield 40–55%

$R = R^1$ = alkyl or

$R + R^1 = (CH_2)_n$, $n = 2$–3

SCHEME 113

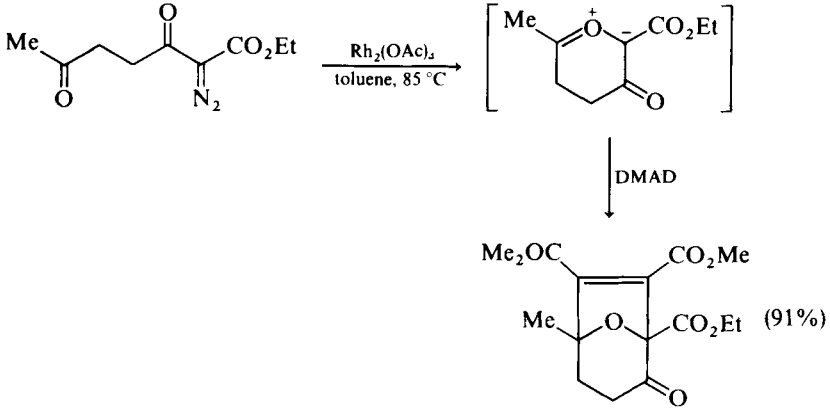
$$BzOCH_2C(=N_2)C(=O)CO_2Me \xrightarrow[CHCl_3]{Rh_2(OAc)_4,\ 20\ ^\circ C} H_2C=C(OBz)CO_2Me \quad (94\%) \qquad (191)$$



(192)

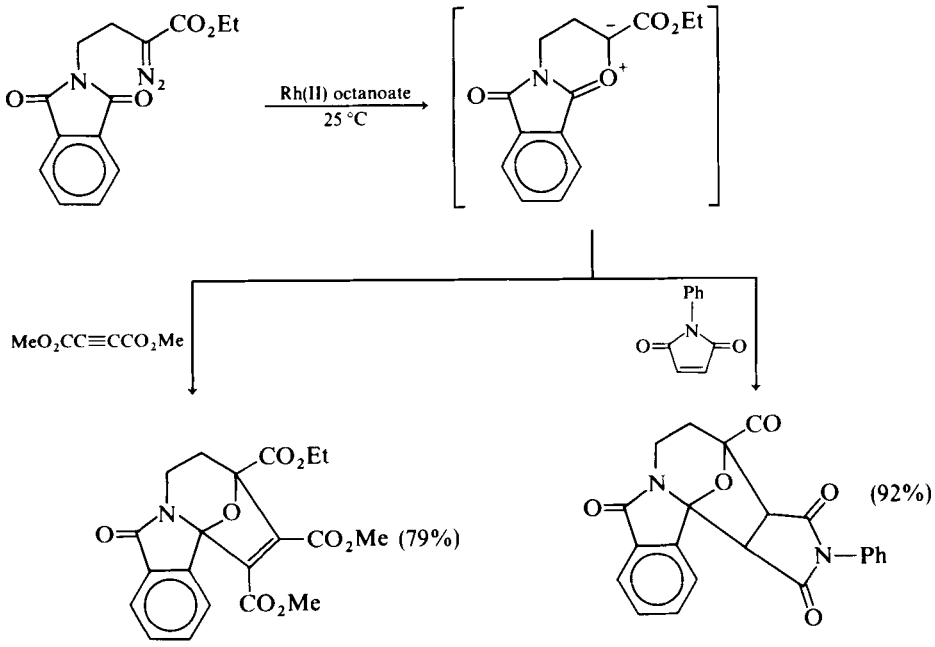
Reactions of intramolecular cyclization of oxodiazoesters are also of great synthetic importance. Thus, Rh-promoted metallocarbene from 6-oxo-2-diazoalkanoates (see Schemes 114[133] and 115[84]) and 2-oxoalkyl α-acetyldiazoacetates or 2-oxoalkyl ethyl diazomalonates (see Scheme 116[84]) lead to six-membered cyclic *O*-ylides, which on [3,2]-cycloaddition to active dipolarophiles give polyheterocyclic compounds used in the synthesis of alkaloids.

A similar Cu(I)-initiated intramolecular transformation of methyl *o*-acylphenyl diazoacetate, containing a carbonyl group in β-position in relation to the diazo group,



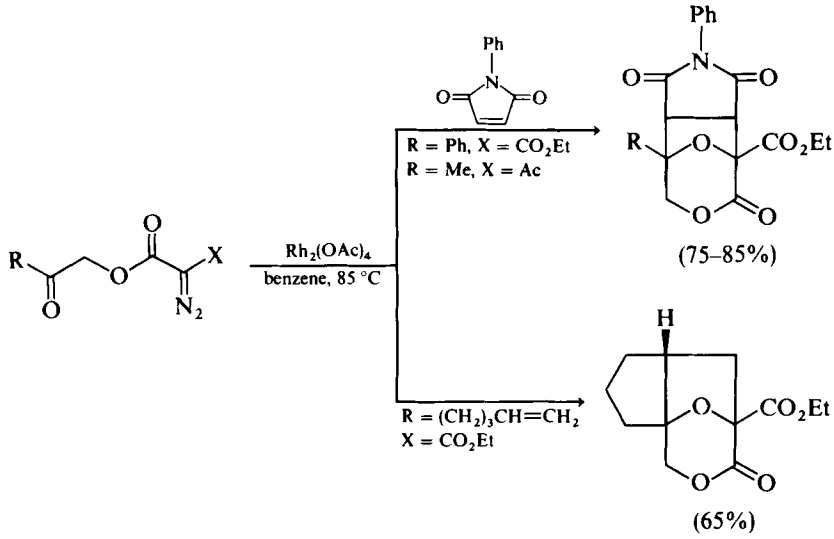
DMAD = $MeO_2CC{\equiv}CCO_2Me$

SCHEME 114

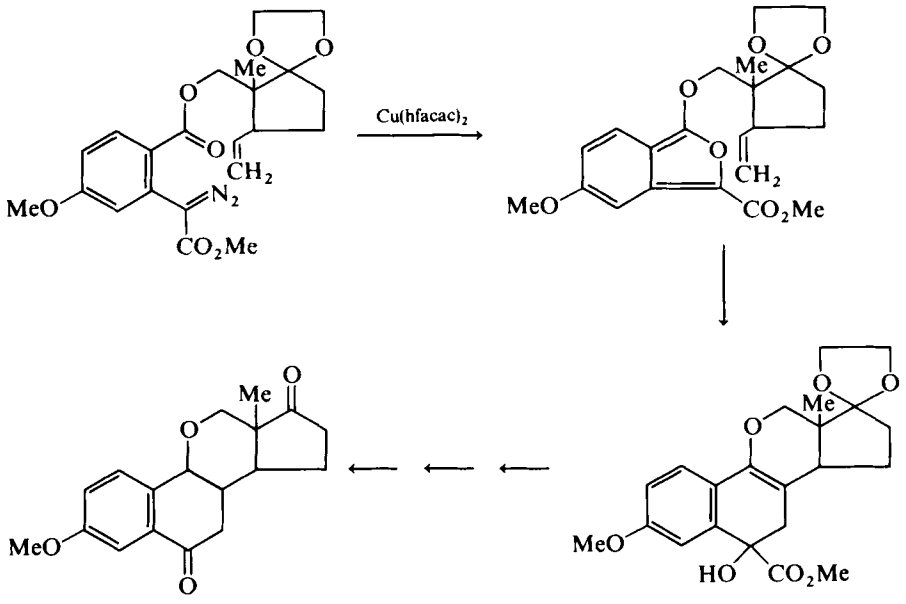


SCHEME 115

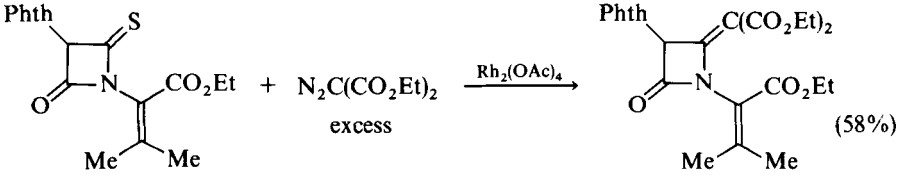
leads to benzo[*b*]furane; a subsequent intramolecular Diels–Alder reaction in the latter results in a high yield of a template for the production of 6-keto-11-oxasteroids[499] (see Scheme 117).



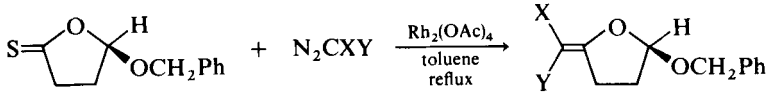
SCHEME 116



SCHEME 117



Phth = phthalimido (193)



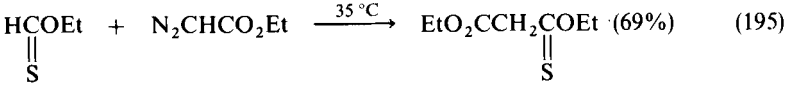
(194)

X = CO_2Et
Y = CO_2Et or $PO(OEt)_2$

Among publications devoted to the study of ADA reactions with compounds containing other C=X bonds, reactions with thiocarbonyl compounds can be mentioned. The preparative potentialities of these reactions have not been sufficiently studied so far. For instance, $Rh_2(OAc)_4$-initiated dediazotation of diazoesters in the presence of cyclic thioketones causes transformation of the latter into methylenecyclanes (see equations 193[500] and 194[501]), supposedly as a result of desulfuration of intermediate thiiranes (see Section IV.B.4.d).

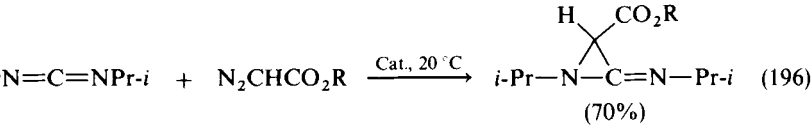
The formation of thiiranes may involve dediazotation of the initially originating 1,3,4-thiadiazoles (i.e. [3,2]-cycloadducts of diazoesters to the C=S bond[500]) though isomerization of *S*-ylides[501] is more likely. Irrespective of the mechanism, this reaction is of a great preparative value as an analogue of the Wittig reaction.

EDA reaction with ethyl thioformate[502] leads to diethyl monothiomalonate with a fair yield. This transformation is a particular case of a general reaction of ethyl thioformate homologization by a wide range of compounds and, apparently, it also proceeds with the participation of thiiranes (see equation 195).



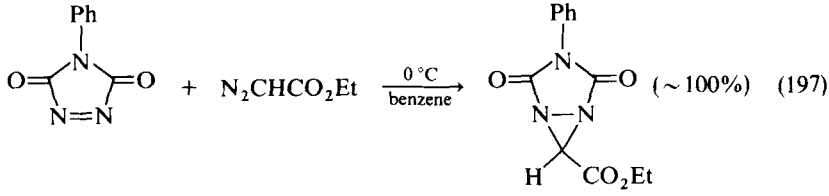
(195)

An example of ADA reactions with compounds containing C=N bonds is the interaction with carbodiimide, catalyzed by $Rh_2(OAc)_4$ or by copper(II) triflate[503] (see equation 196).

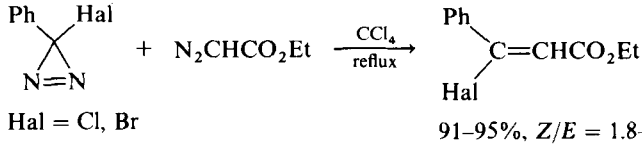


(196)

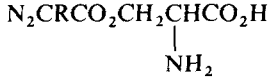
A unique cyclopropanation of the N=N bond in 4-phenyl-3,5-dioxo-1,2,4-triazole proceeds in the absence of catalyst at 0 °C practically with a quantitative yield of the bicyclic diaziridine product[504] (see equation 197). However, in a similar reaction of EDA with diazirines unsymmetrical alkenes were formed practically in quantitative yields and



(197)



(198)



(69) R = H
(70) R = *R*-MeCHOH

with predominance of *Z*-isomer, instead of 1,3-diazobicyclo[1.1.0]butanes[505] (see equation 198).

V. CONCLUSION

The present review demonstrates that interest in all aspects of diazoester chemistry remains high. Analysis of the literature shows, however, that the main attention of researchers is focused on several topics which are crucial for extending the application of these reagents in organic synthesis.

The first of these topics is associated with increasing the selectivity of reactions in which diazoesters participate. In the main, these are investigations in the enantio- and diastereoselective syntheses of cyclic compounds with the use of catalytic dediazotation of the diazoesters. The second topic is directed to broadening the sphere of application of diazoesters in organic synthesis and is developing along three lines: searching for new transformations of the diazoesters, involving them in reactions with new classes of compounds, and synthesizing new diazoesters for the construction of prescribed structures, particularly natural compounds.

We believe that successful development of studies in all the above-cited directions will depend on progress in the development of new catalysts for dediazotation of diazoesters and on elucidation of the detailed aspects of the mechanism of catalytic reactions. This assumption is supported by the surge of studies in diazoester chemistry that followed the discovery of rhodium catalysis.

Studies important in their own right are those directed to broadening the technical applications of the diazoesters in commercial organic syntheses, for instance, for the production of pyrethroid insecticides, drugs, functionalized polymers, etc. There are examples of using diazoesters not only as organic synthetic reagents, but also as excimer

laser resists[506] and antitumor antibiotics, such as azaserine[507] (**69**) and thrazarine[508] (**70**).

Thus, construction of new diazoesters has not only synthetic aspects, but is also of practical interest in the search for substances possessing technically useful properties and biological activity.

VI. ACKNOWLEDGMENTS

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CHAPTER 26

Anion radicals of aromatic carboxylic acids and their derivatives: structure and reactivity

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I. INTRODUCTION

In recent years chemistry of radical anions (RAs) of organic compounds, including carboxylic acids and their derivatives, has received much attention. This interest is due to several reasons. First, the transition into a radical anion state activates organic

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molecules with respect to various transformations, which often are not typical for the starting systems, and opens up new ways of their functionalization[1]. In particular, one-electron reduction enhances nucleophilic and protophilic properties of organic compounds, facilitates their reactions with free radicals and makes their fragmentation and dimerization possible.

Second, RAs are known to be the key intermediates of many reactions of carboxylic acids and their derivatives. For example, a mechanism including formation of these species has been suggested for nucleophilic substitution at a carbonyl group, the transformation of which is traditionally considered to be heterolytic[2].

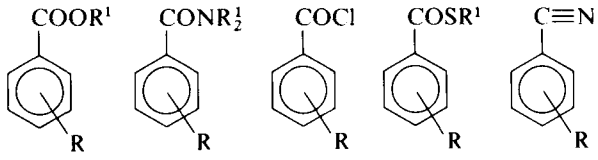
Finally, the determination of RA formation energies in gas phase and in solution and investigation of their electronic and spatial structures make it possible to obtain information on energy and shape of the LUMO of the parent molecules. Thus, the influence of different factors on the reactivity of the latter towards nucleophilic reagents can be analyzed.

In this chapter we will deal mainly with the characterization of the reactivity of RAs of carboxylic acids and derivatives, using their aromatic representatives as examples. Aromatic compounds have been chosen because they are characterized by a diverse variety of chemical properties and undergo transformations involving both the functional group and the aromatic moiety. However, we start with a brief description of the available literature data on the energy of formation of RAs in solutions and of special features of their electronic and spatial structures.

II. ENERGY OF RADICAL ANION FORMATION

Usually, the first half-wave potentials of a reversible electrochemical reduction of organic compounds ($E_{1/2}$, see, e.g., Reference 3) are used as a measure of their capability of transforming to a radical anion state in solutions.

The available literature data allow one to characterize the influence of the structure of the aromatic fragment and of the functional group on $E_{1/2}$ for the various derivatives



(1) (2) (3) (4) (5)

of aromatic carboxylic acids such as esters (**1**)[4–18], amides (**2**)[19], aroyl chlorides (**3**)[20], thioesters (**4**)[7,8,21,22] and nitriles (**5**)[23–49], although sometimes this is not an easy problem.

Specifically, the quantitative estimation of the relative electron-acceptor activity of the above functional groups and characterization of their position in the series of other electron-acceptor substituents are quite difficult, because a direct comparison of the known $E_{1/2}$ values for monofunctional benzene derivatives is not always possible. In most cases these values were measured by different researchers in different solutions and supporting electrolytes and, consequently, reflect not only changes in structure of the functional group but also in conditions of the $E_{1/2}$ measurements. Also, the $E_{1/2}$ values

are often determined relative to different reference electrodes. An approach based on analysis of the difference between reduction potentials of different pairs of compounds (the value which is usually less sensitive to conditions of measurements) seems more reliable. For example, according to the existent literature data the difference between reduction potentials

$$\Delta E_{1/2} = E_{1/2}(C_6H_5COSCH_3) - E_{1/2}(C_6H_5CO_2CH_3)$$

is 0.37 (DMF, Ag/AgCl[7]), 0.34 (MeCN, Ag/$AgNO_3$[8]) and 0.36 (EtOH, SCE[12]) with the solvent and reference electrode given in parentheses. One can hope that the relative values of $E_{1/2}$ listed in Table 1 reflect a true picture of the changes of electron-acceptor properties of different functional groups.

On the whole the data of Table 1 correspond to the expected values and do not need additional consideration. The only surprising fact is that a cyano group introduced into the benzene ring provides a lesser stabilization than a carbomethoxy group. According to quantum-chemical calculations[50] and data on the influence of these substituents on reduction potentials of nitrobenzene[51] and benzonitrile[27] an opposite effect should have been observed. It is possible that the experimental facts under consideration have to be verified; however, such a change in relative electron-acceptor capability of substituents depending on the presence of other electron-acceptor groups in the aromatic molecule is theoretically possible[47,52].

The change in energy of π^* orbitals of benzene under the influence of substituent X (ΔE_X) can be described as a sum of the resonance (Δ_X^r) and induction (Δ_X^i) components[52]:

$$-\Delta E_X^{\pi^*} = \frac{c_i^2}{0.333}\Delta_X^r + \Delta_X^i \qquad (1)$$

where c_i^2 corresponds to the contribution of the substituent-bound carbon atom to LUMO; $c_i = 0.333$ and 0 for orbitals of b_1 and a_2 type, respectively; Δ_X^r and Δ_X^i are positive for electron-acceptor substituents.

If substituent Y is introduced into a molecule that already has substituent X, it is necessary to take into account that the orbital coefficients can change in comparison with an unsubstituted benzene ring and, as a result, the stabilizing effect of the substituent can also change. To consider the nonadditivity effects of substituents, expression 2 for

TABLE 1. Relative reduction potentials (in V) of monofunctional derivatives of benzene (PhX)[7,12,18–20]

X	$E_{1/2}(PhX) - E_{1/2}(PhCN)$
CO_2NMe_2	−0.05
CN	0
CO_2Me	0.07
COMe	0.33
COSMe	0.43
COH	0.44
CSOMe	0.64
COCl	1.00
CS_2Me	1.13
NO_2	1.2
C—CPh ‖ ‖ O O	1.24

disubstituted benzene derivatives has been suggested[52]:

$$-\Delta E^{\pi^*}_{XY} = \frac{c_i^2}{0.333}\Delta^r_X + \frac{c_i^2}{0.333}\Delta^r_Y - 0.5\frac{c_i^2}{0.333}\Delta^r_X \cdot \frac{c_j^2}{0.333}\Delta^r_Y + \Delta^i_X + \Delta^i_Y \qquad (2)$$

From this expression it follows that while the contribution of the induction components of the second substituent remains unchanged on the background of the electron-acceptor substituent present in the ring, that of the resonance component tends to decrease

$$(\Delta^r_Y)_{eff} = \Delta^r_Y - (0.5c_i^2/0.333)\Delta^r_Y\Delta^r_X$$

in comparison with the corresponding monosubstituted benzene. Therefore, if one of the two substituents Y^1 and Y^2 is characterized by a stronger resonance effect ($\Delta^r_{Y^1} > \Delta^r_{Y^2}$) and weaker induction effect ($\Delta^i_{Y^1} < \Delta^i_{Y^2}$) than the other one (carbomethoxy and cyano groups satisfy these conditions), evidently an opposite order of their capability of stabilizing the RA species can occur.

Considerable attention has also been devoted to the study of the influence of the nature of substituent R^1 on the reduction potentials of compounds **1**[4–6,12,17], **2**[19], and **4**[12,22]. The results obtained suggest that this influence is not very significant and, as shown in Reference 6 for compound **1** as an example, can be described quantitatively by Taft's equation. The largest stabilizing effect was observed when a phenyl group was substituted for an alkyl group[4–6,12].

Changes in reduction potential under the influence of the substituent introduced into the aromatic fragment were examined for compounds **1**[9–11,12], **3**[20] and **5**[23,47]. The effect of substituents occupying the *para* and *meta* positions of compound **1** is described satisfactorily by the Hammett equation and is characterized by the high sensitivity coefficient ($\rho = 0.57$)[11], which is much higher than that for compounds containing a group with stronger electron-acceptor properties. For example, for substituted methyl dithiobenzoates $\rho = 0.45$[7]. The possibility to describe the influence of substituent R on $E_{1/2}$ of benzonitrile in the framework of the empirical approach based on the theory of MO perturbations was demonstrated[47].

The effect of *ortho* substituents on $E_{1/2}$ depends on the nature of the functional group. For instance, the introduction of a methyl group into the *ortho* position relative to a —COCl group leads to a more significant destabilization of the RA state than the introduction of the same substituent into the *para* position[20]. This seems to be due to the fact that the *o*-methyl group causes steric hindrance for the disposition of the —COCl group in the plane of the aromatic fragment, which naturally results in additional destabilization of the RA state. Similar phenomena have also been reported for some other benzene derivatives containing strong electron-acceptor groups, e.g., for nitrobenzene[53] and methyl dithiobenzoate[7]. On the other hand, an *o*-methyl group in methyl benzoate has a smaller destabilizing effect on the RA state than the *p*-methyl group[12]. This observation suggests that, unlike the above functional groups, the carbomethoxy group remains in the plane of the aromatic fragment. This conclusion is supported by quantum-chemical calculations[54], as well as by the data on the effect of *o*-methyl and *o*-methoxyl groups on ESR parameters of the RA of methyl benzoate[55,56] and will be discussed in more detail in the next section.

III. THE ELECTRONIC AND SPATIAL STRUCTURES OF RADICAL ANIONS

The electronic and spatial structures of RAs of aromatic benzoic acids and their derivatives have been under active investigation for many years. To give a complete account of the various findings in this field would greatly exceed the scope of this chapter.

Thus here we discuss only those problems which are the most important for understanding the chemical properties of the species of interest, i.e.:

(i) distribution of the unpaired electron density in the aromatic fragment and between this fragment and a functional group;

(ii) spatial structure, i.e. the mutual disposition of the functional group and aromatic fragment;

(iii) special features of the electronic structure of RAs containing several functional groups of the same type.

The discussion is based mainly on the studies of RAs by the ESR method; however, results obtained by other methods, such as quantum-chemical calculations, will also be outlined where necessary. For detailed information on magnetic-resonance parameters of RAs the reader is referred to References 57 and 58 (carboxylic acids), 55, 56 and 59–64 (esters), 19 and 65 (amides), and 23, 42, 62, and 66–69 (nitriles). Table 2 lists ESR parameters of benzoic acid derivatives. For comparison the hyperfine interaction (hfi) constants for RAs of some other monofunctional derivatives of benzene are also shown. Taking into account the McConnell relation $a^1_H = Q_H\rho_c$, where ρ_c is spin density on the carbon atom coupled with the hydrogen atom[72], the tabulated data give an idea about the spin density distribution in the RAs under consideration. Note first that a considerable proportion of spin density is concentrated in the *ortho* and *para* positions relative to the functional group: $|a^H_p| > |a^H_o| > |a^H_m|$. The a^H_o/a^H_p ratio depends on the nature of the substituent and is often regarded as an empirical parameter that characterizes the capability of the substituent of participating in density delocalization of an unpaired electron in RA systems[19,59,62,66,73]. The higher the ratio, the higher the degree of electron density transfer from the aromatic fragment into the substituent. According to the data in Table 2 the degree of density transfer of an unpaired electron into substituent X in the RA of C_6H_5X increases in the following order:

$$CN < CO_2^- < CONH^- < CO_2CH_3 < CON(CH_3)_2 < COCH_3 < CHO < CSOCH_3 < CSN(CH_3)_2 < NO_2 \sim CS_2CH_3$$

The same conclusion can also be reached on the basis of the other empirical parameter, namely the sum of hfi constants with aromatic protons (which is determined by taking into account the sign of these values) (see Table 2). Actually this sum is a

TABLE 2. Hyperfine interaction (hfi) constants for RA of monofunctional derivatives of benzene (PhX)

	hfi constants (GS)							a^H_0	
X	$-a_2$	a_3	$-a_4$	a_5	$-a_6$	a_X	$\lvert\sum a_H\rvert$	a^H_p	Reference
CN	3.63	0.30	8.40	0.30	3.63	$a_N = 2.15$	15.06	0.43	23
CO_2^-	4.24	0.81	7.78	0.81	4.24		14.64	0.54	57
$CONH^-$	4.24	0.81	7.78	0.81	4.24		14.64	0.54	57
CONH –	4.20	0.92	7.57	0.62	3.99	$a_N = 0.98$; $a^{NH}_H = 3.37$	14.22	0.54	65
CO_2Me	4.20	0.94	7.64	0.94	4.20	$a^{Me}_H = 0.94$	14.16	0.55	59
$CONMe_2$	4.16	0.87	6.93	0.77	3.94	$a_N = 0.07$; $a^{Me}_H = 0.59$	13.39	0.59	19
COMe	4.25	1.07	6.60	0.88	3.71	$a^{Me}_H = 6.74$	12.61	0.60	70
CHO	4.68	1.31	6.47	0.75	3.39	$a^{CHO}_H = 8.51$	12.48	0.62	70
COS^-	4.02	1.14	5.53	1.14	4.02		11.29	0.73	57
CSOMe	4.05	1.35	5.34	1.35	4.05	$a^{Me}_H = 1.35$	10.74	0.76	7
NO_2	3.36	1.07	4.03	1.07	3.36	$a^{NO_2}_N = 9.7$	9.61	0.83	71
CSSMe	3.44	1.08	4.48	1.08	3.44	$a^{Me}_H = 1.08$	9.20	0.77	7

measure of localization of an unpaired electron density on a phenyl fragment. Thus, the tendency of variations in this value provides information on density redistribution between the aromatic ring and the substituent[7,19,59,66,73].

In general, the above order of the degree of density transfer coincides with the order of the substituent capability of stabilizing the RA state (see Section II). However, deviations from this correlation can also take place. Particularly, this occurs in case of the $CON(CH_3)_2$ group which stabilizes the RA state to a lesser degree than the CO_2CH_3 group or cyano group but withdraws a significant proportion of the density of an unpaired electron. This is also the case for the $CSN(CH_3)_2$ and $CSOCH_3$ groups (cf data in References 7, 11 and 19). This observation can be explained by the fact that the capability of a substituent participating in delocalization of an unpaired electron density is determined largely by the resonance component of its electronic effect, whereas the degree of stabilization of the RA state is determined by both resonance and induction components[47,52,74]. Support for the above statements comes from quantum-chemical calculations[19,57,59,64,65,70,73,75].

RAs of bifunctional derivatives of benzene, XYC_6H_4, should be considered individually because, as follows from experimental data[7,8,23,57,62,66] and analysis on the basis of qualitative quantum-chemical ideas and calculations[57,62,66,73], the spin density distribution in these systems actually provides information on the relative capability of the substituent stabilizing the RA state. In fact, in accordance with a valence bond superposition model[62,66,76] spin density (ρ_i) on the atom C_i can be described as

$$\rho_i = \{k(X)\}^2\rho_i(X) + \{k(Y)\}^2\rho_i(Y) \tag{3}$$

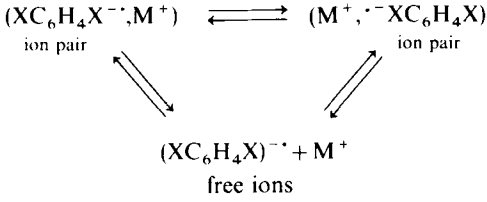
where $\rho_i(X)$ and $\rho_i(Y)$ correspond to spin densities on C_i nuclei in monosubstituted benzene derivatives $PhX^{-\cdot}$ and $PhY^{-\cdot}$, and $\{k(X)\}^2$ and $\{k(Y)\}^2$ correspond to contributions of these derivatives to the ground state of the system $(XC_6H_4Y)^{-\cdot}$. Obviously, $\{k(X)\}^2$ and $\{k(Y)\}^2$ are determined by relative energies of PhX^- and PhY^-, i.e. actually by the relative capability of substituents stabilizing the RA state. The available literature data on the electronic structure of RAs of 1,4- and 1,3-disubstituted benzenes[7,8,23,57,62,66] makes it possible to expand the series of relative stabilizing capabilities of substituents presented in this section. Particularly, there is some evidence that a carboxylate group shows a lower stabilizing capability than a cyano group.

As follows from Table 2 for RAs of benzamide derivatives the *o* and *o'*, as well as *m* and *m'* positions of the benzene ring are not equivalent, which is related to the absence of a free rotation of the functional group. A similar phenomenon is observed for RAs of aromatic aldehydes and ketones. Despite the equivalency of the hfi constants with *o*, *o'* and *m*, *m'* protons in RAs of alkyl benzoates, it is strongly probable that rotation of the functional group in this system is inhibited. This conclusion can be obtained from the following facts. First, an analysis of ESR spectra of RAs of di-*t*-butyl terephthalate indicates the nonequivalency of *o* protons[62]. Second, the quantum-chemical calculations show that, upon transformation of methyl benzoate to the RA state, the bond order for the ester group–benzene ring bond increases approximately by the same magnitude as that for the RAs characterized by a slow rotation of the functional group[59]. In addition, a recent experimental study of vibrational spectra of RAs of terephthalic acid and its mono- and diionized forms has confirmed an increase in $C—CO_2$ bond order[77]. The frequency of $C—CO_2$ bond vibrations, equal to 1128 cm^{-1} for the terephthalic acid dianion, changes to 1422, 1362 and 1404 cm^{-1} when passing to radical-trianion, -dianion and -anion, respectively. This is a clear indication that the $C—CO_2$ binding is of double-bond type in the products of one-electron reduction. Finally, based on quantum-chemical calculations, Sieiro and coworkers[54–56] have shown that the transformation to the RA state leads to an increase in rotation barrier of the carbomethoxy group in methyl benzoate from 5.3 to 19.2 kcal mol^{-1}. Moreover, in accord with the calculations

the introduction of one or two methyl groups into the *ortho* position of methyl benzoate results in rotation of the carbomethoxy group from the plane of an aromatic fragment by 40 and 60°, respectively. However, for RAs a flat structure has a minimal energy, the height of the rotation barrier of the CO_2CH_3 group being independent of the number and position of the introduced methyl groups. These conclusions are confirmed by ESR spectral parameters for RAs of polymethyl- and polymethoxy-substituted methyl benzoates[55,56], which differ only slightly from those for the RA of methyl benzoate. Additional support comes from data on the influence of *o*-methyl groups on the reduction potential of methyl benzoate (see Section II).

Thus in RAs of benzoic acid, its anion, esters and amides a functional group is locked in the plane of the aromatic fragment due to an essentially double-bond type of binding of the functional group to the aromatic carbon atom.

In concluding this section consider some special features of the electronic structure of RAs containing two or more functional groups. ESR spectra of RAs of dialkyl terephthalates, generated by electrochemical reduction of DMF or MeCN solution, correspond to symmetrical distribution of an unpaired electron density between functional groups[60,63,64]. A different picture is observed when dialkyl terephthalates are reduced with alkaline metals in DME or THF. ESR spectra indicate that in these conditions two types of radical species are formed[60]. One type is characterized by symmetrical distribution of the spin density (like in the case of electrochemical generation), and the other by a nonsymmetrical distribution. The ESR spectrum of the latter species shows the hfi with an alkaline metal nucleus, which is direct evidence for the formation of ion pairs. The degree of nonsymmetry is so high that one can speak of a predominant density localization of an unpaired electron on one of the two equivalent functional groups and model the spin density distribution from the electronic structure of RAs of monofunctional derivatives. The formation of such nonsymmetrical forms of RAs has also been reported for dicyanobenzenes[78], di- and polynitrobenzenes[79] and benzenedicarbaldehydes[80]. Note that the asymmetry can be caused not only by the formation of ion pairs, but also by the specific solvation of the functional group carrying a negative charge by a proton-donor solvent[79–81]. All the above data show that to study chemical properties of benzene derivatives containing two or more similar symmetrical electron-acceptor groups, it is necessary to consider the possibility of occurrence of equilibrium 4 in the reaction mixture. The reason is that the forms of the same RA with symmetrical and nonsymmetrical spin density distribution can differ in reactivity.



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IV. CHEMICAL PROPERTIES OF RADICAL ANIONS

Transition of substituted arenes into the RA state is accompanied by activation of the radical, basic and nucleophilic properties of both the functional group and the aromatic moiety. We will characterize below chemical properties of RAs, such as their ability to undergo fragmentation and dimerization, and to react with acidic, electrophilic and free radical reagents.

A. Fragmentation Reactions

The fragmentation is one of the most characteristic features of RAs. All fragmentation reactions of RAs of substituted arenes, including aromatic carboxylic acids and their derivatives, can be divided into two classes. The first class includes transformations connected with bond rupture in the functional group, the structure of which determines reaction route and type of end-products. The second class of reactions involves bond rupture in the aromatic fragment; the functional group affects reaction rate and regioselectivity but does not participate in the reaction. For most radical anion systems studied one of the two main classes of fragmentation reactions is prevailing, which makes their independent consideration possible.

1. Bond rupture in the functional group

a. Esters of aromatic carboxylic acids. Depending on reaction conditions, reduction of esters of aromatic carboxylic acids, $ArCO_2R$, can lead to a wide variety of products (equations 5–9) containing a modified functional group[12,14,16,17,20,82–93].

The treatment of diluted $ArCO_2R$ solutions in ethanol with alkaline metals (Bouveault–Blanc reduction) leads eventually to the formation of the corresponding alcohols[82,93]. When the reduction is carried out in ether solvents, benzene or liquid NH_3, the main products are acyloins[93,94] (equation 6). Solutions of alkaline metals in the systems t-$BuNH_2$–THF–crown ether[82] or HMPA–t-BuOH[85] reduce ethers to the corresponding carboxylic acids $ArCO_2H$ and alkanes RH (equation 7). Such a reaction occurs under UV irradiation of $ArCO_2R$ in an HMPA–H_2O mixture[83,84], as well as in acetonitrile or in alcohol in the presence of amines[86–89]. When the solution of benzhydryl or fluorenyl benzoate is treated with lithium naphthalenide, along with acyloins, phenylbenzhydryl or phenylfluorenyl ketone is formed, respectively, with a relatively good yield[90,91]. The main products of an electrochemical reduction of t-butyl benzoate are benzoic acid and t-butyl p-t-butylbenzoate[17] (equation 9). Conditions governing the above-indicated processes are such that there can be no doubt about the formation of RAs. The electron donors are either alkaline metals or solvated electrons or the RA of naphthalene. In photochemical processes the formation of RAs results from reduction

$$ArCO_2R \xrightarrow[\text{ethanol}]{M} ArCH_2OH + ROH \qquad (5)$$

$$\xrightarrow[\text{ether solvents, benzene or liquid } NH_3]{M} ArC(=O)-CHAr(OH) \qquad (6)$$

$$\xrightarrow[t\text{-}BuNH_2\text{ THF, HMPA } t\text{-BuOH}]{M} ArCO_2H + RH \qquad (7)$$

$$\xrightarrow[THF]{NaNaphH} ArCOR \qquad (8)$$

$$\xrightarrow[(R = t\text{-Bu, Ar = Ph})]{\text{cathode}} R\text{-}C_6H_4\text{-}CO_2R + C_6H_5CO_2H \qquad (9)$$

of the $ArCO_2R$ excited state with amine (equation 10). This fact was confirmed by spectral data in Reference 93.

$$ArCO_2R \xrightarrow{h\nu} ArCO_2R^* \xrightarrow{R_3N} ArCO_2R^{-\cdot} + R_3N^{+\cdot} \quad (10)$$

Formally, the products of reactions 5–9 can result from the rupture of ArCO—OR or $ArCO_2$—R bonds in RAs of esters (equations 11 and 12).

$$ArCO_2R^{-\cdot} \longrightarrow ArCO^{\cdot} + RO^- \quad (11)$$

$$ArCO_2R^{-\cdot} \longrightarrow ArCO_2^- + R^{\cdot} \quad (12)$$

The subsequent paths of transformation of $ArCO^{\cdot}$ and $R^{\cdot}$ radicals to the end-products of reactions 5–9 are quite evident (equations 13–17). Aldehydes (or benzils) formed as a result of abstraction of a hydrogen atom by acyl radical (or, respectively,

$$ArCO^{\cdot} \xrightarrow[-CH_3\dot{C}HOH]{C_2H_5OH} ArCHO \xrightarrow{2e,2H^+} ArCH_2OH \quad (13)$$

$$ArCO^{\cdot} \xrightarrow{ArCO^{\cdot}} ArC(=O)—C(=O)Ar \xrightarrow{2e,2H^+} ArC(=O)—CHAr(OH) \quad (14)$$

as a result of dimerization of $ArCO^{\cdot}$) have higher electron affinity than the starting esters (see Table 1) and can easily be reduced to alcohols(benzoins). $R^{\cdot}$ can be reduced to a carbanion or recombine with RA. In its turn, the carbanion R^- is either protonated or attacks the starting ester via a carbonyl carbon atom.

Note, however, that the literature reports alternative mechanisms for the reactions 5–9 that do not involve fragmentation of RAs of esters as an elementary stage. In particular, according to Reference 82, during the Boveault–Blanc reduction of esters the elimination of RO^- does not occur in RAs, but rather in the product of its subsequent

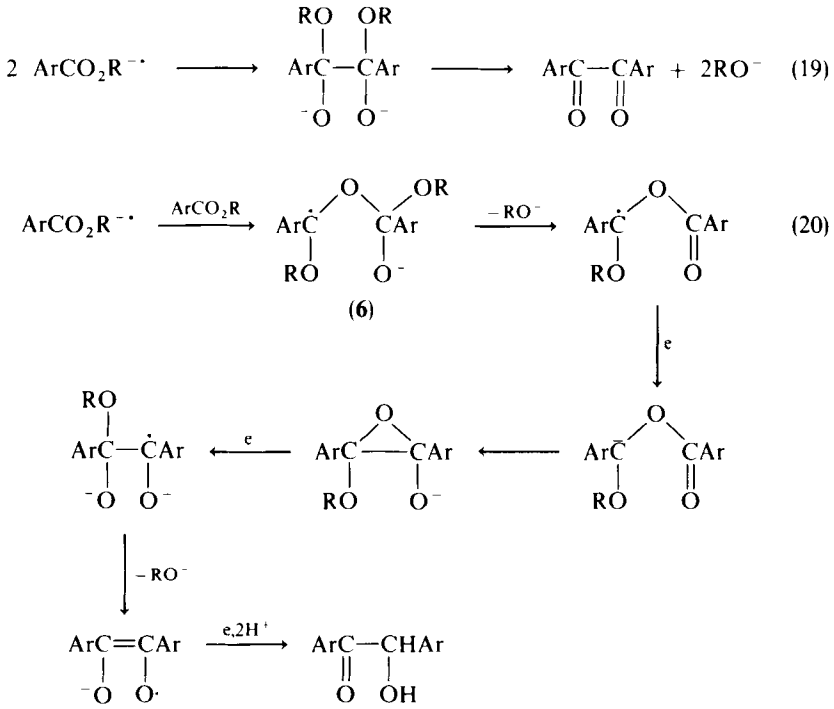
$$R^{\cdot} \xrightarrow[-S^{\cdot}]{SH} RH \quad (15)$$

$$R \xrightarrow{ArCO_2R} ArC(O^-)(R)—OR \longrightarrow ArC(=O)R + RO^- \quad (16)$$

Ar = Ph, R = *t*-Bu

$$ArCO_2R^{-\cdot} \longrightarrow \text{(substituted benzene)}CO_2R \quad (17)$$

$$ArCO_2R^{-\cdot} \xrightarrow{e,H^+} ArC(O^-)(H)—OR \longrightarrow ArCHO + RO^- \quad (18)$$

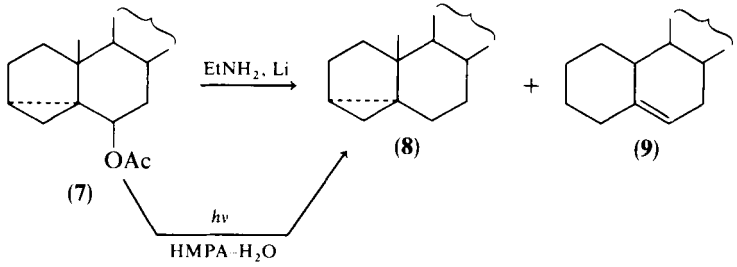


reduction (equation 18). In the conditions of acyloin formation, the elimination of RO^- can be preceded by dimerization of RAs of esters (equation 19) or by addition of the latter to the molecule of the initial ester followed by the formation of an oxygen-bridged RA (**6**, equation 20)[94]. The fragmentation of the oxygen-bridged RA (**6**) producing radical R· (equation 21) is an alternative to the route in equation 12[85,94]:

$$\mathbf{6} \longrightarrow ArCO_2^- + R^{\cdot} + ArCO_2R. \qquad (21)$$

The ability of an ester group to undergo fragmentation after one-electron reduction has been proven only in recent years[17,92,93]. Of special interest in this respect are the works by Massnovi[92,93]. He has shown that pulse radiolysis in alcohol or hexane solutions of various alkylbenzoates produces the corresponding RAs, which further decompose in a first-order reaction. The decay of the RA of benzyl and benzhydryl benzoates gives rise to the appearance of absorption bands ascribed, respectively, to a benzyl or benzhydryl radical. The decay of the RAs and accumulation of free radicals are characterized by the same first-order rate constant.

It should be noted that the possibility of formation of alkyl radicals during reduction of esters was mentioned in the literature before the appearance of the works by Massnovi. For example, during reduction of 3β,5α-cyclocholestane-6-yl acetate (**7**) with alkaline metals[82] or photochemically[83,84] one of the main reaction products was cholest-5-ene (**9**) rather than 3,5-cyclocholestane (**8**) (equation 22). This result fits the supposition of an intermediate formation of an alkyl radical, since it is well known that 3,5-cyclocholestan-6-yl radical **10** can be isomerized very easily to cholest-5-en-3-yl radical **11** (equation 23), which is thermodynamically more stable[95].



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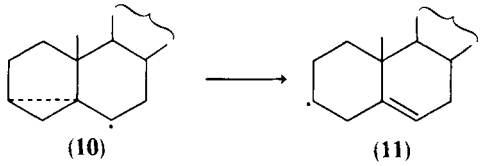


(23)

However, the formation of alkyl radicals alone does not necessarily imply that they are products of fragmentation of ester RAs via equation 12. In principle, alternative routes are not excluded (see, e.g., equation 21). The special advantage of Massnovi's work is that it proves the decay of RAs and the formation of alkyl radicals occur in one elementary act.

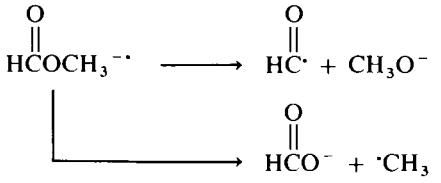
The rate of decay of RAs of $PhCO_2R$ depends on the nature of the alkyl group, R, and generally tends to increase with increasing stability of the free radical formed. The decay of primary alkyl benzoates occurs with $k \sim 5 \times 10^3\ s^{-1}$, higher rates of decay being observed for *t*-butyl and benzyl benzoates ($k \sim 1.9 \times 10^4\ s^{-1}$ and $4.8 \times 10^4\ s^{-1}$) and the highest one for benzhydryl benzoate ($k \sim 5 \times 10^5\ s^{-1}$)[92,93].

A significant effect on the rate of fragmentation of alkyl benzoate RAs is exerted by the medium. According to Massnovi[92,93], when passing from alcohol to hexane solution the rate of fragmentation increases by *ca* one order of magnitude. It is likely that the charge is localized to a larger extent in the initial state than in the transition state of the reaction. For this reason, passing from ethanol to hexane must lead to a stronger destabilization of the initial state than of a transition one and, consequently, to a decrease in the energy barrier of fragmentation[93].

In the light of this concept, data on the rates of fragmentation of alkyl benzoate RAs in MeCN are somewhat surprising. The rates were determined by the various electrochemical methods: cyclic voltammetry, double potential step experiments and rotating disc techniques[17]. The fragmentation rate constants of RAs of ethyl, isopropyl and *t*-butyl benzoates are $1.5 \times 10^{-2}\ s^{-1}$, $1.2 \times 10^{-2}\ s^{-1}$ and $4.3\ s^{-1}$, respectively, i.e., some 4–5 orders of magnitude less than in ethanol. Since aprotic bipolar solvents provide a lesser stabilization of anionoid states than proton-donor media, the fall of the rate constants is rather unexpected. This fact may be explained by the capability of alkyl benzoate RAs forming ion pairs with tetraalkylammonium cations whose salts are used as supporting electrolytes. To verify this supposition, special investigations are needed.

No fully satisfactory experimental evidence for the RA fragmentation producing an aroyl radical and an alkoxy anion (equation 11) has yet been obtained. It is quite possible that this route of fragmentation of the RA of esters does not take place at all. According to quantum-chemical calculations[96] and simple thermodynamic estimates, this route is less favorable than that via reaction 12. For instance, *ab initio* quantum-chemical calculations on STO-3G and STO-4-31G basis for the RA of, e.g., methyl formate[96] show

that the fragmentation via reaction 24 is energetically less favorable [62.9 kcal mol^{-1} (STO-3G) and 75.6 kcal mol^{-1} (STO-4-31G)] than that via reaction 25. The same



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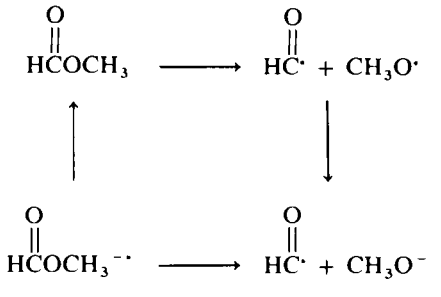
(25)

conclusion can be reached from empirical estimates taking into account thermodynamic cycles 26 and 27. Route 25 is energetically more favorable than route 24, due to both lower energy of the HCO_2—CH_3 bond (81.4 kcal mol^{-1} [97]) in comparison with the HCO—OCH_3 bond (92.6 kcal mol^{-1} [97]) and higher electron affinity of the $HCO_2^{\cdot}$ radical ($E^{\circ}_{CH_3CO_2^{\cdot}/CH_3CO_2^-}$ = 2.4 V[98]) in comparison with $CH_3O^{\cdot}$ ($E^{\circ}_{CH_3O^{\cdot}/CH_3O^-}$ = 1.4 V[98])†.



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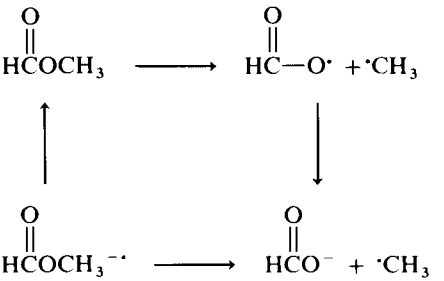


(27)

This conclusion is generally supported by the data on photochemical reduction of acetates of primary[84], secondary[83,84,88] and tertiary[83,84,88] alkyl, as well as allyl[87] and benzyl[86,89,93] alcohols. According to these data the main reaction products are carboxylic acid and the corresponding alkanes.

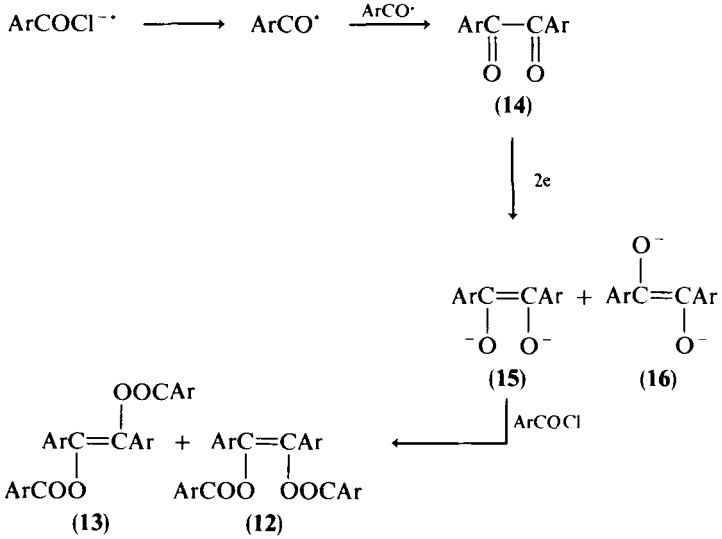
† Data for aqueous solutions. For acetonitrile ($E^{\circ}_{CH_3CO_2^{\cdot}/CH_3CO_2^-}$ = 2.4 V[98]) and ($E^{\circ}_{CH_3O^{\cdot}/CH_3O^-}$ = 1.4 V[98]).

b. Anhydrides and aroyl halides. Radiolysis of benzoic anhydride in hexane at 295 K[93] and benzoyl fluoride and benzoyl chloride in a methyltetrahydrofurane matrix at 77 K[99] gives rise to a species the electron spectrum of which has two intensive absorption bands at 300–325 nm and 450 nm. This species can be attributed to the RA structure because a similar spectrum is characteristic of the RA of benzoic acid[100] and its derivatives such as esters[93] and amides[99].

The case is different for the radiolysis of benzoyl bromide in a methyltetrahydrofurane matrix at 77 K[99]. The electron spectrum indicates the formation of benzoyl radical, probably due to abstraction of Br^- from the RA (equation 28):

$$PhCOBr^{-\cdot} \longrightarrow PhCO^{\cdot} + Br^- \tag{28}$$

Kinetic study of the decay of the benzoic anhydride RA has also proven its transformation to the benzoyl radical[93].

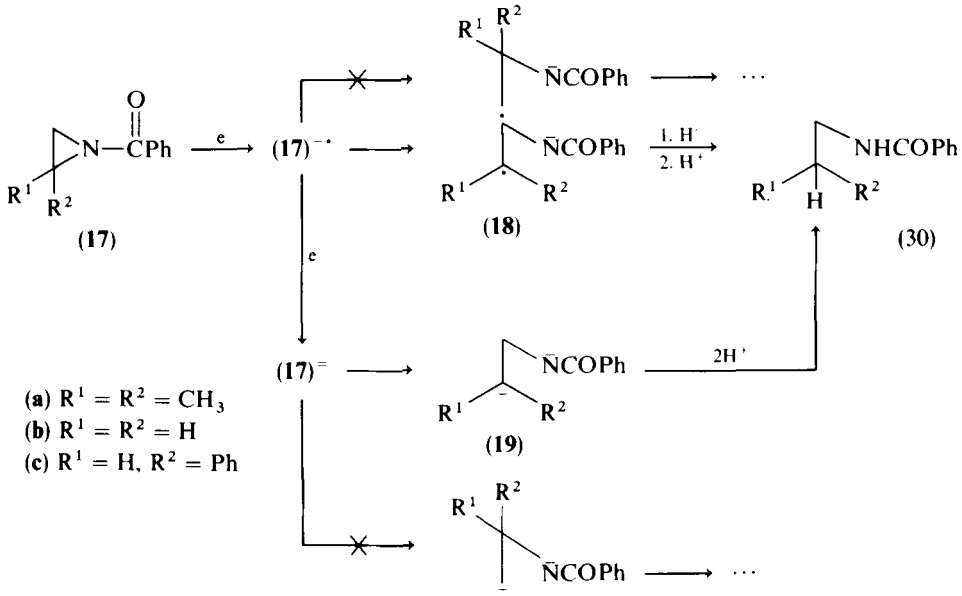


(29)

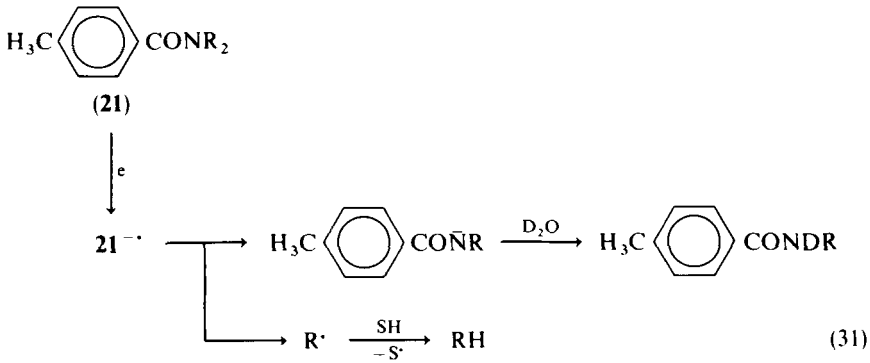
The above facts confirm the mechanism of formation of the products of reduction of aroyl halides, which are esters of *cis* and *trans* enediols (**12** and **13**), postulated in References 20 and 101–105. The key elementary step of this mechanism is that of RAs fragmentation (see equation 29). Dibenzocyclooctatetraene dianion[101], sodium and lithium amalgams[20], mercury cathode[102,103], iron[104] and nickel[105] carbonyls were used as reductants. In some cases benzil (**14**) could be isolated as an intermediate (e.g. when Ar = 2,4,6-$(CH_3)_3C_6H_2$)[20]. However, as a rule, the reaction does not stop at this stage, since benzils have higher affinity for electron than the initial acyl halides (see Table 1). Thus, under the reaction conditions, they are readily reduced to *cis*-**15** or *trans*-**16** enediolates which undergo further acylation to give the final products.

c. N,N-Dialkylcarboxamides. The data suggesting the possibility of fragmentation of RAs of *N,N*-dialkylcarboxamides have appeared only in recent years[106,107]. As reported in Reference 106, the reduction of *N*-benzoylaziridines (**17**) leads to the rupture of the C—N bond of the aziridine ring. Note that it is predominantly the N—CR^1R^2 bond that is broken upon substitution of hydrogen atoms at one of the carbon atoms of the

aziridine fragment by R^1 and R^2 (equation 30). The assumption that RAs are the key intermediates provides a satisfactory explanation of the fact that in the RA those C—N bonds are affected whose rupture gives a more stable alkyl radical (**18**). The same phenomenon is also typical for RAs of alkylbenzoates (see Section IV.A.1.a). An alternative mechanism that involves fragmentation of a dianion of a starting compound as a key elementary stage is less probable, because then it is necessary to assume for compound **17a** that of the two possible fragmentation routes the one that leads to a less stable carbanion **19** is accomplished. However, other mechanisms cannot be ruled out either (for more details see Section IV.A.1.a).



The results obtained in Reference 107 are also in agreement with the supposition that alkyl radicals are formed upon reduction of *N,N*-dialkylcarboxamides. Under the action



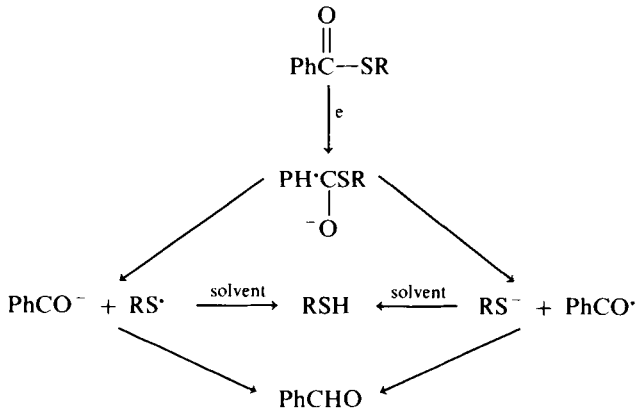
(**a**) R = cyclohexyl; (**b**) R = isopropyl; (**c**) R = benzyl

of alkaline metals on *N,N*-disubstituted benz- (**20**) and toluamides (**21**) the starting compounds are partly dealkylated in THF via the route in equation 31.

For compound **21c** the treatment of the reaction mixture with D_2O produced *N*-benzyltoluamide-*N*-d_1 and unlabelled toluene. The treatment of the reaction mass with CO_2 does not lead to the formation of phenylacetic acid. Based on these facts, the authors of Reference 107 ruled out the possibility of benzyl anion formation and suggested that toluene resulted from abstraction of a hydrogen atom of the solvent by benzyl radical.

All the evidence for the possibility of the C—N bond rupture in RAs of *N,N*-dialkylcarboxamides is indirect and, of course, further work is in order to settle this question.

d. Esters of aromatic thiocarboxylic acids. The existent literature does not provide any reliable data on fragmentation of RAs of esters of thiocarboxylic acids. According to cyclovoltammetry studies[21] a one-electron reduction of esters of thiobenzoic acid PhCOSR (R = Ph, 4-ClC_6H_4, $PhCH_2$, *t*-Bu, Me) in DMF is accompanied by either fragmentation or dimerization of the RAs formed. However, available experimental results are not sufficient to make a choice between the two options. If the fragmentation,



(32)

indeed, takes place, its main route must be the rupture of the PhCO—SR bond, as can be judged from the structure of the main electrolysis product—diphenylacetylene. Using the same assumption the authors of Reference 22 suggest the scheme in equation 32 for the formation of thiols, benzaldehyde and 1,2-diphenylethyleneglycol resulting from the electrolysis of phenyl and benzyl esters of thiobenzoic acid in absolute methanol.

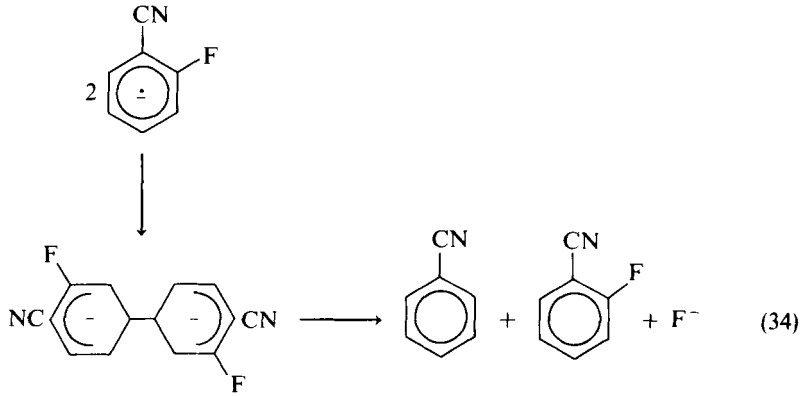
2. Chemical bond rupture in aromatic fragments

The reduction of halogen-substituted carboxylic acids and their derivatives often leads to dehalogenation of the starting compounds[9,11,21,23–26,36,39,48,57,67,108–110]. It has been demonstrated in numerous studies that the rupture of the C_{Ar}—Hlg bond takes place directly in the RA[57,67,108–110]:

$$ArHlg \xrightarrow{e} ArHlg^{-\cdot} \xrightarrow{k_f} Ar + Hlg^- \qquad (33)$$

However, for elimination of slightly mobile groups (X = OR,F) some researchers assumed an alternative fragmentation mechanism that involved dimerization of RAs as

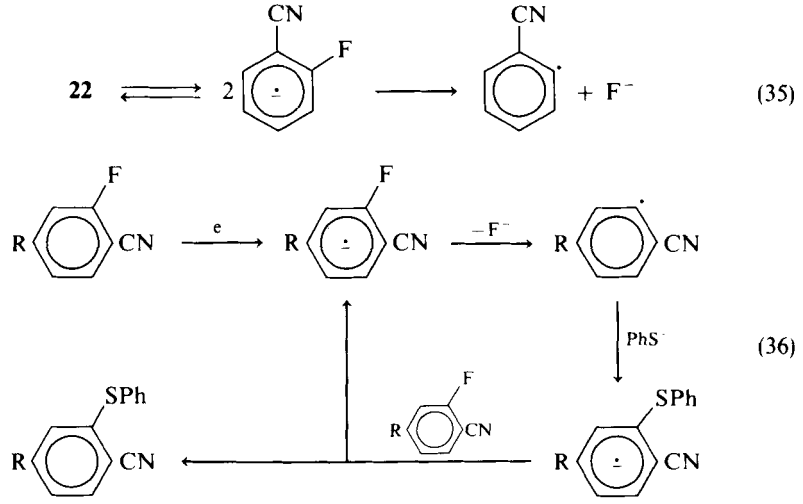
a first step followed by elimination of a group from the dimeric dianion formed[25,38]. In particular, such a mechanism (equation 34) was suggested for the reductive defluorination of *o*-fluorobenzonitrile[25]. However, the data used to support the validity of this mechanism[25] is not in conflict with equation 35. According to this scheme the dimerization is a side equilibrium, while the formation of the fragmentation product, benzonitrile, results from elimination of a fluorine anion from the RA.



(22) (34)

It has been demonstrated that the RA of fluoro-4-methylbenzonitrile, which cannot undergo dimerization, as follows from cyclic voltammetry experiments, can remove a fluorine anion quite easily giving eventually *p*-tolunitrile. In addition, upon electrochemical reduction of 2-fluorobenzonitrile and 2-fluoro-*p*-tolunitrile in the presence of thiophenolate ion a reaction of the $S_{RN}1$ type (equation 36) is initiated. This reaction leads to the substitution of a thiophenyl group for a fluorine atom, which is in agreement with the formation of aryl radicals under the reaction conditions[111].

In our opinion the above facts provide a sufficient basis for giving preference for the scheme in equation 35.



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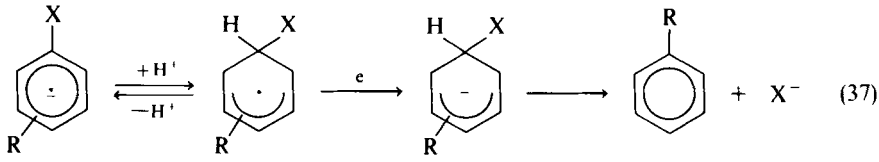
(36)

For the fragmentation of RAs in proton-donor media it is necessary to consider the mechanism that involves the protonation of RA via the *ipso* position relative to the leading group, the reduction of the radical adduct formed to the anionic σ complex and subsequent removal of the group in the form of an anion[14]; see equation 37. The possibility of the occurrence of this mechanism is confirmed by the formation of cyclohexadienyl radicals containing a halogen atom in the geminal node identified by ESR during reduction of halobenzenes and their derivatives in alcohol matrices[112]. However, this mechanism can be ruled out taking into account the fact that for RAs of halobenzoate ions (Hlg = *o*-, *m*-, *p*-F,Cl,Br) the rate of fragmentation is independent of the pH of the aqueous solution within the range 4–12[110].



(37)

Thus, the data concerning the influence of various factors on the rate of RA fragmentation will be considered below, assuming that the reaction follows the mechanism in equation 33.

An analysis of the available literature data shows that the introduction of a carboxylate or cyano group into the RA of chlorobenzene decreases its fragmentation rate constant by 3–5 orders of magnitude depending on the mutual location of the chlorine and the added functional group. In this instance the stabilizing effect of the cyano group is somewhat higher than that of the carboxylate group (see Table 3). The rate of elimination of the halogen anion from the *ortho* and *para* positions of RAs of halogen derivatives of benzonitrile or benzoate ion is much higher than from the *meta* position. Finally, at a fixed position of the halogen relative to a CO_2^- or CN group the rate of fragmentation of the corresponding RAs changes in the order: Br > Cl > F (see Table 3). These facts make it possible to explain using the approach developed in References 36, 39, and 114–119.

The elimination of the halogen anion from π RAs through a planar activated complex is symmetry forbidden, because the initial state has a π symmetry ($\pi^7\ \sigma^2$) and the final

TABLE 3. Rate constants of C—Hlg bond cleavage in aromatic RA[25,108a,b,109,110,113]

Compound	Solvent	Hlg		
		F	Cl	Br
C_6H_5Hlg	EtOH	—	1.8×10^9 [a]	
4-$HlhC_6H_4CN$	CH_3CN	11[b]	1.5×10^8	$>10^{10}$
	H_2O	6.5×10^5	5×10^6	$>3 \times 10^7$
2-$HlgC_6H_4CO_2$	H_2O	1×10^4	8×10^7	5.5×10^8
3-$HlgC_6H_4CO_2$	H_2O	$>3 \times 10^3$	1.2×10^6	4.0×10^7
4-$HlgC_6H_4CO_2$	H_2O	3.3×10^5	5×10^7	3.0×10^8
	H_2O	6.0×10^5	4×10^7	
4-$HlgC_6F_4CO_2$ [c]	H_2O	$>10_9$	$>10_9$	

[a] Similar rate constants were obtained for other solvents: DMF, MeCN, EtCN, MeOH, PrOH.
[b] In DMF.
[c] V. V. Kanovalov, A. M. Raitsimring, Yu. D. Tsvetkov, S. S. Laev, I. I. Bilkis and V. D. Shteingarts, submitted for publication.

state has a σ symmetry $(\pi^6\sigma^3)$[114]. It is plausible to suggest that a transition complex has a nonplanar structure with a halogen atom being removed from the plane of the aromatic ring, which provides mixing of the ground π and dissociative σ^* states of RAs. As follows from the quantum-chemical study of the potential energy surface of the fragmentation reactions, the energy of the system in a transition state depends upon (i) initial splitting of the terms π and σ^* $(\Delta E_{\pi\sigma^*})$[36,39,115–118], (ii) their curvature[118,119] and (iii) stabilization energy of the system in the point of intersection of π and σ^* terms due to an out-of-plane deformation (Q) of the RA ($\Delta E_{st} \cong \langle\pi|\partial\hat{H}/\partial Q|\sigma^*\rangle$)[118].

In line with the above speculations, a decrease in k_f by several orders of magnitude when passing from bromine to chlorine and further to fluor-containing RAs reflects enhancement of both the curvature of the terms (which changes proportionally with the C—Hlg bond energy[120] and the initial energy splitting $\Delta E_{\pi\sigma^*}$[36,119], and consequently the expected activation energy. Note, however, that the governing factor seems to be the change of $\Delta E_{\pi\sigma^*}$. This supposition follows from a comparison of the rates of fragmentation of RAs of monohalobenzoates and their polyfluorinated analogs (see Table 3). The substitution of hydrogen by fluorine leads to an increase in the force constant of stretching vibrations of the C—F bond (the curvature of the terms) and its energy† (which must provide enhancement of the activation energy of the fragmentation reaction), on the one hand, and to a decrease in the initial splitting of the π and σ^* terms[118,124,125] (which must provide a decrease in the activation barrier), on the other. Since the introduction of the fluorine atoms into the RA enhances the rate of its fragmentation, obviously the determining factor is the change of $\Delta E_{\pi\sigma^*}$.

For a given halogen (Hlg = Cl) the introduction of a π-electron-acceptor substituent (e.g. R = CN or CO_2) to C_6H_5Hlg provides a stronger stabilization of the π than the σ^* state[36]. As a result, $\Delta E_{\pi\sigma^*}$ and thus the activation energy of fragmentation tend to increase. The fact that the rate of the fragmentation for RAs of halobenzonitriles is slower than rate for RAs of halobenzoate anions reflects a relative capability of CN and CO_2^- groups stabilizing the ground state (see section III).

The rate constant ratio for RAs of *o*, *m* and *p* derivatives of the benzoate ion is a qualitative indication of the change of the matrix element $\langle\pi|(\partial H/\partial Q)_{Q=0}|\sigma^*\rangle$, whose absolute value increases in the order $m < o < p$ in accord with the change of the corresponding carbon atoms in π^*-SOMO of the RA of the benzoate ion: 0.033 (*meta*) < 0.173 (*ortho*) < 0.318 (*para*). Note, however, that for RAs of chlorobenzoate and bromobenzoate ions the rate of fragmentation of the *o* isomer is higher than that of the *p* isomer. The deviations from the expected correlation can be associated with a partial removal of the CO_2^- group (see, however, Section III) or the chlorine or bromine atoms from the plane of the benzene ring of these RAs due to steric interactions between them[110]. This can further lead to a stronger interaction between the π^* and σ^* states

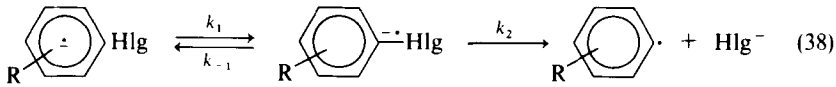
† The increase of the C—Hlg bond strength in RA (D_{C-Hlg}) is due to the increase of the C—Hlg bond energy in the initial arene[121] and its electron affinity (E_{ArX/ArX^-})[48,122,123] upon substitution of fluorine for hydrogen (see the following thermodynamic cycle).

$$\begin{array}{ccc} ArHlg & \xrightarrow{D_{C-Hlg}} & Ar^{\cdot} + Hlg^{\cdot} \\ \uparrow -E_{ArHlg/ArHlg^{-\cdot}} & & \downarrow E_{Hlg^{\cdot}/Hlg^-} \\ ArHlg^{-\cdot} & \xrightarrow{D^{-\cdot}_{C-Hlg}} & Ar^{\cdot} + Hlg^- \end{array}$$

than that anticipated from the values of the unpaired electron density on the *ortho* carbon, and eventually to an increase in k_f.

By inspecting the data in Table 3 one can see that the rate of elimination of the fluorine anion increases when passing from aprotic bipolar solvent to water, while elimination of anions of other halogens is slowed down. Apparently, this is caused by the different degrees of charge localization in the transient states of these reactions and correspondingly the different degrees of their solvation (the difference in solvation of RAs seems insignificant). Transition to a medium with a higher solvation strength must provide stabilization of both initial and transition states. An increase in rate of the fluorine ion elimination with increasing solvation strength of the solvent implies that the transition state is characterized by a greater degree of charge localization and thus undergoes an easier solvation than the initial RA. It is likely that the transition state corresponds to a significant degree of the C—F bond rupture and formation of the fluorine anion. The inhibition of elimination of the chlorine and bromine anions when passing to water solutions is evidence for the occurrence of the opposite events.

The above analysis is based on the assumption that the fragmentation of π RA is a one-step process[36,39,117–119]. Some authors[126,127] believe that the C—Hlg bond rupture is preceded by the transition of the πRA to the σRA (equation 38). The available



π RA σ RA (38)

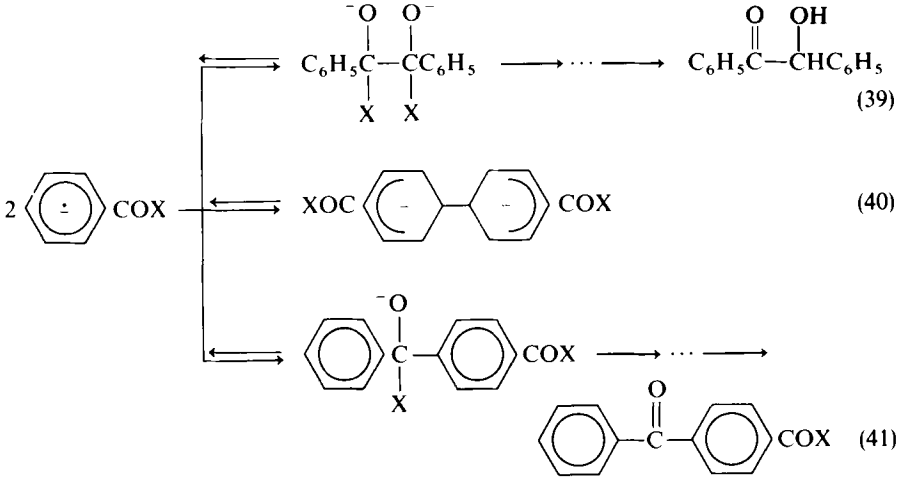
experimental data are not sufficient to draw final conclusions about the reaction mechanism. The difficulty here is that with a rate-determining first step ($k_2 \gg k_{-1}$) the influence of structural factors and medium on the rate of RA fragmentation must be qualitatively the same for one- and two-step mechanisms owing to similar transition states.

As far as the competitive processes of chemical bond rupture in functional groups and aromatic fragments of RAs are concerned, no systematic studies have been carried out so far. The available literature data are as follows. In the course of electrochemical reduction of alkyl esters of *o*- and *m*-chloro- as well as *m*- and *p*-bromobenzoic acids in DMF, the rupture of the C—Hlg bond occurs in the first step[9,11]. It is not excluded, however, that on passing to hydroxyl-containing solvents the situation can change. The reason is that the rate constant for the ester group cleavage increases noticeably (see Section IV.A.1.a), while the rate constant for the halogen ion elimination slightly decreases (see above). RAs of phenyl *o*-chlorothiobenzoate react in the same manner as halogen-substituted alkyl benzoates[21]. However, a different reaction is observed for RAs of 4-bromobenzoyl chloride. From the structure of the reduction products it follows that the C—Hlg bond is broken in the functional group[20].

B. Dimerization of Radical Anions

The dimerization reaction of RAs of aromatic carboxylic acids and their derivatives is due to the radical nature of these species. The density of an unpaired electron in these species is distributed between a functional group ('head') and an aromatic fragment ('tail') (see Section III). Therefore, the formation of dimerization products should correspond to the formation of a chemical bond between functional groups ('head–head' interaction), aromatic fragments ('tail–tail' interaction) and a functional group of one

RA molecule and an aromatic fragment of the other molecule ('head-tail' interaction); see equations 39–41.



(39)

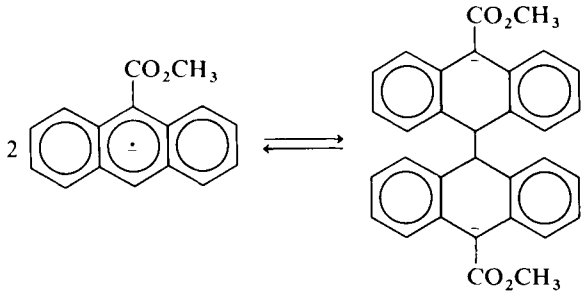
(40)

(41)

(23)

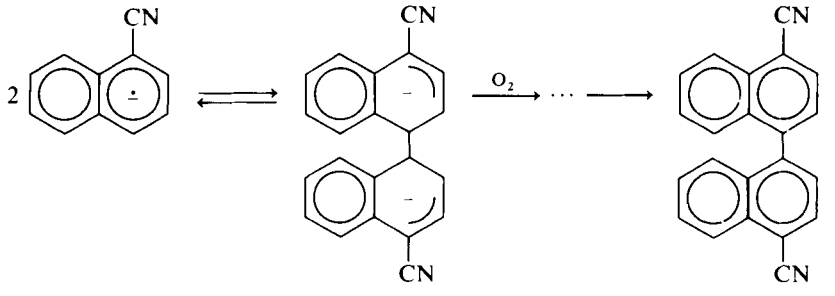
The formation of acyloins by reduction of substituted aromatic carboxylic acids (X = OH)[90,128], their esters (X = OR)[90,91,93,94,129,130] and *N*,*N*-dialkylamides (X = NR_2)[107] suggests that the dimerization can occur via a 'head–head' interaction. Note, however, that alternative mechanisms of the above transformations have also been proposed (see Section IV.A.1.a, equation 20). The same concerns also Reference 107 where the reduction of *N*,*N*-dialkylbenzamides with lithium in THF was reported to yield, along with benzoin, also the amide (**23**, X = NR_2), corresponding to RA dimerization of 'head–tail' type.

Evidence for the 'tail–tail' dimerization of RAs of derivatives of aromatic carboxylic acids has been obtained recently mainly for RAs of aromatic nitriles[25,26,28,30–32,35,37,38,40,42–44,48,49,131–133] and esters[15,16,135,136]. The dimeric dianion (**24**; equation 42) resulting from electrochemical reduction of methyl anthroate was quite convincingly identified by NMR[15]. The products of protonation of the dianion **24** were also isolated[135,134]. The products corresponding to protonation, oxidation or alkylation of dimeric dianions resulting from reduction of 1-naphthonitrile and 9-cyanoanthracene have been characterized[131–133] (equations 43 and 44; (see also Section IV.C).



(42)

(24)



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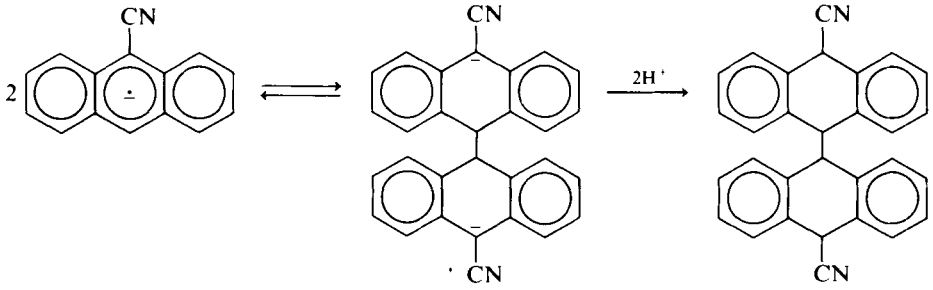
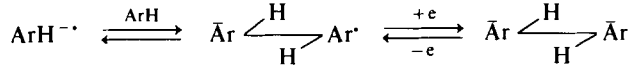
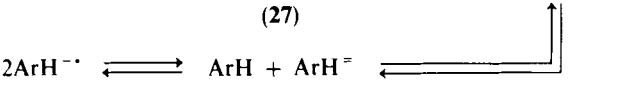


(26) (44)

The mechanisms of formation of dimeric dianions of type **24–26** have been discussed in many studies[30–32,37,136]. Usually three schemes are considered. The first involves a direct recombination of RAs, and the second the interaction of the RA with a molecule of the initial neutral compound yielding a radical anion adduct (**27**), which is further reduced to a dimeric dianion (equation 45). The third scheme consists of disproportionation of the RAs leading to the initial compound and its dianion, whose subsequent interaction gives a dimeric dianion (equation 46). Evidence reported in favor of the first mechanism[30–32,37,136] seems the most convincing.



(27) (45)



(46)

The formation of dimeric dianions is observed when a reduced aromatic compound contains at least one electron-acceptor group, which seems to be due to a larger effect of the substituents on stability of the dimeric dianion than of the corresponding RA. A noticeable effect on the equilibrium point of dimerization is observed upon substitution of a fluorine[25,26,42,48], methoxy[38] or phenoxy[40] group for hydrogen. The data of References 25,26, 42, and 48 suggest that the introduction of a fluorine atom to an *ortho* position relative to a benzonitrile cyano group favors the retaining of the RA dimerization capability. However, the introduction of a fluorine atom into a *meta* position does not yield a dimeric dianion. A similar picture is observed for methoxy and phenoxy derivatives of benzonitrile. These observations may be explained by the fact that the

charged positions in the RA of benzonitrile and dimeric dianion do not coincide, while the above-indicated substituents can stabilize anionoid species from only the non-resonance positions. For *ortho* derivatives, destabilization of the RA and stabilization of the dimeric dianion take place, while for *meta* derivatives the opposite situation prevails.

The RA dimerization rate constant (k_d) depends on many factors. An attempt has been made[137,138] to describe the influence of the RA structure on the RA dimerization rate within the theory of MO perturbations. As follows from these studies, both the density of an unpaired electron and the charge density on chemically bound atoms play an important role in the process. The quantum-chemical calculation of these values is necessary for the quantitative evaluation of the rate constants. The empirical studies have shown that the dimerization rate slightly increases with increasing electron-acceptor properties of the substituent[30,31]. The same correlation seems to occur when passing from benzene and naphthalene derivatives to those of anthracene[32,43].

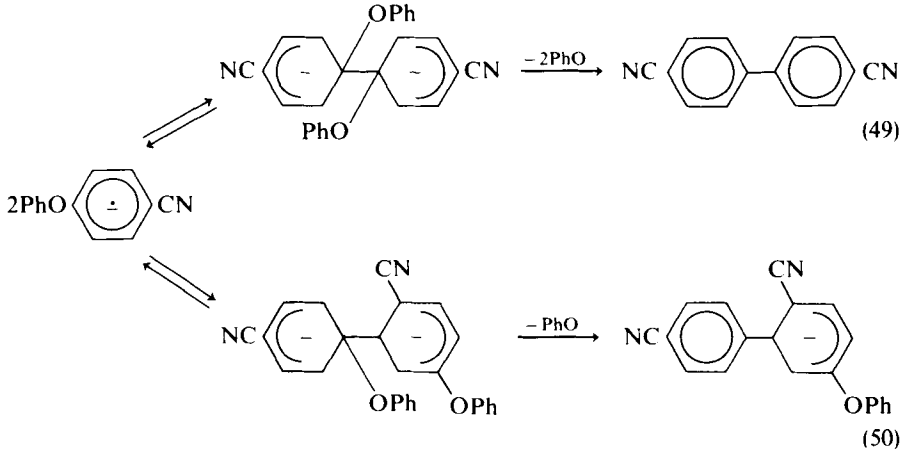
The substitution of a fluorine atom[25,26], a methoxy[38] or phenoxy[40] or methyl group[111] for a hydrogen atom in the intimate vicinity of the reaction site appreciably suppresses the rate of the dimerization process. For example, k_d of the RA of 9-cyano-10-fluoroanthracene is *ca* one order lower than that of the RA of a nonfluorinated analog[139], which may be due to the enhanced steric hindrance for the C—C bond formation.

The RA dimerization rate depends on the content of water in the system in case the reduction is performed in aprotic bipolar solvents[30–32,37,136]. In this instance the dimer is assumed to result from the interaction between the RA and its complex with a water molecule[30–32,37,136] (equations 47 and 48).

$$ArH^{-\cdot} + H_2O \rightleftharpoons (ArH^{-\cdot}, H_2O) \tag{47}$$

$$ArH^{-\cdot} + (ArH^{-\cdot}, H_2O) \rightleftharpoons ([Ar \overset{H}{\underset{H}{\leftrightarrow}} Ar]^{2-}, H_2O) \tag{48}$$

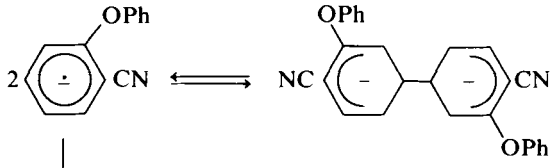
Using an electrochemical reduction of 2- and 4-phenoxybenzonitriles as an example, the possibility has been demonstrated[38,40] of the formation of the 'tail–tail' dimeric dianions corresponding to the formation of a new bond not only between 4- and 4-, but also between 2- and 4- and 6- and 4-carbon atoms (equations 49–53). In the presence



(49)

(50)

of nucleophilic mobile groups (OPh,OCH_3,F) in the geminal node of the dimeric dianion this dimerization route becomes irreversible, because of elimination of a nucleofuge[25,26,38,40,48,139] (equations 49, 50 and 52). As a rule, the main products of reductive dimerization are formed by this latter route.



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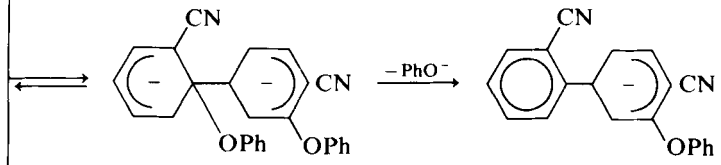

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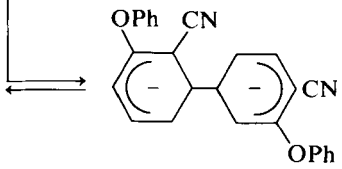


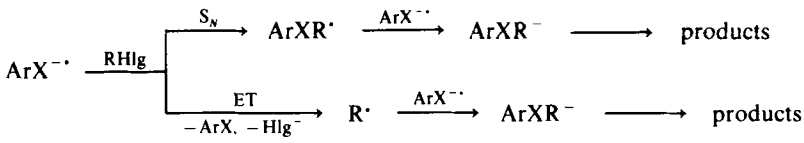
(53)

Taking into account the fragmentation (Section IV.A) and dimerization capabilities, a question arises as to the interrelation of these processes and the possibility of controlling them. In those situations where the dimerization occurs via positions precluding the possibility of a fast transformation of dimeric dianions into reaction products, the main direction of the reaction is that of irreversible fragmentation.

When RAs are dimerized via carbon atoms carrying a nucleophilic mobile group, a dimeric dianion of any type, 'head–head', 'tail–tail' or 'head–tail', undergoes an easy irreversible transformation to the reaction product by eliminating the nucleofuge. In this case the dimerization-to-fragmentation product ratio is controlled by the rate ratio of both reaction routes. Since the dimerization rate is of second order with respect to RA concentration and the fragmentation rate is of first order, a decrease in concentration favors a relative increase in fragmentation rate and proportion of the corresponding products (see, e.g., References 25, 26, 48 and 136). The variation of the solvation capability of the medium opens up another possibility. For instance, one can anticipate an increase in proportion of the fragmentation products when water is added to aprotic bipolar solvents traditionally used for electrochemical reduction of *p*-fluorobenzonitrile. As has been mentioned in Section IV.A.2, when passing from DMF to H_2O the rate of elimination of a fluorine atom increases by several orders of magnitude, while the rate of dimerization must change to a lesser degree, as suggested by data elsewhere[32,37].

C. Radical Anions as Nucleophiles

RAs of many aromatic compounds, including derivatives of aromatic carboxylic acids, can easily be alkylated by alkyl halides[1]. These reactions occur usually with a high rate, which is not necessarily the consequence of the RA high nucleophility. The alkylation products can be formed by either of the two routes—S_N and electron transfer (ET); see Scheme 1. In the former case the formation of a chemical bond between an aromatic

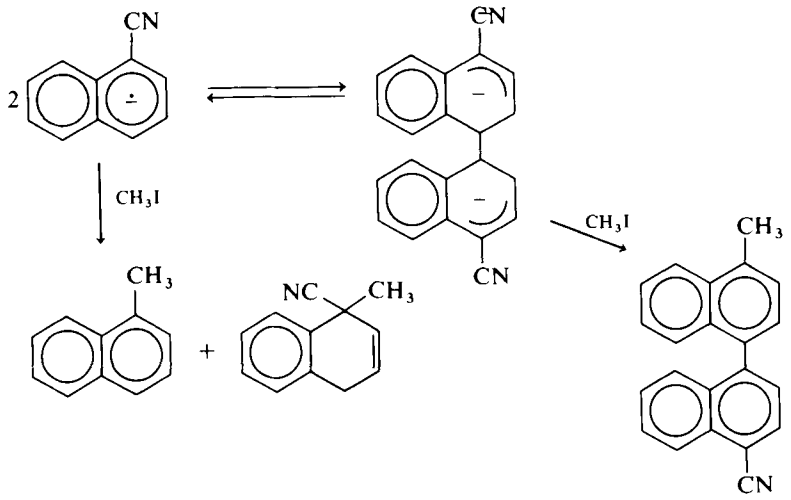


SCHEME 1

compound and an alkyl fragment results directly from the interaction of the RA with an alkylating agent. In the latter case part of a radical anion salt is consumed for the reduction of the alkylating agent. The transformation of arene into reaction products is due to the secondary radical recombination, i.e. it is a consequence of the RA free radical properties. Thus the characterization of nucleophilic reactivity of RAs in reactions with electrophiles and of the effect of various factors on the resulting products is possible, provided that reliable data on the mechanism of each particular process are available. Unfortunately, investigations conducted on the level sufficient for such a characterization are not numerous. The available literature data on reactivity of RAs of aromatic hydrocarbons, ketones and nitro compounds have been discussed at length[1]. Mechanistic studies of the interaction of RAs of derivatives of aromatic carboxylic acids with alkyl halides, performed recently for RAs of cyanoarenes[132,133,140–142], have not been reviewed in Reference 1 and will be dealt with here comprehensively.

The investigation of reactivity of RAs of aromatic nitriles is complicated by their equilibrium with dimeric dianions, the equilibrium being strongly shifted towards these latter (see Section IV.B). For example, the action of methyl iodine on an equilibrium mixture of the RA of naphthonitrile with its dimeric dianion leads to the formation of the methylation product of the dimeric dianion together with RA methylation products (equation 54)[132].

Note, however, that the presence of traces of ammonia in THF results in dramatic changes in product composition: in this medium the yield of the alkylated dimer (**28**) does not exceed 1%[140]. If the reaction is carried out in liquid ammonia, no detectable amounts of dimeric species are formed[140]. In other words, even though the RA of 1-naphthonitrile is dimerized to a large extent in liquid ammonia[43], the only reactive

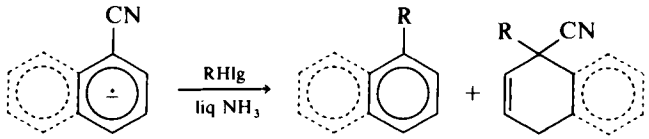


(54)

(**28**)

reduced state of 1-naphthonitrile is the RA. Possible reasons for such a ratio of reactivities of RAs and dimeric dianions may be different types of ionic association of these species and specific features of the spatial structure of the dimeric dianion. However, the whole picture still remains unclear.

The interaction of the RA of benzonitrile and 1-naphthonitrile with alkyl halides in liquid ammonia yields alkylarenes and 1-alkyl-1-cyano-1,4-dihydroarenes, whose ratio depends upon the nature of the halogen and increases when proceeding from iodine to chlorine derivatives. The proportion of dihydroarene can be decreased by carrying out the reaction in the presence of a strong base or by decreasing the amount of the alkylating agent[140,141]; see equation 55. The RA of 9-cyanoanthracene reacts with alkyl halides in



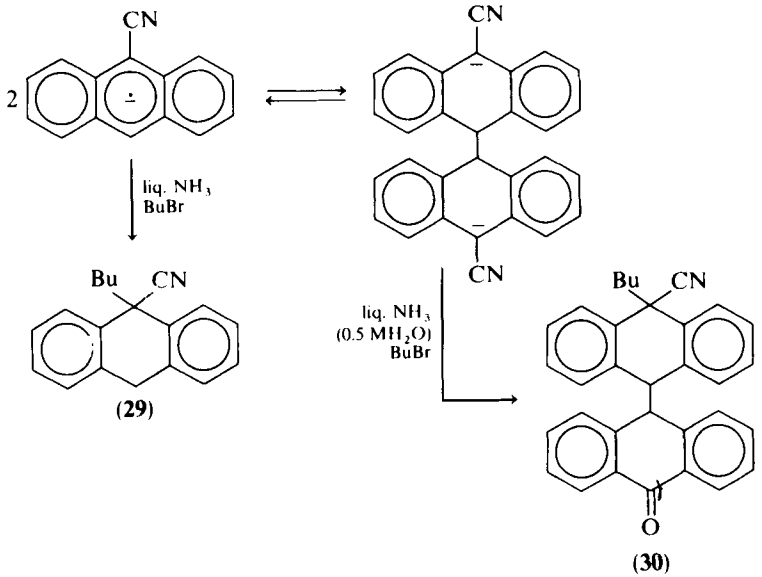
(55)

Yields 54–96% 0–18%

R = CH_3, n-C_4H_9, n-C_8H_{17}

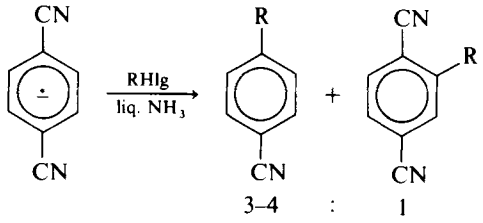
Hlg = I, Br, Cl

liquid ammonia producing only 9-alkyl-9-cyano-9,10-dihydroanthracene (**29**)[133]. This latter can easily be converted to 9-alkylanthracene under the action of a strong base. The interaction of the products of one-electron reduction of 9-cyanoanthracene with alkyl halides is affected by the presence of proton-donor components. For example, the interaction with butyl bromide in the presence of 0.5M H_2O (equation 56) gives 10-(9′-cyano-9′-butyl-10′-dihydroanthracenyl)-anthrone (**30**). Nitrile (**29**), corresponding to the RA alkylation, is not formed in these conditions. Such a change in the direction of the reaction can be caused by an increase in the degree of dimerization of the RA under the influence of water (see Section IV.B). Neither can the change in the relative



(29) (30)

(56)

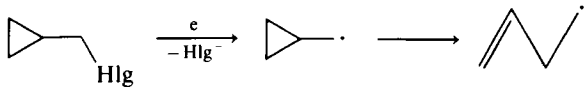


(57)

R = n-Bu, n-Oct; Hlg = I, Br.

reactivity of the anionoid species due to complexation with water be excluded. The interaction of alkyl halides with RAs of terephthalodinitrile yields a mixture of 4-cyanoalkylbenzene and 2-alkyl-1,4-dicyanobenzene[142]; see equation 57.

To elucidate the reaction mechanism, two types of model electrophiles were applied[132,133,140–142]. The common feature of these electrophiles is that, depending on the reaction route, they exist as different structural fragments in reaction products. Cyclopropylmethyl halides belong to the first type of model electrophiles[1,143]. When the ET mechanism operates, they give a cyclopropylmethyl radical which is readily isomerized to a 3-butenyl radical (at $-33°C$, $k_i = 5 \times 10^6\ s^{-1}$, as calculated from data of Reference 144; equation 58). This reaction, in turn, can lead to products containing an isomerized alkyl fragment, except for situations where the rate of interaction of the alkyl radical with the RA significantly exceeds the rate of its isomerization.

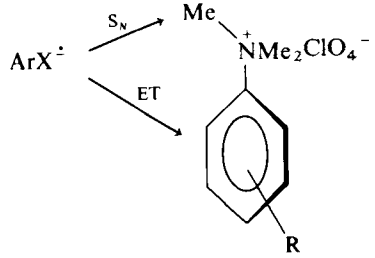


(58)

The second type of model electrophiles includes aryl-*N*,*N*,*N*-trimethylammonium salts. In these salts the N—Me bonds are broken when the reaction follows the S_N mechanism and the N—Ar bonds are broken upon interaction of the ammonium salt with a one-electron reductant[1,145–147]. Consequently, depending on the reaction mechanism, methylation or arylation products of the $ArX^{\cdot-}$ must be formed (Scheme 2).

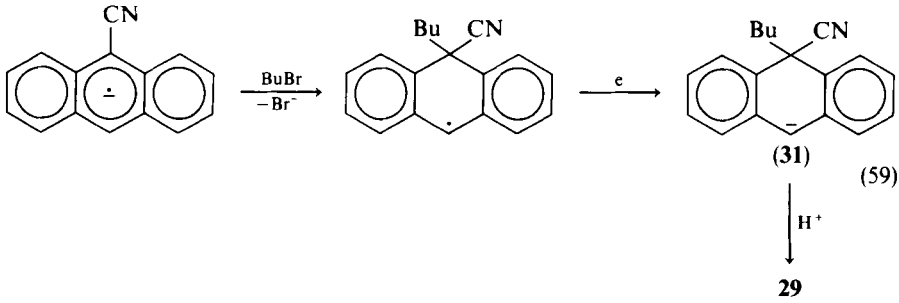
A mechanistic study has shown that RAs of benzonitrile, 1-naphthonitrile and 9-cyanoanthracene react with cyclopropylmethyl bromide and may be with other alkyl halides by the S_N2 route. In the two former cases the main products are cyclopropylmethylarenes and in the latter case 9-cyano-9-cyclopropylmethyl-9,10-dihydroanthracene. The corresponding products with the 3-butenyl fragment were not detected, although under reaction conditions favoring the ET mechanism the fraction of these products should be not less than 30%[133,141].

Different from the above indicated RAs, that of terephthalodinitrile reacts with cyclopropyl bromide by the ET mechanism[142]. The reactivity of this RA will be discussed in more detail in Section IV.E.



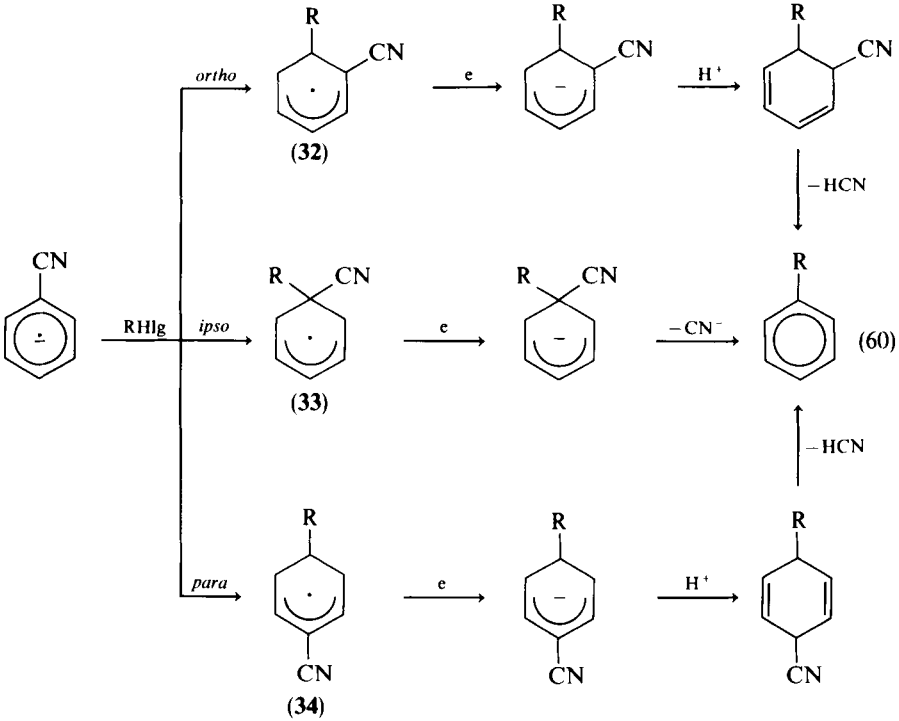
SCHEME 2

The interaction of RAs of 1-naphthonitrile with *p*-methoxyphenyl-*N*,*N*,*N*-trimethylammonium perchlorate in THF, containing ammonia in trace amounts, yields a mixture of basically two compounds: methylnaphthalene and *N*,*N*-dimethylanisidine. This fact is evidence for the electrophilic alklylation of the starting RA. When *m*-methoxyphenyl-*N*,*N*,*N*-trimethylammonium perchlorate having higher electron affinity than the *para* analog is involved in reaction with the RA of 1-naphthonitrile, the reaction mixture contains, along with methylnaphthalene and *m*-*N*,*N*-dimethylanisidine, considerable amounts of anisol, which indicates that both S_N and ET reaction routes are operative[140]. The contribution of the ET route increases when passing from the *p*-methoxy- to the *m*-methoxyphenyltrimethylammonium salt. This observation is in agreement with the conclusion made in References 1 and 146, namely that the rate of this route has a higher sensitivity to the electrophile structure than the S_N rate.

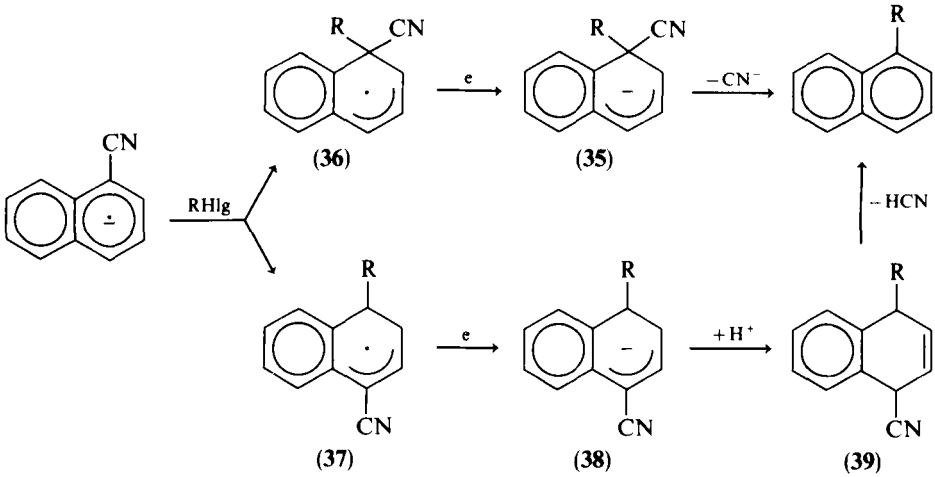


(59)

Consider now the problem of regioselectivity of alkylation of RAs of cyanoarenes. Evidently, for RAs of 9-cyanoanthracene *ipso* alkylation takes place (equation 59). For



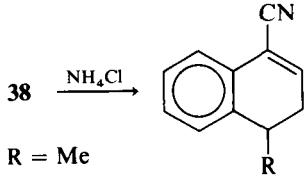
(60)



(61)

RAs of benzonitrile and 1-naphthonitrile the situation is not so unambiguous. For example, the formation of alkylbenzenes can be accounted for by the emergence of an alkyl residue in the *ipso*, *ortho* or *para* positions relative to the cyano group of benzonitrile RAs (equation 60). Several routes of alkylnaphthalene formation can be suggested (equation 61).

A study of the interaction of the RA of 4-deuterobenzonitrile with octyl bromide has shown that the octylbenzene formed has 96% of the deuterium label in the *para* position. Thus one can conclude that the RA of benzonitrile, like that of 9-cyanoanthracene, is alkylated in the *ipso* position. The same is true for the RA of 1-naphthonitrile, as follows from the data on insertion of the deuterium label into alkylnaphthalene. Additional support comes from the fact that the protonation of the anionic σ complex **38** (equation 62) gives the isomeric 1-cyano-4-methyl-3,4-dihydronaphthalene, which does not undergo dehydrocyanation[140], rather than the expected dihydroarene (**39**), as obtained in equation 61.



(62)

If regioselectivity of the above reactions is determined by the first step (see the schemes in equations 60 and 61), which is characterized by an early transition state, the orientation of addition of an alkyl group can be associated with the special features of the electronic structure of the starting RA. For the late transition state the determining factor must be the relative stability of isomeric free radicals **32**–**34** (equation 60) and **36** and **37** (equation 61). Based on the available literature data, it is possible to make the necessary analysis for only the reaction in equation 60. The relative energies of cyclohexadienyl radicals **32**–**34** (R = H) reported elsewhere[148] are 1.74, 9.94 and 0 kcal mol^{-1}, respectively, and do not explain the regioselectivity observed in experiment. Meanwhile, the distribution of the π-electron charge in the RA of benzonitrile is such that *ipso*

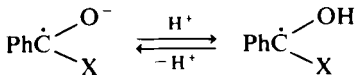
alkylation is the most preferential of all ($\rho_{C_1} = 1.326$, $\rho_{C_2} = 1.060$, $\rho_{C_3} = 1.072$, $\rho_{C_4} = 1.250$)[50]. This direction of the reaction fits also the fact that the deepest minimum of the molecular electrostatic potential in the RA of benzonitrile is near an *ipso*-carbon atom[50]. All data taken together suggest an early transition state of the S_N route of interactions of RAs of benzonitrile and, most probably, of 1-naphthonitrile and 9-cyananthracene with alkyl halides.

In concluding this section we note that the substitution of an alkyl fragment for a cyano group in RAs of cyanoarenes found in References 132, 133, 140 and 141 is actually a new approach to the synthesis of alkyl arenes. For example, the yield of octylbenzene is 96% in reaction of RAs of benzonitrile with octyl bromide, which is much higher than the yields obtained by the traditional Wurz–Fittig method and its modifications (65–80%)[149,150].

D. Radical Anions as Bases

We have demonstrated in Section IV.C that the transformation of aromatic nitriles of carboxylic acids to the radical anion state significantly enhances nucleophility of the starting compound. As a result, reactions with weak electrophiles such as alkyl halides and aryltrimethylammonium salts become possible and occur with noticeable rates. A similar activation effect on basic properties of aromatic compounds (including basicity increases by many orders of magnitude, see Table 4) is exerted by one-electron reduction. The sensitivity of the pK_a values to the nature of substituents markedly increases. When passing from substituted benzoic acids to their RAs the value of ρ in the Hammett equation ($\rho K_a^R - \rho K_a^H = \rho\sigma$) increases from 1 to nearly 10.

According to Neta[153] the RAs of benzoic acid derivatives of general formula PhCOX are protonated via an oxygen atom in aqueous solutions (equation 63). However, it has



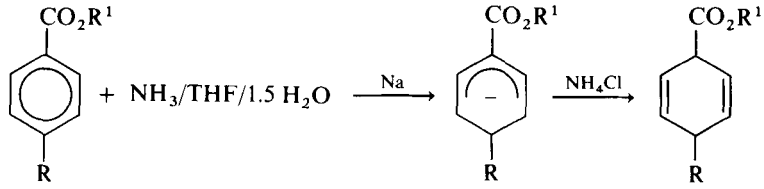
$$X = O^-,\ OCH_3,\ NH_2 \qquad (63)$$

TABLE 4. Influence of one-electron reduction on the basicity of derivatives of benzoic acid

Compound	pK_a		
	AH^{+a}	$AH^{\cdot b}$	ΔpK_a
C_6H_5CN	−10.4	7.3	17.7
$C_6H_5CO_2CH_3$	−7.8	5.5	13.3
$C_6H_5CONH_2$	−1.9	7.7	9.6
$C_6H_5CO_2$	4.2	12.0	7.8
$4\text{-}O_2CC_6H_4CO_2$	4.82	9.3	4.48
$4\text{-}HO_2CC_6H_4CO_2$	3.51	7.2	3.69
$4\text{-}O_2NC_6H_4CO_2$	3.42	3–4	~0–1

[a] Date from References 151 and 152.
[b] Data from References 77, 81, 153 and 154.

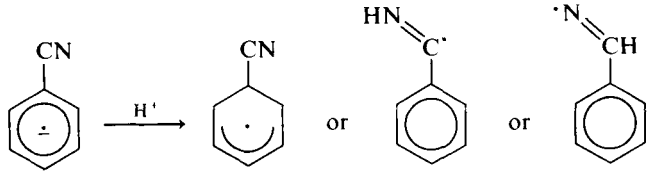
been shown recently that reduction of an aromatic fragment takes place when esters of aromatic carboxylic acids are reduced in liquid ammonia containing H_2O in small amounts. It is supposed[135] that in these conditions the RAs are protonated via the aromatic fragment (see, e.g., equation 64). Numerous studies deal with regioselectivity



(64)

R = H, Me; R^1 = Et, *t*-Bu

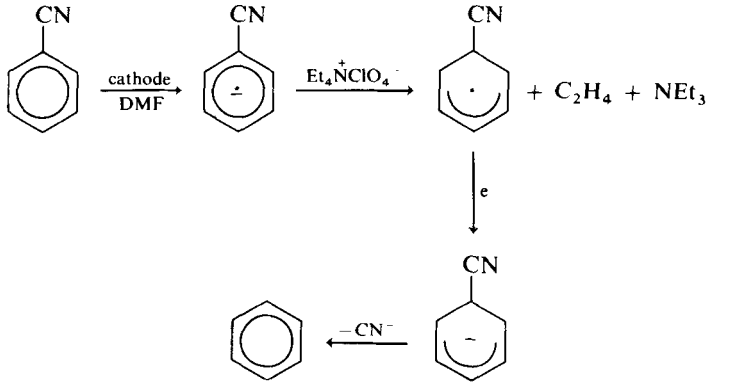
of protonation of RAs of aromatic nitriles[29,40,108a,132,140,154–159]. A pulse radiolysis study of the protonation of RAs of benzonitrile in aqueous solutions suggests that the free radical formed corresponds to proton addition via the *ipso* position or one of the atoms of the cyano group (equation 65). However, the authors have not succeeded in



(65)

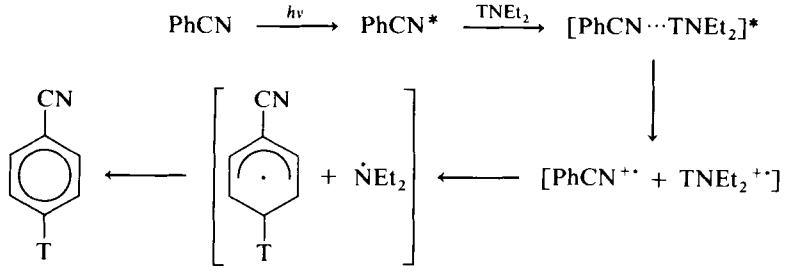
making a choice between the possible paths[108a,154]. The protonation via *ortho*-, *para*- or *meta*-carbon atoms has been ruled out because the electron spectrum of the protonation product is different from those of cyclohexadienyl radicals, which are the products of hydrogen atom addition via the *ortho*, *para* or *meta* position of benzonitrile[108a,154].

A characteristic feature of the interaction of the RAs of benzonitrile with protonating agents in aprotic media is that the reaction center is the benzene ring[29,155]. For example, the main product of electrochemical[29] or photochemical[155] reduction of benzonitrile in DMF or acetonitrile is benzene. Which carbon atoms are the most preferential sites for proton attack is still in dispute. A detailed electrochemical study[29] has led the authors to conclude that the RA of benzonitrile is protonated via the *ipso* position (see equation 66). This opinion is shared by some other scientists[155], and is in agreement with the



(66)

data on the regioselectivity of alkylation of RAs of benzonitrile (see section IV.C). However, an alternative conclusion has been reached by others[156]. Proceeding from the data on a hydrogen–tritium exchange, which occurs under irradiation of the $C_6H_5CN—TNEt_2—C_6H_6$ system and involves an intermediate formation of a radical ion pair, proton transfer from the cation radical to the RA and disproportionation of a free radical pair (equation 67), they concluded that the most preferential positions of protonation are *para* (80–90%) and *ortho* (10–20%).



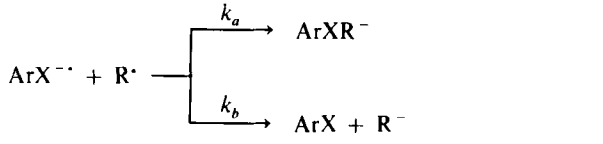
(67)

There is still no certainty about the regioselectivity of protonation of RAs of a series of other cyanoarenes such as 1- and 2-naphthonitrile[132,140,157], dicyanobenzenes[40,155], and 1,4-dicyanonaphthalene[158]. An exception is the RA of 9-cyanophenanthrene for which the addition of a proton was convincingly shown to occur via position 10[159]. However, in general the results of References 29, 40, 132, 140 and 154–159 show that the protonation of RAs of cyanoarenes leads to intermediates or products which can lose a cyanide ion or undergo dehydrocyanation in the reaction conditions or when treated with bases. This seems to be a promising method of removal of a cyano group from aromatic nitriles.

For the study of the interaction of RAs of aromatic esters and nitriles with protonating agents it is necessary to take into account their equilibrium with the corresponding dimeric dianions that can also undergo protonation (see Section IV.B, equations 43 and 44). However, as has been proven with methyl anthroate[135] and 1-naphthonitrile[140], one can find conditions under which only RA transformation products will be formed.

E. Interaction of Radical Anions with Free Radicals

The interaction of RAs of aromatic compounds with free radicals R· has been generally discussed in a review article[1]. This reaction can follow two competitive routes. The first one involves formation of a bond between the RA and R· (equation 68a) and the second a reduction of R· to R^- (equation 68b). The rate ratio of the two routes (k_b/k_a) depends



(68a)

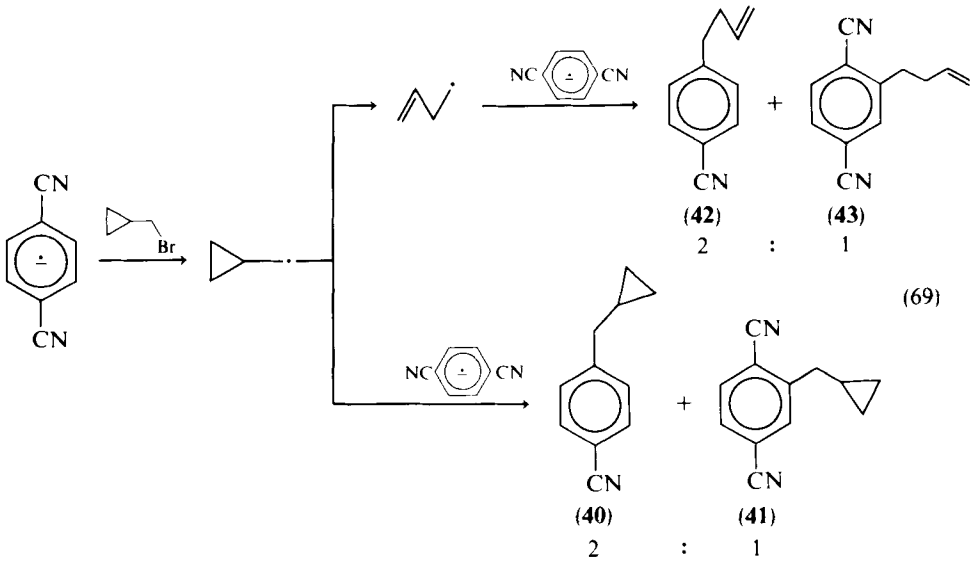
(68b)

on the standard potentials of the $R^{\cdot}/R^{-}$ and $ArX/ArX^{-\cdot}$ pairs, as well as on the type of ionic association of the radical-anion salt. In particular, when proceeding from primary to secondary and then to tertiary alkyl radicals (i.e. with decreasing electron affinity of $R^{\cdot}$), the rate ratio of the competitive reactions k_b/k_a changes in favor of recombination. A similar effect is achieved with increasing the standard potential E^0_{ArX/ArX^-} or passing from free ions to contact ion pairs. Route 68a becomes the main one for aromatic compounds having $E^0_{ArX/ArX^-} > -2.0$ V (rel. SCE)[1,18,160]. Note, however, that for aryl radicals characterized by higher electron affinity than alkyl radicals the contribution of route 68b can be appreciable for reactions with RAs of benzophenone ($E^0 = -1.7$ V)[1,147].

The available literature data on the interaction of free radicals with RAs of derivatives of aromatic carboxylic acids generally agree with the above statements. Route 68a predominates for interactions of RAs of polycyanoarenes ($E^0 < -1.6$ V[34]) with alkyl[34,157,161–167], allyl[34,162,165,168–173], benzyl[34,155,158,169,171,174–186], alkoxyalkyl[34,182,187–191], aminoalkyl[182,190,192], cyanoalkyl[182,193], trimethylsilyl[194] and cyclohexadienyl[195] radicals (see Schemes 3–12). However, the interaction of these RAs with stronger electron-acceptor free radicals of the diphenylmethyl type follows route 68b[162,187,196]. Alkanes as main fragmentation products of RAs of benzoic acid esters (see Section IV.A.1.a) seem to result at least partly from the reaction via route 68b.

The rate constants of addition of alkyl radicals to RAs of aromatic compounds are close to the diffusion limit[1,197,198]. For example, 5-hexenyl radical reacts with sodium naphthalenide and lithium salt of benzophenone RA with $k_a = 1 \times 10^9$ m^{-1} s^{-1} (22–23°C)[197] and $k_a = 1.5 \times 10^8$ M^{-1} s^{-1} (22–23°C)[198], respectively, which is some 5–6 orders of magnitude higher than k_a of interaction between alkyl radicals and parent arenes.

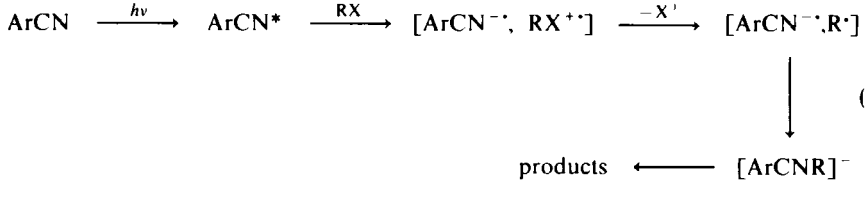
A similar picture is observed for RAs of polycyanoarenes. The investigation of interaction of RAs of terephthalodinitrile with cyclopropylmethyl bromide has indicated that, along with 4-cyano- (**40**) and 2,5-dicyano- (**41**) benzylcyclopropane, compounds **42** and **43** are also formed. These latter contain a 3-butenyl fragment resulting from isomerization of an intermediate cyclopropylmethyl radical (see Section IV.C; also equation 69). The ratio between the products with the cyclopropylmethyl (*P*) and



(69)

3-butenyl (P_i) fragments is $P/P_i = 3$, which corresponds to $k_a \sim 10^9\ M^{-1}\ s^{-1}$ at $-33°C$[142†] for the initial concentration of the RA of about 10^{-2} M. This value is 6 orders higher than the rate constant of methyl-radical addition to benzonitrile ($k \sim 4 \times 10^2\ M^{-1}\ s^{-1}$ [199]).

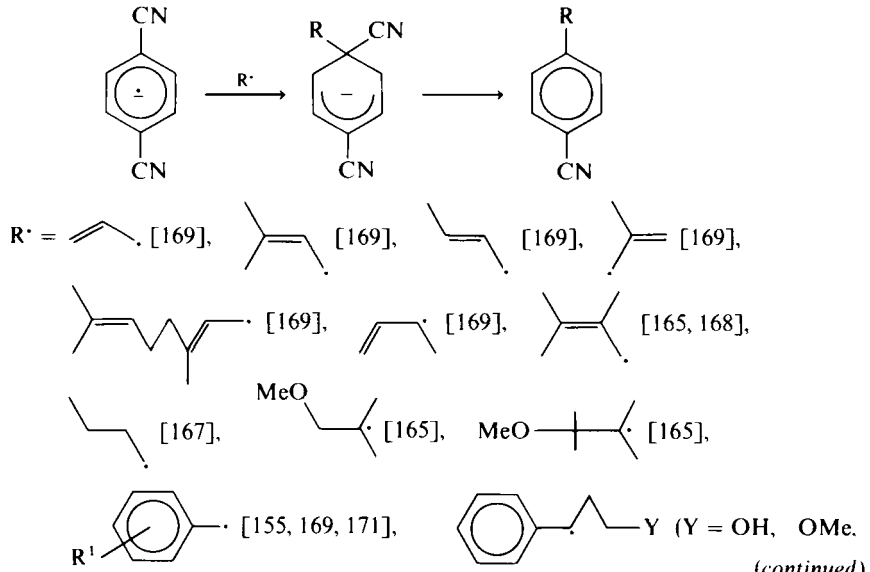
The data in Schemes 3–12 were obtained mainly for photochemical transformations of cyanoarenes in the presence of various electron donors (RX). As a result of electron transfer from the donor molecule into the excited acceptor molecule, the ion-radical pair is formed. Its further fate depends upon the structure of the donor and nucleophilic (basic) properties of the reaction mixture. In most cases with a nucleophilic assistance provided by the solvent, the radical cation (RC) of the donor ($RX^{+\cdot}$) undergoes fragmentation producing the radical $R^{\cdot}$. This latter interacts further with RAs of cyanoarenes to give eventually the reaction products (equation 70)[169–171,184,185,187,190].



(70)

$X = H, SiR^1_3, GeR^1_3, SnR^1_3$

When alkenes or aromatic compounds are used as electron donors, the formation of free radicals may be due to either elimination of a proton (or any other group) or addition of a nucleophile to the RC (equations 71 and 72)[161,162,165,166,173,195]. In those

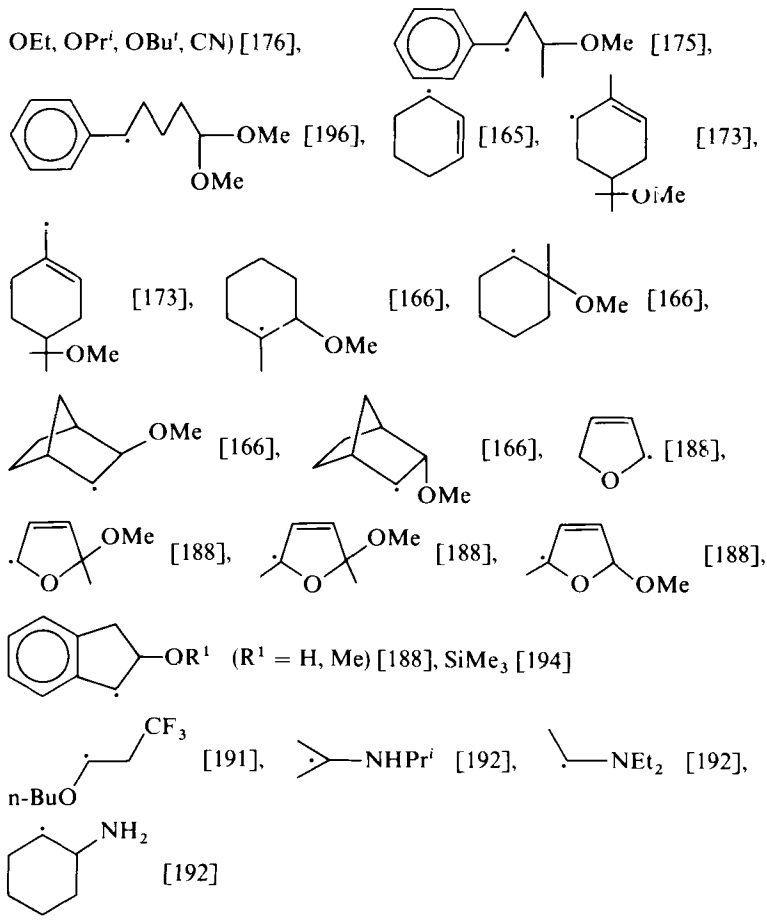


(continued)

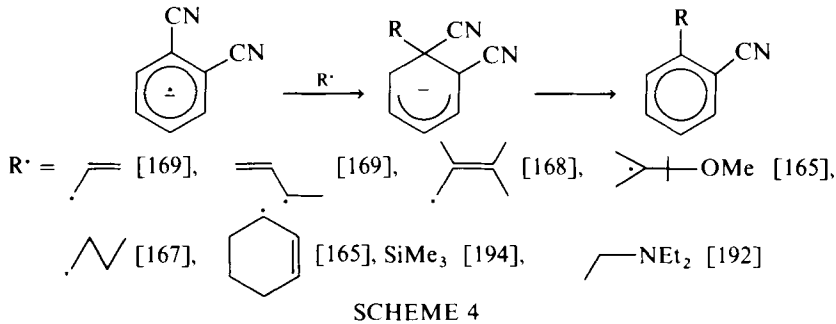
SCHEME 3

(References in Schemes 3–12 in square brackets)

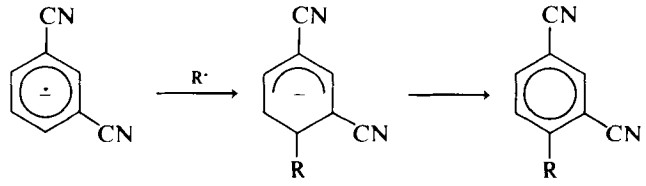
† $P/P_i = \{k_a[ArX^-]_0/k_i \ln(1 + k_a[ArX^-]_0/k_i)\} - 1$[197,198].

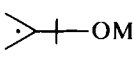


SCHEME 3 (*continued*)

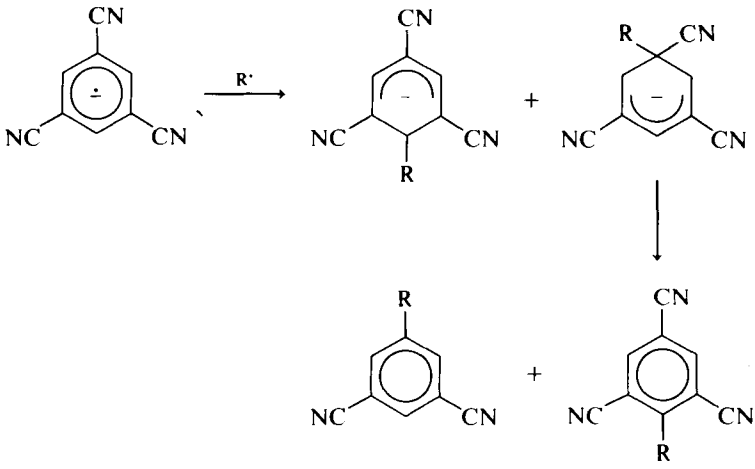


SCHEME 4



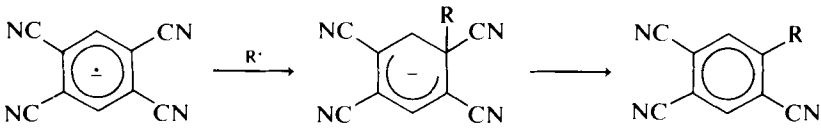
R· = [165],  [165], $SiMe_3$ [194]

SCHEME 5



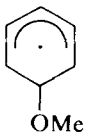
R· = $SiMe_3$ [194], [193]

SCHEME 6

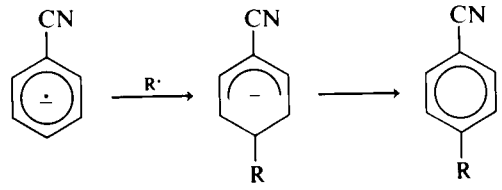


R· = [167], [167], [167], [167],

[167], [187], [187],

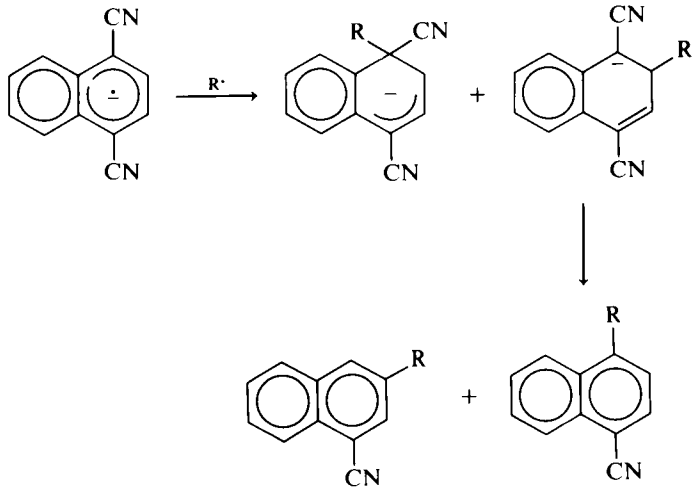
[187],  [195], $SiMe_3$ [194]

SCHEME 7



$R^{\cdot} = SiMe_3$ [194]

SCHEME 8

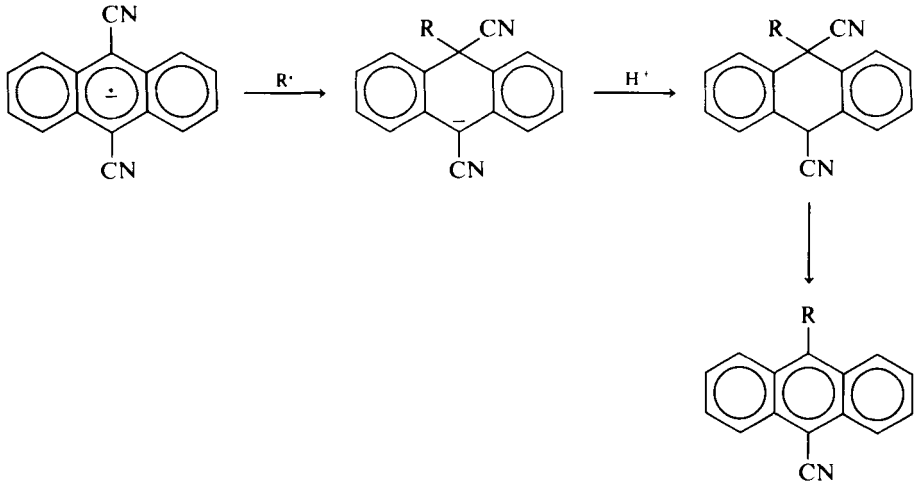


$R^{\cdot} = Me^{\cdot}$ [163], [164], [164], [168],

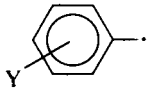
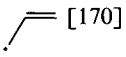
[170], [163, 177–184], [184],

[184], [189]

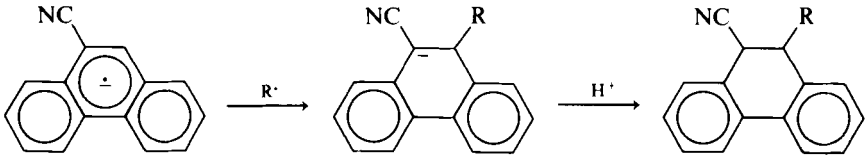
SCHEME 9



R· = ·CH_2X (X = OEt, SEt, NMe_2, NEt_2) [190], [190],

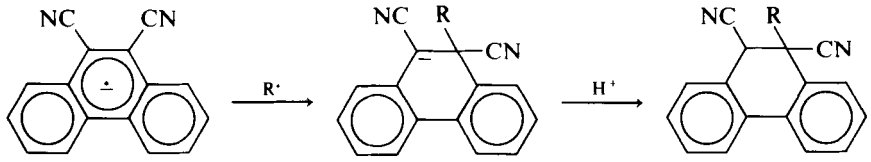
[190],  [185],  [170]

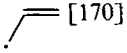
SCHEME 10



R· = [162], OMe [162]

SCHEME 11

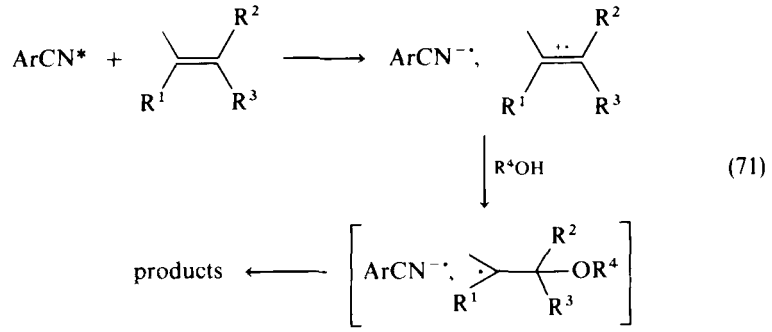


R· =  [170]

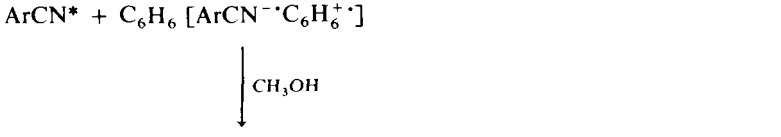
SCHEME 12

cases where the compounds containing a cyclopropane or cyclobutane or cyclopentane fragment serve as electron donors, the RCs undergo cleavage via one of the bonds giving free radicals in the presence of nucleophilic reagents[175,176,196,200]; see equation 73.

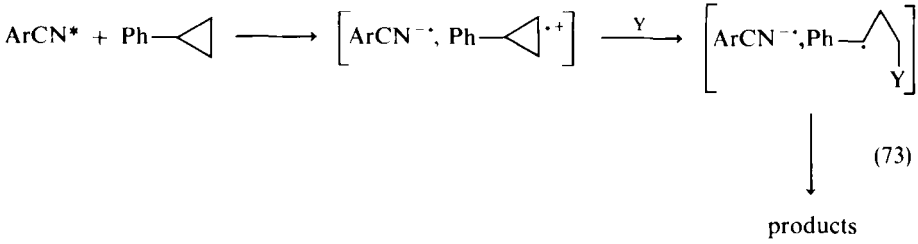
The data displayed in Schemes 3–12 indicate that the interaction of RAs of cyano-



(71)



(72)

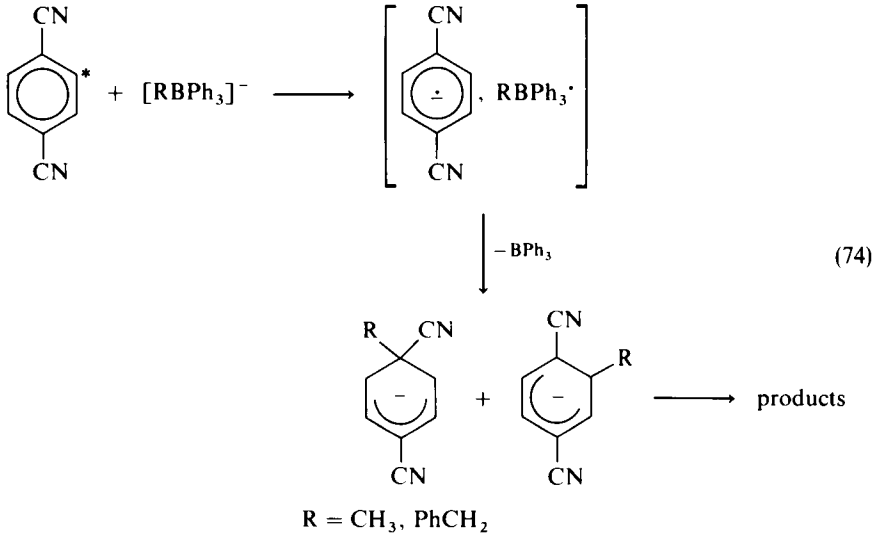


(73)

arenes with free radicals opens up a new possibility of introducing various structural fragments in the aromatic ring. As a rule, a free radical R$^{\cdot}$ attaches via the carbon atom having a maximum spin density[73,168]. For RAs of terephthalodinitrile, 1,4-dicyanonaphthalene, 9,10-dicyanoanthracene and 1,2,4,5-tetracyanobenzene this is the *ipso* position, for RAs of 1,3,5-tricyanobenzene—both substituted and nonsubstituted positions, and for RAs of benzonitrile—the *para* position[66,73,168].

It should be noted here that the relative reactivity of the different positions in the aromatic fragment of RAs of cyanoarenes can change as a function of reaction conditions. For example, unlike the data in Scheme 3, the products resulting from the interaction of the RA of terephthalodinitrile with alkyl halides (equation 69 and equation 57 in Section IV.C) and from photoalkylation of terephthalodinitrile by alkyltriphenylborate salts[163,164] (equation 74) correspond to the alkylation of this RA via both the *ipso*- and *ortho*-carbon atoms.

The above facts can be explained as follows. Most probably, the data presented in Scheme 3 describe the reactivity of a free RA of terephthalodinitrile. Simultaneously the

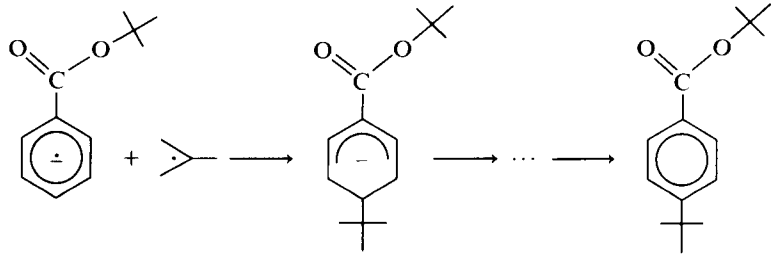


(74)

R = CH_3, $PhCH_2$

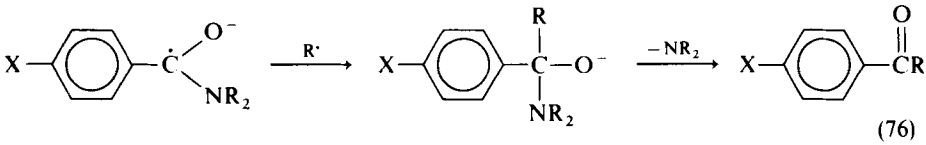
potassium salt of this RA, which exists as an ion associate at concentrations of *ca* 10^{-2} M[201], is involved in reaction with alkyl halides. In the terephthalodinitrile RA–potassium cation ion pair, the density distribution of the unpaired electron should resemble that of the RA of benzonitrile (see Section III); in other words, it should be characterized by a lesser difference in spin density in the *ipso* and *ortho* positions relative to the cyano group coordinated to the alkaline metal cation. According to quantum-chemical calculations for the terephthalodinitrile RA, $\rho(C_1)/\rho(C_2) = 0.2$, whereas for the benzonitrile RA the value is 0.44[73]. The change of the spin density ratio leads to the change of the relative reactivity of the *ipso* and *ortho* positions towards free radicals, and consequently, to the increase in the yield of products originating from the *ortho* attack. In photoalkylation of terephthalodinitrile by alkyltriphenylborate salts, the formation of a complex between the RA and the triphenylboron molecule can lead to a similar effect. It must be understood that the above speculations still need experimental verification.

As distinct from RAs of cyanoarenes, the regioselectivity of interactions of free radicals with RAs of other derivatives of aromatic carboxylic acids has almost not been characterized. The formation of *t*-butyl *p*-*t*-butylbenzoate during reduction of *t*-butyl benzoate was reported elsewhere[17]. This can be explained assuming that the *t*-butyl radical, a product of the fragmentation of the RA (see section IV.A.1.a), adds to the other molecule of this RA (equation 75). However, the authors of this work[17] suppose that the final reaction product results from the interaction of the *t*-butyl radical with the initial *t*-butyl benzoate.



(75)

In a recently published work[107] the authors suggest that the formation of aryl benzyl ketones during reduction of *N,N*-dibenzyl-substituted benzamide and toluamide is caused by addition of the benzyl radical—a product of fragmentation of the RA of the initial compound (see Section IV.A.1.c)—to the RA (equation 76). However, the reported data[107] do not rule out an alternative mechanism that involves the interaction of the initial amide with a benzyl anion.



(76)

X = H, CH_3; R = $C_6H_5CH_2$

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Antebi, S. 813, 814 (114, 115), *841*
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Apasov, E.T. 896, 907 (182), *958*
Apeloig, Y. 148, 149 (58), *151*
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Armstrong, V.C. 360, 361 (170), *369*, 782, 783, 790 (139a), *801*
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Boger, D.L. 565 (77), *610*, 686 (614), *701*
Bögge, H. 1569 (389), *1634*
Bögl, K.W. 1200, 1201, 1222, 1223 (4a), *1244*
Bogorad, L. 1050 (89), *1060*
Bogusky, M.J. 177 (188), *220*
Boguta, G. 1239 (167, 168), *1248*
Bohlmann, F. 1570 (391), *1634*
Bohm, H.J. 23 (132), *48*
Böhm, S. 214 (474), *226*
Bohme, D.K. 740 (149), *746*
Böhme, H. 820 (184, 185), *842*, 1004 (156), *1029*
Böhmert-Süss, S. 81 (184), *94*
Bohn, B.D. 674 (545), *700*
Bohonek, J. 972–974, 976, 980 (18), *1026*
Bohrer, G. 652 (381), *696*
Bohrmann, L. 913 (303), *960*
Böhshar, M. 1487 (117), 1538 (117, 315, 316), *1627*, *1632*
Boicelli, A. 886, 898, 933 (142), *957*
Boire, B.A. 1135 (4e), *1146*
Boisdon, M.-Th. 928 (369), *961*
Boisdon, M.Th. 949 (415), *962*
Boix, J. 1176 (20), *1198*
Boland, W. 141, 143 (34), *150*
Bolesov, I.G. 1519, 1566 (246), *1630*
Bolestova, G.I. 641 (283), *694*
Bolitt, V. 687 (628), *701*
Bollinger, F.W. 634 (218), *693*, 1482 (79), *1627*
Bollish, F.R. 294 (58), *303*
Bolm, C. 1567 (385), *1634*
Bolsing, F. 1352 (400), *1391*
Bolsterli, J.J. 1448 (237), *1472*
Boltanski, A. 557 (35), *609*
Boltansky, A. 1459 (281, 282), *1473*
Bolte, J. 1428 (174), *1470*
Bolton, J.R. 228, 229 (1), *264*
Bolton, P.D. 313 (38), 321, 322 (66), *366*, *367*
Bonaventura, C. 953 (487), *964*
Bonaventura, J. 953 (487), *964*
Bonavoglia, F. 663 (464), *698*
Bonazzola, L. 236 (61), *266*
Bond, P.M. 753, 760, 761 (28), 775, 776 (115), *799*, *800*
Bondarenko, L.I. 760 (63), *799*
Boned, M.L. 62 (55), 63 (55, 57, 59, 61), *91*
Bonet, J.-J. 1175 (18), 1176 (20, 21), *1198*
Bonetskaya, A.K. 60, 81 (43), *91*
Bonhoeffer, K.F. 510 (377), *544*
Bonin, W. 954 (597), *966*
Bonnans-Plaisance, C. 817, 826, 835 (150), *841*
Bonnaud, B. 432 (165), *539*
Bonner, D.P. 859 (49), *872*, 1087 (145), *1104*
Bonner, W.M. 1054 (112), *1060*
Bonnet, A. 679 (583), *700*
Bonnier, M. 482 (309), *542*
Booth, P. 827 (270), *844*
Booth, P.M. 676 (555), *700*
Booth, R.J. 232 (28), *265*
Bopegedera, A.M.R.P. 24 (155), *49*
Borden, W.T. 6, 10 (42), *47*, 578 (126), *611*, 1367 (473), *1393*
Bordner, J. 1359 (433), *1392*
Borer, R. 976 (43), *1026*
Borg, R.M. 1670–1673 (165), *1681*
Borggrefe, G. 1492 (140), *1628*
Borgström, B. 1399 (23), *1467*
Borisov, S.B. 77 (148), *93*

Borisova, A.I. 1510 (214), *1629*
Börjesson, B. 78 (149), *93*
Bormans, G. 470 (246), *541*
Born, M. 325 (92), *367*
Bornah, R.C. 1315 (245), *1388*
Bornemann, E. 877 (33), *955*
Borner, P. 972, 1002 (19), *1026*
Bornowski, B. 176 (211b), *220*
Bórquez, T.M. 775, 776 (116), *800*
Borrell, P. 1135 (1), *1146*
Borrelli, A.R. 1274 (15), *1383*
Bors, W. 1201 (20), 1203 (47), 1204 (38), 1217 (20), *1244, 1245*
Borthwick, D. 877, 878, 881 (58), *955*
Boruah, R.C. 1288 (85), *1384*
Bory, S. 1040 (39), *1059*
Borzekovski, J. 953 (546), *965*
Bos, H.J.T. 818 (172–174), 819 (172, 173), *842*
Bos, W. 649 (356), *696*
Bosch, E. 564 (72, 73), *610*
Bosco, M. 638, 682 (251), *694*
Bose, A.K. 589 (179), *612*
Bose, H.S. 1275 (26), *1383*
Böshagen, H. 925 (350), *961*
Böss, M. 1318 (268), *1388*
Bossuyt, A. 466 (230), *540*
Bothe, E. 794, 798 (185a), *802*
Bothner-By, A.A. 207 (411), *224*
Botta, A. 946 (407a), *962*
Botta, L. 1080 (117), *1103*
Botting, R. 1075 (77), *1102*
Bouab, O. 976 (39), *1026*
Boucherle, A. 1337, 1342 (342), *1390*
Bouchoux, G. 144 (39, 40), *151*, 737, 738 (139), *746*
Boudjouk, P. 645 (319), 654 (402), *695, 697*
Bouffard, F.A. 679 (575), *700*
Bouloussa, O. 473 (262), *541*
Boulton, A. 892 (169), *958*
Boulton, A.J. 428, 429 (143b), *538*
Bouma, W.J. 145 (46), *151*
Bouman, T.D. 96 (3), *127*, 158 (4), 159, 163 (41), 170 (106), *215, 216, 218*
Bourdon, F. 811 (62), *840*
Bourdonneau, M. 180 (210), *220*
Bourgeois, B.F.D. 1092 (180), *1104*
Bourgery, G. 954 (569), *966*
Bouska, J.B. 851 (11), *871*
Boutagy, J. 479 (282), *542*
Boutin, R.H. 1296, 1297 (163, 164), *1386*
Bouwman, T.D. 179 (202), *220*
Bovara, R. 1452 (256), *1472*
Bovey, F.A. 1, 26 (7), *46*, 203 (381), *224*
Bovy, P. 855 (28), *871*
Bovy, Ph. 496 (338), *543*
Bowden, K. 419 (134b), 512 (388), *538, 544*, 1273 (3), *1383*
Bowden, M.J.S. 1362 (453), *1392*
Bowers, A. 419 (134a), *538*
Bowers, M.T. 737 (137), *746*
Bowie, J.H. 740 (148, 150, 151), 741 (157a, 157b), *746*, 1316 (257), *1388*
Bowles, T. 1604 (474), *1636*
Bowman, R.L. 112, 119 (85), *129*
Box, H.C. 234 (45), 260 (195), 264 (221), *265, 268, 269*, 1242 (193, 194, 197), *1248*
Boyd, D.B. 108 (63), *129*, 589 (172), *612*
Boyd, G.V. 548, 578 (1), *608*, 1278 (45, 46), *1384*
Boyd, N.F. 1201 (12), *1244*
Boyd, R.H. 308 (10), *365*
Boyd, R.K. 135 (9), *150*
Boyer, H. 913 (306), 932 (386), *960, 962*
Boyer, H.J. 882, 900, 932 (110), *956*
Boyer, J. 618 (38), *690*, 925 (353), 935, 936 (392), *961, 962*
Boyer, S.K. 1357 (428), *1392*, 1482 (57), *1626*
Boykin, B.W. 183 (239), *221*
Boykin, D.W. 181 (226, 231), 183 (221, 224, 226, 231, 236–238), 184 (236, 241), *220, 221*
Boykin, L.W. 183, 185 (235), *221*
Boylan, M. 1049 (78), *1059*
Boyle, P.H. 1505 (200), *1629*
Boys, S.F. 3 (28), 20 (114), 22 (128), 25 (28), *46, 48*
Boyse, E.A. 1053 (97), *1060*
Braams, R. 1224, 1233 (105), *1247*
Brachwitz, H. 892 (170), 904 (251), 908, 913 (283–285), 919 (284, 285), 924 (283), *958–960*
Bradamante, S. 1363 (457), *1392*
Bradbury, A.F. 1056 (126), 1057 (127), *1060, 1061*
Bradley, C.H. 177, 178 (180), *219*
Bradley, M.O. 454 (196), *539*
Bradley, R.J. 169 (92), *217*
Bradley, R.S. 60 (45), 66 (94), 74 (141), 81 (45), *91–93*
Bradshaw, J.S. 620 (49), *690*, 803 (5), 815 (127, 135, 136), 816, 829 (136), *838, 841*
Bradshow, W.W. 1243 (199), *1248*
Brady, F. 374 (2), 382 (23), *534, 535*
Brady, L. 1405 (70), *1468*
Brady, O. 905, 909, 925 (261), *959*
Brady, W.T. 578 (124a, 124b), *611*, 1329 (313), *1389*
Braham, J.N. 1498 (174), *1629*
Bram, G. 630 (175), *692*
Branca, S.J. 1359 (437–439), 1360 (438), 1361 (438, 439), *1392*
Brand, M. 632 (198), *693*

Brandänge, S. 193 (323), *222*
Brander, A. 1300 (185), *1387*
Brandes, B.D. 1567 (386), *1634*
Brandsma, L. 822 (218), 831 (368–370), *843, 846*
Brandt, W. 1357 (425), *1392*
Branston, R.E. 787, 789 (150), *801*
Brasca, M.G. 1313 (236), *1388*
Brater, D.C. 1077 (97), *1103*
Bratz, M. 653 (394, 395), *697*
Braumann, J.I. 740 (155), 741 (156), *746*
Braun, D. 158, 160 (6), *216*
Braun, J. 1443 (223), *1471*
Braun, M. 655 (411), 674 (541), *697, 700*
Braun, S. 205 (390), *224*
Braun, W. 205 (402), *224*, 244 (115), *267*, 1251 (15), *1268*
Brauner, A. 141 (34), 143 (34, 38), *150, 151*
Bräuner, H.-J. 1014 (180, 181), 1015 (181–183), 1021 (182), 1024, 1025 (203), *1029, 1030*
Bravdo, T. 556 (33), 557 (35), *609*, 1459 (282–284), *1473*
Bravo, P. 1414 (127), *1469*
Brazier, C.R. 24, 43 (154), *49*
Breanger, E. 1043 (55), *1059*
Bredereck, H. 973 (24), 989 (94), 1009 (175, 176), 1011 (176), 1016 (24), 1024 (199), *1026, 1027, 1029, 1030*
Bredt, J. 415 (126), *538*
Breitenbach, J.W. 66 (98), 79 (168), *92, 93*
Breitenstein, W. 394 (69), *536*
Breitgoff, D. 1429 (175), 1441 (214), 1446, 1448 (232), *1470–1472*
Breitmaier, E. 158 (7), *216*, 989 (92), *1027*
Breitman, T.R. 439 (172), *539*
Brembilla, A. 787 (156), *801*
Brennan, J. 598 (217), *613*, 646 (332), *695*
Brennan, M.P. 1254, 1266 (76), *1269*
Brenner, D. 470 (244, 245), *541*
Breslav, I.I. 1641, 1642, 1644 (47), *1679*
Breslow, J.L. 1098 (214), *1105*
Bressloff, P. 1072 (48), *1102*
Bretschneider, H. 878 (76), *956*
Brettle, R. 1254, 1266 (76), *1269*, 1276 (33), *1383*
Breuer, E. 1162 (2), *1164*
Breuer, H. 954 (553), *965*
Brevard, C. 180 (210), *220*
Brewster, A. 686 (623), *701*
Brewster, A.I.R. 173 (133), *218*
Brewster, J.H. 97 (26), 98 (27), *128*
Brey, W.S. 215 (476), *226*
Brianso, J.S. 1176 (20), *1198*
Brianso, M.C. 1176 (20), *1198*
Bricas, E. 197 (349), *223*
Brickner, S.J. 575 (108), *611*
Bridge, M.R. 711 (42), *744*
Bridon, D. 618 (26, 28), 623, 626 (28), *689*
Brieva, R. 1435 (193), 1464 (304, 306), *1471, 1473*
Briggs, A.J. 621 (65), *690*
Briggs, L. 884 (124), *957*
Bright, D. 898 (231), *959*
Brillon, D. 606 (251), *614*
Brimblecombe, R.W. 434 (166), *539*
Brine, G.A. 1300 (190), *1387*
Briner, E. 67 (107), *92*
Brinker, D.A. 1565 (370), *1633*
Brinkmeyer, R.S. 1009, 1015, 1016 (174), *1029*
Brinn, J. 923 (341), *961*
Brint, P. 100 (35), *128*
Briody, J.M. 758 (57), 797 (194), *799, 802*
Brion, J.D. 829 (319), *845*
Bristol, J.A. 419 (137), *538*
Brockehurst, B. 1116 (14), *1134*
Brockerhoff, H. 1399 (22), *1467*
Brockhart, T. 402 (92), *537*
Brockman, F.G. 321, 322 (61), *367*
Brockman, H.L. 1399 (23), *1467*
Brodersen, R. 170 (105), *218*
Brodgen, R.N. 1080 (108), *1103*
Brodie, B.B. 1067 (17, 18), *1101*
Brodskaya, E.I. 1535, 1536 (314), 1561 (364a), *1632, 1633*
Brodskaya, G.A. 1225 (106, 107), 1228 (125), *1247*
Broekema, R.J. 978 (49), *1026*
Brogden, R.N. 1096 (198), 1097 (206), *1105*
Brokhovetskii, D. 898, 908, 913 (208), *958*
Bromilow, J. 164 (56, 57), *217*
Bronsted, J.N. 306 (7), 327 (97), *365, 367*
Brook, M.A. 488 (319), *542*
Brookhart, T. 1168 (7), *1198*
Brooks, B. 210 (444), *225*
Brooks, C.L.III 2 (10), *46*
Brooks, D.W. 851 (11), *871*
Brooks, P.M. 1077 (96), *1103*
Brooks, V.L. 254, 257 (151), *268*
Brosch, D. 1378, 1379 (531), *1394*
Brossi, M. 1275 (21), 1375 (505), *1383, 1393*
Brotherton, C.E. 686 (614), *701*
Broughton, H.B. 676 (555), *700*
Brouw, P.M.op den 973 (25), *1026*
Brouwer, A.C. 818 (172–174), 819 (172, 173), *842*
Browh, H.C. 618 (35), *690*
Brown, A.C. 1251 (12), *1268*
Brown, A.G. 589 (169), *612*
Brown, D.A. 856 (33), *872*
Brown, D.F. 709 (33), *743*
Brown, D.J. 1256 (83), *1269*
Brown, D.W. 116 (104), *130*

Brown, E. 631 (188), 656 (425–428), *693, 697*
Brown, E.L. 466 (235), *540*
Brown, H. 878, 880, 897, 907, 915, 918, 926 (77a), *956*
Brown, H.C. 183 (232), *221*, 618 (22, 31, 37), 621 (54, 55, 60, 70), 633 (217), *689, 690, 693*, 1667 (152), *1681*
Brown, J.J. 441 (174), *539*
Brown, J.M. 78, 79 (150), *93*, 481 (295), *542*
Brown, L.E. 466, 467 (236), *541*
Brown, M.J. 594 (204a), *613*
Brown, M.S. 1100 (224, 225), *1105*
Brown, P.R. 815 (127), *841*
Brown, R. 1345 (365), *1390*
Brown, R.S. 16 (84), *47*, 781 (131), 782 (141), 784 (131, 141), 785 (131), 786 (131, 141), 787 (131), *801*, 1014 (179), *1029*, 1308 (219), *1387*
Brown, S.P. 634 (220), *693*
Brown, T.H. 1644 (76), *1679*
Brown, W.G. 481 (296), *542*
Brownbridge, P. 976 (42), 982, 984 (42, 66), 1022 (42), *1026, 1027*
Browne, E. 465 (226), *540*
Browne, L.J. 674 (540), *699*
Brownel, G. 506 (364), *544*
Brownell, G.L. 384 (28), *535*
Brownlee, R.T.C. 164 (54, 56, 57), 166 (70, 71), 179 (207), 183 (233), *217, 220, 221*
Brubaker, M.J. 1305 (204–206), *1387*
Brubaker, W.F.Jr. 454 (197), *539*
Brucat, P.J. 24 (153), *49*
Brucato, L. 1600 (469), *1636*
Bruce, I. 616 (4), *689*
Bruce, M.I. 481 (292), *542*
Bruce, M.R. 811 (103), *840*
Bruck, D. 170, 171 (108), 175 (144, 145), *218, 219*
Brucke, T. 387 (42), *536*
Brückman, R. 1358 (430), *1392*
Bruckner, C. 685 (611), *701*
Brüggen, U.v.d. 982 (65), *1027*
Bruhn, F.R. 1640–1644 (19), *1678*
Bruice, T.C. 751 (17), 752 (17, 22a), 778 (120), 790 (167), 791 (167, 170), 792 (170), 793 (170, 178, 179), 794 (167, 178, 179), *798, 801, 802*
Brumby, S. 233 (40, 41), 243 (113), *265, 267*
Brumfield, M. 1670, 1671, 1675 (190), *1682*
Brummel, Ch.L. 323, 324 (85), *367*
Brummond, D.D. 1032 (4), *1058*
Brundish, D.E. 495 (337), 498 (345), 500 (353, 355, 356), *543*
Brune, K. 1076 (93), *1103*
Brunet, P. 1336 (338, 339), *1390*
Brunner, A. 1567 (378), *1633*
Brunner, H. 1567 (383, 384), *1634*
Brunner, H.R. 458 (204), *540*, 1097 (202, 208), *1105*
Bruno, F. 1252, 1260 (67), *1269*
Brunsvold, W.R. 573 (101), *611*
Brüntrup, G. 579 (127), *611*
Bruntrup, G. 628 (146), 652 (381, 382), *692, 696*
Brunwin, D.M. 591 (187), *613*
Brus, L.E. 1292 (109), *1385*
Brusich, M.J. 24 (147), *49*
Bruylants, A. 789 (160), *801*
Bruyn, R.G.M.de 632 (205), *693*
Bryan, P.N. 1405, 1456 (76), *1468*
Bryant, F. 1238 (163), *1248*
Bryant, T. 668 (493), *699*
Brykina, E.P. 59, 60 (40), 78, 79 (153), *91, 93*
Bryson, N. 470 (244, 245), *541*
Bryson, T.A. 548 (2b), *608*
Brzezinski, B. 211 (457), *225*
Brzozowski, A.M. 1405 (70), *1468*
Bubb, J.E. 493 (329), *543*
Bubnov, N.N. 1256, 1264 (85), *1269*
Bucciarelli, M. 1443 (224), *1471*
Buchanan, G.L. 645 (324), *695*
Buchanan, M.V. 343 (133), *368*
Buchardt, O. 683 (596), *701*
Bucher, T. 1041 (47), *1059*
Buchholz, G. 1128 (40, 41), *1134*
Büchi, G. 1135 (4c), *1146*
Buchman, O. 495 (335, 336), *543*
Büchner, E. 1484 (92), *1627*
Buchner, E. 1499 (178), *1629*
Bucholz, B. 1651 (106), *1680*
Buchsbaum, D.J. 470 (243), *541*
Buchwald, S.L. 582 (141), *611*, 974 (29), *1026*
Buckell, V.F. 466 (234), *540*
Buckingham, A.D. 20 (113), 21 (116, 119), *48*, 168 (87), *217*
Buckner, S.W. 24 (143), *49*
Buckwald, S.L. 573 (100), *611*
Buddrus, J. 1408 (100), *1469*
Budesinsky, M. 109 (68–70), 110 (68), 111 (79), 112 (81), 113 (90), *129*, 1349 (385), *1391*
Budzikiewicz, H. 141 (34), 143 (34, 38), 149 (59), *150, 151*, 215 (480), *226*
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Buhler, R.A. 1227, 1235 (120), *1247*
Buhr, G. 1361 (452), *1392*
Buhrer, M. 1075 (75), *1102*

Buhro, W.E. 1519 (245a), 1574 (403), 1589, 1590 (447), *1630, 1634, 1635*
Buick, A.R. 1643 (57, 67), 1644 (57), 1653 (57, 67), *1679*
Bukatin, M. 23 (135), *49*
Bukownik, R.R. 827 (255), *844*
Bulat, A.D. 375 (7), *534*
Bull, H.G. 980 (54), *1027*
Bull, L.B. 504, 506 (361a), *543*
Büllesbach, E. 177 (196), *220*
Bulman Page, P.C. 616 (6), *689*
Bülow, C. 831 (336), *845*
Bulow, G. 1406 (92), *1469*
Bumagin, N.A. 643 (297), *695*
Buncel, E. 626 (123), *691*, 774 (108), *800*
Bundgaard, M. 1066 (16), *1101*
Bunkina, T.A. 1496, 1529, 1531 (167), 1584 (434), *1628, 1635*
Bunnelle, W.H. 641 (281), *694*
Bunnett, J.F. 308, 312, 332, 353 (15), *366*
Bunton, C. 947 (410), *962*
Bunton, C.A. 727 (100), *745*, 770 (88), 782 (142), 796 (186), *800–802*, 953 (459), *963*, 1640 (2), *1678*
Buono, G. 1428 (173), 1438 (173, 201), *1470, 1471*
Burakevich, J. 926 (356), *961*
Burgar, M.I. 183 (223), 184 (242–245, 251), 186 (243), *220, 221*
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Burger, W. 490 (326), *543*
Burgers, P.C. 136 (17), 147 (53, 54), *150, 151*
Burgess, G. 781 (136), *801*
Burgess, J. 313 (39), *366*, 770 (89), *800*
Burgess, K. 1426 (168), 1431 (181), 1432 (183), *1470, 1471*
Burgess, M.L. 567 (80), *610*
Burglass, A.J. 781 (135), *801*
Burguet, M. 1316 (251), *1388*
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Burke, T.R.Jr. 483 (310), *542*
Burkert, U. 96, 100 (6), *127*, 968 (7), *1025*
Burkhard, J. 1378 (530), *1394*
Burnett, W.E. 829 (305), *845*
Burns, J. 413 (120), *537*
Burrows, H.D. 241 (100), *267*, 1273 (2), *1383*
Bursey, M.M. 343 (132), *368*
Bursics, L. 488 (320), *542*
Burt, R.A. 980 (60), *1027*
Burt, S.K. 16 (83), *47*, 755, 776 (44), *799*
Burton, D.H.R. 870 (86), *873*
Burton, G.W. 1215 (64), 1216 (69), *1246*
Burum, D.P. 173 (137), *218*
Busch, H. 1053, 1054 (99), *1060*
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Ferre, E. 1438 (202), *1471*
Ferreira, B. 618 (41), *690*
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Finley, D. 1054 (102, 107), *1060*
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Fischer, G. 1347 (373), *1390*
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Fischer, K. 904, 933, 950 (254), *959*
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