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THE REACTION OF ISOXAZOLIUM SALTS WITH NUCLEOPHILES[1]

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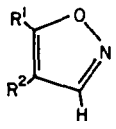
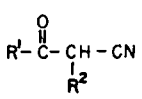
Abstract—A number of facile reactions of 3-unsubstituted isoxazolium salts with bases have been studied and are shown to proceed *via* the primary intermediacy of α-ketoketenimines. These experiments have resulted in the development of a general method for the synthesis of a variety of different heterocyclic systems. The reaction of isoxazolium salts with simple carboxylates has been examined in some detail, in view of the fact that the product enol esters are excellent acylating agents.

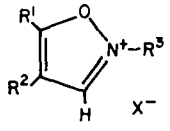
SOME years ago we were led, through a consideration of the well-known base-catalyzed cleavage of 3-unsubstituted isoxazoles (*aaa*) to β-ketonitriles (*aab*), to postulate that similarly constituted isoxazolium salts (*aac*) should be readily transformable into the hitherto unknown α-ketoketenimines (*aad*). Our interest in this hypothesis was



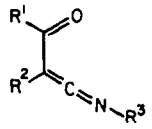
aaa



aab

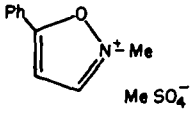


aac

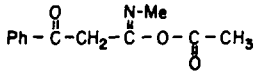


aad

heightened by the structural similarity between the ketoketenimines and the carbodiimides—a relationship which suggested the possible utility of the former as reagents for peptide synthesis. We next discovered that in 1902, in a dissertation describing work carried out with Claisen at Kiel, Mumm[2] recorded the striking observation that N-methyl-5-phenylisoxazolium methosulfate (*aae*) reacts with extraordinary facility with sodium acetate in aqueous solution at room temperature. The crystalline product which precipitated within a few minutes was formulated at the time as the



aae



aaf

iminoanhydride (*aaf*). Further, over a thirty-five year period Claisen, Mumm, and their students reported a number of reactions of 3-unsubstituted isoxazolium salts with various nucleophiles in aqueous solution.[2–15]

[1] For preliminary communications see: R. B. Woodward and R. A. Olofson *J. Amer. Chem. Soc.* **83**, 1007 (1961); R. B. Woodward, R. A. Olofson and H. Mayer, *Ibid.* **83**, 1010 (1961).

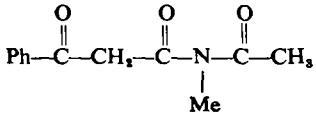
[2] O. Mumm, *Dissertation.* Kiel (1902).

[3] K. Meyer, *Dissertation.* Kiel (1903).

[4] G. Münchmeyer, *Dissertation.* Kiel (1910).

[5] C. Bergell, *Dissertation.* Kiel (1912).

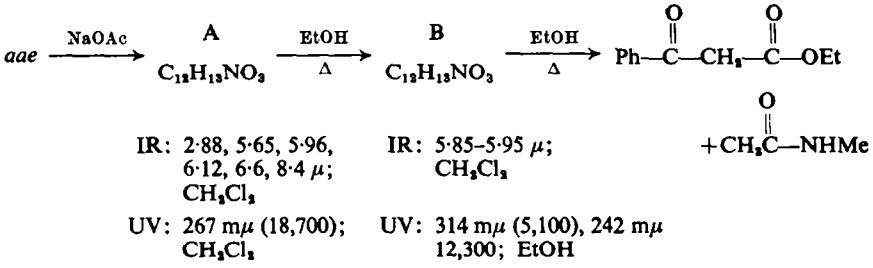
Our own studies began with a re-examination of the reaction of the isoxazolium salt (*aae*) with sodium acetate. Mumm himself[2] had provided one clue to the actual structure of the product when he reported that it rearranged to an isomer on recrystallization from ethanol. The isomer was assigned the imide structure (*aag*). We were



aag

able to verify this observation, and in addition we obtained the expected cleavage products, N-methylacetamide and ethyl benzoylacetate, when the rearrangement product was heated in ethanol. However one of Mumm's structural assignments is not in accord with the newly obtained spectroscopic data. The known facts are summarized in Scheme I. In particular the IR band of A at 2·88 μ cannot be reconciled with the

SCHEME I



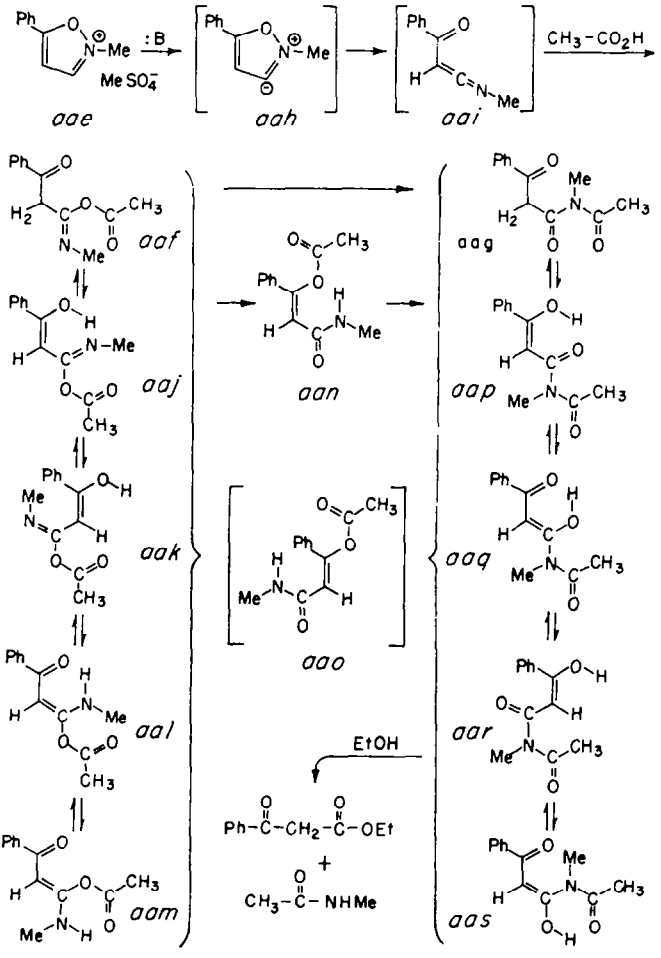
iminoanhydride structure (*aaf*). Further the single UV maximum at 276 mμ is not suggestive of the expected acetophenone absorption.

Possible structures for A and B are limited to formulations in which the groups on the 4 and 5 positions of the isoxazole ring and the alkyl group on the nitrogen retain their structural integrity during the reactions which take place. A series of possible transformations based on the initial mechanistic speculations was postulated in order to expose potential structures for A and B to further scrutiny (Scheme II). Of these structures *aaf* has already been excluded. It may further be noted that the enol ester structure (*aao*) need not be considered; the *trans* substitution of the double bond and the absence of a mechanistic path to eliminate that double bond doom the acyl residue in *aao* to an existence uncomplicated by the possibility of further rearrangement to nitrogen—a necessary requirement if the formation of N-methylacetamide on ethanolysis of B is to be explained.

[6] A. Wirth, *Dissertation.* Kiel (1914).
[7] W. Stülcken, *Dissertation.* Kiel (1935).
[8] H. Hornhardt, *Dissertation.* Kiel (1937).
[9] L. Claisen, *Ber. Dtsch. Chem. Ges.* **42,** 59 (1909).
[10] O. Mumm and G. Münchmeyer, *Ber. Dtsch. Chem. Ges.* **43,** 3335 (1910).
[11] O. Mumm and G. Münchmeyer, *Ber. Dtsch. Chem. Ges.* **43,** 3345 (1910).
[12] O. Mumm and C. Bergell, *Ber. Dtsch. Chem. Ges.* **45,** 3040 (1912).
[13] O. Mumm and C. Bergell, *Ber. Dtsch. Chem. Ges.* **45,** 3149 (1912).
[14] A. Knust and O. Mumm, *Ber. Dtsch. Chem. Ges.* **50,** 563 (1917).
[15] O. Mumm and H. Hornhardt, *Ber. Dtsch. Chem. Ges.* **70,** 1930 (1937).

The postulated cleavage mechanism as it applies in this specific reaction is also outlined in Scheme II; the isoxazolium salt (*aae*) reacts with some base in the solution to produce the ylide (*aah*) which isomerizes to the ketoketenimine (*aai*) and then is attacked by acetic acid to form one or more of the tautomers (*aaf*, $j \rightarrow m$) in analogy with the reactions of carbodiimides and ketenimines with carboxylic acids. These tautomers can rearrange *via* a cyclic six-membered ring intermediate to the enol acetate (*aan*) and again through a similar intermediate to the N-acyl tautomers (*aag*, $p \rightarrow s$). However, *aan* is not an obligatory precursor to this series; *aaf*, $j \rightarrow m$ might rearrange directly via a four-center reaction to *aag*, $p \rightarrow s$.[16]

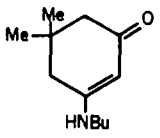
SCHEME II



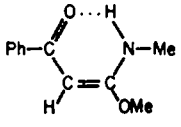
[16] F. Zetzsche, E. Lüscher and H. E. Meyer, *Chem. Ber.* **71**, 1089 (1938); J. C. Sheehan and G. P, Hess, *J. Amer. Chem. Soc.* **77**, 1067 (1955); H. G. Khorana, *Chem. & Ind.* 1087 (1955); C. L. Stevens and M. E. Munk, *J. Amer. Chem. Soc.* **80**, 4065 (1958); D. Y. Curtin and L. L. Miller, *Tetrahedron Letters* 1869 (1965).

It is very difficult, and in many cases impossible, to distinguish the structures of Scheme II by chemical test, and even where the possibility of such differentiation exists, the probability of rearrangement to another structure or tautomer of the series during reaction would cast great doubt upon the results obtained. Spectroscopic analysis is not subject to this deficiency, and though the number of structures to be differentiated is large, we believe the IR and UV spectra uniquely determine the structures of A and B.

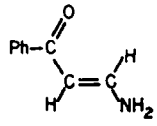
Let us first consider A. The IR band at 2·88 μ, which we have already used to eliminate structure *aaf*, also excludes structure *aag* which has no N—H or O—H. It also argues against *aaj*, *aal*, *aap* and *aaq* in which the active hydrogen should be highly hydrogen-bonded and should give rise to a broad weak band at relatively long wavelength. The IR band at 5·65 μ excludes *aar* and *aas*, neither of which can have such a short wavelength carbonyl band, and further confirms the impossibility of the other structures of series *aag*, $p \rightarrow s$. Structure *aak* does not have the secondary N—H required by the definitive band at 6·6 μ so we are left only with *aam* and *aan*. One would expect that the bands associated with the double bond and the benzoyl carbonyl of *aam* would be at much longer wavelength than 5·96 μ and 6·12 μ. Two models, the cyclohexenone (*aat*)[17] and the iminoether (*aau*) (structure proved later) absorb at 6·20 μ, 6·64 μ and 6·78 μ and at 6·15 μ and 6·5–6·6 μ respectively. Also structures with the



aat



aau



aav

the conjugation of *aam* would not have the simple UV spectrum of A (cf. *aau* λ_{max} (ϵ), MeOH: 235 mμ (10,500), 321 mμ (19,600) and *aav*[18] EtOH: 242 mμ (11,000), 324 mμ (18,000)).

The UV spectrum of A is similar to that of cinnamamide (EtOH: 269 mμ (24,000))[19] and structure *aan* is the N-methyl-β-acetoxy derivative of cinnamamide. Its IR spectrum is also completely in accord with structure *aan*: 2·88 μ—secondary N—H, 5·65 μ—enol ester, 5·96 μ—unsaturated secondary amide, 6·12 μ—double bond, 6·6 μ—amide II band, and 8·4 μ—ester group. Therefore we conclude that compound A has the enol ester structure *aan*.

The UV spectrum of compound B suggests a simple acetophenone chromophore (EtOH: 242 mμ (12,000), 280 mμ (1,000))[20] thus eliminating all structures except *aaf* and *aag*. The unlikelihood of *aaf* is suggested by mechanistic considerations, since its formation would involve a reversal of the original path to *aan*. The iminoanhydride (*aaf*) would also be expected to have a much more highly resolved carbonyl region than is found in B and in particular should have a very low-wavelength band. Further, simple iminoanhydrides are not stable with respect to the corresponding imides and can ordinarily not be isolated.[16,21] We can therefore with assurance assign structure

[17] R. B. Woodward and M. Smith, unpublished results.

[18] K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.* 945, 948 (1946).

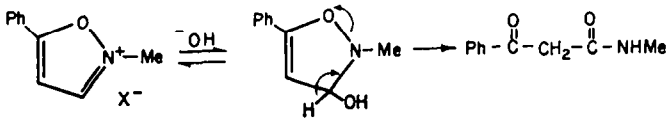
[19] G. Tsatsas, *Bull. Soc. Chim. Fr.* 1011 (1947).

[20] R. P. Mariella and R. R. Raube, *J. Amer. Chem. Soc.* **74**, 521 (1952).

[21] O. Mumm, H. Volquartz and H. Hesse, *Ber. Dtsch. Chim. Ges.* **47**, 751 (1914); **48**, 379 (1915).

aag—Mumm's original structure—to compound B. However, the abnormally high intensity of the long wavelength band in the UV may be associated with the presence of some enol tautomer.

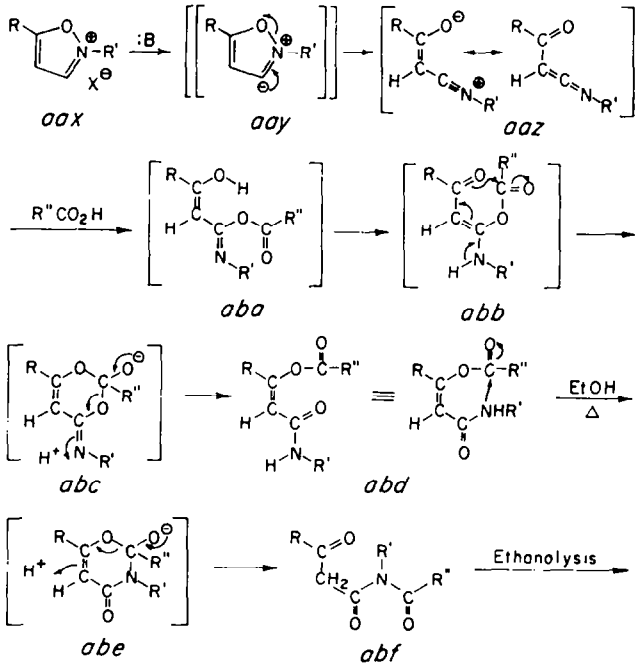
Mechanisms for the general reaction of isoxazolium salts with nucleophiles are only hinted at in the published work of Mumm and his students, and it was not until 1928 that Kohler[22] proposed what can be regarded as a mechanism for the reaction in the case of attack by hydroxide ion. His mechanism as it would be drawn today involves addition of the anion to the isoxazolium cation to form a *pseudo* base (*aaw*) followed by elimination of a proton with opening of the ring to afford the product. We may



aaw

note that from the vantage point of the present day, the second stage (cf. (*aaw* arrows) of the suggested path is one for whose ready activation it is difficult to discern a justifiable basis in principle or analogy.[23,24] We are, however, in the fortunate position of having the alternative mechanism delineated in Scheme III.

SCHEME III



aax *aay* *aaz* *aba* *abb* *abc* *abd* *abe* *abf*

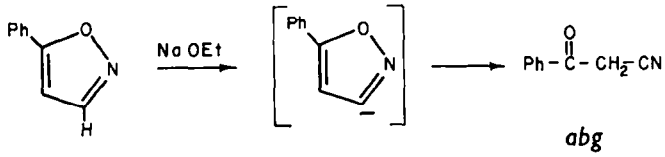
[22] E. P. Kohler and A. H. Blatt, *J. Amer. Chem. Soc.* **50**, 1217 (1928); E. P. Kohler and W. F. Bruce, *Ibid.* **53**, 644 (1931).

[23] D. S. Kemp and R. B. Woodward, *Tetrahedron* **21**, 3019 (1965).

[24] D. S. Kemp, *Dissertation*. Harvard University (1964).

The isoxazolium salt (*aax*) reacts with some base in the solution to produce the ylide (*aay*) which isomerizes to the ketenimine (*aaz*) and finally is attacked by the nucleophile or its conjugate acid to give either the product isolated or its precursor. In the case of carboxylate as nucleophile, we believe that the free acid adds to the ketenimine to yield the iminoanhydride (*aba*) which can rearrange *via* the cyclic intermediate (*abc*) to the enol ester (*abd*). When it is heated in ethanol, the latter is transformed *via* a similar intermediate (*abe*) to the imide (*abf*).

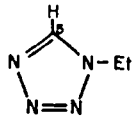
The initial step in the mechanism involves the abstraction of the proton at C-3 of the isoxazolium cation to form an ylide (*aay*); there are a number of lines of argument favoring such a step. First, isoxazolium salts react with all sorts of nucleophiles in either aqueous or non-aqueous media (*vide infra*)—but only when the 3-position is unsubstituted. Second, the reaction solution must contain some base or hydrogen abstractor; the reaction slows down with increasing acidity. Third, there is the very close analogy with some ring cleavage reactions of isoxazoles which must involve the formation of at least partial nagative charge on the 3-position of the isoxazole ring.[25,26] Of these the most straightforward is the reaction of 5-phenylisoxazole with cold sodium ethoxide in ethanol or with aqueous sodium hydroxide (ca. pH 10) to yield benzoylacetonitrile (*abg*).[25]



abg

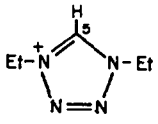
Whether this reaction proceeds stepwise or in a concerted fashion, it would be expected that in analogous reactions of isoxazolium salts proton elimination should be more facile by several powers of ten as a result of the proximity of the positive charge. This conclusion is justified by observations made, in the tetrazole series; 1-ethyl

TABLE 1. KINETICS AT 31°



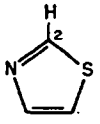
abh

$t_{1/2}$ = 22 min at pD 10·1



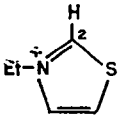
abi

$t_{1/2}$ = 5·1 min in 2·04N DCl—D_2O



abj

$k_2 = 5{\cdot}8 \times 10^{-5}$ l/mol sec.



abk

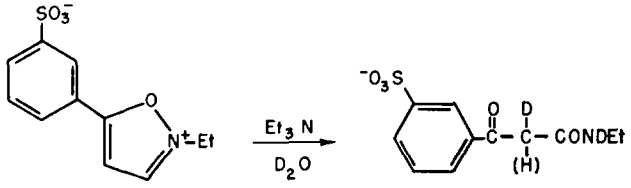
$k_2 = 9{\cdot}8 \times 10^{5}$ l/mol sec.

[25] L. Claisen, *Ber. Dtsch. Chem. Ges.* **36**, 3672 (1903).

[26] S. Cusmano and T. Tiberio, *Gazz. Chim. Ital.* **78**, 896 (1948); A. Quilico, R. Fusco and V. Rosnali, *Ibid.* **76**, 30 (1946); W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).

tetrazole (*abh*) undergoes base induced exchange of its C-5 proton for deuterium in heavy water solution 10^{10-12} times more slowly than the 1,4-diethyl tetrazolium cation (*abi*).[27] An analogous phenomenon is observed in the thiazole series (C-2 proton—*abj* and *abk*) and in other systems.[28]

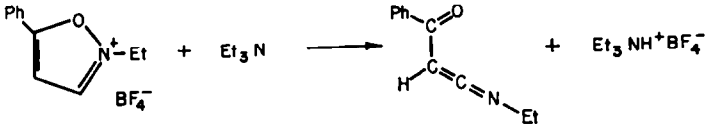
We carried out a similar deuterium exchange experiment on the isoxazolium salt, N-ethyl-5-phenylisoxazolium-3′-sulfonate (*abl*).[29] This compound was dissolved in heavy water and allowed to react with the base produced by addition of one-half equivalent of triethylamine in a reaction which should yield the amide (*abm*). The



abl *abm*

unreacted isoxazolium salt (*abl*) was then isolated. However, using NMR spectroscopy as the analytical tool, we were unable to find any deuterium incorporated in *abl*. This observation shows that (1) the initial step in our mechanism is irreversible—that is, formation of the ylide (*aay*) is slower than subsequent ring-opening to the ketoketenimine (*aaz*), or (2) the ylide is only part of a transition state in a concerted elimination of the proton at C-3 and the ring scission to form the ketenimine.[30]

Unlike many other ylides, that from isoxazolium salts can isomerize to an open form, a ketoketenimine (*aaz*). We have direct proof for this species. N-Ethyl-5-phenylisoxazolium fluoborate (*abn*) was dissolved in methylene chloride containing one equivalent of triethylamine, and an IR spectrum was taken of the reaction solution immediately after mixing. The IR spectrum has strong bands at 4·85 μ, corresponding to the cumulated double bond system of a ketenimine, and at 6·17 μ, corresponding to a cross-conjugated benzoyl carbonyl. The species in solution is undoubtedly the ketoketenimine (*abo*).[31,32] Over a period of hours the ketoketenimine



abn *abo*

[27] R. A. Olofson, W. R. Thompson and J. S. Michelman, *J. Amer. Chem. Soc.* **86**, 1865 (1964); R. A. Olofson and A. C. Rochat, unpublished results.

[28] R. A. Olofson and J. M. Landesberg, unpublished results; see also the classic paper of R. Breslow (*J. Amer. Chem. Soc.* **80**, 3719 (1958)) on the exchange of the thiazolium cation.

[29] R. B. Woodward, R. A. Olofson and H. Mayer, *Tetrahedron*, in press.

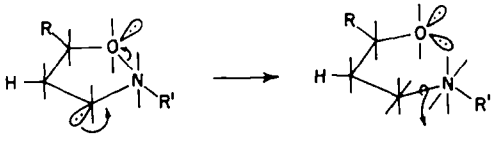
[30] Recent experiments confirm the correctness of this second formulation of the reaction course; R. A. Olofson and J. S. Michelman, unpublished results. The ring scission mechanism for the benzisoxazolium cation is also regarded as a concerted elimination.[24]

[31] Some deuterium exchange experiments which will be described later in connection with the direction of attack of acetate on the ketenimine eliminate the tautomeric structure, Ph–CO—C≡C—NHEt.

[32] Recently the ketoketenimine, Me—CO—CH=C=N—^{t}Bu, derived from N-t-butyl-5-methyl-isoxazolium perchlorate has been isolated and characterized by D. J. Woodman, *Dissertation* Harvard University (1965).

(*abo*) decomposes to unidentified products, probably by reaction with impurities in the methylene chloride or in the tertiary amine, but when acetic acid is added to the reaction medium a very fast reaction takes place to yield the enol ester analogous to *abe*. Though by breaking the reaction to form the enol ester into two parts experimentally, we do not retain the same reaction environment as far as acidity and basicity are concerned, it is most unlikely that another mechanism should be involved when the reactions take place without interruption.

It is of special interest that in the ring cleavage of the isoxazolium salt, stereoelectronic considerations dictate that the direction of electron flow must be counterclockwise as in *abp* (for simplicity using the ylide rather than a transition state as a model) rather than in the alternative direction, though superficially the same product is formed in both cases. When the electronic movement is in the counterclockwise direction, we have a simple *trans* elimination without disruption of the resonant π cloud and with direct formation of the ketoketenimine (*abq*) in its correct molecular orbital representation (except for simultaneously corrected displacements in atomic geometry and molecular polarity). If the electron flow is in the clockwise direction, we do not



abp *abq*

start with an electronic probe onto the electronic-acceptor oxygen, and a main driving force for the reaction is not utilized; in addition, the coupling of the orthogonal π cloud must be disrupted with a concomitant change in atomic and electronic geometry and loss of resonance energy in the transition state.

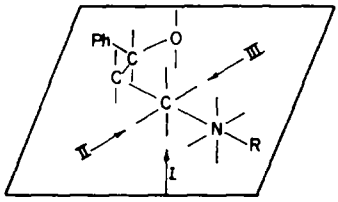
The next step in our general mechanism is reaction of the ketoketenimine with the nucleophile or its conjugate acid. Because of our interest in the reaction with carboxylate, we have studied the reaction of isoxazolium salts with acetate in detail.

In order to determine the nature of the species attacking the substrate, ketenimine *abo* (the methylene chloride solution also contained an equivalent of triethylammonium fluoborate), we carried out some crude relative rate studies. The decrease in the intensity of the 4·85 μ IR band served as a measure of the reaction rate. The relative rates follow:

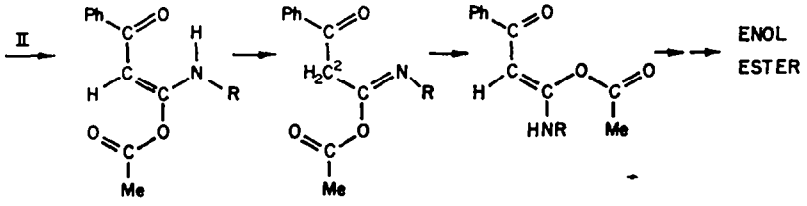
$$1\cdot5 \text{ eq. HOAc} \gg 1\cdot0 \text{ eq. HOAc} > 1\cdot0 \text{ eq. HOAc plus } 0\cdot25 \text{ eq. } Et_3N > 1\cdot0 \text{ eq. HOAc plus } 0\cdot5 \text{ eq. } Et_3N > 1\cdot0 \text{ eq. HOAc plus } 0\cdot75 \text{ eq. } Et_3N \sim 1\cdot0 \text{ eq. HOAc plus } 1\text{–}2 \text{ eqs } Et_3N.$$

Only the acetic acid and triethylamine concentrations were varied. A 0·1 molar solution of triethylammonium acetate in methylene chloride contains about 0·015 moles each of acetic acid and triethylamine. The results of the relative rate experiments in methylene chloride are compatible with either a protonation or an addition of free acetic acid to the ketenimine as the rate determining step in this solvent. The data are not consistent with a rate determining addition of acetate ion or a more complex analogue, i.e. triethylammonium acetate. More will be written about the significance of these results shortly.

There are three possible directions from which acetic acid or acetate anion could attack the ketenimine. Path I (attack from above or below) is unlikely on stereo-

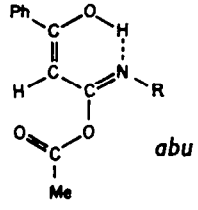


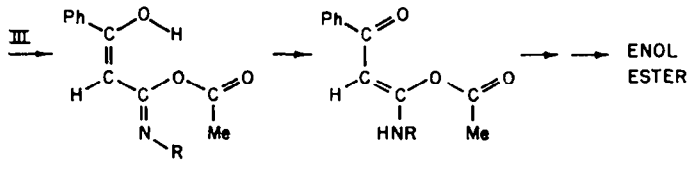
electronic grounds, since addition in that sense would involve disruption of the π cloud with a simultaneous loss in resonance energy. Though one might argue about the exact amount of resonance energy lost by removing the C=N double bond from the π system in the transition state, there is no doubt that enough energy would be lost to give such a transition state an appreciably higher energy than one involving attack *via* path II or path III. Of these latter two, path II seems favored on steric grounds, but there is an experiment which can distinguish between these two directions of attack. If attack takes place *via* path II, the initial product should be *abr* or its anion, and in order to remove the restriction of *trans* substitution on the double bond and allow acetate to migrate to the carbonyl oxygen *via abt* or a similar intermediate, it is necessary to go through a species (*abs*) in which the α-carbon atom (C-2) has become tetrahedral.[33] If on the other hand attack is by path II, a tautomer or anion



of *abv* is formed directly and such a species would be capable of undergoing rearrangement to the isolated enol ester without passing through an intermediate in which C-2 is tetrahedral.

[33] The only other iminoanhydride tautomer which bears a formal single bond in the correct position for rotation is the unfavorable or enol tautomer (*abu*) which must have a considerable barrier to rotation under the reaction conditions: (1) because it should be an exceedingly short-lived species as a result of its instability with respect to the tautomer (*abr*) (cf. —C(OH)=N-*vis-à-vis*-C(=O)—NH—; this is a vinylogue), (2) because the formal single bond has double bond character in consequence of a butadiene-like resonance stabilization, and (3) because of the presence of a very stable hydrogen bond.

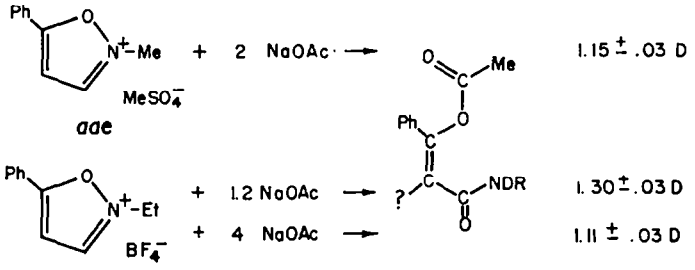




abv

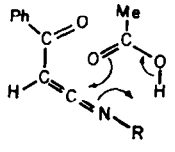
We can differentiate between path II and path III by preparing the enol ester in heavy water. If path II is operative, the enol ester should contain 1·5–2 deuterium atoms—one atom on the amide nitrogen and 0·5–1 atom on the α-carbon atom (depending on how many exchanges there are before the enol ester is formed). If path III is operative, the enol ester should contain 1–2 atoms of deuterium—one atom on the amide nitrogen and 0–1 atom on the α-carbon atom (though exchange is not obligatory it may take place). The only significant result then is 1–1·5 atoms of deuterium per molecule of enol ester. The results are presented in Scheme IV.

SCHEME IV



Studies of the IR spectra of the crude and of the purified enol ester indicate that the amide nitrogen is completely deuterated, and that deuterium is not exchanged out of the molecule during the purification procedure. Sodium acetate does not exchange its methyl hydrogen atoms for deuterium under the reaction conditions. Our experimental results, therefore, indicate that path III is the preferred direction of attack; the change in deuterium content with sodium acetate concentration may be a pH effect on the rate of ketonization of *abv* to *abs*.[34]

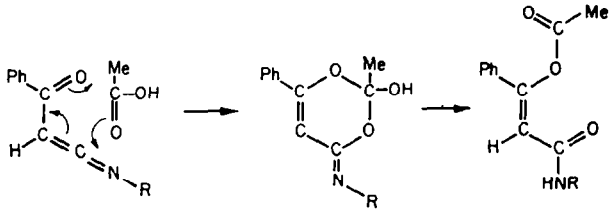
What then can be said about the mechanism of addition of acetate to the ketenimine? First, addition of acetic acid 1,2 or 1,4 (*abw*) across the C=N bond from direction III is unlikely, since then no alternative to a steric effect could be operating and attack *via* path II would be preferred.



abw

[34] A further argument is in accord with attack of acetic acid *via* path III. If attack is by path II, one would not expect to obtain the enol ester as the isolated product. The iminoanhydride first formed should rearrange directly to the imide in the facile four-center O → N acyl migration previously discussed.[16,31]

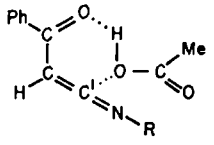
Another possibility would involve addition of acetic acid across the benzoyl carbonyl to give the cyclic intermediate (*abx*) directly. However, in the reaction of other



abx

nucleophiles besides carboxylate with isoxazolium salts where further rearrangement is not possible, the product always contains the nucleophile on the carbon next to nitrogen (*vide infra*).

We propose therefore that the reaction takes place through a cyclic transition state by what might be formally considered a 1,4-addition of the O—H of acetic acid across a diene system as in *aby*. It may be noted that initial interaction between the



aby

reacting species involves formation of a strong hydrogen bond between the benzoyl oxygen (the most basic position) and the acidic proton of acetic acid.[35] This interaction requires that later attack at C^1 takes place from direction III.

The cyclic intermediates (*abc* and *abe*) are the normal ones postulated for ester, anhydride, and amide hydrolysis, aminolysis, and exchange, and for which there is an abundance of evidence.[36] A final note might be added: the rearrangement of the enol ester to the imide is base-catalyzed as is expected. The O to N acyl migration of β-acetoxy-N-methylcinnamamide (*aan*) to the imide (*aag*) has a half-life of about twelve minutes in ethanol at 30°.

This completes the initial study of the mechanism of action of carboxylate ions on isoxazolium salts. Although many points of detail are still obscure and are receiving further investigation[37,38] there is little doubt that in general outline the mechanism presented here is correct.

The final topic to be treated in this paper is a survey of the reactions of isoxazolium salts with other nucleophiles besides carboxylate and also some reactions with carboxylate in which further transformations are involved. With only a very few exceptions

[35] Two very closely related pathways are not distinguished here: acetate ion could react with a protonated ketoketenimine or acetic acid could interact directly with the ketoketenimine, in either case the same cyclic intermediate (*aby*) must be formed.

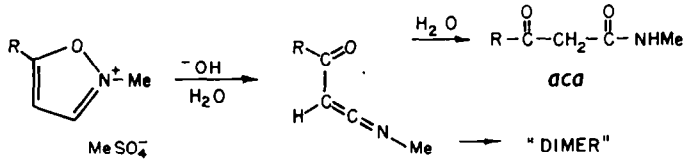
[36] E. S. Gould, *Mechanism and Structure in Organic Chemistry* Chap. 9; pp. 314 *et seq.* Holt, New York (1959).

[37] A complete kinetic study of the analogous reactions of the benzisoxazolium cation has been completed; D. S. Kemp, *Tetrahedron* (1966) and Ref. 24.

[38] Additional mechanistic studies on the reactions of isoxazolium salts have been carried out by D J. Woodman.[22]

these reactions were discovered by the Kiel school, and a substantial proportion were formulated correctly without knowledge of mechanism. Although we have verified experimentally only a few of these reactions, new conclusions are presented in a number of cases.

Reaction with hydroxide.[2,3,9] Two products are isolated, the expected acyl acetamide (*aca*) arising from addition of water to the ketenimine and a compound of unknown structure whose analysis and mol. wt. correspond to a dimer of the intermediate ketoketenimine (*abz*). Two examples are described in the early literature,

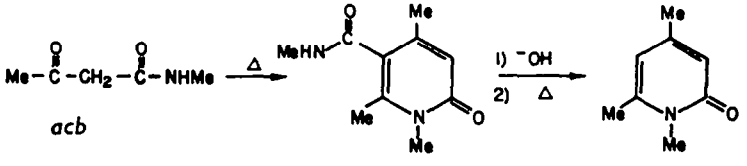


abz

"Mumm's" dimer, R = phenyl,[2] and "Meyer's dimer", R = methyl,[3]

Mumm's dimer	Meyer's dimer
IR: 6·11–6·18 μ (broad) 6·25 μ (short) 6·40 μ; CH_2Cl_2	IR: 6·08–6·18 μ (broad) 6·28 μ (short), 6·41 μ; CH_2Cl_2
UV: 339 mμ (12,800), 225 mμ (29,000); EtOH	UV: 315 mμ (13,800), 232 mμ (27,500); EtOH

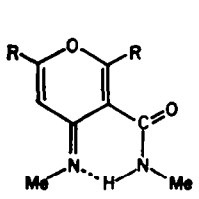
Meyer's dimer is not the lutidone (*acc*), which has been obtained by heating N-methylacetoacetamide (*acb*).[3] The structure of *acc* is proven by conversion on hydrolysis and



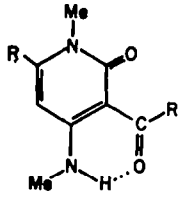
acb *acc* *acd*

decarboxylation to the known N-methyllutidone (*acd*).[39] And Meyer's dimer does nor release methylamine when it is heated in aqueous potassium hydroxide under conditions in which the amide (*acc*) is hydrolyzed to the carboxylic acid.[3] This eliminates from consideration structure *ace* and may of the structures available from Diels-Alder dimerizations of the ketoketenimine. We do not believe that the reaction is of the Diels-Alder type, since a solution of the ketoketenimine in methylene chloride does not undergo this reaction even in the presence of excess triethylamine. The reaction may be one of the ketoketenimine with the anion of the acetoacetamide (*aca*) followed by dehydration; and a structure which we regard as probable is that of the pyridone (*acf*).

[39] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **17**, 1019, 2903 (1884).

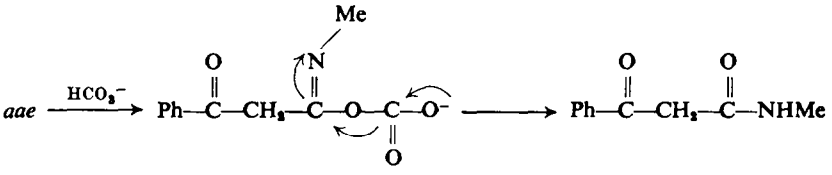


ace



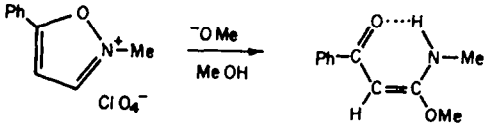
acf

Reaction with bicarbonate.[4] When bicarbonate rather than hydroxide is used as the nucleophile, the acylacetamide (*ach*) is isolated in almost quantitative yield. It is probable that the species *acg* is an intermediate in its formation.



acg *ach*

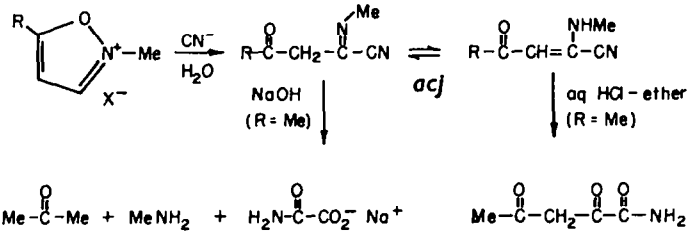
Reaction with alkoxide.[2,4,10,14] The simple addition product between the alcohol and the ketenimine is formed. We have repeated Mumm's work on the reaction of methoxide in methanol with the isoxazolium salt (*aci*) and assign structure *aau* (a tautomer of Mumm's original structure) to the product. The compound is basic; it



aci *aau*

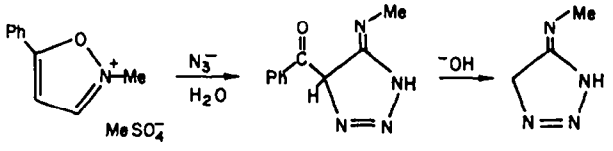
yields methylamine and methyl benzoylacetate on treatment with acid and methylamine and benzoic acid on heating in strong base.[2] Its UV spectrum is very much like that of the model (*aav*) while the IR bands at 6·15 μ—eneamine, and 6·5–6·6 μ—cross conjugated aromatic carbonyl and N—H are as expected (*vide supra*). The *cis* substitution about the double bond is demanded by the absence of a visible N—H stretching vibration in the IR spectrum, which indicates that the proton is strongly hydrogen bonded. An analogous reaction seems to take place with phenoxide ion.[14]

Reaction with cyanide.[5,6,8,10–12,15] Once again the simple addition product (*acj*) is formed, though sometimes both enol and keto tautomers can be isolated.[10] We



have not repeated this work but excellent evidence for the position of cyanide substitution (R = methyl) has been obtained from hydrolytic studies.

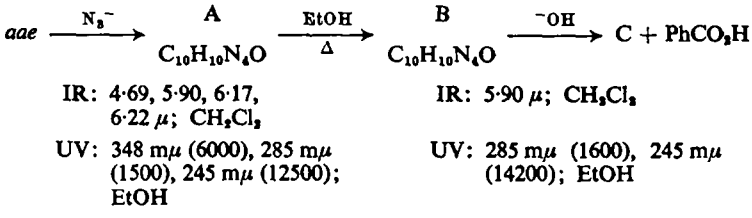
Reaction with azide.[7] When Stülcken treated the isoxazolium salt (*aae*) with sodium azide in water and filtered the precipitate after 24 hr, he obtained a white solid to which he assigned the triazole structure (*ack*) on the basis of analytical data, phenylhydrazone formation, and alkaline hydrolysis to yield benzoic acid and another compound to which he gave the structure *acl*. We repeated this work and obtained



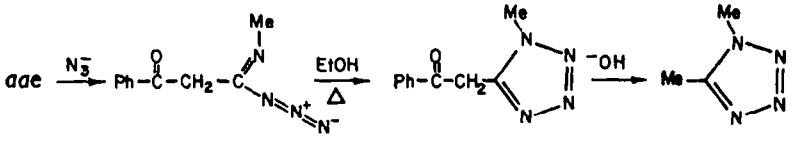
aae *ack* *acl*

all of Stülcken's products. We also isolated an additional unstable compound by filtering the product precipitated within 30 min of mixing the isoxazolium salt and azide in water. This new substance rearranged to Stülcken's initial product on recrystallization from ethanol. The accumulated evidence is diagrammed in Scheme V.

SCHEME V



On the basis of our general mechanism. A should be the iminoazide or azidoazomethine (*acm*), B the tetrazole (*acn*) and C 1,5-dimethyltetrazole (*aco*). And as



acm *acn* *aco*

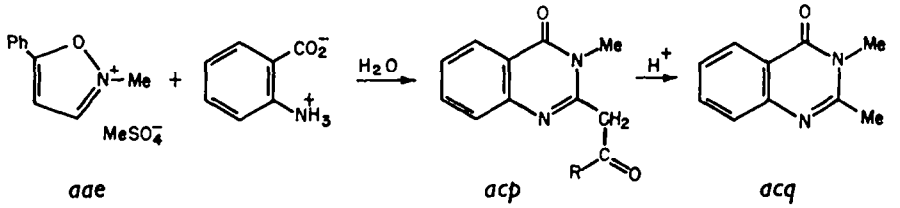
expected the hydrolysis product C is identical with authentic 1,5-dimethyltetrazole, obtained by heating the O-benzenesulfonyloxime of acetone with sodium azide in ethanol-water.[40] The bands in the IR spectrum at 4·69 μ, characteristic of the cumulated double bond azide system, and at 5·90 μ, characteristic of a simple acetophenone carbonyl, together with an acetophenone-like UV spectrum constitute strong evidence in favor of the assigned structure for A. The weak 348 mμ band of A is very probably associated with the presence of a certain proportion of enolic (or enaminic) tautomer in solution. The acetophenone like IR and UV spectra of B are in accord with its assigned structure (*acm*).

[40] A. G. Knoll, Chemische Fabriken, Ger. Pat. 538981, Nov. 11, 1926; *Chem. Abstr.* **26**, 2199 (1932).

[41] For more complex cases ane background information, see J. H. Boyer and E. S Miller, Jr., *J. Amer. Chem. Soc.*, **81**, 4671 (1959).

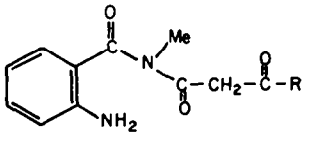
We believe that this is the first time that a compound with the simple iminoazide system (or open form of a tetrazole) has been isolated,[41] although such an intermediate is postulated in the formation of tetrazoles from nitriles and hydrazoic acid. Cyclization to the tetrazole (*acn*) takes place with a half-life of approximately 100 min in 1:1 methanol-water at 27°.

Reaction with anthranilate.[2,5,13,42] We have not repeated this reaction which is reported by Mumm (R = phenyl)[2] and Bergell (R = methyl)[5] to yield the quinazolone (*acp*) on the basis of acidic hydrolysis to the known 2,3-dimethylquinazolone (*acq*).[43]



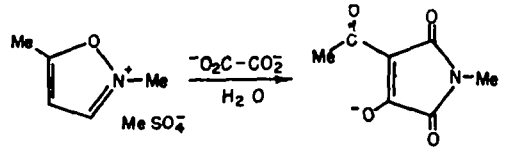
aae *acp* *acq*

The product can be visualized as being produced by a dehydrative cyclization of the expected intermediate imide (*acr*).

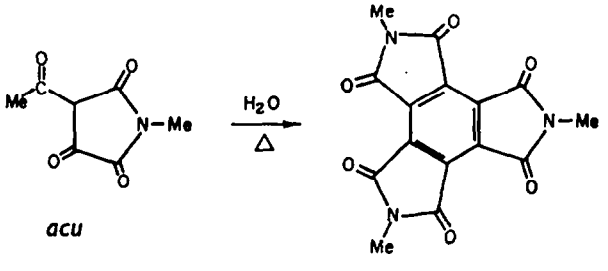


acr

Reaction with oxalate.[5,7,11,13,14] Probably the most fascinating of the reactions reported by Kiel school is that of N-methyl-5-methylisoxazolium methosulfate (*acs*)



acs *act*

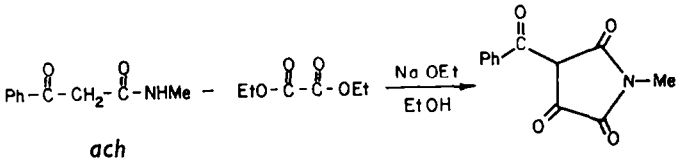


acu *acv*

[42] Before we describe reactions with carboxylates in which special rearrangements take place, it is useful to list those carboxylic acids which yield simple products which must now be assigned enol ester structures analogous to *abd*. These are acetic acid,[8] formic acid,[8] benzoic acid,[2,5,9] *p*-toluic acid,[5,7] *m*- and *p*-nitrobenzoic acid,[7] chloroacetic acid,[7] phenylacetic acid,[7] crotonic acid,[7] and cinnamic acid.[7,14]

[43] A. Weddige, *J. Prakt. Chem.* **36**, 141 (1887)

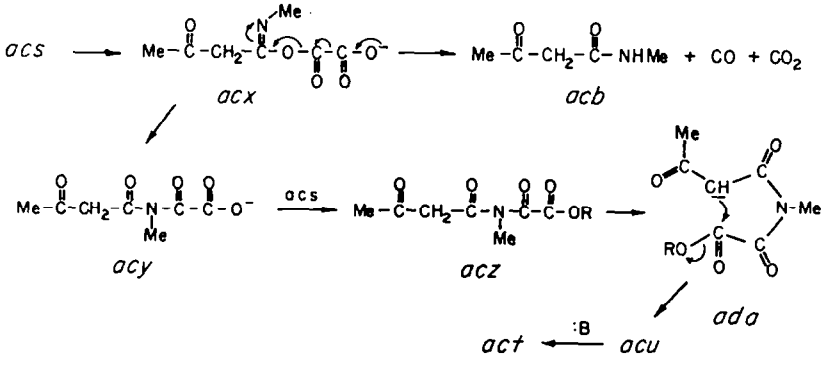
with potassium oxalate in water. The initial product isolated is the salt (*act*) which on acidification affords the free pyrrolidinetrione (*acu*); the latter, when boiled in water, yields trimethylparamide (*acv*), probably *via* a cleavage of the acetyl group followed by three aldol condensations. This final product (*acv*) constitutes the main literature evidence for the structure of the pyrrolidinetrione; trimethylparamide was compared by Mumm[44] with an authentic sample of the material. Since the IR and UV spectra are not definitive, we have checked the pyrrolidinetrione structure by synthesis. A similar reaction to yield a pyrrolidinetrione (*acw*)[5,7,11,13,14] is given by the 5-phenyl-isoxazolium salt (*aae*), and we choose to synthesize this compound following the general procedure of Howard[45] from N-methylbenzoylacetamide (*ach*) and ethyl oxalate. The product (*acw*) is identical in all respects with the one obtained from the



ach *acw*

isoxazolium salt. The methyl compound (*acu*) has an IR spectrum: 5·64, 5·81, 6·01, 6·29 and 6·40 μ in CH_2Cl_2 and an UV spectrum; 305 mμ (1,900), 258 mμ (18,300), and 241 mμ (13,800) in ethanol, while the phenyl analogue (*acw*) has an IR spectrum: 5·63, 5·79, 5·92, 5·98 and 6·23 μ in CH_2Cl_2 and an UV spectrum: 334 mμ (6,700), 285 mμ (10,100), and 235 mμ (12,200) in ethanol. The spectra do not tell us which tautomers are isolated.

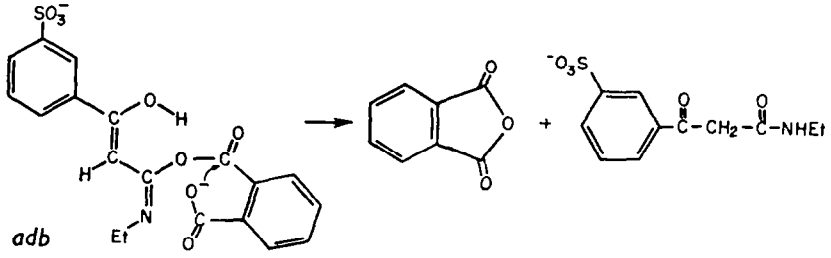
A few mechanistic gymnastics are required to rationalize the formation of a pyrrolidinetrione. The first intermediate is probably the iminoanhydride (*acx*) which can undergo two reactions. The first of these is decomposition to N-methylaceto-acetamide (*acb*) with concomitant evolution of carbon monoxide and carbon dioxide. And, in fact this is a major side reaction; it has been shown that the two gases are given off in equivalent amounts.[5,7] Alternatively (*acx*) can undergo the normal rearrangement to the imide (*acy*) which can react with another mole of isoxazolium salt to yield a carboxyl-activated species of type *acz*. The anion of this intermediate (*ada*) can cyclize with elimination of N-methylacetoacetamide (*acb*) to yield the pyrroli-dinetrione (*acu*) which ionizes to the isolated salt (*act*).



[44] O. Mumm, *Liebig's Ann.* **411**, 244 (1916).

[45] E. G. Howard, A. Kotch, R. V. Lindsey, Jr. and R. E. Putman, *J. Amer. Chem. Soc.* **80**, 3924 (1958).

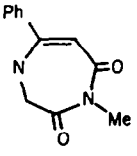
Anhydride formation. Stülcken[7] reported the formation of N-methylbenzoylacetamide (*ach*) when the isoxazolium salt (*aae*) is treated with the dianion of hydroxysuccinic acid in water. Thinking there might be simultaneous cyclic anhydride formation, we ran a few experiments to check this hypothesis. As expected, when the dianion of phthalic acid is treated with a zwitterionic isoxazolium salt (*abl*)[29] in acetonitrile, phthalic anhydride is formed though in only moderate yield (61%). The yield indicates that rearrangement of *adb* to the imide is competitive with anhydride formation. From the aliphatic acid, phthaloylglycine, no anhydride is formed, a



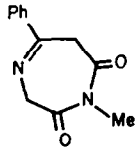
adb

result which is substantiated by our results in peptide synthesis[29] where anhydride formation would lead to a drastically reduced yield.

Reaction with glycine.[7] The enamine tautomer (*adc*) of the Schiff base structure (*add*) which Stülcken favored for the product from the treatment of N-methyl-5-phenylisoxazolium methosulfate (*aae*) with glycine in water is in agreement with the spectroscopic results (IR: 3·06, 5·78, 6·16, 6·25, 6·35 and 6·55 μ in KBr; UV: 240 mμ (14,100), 327 mμ (25,300) in EtOH) though other structures are not ruled out. A

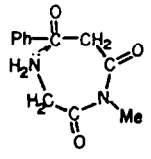


adc

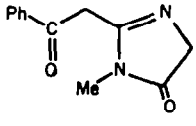


add

species of this structure could be formed by dehydration of the normal imide (*ade*). When the sodium salt of glycine was used rather than the free zwitterion, Knust[14] obtained a different acidic product to which he assigned structure *adf*. We have not



ade

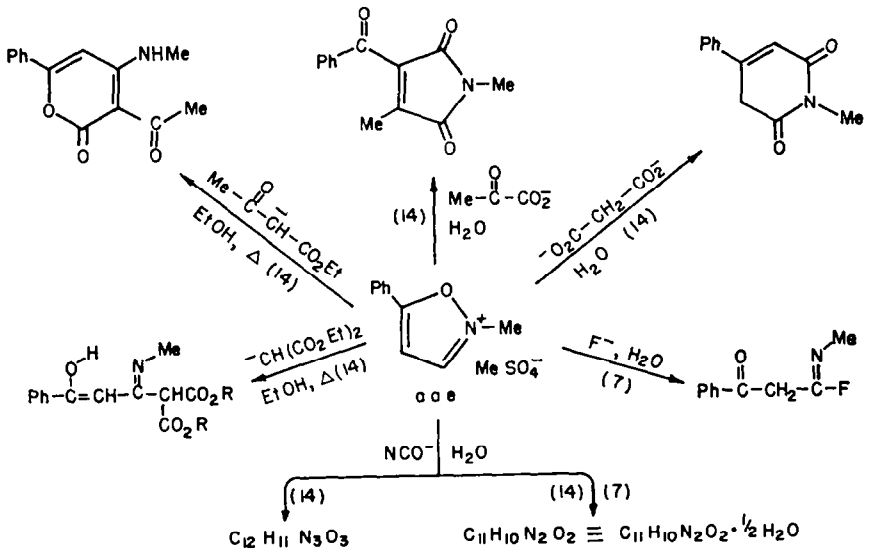


adf

verified this experiment.

Other reactions. The remaining reactions examined by the Kiel school are diagrammed in Scheme VI. We have not repeated these reactions and suggest that though many of the structures postulated by Mumm and his students are in accord with our

SCHEME VI



mechanistic interpretation, these should only be considered working hypotheses; evidence in favor of many of them is very meager. Nevertheless, the variety of heterocyclic systems produced, under very mild conditions, in the reactions involving bifunctional nucleophiles, is striking, and promises that further exploration of this area will be rewarding.

EXPERIMENTAL

All m.ps were taken in soft glass capillary tubes in a Hershberg m.p. apparatus using Anschütz thermometers. The IR spectra were run on a Perkin–Elmer Model 21 Double Beam Recording Spectrophotometer equipped with NaCl optics, and bands in the 5–7 μ region were calibrated against the 5·88 μ band of atmospheric water vapor; the UV spectra were run on a Cary Model 11 Recording Spectrophotometer. NMR spectra were measured on a Varian 60 megacycle Model V 4300B Spectrometer.

N-*Methyl-5-phenylisoxazolium methosulfate* (aae)

Using Mumm's original procedure,[8] redistilled dimethyl sulfate (2·00 g) and 5-phenylisoxazole[46] (2·216 g) were placed in a cork-stoppered 25 ml test tube. The mixture was first heated to 60°, then to 80° over a period of 1·5 hr, and finally to 100° and allowed to stand at that temp for 30 min. If the heating process was hastened, the reaction proceeded with such vigor that an explosion occurred; the critical mass is probably not more than 5 times that used here. On cooling, the product solidified to a yellow-brown glass. This was usually dissolved in a small amount of water, extracted with ether, and used directly. It could be crystallized by trituration with ether, but purification was difficult because the methosulfate was exceedingly hygroscopic.

N-*Methyl-5-phenylisoxazolium perchlorate* (aci)

An aqueous solution of *aae* was added to a saturated solution of potassium perchlorate in water to which a little perchloric acid had been added (to pH 2–3), and the precipitated perchlorate salt was filtered off, washed with water and dried. It was recrystallized twice from acetonitrile–ether before use. The compound explodes on heating.

[46] An improved procedure for the synthesis of this compound is reported in Ref. 29.

N-*Methyl-5-phenylisoxazolium bisulfate*

The crude *aae* was refluxed in acetone (to which a few drops of water had been added) for 3 hr. When the solution was cooled, the bisulfate crystallized. It could be recrystallized from MeCN–pet. ether; m.p. 133–134·5° (Lit.[7] 135°).

N-*Methyl-5-methylisoxazolium methosulfate* (acs)

This was prepared in the same way as the 5-phenyl analogue from 5-methylisoxazole (gift from Chas. Pfizer and Co., Inc.). The highest required temp was 80° and the mixture was left at that temp for 30 min. The crude oil was dissolved in water, extracted with ether, and the aqueous solution used directly.

N-*Ethyl-5-phenylisoxazolium fluoborate* (abn)

Triethyloxonium fluoborate[47] (7·60 g, 0·04 M) and 5-phenylisoxazole[46] (5·80 g, 0·04 M) were dissolved in 50 ml CH_2Cl_2 and the mixture allowed to stand overnight at room temp protected by a $CaCl_2$ drying tube. After the solvent had been removed at reduced press., the solid residue was crystallized twice by being dissolved in warm acetone and precipitated with ether; m.p. 100–100·5°; yield 9·83 g or 94%. The product slowly decomposes and etches glass containers on standing; UV: λ_{max} (ε) 295 mμ (21,000) in CH_2Cl_2. (Found: C, 50·74; H, 4·85; N, 4·92. $C_{11}H_{12}NOBF_4$ requires: C, 50·61; H, 4·64; N, 5·37%.)

β-Acetoxy-N-*methylcinnamamide* (aan)

Following the procedure of Mumm,[8] the crude *aae* obtained from 2·9 g of 5-phenylisoxazole was dissolved in 10 ml water and extracted with ether. The aqueous solution was then added to a cold solution of AcONa (3·28 g) in water (20 ml), and the clear solution placed in an ice bath. After 1 hr the precipitate was filtered off, washed with water, and dried *in vacuo;* yield: 3·6 g or 82%. Further crops contained substantial quantities of the imide (*aag*). The product was twice dissolved in CH_2Cl_2 and precipitated with pet. ether to give pure material of m.p. 105–106° (Lit.[1] 107°). The enol ester is not stable and decomposes over a period of days at room temp to a brown tar; IR: 2·88, 5·65, 5·96, 6·12, 6·6, 8·4 μ in CH_2Cl_2 (Fig. 1); UV: λ_{max} (ε) 267 mμ (18,700) in CH_2Cl_2.

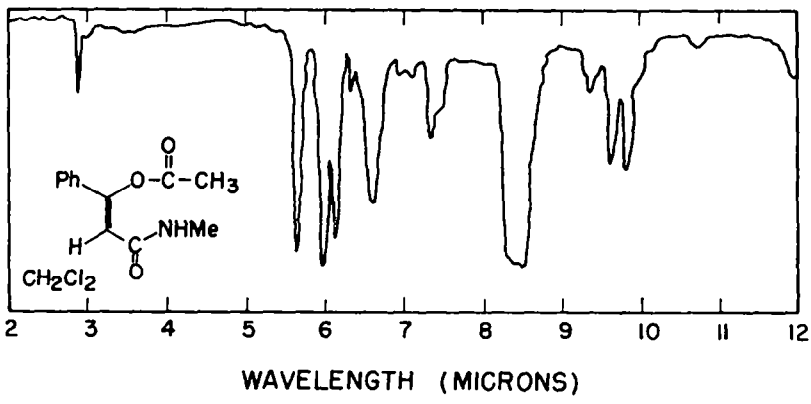


FIG. 1.

Reaction in EtOH at similar concentrations afforded 80–90% of the product in which EtOH had added to the ketenimine and a small quantity of a mixture of enol ester and imide (product ratios determined with the aid of IR spectra). Treatment of the bisulfate salt with AcOH in water followed by titration with NaOHaq and treatment of the perchlorate salt with AcOK in MeCN also gave moderate yields of the enol ester.

[47] H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).

N-*Acetyl*-N-*methylbenzoylacetamide* (aag)

The enol ester (*aan*) was recrystallized 3 times from warm EtOH to yield its isomer (*aag*); m.p. 100–101° (Lit.[3] 101°); 60%; IR: 5·85–5·95 μ in CH_2Cl_2 (Fig. 2); UV: λ_{max} (ε) 242 mμ (12,300), 314 mμ (5,100) in EtOH. A better yield could be obtained by crystallization of the enol ester from

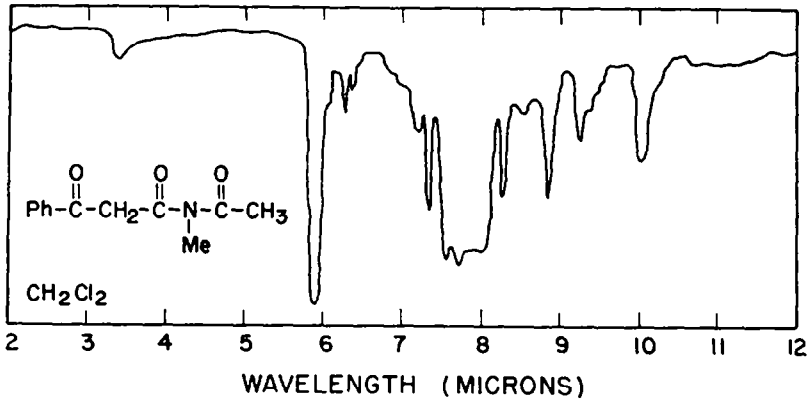


FIG. 2.

boiling MeCN. Using the decrease of the 267 mμ band of the enol ester as a measure of rate, and applying a Guggenheim analysis[48] to the results, a crude half-life for the rearrangement of 12 min in abs EtOH at 30° was determined.

Ethanolysis to ethyl benzoylacetate and N-*methylacetamide*

The imide (*aag*) was refluxed in EtOH for 2 hr. Removal of the solvent at reduced press afforded a residue whose IR spectrum showed the presence of N-methylacetamide and ethyl benzoylacetate. Upon prolonged evacuation the volatile N-methylacetamide was also evaporated, and the final residue had the same IR spectrum in all details as an authentic sample of ethyl benzoylacetate.

Deuterium exchange experiments on the isoxazolium salt (abl)

The zwitterionic isoxazolium salt, N-ethyl-5-phenylisoxazolium-3′-sulfonate[39] (*abl*) (2 g), was dissolved in 100 ml D_2O, and one-half equiv. Et_3N was added. The mixture was allowed to stand at room temp overnight; the D_2O was then removed at reduced press. The product was precipitated 4 times from an almost saturated 1N solution of HCl in D_2O with acetone to yield isoxazolium salt of the same decomposition point as the starting material (30% recovery). It is expected that no further possible exchange occurs in acid solution.[37,38] NMR spectra of the starting material and the reisolated isoxazolium salt were taken in deuterotrifluoroacetic acid and these were identical; there was no noticeable loss in the relative intensity of any peak.

A similar experiment was run in which *abl* was diluted to 0·001M in D_2O without adding any Et_3N, then left overnight, and finally recovered. Again no deuterium was exchanged into the isoxazolium salt.

Formation and decomposition of N-*ethyl-benzoylketenimine* (abo)

Compound *abn* (261 mg, 1 mM), was dissolved in CH_2Cl_2 in a 10 ml volumetric flask; 1 mM Et_3N in the same solvent was then added, the flask filled to the mark with CH_2Cl_2 and an IR spectrum immediately taken; IR: 4·85, 6·17 μ in CH_2Cl_2 (Fig. 3).

The mixture was left in the IR cell and additional spectra were taken of the 4–7 μ region over the next 3 hr (Fig. 4). A complete spectrum taken after 40 hr was not very informative; it did however show the absence of a "Mumm's dimer" like compound.

In another series of experiments, the initial concentration of Et_3N was 0·15 M (1·5 mM added), and a similar set of spectra of the 4–7 μ region indicated a slightly increased rate of decomposition of the ketenimine, possibly as a result of reaction with impurities in the Et_3N.

[48] A. A. Frost and R. G. Pearson, *Kinetics and Mechanism* p. 48. Wiley, New York (1953).

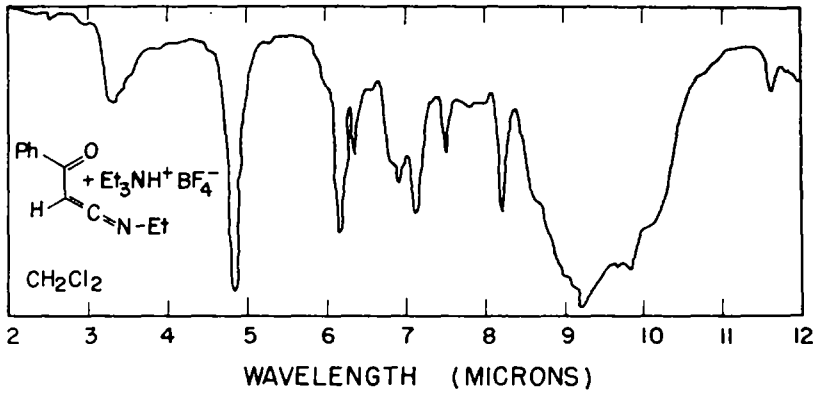


FIG. 3.

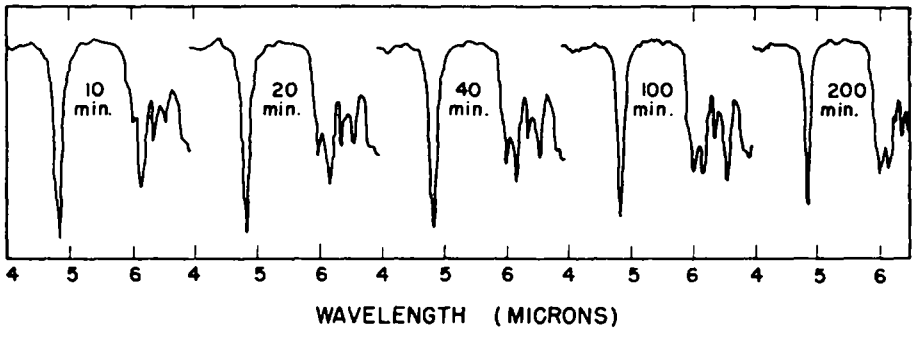


FIG. 4. Reaction with 1·0 equiv Et_3N in CH_2Cl_2.

Addition of AcOH to the solution of the ketenimine afforded the enol ester in a very fast reaction (*vide infra*).

Relative rate studies on the reaction of N-*ethyl-benzoylketenimine* (abo) *with acetic acid*

A solution of the ketenimine was prepared by weighing 65 mg (0·25 mM) *abn* into a 10 ml volumetric flask and dissolving it in a little CH_2Cl_2; one equiv (0·25 mM) Et_3N in the same solvent was added to give a total volume of about 7 ml, and the mixture was shaken for 1 min. Then 1 equiv AcOH in CH_2Cl_2 was added (Time Zero) and the volumetric flask filled to the mark and shaken for 15 sec. A portion of the solution was put in an IR cell and speedily placed in the IR machine; the rate of enol ester formation was followed by watching the decrease in the intensity of the ketenimine band at 4·85 μ with time. Additional experiments were performed in which 1 equiv of AcOH plus 0·1-1 equiv Et_3N were added at Time Zero. The results are tabulated in Table 2. The rates are very crude, the only temp control being that of the room.

TABLE 2

No. equiv HOAc	No. equiv Et_3N	% Reaction after one min	two min	five min
1	0·00	72	85	95
1	0·10	63	76	90
1	0·25	51	68	85
1	0·50	39	56	79
1	0·75	33	51	78
1	1·00	31	49	77

In other reaction series we found that addition of 1·5 equivs of AcOH with no added Et_3N gave an exceedingly fast rate, but addition of 1·5 equivs of AcOH plus 1·5 equivs of Et_3N did not give as fast a rate as one equiv of AcOH alone. Use of 2–3 equivs rather than one equiv of Et_3N to one equiv of AcOH did not change the rate within experimental error.

In a 0·1 M solution of triethylammonium acetate in CH_2Cl_2, the dissociated salt accounts for about 85% of the species in solution (estimated from the IR spectrum).

The formation of β-acetoxy-N-ethylcinnamamide in heavy water

Compound *abn* (1·04 g, 4 mM) was added to a cold solution of 1·31 g (16 mM) of AcONa in 15 ml of D_2O, and the mixture was stirred in an ice bath for 30 min. The precipitate was filtered off, washed with D_2O, dried under vacuum at room temp for 1 hr, and finally precipitated 5 times from CH_2Cl_2 with pet. ether to yield material m.p. 105–106°. The conditions were not optimum for the best yield, the purpose of the experiment being only to determine the amount of deuterium in the product; IR: 3·96, 5·66, 5·98 (shoulder), 6·01, 6·13 μ in CH_2Cl_2; UV: $\lambda_{max}(\varepsilon)$ 268 mμ (20,100) in CH_2Cl_2. (Found: C, 66·50; H + D, 6·51; N, 5·95. $C_{13}H_{14}DNO_2$ requires: C, 66·65; H + D, 6·88, N, 5·98%.)

$$\text{D Anal.: } \frac{100 \times \#D}{\#H + \#D} = 7{\cdot}37 \text{ excess atom \% or } 1{\cdot}11 \text{ D per molecule.}$$

This deuterated enol ester (20 mg) was dissolved in 50 ml CH_2Cl_2 which had been saturated with H_2O, and the mixture was allowed to stand at room temp overnight. The solution was dried (Na_2SO_4), the solvent removed at reduced press, and an IR spectrum taken of the residue. The identity of this spectrum with that of the starting material indicated that there was no exchange of deuterium for hydrogen on the amide nitrogen during the isolation procedure for the enol ester.

Another experiment was run under exactly the same conditions and workup procedure as the enol ester formation reaction above, except that 0·39 g (4·8 mM) of AcONa was used, again giving material of m.p. 105–106°. (Found: C, 66·37; H + D, 6·45; N, 5·91. $C_{13}H_{14}DNO_2$ requires: C, 66·65; H + D, 6·88; N, 5·98%.)

D Anal.: 8·66 excess atom % or 1·30 D per molecule.

The procedure described for the initial synthesis of *aan* (*vide supra*) was used for the synthesis of this compound in D_2O; m.p. 105·5–106·5°.

D Anal.: 8·85 excess atom % or 1·15 D per molecule.

The following control experiment was also performed. AcONa (200 mg) was dissolved in 25 ml D_2O, and the solution left at room temp for 1 hr. Then 25 mg AcOH was added and the solution left for another hr at room temp. The solvent was stripped off at reduced press at 35°, and the AcONa dried overnight at 60° and for 4 hr at 130° under high vacuum.

D Anal.: less than 0·02 excess atom % D.

Reaction with hydroxide

(a) N-*Methylbenzoylacetamide* (ach). Mumm's original procedure[8] was used to give, in small yield, a product identical with the one isolated from bicarbonate treatment of *aae*; its properties will be described later in this section.

(b) "*Mumm's dimer*". In addition to *ach* another product was obtained on treatment of the crude *aae* with two equivs of KOH in water, using the general procedure for reaction with acetate described above. The reaction mixture was left in the refrigerator overnight; then the yellow product was filtered, washed with water and dried. Two recrystallizations from EtOH yielded a light yellow solid of m.p. 198–199° (Lit.[8] 198°); 41%; IR: 6·11–6·18, 6·25, 6·40 μ in CH_2Cl_2 (Fig. 5); UV: $\lambda_{max}(\varepsilon)$ 225 mμ (29,200), 339 mμ (12,800) in EtOH.

(c) "*Meyer's dimer*". This compound was prepared in 47% yield from crude oil obtained on heating 5-methylisoxazole with dimethyl sulfate, using the same procedure as in the preparation of Mumm's dimer; m.p. 176–177° (Lit.[8] 176–177°); IR: 6·09–6·18, 6·28, 6·41 μ in CH_2Cl_2 (Fig. 6); UV: $\lambda_{max}(\varepsilon)$ 232 mμ (27,500), 315 mμ (13,800) in EtOH.

Reaction with bicarbonate-N-methylbenzoylacetamide (ach)

Reaction of crude *aae* with two equivs $NaHCO_3$aq in the refrigerator overnight gave a yellow precipitate, which after 2 recrystallizations from EtOH–water yielded 83% of an off-white solid

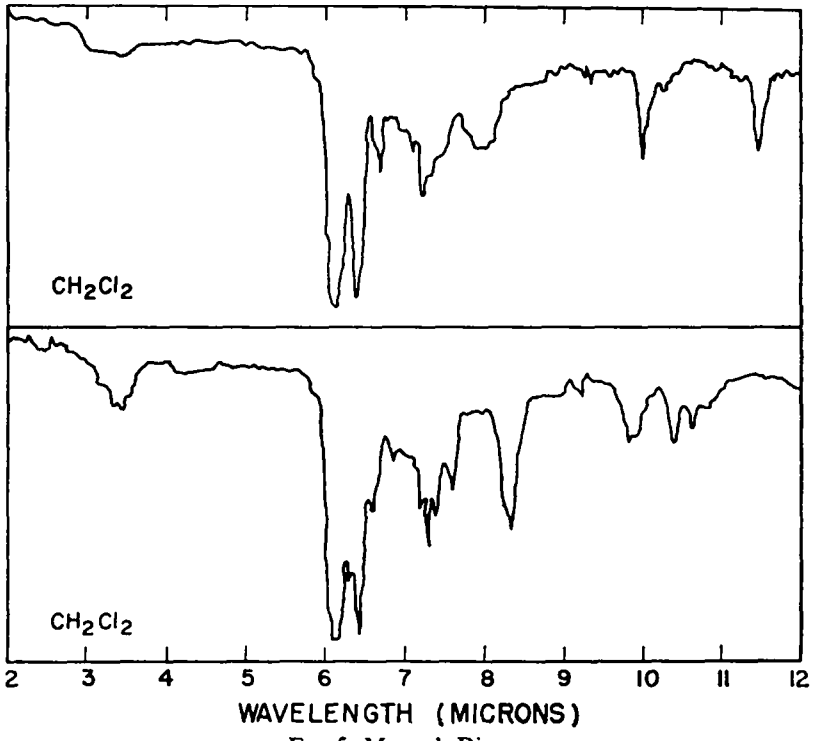


FIG. 5. Mumm's Dimer.
FIG. 6. Meyer's Dimer.

of m.p. 103–104° (Lit.[3] 101–102°); IR: 2·86, 2·93, 5·92 (shoulder), 5·95, 6·5 μ in CH_2Cl_2; UV: $\lambda_{max}(\varepsilon)$ 244 mμ(10,800), 286 mμ(5,300) in EtOH.

Reaction with methoxide

Compound *aci* was dissolved in MeOH and 1·1 equivs MeONa in the same solvent was added. The MeOH was removed *in vacuo*, the product partitioned between AcOEt and water, the water layer discarded, and the organic layer extracted once with water and finally dried (Na_2SO_4). When the AcOEt had been stripped off at reduced press and the product crystallized twice from CH_2Cl_2–pet. ether, an 83% yield of *aau* was obtained as a white solid of m.p. 67·5–68° (Lit.[3] 68–69°); IR: 6·15, 6·5–6·6 μ in CH_2Cl_2 (Fig. 7); UV: $\lambda_{max}(\varepsilon)$ 235 mμ (10,500), 321 mμ (19,600) in MeOH.

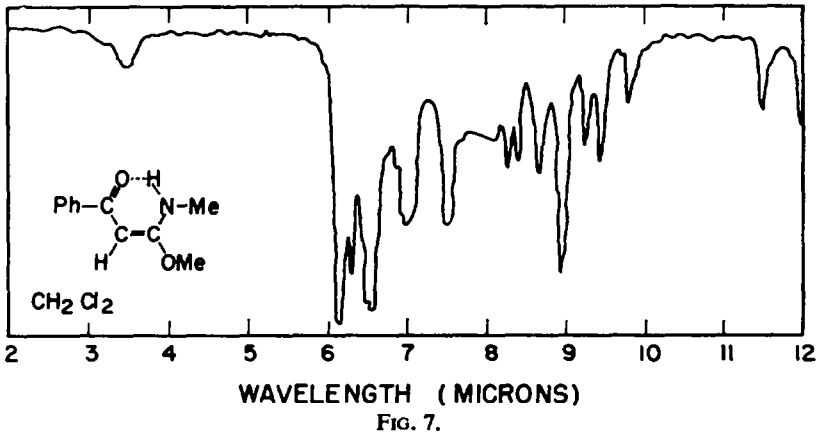


FIG. 7.

Reaction with azide

(a) *The iminoazide* (acm). The crude *aae* from 2·9 g 5-phenylisoxazole was dissolved in 10 ml water and extracted with ether. The last traces of ether were removed from the aqueous solution under vacuum. Then this solution was added to an icy solution of sodium azide (3·0 g) in 20 ml water, and the mixture placed in an ice bath. After about 30 min the precipitated solid was filtered, washed with cold water, and dried under vacuum at room temp; yield: 52%. An analytical sample was prepared by partly dissolving the material in CH_2Cl_2, filtering, and precipitating the product with pet. ether; IR: 4·69, 5·90, 6·17, 6·62 μ in CH_2Cl_2 (Fig. 8); UV: λ_{max} (ε) 245 mμ (12,500), 285 mμ (1,500), 348 mμ (6,000) in EtOH. (Found: C, 59·30; H, 5·06; N, 28·18. $C_{10}H_{10}N_4O$ requires: C, 59·50; H, 4·89; N, 27·71.)

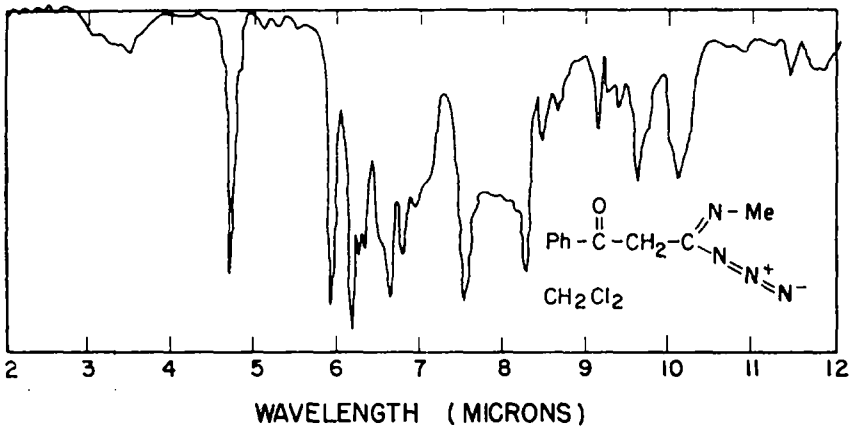


FIG. 8.

Further crops from the aqueous solution contained varying amounts of *acn*.

(b) 1-*Methyl-5-phenacyltetrazole* (acn). When *acm* was boiled for 10 min in a small amount of EtOH, the solution cooled, and the crystals filtered and dried, an 88% yield of the isomer of m.p. 157–158° (Lit.[7] 158°) was obtained. Further crystallization did not change the m.p. Cyclization to the tetrazole has a half-life of approximately 100 min in 1:1 MeOH–water (by volume) at 27° as determined by using the decrease in the 348 mμ band of the iminoazide as a measure of rate; IR: 5·90 μ in CH_2Cl_2 (Fig. 9); UV: λ_{max} (ε) 245 mμ (14,200), 285 mμ (1,600) in EtOH.

(c) *Hydrolysis of* acn *to benzoic acid and* 1,5-*dimethyltetrazole* (aco). The tetrazole (*acn*) was boiled in 2N NaOH for 1 hr, the solution cooled and acidified with HCl, and the precipitated

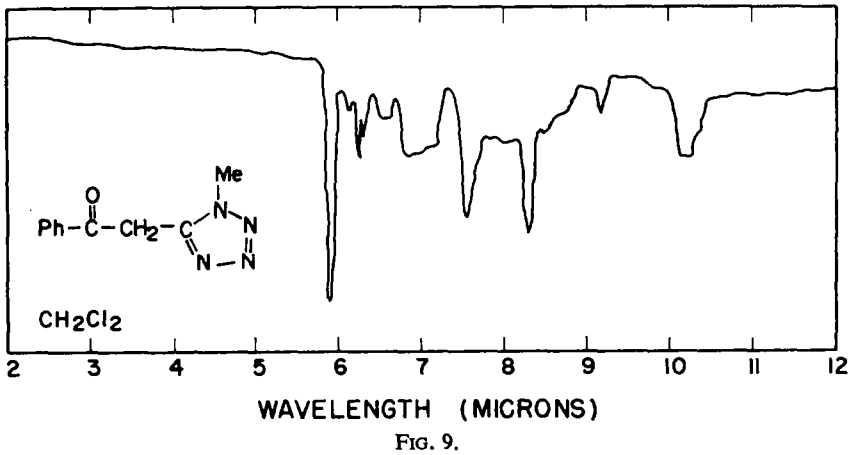


FIG. 9.

benzoic acid filtered off and dried (identical with authentic benzoic acid). Then the aqueous filtrate was neutralized to pH 7 with NaOHaq and taken to dryness at reduced press. The residue was triturated with EtOH, filtered, the EtOH removed, and the product crystallized 3 times from the same solvent to yield 1,5-dimethyltetrazole m.p. 69·5–70·5°.

A comparison sample of 1,5-dimethyltetrazole (the procedure is described here since none is given in the abstract[40]) was prepared by heating the O-benzenesulfonyloxime of acetone (m.p. 51–52°) slowly with 1·3 moles sodium azide in aqueous EtOH on a hot water bath (if the solution is heated too fast the mixture explodes) over a period of 1 hr to reflux; the solution was cooled and taken to dryness at reduced press. Finally the residue was triturated with AcOEt and filtered. The organic layer was shaken with a small amount of water, dried (Na_2SO_4), the solvent removed, and the product crystallized twice from EtOH to give 68% of material, m.p. 70–71° (Lit.[40] 70–71°). This was identical with the material obtained from alkaline treatment of *acn;* the IR spectra were superimposable and the mixture m.p. was not depressed (69·5–71°).

Reaction with oxalate

(a) 3-*Acetyl*-1-*methylpyrrolidinetrione, potassium salt* (act). The published procedure of Mumm and Bergell[18] was used to give the K salt in 41% yield; IR: 5·64, 5·75 (shoulder), 5·80–5·85, 6·09 μ in KBr; UV: λ_{max} (ε) 242 mμ (14,900), 258 mμ (21,400), 348 mμ (2,200) in H_2O.

(b) 3-*Acetyl*-1-*methylpyrrolidinetrione* (acu). The published procedure[18] was used to give an almost white solid, m.p. 122–124° (Lit.[18] 120–124°) in 85% yield; IR: 5·64, 5·81, 6·01, 6·29, 6·40 μ in CH_2Cl_2 (Fig. 10); UV: λ_{max} (ε) 241 mμ (13,800) inflection, 258 mμ (18,300), 305 mμ (1,900) in EtOH.

(c) *Trimethylparamide* (acv). When *acu* was boiled in water, the solution slowly turned dark red and a light tan solid precipitated. After 3 hr the mixture was cooled, filtered, the solid washed with water, dried, and recrystallized from boiling nitrobenzene to yield a product with the properties of trimethylparamide as described by Mumm and Bergell;[18] 52%; IR: 5·73, 5·85 (shoulder), 5·95, 6·05, 6·38 μ in KBr.

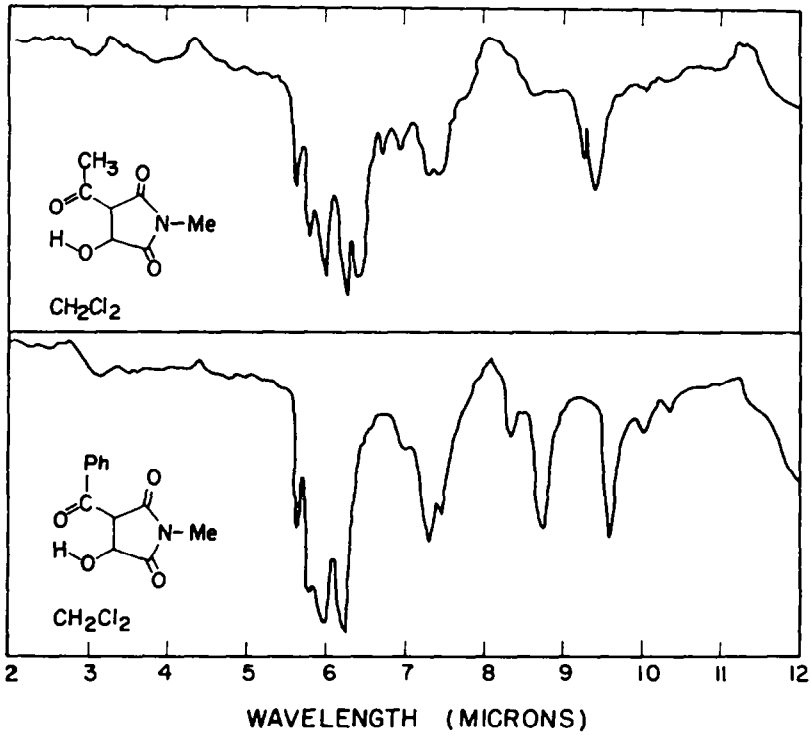


FIG. 10.

FIG. 11.

(d) 3-*Benzoyl*-1-*methylpyrrolidinetrione* (acw). The published procedure of Mumm and Bergell[13] and of Knust and Mumm[14] was repeated to give a 21% yield of product, m.p. 106–107° (Lit.[13] 107°). When the mole ratio of oxalate was decreased to 1·3, the yield was 33%; IR: 5·63, 5·79, 5·92 (shoulder), 5·98, 6·23 μ in CH_2Cl_2 (Fig. 11); UV: λ_{max} (ε) 235 mμ (12,200), 285 mμ (10,100), 334 mμ (6,700) in EtOH.

This compound was also prepared by the general procedure of Howard[45] for pyrrolidinetriones by dissolving 1·78 g (0·01 M) N-methylbenzoylacetamide in 20 ml EtOH and adding 2·02 equivs of EtONa (from NaH in a mineral oil dispersion) in 10 ml EtOH followed by 1·50 g of ethyl oxalate. When the temp stopped rising, the solution was warmed further to 60° for 15 min, cooled, the solvent removed *in vacuo*, the residue dissolved in water, and acidified to precipitate the pyrrolidinetrione, which was filtered off, dried, and recrystallized twice from EtOH to give 10% (0·23 g) of an off-white solid, m.p. 106–107°.

The IR spectrum of the pyrrolidinetrione was identical with that obtained from the isoxazolium salt, and the mixture m.p. was not depressed (105·5–107°).

Anhydride formation

(a) *From phthalic acid.* Compound *abf*[39] (1·012 g) was placed in a 25 ml Erlenmeyer flask along with 10 ml MeCN. A solution of 0·665 g phthalic acid plus 0·810 g Et_3N in the same solvent was added and the mixture stirred with a magnetic stirrer overnight. The solvent was stripped off at reduced press and the residue partitioned between AcOEt and water, the aqueous layer discarded, the organic layer extracted once with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. The product was crystallized twice from CH_2Cl_2–pet. ether to give 0·361 g (61%) pure phthalic anhydride, m.p. 130–131°, identical with commercial material.

(b) *From phthaloylglycine.* A parallel experiment was run with phthaloylglycine (1·026 g), N-ethyl-5-phenylisoxazolium-3′-sulfonate[39] (0·633 g) and Et_3N (0·506 g). After the MeCN had been stripped off, an IR spectrum was taken of the total residue. No anhydride could be detected (no carbonyl band below 5·62 μ).

Reaction with glycine

To the usual solution of the crude *aae* 1·2 equivs glycine were added. The mixture was allowed to stand overnight at room temp; then NaOHaq was added over a 1 hr period to bring the pH up to 7 and the mixture was left in the refrigerator overnight. Finally the precipitate was filtered off, washed with water, dried, and recrystallized twice from hot pyridine to give needles m.p. 222–223·5° (Lit.[7] 223°) in 53% yield. Use of a greater excess of glycine led to a reduced yield; IR: 3·06, 5·76, 6·16, 6·25, 6·35, 6·55 μ in KBr (Fig. 12); UV: 240 mμ (14,100), 327 mμ (25,300) in EtOH.

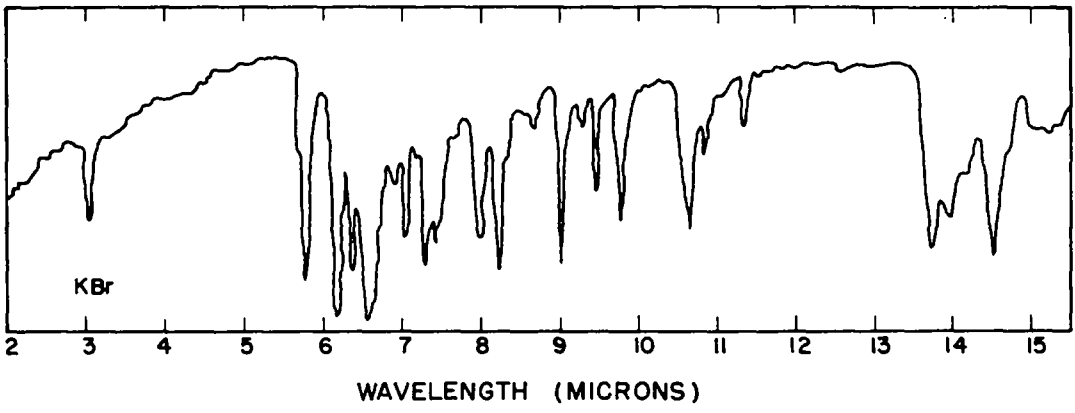


FIG. 12. Glycine product.

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