THE CHEMISTRY OF IMIDATES

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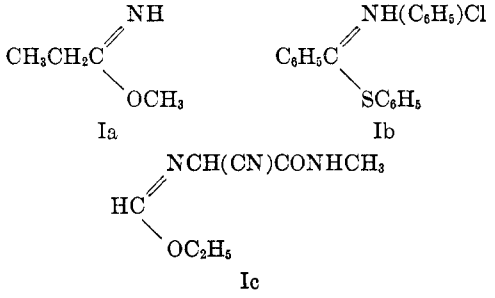
I. Nomenclature and Scope of the Review

This review covers the type of compounds variously described as imino ethers, imido esters, imidic esters, imidoates, and imidates as well as their *N*-substituted derivatives (alkyl isoanilides) and thio analogs. Throughout this article, it is proposed that compounds of this class should be named after the parent imidic acids and termed imidates: thus, compound Ia is methyl propionimidate, Ib is phenyl *N*-phenylbenzthioimidate hydrochloride, and Ic is ethyl *N*-(cyano-*N'*-methylcarbamoylmethyl)formimidate.

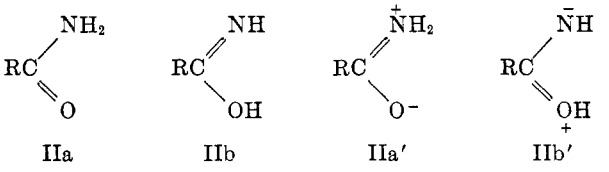


Many imidates have been prepared but merely as intermediates in syntheses; consequently studies of their properties and reactions have often been neglected. It is *not* claimed, therefore, that this review is exhaustive nor that it refers to all known imidates but rather that the general methods of preparation as well as the properties of these compounds are discussed. Further, the review does not cover compounds such as the oxazoles and benzoxazoles, which contain the imidate system within the ring, except when these compounds arise during typical imidate preparations or can be synthesized from imidates. Derivatives of urea, thiourea, and related compounds are not reviewed unless they are of special interest.

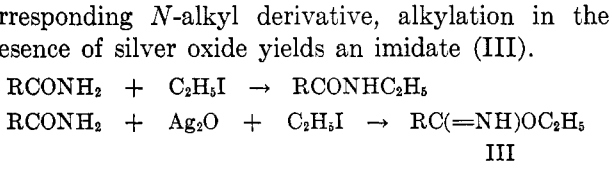
A previous survey of this subject is in A. Pinner's book, *Die Imidoäther und ihre Derivate* (252). However, in view of the difficulty in obtaining this volume at the present time and as Pinner's work still constitutes a landmark in imidate chemistry, this review covers work published on these compounds from the first real recognition of their nature by Pinner and includes references to papers published by the fall of 1959 by later workers in this field.

II. Introduction

The lactam–lactim (amide–iminol) tautomerism of the amides of carboxylic acids is an example of prototropy that may be represented by the structures IIa and IIb, which are considered to be stabilized



by resonance with the polar forms IIa′ and IIb′, respectively. Formula IIa is that usually ascribed to the acid amide (lactam), but the tautomeric imidic acid structure (lactim) IIb is also feasible because, although direct alkylation of an amide gives the corresponding *N*-alkyl derivative, alkylation in the presence of silver oxide yields an imidate (III).

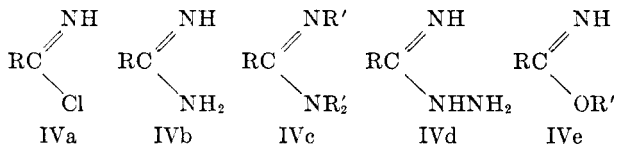


Although no substantiated claim has been put forward for the isolation of free imidic acids (103, 131, 206, 287), a typical acid amide could be an equilibrium mixture of lactam and lactim forms. Early work by Hantzsch (130) on the ultraviolet absorption spectra of solutions of benzamide and trichloroacetamide suggested that the lactim forms predominated in these cases, but these conclusions have been criticized by Grob and Fischer (121). These workers argue that abnormal light absorption (due to steric hindrance of resonance involving a substituted amide group) causes the ultraviolet absorption spectra of amides to resemble the spectra of the corresponding imidates more closely than those of the *N,N*-disubstituted amides, which are incapable of tautomerism and hence are of unambiguous structure. A study of the ultraviolet spectra of amides and imidates of α,β-acetylenic acids, where no disturbance of resonance of the amides is possible as a result of the linearity of the acetylenic bond, led these workers (121) to conclude that no significant amounts of the lactim forms of the amides were present. This supports earlier evidence by Richards and Thompson (274) on infrared spectra which pointed to a predomi-

nance of the lactam form of the amide which, however, in the solid state was associated owing to hydrogen bonding (for a fuller discussion see Bellamy (27)).

X-ray measurements on acetamide show that while the occurrence of the lactim form is unlikely, this amide is associated in the solid state, existing as a ring polymer (295), but evidence from other measurements points to considerable shortening, due to resonance, of the carbon–nitrogen bond length within the terminal amide group of glycyl-L-asparagine (249) and to as much as 80 per cent double-bond character in the amide group of glutamine (70).

The dubiety which has existed, and may even yet exist, regarding the lactam–lactim structure of even the simplest of the amides has not prevented detailed study of the derivatives of the lactim forms, as the chlorides IVa (imino chlorides or imidyl chlorides), the simple and substituted amides IVb and IVc (amidines), the hydrazides IVd (amidrazones or hydrazidines), and the esters IVe (imidates) of the imidic acids are, in the main, well-defined chemical compounds.



III. Methods of Synthesis of Imidates

A. The Pinner Synthesis

1. Scope and limitations

The Pinner synthesis consists in condensing a nitrile and an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide (252).

$$RCN + R'OH + HCl \rightarrow RC(=NH_2Cl)OR'$$

An early literature reference to the attempted preparation of an imidate by this method is to be found in the work of Beckurts and Otto (25), but credit for the elucidation of the nature of this reaction and for detailed study of these compounds must be reserved for Pinner (252, 268).

The reaction is normally carried out at 0°C., and anhydrous chloroform (12), nitrobenzene (12), dioxane (38, 178), dimethyl Cellosolve (349), and, in particular, benzene (7, 12, 252) and ether (228, 252, 275) have been used as diluents. It has been established, however, that use of a solvent may be detrimental to the yield and that better results accrue in certain cases when the anhydrous diluent is added after several days or when the imidate is on the point of crystallization (222, 285, 308).

Excess alcohol has also found use as diluent (12, 22, 64), but this would be conducive to formation of the ortho ester in certain instances (*cf.* Section IV,D).

After filtration and washing with more anhydrous solvent, the imidate hydrohalide is best stored *in vacuo* over concentrated sulfuric acid or solid sodium hydroxide, which remove any excess hydrogen halide and also maintain anhydrous conditions.

Hydrogen chloride has been employed in almost every instance of imidate formation by this method, but the use of hydrogen bromide has also been reported (182, 304). Moreover, adiponitrile and ethanol in sulfuric acid at 70°C. are said to give the hemisulfate salt of ω-cyanovalerimidate (124).

$$NC(CH_2)_4CN + C_2H_5OH + H_2SO_4 \rightarrow NC(CH_2)_4C(=NH\cdot 0.5H_2SO_4)(OC_2H_5)$$

Of the alcohols, methanol and ethanol are the most used and in general give satisfactory yields of imidate hydrohalides in the Pinner synthesis, but propyl (133), isopropyl (82), butyl (133), isobutyl (268), *dl*- and optically active *sec*-butyl (308), and benzyl (149) alcohols, among the simpler members, have all been utilized. Octyl and decyl alcohols are also reported to furnish substituted benzimidates in high yields (250).

Glycols have received less attention, but Pinner (253) was able to prepare an imidate from ethylene glycol and hydrogen cyanide.

$$2HCN + 2HCl + (CH_2OH)_2 \rightarrow \begin{matrix} CH_2OCH{=}NH_2Cl \\ | \\ CH_2OCH{=}NH_2Cl \end{matrix}$$

1,2- and 1,3-propanediols as well as 2,3-butanediol react with cyanogen to give symmetrical oxaldiimidate dihydrochlorides (349),

$$2HO(CH_2)_3OH + (CN)_2 + 2HCl \rightarrow HO(CH_2)_3OC(=ClH_2N)\text{—}CO(=NH_2Cl)(CH_2)_3OH$$

but 1,2-, 1,3-, and 1,4-butanediols, all of which have primary alcoholic groupings and were expected to be reactive, failed to furnish the desired products.

Thioimidate salts can be derived by replacement of the carbinol with the corresponding mercaptan (14, 16, 33, 72, 270),

$$RCN + HCl + R'SH \rightarrow RC(=NH_2Cl)SR'$$

and it has been suggested that the crystalline thioimidate salts prepared from thioglycolic acid might be used to characterize nitriles (72).

$$RCN + HCl + HSCH_2COOH \rightarrow RC(=NH_2Cl)SCH_2COOH$$

Hartigan and Cloke (133), as well as Marvel, de Radzitzky, and Brader (209), have prepared thioimidate hydrochlorides in poor yield by the use of *tert*-butyl mercaptan, although no reference to the use of analogous tertiary alcohols in direct syntheses has been noted.

Simple phenols (147, 218) and their thio analogs (14, 133) also undergo the Pinner synthesis satisfactorily.

$$RCN + HCl + \beta\text{-}C_{10}H_7OH \rightarrow RC(=NH_2Cl)OC_{10}H_7\text{-}\beta$$

This method, moreover, can utilize a wide variety of nitriles, and Pinner has prepared imidates from hydrogen cyanide (252, 253), although recently Hinkel and Hullin (142), from a study of the Gattermann reaction using hydrogen cyanide, have criticized the generally accepted structure of formimidates and suggested the following alternative formula:

$$ROCHClNHCH(OR)NH_2Cl$$

Few cases of failure (177), except for certain acetonitriles substituted with a nitro group or two or more halogen atoms (306), have been noted in the synthesis of imidates from simple and substituted aliphatic nitriles (48, 55, 95, 222, 252, 326), and the preparation of imidates from palmito- (96), stearo-, and lauronitriles (105) has been recorded. The method has been extended to give α-hydroxyimidate hydrohalides from simple aldehyde and ketone cyanohydrins (23, 182, 227, 261, 285), and ethyl mandelimidate hydrochloride is now available commercially.

Acyl nitriles have received scant attention and no general conclusions can be drawn regarding the course of the reaction for, while Pinner (252) obtained ethyl benzoate and hydrogen cyanide from benzoyl cyanide,

$$C_6H_5COCN + C_2H_5OH + HCl \rightarrow C_6H_5COOC_2H_5 + HCN$$

Roger and Harper (284) regard the somewhat unstable ethyl *o*-toluoylimidate hydrochloride as the intermediate in the preparation of ethyl *o*-toluoylformate.

$$o\text{-}CH_3C_6H_4COCN + C_2H_5OH + HCl \rightarrow o\text{-}CH_3C_6H_4COC(=NH_2Cl)OC_2H_5$$

Should the nitrile have an amino group as a substituent, it is customary to protect that group, e.g., through its *p*-toluenesulfonyl derivative, and so prevent precipitation of the aminonitrile hydrohalide (228). Recently, however, a general method for the preparation of imidates of amino acids has been developed by Baksheev and Gavrilov (18), who allowed methanol saturated with hydrogen chloride to react with aminonitrile hydrochlorides. The contact time had to be short or the final product consisted mainly of ammonium chloride. Turner and Djerassi (321) have been similarly successful in converting *N*-benzyl-*N*-phenylglycinonitrile into an imidate salt, using chloroform as diluent, whereas ether gave a precipitate of the aminonitrile salt.

When the nitrile contains an unsaturated center, addition of hydrogen halide across the double or triple bond can proceed simultaneously with imidate formation (110, 172, 259),

$$C_6H_5C{\equiv}CCN + CH_3OH + HCl \rightarrow C_6H_5C(Cl){=}CHC(=NH_2Cl)OCH_3$$

but recently imidates containing unsaturated linkages have been prepared from cyano-substituted triphenylethylenes. Of these, the stereoisomeric imidates prepared from the cis and trans forms of the nitrile (V) are

$$m\text{-}CNC_6H_4C(C_6H_5){=}CHC_6H_5$$

V

of special interest (7). The nitriles VIa and VIb were recovered unchanged after treatment with an alcoholic

$$p\text{-}(CH_3OC_6H_4)_2C{=}CHC_6H_4CN\text{-}o$$

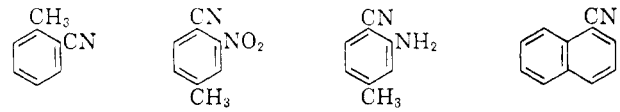
VIa

$$p\text{-}CH_3OC_6H_4C(CN){=}C(C_6H_4OCH_3\text{-}p)_2$$

VIb

solution of hydrogen halide (7), a result which could be reasonably expected in the case of the ortho-substituted nitrile (*cf.* later in this section).

Simple and substituted benzimidate hydrohalides are also well-defined crystalline compounds (65, 91, 111, 161, 268, 271), and substituents do not generally alter the course of the reaction unless they are ortho to the cyano group, when steric hindrance occurs. This proximity effect was first discovered by Pinner (252, 260), who was unable to obtain imidates in the normal way from the *o*-substituted benzonitriles VIIa, VIIb, and VIIc or from α-cyanonaphthalene (VIId),

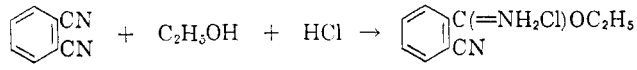


VIIa VIIb VIIc VIId

although the other positional isomers readily yielded imidates (269).

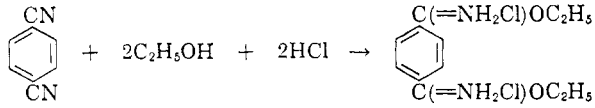
$$\beta\text{-}C_{10}H_7CN + C_2H_5OH + HCl \rightarrow \beta\text{-}C_{10}H_7C(=NH_2Cl)OC_2H_5$$

Extending his investigations, Pinner (260) discovered that phthalonitrile gave rise to a monoimidate salt only,

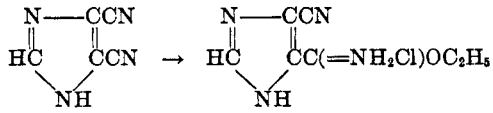


Phthalonitrile

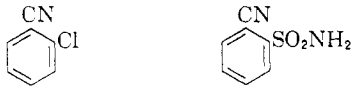
whereas the iso- and terephthalonitriles furnished diimidate salts.



Bredereck and Schmötzer (45) noted similar behavior with vicinal dicyano-substituted heterocyclic compounds,



and King and Wright (178) found that whereas both cyano groups of 2,7-dicyanonaphthalene underwent conversion into the imidate, only the 7-cyano group of 1,7-dicyanonaphthalene was reactive under the conditions of the Pinner synthesis. Other examples of this proximity effect were discovered by Lander and Jewson (199), who failed to convert *o*-chlorobenzonitrile into an imidate, and by Guy and Paris (123), who were similarly unsuccessful in the case of *o*-cyanobenzenesulfonamide.

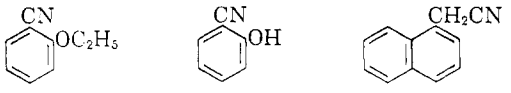


o-Chlorobenzonitrile *o*-Cyanobenzenesulfonamide

Moreover, steric inhibition of imidate formation of a not dissimilar character has been noted with 3-chloro- and 3-bromo-1,1-diphenylpropyl cyanides (VIII: X = Cl or Br), which failed to give imidates via the Pinner method within forty-four days (177).

$$XCH_2CH_2C(C_6H_5)_2CN$$
VIII

The extent of the limitations of this proximity effect has never been fully studied, but it is of interest to note that *o*-ethoxybenzonitrile (IXa) (261), *o*-hydroxybenzonitrile (IXb) (97), and α-naphthylacetonitrile (IXc) (16) all formed imidates in the normal manner indicated by Pinner.



IXa IXb IXc

Although a cyano group does not appear to condense with alcohol and hydrogen halide when adjacent to a bulky ortho-substituent, several imidate salts have been successfully isolated by alkylation of the corresponding *o*-substituted amides in the presence of silver oxide (*cf.* Section III,C).

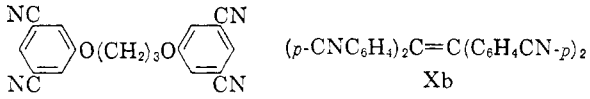
Conversion into imidate salts of cyano groups attached to heterocyclic residues which are stable under the conditions of the reaction also proceeds smoothly (20, 21, 45, 54, 120, 238, 262), and investigations of this type relate, in the main, to potential chemotherapeutic agents.

Dinitriles, with the few exceptions mentioned earlier, undergo the Pinner synthesis, furnishing diimidates (49, 220, 252, 254, 349),

$$\begin{matrix} CN \\ | \\ CN \end{matrix} + 2C_2H_5OH + 2HCl \rightarrow \begin{matrix} C(=NH_2Cl)OC_2H_5 \\ | \\ C(=NH_2Cl)OC_2H_5 \end{matrix}$$

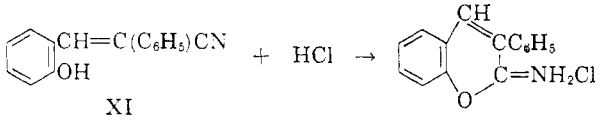
but, although many diamidines of potential trypanocidal action have been synthesized via diimidates, the imidates themselves have not been well characterized (12, 178).

In a study of polyamidines, Barber and Slack (22) found that only a triimidate salt was formed from the tetracyano compound (Xa) and this, owing to its great insolubility, separated out and did not undergo further condensation, whereas the nitrile (Xb) formed a tetraimidate salt on prolonged standing.



Xa Xb

Treatment with hydrogen chloride of a nitrile which contains a hydroxy group as a substituent so oriented that interaction of the functional groups can occur gives rise to cyclic imidates; thus, 2-imino-3-phenylcoumarin hydrochloride was prepared from the nitrile XI (148), and the γ-hydroxycyanohydrin XII produced



XI

a γ-lactone system on treatment with hydrogen chloride (292, 342).

$$\underset{XII}{HOCH_2C(CH_3)_2CHOHCN} + HCl \rightarrow \overbrace{CH_2C(CH_3)_2CHOHC}^{O}{=}NH_2Cl$$

An elegant synthesis of furan derivatives (118) consists in subjecting various cyano-substituted 1,2-benzoylethylenes to the Pinner reaction, when cyclization and imidate formation occur simultaneously.

Trichloroacetonitrile reacts directly when refluxed with alcohol to yield trichloroacetimidate (305), this

$$CCl_3CN + ROH \rightarrow \underset{\text{Trichloroacetimidate}}{CCl_3C(=NH)OR}$$

modification being made possible by the electronegative character of the trichloromethyl group, and it is also claimed that allyl alcohol combines directly with cyanogen to yield allyl cyanoformimidate (325).

2. *Practical aspects*

The yield of imidate hydrohalide may be markedly affected, subsequent to its formation, by three factors: hydrolysis, temperature, and alcoholysis.

(a) Hydrolysis by moisture

By far the most serious of these is hydrolysis by moisture to the normal ester and, as this is accelerated by hydrogen ions, the use of anhydrous diluents and reactants is necessitated.

$$RC(=NH_2Cl)OC_2H_5 + H_2O \rightarrow RCOOC_2H_5 + NH_4Cl$$

The reaction is fast and complete in the case of the lower aliphatic members, which tend to be hygroscopic

in nature (95, 252), but the use of aromatic nitriles or phenyl-substituted aliphatic nitriles confers greater toleration.

(b) Temperature

The synthesis normally proceeds smoothly at 0°C. but rise in temperature may result in decomposition of the imidate salt into amide and alkyl halide (*cf.* Section IV,A for a fuller discussion).

$$RC(=NH_2Cl)OC_2H_5 \rightarrow RCONH_2 + C_2H_5Cl$$

(c) Alcoholysis

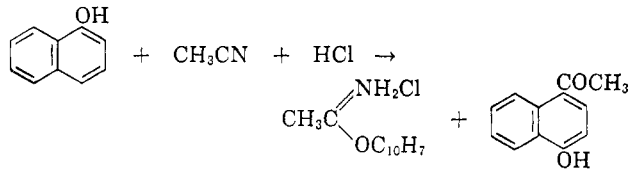
Excess alcohol may give rise to ortho esters (*cf.* Section IV,D), but at 0°C. this appears to be trouble some only in the case of the formimidates (252).

$$RC(=NH_2Cl)OC_2H_5 + 2C_2H_5OH \rightarrow RC(OC_2H_5)_3 + NH_4Cl$$

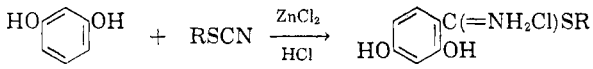
B. SYNTHESIS OF IMIDATES VIA IMINO CHLORIDES

1. The Hoesch reaction

The Hoesch reaction (303) for the preparation of hydroxyaryl ketones is very similar in procedure to the Pinner reaction. Essentially, the method consists in condensing a nitrile with a phenol or a phenolic ether in the presence of zinc chloride and anhydrous hydrogen chloride in a suitable solvent, the reaction proceeding via the imino chloride and then the ketimine hydrochloride to the ketone. In certain cases, however, imidate formation proceeds simultaneously and may even form the main reaction trend.



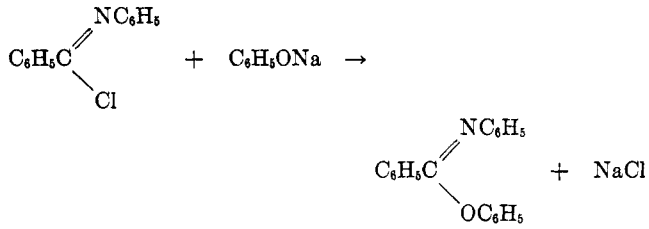
A modified Hoesch synthesis is to be found in the work of Kaufmann and Adams (169) and of Borsche and Niemann (37), who synthesized thioimidates by substituting an alkyl or aryl thiocyanate for the nitrile.



The reactions of cyanogen under the Hoesch and Pinner syntheses have been reviewed recently (49).

2. Reaction with alkoxides and phenoxides

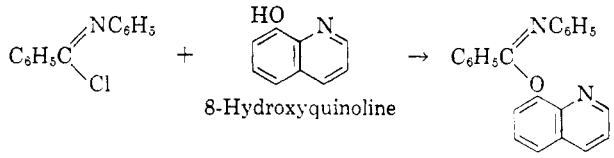
The action of imino chlorides with alkoxides or phenoxides may be regarded as a modification of the Pinner synthesis, resulting again in the formation of imidates (58, 59, 60, 61, 62, 87, 129, 165, 196, 197, 340). The product can be isolated either directly, by removal of the solvent *in vacuo* and trituration of the residue with water, or as the hydrochloride by addition



of hydrogen chloride in an anhydrous solvent. The *O*-methyl imidates derived in this way are free from contaminant *N*-disubstituted amides, which are troublesome by-products in the alkylation of the silver derivatives of anilides with methyl iodide (196) (*cf.* next section). Moreover, Chapman (61), utilizing an atmosphere of nitrogen, introduced the use of thiophenoxides and obtained *N*-substituted thioimidates.

$$C_6H_5C(=NC_6H_5)Cl + C_6H_5SNa \rightarrow C_6H_5C(=NC_6H_5)SC_6H_5$$

Likewise Hall has employed 8-hydroxyquinoline (125).

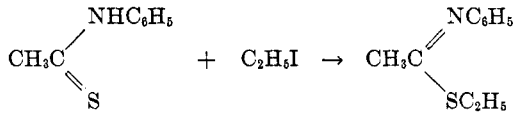


The condensation of an imino halide is also reported to take place directly with a phenol when pyridine is used as solvent, provided the imino halide is free from phosphorus halides (78).

C. SYNTHESIS OF IMIDATES FROM AMIDES

1. Direct alkylation

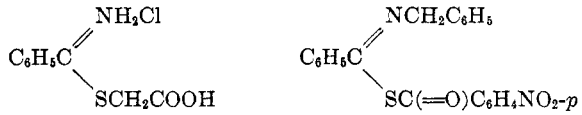
Wallach and Bleibtreu (327, 328) found that thioacetanilide with ethyl iodide in the presence of sodium ethoxide formed ethyl *N*-phenylthioacetimidate.



Later Bernthsen (33) was able to alkylate benzthioamide directly with alkyl iodides at 100°C. and obtained thiobenzimidates as products.

$$C_6H_5CSNH_2 + C_2H_5I \rightarrow C_6H_5C(=NH_2I)SC_2H_5$$

The method has been extended to give thioformimidates (44), thioacetimidates (40), and thiobenzimidates (39), as well as carboxymethylthiobenzimidate hydrochloride (XIIIa) (72) and compound XIIIb (41) by the use of chloroacetic acid and *p*-nitrobenzoyl chloride, respectively.



XIIIa XIIIb

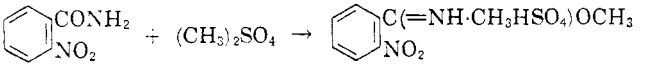
Further, *S*-benzylthiuronium chloride, prepared by the direct *S*-alkylation of thiourea with benzyl chloride, is a useful reagent for the characterization of carboxylic and sulfonic acids (57, 146).

$$H_2NCSNH_2 + C_6H_5CH_2Cl \rightarrow NH_2C(=NH_2Cl)SCH_2C_6H$$

In the case of the *O*-amides, however, direct alkylation normally gives the *N*-alkyl derivative, but recently a patent (135) described the formation of *O*-imidates from primary and secondary amides by interaction with chloroformates in benzene at room temperature.

$$HCONH_2 + ClCOOC_2H_5 \rightarrow HC(=NH_2Cl)OC_2H_5$$

Amides and thioamides may also be alkylated directly with dimethyl sulfate at temperatures below 100°C. to give the methyl hydrogen sulfate salts of the imidates or thioimidates (52, 211), and Matsui (211) prepared *o*-nitrobenzimidates in this way, although *o*-nitrophenyl cyanide did not undergo the Pinner reaction.



Alkylation with dimethyl sulfate has been applied to the *O*-alkylation of urea (156) and to the preparation of *O*-methylcaprolactim (32).

$$\underbrace{CH_2(CH_2)_4CONH} + (CH_3)_2SO_4 \rightarrow \underbrace{CH_2(CH_2)_4C(OCH_3)=N}\cdot CH_3HSO_4$$

Formanilide yielded a substituted formamidine with this reagent (42), and diversity of opinion arises on the nature of the product of the reaction between formamide and dimethyl sulfate, for while Matsui (211) claims to have isolated the imidate, other workers state that their product was a formamidine (43).

2. *Alkylation of silver salts*

Tafel and Enoch (317, 318) prepared the silver derivatives of amides and found that they yielded imidates on treatment with ethyl iodide,

$$C_6H_5CONH_2 \rightarrow C_6H_5C(=NH)OAg \xrightarrow{C_2H_5I} C_6H_5C(=NH)OC_2H_5$$

the product being obtained finally by lixiviating the mass with ether and saturating with hydrogen chloride. Use of this method was made to synthesize ethyl *o*-chloro- and *o*-methylbenzimidates (199), which could not be prepared by the Pinner method, and it has also been found possible to synthesize imidates from amides containing acetylenic systems, thus avoiding any complication of addition of hydrogen halide over the triple bond (110).

Lander (194, 195, 196), extending the work of Comstock and Kleeberg (71), isolated *N*-substituted imidates by the alkylation of the silver derivatives of anilides.

$$CH_3C(=NC_6H_5)OAg + C_2H_5I \rightarrow CH_3C(=NC_6H_5)OC_2H_5$$

However, he discovered that the reaction gave no significant yield when the *N*-substituent was alkyl in character (197) and that whereas the use of ethyl iodide gave exclusively the imidate XIVa, methyl iodide gave a mixture of the *N*-substituted imidate and the *N*,*N*-disubstituted amide (XIVb).

$$CH_3CONHC_6H_5 + Ag_2O + C_2H_5I \rightarrow \underset{\text{XIVa}}{CH_3C(=NC_6H_5)OC_2H_5}$$

$$CH_3CONHC_6H_5 + Ag_2O + CH_3I \rightarrow CH_3C(=NC_6H_5)OCH_3 + \underset{\text{XIVb}}{CH_3CON(C_6H_5)CH_3}$$

Ethyl *N*-phenylformimidate, a useful intermediate in the synthesis of aldehydes, has heretofore been prepared in this way but may now be prepared more conveniently from aniline and ethyl orthoformate (*cf.* the following section).

D. SYNTHESIS OF IMIDATES FROM ORTHO ESTERS

Claisen (66) suggested a two-stage mechanism for the interaction of ethyl orthoformate and aniline, with the intermediate formation of *N*,*N'*-diphenylformamidine.

$$\text{A: } 2C_6H_5NH_2 + HC(OC_2H_5)_3 \rightarrow HC(=NC_6H_5)NHC_6H_5 + 3C_2H_5OH$$

$$\text{B: } HC(=NC_6H_5)NHC_6H_5 + HC(OC_2H_5)_3 \rightarrow 2HC(=NC_6H_5)OC_2H_5 + C_2H_5OH$$

He postulated step A to be rapid and step B slow, on the grounds that the imidate was isolated only after prolonged heating, whereas the amidine formed readily. Improved yields resulted when hydrogen chloride was introduced into the reaction in the form of the amine hydrochloride (127, 192), and Roberts (276) has since shown that the yield of imidate is markedly dependent on acid catalysis and that in basic media the yield of imidate is zero. Sulfuric (276, 282) and *p*-toluenesulfonic (116, 276) acids also catalyze the reaction effectively. On the basis of further investigations (277), Roberts and DeWolfe (278) suggest that the overall reaction mechanism may be represented by the two equations C and D.

$$\text{C: } C_6H_5NH_2 + HC(OC_2H_5)_3 \underset{r}{\overset{f}{\rightleftharpoons}} HC(=NC_6H_5)OC_2H_5 + 2C_2H_5OH$$

$$\text{D: } HC(=NC_6H_5)OC_2H_5 + C_6H_5NH_2 \underset{r}{\overset{f}{\rightleftharpoons}} HC(=NC_6H_5)NHC_6H_5 + C_2H_5OH$$

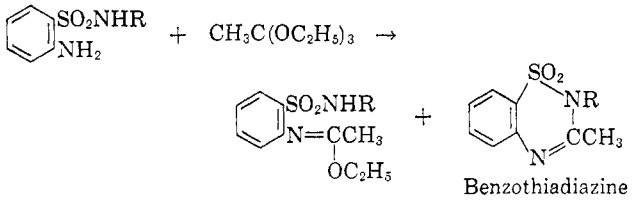
Addition of equations Cf and Df gives Claisen's equation (step A), and it was shown by ultraviolet spectrophotometry, using high-dilution techniques, that ethyl *N*-phenylformimidate was in fact the primary reaction

product but that it reacted immediately with excess aniline, giving the amidine, i.e., reaction Df is faster than Cf and, furthermore, in the absence of acid catalysts, reaction Dr is slow (278). The Claisen reaction (step B) may then be looked on as proceeding via alcoholysis of the amidine (reaction Dr); this is a fast reaction in the presence of acid catalysts, which catalysts also produce, by breakdown of the ortho ester, the alcohol necessary for reaction Dr. As reaction Dr also produces aniline, this reacts with ortho ester to furnish more imidate (reaction Cf).

The method has been utilized to prepare various alkyl *N*-phenylformimidates (280) and, in particular, ethyl *N*-phenylformimidate (281) as well as dye intermediates of the type shown below, where Z is a heterocyclic residue (170).

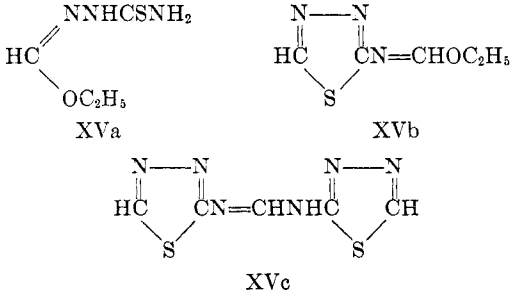
$$\overbrace{N{=}CHCH{=}C}^{Z}N{=}C(OC_2H_5)CH_3$$

The interaction of ethyl orthoacetate with *o*-aminobenzenesulfonamides gave principally the imidate as well as smaller quantities of benzothiadiazine

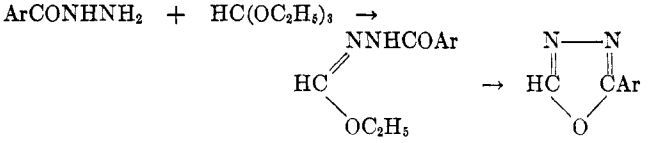


but ethyl orthoformate, on the other hand, led with uniform success to the formation of the thiadiazine system (112).

It is of interest to compare the reaction of ortho esters on amines with that on other substituted ammonias; thus thiosemicarbazide reacts with ethyl orthoformate giving either ethyl formate thiosemicarbazone (XVa) at 100°C. or ethyl *N*-(1,3,4-thiadiazole)-2-formimidate (XVb) at 140°C., both of which may be intermediates in the formation of the final product, *N,N'*-bis(1,3,4-thiadiazole)-2-formamidine (XVc) (6).



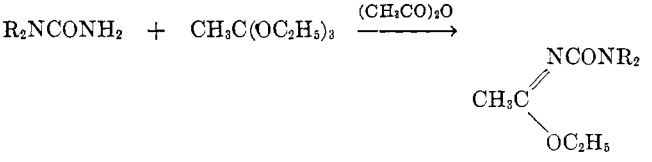
Similarly, 2-substituted 1,3,4-oxadiazoles are conveniently synthesized by warming ethyl orthoformate with carboxylic acid hydrazides, the reaction proceeding via an imidate intermediate which was isolated in two instances (5).



Urea and *N*-alkylureas react with ethyl orthoformate to give *N,N'*-dicarbamylformamidines (338),

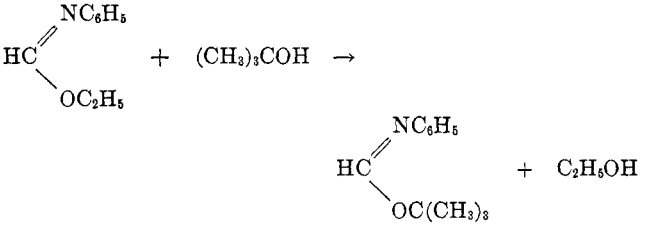
$$2RNHCONH_2 + HC(OC_2H_5)_3 \rightarrow RNHCON{=}CHNHCONHR$$

but when acetic anhydride is introduced into the reaction, imidates become the major product, and in the case of ethyl orthoacetate, the exclusive one (339), thus demonstrating the effect of acid catalysis.



E. SYNTHESIS OF IMIDATES BY TRANSESTERIFICATION

Imidates may be transesterified by refluxing with an alcohol of higher boiling point than that used in their formation (31). Absence of acid has been shown to be advantageous, and the method has been used to give *tert*-butyl *N*-phenylformimidate (280), although no direct synthesis using a tertiary alcohol has been noted.

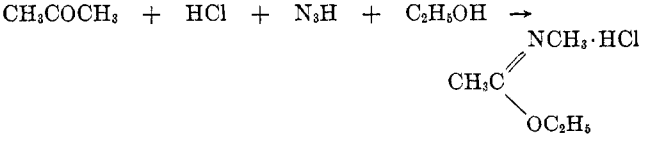


Similarly, *O*-imidates have been derived from thioimidates (169).

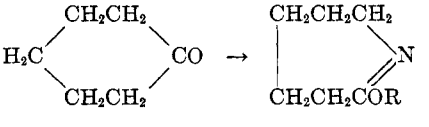
$$RC({=}NH)SR' + R''OH \rightarrow RC({=}NH)OR'' + R'SH$$

F. SYNTHESIS OF IMIDATES FROM ALDEHYDES AND KETONES

Ketones in the presence of alcohol, hydrogen chloride, and hydrazoic acid yield imidates.

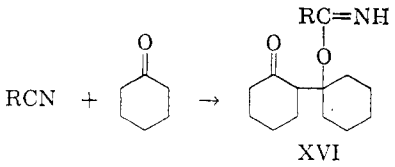


Furthermore, cyclic ketones (e.g., cyclohexanone) react with ring expansion and formation of a heterocyclic compound (185).



Cyclohexanone also reacts with nitriles in the pres-

ence of aluminum chloride to give imidates assigned the structure shown in formula XVI (50).

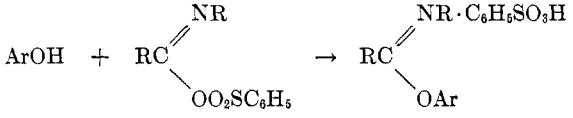


XVI

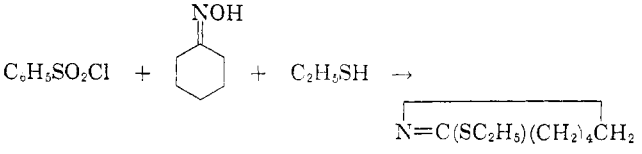
R = CH_3—, C_2H_5—, C_6H_5—.

Aldonitrones, formed by the condensation of aldehydes with *N*-substituted hydroxylamines, react with methanolic potassium cyanide to give imidates (28, 29).

The fact that imidosulfonates (derived from ketoxime sulfonates undergoing Beckmann transformations) behaved as alkylating agents prompted Oxley and Short (246) to examine their behavior toward phenols; they obtained good yields of imidates when the reactants were heated in boiling toluene.



In like manner, cyclohexanone oxime undergoes a Beckmann rearrangement in the presence of ethanethiol and benzenesulfonyl chloride, yielding a cyclic thioimidate (173).



G. SYNTHESIS OF IMIDATES FROM UNSATURATED SYSTEMS

The addition of primary amines to ethoxyacetylene in refluxing ethanol gives rise to imidates, but amidines may also be formed by the further interaction of the amine (11).

$$RNH_2 + C_2H_5OC{\equiv}CH \rightarrow CH_3C(=NR)OC_2H_5 + CH_3C(=NR)NHR$$

Secondary amines, on the other hand, do not give imidate formation, as the intermediate (XVII) is incapable of undergoing the required tautomeric shift (11).

$$R_2NH + C_2H_5OC{\equiv}CH \rightarrow \underset{\text{XVII}}{H_2C{=}C(OC_2H_5)NR_2}$$

Likewise, ethoxyethylene reacts with compounds of the type $AcNH_2$ under the influence of acid catalysts in acetone to yield diimidates (323),

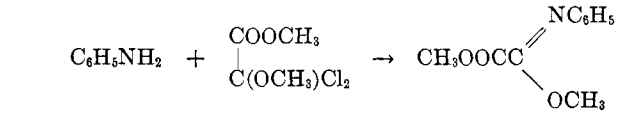
$$C_2H_5OCH{=}CH_2 + AcNH_2 \rightarrow CH_3CH[OC(=NH)CH_3]$$

and the imene (XVIII) readily undergoes nucleophilic addition upon being heated with alcohol containing a trace of alkali (92).

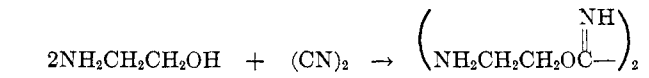
$$\underset{\text{XVIII}}{(CH_3SO_2)_2C{=}C{=}NCH_3} + CH_3OH \rightarrow (CH_3SO_2)_2CHC(=NCH_3)OCH_3$$

H. MISCELLANEOUS SYNTHESES OF IMIDATES

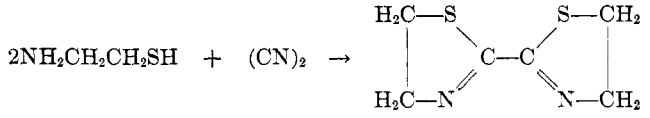
Methyl *N*-phenylcarbomethoxyformimidate has been prepared by the action of methyl methoxydichloroacetate on aniline in boiling xylene (9, 10).



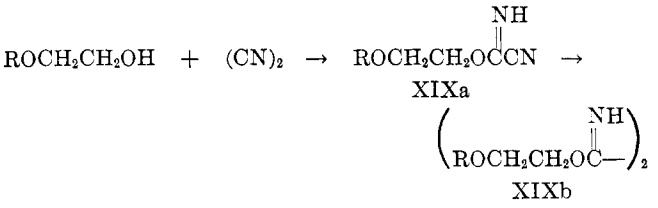
Ethanolamine in dilute potassium cyanide solution reacts with cyanogen giving an oxaldiimidate (346),



but 2-mercaptoethylamine reacts directly in aqueous solution to form a bisthiazoline (347).



Moreover, cyanogen reacts with methyl Cellosolve under similar conditions to form a cyanoformimidate (XIXa), which on treatment with further methyl Cellosolve and sodium is converted into an oxaldiimidate (XIXb) (349).



Basic catalysts also promote reaction between cyanogen and thiols, giving oxaldithioimidates (348), and α-chloro- and α,α-dichloronitriles react with alcohols in sodium cyanide solutions (pH 9.5) at 80°C. to furnish imidates (239).

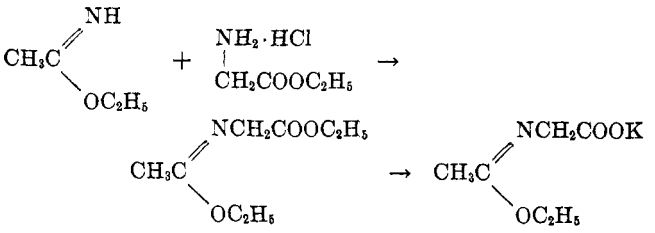
Chlorothioformimidates are reported to be formed from the interaction of isocyanides and sulfenyl chlorides (134).

$$RNC + R'SCl \rightarrow ClC(=NR)SR'$$

I. SYNTHESIS OF *N*-SUBSTITUTED IMIDATES FROM SIMPLE IMIDATES

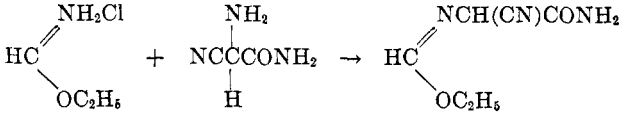
The observation by Schmidt (293) that *N*-substituted imidates could be derived by the action of esters of amino acids on simple imidates has of late received much attention, and the reaction has been shown to be more general and the products more stable than Schmidt supposed (82, 174, 292); e.g., it was found possible to saponify ethyl *N*-carbethoxymethylacetimidate (XX) (82).

One equivalent of acid must be present—usually intro-

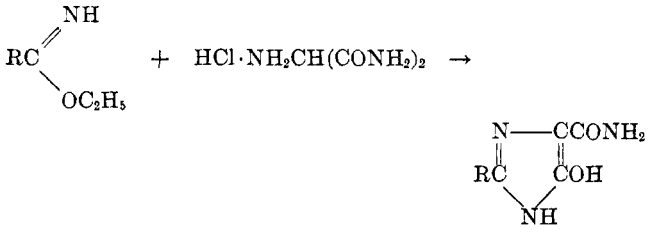


XX

duced as the hydrochloride of the amino ester—or the reaction produces an imidazole (*cf.* Section IV,E). The reaction has been varied to embrace aminonitriles (86) and aminoamides (297).



In general thioimidates appear to give imidazoles even in the presence of acid (17, 74), but several *N*-substituted thioimidates have been reported from reactions of this type (16). Aminomalonamide also reacts in the presence of acid to give an imidazole in place of the expected *N*-substituted imidate (231).



J. PREPARATION OF IMIDATE BASES FROM THEIR SALTS

Imidates are often derived from the foregoing reactions in the form of their salts, in particular the hydrochlorides, but it is sometimes more convenient to handle them as the free bases. These bases may be obtained by treating the salts with 33 per cent potassium carbonate solution and extracting immediately with ether. Sodium or potassium hydroxide solutions may also be used satisfactorily (252).

$$RC(=NH_2Cl)OR' \rightarrow RC(=NH)OR'$$

Imidate bases are either liquids, which in the case of the lower aliphatic members can be distilled, e.g., ethyl acetimidate, which boils at 92–95°C. (252), or low-melting solids, e.g., ethyl atrolactimidate, which melts at 56–57°C. (285). Aromatic imidates tend to revert on being heated to the parent nitriles and alcohols (252); hence they cannot be distilled. Imidate bases are insoluble in water, but unlike their salts they are only slowly attacked by that reagent.

IV. Properties of Imidates

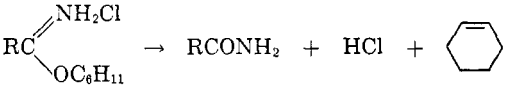
A. Stability of Imidate Salts and Their Decomposition by Heat

1. *Unsubstituted imidate salts*

Unsubstituted imidate hydrohalides normally decompose when heated into the corresponding amides and alkyl halides (252); thioimidate salts give similarly thioamides (271).

$$RC(=NH_2X)OR' \rightarrow RCONH_2 + R'X$$

Use has been made of this irreversible pyrolysis to prepare pure samples of alkyl halides (106); it might also prove suitable for the dehydration of some secondary alcohols, since Mengelberg (227) has shown that imidate salts derived from cyclohexanol undergo pyrolysis to the amide, hydrogen chloride, and cyclohexene.

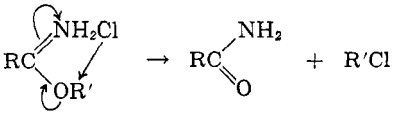


No claim for the isolation of aryl halides from imidates derived from phenols has been found, but the pyrolysis of phenyl thiobenzimidate hydrochloride yields benzonitrile, thiophenol, and hydrogen chloride (133).

$$C_6H_5C(=NH_2Cl)SC_6H_5 \rightarrow \underset{\text{Benzonitrile}}{C_6H_5CN} + \underset{\text{Thiophenol}}{C_6H_5SH} + HCl$$

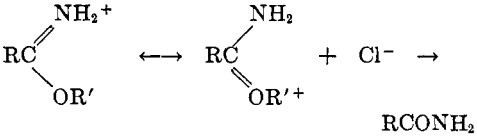
Hartigan and Cloke (133) studied the thermal behavior of various crystalline alkyl thiobenzimidate hydrochlorides by means of a differential thermocouple method and found for each a "mean temperature of pyrolysis" with the order methyl (194°C.) ≫ ethyl ≫ propyl > butyl > amyl (159°C.) for these alkyl thioimidate salts, which had no true melting point prior to pyrolysis. In the case of the *O*-imidates, ethyl isobutyrimidate hydrochloride exhibited a true melting point and a pyrolysis point about 10°C. above this, whereas ethyl acetimidate hydrochloride decomposed without melting. In general the thio compounds were more stable toward heat (133).

McElvain and Tate (224) studied the rates of decomposition of several imidate hydrohalides in chloroform and *tert*-butyl alcohol solutions at 60°C. These decompositions followed first-order kinetics with respect to the disappearance of the halide ion, giving straight-line plots of log [Cl^-] vs. time. Thus, either an intramolecular attack by the halogen (equation 1),



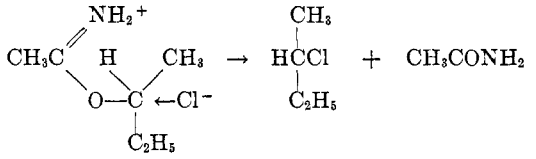
(1)

or a bimolecular process (wherein the ionization of the imidate salt is considered to be slight)



$$RCONH_2 + R'Cl \quad (2)$$

are feasible reaction mechanisms (224). Support for the S_N2 mechanism (equation 2) was established when it was found that the rates of decomposition of alkyl acetimidate salts were of the same order as for other recognized S_N2 reactions (224). Subsequently, Stevens, Morrow, and Lawson (308) obtained a *sec*-butyl chloride of high optical purity but with inverted configuration from the thermal decomposition of optically active *sec*-butyl acetimidate hydrochloride, thereby confirming the S_N2 mechanism.

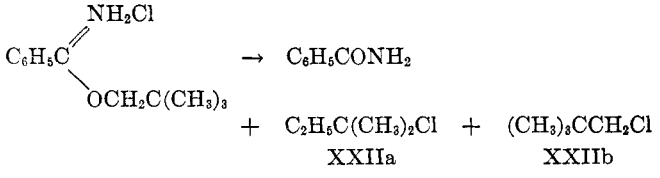


Pyrolytic studies on imidate salts in the solid phase have also been carried out by McKenzie and Webb (226), but they found the results difficult to interpret and did not propose a definite mechanism. For the imidate XXI, when R = CH_3—, a stabilizing effect was noted as compared with R = C_6H_5— or $ClCH_2CH_2$—;

$$\underset{\text{XXI}}{RC(=NH_2Cl)OR'}$$

further, when R′ = Ar, a greatly enhanced stability ensued as prolonged heating at 70°C. gave little decomposition (226). When, for XXI, R = $CHCl_2$—, CCl_3—, CBr_3—, NO_2CH_2—, or $CCl_2(NO_2)$—, the instability of the imidate salts was such that the corresponding substituted acetamides were isolated instead of the methyl imidate salts (306). Similarly, attempts to prepare mandelimidate hydrochlorides from secondary alcohols via the Pinner synthesis have resulted in the formation of mandelamide (329), and benzyl β-chloropropionimidate hydrochloride decomposed spontaneously into β-chloropropionamide within a few days at room temperature (226).

Anomalous reactions were observed during the pyrolysis of neopentyl benzimidate hydrochloride, which gave rise at 200°C. to the isomeric chlorides (XXIIa and XXIIb), suggesting that the normal bimolecular process may be inhibited by steric hindrance (63).



2. *N-Substituted imidate salts*

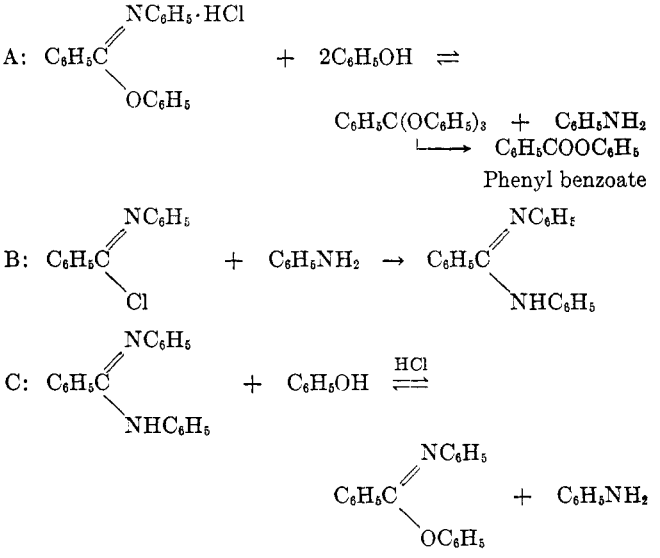
The thermal decomposition of *N*-substituted imidate salts is more complex and not easy to explain. Chapman (59) found that phenyl *N*-phenylbenzimidate hydrochloride, on being heated, gave the imidate base as the main product along with *N,N′*-diphenylbenzamidine hydrochloride, hydrogen chloride, phenol, benzanilide, and phenyl benzoate. He thought that the decomposition would give initially the imino chloride and phenol,

$$C_6H_5C(=NC_6H_5\cdot HCl)OC_6H_5 \rightarrow C_6H_5C(=NC_6H_5)Cl + C_6H_5OH$$

which would recombine to furnish the imidate base.

$$C_6H_5C(=NC_6H_5)Cl + C_6H_5OH \rightarrow C_6H_5C(=NC_6H_5)OC_6H_5 + HC$$

The anilide, he suggested, would be formed by the action of traces of moisture on the imino chloride, but he could offer no satisfactory explanation for the formation of the amidine. In the light of work by Knott (188) and by Roberts and DeWolfe (278), the authors suggest that the amidine may have arisen by a series of reactions (A, B, and C) which would still give the imidate as principal product, owing to the presence of hydrogen chloride.



Only a trace of aniline need be formed by reaction A in order that reactions B and C should proceed, as aniline is regenerated in reaction C. Either the action of moisture on the imidate, or the ortho ester (equation A), would be possible sources of phenyl benzoate.

B. STABILITY OF IMIDATE BASES AND THEIR DECOMPOSITION BY HEAT

1. *Unsubstituted imidates*

The simpler aliphatic imidate bases are usually liquids which can be distilled unchanged; aromatic imidates, however, decompose when heated into the corresponding nitriles and alcohols (252).

$$ArC(=NH)OR \rightarrow ArCN + ROH$$

Storage over a period of twenty-two years resulted in the formation of cyaphenine from alkyl benzimidates (163).

2. N-Substituted imidates; the Chapman rearrangement

N-Substituted imidates, if liquids, may usually be distilled *in vacuo* but undergo rearrangement to *N,N*-disubstituted amides on being heated at elevated temperatures.

$$CH_3C(=NC_6H_5)OCH_3 \rightarrow CH_3CON(C_6H_5)CH_3$$

This reaction has become known as the Chapman rearrangement, despite earlier work in this field. For example, Lander (198) studied the effect of the presence of alkyl halides on this reaction and found that replacement of a higher by a lower alkyl group took place when such an imidate was heated with a lower alkyl halide.

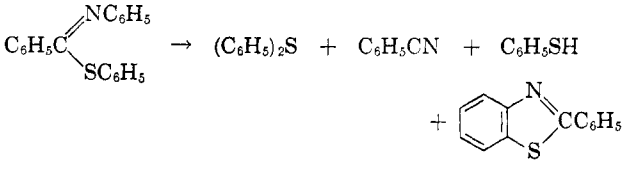
$$CH_3C(=NC_6H_5)OC_2H_5 + CH_3I \rightarrow CH_3CON(C_6H_5)CH_3 + C_2H_5I$$

He also noted that *N*-substituted imidates derived from methanol underwent rearrangement almost quantitatively at 100°C., while those prepared from ethanol had enhanced stability.

The reaction proceeds equally well, however, in the absence of alkyl halide, and the first quantitative studies were undertaken by Chapman (60). From a study of freezing-point diagrams for a mixture of reactant (imidate XXIII: R = R′ = aryl) and pyrolysis

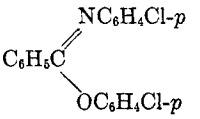
$$RC(=NR'')OR'$$
XXIII

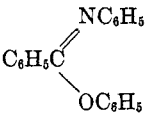
product (amide), he concluded that the reaction was monomolecular, complete, and without by-products in the cases examined. In contrast to the *O*-aryl imidates (XXIII: R = R′ = aryl), the *O*-alkyl compounds did not give good yields of reaction products and required a higher temperature for rearrangement (62, 198). When the corresponding *N*-substituted thioimidates were pyrolyzed, higher temperatures were again required and the products were more diverse (61).



The reaction was described by Chapman (61, 62) as being intramolecular and reversible but with the equilibrium biased in favor of amide formation in the case of the *O*-imidates. Recently, elegant kinetic experiments by Wiberg and Rowland (340) have confirmed that this 1,3-shift is in fact intramolecular, since pyrolysis of a mixture of the imidates XXIVa and XXIVb in diphenyl ether solution gave no detectable mixed products.

The mechanism points to the electron pair of the nitrogen being involved with the migrating group, giving nucleophilic displacement on the ring when for XXIII R′ = aryl. However, a free-radical (i.e., intermolecular) process is feasible when for the imidate XXIII R′ = alkyl, as methyl-C^{13} *N*-*p*-tolylformimidate and methyl *N*-*p*-ethylphenylformimidate did give rise to mixed reaction products (341).

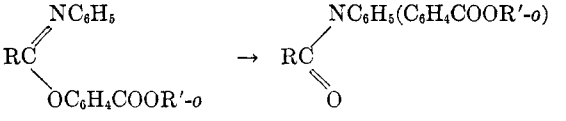

XXIVa


XXIVb

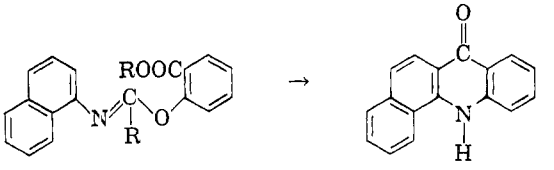
Use of this pyrolysis has been made in the synthesis of *N*-substituted amides (78), and subsequently secondary amines, by hydrolysis (165, 203). The preparation of *N*-alkylarylamines from primary aromatic amines has been achieved by treating the amine in the presence of sulfuric acid below 140°C. with an alkyl orthoformate; the imidate intermediate was then decomposed *in situ* above 140°C. (282).

$$HC(OCH_3)_3 + C_6H_5NH_2 \rightarrow HC(=NC_6H_5)OCH_3 \rightarrow HCON(C_6H_5)CH_3 \rightarrow C_6H_5NHCH_3$$

Moreover, the Chapman rearrangement proceeds readily in the presence of electron-attracting substituents on the migrating group and a series of sixteen acids of the general type shown in formula XXV has been prepared, these acids being of interest as they exhibit labile optical activity when suitably substituted (132, 154, 155).


XXV

Acridones (154) and benzacridones (XXVI) (87) have also been obtained.


XXVI

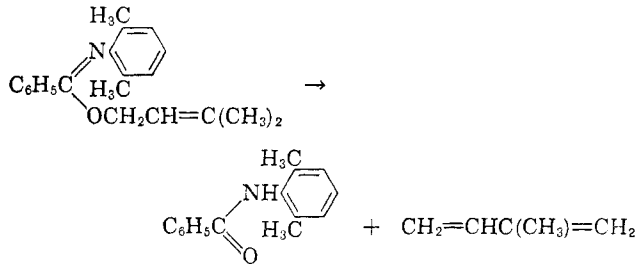
The rearrangement of *N*-substituted benzimidates prepared from allyl alcohols does not always follow the typical Chapman rearrangement. Thus Mumm and Möller (235) found that γ-methylallyl *N*-phenylbenzimidate rearranged with inversion of the allyl group to give *N*-(α-methylallyl)benzanilide,

$$C_6H_5C(=NC_6H_5)OCH_2CH=CHCH_3 \rightarrow C_6H_5CON(C_6H_5)CH(CH_3)CH=CH_2$$

but Lauer and Lockwood (201) demonstrated that the oxygen-to-carbon migration of the γ,γ-dimethylallyl group of γ,γ-dimethylallyl *N*-phenylbenzimidate occurred without inversion as follows:

$$C_6H_5C(=NC_6H_5)OCH_2CH=C(CH_3)_2 \rightarrow C_6H_5CONHC_6H_4[CH_2CH=C(CH_3)_2]\text{-}o$$

When oxygen-to-carbon migration was hindered by substitution on the aromatic nucleus, decomposition took place thus:



giving no justification for assuming that the migration of a group from oxygen to carbon is a two-step process involving double inversion of the migrating group (200).

C. REACTION OF IMIDATES WITH WATER AND WITH HYDROGEN SULFIDE

1. *Reaction of imidates with water*

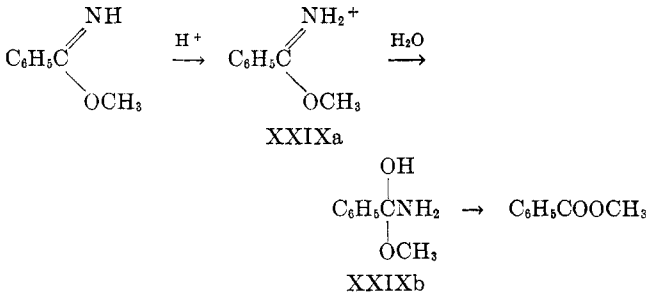
Imidate salts are hydrolyzed in water to the corresponding esters and ammonium salts (252),

$$\underset{\text{XXVII}}{RC(=NH_2X)OR'} + H_2O \rightarrow RCOOR' + NH_4X$$

and, as the reaction is markedly accelerated by hydrogen ions, this necessitates the formation and storage of such salts under anhydrous conditions. In the experience of the authors, when R = alkyl in XXVII the compounds tend to be hygroscopic and hence bring about their own decomposition, but when R carries an aromatic substituent, greater resistance to hydrolysis is noted. A second decomposition into the parent nitrile and alcohol (or phenol) is reported to take place in alkaline media (133) but this is not so prevalent as the acid hydrolysis except at elevated temperature or when, for XXVIII, R′ = Ar.

$$\underset{\text{XXVIII}}{RC(=NH)OR'} \rightarrow RCN + R'OH$$

Using the method of Stieglitz (311, 312, 313, 314), Cloke and his associates (68, 69, 133) measured the rates of hydrolysis of imidate and thioimidate salts by maintaining aqueous solutions of known molarity of these salts at controlled temperatures. Portions of the solution, withdrawn at intervals, were added to a known volume of standard alkali, the imidate base so formed was extracted with carbon tetrachloride, and the excess alkali was estimated by titration with standard acid. The rate of interaction of imidate salt with water was then calculated and the reaction was found to be monomolecular. Further, thiobenzimidates were found to be less sensitive to decomposition than the corresponding *O*-imidates. Salts of *O*-imidates, having a high velocity constant of hydrolysis, had a low dissociation constant, but this relationship was not so clean-cut in the case of the thiobenzimidates (133). Recent work by Edward and Meacock (99) has shown that the rate of hydrolysis of methyl benzimidate ($pK_a' = 5.68$–5.8)—the protonation of which nears completion in solutions more acid than pH 3—would be expected to become constant with increasing acidity. However, it does in fact drop in solutions of hydrochloric acid above 0.1 *N*. It is predicted that this is consistent with a reaction mechanism of the type



in which the rate-determining step is the attack of the water molecule on the ion XXIXa, giving the labile intermediate XXIXb. Moreover, the hydrolysis of methyl benzimidate was found to be almost 400 times faster than that of benzamide, owing chiefly to the almost complete protonation of the former compound.

Practical use of this hydrolysis has been made in the preparation of esters with insect-repellent properties (23) and in the synthesis of 2-substituted acrylic esters (172), among others (250, 275).

It was claimed by Eschweiler (103) that "imino-hydrins" or isoamides

$$RC(=NH)OH$$

arose when imidate salts (especially α-hydroxyimidate salts) reacted with silver oxide or the bases were shaken with water. These compounds were found to be neutral, to have twice the molecular weight assigned to them by Eschweiler, and to have conductivities in aqueous media approximating to those of salts (131). MacKenzie (206) and Rule (287) have since shown these compounds to be amidine salts of the general formula (XXX) shown below:

$$\underset{\text{XXX}}{RC(=NH)NH_2 \cdot RCOOH}$$

An example would be mandelamidine mandelate. Rule proposed that the hydrolysis of the imidate took place, giving an ammonium salt which reacted with a further molecule of imidate to give the amidine salt.

$$RC(=NH)OC_2H_5 + 2H_2O \rightarrow RCOONH_4 + C_2H_5OH$$

$$RC(=NH)OC_2H_5 + RCOONH_4 \rightarrow RC(=NH)NH_2 \cdot RCOOH + C_2H_5OH$$

Reference to these "imino-hydrins" is still to be found, however, in modern literature (283).

2. Reaction of imidates with hydrogen sulfide

Ethereal solutions of imidates react with dry hydrogen sulfide to give thion esters along with some thioamide (210, 212, 290).

$$CH_3C(=NH)OC_2H_5 + H_2S \rightarrow CH_3CSOC_2H_5 \xrightarrow{NH_3} CH_3CSNH_2 + C_2H_5OH$$

The method is fairly general in scope (159), and McElvain and Karjala (167) were able to prepare γ-(2-methylpiperidino)propyl thionbenzoate by the action of hydrogen sulfide on the corresponding imidate. The pesticide rubeanic acid was similarly prepared from oxaldiimidate (322).

$$\begin{array}{l} C(=NH)OC_2H_5 \\ | \\ C(=NH)OC_2H_5 \end{array} + H_2S \rightarrow \begin{array}{l} CSNH_2 \\ | \\ CSNH_2 \end{array}$$

Rubeanic acid

On the other hand, thiol esters are readily synthesized by the action of water on thioimidate salts (133).

$$C_6H_5C(=NH_2Cl)SC_2H_5 + H_2O \rightarrow C_6H_5COSC_2H_5 + NH_4Cl$$

Dithio esters can be formed from the action of hydrogen sulfide with thioimidates but, whereas benzyl thioformimidate was obtained in this way (151),

$$\underset{\text{XXXI}}{2RC(=NH)SCH_2C_6H_5} + 3H_2S \rightarrow 2RCSSCH_2C_6H_5 + (NH_4)_2S$$

Jepson, Lawson, and Lawton (159) found no evidence for the formation of other dithio esters (XXXI: R = CH_3— or $C_6H_5CH_2$—), thioamides being isolated instead. Similarly, dithioöxamide was isolated from the action of hydrogen sulfide on methyl oxaldithioimidate (348). Marvel, de Radzitzky, and Brader (209) have modified the foregoing procedure (291) and obtained dithio esters in good yields by treating a solution of the thioimidate salt in pyridine at 0°C. with hydrogen sulfide. After acidification of the reaction mixture, the product was obtained on extraction with ether.

D. PREPARATION OF ORTHO ESTERS BY ALCOHOLYSIS OF IMIDATES

Pinner (252, 253) prepared simple and mixed ortho esters by the interaction of alkyl formimidate salts with excess alcohol at room temperature.

$$HC(=NH_2X)OR + 2R'OH \rightarrow HC(OR')_2R + NH_4X$$

Alcoholysis of imidate salts of other monobasic acids gave later workers ortho esters of acetic (273, 288), phenylacetic (289), propionic (299), butyric, valeric, caproic, isocaproic, and benzoic (48) acids.

In these cases the reaction period varies from a few days (methyl orthopropionate) to six weeks (ethyl orthobenzoate), but the reaction time has been cut to a few hours and the yields materially increased by carrying out the reaction in boiling ether (219) or petroleum ether (214). Such conditions ensure reaction temperatures below those at which decomposition of the imidate salt into the amide would predominate over formation of ortho ester.

$$\underset{\text{XXXII}}{RC(=NH_2Cl)OR'} \rightarrow RCONH_2 + R'Cl \qquad (1)$$

The modified reaction is considered to give a cleaner product than the Tschitschibabin synthesis of ortho esters (219).

$$RMgBr + C(OC_2H_5)_4 \rightarrow RC(OC_2H_5)_3$$

Amide formation was found to be least for imidates of the type of XXXII when R carried only one substituent, e.g., alkyl, halogen, or ethoxy (218). Where R had two or more α-substituents, amide was the major reaction product (218, 251). When for the imidate XXXII, R′ = C_6H_5—, however, greater stability to formation of ortho ester was noted and amide formation lessened, presumably because the C_6H_5—O bond did not rupture as readily as an alkyl-oxygen bond (218). Moreover when R carried two or more α-substituents, normal esters and ethers were identified among the products of alcoholysis (216, 222).

$$RC(=NH_2Cl)OR' + 2R'OH \rightarrow RCOOR' + NH_4Cl + R'OR' \qquad (2)$$

This latter reaction course was also evident when an imidate-boron trifluoride coördination compound was subjected to alcoholysis (222),

$$RC(=NH\cdot BF_3)OR' + 2R'OH \rightarrow RCOOR' + NH_3BF_3 + R'OR'$$

the boron trifluoride-ammonia having catalyzed the decomposition of the ortho ester as soon as it was formed. The presence of normal esters in the other cases (equation 2) indicated that similar decompositions of the ortho esters were taking place, owing to the catalytic action of imidate salts. In support of this, McElvain and Clarke (217) isolated pentaethoxyethane (XXXIIIb) when excess of the imidate salt (XXXIIIa) was neutralized with sodium ethoxide just before fractional separation of the products, whereas distillation without neutralization gave the normal ester (XXXIIIc) and diethyl ether.

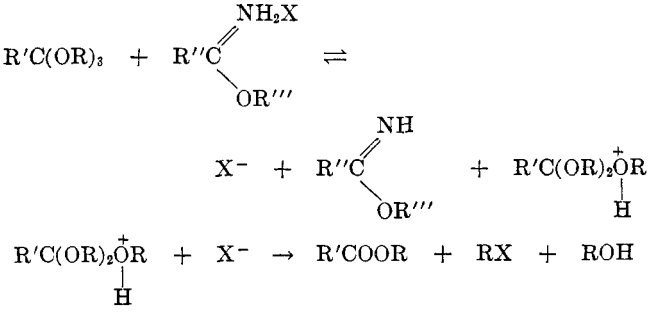
$$\underset{\text{XXXIIIa}}{(C_2H_5O)_2CHC\begin{matrix} NH_2Cl \\ \diagup\!\!\!\diagdown \\ OC_2H_5 \end{matrix}} + C_2H_5OH \rightarrow \begin{cases} \underset{\text{XXXIIIb}}{(C_2H_5O)_2CHC(OC_2H_5)_3} \\ \underset{\text{XXXIIIc}}{(C_2H_5O)_2CHCOOC_2H_5} + (C_2H_5)_2O \end{cases}$$

At first sight the size of the α-substituents seemed to be exerting a marked effect on formation of normal ester (222), but kinetic studies on ortho ester/imidate salt

pairs in chloroform solution at 25°C. led to very different conclusions (224). From these experiments—in which amide formation (equation 1 above) was minimized by the choice of temperature and solvent—McElvain and Tate (224) gave this picture of the reaction:

$$R'C(OR)_3 + R''C(=NH_2Cl)OR''' \rightarrow R'COOR + R''C(=NH)OR''' + RCl + ROH$$

and concluded that (*a*) the α-substituents of ortho esters had no significant effect on their rates of cleavage, (*b*) the reaction was acid catalyzed (the less basic the imidate, the higher the rate of cleavage of the ortho ester), (*c*) methyl ortho esters were more rapidly cleaved than their ethyl analogs, and (*d*) the reaction proceeded faster when the imidate anion was bromide rather than chloride. An S_N2 reaction mechanism was therefore postulated, involving a reversible proton transfer from imidate salt to ortho ester, followed by a rate-determining interaction of the resultant cation and halide anion.



McElvain and Tate (224) have been careful to point out, however, that these results may not be strictly applicable to the formation of normal ester during the alcoholysis of imidate salts, which takes place in alcohol and not in chloroform solution.

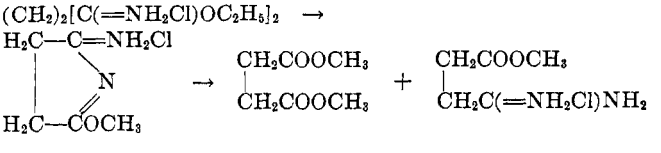
The monoimidate salts of malononitrile and succinonitrile gave on alcoholysis good yields of the corresponding ortho esters (220),

$$NC(CH_2)_nC(=NH_2Cl)OCH_3 \xrightarrow{CH_3OH} NC(CH_2)_nC(OCH_3)_3$$
$n = 1$ or 2.

but these were cleaved to the normal esters on treatment with alcohol and hydrogen chloride.

$$NC(CH_2)_nC(OCH_3)_3 \xrightarrow[CH_3OH]{HCl} NC(CH_2)_nCOOCH_3 + (CH_2)_n(COOCH_3)_2$$

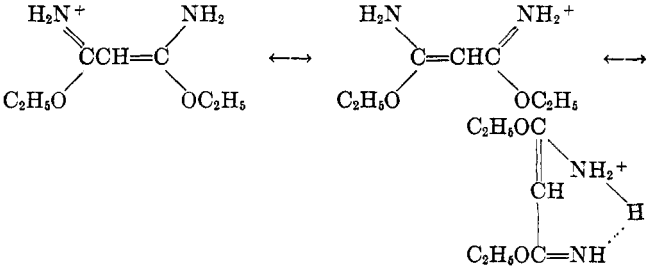
Application of alcoholysis to simple diimidate salts showed that methyl succindiimidate dihydrochloride yielded dimethyl succinate, ammonium chloride, and β-carbomethoxypropionamidine hydrochloride.



If, however, the reaction mixture was neutralized prior to fractional distillation, then the desired methyl orthosuccinate was obtained (220).

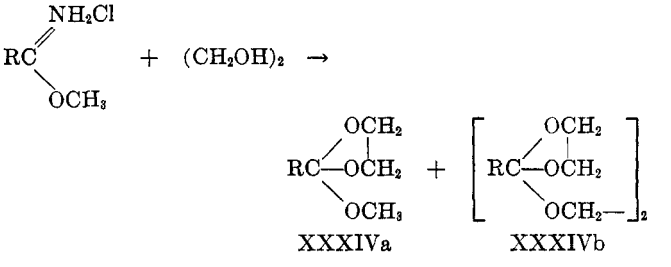
$$(CH_3O)_3CCH_2CH_2C(OCH_3)_3$$

Malondiimidate monohydrochloride gave, on alcoholysis, malondiamidine dihydrochloride and 2-carbethoxy-4,6-diethoxypyrimidine (225). McElvain and Tate (225) suggest that resonance of the malondiimidate cation



gives the malondiimidate monohydrochloride a stability to alcoholysis much more akin to that of an imidate base, which will not undergo any noticeable alcoholysis even in boiling alcohol (223).

Alkyl ethylene ortho esters (XXXIVa) have been prepared by the alcoholysis of imidate salts with one equivalent of ethylene glycol but some diortho ester (XXXIVb) is formed simultaneously (215, 221).



The ready alcoholysis of imidates offers a new route for the conversion of nitriles into aldehydes, the nitrile being first converted into the imidate, then to the ortho ester, and finally with lithium aluminum hydride through the acetal to the aldehyde (67).

$$RCN \rightarrow RC(=NH_2Cl)OR' \rightarrow RC(OR')_3 \rightarrow RCH(OR')_2 \rightarrow RCHO$$

E. REACTION OF IMIDATES WITH AMMONIA AND SUBSTITUTED AMMONIAS

1. Formation of amidines by reaction of imidates with ammonia

Amidines, the subject of a comprehensive review by Shriner and Neumann (298), have been synthesized extensively by the interaction of imidate salts with alcoholic ammonia solutions (7, 12, 38, 47, 228, 252),

$$RC(=NH_2Cl)OR' + NH_3 \rightarrow RC(=NH_2Cl)NH_2 + R'OH$$

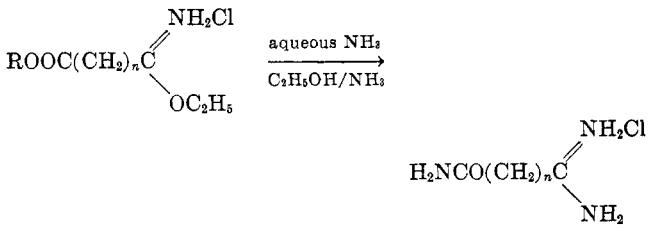
or by heating imidates with ammonium salts in aqueous alcohol at 50–70°C. (20, 21, 22, 120).

$$RC(=NH)OR' + NH_4X \rightarrow RC(=NH_2X)NH_2 + R'OH$$

This latter method appears of particular value when the imidate has as a substituent a normal ester grouping (91)

$$\underset{\text{XXXV}}{ROOCC_6H_4C(=NH)OR'} + NH_4X \rightarrow ROOCC_6H_4C(=NH_2X)NH_2$$

which can otherwise enter into reaction (162).



Amidine formation with imidates of the type of XXXV has also been achieved by controlled addition of ammonium hydroxide to an alcoholic solution of the imidate, followed by gentle heating (91).

The reaction mechanism remains obscure, but Pinner (252) suggested that it was threefold: first the formation of the base,

$$RC(=NH_2Cl)OC_2H_5 + NH_3 \rightarrow RC(=NH)OC_2H_5 + NH_4Cl \quad (3)$$

which reacted with excess free ammonia,

$$\underset{\text{XXXVI}}{RC(=NH)OC_2H_5} + NH_3 \rightarrow RC(=NH)NH_2 + C_2H_5OH$$

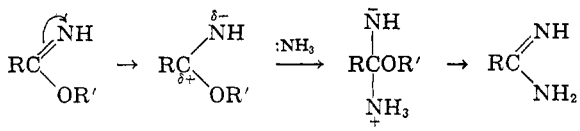
giving finally the amidine salt.

$$RC(=NH)NH_2 + NH_4Cl \rightarrow RC(=NH_2Cl)NH_2 + NH_3$$

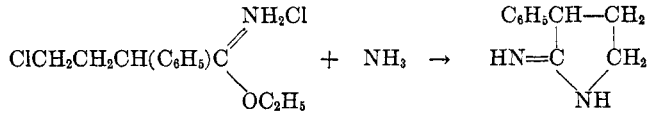
Experimental support for such a mechanism can be drawn from the preparation of benzamidine from benzimidate (XXXVI: R = C_6H_5—) (12) and from the fact that amidines are in general stronger bases than ammonia (298). In contradistinction, Knorr (187) suggested that the imidate base on formation (equation 3 above) reacted directly with the ammonium salt formed along with it:

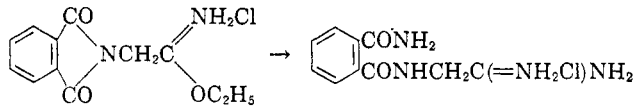
$$RC(=NH)OC_2H_5 + NH_4Cl \rightarrow RC(=NH_2Cl)NH_2 + C_2H_5OH$$

this being, in fact, a general method of amidine formation (20, 22, 120). Shriner and Neumann (298) have proposed a mechanism similar to that suggested for the hydrolysis of esters.



Few exceptions (238) to the formation of amidines by this method have been noted, but γ-chloro-α-phenylbutyrimidate hydrochloride cyclized to 2-imino-3-phenylpyrrolidine when treated with ammonia (177), and ethyl phthalimidoacetimidate hydrochloride gave a phthalamidoamidine with the same reagent (38).





The synthesis of amidines via imidates has been criticized, however, on the grounds that large volumes of anhydrous solvents are required during the reactions, and more direct syntheses from other starting materials have recently been devised (152, 243, 244, 245, 246, 247).

2. *Formation of amidines by reaction of imidates with sulfonamides*

Simple or *N*-substituted imidates refluxed in benzene or alcohol with sulfonamides condense to sulfonyl derivatives of amidines (138, 188).

$$CH_3C(=NR)OC_2H_5 + R'SO_2NH_2 \rightarrow CH_3C(=NSO_2R')NHR$$

R = H or Ar.

These sulfonylamidines are of considerable interest, as it is possible to isolate two isomeric forms (XXXVIIa and XXXVIIb) (8, 19).

XXXVIIa XXXVIIb

On the basis of their hydrolysis products, Barber (19) assigned the formula XXXVIIa to the stable tautomer, but Angyal and Warburton (8), from their work on the ultraviolet spectra of these compounds, claim that compound XXXVIIb is in fact the stable tautomer.

An imidate condenses preferentially with the sulfonamide group when the reactant carries both sulfonamide and primary amine groupings (113, 233).

$$H_2NC_6H_4SO_2NH_2 + RC(=NH)OR' \rightarrow RC(=NSO_2C_6H_4NH_2)NH_2$$

3. *Preparation of amidines by reaction of imidates with primary amines*

Imidate salts condense with primary amines to produce monosubstituted amidines (252, 298).

$$\underset{\text{XXXVIII}}{RC(=NH_2Cl)OR'} + R''NH_2 \rightarrow RC(=NH_2Cl)NHR'' + R'OH$$

The basic strength of the amine plays an important role, and it would appear that the conditions of reaction are most favorable when for compound XXXVIII R″ is aliphatic (7, 47, 140, 161, 252, 349, 351). The salts of the weakly basic 2-nitrobutyl imidates (XXXVIII: R′ = $C_2H_5CH(NO_2)CH_2$—) readily undergo aminolysis (79) and good yields are also reported from

refluxing an imidate salt (one part) with an amine (two parts) in dioxane (24).

Excess primary amine reacting at a higher temperature over a longer period of time furnishes an *N,N'*-disubstituted amidine (44, 140, 252, 298).

$$RC(=NH_2Cl)OC_2H_5 + 2R'NH_2 \rightarrow RC(=NR')NHR' + NH_4Cl + C_2H_5OH$$

4. Formation of amidines by reaction of imidates with secondary amines

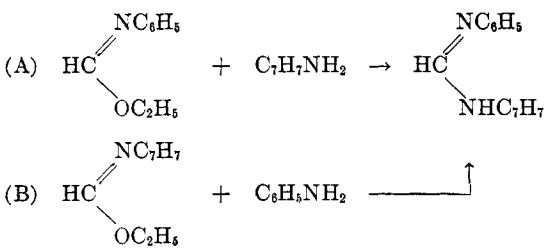
Unsymmetrical disubstituted amidines are formed when imidate salts are treated with secondary amines (53, 161, 252, 298).

$$RC(=NH_2Cl)OC_2H_5 + R'R''NH \rightarrow RC(=NH_2Cl)NR'R'' + C_2H_5OH$$

Imidates do not react with tertiary amines (252, 351).

5. Formation of amidines by reaction of N-substituted imidates with amines

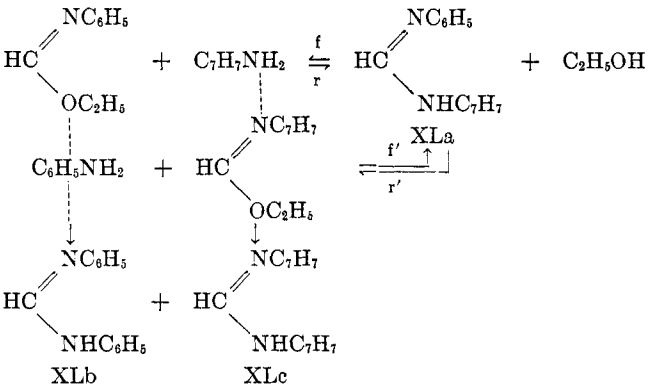
Repeating earlier work on the reaction between arylamines and ethyl *N*-arylformimidates (333, 334), Roberts (277) found the reaction to be extremely sensitive to acid catalysis.



When great care was taken to exclude all traces of acid, reactions A and B gave the same high-melting product, *N*-phenyl-*N'*-(*p*-tolyl)formamidine, but in the presence of acid (introduced as the amine salt), a disproportionation reaction took place and the product was a mixture of the foregoing amidine along with *N,N'*-diphenylformamidine (XXXIXa) and *N,N'*-di(*p*-tolyl)formamidine (XXXIXb).

$HC(=NC_6H_5)NHC_6H_5$ XXXIXa $HC(=NC_7H_7)NHC_7H_7$ XXXIXb

This mixture could not be separated by crystallization and had a sharp melting point (86°C.)—hence the confusion in the earlier work (333, 334). Roberts and DeWolfe (278) have since shown that these results may be interpreted on the basis of the following reaction picture:



The reverse reactions (r and r') do not occur to any appreciable extent in the absence of acids; hence *N*-phenyl-*N'*-(*p*-tolyl)formamidine is formed almost irreversibly. In the presence of acids, however, reactions r and r' have an appreciable rate; hence aniline and toluidine are formed from the *N*-phenyl-*N'*-(*p*-tolyl)formamidine and these undergo further reaction, giving a mixture of products (XLa, XLb, and XLc).

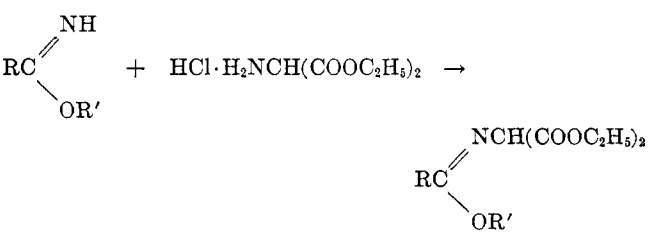
The reactions of *p*-nitroaniline (279) and of *o*- and *p*-chloroanilines (192, 279) have also been studied. Since a higher temperature is required for the interaction of the imidate and *p*-nitroaniline, there is always some disproportionation reaction, resulting in a mixture of products, even when acids are excluded. In this case, however, it is feasible to separate the three amidines by crystallization.

6. Formation of amidines by reaction of imidates with acids

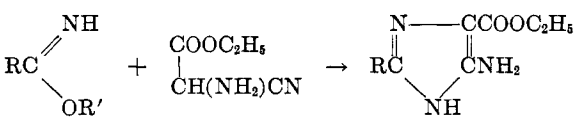
Amidines are formed when imidates react with specific acids (*cf.* Section IV,H).

7. Preparation of imidazoles from imidates

An imidate base in a suitable organic solvent, when shaken with an aqueous solution of a salt of an α-amino ester, furnishes an *N*-substituted imidate (16, 82, 86, 174, 180, 292, 293, 296, 297).



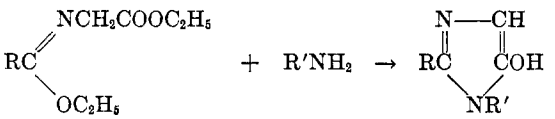
but condensation of the free base of the imidate with the α-amino ester itself gives rise to an imidazole (74).



Thioimidates and their *salts* react in chloroform solu-

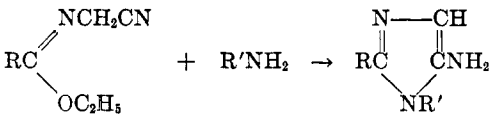
tion with α-amino nitriles to give imidazoles in yields superior to those from the *O*-imidates (17, 74), but in certain cases the formation of *N*-substituted thioimidates is reported (16, 74).

N-Substituted imidates of the type of XLI react smoothly with simple aliphatic amines to give hydroxyimidazoles (297),

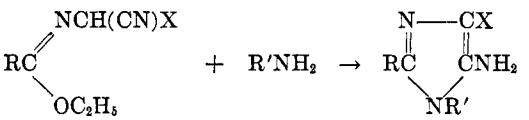


XLI

although Kjær failed to cyclize an imidate of similar type using ammonia (180). Slight modifications of this reaction have led to the formation of aminoimidazoles (297),

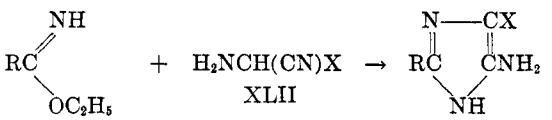


and to 4-amido- or 4-thioamido-5-aminoimidazoles (296).



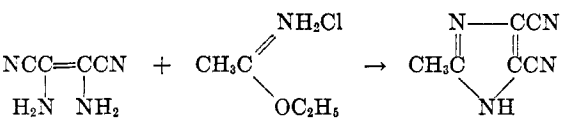
X = —CONH₂ or —CSNH₂.

Similar amino amides were obtained by direct condensation of imidates or thioimidates with compounds of the type of XLII (77, 231, 296).

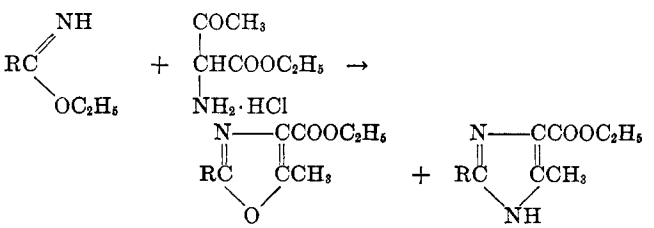


X = —CONH₂ or —CSNH₂

Other syntheses include the preparation of 4,5-dicyano-2-methylimidazole from acetimidate and tetrameric hydrocyanic acid (45),

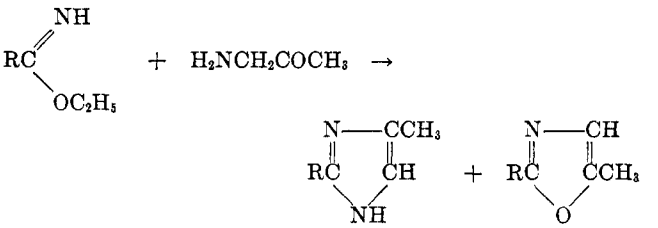


and the condensation of α-aminoketone hydrochlorides with imidates in glacial acetic acid to give a neutral fraction, the oxazole (XLIIIa), and a basic fraction identified as the imidazole (XLIIIb) (85).



XLIIIa XLIIIb

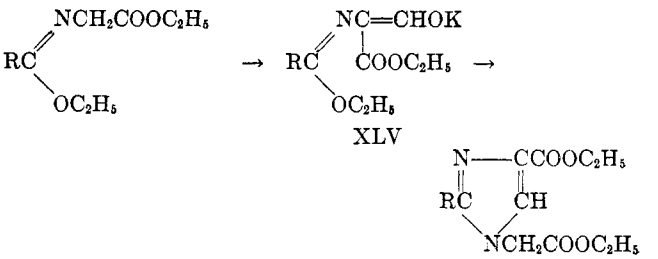
Use of aminoacetone gives, similarly, 4-methylimidazoles (XLIVa) (100)



XLIVa XLIVb

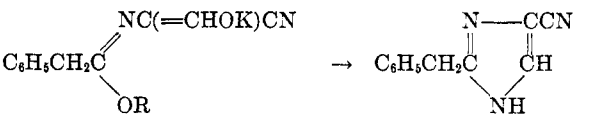
along with considerable quantities of oxazole (XLIVb).

Finally, *N*-substituted imidates can be formylated to give imidates of the type of XLV, which condense with glycine ethyl ester to yield 1-substituted imidazoles (82).



XLV

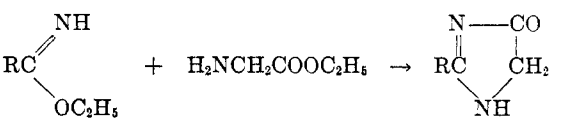
Modification of this procedure, using the potassium salt (XLVI) and ammonium sulfate, led to the formation of 2-benzyl-4-cyanoimidazole (84).



XLVI

8. Preparation of 4(5)-imidazolones from imidates

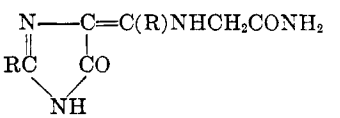
The work of Finger and Zeh (108, 109) on the preparation of 4(5)-imidazolones has been reinvestigated; Kjær (179) found that glycine ethyl ester and ethyl phenylacetimidate in ether solution at room temperature deposited 2-benzyl-4(5)-imidazolone (XLVII) on standing,



XLVII

R = C₆H₅CH₂—.

whereas these reactants on being heated in the absence of solvent gave the dimer (XLVIII).

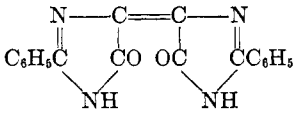


XLVIII

R = C₆H₅CH₂—.

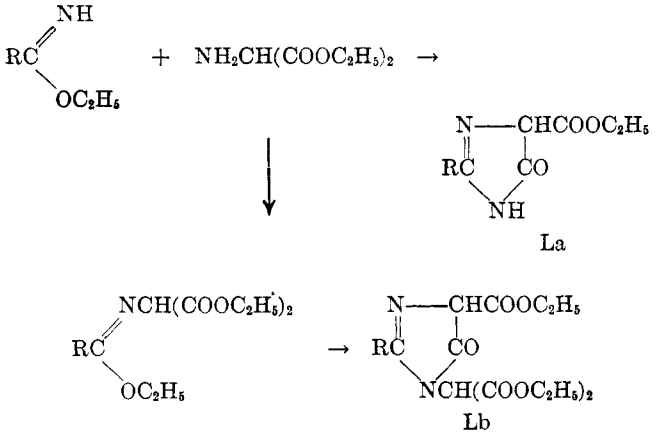
The somewhat unstable 2-phenyl-4(5)-imidazolone (XLVII: R = C_6H_5—) could only be obtained by letting

the reactants stand in ether under nitrogen to reduce side products formed by oxidation; glyoxaline red (XLIX) was formed simultaneously and a chromatogram of the reaction mixture pointed to the presence of further products (181).

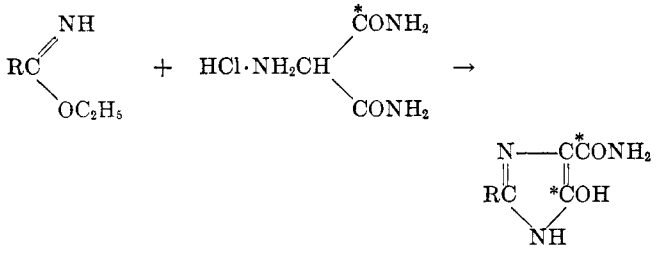


XLIX
Glyoxaline red

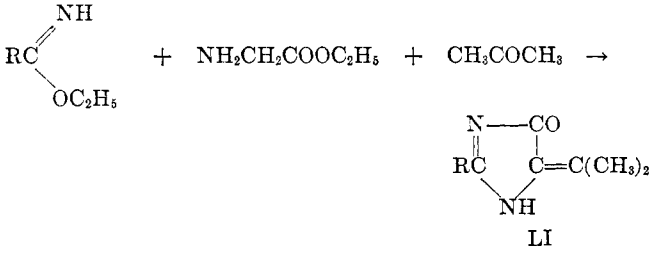
Ethyl aminomalonate condenses similarly with imidates to give either the imidazolone (La) or, by interaction of two molecules of ester, the compound Lb (82, 231),



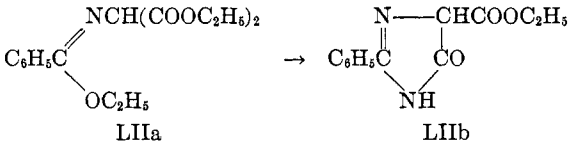
and C^{14}-labeled aminomalonamide hydrochloride gives 5(4)-hydroxy-4(5)-imidazolecarboxamides (231).



In their attempts to improve the yields in the Finger condensation (108, 109), Lehr, Karlan, and Goldberg (202) used acetone as the condensing solvent and isolated not the expected imidazolones but their 5(4)-isopropylidene derivatives (LI). Other ketones underwent similar condensation reactions.



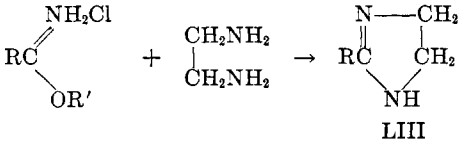
Work in the penicillin field (80) had shown that the imidate LIIa on treatment with ammonia and subsequent heating cyclized to 2-phenyl-5(4)-carbethoxy-4-(5)-imidazolone (LIIb),



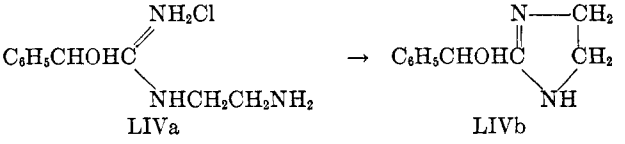
but Kjær (180) found that ethyl *N*-carbethoxymethylphenylacetimidate gave the dimer XLVIII (R = $C_6H_5CH_2$—) under similar conditions.

9. *Preparation of imidazolines from imidates*

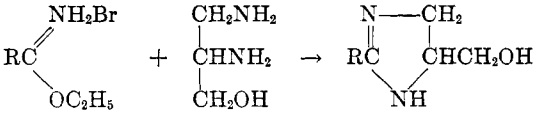
2-Imidazolines have been prepared extensively by heating 1,2-alkyldiamines with imidates or their salts.



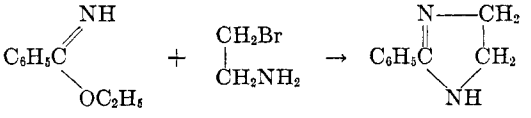
A review by Ferm and Riebsomer (107) covers work published up to 1952, but more recent workers have prepared 2-imidazolines of the type of LIII, where R = C_6H_5— and *p*-$CH_3C_6H_4$— (139), $C_6H_5COCH_2$— (184), 2,6-$(CH_3)_2C_6H_3NHCOCH_2$— (204), and α-aminoalkyl (229), among others (7, 117, 118, 153). From a preparation of this type, Bristow (47) was able to isolate and characterize the intermediate *N*-(2-aminoethyl)mandelamidine hydrochloride (LIVa), which lost ammonia slowly at room temperature (more readily in hot alcohol) to give the corresponding 2-imidazoline (LIVb).



The use of 2,3-diamino-1-propanol gives rise to 2-imidazoline-5-methanols (304).



Modification of the foregoing procedure by the use of 2-bromoethylamine leads to inferior yields of product (316).

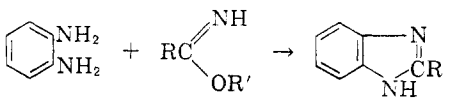


The claim by Drozdov and Bekhli (96) to have synthesized an imidazoline from 2-hydroxy-3-piperidinopropylamine and an imidate is criticized by King and Acheson (175), who point out that the

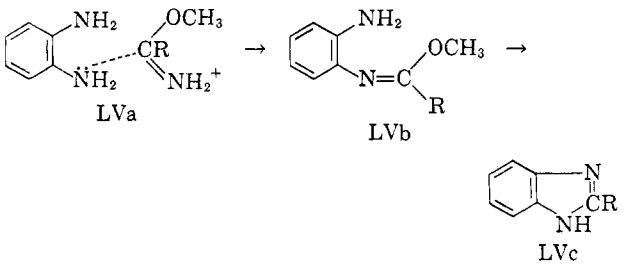
recorded analytical figures do not exclude the oxazoline structure. King and Acheson's statement is supported also by more recent work on the interaction of ethanolamines and imidates (*cf.* Section IV,E,12).

10. Preparation of benzimidazoles from imidates

King and Acheson (175) reinvestigated the preparation of benzimidazoles (350) from imidates or thioimidates and *o*-phenylenediamine (332)

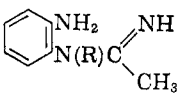


and found that optimum conditions required the presence of one or at the most two equivalents of acid. They suggested that the reaction proceeded by attack of an imidate cation on the lone pair of electrons of one of the amino groups (LVa), with subsequent formation of the *N*-substituted imidate (LVb) which, by elimination of alcohol, cyclized through intramolecular condensation to give LVc (175).



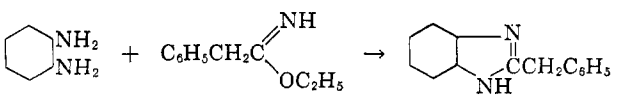
The reaction is well suited for the preparation of 2-arylbenzimidazoles but is not so useful for the 2-alkyl compounds, especially when the *o*-diamine possesses an electrophilic substituent, e.g., a $—NO_2$ or $—COOCH_3$ group in the 4-position (320). Illustrative of other preparations of this type is the work of Mengelberg (230) on 2-(α-aminoalkyl)benzimidazoles and of King, Acheson, and Spensley (176) on 2-chloromethylbenzimidazoles among others (26).

N-Substituted *o*-phenylenediamines can replace the simple diamine, but in these cases side reactions leading to the formation of amidines (LVI) can reduce the yield of benzimidazole, and it has been suggested



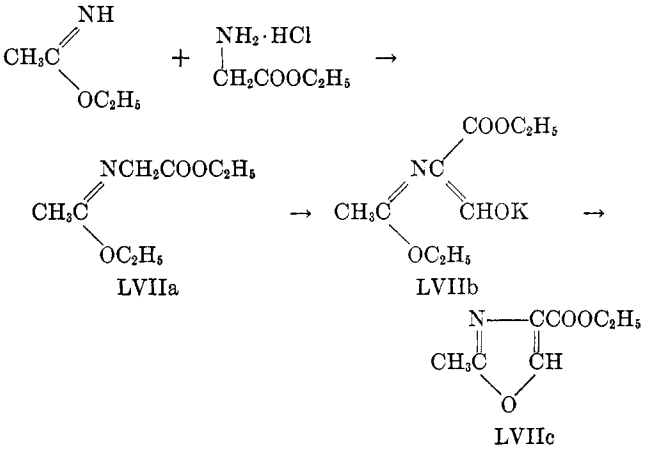
that the basicity of the amino or substituted amino groups is a controlling factor in the course of this reaction (175).

The use of hexahydro-*o*-phenylenediamine with ethyl phenylacetimidate gives in like manner 2-benzylhexahydrobenzimidazole (302).

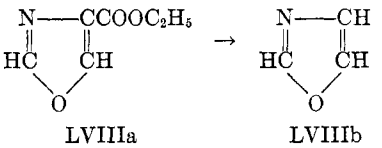


11. Preparation of oxazoles from imidates

In recent times the chemistry of the oxazoles has been extensively studied by Cornforth (81) and has also been the subject of an earlier review by Wiley (343). Representative of the work on these compounds is the preparation of ethyl 2-methyloxazole-4-carboxylate (LVIIc) from ethyl acetimidate and glycine ethyl ester hydrochloride through the intermediate LVIIa; this compound, on formylation with ethyl formate and potassium ethoxide, gave LVIIb, which cyclized in boiling acetic acid to the oxazole (82, 83).

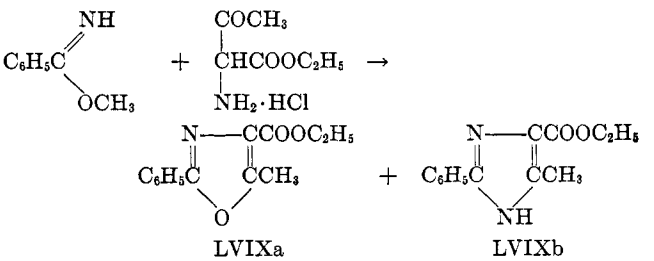


Using this method, Cornforth and Cornforth (82) went on to synthesize the hitherto unknown compound, oxazole (LVIIIb), from isopropyl formimidate and glycine ethyl ester hydrochloride by subsequent hydrolysis and decarboxylation of the resultant 4-carbethoxyoxazole (LVIIIa).

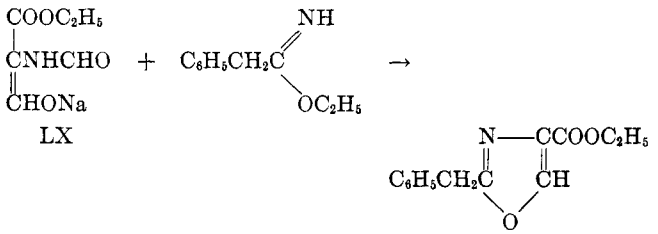


Later the method was adapted to give 4-cyanoöxazoles by replacing the amino ester with aminoacetonitrile (84, 86).

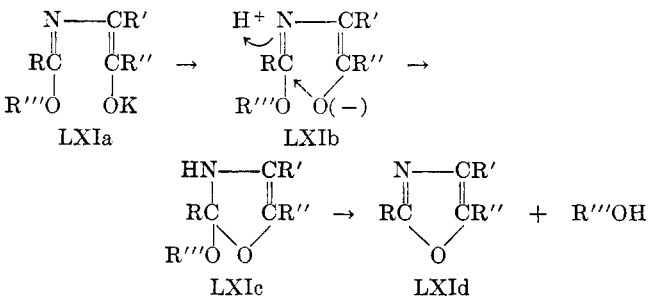
It was found, moreover, that imidates and the salts of α-amino ketones would condense to a mixture of oxazole and imidazole; in this way ethyl 5-methyl-2-phenyloxazole-4-carboxylate (LVIXa) and the corresponding imidazole (LVIXb) were the products of the condensation of methyl benzimidate and ethyl aminoacetoacetate hydrochloride (85).



A further illustration of oxazole synthesis arises in the condensation of the enolate LX with ethyl phenylacetimidate in the presence of mineral acid (2, 3).

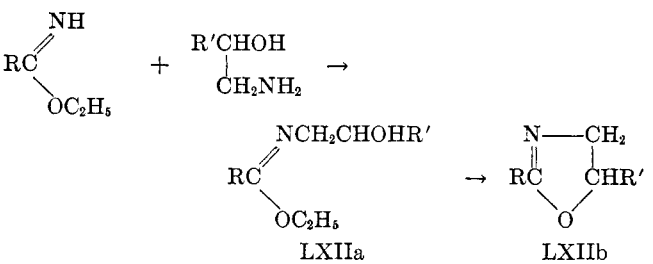


It has been suggested that since enolates of the type of LXIa showed no tendency to cyclize spontaneously, the reaction might be initiated by the acceptance of a positive ion by the nitrogen atom of the enolate ion (LXIb) which, via the intermediate LXIc, then furnished the oxazole (LXId) by loss of a molecule of alcohol (85).



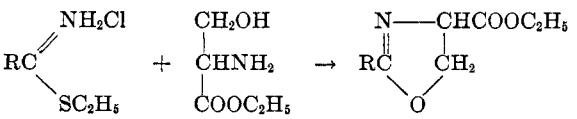
12. Preparation of oxazolines from imidates

2-Oxazolines (81, 344) result when imidates or their salts are heated with α-hydroxy-β-alkylamines with or without diluent present (36).

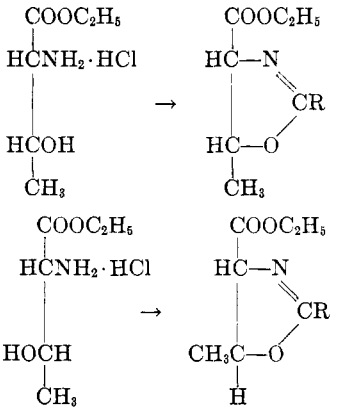


The initial step is thought to be the formation of the *N*-substituted imidate (LXIIa), which cyclizes under the experimental conditions to the oxazoline (LXIIb) (36).

2-Alkyl- or 2-aryl-4-carbethoxyoxazolines are readily obtained by replacing the alkylamine with serine ethyl ester (46, 101, 144, 145, 242),

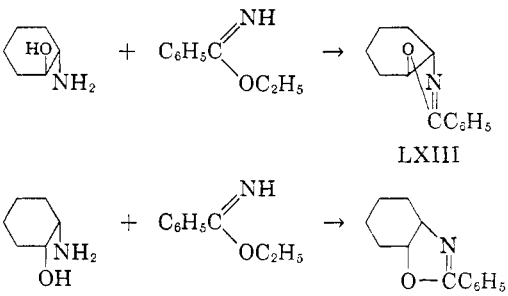


and 5-substituents have been introduced by the use of substituted serines. Increasing the size of the serine ester group from methyl to isopropyl was found to give substantially better yields of oxazoline (101). Moreover the reaction proceeds with retention of configuration at both asymmetric centers in the threonine series (101).

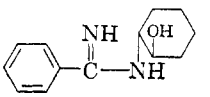


Similar results are discussed in the patent literature (300).

Likewise, other workers (164) describe the preparation of *cis*- and *trans*-2-phenyl-4,5-cyclohexanoöxazolines by heterocyclization of the corresponding 2-aminocyclohexanol hydrochlorides with imidates.

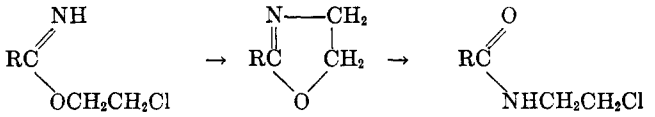


Retention of configuration was once again noted (164). Although the *trans*-oxazoline (LXIII) was found to be quite stable, there was formed simultaneously with it a considerable quantity of *N*-(*trans*-2-hydroxycyclohexyl)benzamidine hydrochloride (213).



In the case of the *cis*- and *trans*-aminocyclopentanols, which have greater coplanarity and rigidity than the corresponding cyclohexanols, only the cis compound yields an oxazoline, whereas the trans compound gives a substantial precipitate of *N*-(*trans*-2-hydroxycyclopentyl)benzamidine hydrochloride (213).

Following the early work of Gabriel and Neumann (114), 2-oxazolines have been synthesized in fair yields by treating imidate salts derived from β-chloroalcohols with ethereal or alcoholic ammonia solutions (248, 319). Wislicenus and Körber have shown that the oxazoline formed from the imidate in this way was an intermediate in the formation of the corresponding amide (LXIV) (345).

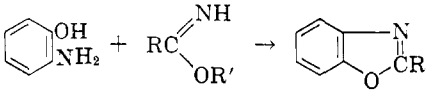


LXIV

Although imidates prepared from β-fluoroalcohols are known (51), there is no record as to whether they cyclize to oxazolines.

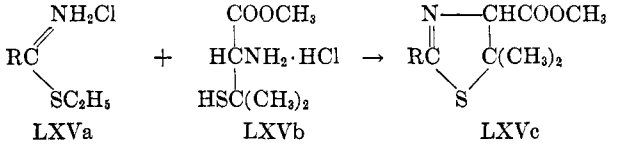
13. Preparation of benzoxazoles from imidates

o-Aminophenols condense with many acid derivatives to give 2-substituted benzoxazoles. Imidates are no exception to this behavior (175, 332).



14. Preparation of thiazolines and related compounds from imidates

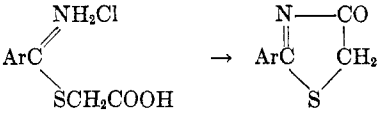
Studies within the penicillin field initiated an investigation of the products derived from the interaction of α,β-mercaptoamines and imidates or thioimidates (15, 73); thus the penicillamine ester LXVb and ethyl cyanothioacetimidate hydrochloride (LXVa: R = —CH_2CN) condensed in dry chloroform to produce methyl 2-cyanomethyl-5,5-dimethylthiazoline-4-carboxylate (LXVc: R = —CH_2CN) (76).



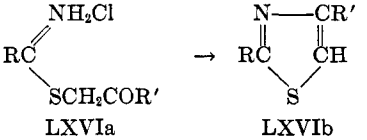
LXVa LXVb LXVc

The reaction was found to be far from general however, owing, on the one hand, to the instability of the desired imidate intermediates or, on the other hand, to the great stability of the corresponding thioimidates, which led to their recovery unchanged from the reaction (75).

Syntheses of a somewhat different character are the cyclization reactions in boiling toluene of aryl imidates derived from thioglycolic acid (307) or its esters (232), giving rise to 2-substituted thiazolin-4-ones.

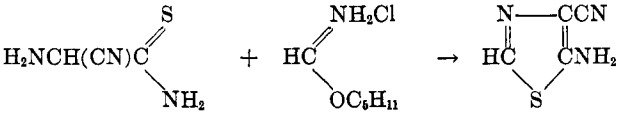


Related compounds of the type of LXVIa (R′ = CH_3— or C_6H_5—) cyclized in like manner to 4-methyl- and 4-phenylthiazoles, respectively (LXVIb: R′ = CH_3— or C_6H_5—) (232).



LXVIa LXVIb

Recently the thioamide LXVIIa was found to condense with isopentyl formimidate to furnish the aminothiazole LXVIIb, although other formimidate and thioformimidate salts gave no definite products (296).



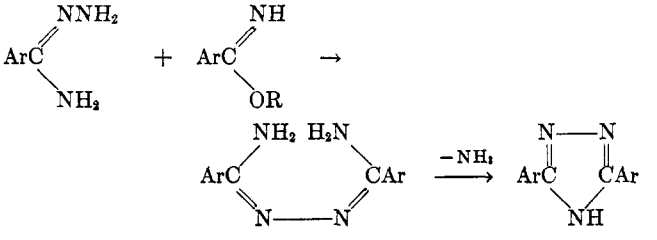
LXVIIa LXVIIb

15. Reaction of imidates with hydrazine

Pinner directed attention to the examination of products obtained from aromatic imidates and hydrazine and showed that the direct reaction products were amidrazones (252, 263, 264, 265, 266, 267).

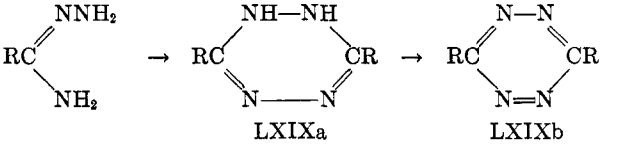
$$ArC(=NH)OR + NH_2NH_2 \rightarrow ArC(=NNH_2)NH_2$$

Pinner's studies of aliphatic systems, however, met with little success. Moreover, amidrazones could react with excess imidate to give dihydrazidines (LXVIIIa), which by elimination of ammonia gave rise to triazoles (LXVIIIb).



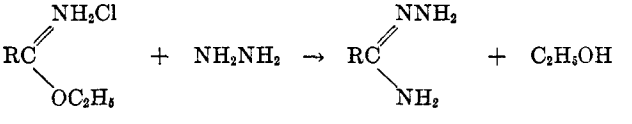
LXVIIIa LXVIIIb

Further, condensation between two molecules of amidrazone could give a dihydrotetrazine (LXIXa), which was readily oxidized to a tetrazine (LXIXb) (263, 264, 265, 266, 267).

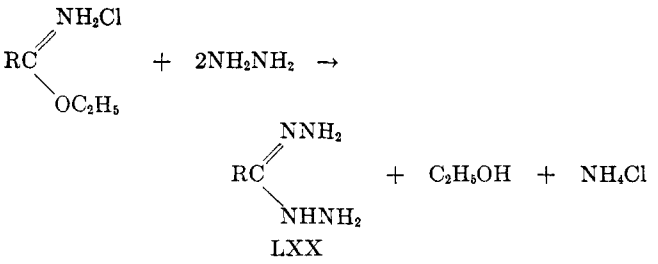


LXIXa LXIXb

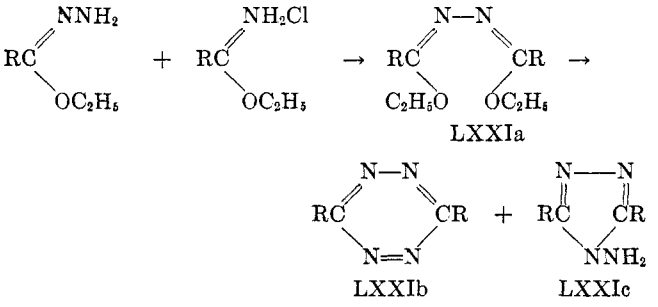
Oberhummer (240, 241) succeeded where Pinner had failed and obtained products from the condensation of aliphatic imidates and anhydrous hydrazine. He showed that the reaction would follow three different courses: firstly, equimolar quantities of imidate salt and hydrazine at temperatures below 0°C. gave the amidrazone,



whereas two molecules of hydrazine to one of imidate salt yielded a hydrazidine (LXX). Finally, if the temperature was raised to 40–50°C., secondary reaction products (LXXIb and LXXIc) derived from



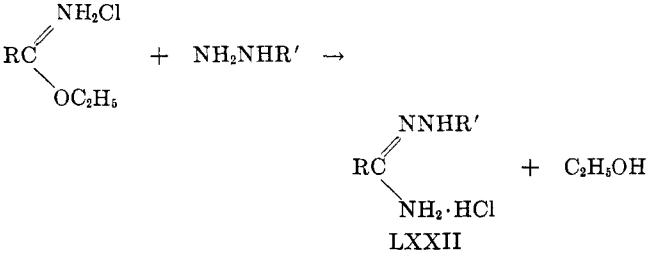
the hydrazino ether (LXXIa) were formed.



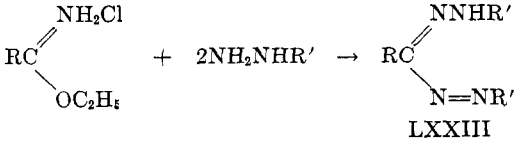
Amidrazones have also been synthesized as intermediates in the preparation of tetrazoles (4, 30, 102), but in these instances the amidrazones need not be isolated in a pure state.

16. Reaction of imidates with monosubstituted hydrazines

N_1-Substituted amidrazones (LXXII) have been synthesized extensively from imidates and monosubstituted hydrazines (13, 160, 193, 237, 252, 255, 258, 324).

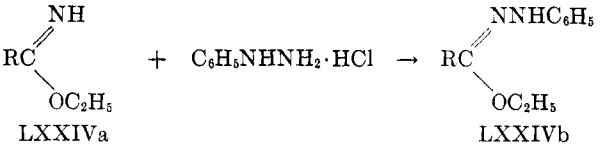


The reactants are usually allowed to stand at room temperature in alcohol solution and the amidrazone may be accompanied by formazan (LXXIII), especially if excess hydrazine is employed.

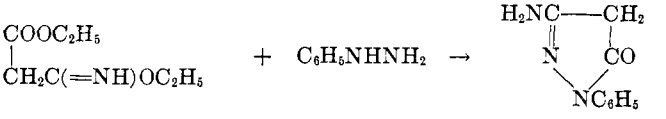


On the other hand, Schmidt (293) records the isolation of hydrazino ethers (LXXIVb) from simple imidates (LXXIVa: R = CH_3— or C_2H_5—) by condensation with phenylhydrazine hydrochloride.

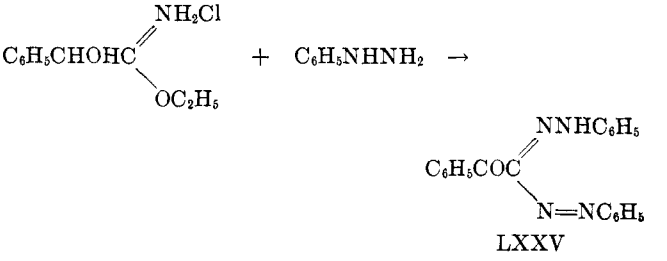
The method also embraces the preparation of certain pyrazolones (193); thus Weissberger, Porter, and Gregory (330) have described the preparation of



3-amino-1-phenyl-5-pyrazolone from the condensation of ethyl malonato monoimidate and phenylhydrazine.

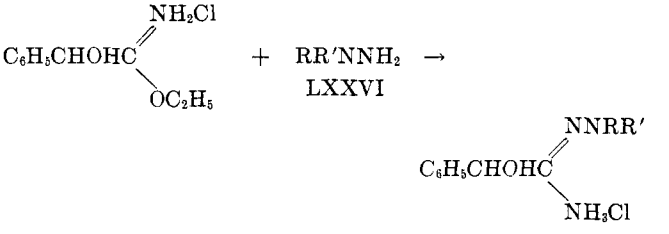


Roger and Newlands (237) found that ethyl mandelimidate hydrochloride reacted with phenylhydrazine in an atmosphere of nitrogen to give not the expected *N,N'*-diphenylmandeloformazan but *N,N'*-diphenylbenzoylformazan (LXXV).



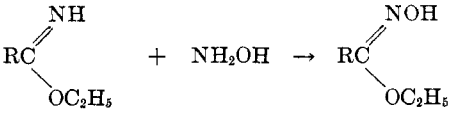
17. Reaction of imidates with disubstituted hydrazines

Roger and Newlands (237) investigated the reaction between hydrazines of the type of LXXVI (R = R' = C_6H_5— and R = CH_3—, R' = C_6H_5—) and ethyl mandelimidate hydrochloride and characterized the products as N_1,N_1-disubstituted amidrazones.

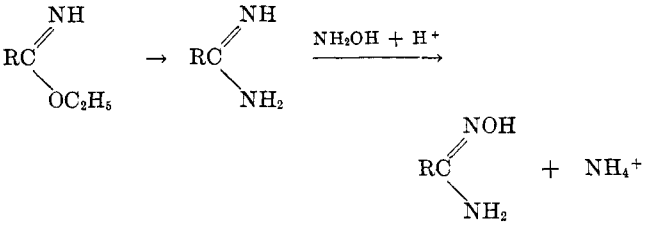


18. Reaction of imidates with hydroxylamines

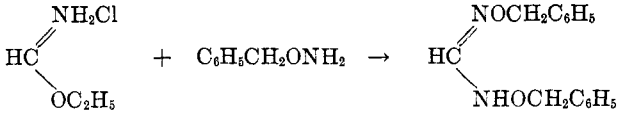
Pinner (256, 257) discovered that the imino groupings of imidates were readily replaced by the oximino group, and Houben, Pfankuch, and Zivadinovitsch (149, 150, 151) showed that good yields of hydroxamic esters resulted when hydroxylamine in aqueous solution was shaken with ethereal solutions of imidates or thioimidates.



The corresponding amidoximes are better synthesized via amidines (298),

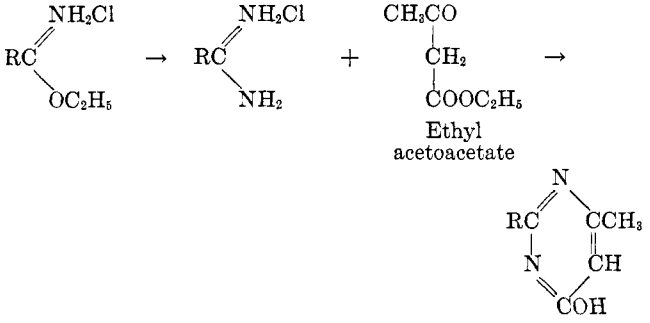


although the action of an ethanolic pyridine solution of hydroxylamine on an imidate salt is claimed in at least one instance to give an amidoxime (56). Both the imino and the ether groups of ethyl formimidate hydrochloride are replaced by interaction with phenylmethoxyamine (294).

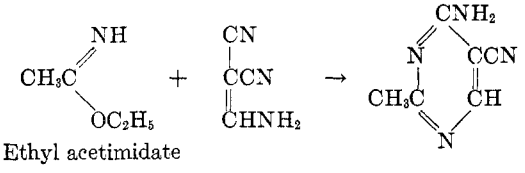


F. SYNTHESIS OF AZINES FROM IMIDATES

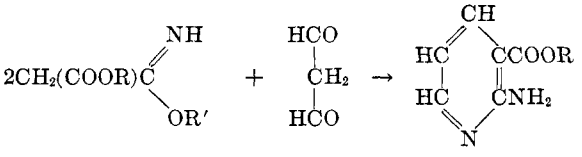
Pyrimidines are readily obtainable from imidates through the condensation, in basic media, of amidines with malonic acid derivatives and related compounds (171, 298); e.g., ethyl acetoacetate.



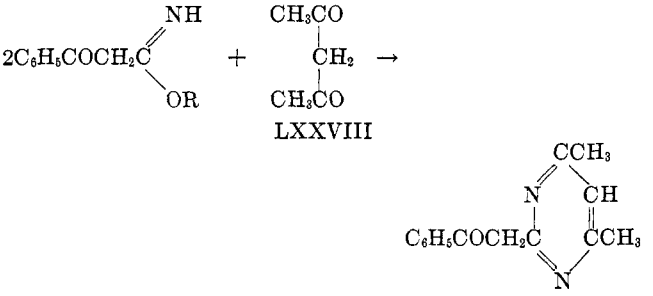
Direct syntheses from imidates include the preparation of 4-amino-5-cyano-2-methylpyrimidine, an intermediate in the synthesis of vitamin B_1, from the interaction of ethyl acetimidate and aminomethylenemalononitrile (205).



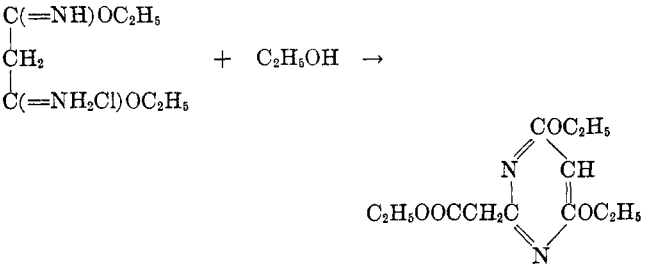
Also the work of Dornow, Karlson, and Neuse (93, 94), who showed that α-carbethoxyacetimidate and the 1,3-dialdehyde LXXVII formed an α-aminonicotinate,



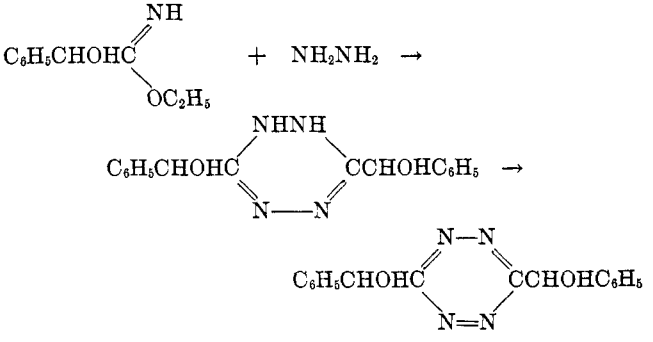
and that benzoylacetimidate and the 1,3-diketone LXXVIII gave similarly 4,6-dimethyl-2-phenacylpyrimidine, is further evidence of direct azine synthesis from imidates.



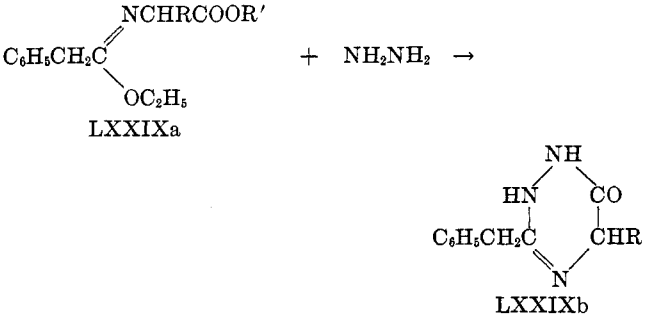
2 - Carbethoxymethyl - 4,6 - diethoxypyrimidine has been found among the products formed during the alcoholysis of diethyl malondiimidate monohydrochloride (225).



Of a somewhat different character is the reaction of hydrazine with specific imidates, e.g., ethyl mandelimidate, to form in the first instance a dihydrotetrazine, easily oxidizable to a tetrazine (263, 264, 265, 266, 267).

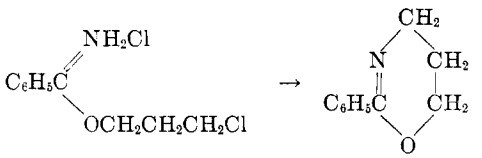


Kjær (180) noted a somewhat similar reaction between imidates of the type of LXXIXa and hydrazine hydrate in alcohol solution. He formulated the products as 3-benzyl-1,2-dihydro-4-triazones (LXXIXb: R = H, CH_3—, or $C_6H_5CH_2$—).



G. SYNTHESIS OF DIHYDROÖXAZINES FROM IMIDATES

What may be looked on as an extension of the Gabriel and Neumann oxazoline synthesis (*cf.* Section IV,E,12) is to be found in work by Cloke and Keniston (68), who claim the formation of 2-phenyl-5,6-dihydro-1,3,4-oxazine from the pyrolysis of γ-chloropropyl benzimidate; γ-chloropropylbenzamide was formed simultaneously.

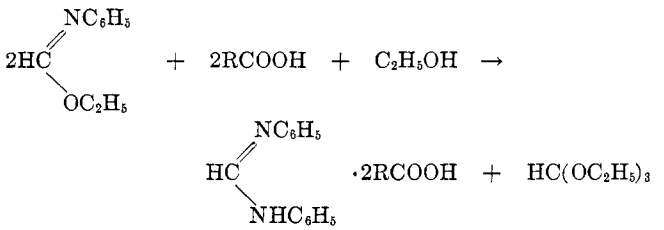


The hydrobromide of this oxazine also resulted from the interaction of hydrogen sulfide and γ-bromopropyl benzimidate (167).

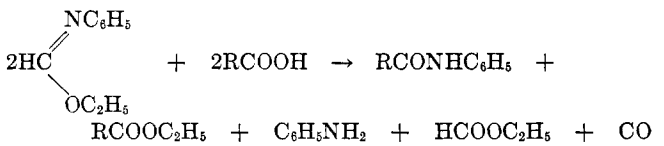
H. REACTION OF IMIDATES WITH ACIDS

1. Reaction with carboxylic and sulfonic acids

Knott (188) has shown that ethyl *N*-phenylformimidate reacts with carboxylic and sulfonic acids in alcohol solution to form mono- or diacid salts of *N,N'*-diphenylformamidine. In one instance a by-product was

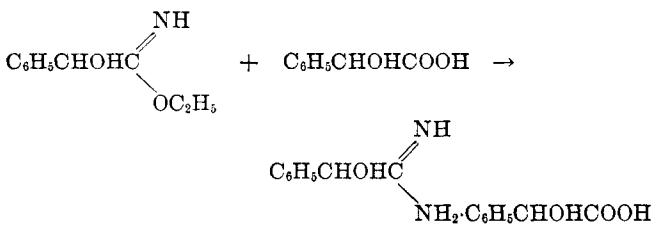


identified as ethyl orthoformate, but the reaction was found not to proceed with the fatty acids from isobutyric acid upwards. If, on the other hand, the imidate and acid were heated together without solvent, the principal product was the corresponding anilide.

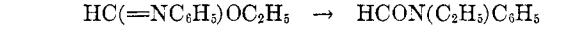


All the normal fatty acids from acetic to lauric as well as isobutyric, isovaleric, and isocaproic underwent reaction in this manner (188).

In these laboratories heating ethyl mandelimidate was found to furnish mandelamidine mandelate along with mandelic acid, either in the presence of diluent (dioxane) or in its absence (286).



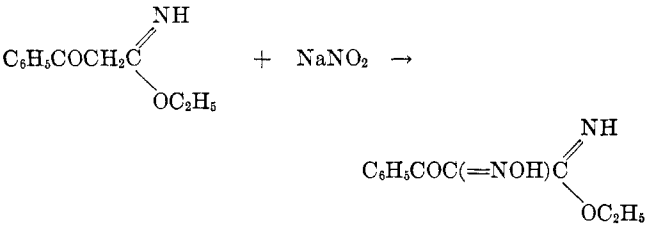
Reactions of this type have also been studied by Roberts, DeWolfe, and Vogt (278, 282), who noted that ethyl *N*-phenylformimidate when treated with sulfuric acid at 170°C. gave *N*-ethylformanilide as the main product.



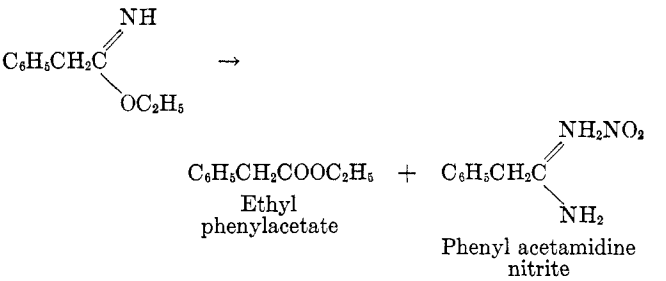
When an alcohol/ether solution of either hydrogen chloride or picric acid was used, however, the product was the corresponding *N,N'*-diphenylformamidine salt. Methyl *N*-phenylformimidate and ethyl *N*-(*p*-chlorophenyl)formimidate rearranged similarly in hot sulfuric acid (282).

2. Reaction with nitrous acid

Bernton (34) observed that ethyl oximinobenzoylacetimidate was formed when cold solutions of sodium nitrite and ethyl benzoylacetimidate were mixed,

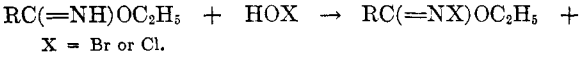


but that the action of nitrous acid converted ethyl phenylacetimidate into ethyl phenylacetate and phenylacetamidine nitrite.



3. Reaction with hypohalous acids

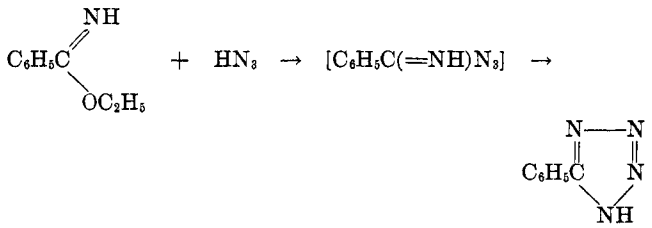
Hypobromous and hypochlorous acids convert imidates into their *N*-bromo and *N*-chloro derivatives, respectively (141, 309, 310, 315).



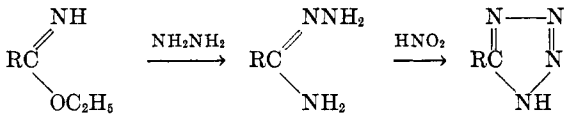
It is claimed that syn and anti forms of these imidates may sometimes be separated by fractional crystallization.

4. Reaction with hydrazoic acid

Tetrazoles may be synthesized by the action of hydrazoic acid on imidates (4, 173, 186). It is more customary, however, to synthesize tetrazoles from



imidates via amidrazones, which are treated with acidified solutions of a nitrite (4, 30, 102, 264).



I. REACTION OF IMIDATES WITH ACID CHLORIDES AND ANHYDRIDES

Acetic anhydride reacts with imidates forming acetylated amides (252, 269).

$$RC(=NH)OR' + (CH_3CO)_2O \rightarrow RCONHCOCH_3$$

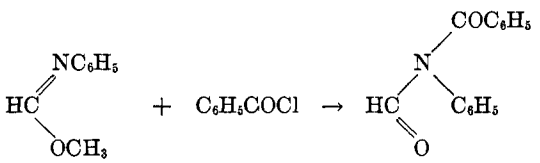
Acid chlorides (LXXX: R′ = CH_3—, C_2H_5—, C_6H_5—) give acyl derivatives of imidates (335, 336, 337),

$$RC(=NH)OC_2H_5 + \underset{\text{LXXX}}{R'COCl} \rightarrow RC(=NCOR')OC_2H_5$$

which, however, readily undergo hydrolysis by water to diacid anilides.

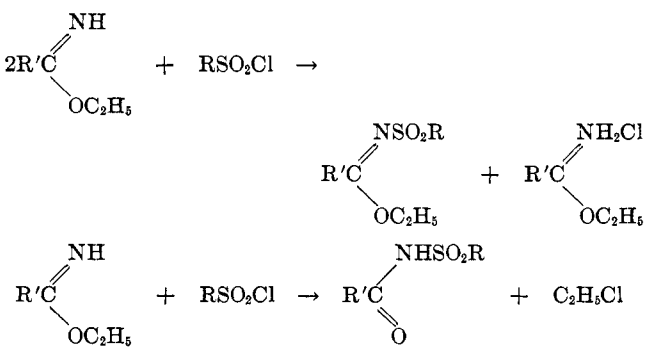
$$RC(=NCOR')OC_2H_5 \rightarrow RCONHCOR'$$

Diacid anilides also result from the interaction of acyl chlorides and *N*-substituted imidates (335).



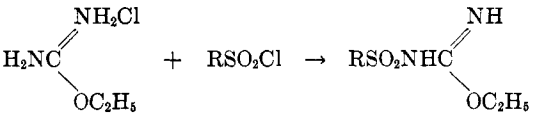
J. REACTION OF IMIDATES WITH SULFONYL HALIDES

Barber (19) records the condensation of imidate bases with sulfonyl halides to give sulfonyl derivatives of the imidates. The reaction is best effected in the presence of two moles of imidate to one of halide; amides are formed simultaneously.

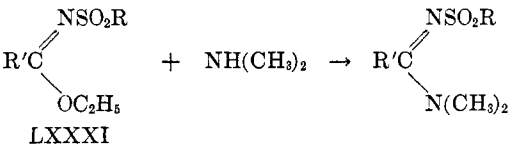


The use of pyridine in this condensation, although found unsuitable by Barber (19), is recommended by other workers (8, 89, 90).

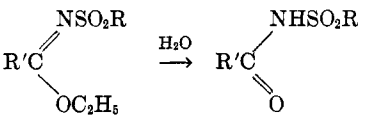
The condensation of ethyl aminoformimidate hydrochloride and a sulfonyl halide in aqueous caustic soda is claimed to leave the imidate grouping unaffected (126).



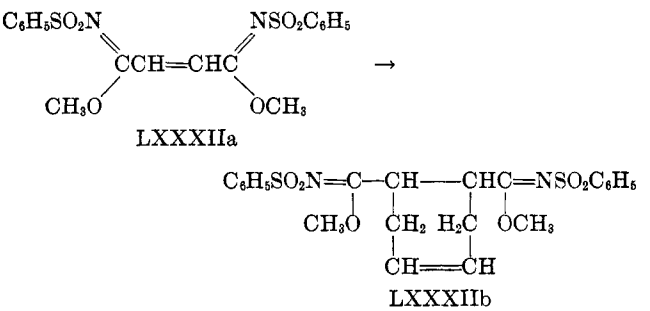
Imidates of the type of LXXXI react in the typical way with amines or ammonia to give the corresponding amidines (8),



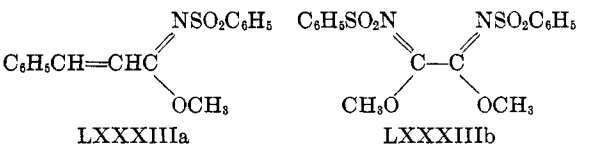
but undergo hydrolysis in the following manner (89, 90):



A study of the unsaturated character of certain sulfonyl derivatives of imidates (1) showed that the imidate LXXXIIa formed an adduct (LXXXIIb) with butadiene,



but that the compounds LXXXIIa, LXXXIIIa, and LXXXIIIb exhibited no diene character and failed to react with maleic anhydride.



K. REACTION OF IMIDATES WITH GRIGNARD REAGENTS

Marquis (207) reported that methyl *N*-phenylbenzimidate on being heated at 200°C. in toluene with phenylmagnesium bromide yielded a substituted ketimine and subsequently benzophenone on treatment with acid, but he described the reaction as being far from general.

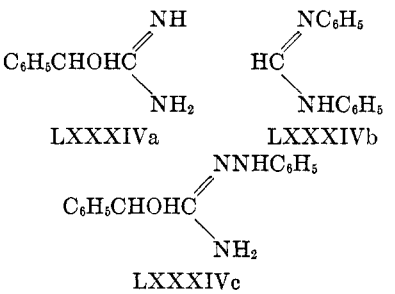
$$C_6H_5C(=NC_6H_5)OCH_3 + C_6H_5MgBr \rightarrow C_6H_5C(=NC_6H_5)C_6H_5 \rightarrow \underset{\text{Benzophenone}}{C_6H_5COC_6H_5}$$

A series of substituted ketols has been prepared by the action of Grignard reagents on ethyl mandelimidate (166, 208, 272) and ethyl atrolactimidate (236) or their hydrochlorides, giving yields comparable with the syntheses of these compounds from the corresponding amides. Moreover, (−)-benzoin was synthesized from ethyl (−)-mandelimidate (from amygdalin) and phenylmagnesium bromide (272).

In contrast to the addition reaction formulated as the first stage of the reaction between an amide and a Grignard reagent, the following substitution mechanism has been proposed in the case of the imidate (208, 272).

$$RC(=NH)OC_2H_5 + C_6H_5MgBr \rightarrow RC(=NH)C_6H_5 \rightarrow RCOC_6H_5$$

Evidence for this substitution mechanism may be adduced from the fact that Grignard reagents fail to react with mandelamidine or its hydrochloride (LXXXIVa) (272), with *N,N'*-diphenylformamidine (LXXXIVb) (301), or with N_1-phenylmandelamidrazone (LXXXIVc) (237),



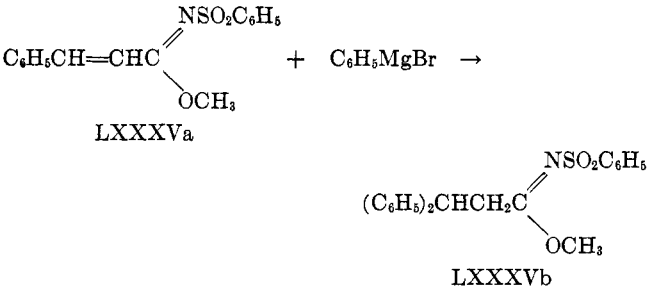
and hence it is suggested that as the imino groups of these compounds do not react with the reagent, it is logical to infer that the imino group of the imidate is also unreactive and that the above substitution mechanism is the correct one.

Aromatic aldehydes are produced by the addition of Grignard reagents to ethyl *N*-phenylformimidate (115, 234, 301) and, as the reaction proceeds smoothly and without great evolution of heat, the yields are superior to those obtained from the ethyl orthoformate synthesis of aldehydes (301).

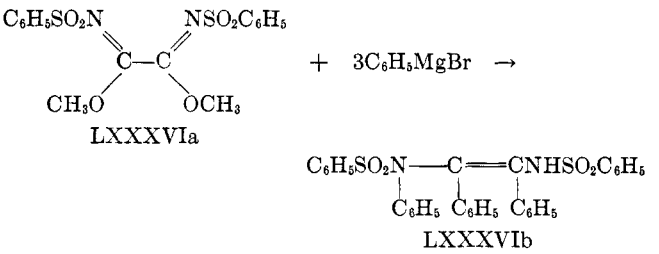
$$C_6H_5MgBr + HC(=NC_6H_5)OC_2H_5 \rightarrow C_6H_5CH{=}NC_6H_5 \rightarrow \underset{\text{Benzaldehyde}}{C_6H_5CHO}$$

This synthesis of aldehydes is now even more feasible in view of the availability of ethyl *N*-phenylformimidate from aniline and ethyl orthoformate (281), as this eliminates the expensive silver salt method used by Smith and Nichols (301).

The reactions of several sulfonyl derivatives of imidates have been examined. Thus, the cinnamimidate LXXXVa gave the saturated imidate LXXXVb on treatment with phenylmagnesium bromide,

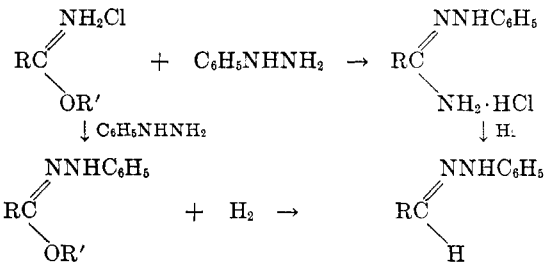


but the substituted oxaldiimidate (LXXXVIa) had a complex reaction, giving with one mole of Grignard reagent, replacement of one —OCH_3 group; with two moles of Grignard reagent, replacement of both —OCH_3 groups; with three moles of Grignard reagent, replacement of both —OCH_3 groups and 1,4-addition (to yield LXXXVIb); or finally, with four moles of Grignard reagent, a mixture of products (1).



L. REDUCTION OF IMIDATES

Reduction of imidate salts with 3 per cent sodium amalgam and dilute mineral acid furnishes aldehydes; the reaction, according to Henle (136, 137), is best carried out in the presence of a substituted hydrazine, when the aldehyde is obtained as its hydrazone.



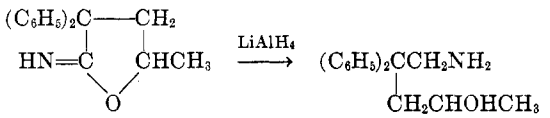
An inferior yield resulted when the reaction was carried out with sodium in alcohol/ammonia, but as only one result has been recorded, no general rule can be formulated (35).

According to Kaufmann and Kirschnek (168), the reduction of imidate salts with lithium aluminum hydride does not give aldehydes, but unfortunately the abstract of their paper makes no mention of any other product. Recently, however, ethyl *N*-ethylbenzimidate has been reduced with this reagent in tetrahydrofuran solution to give benzylethylamine in 50 per cent yield (143).

$$C_6H_5C(=NC_2H_5)OC_2H_5 + LiAlH_4 \rightarrow C_6H_5CH_2NHC_2H_5$$

Benzylethylamine

Moreover, 5-methyl-3,3-diphenyl-2-tetrahydrofuranoneimine (LXXXVIIa), which contains the imidate system partly within the ring, is reduced smoothly to the amino alcohol (LXXXVIIb) by the same reagent (98).



LXXXVIIa LXXXVIIb

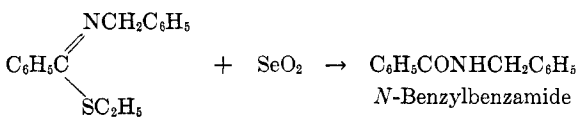
Amines are also formed when imidate salts are hydrogenated at 40 atm. pressure in the presence of noble metal catalysts (183),

$$C_6H_5C(=NH_2Cl)OC_2H_5 \rightarrow C_6H_5CH_2NH_2 \cdot HCl$$

and when the salts are subjected to electrolytic reduction with lead electrodes in dilute sulfuric acid (331). This latter reaction is most suited to aromatic imidates.

M. OXIDATION OF IMIDATES

A search of the literature has revealed little work on this subject, although Boudet (40) has shown that ethyl *N*-benzylthiobenzimidate was oxidized by selenium dioxide or by iodine in alcohol to the substituted amide.

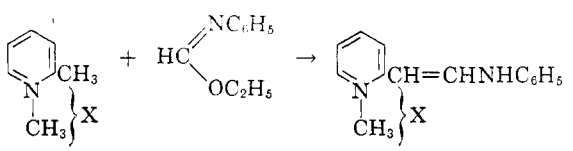


N-Benzylbenzamide

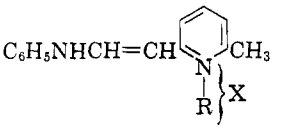
The oxygen of the atmosphere converted the same imidate to benzamide.

N. CONDENSATION REACTIONS OF *N*-PHENYLFORMIMIDATES

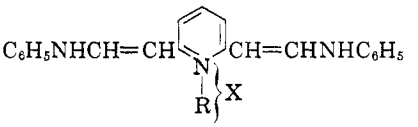
Knott (189) demonstrated that ethyl *N*-phenylformimidate could condense with quaternary salts of mono- and polymethylpyridines, thereby converting methyl groups in the 2- and 4-positions into β-anilinovinyl groups.



When the preparation of mono-β-anilinovinyl compounds was desired from pyridines having two reactive methylene groups, the mildest possible conditions compatible with good yields were required; thus 2,6-dimethylpyridine—having two groups of equal reactivity—gave either the mono derivative (LXXXVIIIa) when the reactants were refluxed in butanol or the di-β-anilinovinyl compound (LXXXVIIIb) when the reactants were fused together.

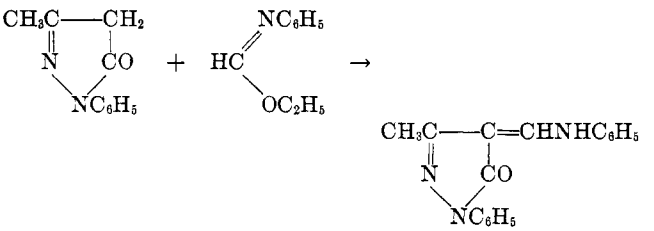


LXXXVIIIa

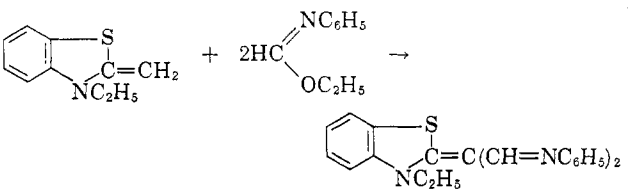


LXXXVIIIb

Heterocyclic systems owing their reactivity to reactive methylene groups within the ring systems were also found to condense with this reagent (191).

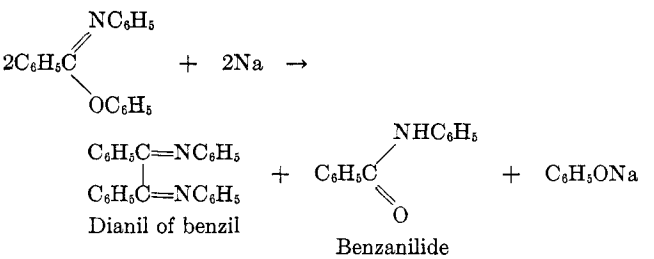


Studies of trinuclear cyanine dyes also prompted an investigation of the reaction of thiazolines and benzthiazolines containing methylene groups in the 2-positions with ethyl *N*-phenylformimidate in the presence of zinc chloride (127, 128), when condensation reactions of the following type were observed.



O. MISCELLANEOUS REACTIONS OF IMIDATES

Jaunin and Séchaud (157, 158) isolated the dianil of benzil from the reaction of sodium with phenyl *N*-phenylbenzimidate in an inert solvent.



Dianil of benzil Benzanilide

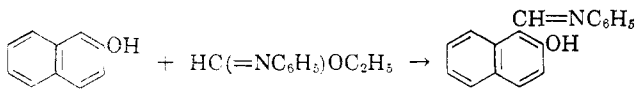
Benzanilide was formed simultaneously. With phenyl *N*-phenyl-*p*-methoxybenzimidate, however, little reaction was observed and the starting material was recovered in 80 per cent yield.

Sodium amide in the presence of an alkyl halide con-

verts *N*-arylformimidates into *N,N,N'*-trisubstituted formamidines, among other products (122).

$$HC(=NAr)OC_2H_5 + NaNH_2 + RX \rightarrow HC(=NAr)NRAr + HCONRAr$$

Moreover, ethyl *N*-phenylformimidate shows reactivity toward many phenols and, as the anils so produced are highly colored and readily formed by direct interaction over a free flame, it has been suggested that this reaction would serve as a good qualitative test for phenols (190).



P. STUDIES ON THE SPECTRA OF IMIDATES

Study of the infrared spectra of imidates has shown that the C=N bond of methyl *N*-phenylbenzimidate absorbs at 1666 cm.$^{-1}$ (104), and Grob and Fischer (121) have found an N—H band occurring at 3311 cm.$^{-1}$ and a C=N band at 1621 cm.$^{-1}$ for the imidate LXXXIX.

$$CH_3(CH_2)_5C{\equiv}CC(=NH)OC_2H_5$$
LXXXIX

It has also been shown that the C=N frequencies for the thioimidates (XC: R = CH_3— or C_6H_5—) occur at 1622 and 1611 cm.$^{-1}$, respectively, but that quaternization of the nitrogen leads to a fall in these values (119).

$$C_6H_5C(=NR)SCH_3$$
XC

Moreover, mention is made of the infrared spectra of imidates of the types R_2S_2 and RSO_2SR, where R = p-$C_6H_4C(=NH_2Cl)OC_2H_5$, but the results are discussed in terms of the C—S and S—S bonds of the disulfides and thiolsulfonates rather than in terms of the imidate groupings (88).

Examination by Grob and Fischer (121) of the ultraviolet spectra of a series of imidates of the type of XCI showed absorption maxima for compound XCIa

$$RC(=NH)OCH_3$$

XCIa: R = $C_6H_5C{\equiv}C$—
XCIb: R = $(CH_3)_3CC{\equiv}C$—
XCIc: R = $CH_3(CH_2)_4C{\equiv}C$—
XCId: R = $CH_3(CH_2)_5C{\equiv}C$—

at 260 mμ, for compound XCIb at 205 mμ, and for compounds XCIc and XCId at 207 mμ, respectively, giving molar extinction coefficients lying between 1.0×10^4 and 2.6×10^4 for these compounds.

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