HETEROCYCLIC NITROGEN COMPOUNDS[1]

EDWARD CURTIS FRANKLIN AND F. W. BERGSTROM

PART II A. HEXACYCLIC COMPOUNDS: PYRIDINE, QUINOLINE, AND ISOQUINOLINE

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CONTENTS

[1] Part I, dealing with pentacyclic nitrogen compounds, appeared in Chemical Reviews **16**, 305 (1935). Part IIB, which will follow, is to include acridine, the benzoquinolines, and heterocycles with two nitrogens in the ring. See also reference 323.

In this article "ammono aquo" is used rather than "aquo ammono", in order to conform to the usage adopted by *Chemical Abstracts*.

I. Introduction

It is the purpose of the present review to summarize a portion of the chemistry of six-membered heterocyclic compounds containing nitrogen and to interpret the reactions insofar as possible from the standpoint of the nitrogen or ammonia system of compounds (323). The extent of the field to be covered imposes necessary limitations upon the number of heterocyclic types to be discussed, in order to prevent an unwieldy review. Accordingly there will be considered only compounds containing one heterocyclic ring with either one or two hetero nitrogen atoms; omissions will be dealt with in a future paper.

Careful reading of the chemical literature soon makes it apparent that the explanation of reactions of pyridine, quinoline, and isoquinoline in terms of an ammonia system is often merely a restatement—in different language—of theories that have long before been expressed, or have otherwise acquired common acceptance as the result of the work of a number of investigators. Thus, the

similarity of the reactions of α- and γ-methylpyridines or α- and γ-methylquinolines to those of the methyl ketones was recognized as long ago as 1901 by Koenigs (493) and has since been commented upon by numerous observers, including Chichibabin (115) and Mills and Smith (621a). Furthermore, pyridine and quinoline have from time to time been called cyclic Schiff bases, with the implication that, like the latter, they may have certain chemical properties in common with the aldehydes and ketones.

A proper understanding of the viewpoint of this article makes desirable a brief explanation of the nitrogen or ammonia system of compounds. Within the next few pages, therefore, will be discussed the majority of the chemical types that will be encountered further on.

A. BASES OF THE AMMONIA SYSTEM

Bases of the water system, such as potassium hydroxide, KOH, and sodium hydroxide, NaOH, are derived from the parent solvent, water, by replacement of one hydrogen atom by an univalent metal. Similarly, by replacement of a hydrogen atom of ammonia, one obtains the ammono bases, potassium amide, KNH_2, and sodium amide, $NaNH_2$. Ammono bases are as a rule much more reactive than aquo bases, and for this reason are of considerable value in organic synthesis. The following comparison will illustrate this point.

Aryl halides are rapidly attacked by the alkali amides in liquid ammonia solution at $-33°C.$ or at room temperatures to give metallic salts of the corresponding aryl amines, in accordance with the equation (65a, 820a):

$$C_6H_5Cl + 2KNH_2 \rightarrow C_6H_5NHK + KCl + NH_3 \qquad (1)$$

Diphenylamine, triphenylamine, and *p*-aminobiphenyl are formed simultaneously by reactions that are dependent upon the catalytic effect of the potassium amide.

The related reaction of the water system, the conversion of chlorobenzene to phenol or sodium phenoxide by sodium carbonate or sodium hydroxide, requires a temperature of about 320°C. and a pressure of 3000 pounds per square inch (380).

B. ACIDS OF THE AMMONIA SYSTEM

Substances having acidic properties in water will behave as acids in liquid ammonia if they have sufficient solubility. In water and in liquid ammonia the hydrogen ion is solvated to the oxonium and ammonium ions, respectively. The oxonium or "hydrogen" ion in water has an abnormally high conductance, several times that of other ions, while the ammonium ion in liquid ammonia is normal in behavior. It is therefore not surprising to find that all ammonium salts in liquid ammonia are very weak acids.

The true acids of the ammonia system contain nitrogen and are related to ammonia as are the familiar oxygen acids to water. The "hydrogen ions" into which these acids dissociate are, of course, solvated to ammonium ions, though generally the ammonium salts of these ammono acids cannot be isolated under ordinary conditions. Although the acids listed below all show definite acidic properties in liquid ammonia, several behave as bases when dissolved in water (guanidine, the amidines):

Benzoic acids

C_6H_5COOH	$C_6H_5C(=NH)NH_2$	$C_6H_5CONH_2$
Aquobenzoic acid	Ammonobenzoic acid or benzamidine	Ammonoaquobenzoic acid or benzamide

In ammonobenzoic acid, the divalent oxygen and the monovalent hydroxyl group have been both replaced by the corresponding valence-equivalent residues of ammonia; in benzamide, this replacement is only partial.

It will be noted that ammonobenzoic acid is formally tribasic, although it is possible only to prepare a monopotassium salt, $C_6H_5C(=NH)NHK$. The trivalence of nitrogen, as contrasted with the divalence of oxygen, increases the complexity of the compounds of the ammonia system.

Carbonic acids

$CO(OH)_2$	$NH=C(NH_2)_2$	$N\equiv C-NH_2$	$NH=C(NH_2)(NHCN)$
Aquocarbonic acid (unstable)	Guanidine	Cyanamide	Dicyanodiamide

Ammonocarbonic acids

$CO(NH_2)_2$	$HNCO$	$NH_2CONHCONH_2$
Urea	Cyanic acid	Biuret

Ammonoaquocarbonic acids

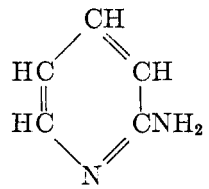
While there is but one aquocarbonic acid (this can exist only in solution), there are many ammonocarbonic acids, of which only three are listed (322).

Dicyanodiamide and biuret represent a class of compounds often encountered in the water system,—the pyro acids, of the type of pyrosulfuric acid, $H_2S_2O_7$, or pyrophosphoric acid, $H_4P_2O_7$. Just as pyrosulfuric acid is formed by loss of water between two molecules of sulfuric acid, so dicyanodiamide may be regarded as formed by the loss of ammonia between two ammonocarbonic acids, cyanamide and guanidine. The parallel relationships are shown below:

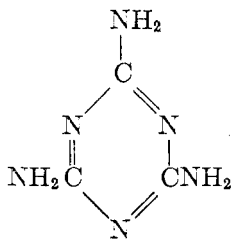
$$2HOSO_2OH = H_2O + HOSO_2—O—SO_2OH$$

$$CNNH_2 + NH_2C(=NH)NH_2 = CNNHC(=NH)NH_2 + NH_3$$

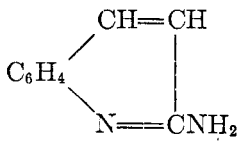
A few heterocyclic nitrogen compounds that may be regarded as acids of the ammonia system are listed below:



2-Aminopyridine



Melamine



2-Aminoquinoline

2-Aminopyridine and 2-aminoquinoline contain the grouping —C(NH$_2$)=N—, characteristic of ammonobenzoic acid and related compounds. One hydrogen attached to nitrogen has, however, been replaced by a group (that is, by one side of the ring), and so both of the substances above are cyclic ammono acid esters.

Melamine is a cyclic ammonopyrocarbonic acid, formed theoretically by the loss of three molecules of ammonia from three molecules of the ammonocarbonic acid, guanidine. It is actually best prepared from cyanamide or dicyanodiamide.

C. ALCOHOLS OF THE AMMONIA SYSTEM

The alkylamines are alcohols of the ammonia system.

C_2H_5OH	$C_2H_5NH_2$	$(C_2H_5)_2NH$
Primary aquo alcohol	Primary ammono alcohols	
$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_2CHNHCH(CH_3)_2$
Secondary aquo alcohol	Secondary ammono alcohols	
$(CH_3)_3COH$	$(CH_3)_3CNH_2$	$(CH_3)_3CNHC(CH_3)_3$
Tertiary aquo alcohol	Tertiary ammono alcohols	

$CH_3CH_2NHCH(CH_3)_2$

Mixed primary–secondary ammono alcohol

It is evident that in the ammonia system, as in the water system, the class to which an alcohol belongs is dependent upon the carbon atom to which the amino or imino group is attached. Mixed ammono alcohols of the type of ethylisopropylamine (above) may exist.

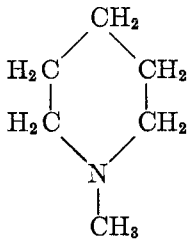
Diethylamine is really an alcohol rather than an ether, because of the hydrogen attached to nitrogen, which makes reactions similar to that of equation 2 possible (824).

$$(C_2H_5)_2NH + LiC_6H_5 = C_6H_6 + (C_2H_5)_2NLi \qquad (2)$$

The formation of lithium diethylamide is to be compared to the action of an alkali-metal aryl upon an aquo alcohol to give a hydrocarbon and a metal alkoxide.

D. ETHERS OF THE AMMONIA SYSTEM

When both hydrogen atoms of water are replaced by groups, an ether is formed; similarly, when all three hydrogens of ammonia are replaced, an ammono ether is obtained.

$(C_2H_5)_2O$	$(CH_3)_3N$	
Aquo ether	Ammono ether	Ammono ether

Strictly speaking, a secondary amine might be considered as a mixed ammono ether alcohol.

E. ALDEHYDES, MEROACETALS, ACETALS

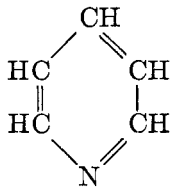
C_6H_5CHO	$C_6H_5CH{=}NH$	$C_6H_5CH{=}NC_6H_5$
Aquo aldehyde	Ammono aldehyde alcohol (benzylidenimine)	Ammono aldehyde ether (benzalaniline)

Since nitrogen is trivalent, while oxygen is divalent, all aldehydes of the ammonia system are mixed compounds of the kind shown above. It should be noted that the hydrogen attached to nitrogen in benzylidenimine is arbitrarily called "alcoholic"; it may be replaced by an alkali metal, but this replacement has considerable influence on the aldehydic reactivity (781).

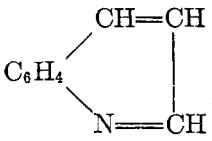
Strain has thus found that benzylidenimine undergoes the Cannizzaro reaction when heated with a solution of potassium amide in liquid ammonia at 210°C. for 1 day. Benzalaniline will, however, react similarly at room temperatures (783).

The negative charge on the anion of the alkali-metal salt, $(C_6H_5CH{=}N^-)K^+$, doubtless is responsible for slowing down a reaction that involves the highly active amide ion, NH_2^-, of potassium amide.

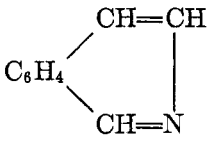
Many cyclic nitrogen compounds, including pyridine, quinoline, and isoquinoline, are to be regarded as cyclic ammono aldehyde ethers.



Pyridine

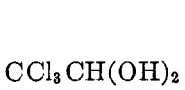


Quinoline

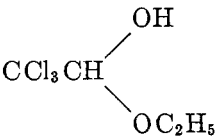


Isoquinoline

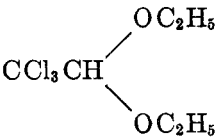
Some aldehyde derivatives are listed below:



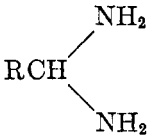
Aquo aldehyde hydrate

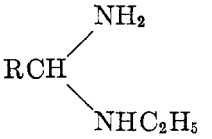


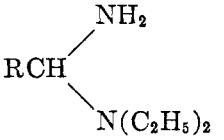
Aquo aldehyde alcoholate (hemiacetal)

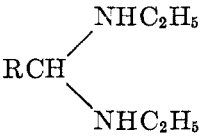


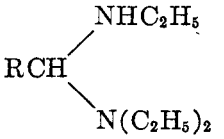
Aquo acetal





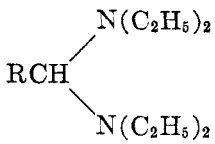




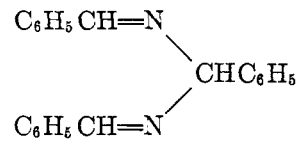


Ammono aldehyde ammonate

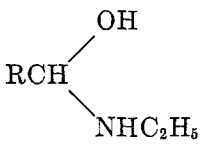
Ammono meroacetals

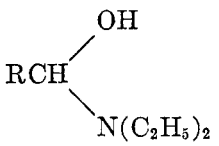


Ammono acetal

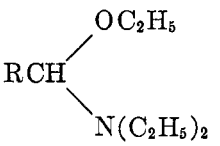


Ammono aldehyde acetal
(hydrobenzamide)





Ammono aquo meroacetals

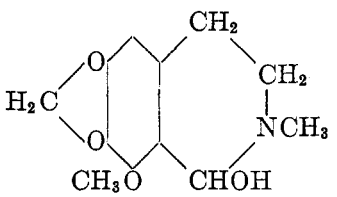


Ammono aquo acetal

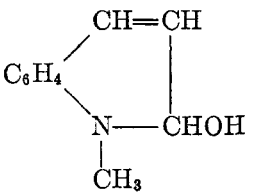
While chloral alcoholate (above) is a true half- or hemi-acetal, the related compounds of the ammonia system, or the mixed ammono aquo compounds, are quarter-, third-, three-quarter-, or half-acetals. It is proposed, for the purposes of a simplified nomenclature, to call all substances between the aldehyde solvate (such as chloral hydrate) and the acetal, meroacetals, from the Greek *meros*, meaning a part or a fraction.

Hydrobenzamide contains two —CH=N— groups and is therefore an ammono aldehyde; since one of the three C_6H_5CH groups is attached to two nitrogens, hydrobenzamide is at the same time an acetal.

Heterocyclic compounds which are to be considered aldehyde derivatives are known in abundance; a few are listed.

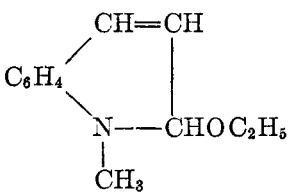


Cotarnine



1-Methyl-2-hydroxy-
1,2-dihydroquinoline
(a pseudo base)

Cyclic ammono aquo meroacetals

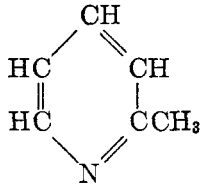


1-Methyl-2-ethoxy-1,2-
dihydroquinoline (a cyclic
ammono aquo acetal)

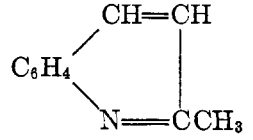
F. KETONES OF THE AMMONIA SYSTEM

$(CH_3)_2CO$	$(C_6H_5)_2C{=}NH$	$(C_6H_5)_2C{=}NC_6H_5$
Aquo ketone (acetone)	Ammono ketone alcohol (benzophenonimine)	Ammono ketone ether (benzophenone anil)

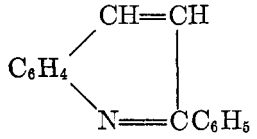
Some cyclic ammono ketone ethers are 2-picoline, quinaldine, 2-phenylquinoline, and 2,3-dimethylquinoxaline, whose formulas are given below:



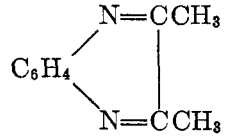
2-Picoline



Quinaldine



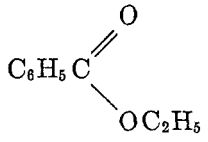
2-Phenylquinoline



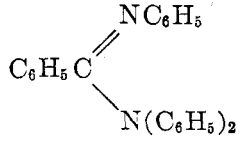
2,3-Dimethylquinoxaline

Of these four compounds, all but 2-phenylquinoline are analogues of a methyl ketone of the water system.

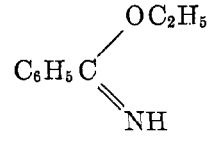
G. ESTERS OF THE AMMONIA SYSTEM



Ethyl benzoate (an aquo ester)



Triphenylbenzamidine (an ammono ester)



Benzimino ethyl ether (an ammono aquo ester)

$CO(OC_2H_5)_2$

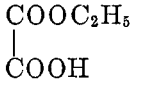
Diethyl carbonate (an aquo ester)

$CO(NR_2)_2$

A tetrasubstituted urea (an ammono aquo ester)

$N{\equiv}CN(C_2H_5)_2$

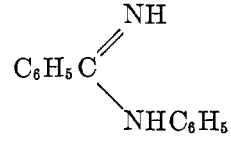
Diethylcyanamide (an ammono ester)



Monoethyl oxalate (an aquo acid ester)

$CO(NHCH_3)_2$

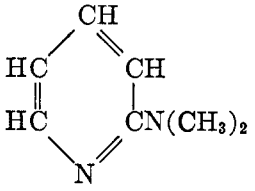
sym-Dimethylurea (an ammono aquo acid ester)



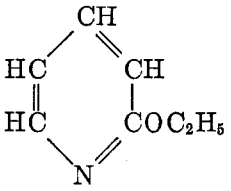
N-Phenylbenzamidine (an ammono acid ester)

The simplest acid ester of the water system is monoethyl oxalate; similar compounds of the ammonia or mixed water–ammonia systems will also be acid esters, as will substances of the type of *sym*-dimethylurea and *N*-phenylbenzamidine,

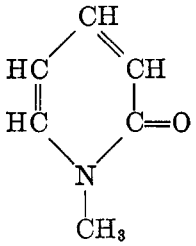
which still have hydrogens attached to nitrogen. Some analogues of the above among the cyclic compounds are the following:



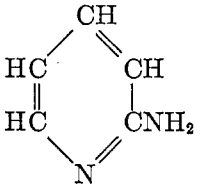
2-Dimethylaminopyridine
(a cyclic ammono ester)



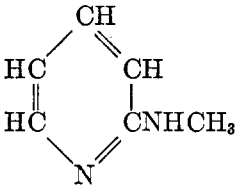
2-Ethoxypyridine
(a cyclic ammono aquo ester)



1-Methyl-2-pyridone
(a cyclic ammono aquo ester)



2-Aminopyridine



2-Methylaminopyridine

(cyclic ammono acid esters)

It is desirable to emphasize again the fact that the ammono acids analogous to the carboxylic acids, RCOOH, have the formula $RC(=NH)NH_2$ and are tribasic. 2-Aminopyridine has one of these hydrogens replaced by a group, and is therefore an acid ester.

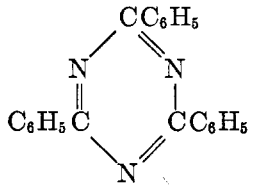
H. ACID ANHYDRIDES AND ACID ANAMMONIDES

An acid anhydride, such as acetic anhydride, is derived from two molecules of a carboxylic acid by loss of one molecule of water; related acids of the ammonia system, the amidines, can lose ammonia intramolecularly to give an acid anammonide, in this case, a nitrile.

$$2CH_3COOH - H_2O = CH_3CO{-}O{-}COCH_3$$

$$CH_3C(=NH)NH_2 - NH_3 = CH_3CN$$

Triacetamide, $(CH_3CO)_3N$, is an acid anhydride anammonide, while cyaphenine



is a cyclic anammonide of ammonobenzoic acid (or benzamidine).

I. TRANSMISSION OF EFFECTS ALONG A CONJUGATED CHAIN; EXPANDED SYSTEMS; THE PRINCIPLE OF VINYLOGY

During the period from 1917 to 1924, Angeli (12) wrote a series of articles in which he showed that the behavior of an ortho- or para-disubstituted benzene could be approximated by joining the two substituent groups together. The *o*- and *p*-nitrochlorobenzenes, accordingly, should behave like nitryl chloride, NO_2Cl, the acid chloride of nitric acid (doubt has been expressed as to whether or not this has ever been isolated in the pure condition, so its properties are not known with certainty). Nevertheless, although their reactivity is above that of *m*-nitrochlorobenzene, it is considerably below that of a typical acid chloride. One might say that the chlorine and the nitro group mutually affect each other across the conjugated system of the benzene ring, but with considerable damping. The *o*- and *p*-nitrotoluenes should have reactive methyl groups because of resemblance in this sense to nitromethane, CH_3NO_2; to some extent the predicted reactivity has been observed.

Fuson (359) has generalized this phenomenon in the following words:

"When in a compound of the type, A—E_1=E_2, or A—E_1≡E_2, a structural unit of the type, —(C=C)$_n$— is interposed between A and E_1, the function of E_2 remains qualitatively unchanged but that of E_1 may be usurped by the carbon atom attached to A. The resulting compound will have the form, A—(C=C)$_n$—E_1=E_2 or A—(C=C)$_n$—E_1≡E_2, and in any given series of this type the members will differ from each other by one or more vinylene residues (disposed in a linear arrangement). It is proposed to term such a group of compounds a vinylogous series. The members of a vinylogous series will be vinylogues of each other."

This rule will therefore not only cover such cases as those of the *o*- and *p*-nitrochlorobenzenes, but also straight-chain compounds of the type of ethyl crotonate (I), ethyl sorbate (II), and crotononitrile (III), all of which contain reactive methyl groups.

$CH_3CH{=}CHCOOC_2H_5$ (I) $\qquad$ $CH_3CH{=}CH{-}CH{=}CH{-}COOC_2H_5$ (II)

$CH_3CH{=}CHCN$ (III)

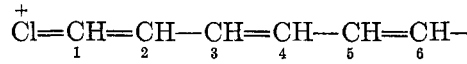
The first two are "vinylogues" of ethyl acetate, the latter a vinylogue of acetonitrile (360). Their behavior is approximated by uniting the two groups attached to the ends of the conjugated system.

The English chemists have for years recognized the fact that effects could be transmitted along a conjugated chain; the following explanation of this transmission is worthy of repetition (442a, 472a, 713a, 713b):

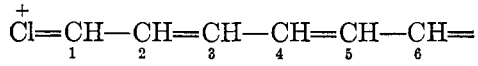
In the compound

$$\underset{1}{Cl{-}CH}{=}\underset{2}{CH}{-}\underset{3}{CH}{=}\underset{4}{CH}{-}\underset{5}{CH}{=}\underset{6}{CH}{-}$$

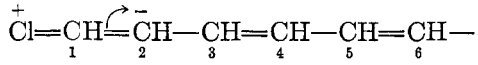
the chlorine has three pairs of unshared electrons. Under certain circumstances, two of the unshared electrons of the chlorine may become shared with carbon atom 1, giving at first:



The chlorine has lost a half interest in two electrons, and so bears a positive charge, but carbon atom 1 now has a decet of electrons around it. Since carbon in combination normally has an octet of electrons in its outer shell, further changes must occur. Two things may happen: (*a*) Two electrons, shared originally by C-1 and C-2 may be shifted so that they are shared between C-2 and C-3, that is to say, the double bond shifts and the shift will continue along the chain to give



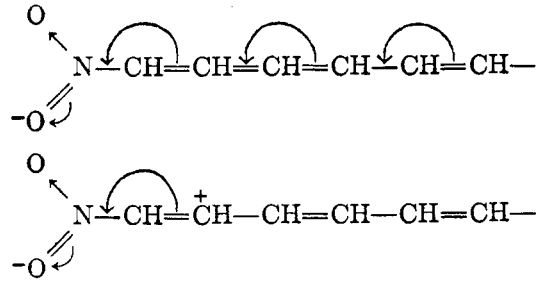
(*b*) An electron pair of a double bond may become unshared on one of the even-numbered carbon atoms, as in the example:



The curved arrow is intended to show this unsharing, which gives an integral (−) charge to C-2. The electron pair concerned has at no time left the octet of C-2, yet it is not now a part of the octet of C-1.

Groups such as methyl repel electrons slightly (+*I* effect; see references 442, 442a, 713a, 713b) and initiate a change that is similarly transmitted along the conjugated chain.

The effect of a nitro group is, conversely, to attract electrons and either cause a shift of the double bonds or the appearance of positive charges (at intervals, of course) upon the even-numbered carbons of the chain. These carbons will then have only a sextet of electrons. The changes may be represented in the abbreviated fashion of the English chemists in the manner shown below:



In the lower formula, carbon No. 2 has a positive charge.

In view of the foregoing, it often happens that heterocyclic nitrogen compounds show reactivity at points other than those predicted from their relation-

ship to the nitrogen system. 4-Methylpyridine and lepidine have many of the ketonic properties of 2-methylpyridine and of quinaldine. 2-Phenylquinoline is a cyclic ammono ketone ether, yet the 4-position often behaves like the 2-position in quinoline itself, as is shown by the reactions with potassium amide and potassium nitrate in liquid ammonia (see Section IV, K).

J. RESONANCE AND RING STABILITY

Nearly all of the ring compounds discussed in this review have the bond system of benzene or its homologues, and consequently have considerable resonance energy. The values in the table below have been taken from Pauling (673) and from Miss Wrinch (in parentheses (821); these are estimated minimum values).

Resonance energy

	kilocalories per mole	
Benzene	39	(56)
Pyridine	43	(54)
Naphthalene	75	(103)
Quinoline	69	(91)

The resonance energy of a nitrogen heterocycle is not far from that of its closest carbocyclic analogue. It follows that pyridine, quinoline, isoquinoline, and related compounds will have a reactivity much less than that of open-chain analogues of either the water or the ammonia system, even though the syntheses of these heterocyclic compounds are in full agreement with their assumed relationship to the ammonia system.

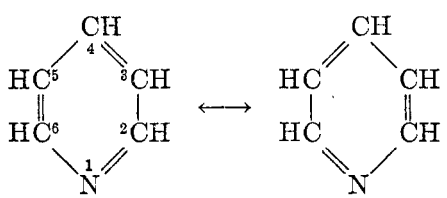
It is unfortunate that many of the original journals, including the Russian, have been unavailable during the writing of this review. It has been necessary to depend upon abstracts not only for these but also for patents.

II. PYRIDINE

A. RELATIONSHIP TO THE NITROGEN OR AMMONIA SYSTEM

The true relationship of pyridine to the ammonia system is shown by its formation from glutacondialdehyde in accordance with the equation:

$$CHOCH_2CH{=}CHCHO \rightleftarrows CHOH{=}CHCH{=}CHCHO \xrightarrow[-2H_2O]{NH_3}$$

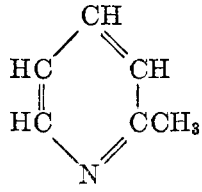


(3)

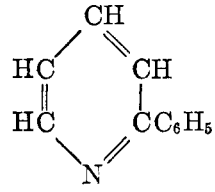
(see also Section II, B, (1) and (2)). Pyridine is therefore to be regarded as an anammonide of the ammono aldehyde enol, $NH_2CH{=}CHCH{=}CHCH{=}NH$. It is simpler and sufficiently accurate, however, to regard pyridine as a cyclic

ammono aldehyde ether, since it contains the grouping —CH=NR, characteristic of these compounds. The equivalence of the 2- and 6-positions may then be explained on the basis of a resonance between the two forms shown above.

2-Alkylated (I) or 2-arylated (II) pyridines are cyclic ammono ketone ethers, but because of the transmission of effects along a conjugated chain, the 4- and 6-positions will have some of the function of the 2-position of unsubstituted pyridine.



I
2-Picoline

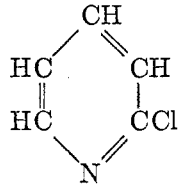


II
2-Phenylpyridine

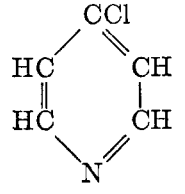
This is readily seen if one or two —C=C— groups are removed from the formulas of 2-picoline (I) or 2-phenylpyridine (II), respectively, leaving $CH_3CH{=}N-$ and $C_6H_5CH{=}N-$, which are ammono aldehyde ethers.

Along the same lines, an alkyl or aryl group in position 4 will have the function of the same group in position 2, while both groups of a 2,6-disubstituted pyridine will be equivalent, if they are the same. 4-Methylpyridine (4-picoline), as anticipated, has pronounced ketonic properties, though there has been some loss in the effect of the —C=N— linkage on the methyl by damping; both methyl groups of 2,6-dimethylpyridine are equally reactive.

2-Chloropyridine (III) is a cyclic ammono acid chloride ester, while 4-chloropyridine (IV) is its vinylogue.



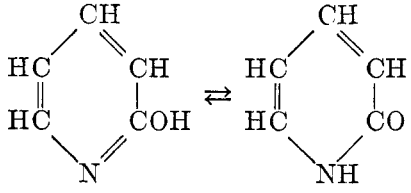
III
2-Chloropyridine



IV
4-Chloropyridine

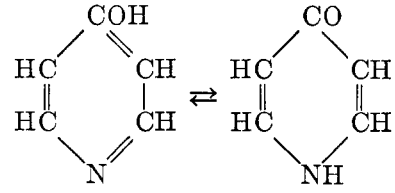
Because of the trivalence of nitrogen it is not possible to have a strict nitrogen analogue of an aquo acid chloride, RCOCl, since one hydrogen will remain as in RC(=NH)Cl (an ammono acid chloride acid) or else the nitrogen will be attached to a group, RC(=NR)Cl, to give an ammono acid chloride ester.

Some additional pyridine derivatives are listed below, with indicated relationship to the ammonia system.



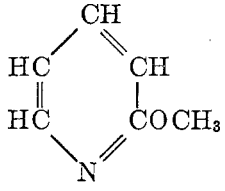
V

2-Hydroxypyridine or 2-pyridone
(cyclic ammono aquo acid esters)

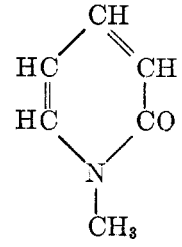


VI

4-Hydroxypyridine or 4-pyridone
(vinylogues of V)



2-Methoxypyridine



1-Methyl-2-pyridone

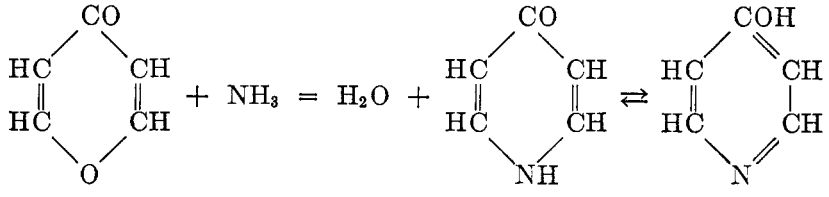
(cyclic ammono aquo esters)

B. METHODS OF SYNTHESIS

Here and later no attempt will be made to cover completely the syntheses of the heterocyclic compounds. Generally, the methods given will be of somewhat greater interest from the point of view of the ammonia system.

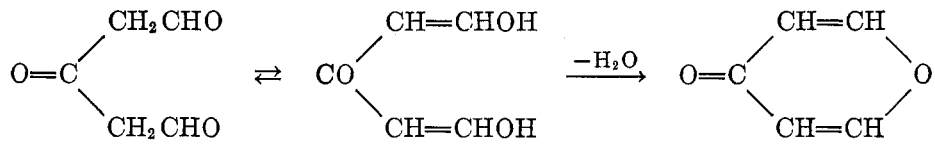
(*1*) Glutacondialdehyde and its derivatives are readily converted to pyridines by the action of ammonia under rather mild conditions. This reaction has previously been discussed, and is represented by equation 3.

(*2*) γ-Pyrone and substituted pyrones are ammonolyzed when heated with aqueous or alcoholic ammonia with the formation of γ-pyridones in accordance with the equation:



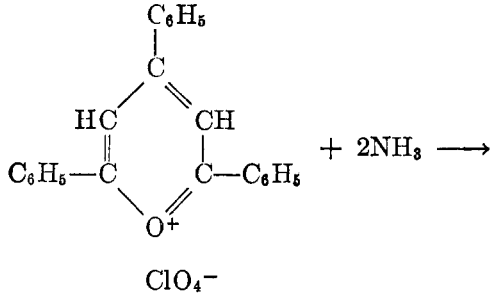
(4)

Pyridone is thus made by heating γ-pyrone with aqueous ammonia at 120–140°C. for 6 hr. (382, 473a, 683), while 2,3-dimethyl-γ-pyridone is similarly prepared from 2,6-dimethyl-γ-pyrone (766) (for the preparation of α-pyridone, see reference 677). In these reactions, the ring is presumably opened by the action of ammonia, and then closed again with the elimination of water. γ-Pyrone is to be regarded as the cyclic anhydride of the dienol form of 1,5-pentanedial-3-one.

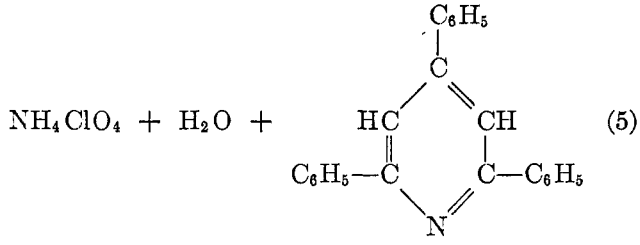


The relationship to synthesis (*1*) is readily seen.

(*3*) Pyrylium salts, when warmed with ammonia, give pyridines in the manner of the following equation (27a, 247, 248, 248a; + $C_6H_5NHNH_2$, 745):



2,4,6-Triphenylpyrylium perchlorate

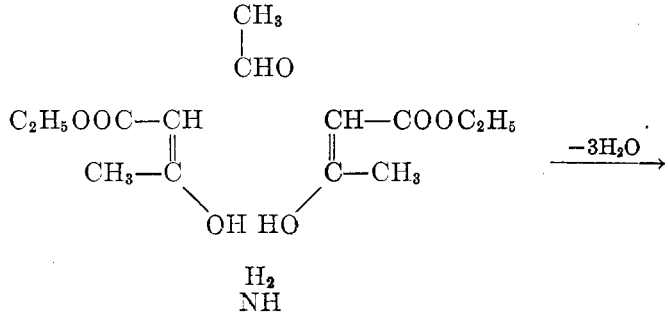


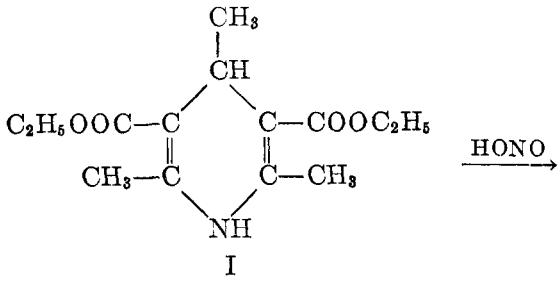
(5)

2,4,6-Triphenylpyridine

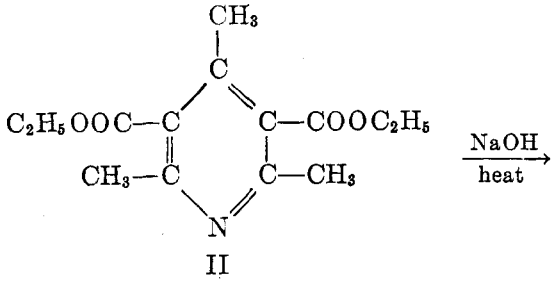
The relationship of pyrylium salts to the pyridines is accordingly a close one; a more extended discussion will be found in Section III.

(*4*) The classical pyridine synthesis of Hantzsch (404b; *cf.* 405a) is illustrated by the preparation of 2,4,6-trimethylpyridine (*sym*-collidine), which proceeds in accordance with the equations below:





I



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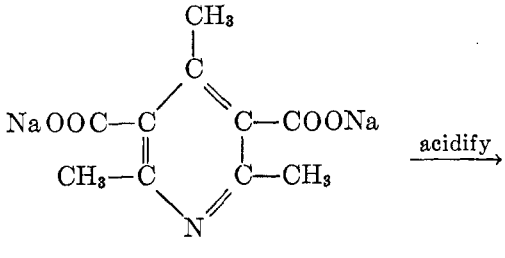
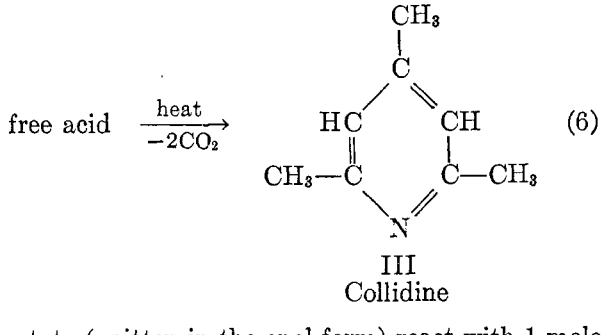




(6)

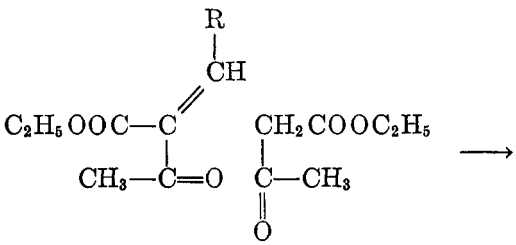
III
Collidine

Two moles of ethyl acetoacetate (written in the enol form) react with 1 mole each of acetaldehyde and ammonia (=aldehyde-ammonia) to form dihydrocollidinedicarboxylic ester (I), which is generally considered a derivative of 1,4-dihydropyridine (*cf.* 763c; for the relationship of 1,4-dihydropyridines to the nitrogen system, see Section II, C, (g)). Oxidation with nitrous acid ("nitrous fumes") gives collidinedicarboxylic ester (II), and this may be converted to collidine (III) by saponification and subsequent decarboxylation of the resulting acid.

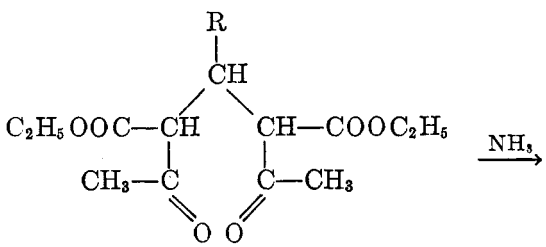
Oxidation of the dihydro ester (I) to the pyridinedicarboxylic acid ester (II) often cannot be accomplished by nitrous acid; the use of nitric acid, chromic acid, hydroxylamine hydrochloride, and even of sulfur (at 150°C.) (but not of potassium permanganate or iodine) has been recommended (*cf.* 43d, 426a, 763a).

The Hantzsch synthesis is capable of considerable variation, both in the nature of the aldehyde and the β-ketonic ester or β-diketone used, and in the details of carrying out the reactions. The mechanism is expressed by one or the other of the two sets of equations below:

$$CH_3COCH_2COOC_2H_5 + RCHO \rightarrow \underset{\text{IV}}{CH_3COC(=CHR)COOC_2H_5} + H_2O$$



IV V



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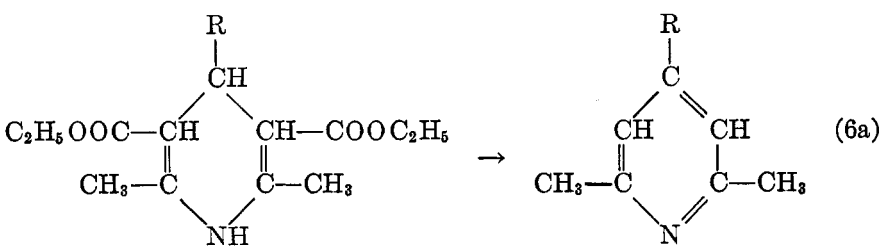


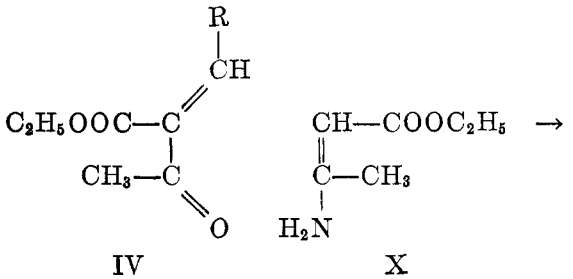
VII VIII

(*cf.* II → III, equation 6)

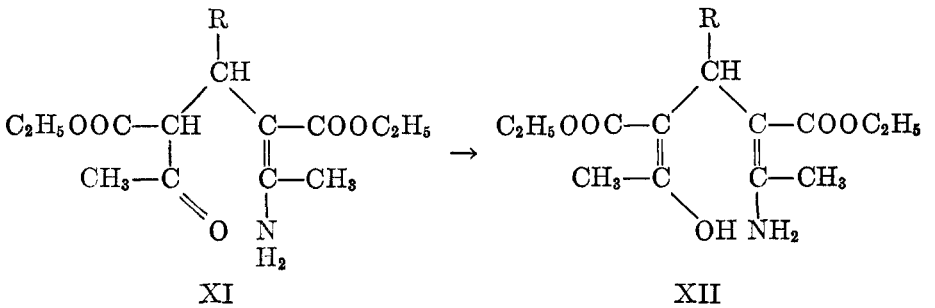
(6a)

$$\underset{\text{V}}{CH_3COCH_2COOC_2H_5} + NH_3 \rightarrow$$

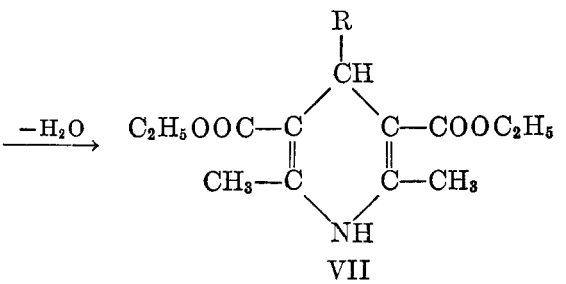
$$\underset{\text{IX}}{CH_3C(=NH)CH_2COOC_2H_5} \rightleftarrows \underset{\text{X}}{CH_3C(NH_2)=CHCOOC_2H_5}$$



IV X



XI XII



(6b)

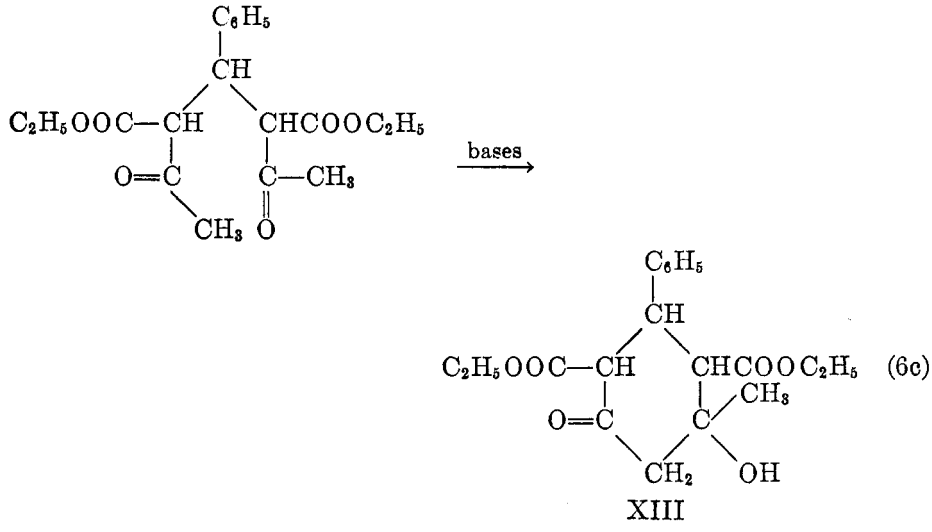
VII

VII → VIII, as above (equation 6a) (68, 478, 478e)

It will be seen that these proposed mechanisms are the same in principle, but differ in the order of the assumed steps. In accordance with equation 6a, an alkylidene or arylidene bisacetoacetic ester (IV) is first formed, probably by the addition of a molecule of acetoacetic ester (V) to the carbon–carbon double bond of IV. Reactions of this type have of course been the subject of extensive investigation (Michael reaction: recent references, 603a; see also 697e). Equation 6b represents the formation of a partially ammonolyzed alkylidene or arylidene bisacetoacetic ester (XI) by addition (173a) of β-aminocrotonic ester (X) to an alkylidene or arylidene acetoacetic ester (IV). Ammonolysis—externally, as in equation 6a by ammonia itself, or intramolecularly, as in equation 6b by a substituted ammonia—results in ring closure and the formation of a dihydropyridine (VII).

The Hantzsch synthesis has been successfully carried out by heating β-aminocrotonic esters with alkylidene or arylidene bisacetoacetic esters in the

manner of equation 6b (478, 478e). However, several investigators (697d) have recorded failure to prepare dihydropyridines by the ammonolysis of alkylidene or arylidene bisacetoacetic esters (equation 6a), because, as Rabe and Elze (697c) have shown, the latter may instead undergo an intramolecular aldol condensation in accordance with the equation:



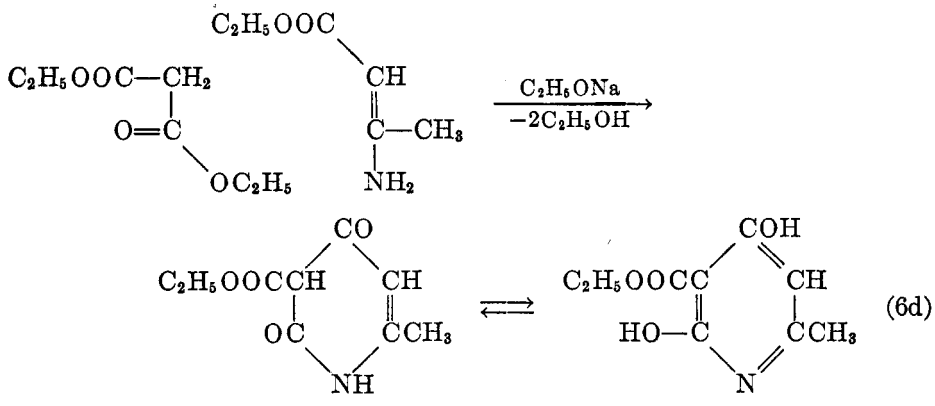
(6c)

XIII

Loss of water from the aldol (XIII) gives a cyclohexene derivative representative of the type prepared by Knoevenagel (476b) by self-condensation of the same alkylidene or arylidene bisacetoacetic esters in the presence of a basic catalyst.

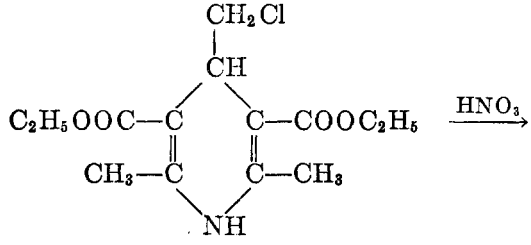
Some modifications of the Hantzsch synthesis, other than those mentioned above, are the following:

(*a*) Malonic esters react with β-aminocrotonic ester in the presence of alcoholic sodium ethylate to give dihydroxypyridine derivatives directly (478a, 478b, 480, 481a, 482; *cf.* 768a), as shown in the equation:

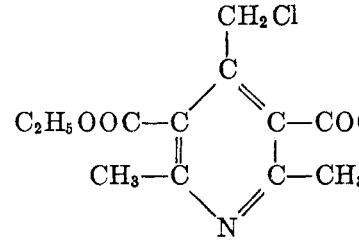


(6d)

(*b*) Benary (43d) dissolved β-aminocrotonic ester and an equivalent of 1,2-dichloroethyl ether in benzene; a vigorous reaction occurred on short standing, to give the dihydropyridine derivative (XIV) below:



XIV

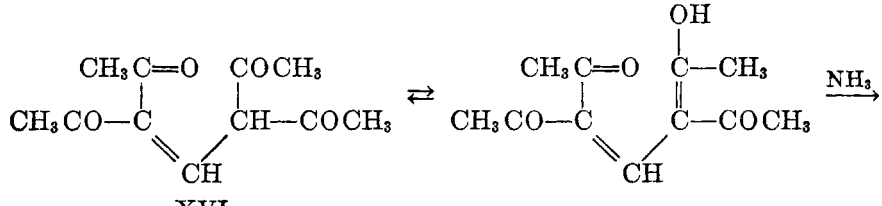


(6e)

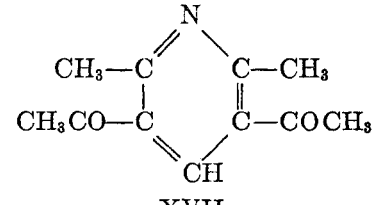
XV

It is oxidized by dilute nitric acid to the corresponding pyridine (XV), which has a chlorine activated by carbonyl and carbimide groups (C=N) and therefore very mobile. The dichloroethyl ether has acted only as a source of monochloroacetaldehyde.

(*c*) Claisen (161b) obtained 2,6-dimethyl-3,5-diacetylpyridine (XVII) by ammonolysis of methenylbisacetylacetone (XVI):



XVI



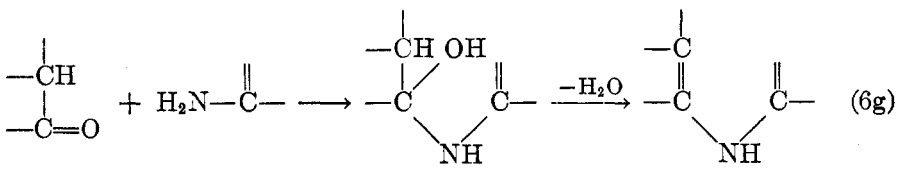
(6f)

XVII
Diacetyllutidine

The methenylbisacetylacetone (XVI) was obtained by the action of the potassium salt of acetylacetone on ethoxymethyleneacetylacetone, which was, in turn, prepared from acetylacetone, ethyl orthoformate, and acetic anhydride.

It is worth while pointing out that aldehydes and ketones are often very readily ammonolyzed—either by ammonia itself, or by a substituted ammonia. In many cases, these reactions can lead to ring closure, as in the pyridine syntheses under discussion. While esters ammonolyze fairly readily (see Claisen's reaction (6d) above), acids do so with some difficulty. Cyclization rarely takes place because of an intramolecular ammonolysis that involves an alcoholic hydroxyl, RCH_2OH.

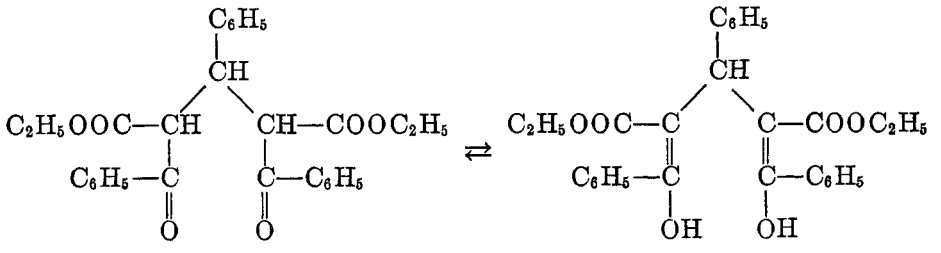
The fine details of the action of ammonia or a substituted ammonia on the carbonyl group are unknown; it is not necessary to assume that enolization precedes ammonolysis, as has been done in equations 6b and 6f. Perhaps an addition to the carbonyl group is followed by loss of water, in the sense of the equation below:



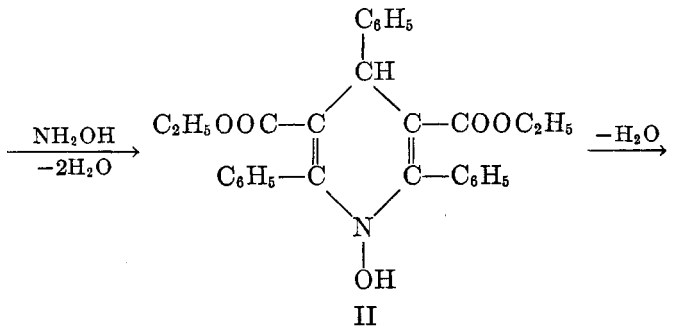
(6g)

The effect of different groups on the ring closure of the Hantzsch synthesis has been investigated by Hinkel, Ayling, Morgan, and Cremer (426).

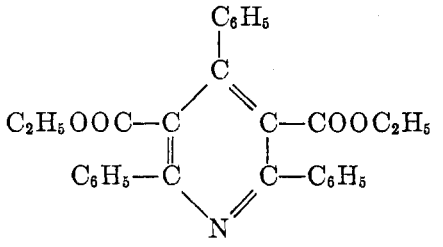
(*5*) Pyridine derivatives may be formed directly by heating 1,5-diketones with hydroxylamine (476a), as Knoevenagel has shown in the two examples below:



I



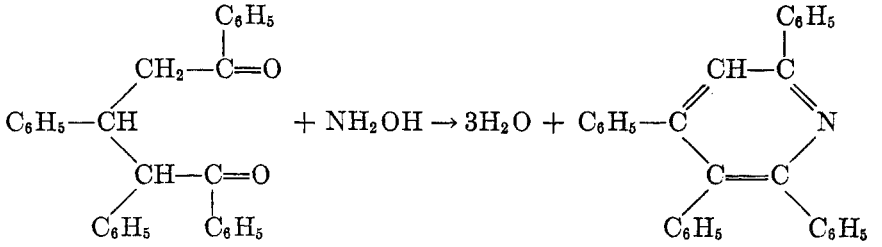
II



(7)

III

The ethyl ester of 2,4,6-triphenylpyridine-3,5-dicarboxylic acid (III) is formed by heating benzylidenedibenzoylacetic ester (I) with aqueous hydroxylamine for 4 hr. at 120–130°C. It has been assumed, in accordance with the work of S. Skraup (763b), that there is formed an intermediate (II) with hydroxyl attached to nitrogen. 1,2,3,5-Tetraphenyl-1,5-pentanedione (IV) is converted to tetraphenylpyridine (V) by the action of hydroxylamine hydrochloride at 140–150°C. (477).

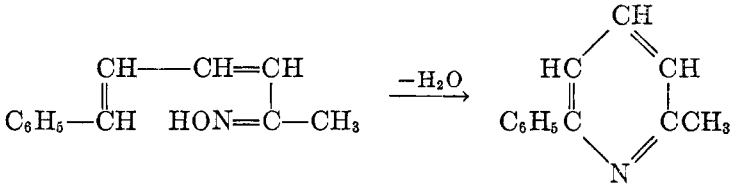


(8)

IV V

The applicability of this synthesis is rather limited.

A somewhat related reaction is the formation, in 25 per cent yield, of 2-methyl-6-phenylpyridine by the dry distillation of the oxime of cinnamylideneacetone (750).



(8a)

2-Methyl-6-phenylpyridine

(*6*) Aliphatic aldehydes, when heated with ammonia, form a mixture of pyridine homologues. There are many ways in which these reactions may be carried out.

(*a*) When acetaldehyde-ammonia is heated for 12 hr. with double its volume of absolute alcohol at 120–130°C., there is formed 2-methyl-5-ethylpyridine (aldehyde collidine), together with other bases (2).

(*b*) Pläth (691), Chichibabin (119), Chichibabin and Oparina (150), and

others heated aldehyde-ammonia, or paraldehyde, with ammonia to temperatures of 200°C. and above, obtaining aldehyde collidine in yields of 50 per cent of the theoretical or over. At the same time, smaller amounts of 2- and 4-methylpyridines and β-collidine (4-methyl-3-ethylpyridine) were formed (20, 119, 150, 263, 489, 691; *cf.* 151).

Similar heating of propionaldehyde with ammonia at 205–210°C. (263a), or with ammonia in the presence of aluminum trioxide at 310–320°C. (151), gave 2-ethyl-3, 5-dimethylpyridine, 3,5-dimethylpyridine, and 3,5-dimethyl-4-ethylpyridine.

(*c*) Several patents have been granted for the preparation of aldehyde collidine by heating paraldehyde with aqueous ammonia; yields of crude base up to 80 per cent of the theoretical are claimed (378).

(*d*) Mixed pyridine bases may be formed by passing aldehydes and ammonia over a contact catalyst, such as alumina (130, 136, 146, 148, 151, 661). Pyridine itself may be made, though in poor yield, by passing ammonia, acetaldehyde, and acrolein over heated alumina (152).

Chichibabin has discussed the mechanism of these reactions in a recent article which is not available because of conditions imposed by the war (120; see also 123 and 119).

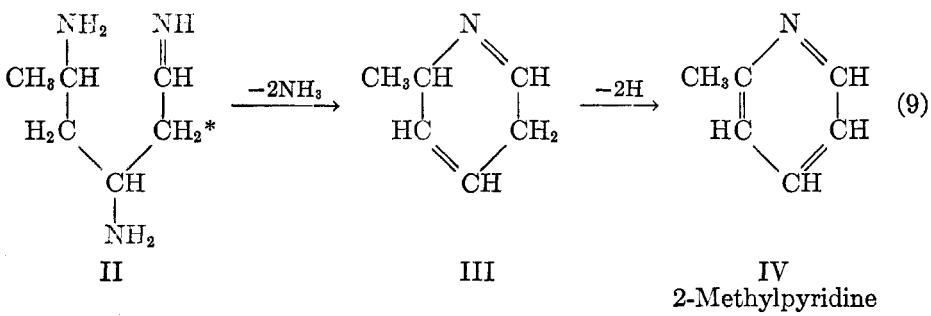
Strain (784) is of the opinion that the formation of 2-methylpyridine and aldehyde collidine is best explained by assuming a series of aldol condensations, followed by a cyclization and dehydrogenation in the sense of the equations below:

$$CH_3CHO + NH_3 = H_2O + CH_3CH{=}NH$$

I

$$3CH_3CH{=}NH \longrightarrow CH_3CH(NH_2)CH_2CH(NH_2)CH_2^*CH{=}NH$$

II

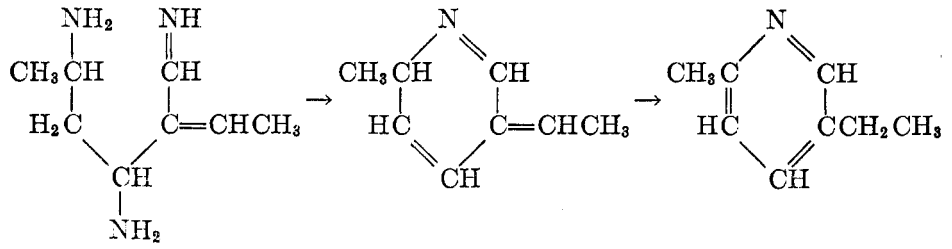


(9)

II III IV

2-Methylpyridine

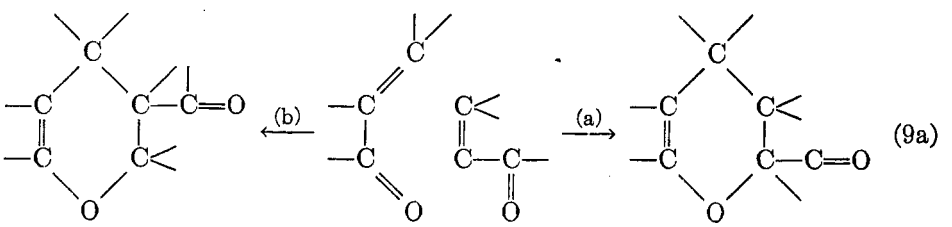
To explain the formation of aldehyde collidine (VII), it may be assumed that acetaldehyde undergoes a Claisen reaction with the trialdol (II) at the point indicated by the asterisk, to form V.



V VI VII

The grouping —CH_2CH=NH— is present in an ammono aldehyde alcohol or ammono aldehyde ether, and the hydrogens of the methylene group will be reactive in the sense that the alpha hydrogens of an aldehyde or ketone are reactive. The acetaldehyde may of course condense with the dihydropyridine derivative (III) to form VII.

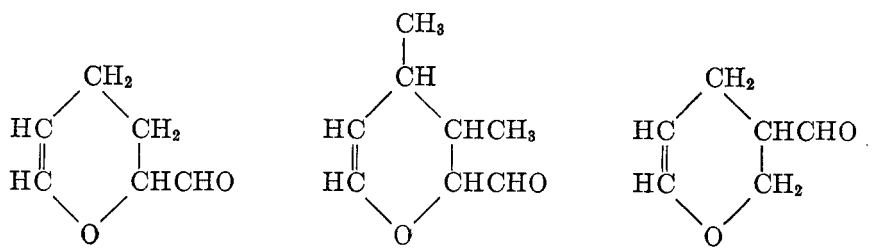
The investigations of Sherlin (759a), Alder (7a, 7b, 7c), and coworkers suggest another manner in which aldehydes and ketones may be converted to pyridine derivatives. Normally, an α,β-unsaturated aldehyde or ketone will readily undergo an extensive polymerization, but this may be limited to the first stage by adding an inhibitor, hydroquinone. Under these circumstances a dimer may be isolated. According to Alder (7b), the reaction always follows the course (a) of the equation below:



(9a)

VII VIII IX

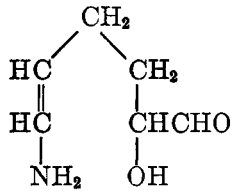
Acrolein and crotonaldehyde thus give X and XI, respectively, although Sherlin (probably erroneously) considers that the dimer of the former is XII.



X XI XII

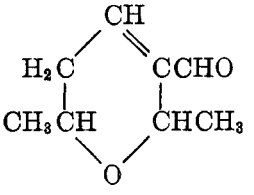
The heterocyclic oxygen of VII, IX, X, XI, or XII can be replaced by an —NH group by the action of ammonia, as is the case in the pyrone series (Section II,

B, (2)), but undoubtedly with more difficulty and at a higher temperature, since the ring closure of the hypothetical intermediate



will involve the loss of water from an alcoholic hydroxyl. Acrolein-ammonia, $C_6H_9ON \cdot 0.5H_2O$, may have a structure corresponding to either X or XII, with —NH— replacing the heterocyclic oxygen (*cf.* 162a). If the formula resembles XII, an intramolecular oxidation–reduction (ring → aromatic, —CHO → CH_3) would give the β-methylpyridine which is known to be the principal product formed when acrolein-ammonia is heated (26a, 162a), or when glycerol is heated with ammonium phosphate (779a). By-products of the reaction are reported to be 3-ethylpyridine, 3-propylpyridine, pyridine, and small quantities of 2-substituted pyridines (2-picoline, etc.) (779a).

It is interesting that Delépine and Horeau (235a) have obtained a dimeric crotonaldehyde of the structure below (XIII), by treating crotonaldehyde with hydrochloric acid.



XIII

A molecular rearrangement must have occurred at some stage of its formation, if this formula is correct. It is entirely reasonable to suppose that the reactions between ammonia and aldehydes to give pyridine derivatives are also complicated by molecular rearrangements that may occur in an intermediate step. A good discussion of the mechanism is given by Chichibabin (119, 120, 123).

(7) Acetylene, when heated with ammonia in the presence of a contact catalyst (alumina, carbides of iron, aluminum, chromium, tungsten, and uranium, etc.) at about 250°C. and 50 atmospheres, gives acetonitrile, together with a quantity of mixed pyridine bases and very small amounts of pyrroles (126, 144, 145, 745a). It is known that acetaldehyde is formed by the catalytic hydration of acetylene in dilute sulfuric acid with mercuric salts as catalysts; one may speculate and say that the approximate ammonia system equivalent of acetaldehyde, ethylidenimine, $CH_3CH{=}NH$ (an ammono aldehyde alcohol), is an intermediate in these reactions. Dehydrogenation would give an acid anammonide, acetonitrile,

CH_3CN, while condensation in the manner of method (*6*) above would give pyridine bases. Many patents have been granted on this method (660).

(*8*) Alkylpyridinium halides, when heated to temperatures not far removed from 300°C., give mixtures of the hydrohalides of 2- and 4-alkylpyridines. Ladenburg, the originator of this synthesis, thus prepared (among other compounds) 2- and 4-ethylpyridines and 2,4-diethylpyridine by heating pyridine ethiodide in sealed tubes (551). Chichibabin (111) records that a small amount of β-ethylpyridine is also formed. Obviously, the Ladenburg rearrangement offers a rather inconvenient way of preparing pure homologues of pyridine. Nevertheless, the method seems to have been used a number of times for making 2- and 4-benzylpyridines, with copper bronze as a catalyst (157, 630a, 553; *cf.* 124). A small amount of 3-benzylpyridine is also formed (111).

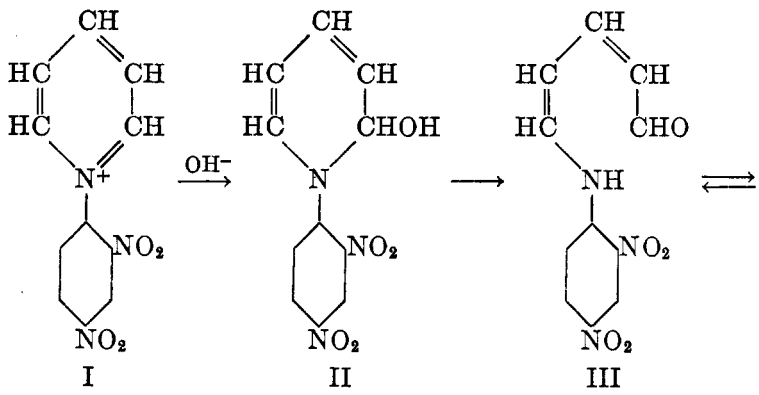
(*9*) Yields of 2-, 3-, and 4-substituted pyridines totalling 70–80 per cent of the theoretical are formed from aryldiazonium salts and pyridine at temperatures up to 70°C. (129, 129a, 171a, 414). As an example, a mixture of the three *p*-nitrophenylpyridines is formed by adding 435 parts of an aqueous acid solution of *p*-nitrobenzenediazonium chloride to 500 parts of pyridine, stirring during 3 hr. at 24–26°C., pouring into water, and filtering. The mechanism of this rather interesting reaction is not known, but it is presumably similar to that of the synthesis of diphenyl derivatives from diazonium salts and benzene hydrocarbons in alkaline solution (376a).

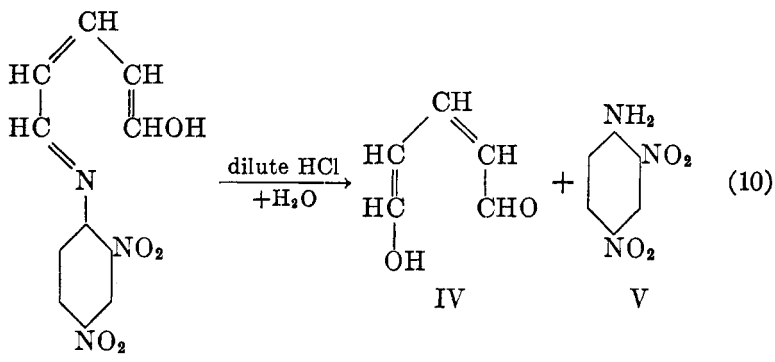
C. RING OPENINGS

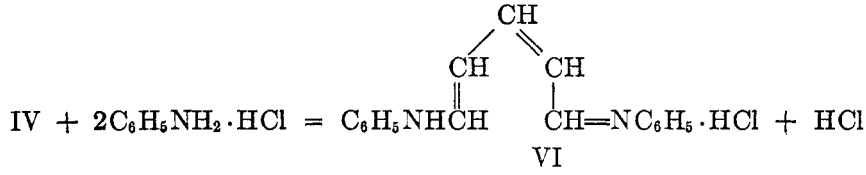
The pyridine nucleus is normally difficult to rupture. Oxidation of quinoline (benzopyridine) gives pyridine-2,3-dicarboxylic acid (quinolinic acid) with destruction of the benzene ring. Determination of nitrogen in pyridine derivatives by the usual Kjeldahl method is apt to lead to low results because of incomplete destruction of the pyridine ring.

There are, however, many methods of opening the ring that depend as a general rule upon the decomposition of quaternary salts of pyridine by means of alkalies, amines, or other bases. The reaction of Bucherer and Schenkel (103) does not follow this scheme, since pyridine is first heated with sodium bisulfite to form the addition compound, $C_5H_5N \cdot 3NaHSO_3$, which is split by alkali into the sodium salt of glutacondialdehyde, $NaOCH{=}CHCH{=}CHCHO$, ammonia, and sodium sulfite.

(*a*) Pyridine and 2,4-dinitrochlorobenzene react when heated to give a quaternary ammonium salt, 2,4-dinitrophenylpyridinium chloride (cation = I) which undergoes ring cleavage in the presence of alkali to form a red compound (III) as an intermediate. Dilute hydrochloric acid hydrolyzes it to dinitroaniline (V) and glutacondialdehyde (IV), which is isolated as the product of its reaction with aniline, glutacondialdehyde anil anilide hydrochloride (VI). It is interesting that in the absence of water in glacial acetic acid solution, hydrochloric acid converts III to dinitrophenylpyridinium chloride (I). The equations follow.







The intermediate (II), which has not been isolated, has been added for purposes of explanation; it is formed by the attack of the hydroxyl ion of the alkali upon the 2-carbon atom of the pyridine ring, and belongs to the class of pseudo bases (Section II, I, 7) or ammono aquo meroacetals. The enol form of III will be at least partly converted to a salt (=CHOH → =CHO$^-$ Na$^+$) in alkaline solution. It will be noted that resonance will allow the anionic charge to appear upon the nitrogen attached to position 1 of the benzene ring, or upon the oxygen atoms of the two nitro groups, thereby accounting for the stability and for the red color observed. As extensive a resonance is not possible with the cyclic form (II), as might have been inferred from the fact that the simple pseudo bases of the pyridine and quinoline series are colorless. However, the pseudo base from 2,4-dinitrophenylisoquinolinium chloride is red (Section V, G, 1).

The two tautomeric forms of III may be represented by the partial formulas below, which represent, respectively, an ammono enol (or, better, an ammono enol ether) and an ammono aldehyde ether or Schiff base. The latter, as is well

—CH=CH—NHC$_6$H$_4$(NO$_2$)$_2$ =CH—CH=NC$_6$H$_4$(NO$_2$)$_2$

known, may be readily hydrolyzed by acids (702c); that the former behave similarly follows from the work of Mannich and his students (575), who find that the ammono enol ether, or enamine, *N*-butenylpiperidine (VII), is readily hydrolyzed in accordance with the equation,

$$\underset{\text{VII}}{CH_3CH_2CH{=}CH\cdot NC_5H_{10}} + HOH \xrightarrow{\text{acids}} C_5H_{10}NH\cdot HX + CH_3CH_2CH{=}CHOH \rightarrow C_5H_{10}NH\cdot HX + CH_3CH_2CH_2CHO \quad (11)$$

The related water system compounds, vinyl ethyl ether (286a, 816), $CH_2{=}CHOC_2H_5$, and α-methoxystyrene (630), $C_6H_5C(OCH_3){=}CH_2$, are easily hydrolyzed by acids, the former even at room temperatures, to give acetaldehyde and acetophenone, respectively, together with ethyl and methyl alcohols. Ethyl styryl ether, $C_6H_5CH{=}CHOC_2H_5$, is converted to ethanol and phenylacetaldehyde by boiling with dilute sulfuric acid (638). Enamines of the general formula $RCH(NR_2)CH{=}CHNR_2'$ are hydrolyzed under acid conditions in a similar manner (575, 577, 579, 580, 601c).

Meyer and coworkers (601b, 601c, 601d) have given other examples of the reactivity of compounds with an amino or substituted amino group directly attached to a doubly bound carbon atom.

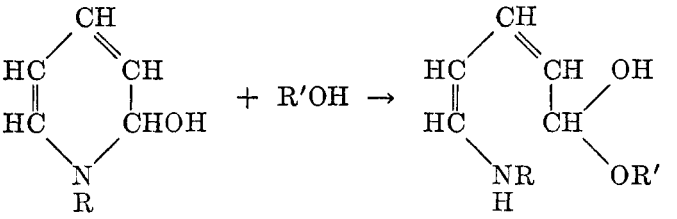
All in all, the net result of these transformations is the hydrolysis of pyridine to glutacondialdehyde and ammonia, a reaction that is in effect a reversal of its synthesis (see method (*1*), Section II, B). The reaction has been fully investigated by Zincke and his coworkers (709, 833, 834, 835, 836, 838, 840). W. König has observed that a similar ring opening occurs when *p*-nitrophenylpyridinium chloride is boiled with alkali (510; *cf.* 515).

Pyridine methiodide, when treated with alkali, gives a mixture of *N*-methylpyridinium hydroxide and 1-methyl-2-hydroxy-1,2-dihydropyridine, with the equilibrium favoring the former. Nevertheless, Decker and Kaufmann (217) have observed that some methylamine is formed by boiling pyridine methiodide with 10 per cent sodium hydroxide solution, indicating that ring opening has taken place to some extent.

(*b*) Ring openings have been observed when alkali reacts with quaternary pyridinium salts formed from sulfur trioxide (pyridine-*N*-sulfonic acid (37, 38)), cyanogen bromide (508, 515), chlorosulfonic acid ethyl ester (36), phosphorus pentachloride, benzanilidenimidochloride, and others (710).

(*c*) Freytag (345) and coworkers discovered in 1932 that pyridine slowly turns yellow in ultraviolet light, particularly at wave lengths of 248–266 millimicrons. Paper impregnated with pyridine and then exposed to ultraviolet light gave with primary amines characteristic colors which serve as a test not only for the amines in question but also for pyridine. Some pyridine derivatives undergo this reaction (e.g., 3-aminopyridine, particularly at 313 millimicrons), while others do not or do so slowly (2-aminopyridine, 2, 4, 6-trimethylpyridine). It was shown definitely that the pyridine ring was opened to form the enol of glutacondialdehyde, or a substitution product, which reacted with the primary aromatic amines to give the colors observed.

(*d*) König (513) believes that the products of the action of alcohol upon some pseudo bases of the pyridine series have open-chain formulas.



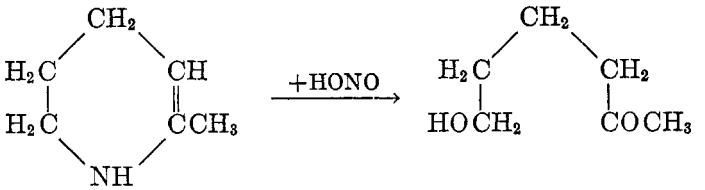
(12)

R′ is an alkyl group.

(*e*) Shaw (756) finds that little if any piperidine is formed when pyridine is reduced by sodium in boiling 95 per cent alcohol; ammonia is evolved and the main product is a nitrogen-free resin. The ring fission takes place at the 1,4-dihydro stage of the reduction and does not appear to occur to any extent in absolute alcohol, as piperidine is formed in good yield. The following experiment is described by Shaw (757): When a solution of 80 g. of pyridine in 400 cc. of boiling 95 per cent alcohol was treated with sodium (24 g.), no ammonia was evolved. Hydroxylamine hydrochloride (36 g.) in dry alcohol was added and the mixture boiled for a few minutes, whereupon ammonia was evolved copiously. From this solution, 28 g. of the oxime of glutardialdehyde was obtained, or 65 per cent, calculated on the basis of the hydroxylamine.

A similar reduction of 2-stilbazole ($C_5H_4NCH{=}CHC_6H_5$-2) gives β-phenethyltetrahydropyran (a ring opening, followed by a ring closure) (756, first reference).

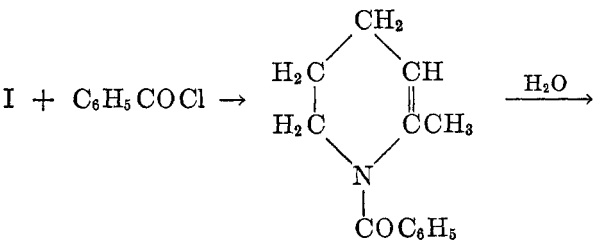
(*f*) Partially hydrogenated pyridine derivatives often undergo ring cleavage rather readily. 1,4,5,6-Tetrahydro-2-methylpyridine (I) thus reacts with nitrous acid to form acetylbutyl alcohol (II), as represented by the following equation (86, 565, 626):

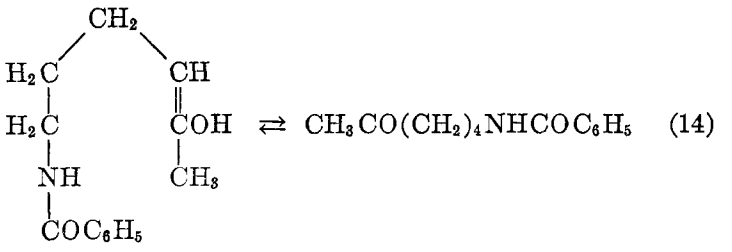


(13)

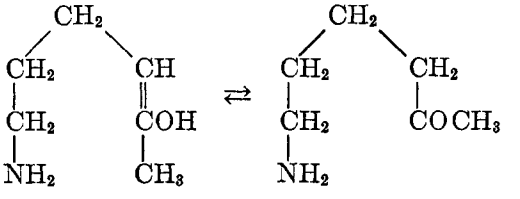
I II

The ring may also be opened by benzoyl chloride, in the manner of the equation below:





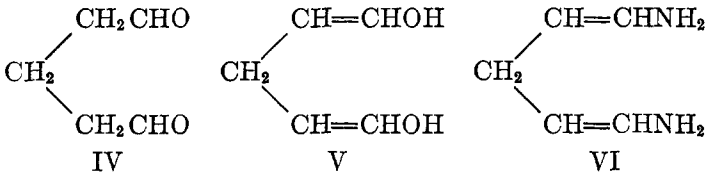
The tetrahydromethylpyridine above (I) is an ammono enol ether, because of the grouping —CH=C(CH_3)—NH—, and is easily hydrolyzed, as are the related compounds of Zincke (see Section II, C, (a)). The reactions of equations 13 and 14 may be remembered by assuming a reaction of I with water to give 6-amino-2-hexanone (III).



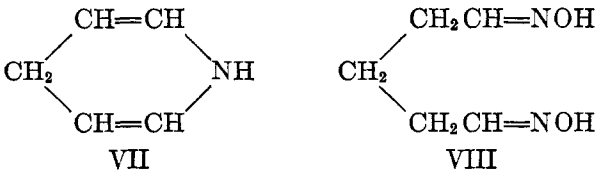
III

The reaction of III with nitrous acid will give the ketone alcohol (II), while reaction with benzoyl chloride will give a benzoyl derivative of III, as shown in equation 14. The conversion of I to III is the hydrolysis of an ammono enol ether to an ammono alcohol-aquo ketone or its enol.

(*g*) Ring scission has often been noticed with the 1,4-dihydropyridines obtained as intermediates in the Hantzsch synthesis (405, 483, 476, 743, 763; see Section II, B). That 1,4-dihydropyridine itself may readily be converted to the open-chain glutardialdehyde dioxime has been shown by the work of Shaw, which was discussed in section II, C, (e). 1,4-Dihydropyridine is a partial anammonide of an ammono dienol, as may be seen from the scheme below; no strictly analogous derivatives of the water system exist.

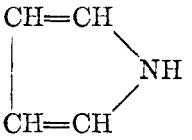


IV V VI



VII VIII

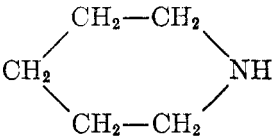
Glutardialdehyde (IV) is tautomeric with the dienol form (V). The corresponding (hypothetical) ammono dienol is VI, and its anammonide, 1,4-dihydropyridine, is VII; because of the hydrogen attached to nitrogen it still should have the properties of an enol. This fact, coupled with the diminished resonance of a six-membered ring with two isolated double bonds, is responsible for the ready formation of glutardialdoxime (VIII) by reaction with hydroxylamine. Pyrrole



is closely related to 1,4-dihydropyridine, but it is not as reactive because of an increase in the resonance energy.

D. REDUCTION OF PYRIDINE BASES

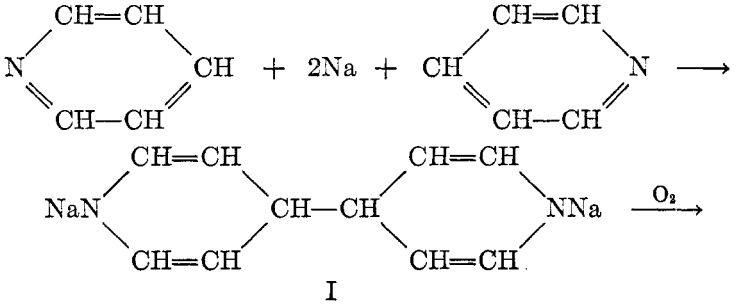
Complete reduction of pyridine, either by sodium in absolute alcohol or by hydrogen in the presence of a catalyst (262, 588, 651, 736, 737a) or electrolytically (5, 262) gives piperidine,



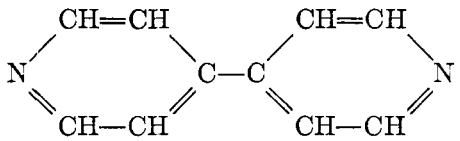
a saturated ammono alcohol. Partial reduction of pyridine to dihydro and tetrahydro derivatives has been accomplished (see Section II, C, (e); *cf.* 494, 738), but no attempt will be made to cover the literature on this subject.

Metallic sodium, potassium, and lithium reduce pyridine (in the absence of other solvent) to alkali-metal substitution products of hydrogenated dipyridyls; when pyridine is oxidized with atmospheric oxygen at somewhat elevated temperatures, a mixture of dipyridyls is formed (11, 278, 659, 767a, 807a, 814a).

Sodium thus reacts with pyridine at room temperatures to form a greenish solution, from which a black-green substance of the composition $(C_5H_5N)_2Na$ can be isolated by removal of excess of pyridine in a vacuum. When this is heated in a vacuum at 130°C., monopyridine sodium, C_5H_5NNa, is formed, though this probably has double the formula indicated. Both substances are spontaneously inflammable in air, and when hydrolyzed with water (moist ether) give tetrahydrodipyridyls, which air oxidation converts to 4,4′-dipyridyl (II) with smaller amounts of the 2,2′-isomer. The reactions may be represented by the following equations:



I

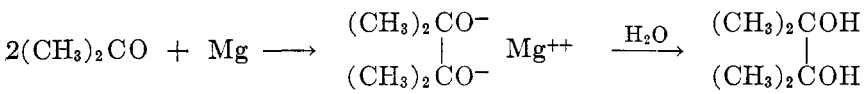


(15)

II

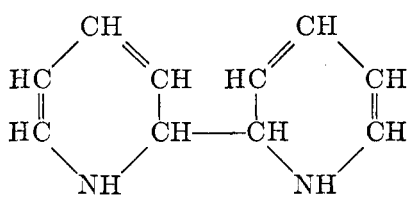
2,2′-Dipyridyl is formed similarly. If sodium in a large excess of pyridine is heated for some time at 114–115°C., and then oxidized with dry air or oxygen at 90–100°C., 2,2′-, 4,4′-, 3,3′-, and 2,3′-dipyridyls result (767a). The isomerization probably occurs at the tetrahydrodipyridyl (I) stage.

The formation of either 2,2′- or 4,4′-tetrahydrodipyridyl may be compared to the reduction of acetone by magnesium amalgam to tetramethylethylene glycol, or pinacol, in accordance with the equation:



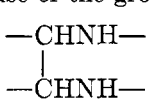
(16)

The reactions are of course not strictly analogous, because acetone is a ketone, while pyridine is an ammono aldehyde ether. Tetrahydro-2,2′-dipyridyl (III)



III

is an ammono glycol ether, because of the grouping



while tetrahydro-4,4′-dipyridyl (I, Na replaced by H) is its vinylogue; it is at the same time a 1,4-dihydropyridine derivative (see Section II, C, (g)).

4,4′-Dipyridyl is probably most readily prepared by reducing pyridine with zinc dust and acetic anhydride to the diacetyl derivative of tetrahydro-4,4′-dipyridyl (249), and oxidizing this, preferably with oxygen gas, to the dipyridyl. The preparation of 2,2′-dipyridyl is described in the next section.

E. OXIDATION OF PYRIDINE

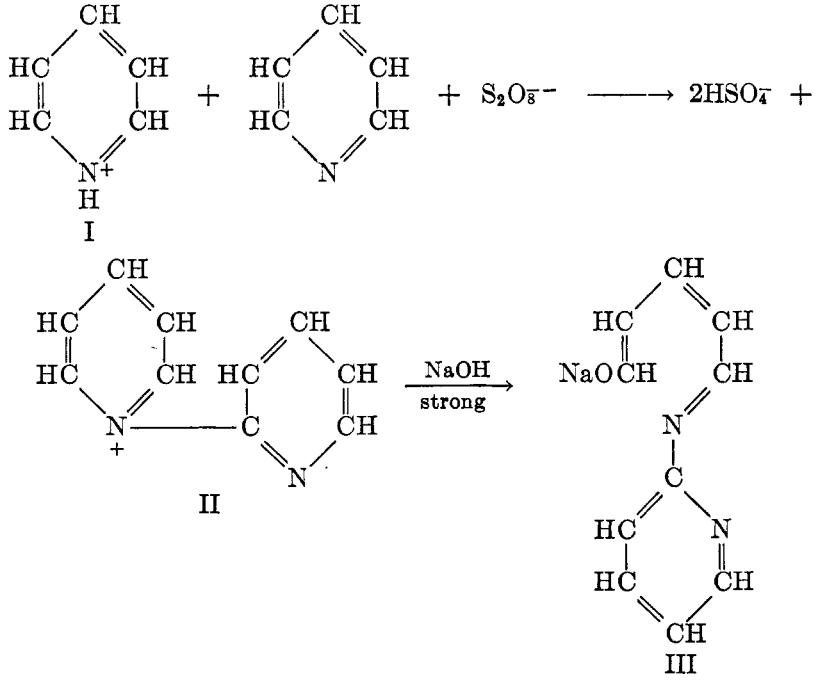
Pyridine is stable or resistant toward neutral permanganate in the cold (375) or towards warm chromic acid (1, 10). Chemical oxidation under other conditions may lead to more or less complete rupture of the pyridine ring, with the formation of carbon dioxide and ammonia (235, 758, 822). Oxidation of pyridine—a cyclic ammono aldehyde ether—to the corresponding cyclic ammono aquo acid ester, 2-hydroxypyridine, is accomplished by dry potassium hydroxide at an elevated temperature (see Section II, G).

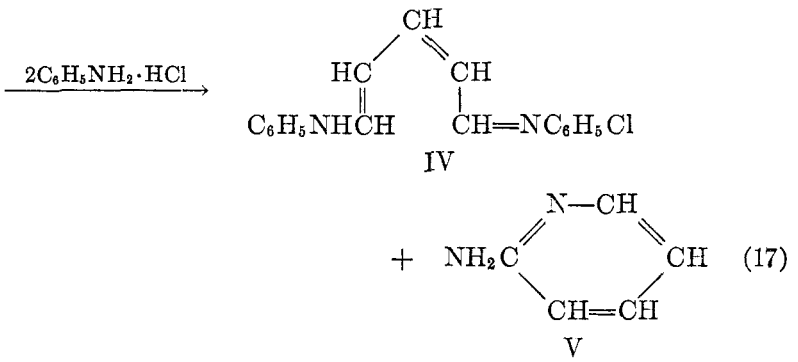
2,2′- and 4,4′-dipyridyls may be regarded as oxidation (or nitridation) products of pyridine in the sense that diacetyl, $CH_3COCOCH_3$, may be considered an oxidation product of acetaldehyde, CH_3CHO. Hein and Retter (417, 418), followed by Morgan and Burstall (627), oxidized pyridine with anhydrous ferric chloride at temperatures around 340°C., and obtained 2,2′-dipyridyl in fair yield, together with other dipyridyls and 2,2′,2″-tripyridyl. 2,2′-Dipyridyl is also formed, though in less satisfactory yields (14–20 per cent), by heating pyridine for 4–5 hr. with an alumina–nickel catalyst at 320–325°C. (814).

Oxidation of pyridine homologues when properly carried out will give pyridinecarboxylic acids, though sometimes in poor yield because of destruction of the ring, which can be brought about by overheating with the oxidizing agent (758, 796, 822).

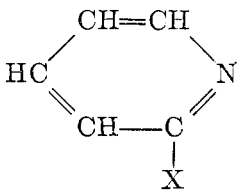
Perbenzoic acid oxidizes pyridine to pyridine *N*-oxide, $C_5H_5N\rightarrow O$ (591), while alkali persulfates may lead to complete oxidative degradation (261). Baumgarten and Dammann (39, 40) have, however, found that oxidation with aqueous potassium persulfate under milder conditions (heating for 2–3 hr.) gives as the chief product 2-pyridylpyridinium sulfate (II), which was isolated as the perchlorate. Autoöxidation of aqueous sulfite solutions for several hours in the presence of pyridine gives a mixture of 2- and 3-pyridylpyridinium salts (40, 41).

The formation of a 2-pyridylpyridinium salt is given below in equation 17. It will be noted that one pyridine ring can readily be opened, as with Zincke's dinitrophenylpyridinium chloride (see Section II, C, (a)), while the simultaneous formation of 2-aminopyridine (or of 3-aminopyridine in the case of the 3-pyridylpyridinium salts) is indicative of its structure. The resemblance to the reactions undergone by the analogous 4-pyridylpyridinium salts (see Section II, I, 5) is marked.





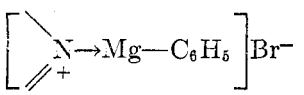
Baumgarten and Dammann (39) interpret the reaction as follows: The hydrogen attached to the nitrogen of the pyridinium ion (I) and an alpha hydrogen of a molecule of pyridine are removed by the persulfate; this is followed by a coupling of the two residues so formed. One can regard the 2-pyridylpyridinium salts (II) as quaternary ammonium salts formed by adding to a molecule of pyridine a second molecule of pyridine with an ionizable substituent in the 2-position:



where X may be HSO_4, or a related group.

F. THE ACTION OF METALLOÖRGANIC COMPOUNDS ON PYRIDINE

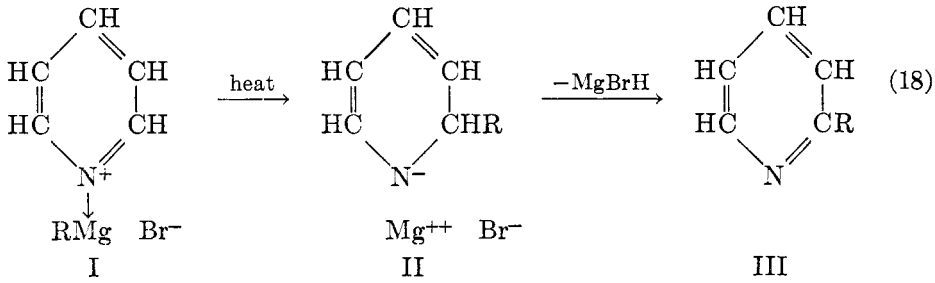
The action of the Grignard reagent on pyridine in ether under ordinary conditions gives addition compounds of low solubility, such as ($2C_5H_5N + CH_3MgI + (C_2H_5)_2O$) and ($2C_5H_5N + C_6H_5MgBr + (C_2H_5)_2O$) (641a, 642, 643). It is probable that one pyridine molecule, at least, becomes attached to the heterocyclic nitrogen by a coördinate bond, as in the partial formula:



The nitrogen will therefore bear a positive charge, and it is possible that this may exert some activating effect on the reactions that are to be described, in the same manner that the ketonic reactivity of 2-methylpyridine is increased by the formation of a quaternary salt of the type of the methiodide (see Section II, I).

If an excess of Grignard reagent is heated with pyridine in diethyl ether at temperatures of 150–160°C. (62), alkyl- and aryl-pyridines are formed, though in rather variable yields. It is interesting to find 2,6-diphenylpyridine among the products of this high-temperature Grignard reaction (820); presumably it signifies that the addition compound (II below) loses MgBrH or its equivalent and gives free 2-phenylpyridine, which in turn reacts with phenylmagnesium

bromide to give diphenylpyridine. The related preparation of 2-phenylquinoline from quinoline was carried out some years ago by Oddo (641). The reactions probably follow the equation:



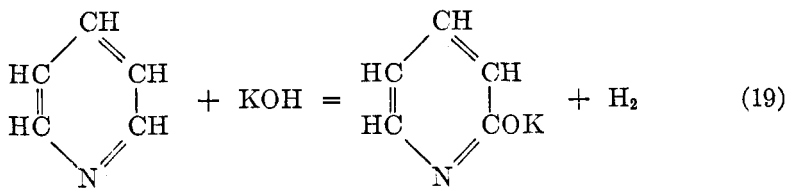
I II III (18)

It is assumed, for the purposes of writing the equation, that the addition compound (I) first formed between pyridine and the Grignard reagent contains only one molecule of each. The loss of MgBrH or of $MgBr_2$ and MgH_2 from II is in agreement with Ziegler's proposed mechanism for the reaction between pyridine and the lithium alkyls and aryls (831a). Certainly, magnesium bromohydride or magnesium hydride have never been isolated in these reactions, because they doubtless reduce organic matter that is present.

Lithium alkyls and aryls react more smoothly and at a lower temperature with pyridine than do the Grignard reagents. Ziegler and Zeiser (825) thus treated 2-butylpyridine with an excess of butyllithium at 100°C. and prepared 2,6-dibutylpyridine. Evans and Allen (285; *cf.* 831b) heated the product of action of phenyllithium on pyridine for 8 hr. in toluene and obtained 2-phenylpyridine in 40–50 per cent yield. 2-Butylpyridine was similarly prepared from pyridine and butyllithium in a nitrogen atmosphere at 90–100°C., together with lithium hydride, which separated during the heating (831a). Although the latter was not actually isolated, its presence was inferred from the almost theoretical amount of hydrogen that was obtained on hydrolysis.

G. THE ACTION OF BASES ON PYRIDINE

Chichibabin (114, 121, 131) prepared the potassium salt of 2-hydroxypyridine (2-pyridone) by heating pyridine with dry potassium hydroxide at 300–320°C., in the manner shown by the equation:

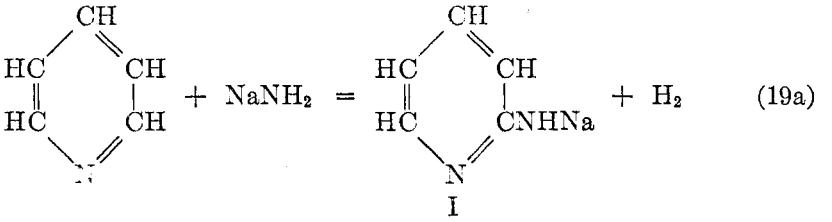


(19)

Potassium hydroxide has oxidized a cyclic ammono aldehyde ether to the potassium salt of a cyclic ammono aquo acid ester, 2-hydroxypyridine. Previously, Kudernatsch (547) melted 3-hydroxypyridine with sodium hydroxide and a little

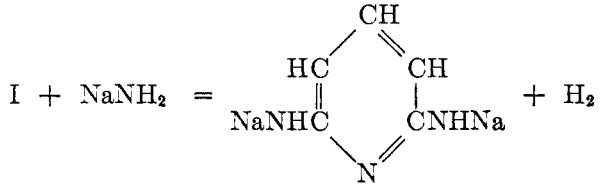
water and obtained 2,5-dihydroxypyridine. The hydrogen evolution begins at about 290°C., and is over in about 35 min.

Chichibabin and Seide (158) in 1914 prepared 2-aminopyridine and 2,6-diaminopyridine (as sodium salts, I and II) by heating pyridine with sodium amide under xylene or other inert liquids. The reaction may be expressed as follows:



(19a)

I



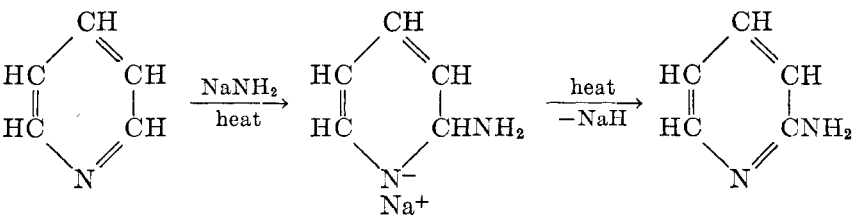
II

The preparation of the diaminopyridine requires a higher temperature and a larger amount of sodium amide than is necessary in making monoaminopyridine.

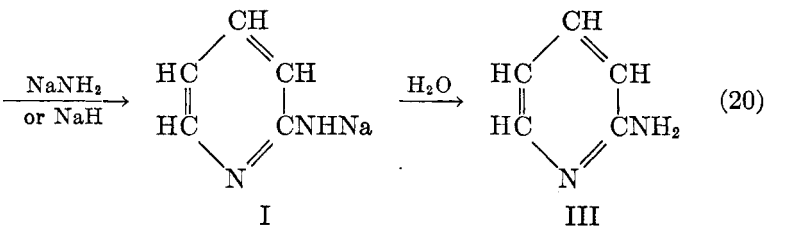
Generally this reaction and others of its type are carried out by heating pyridine and its homologues with sodium amide in boiling toluene, xylene, or in mineral oil at temperatures that may go as high as 160–180°C. Recently, Leffler (556), following a suggestion of Ostromislenski (649), has recommended the use of dimethylaniline as a reaction medium.

The introduction of an amino group into the 4-position of the pyridine ring proceeds with more difficulty than in the 2- or 6-position. The preparation of 2,4,6-triaminopyridine has been disclosed in a foreign patent (668). Further references to this important type of reaction must be omitted here, but they can be found in articles by Leffler (556) and by Fernelius and the author (61, 61a; *cf.* 116).

There seems to be a fairly general agreement that the reaction between sodium amide and pyridine is to be represented essentially by the following series of reactions:



II III



(20)

The formation of II is reasonable, since sodium amide has been found to add to the related carbonyl group of some aquo ketones (391).

Objection might be raised to assuming that 2-aminopyridine (III) is itself an intermediate in this reaction, rather than its sodium salt (I); a mechanism has been given (see under quinoline, Section IV, H, 4; reference 56) which avoids this difficulty. The 2- and 6-positions of pyridine are equivalent because of resonance in the ring, while the reactivity of the 4-position will be somewhat less because of damping in transmission of the effect of the —C=N— grouping along a conjugated chain. From the standpoint of the ammonia system, pyridine, a cyclic ammono aldehyde ether, has been nitridized to 2-aminopyridine, a cyclic ammono acid ester.

2-Methylaminopyridine is formed (786) when pyridine and methylamine are heated with the eutectic of sodium amide and potassium amide (541) for several hours at 80°C.; similar reactions have been carried out with quinoline (see section IV, H, 4). Two interpretations of the reaction mechanism may be given: (*1*) The mixed alkali amides (=MNH_2) react with methylamine, possibly reversibly, to form an alkali methylamide, as expressed by the equation:

$$CH_3NH_2 + NaNH_2 \rightleftarrows CH_3NHNa + NH_3 \qquad (21)$$

It was, however, found experimentally that the higher amines ($C_4H_9NH_2$ and others) gave off very little ammonia when heated with sodium amide, owing either to the formation of a coating of insoluble alkali alkylamide on the mixed amides that prevented further reaction, or to the retention of ammonia by the alkali alkylamide as ammonia of "crystallization." The equation for the synthesis of methylaminopyridine would then be the following:

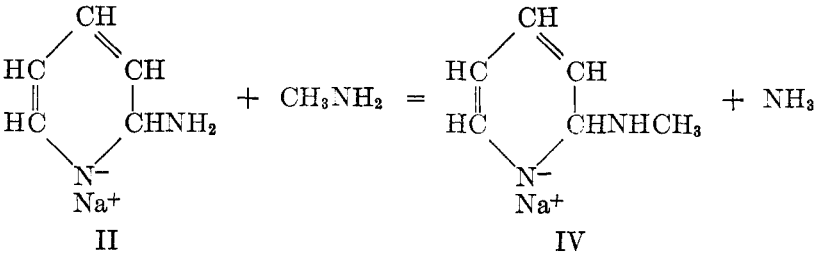
$$C_5H_5N + CH_3NHM = C_5H_4NN(M)CH_3 + H_2 \qquad (22)$$

When hydrolyzed,

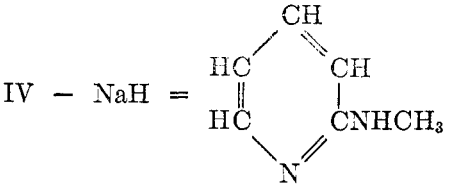
$$C_5H_4NN(M)CH_3 + H_2O = MOH + C_5H_4NNHCH_3$$

where M is sodium or potassium.

(*2*) It is perhaps a little more plausible at present to say that sodium amide (or potassium amide) adds normally to the pyridine to give an addition compound (II of equation 20 or 23), which reacts with methylamine in the manner below to form an intermediate (IV). This passes into methylaminopyridine or an alkali salt by loss of sodium hydride.

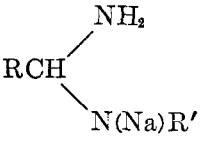


II IV (23)



$$-NHCH_3 + NaH \rightarrow H_2 + -N(Na)CH_3$$

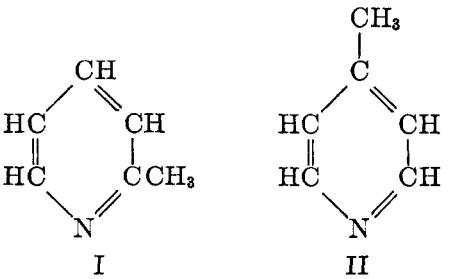
The conversion of II to IV may be reversible. Compound II is a salt of an ammono meroacetal,



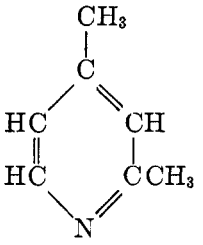
and is therefore sufficiently reactive to undergo the above changes with ease. It will be shown subsequently that many similar reactions are known, particularly among the ammono aquo meroacetals, such as the pyridine and quinoline pseudo bases and cotarnine (see Sections II, I, 7; IV, N, 2; V, I).

H. ALKYLATED AND ARYLATED PYRIDINES

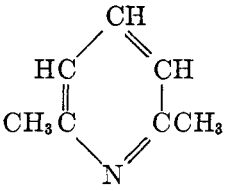
2-Methylpyridine (α-picoline, I) and 4-methylpyridine (γ-picoline, II) are cyclic ketone ethers of the ammonia system; furthermore, in view of the previous discussion of vinylogy (Section I, I) it will be seen that the 4- and 6-hydrogens of I and the 2- and 6-hydrogens of II will behave much as do the 2-, 4-, or 6-hydrogens of unsubstituted pyridine. 2,4-Dimethylpyridine (III), 2,6-dimethylpyridine (IV), and 2,4,6-trimethylpyridine (*sym*-collidine, V) all should show ketonic reactivity similar to that of the α- and γ-picolines.



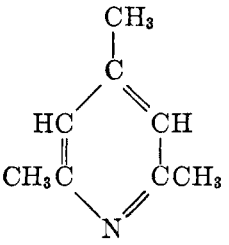
I II



III

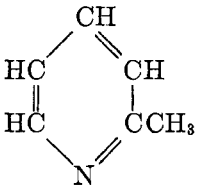


IV

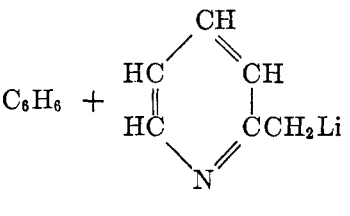


V

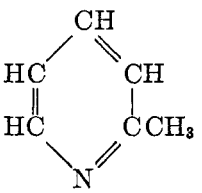
Among the large number of reactions of these compounds are the following: (*1*) Like the aquo methyl ketones of the type of acetone or acetophenone, 2- and 4-methylpyridines form alkali-metal salts when they are treated with sufficiently strong bases, as shown by equations 24 and 25 (54, 117, 669, 827):



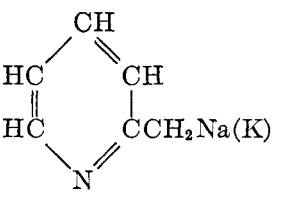
$+ \ LiC_6H_5 \xrightarrow{\text{ether}}$



$C_6H_6 +$ $\rightleftarrows$ (24)



$+ \ NaNH_2 \ (\text{or } KNH_2) = NH_3 +$



$\rightleftarrows$ (25)

Presumably the alkali-metal salts of the picolines are tautomeric in the sense that the sodium salt of acetoacetic ester is. The tautomerism of the parent compound, 2-picoline, was discussed some time ago by Chichibabin (115; *cf.* Mills and Smith (625)).

A number of examples of the type of syntheses that can be carried out with these highly reactive salts follow.

(*a*) $C_5H_4NCH_2Na + RX = C_5H_4NCH_2R$ (or $C_5H_4NCHR_2$) + NaX

where RX is an alkyl halide. The method of Chichibabin for carrying out this reaction is the following (117a):

The pyridine base, with a methyl group in the 2-, 4-, or 6-position, is mixed, without other solvent, with an excess (calculated on the basis of alkyl halide) of finely pulverized sodium amide of good quality; the liquid becomes yellow, yellow brown, or brown violet. The appropriate alkyl halide is slowly added with cooling, and the reaction products fractionally distilled, after hydrolysis destroys the sodium salts. The yields are usually from 50 to 60 per cent of the monosubstitution product and up to about 20 per cent of the disubstitution product. The ease of formation of metallic derivatives decreases in the order 4-picoline (4-methyl-3-ethylpyridine, 2-picoline), 2,6-dimethylpyridine.

2- and 4-Picolines have similarly been converted to phenylethylpyridines and phenylpropylpyridines through the potassium salt in liquid ammonia (65b). 12-(2-Pyridyl)-1-decene (or -2-decene) has been made from undecylene chloride, 2-picoline, and sodium amide (87a), following Chichibabin's method as modified by Knight and Shaw (474a), who operated at a temperature of 100°C. Ziegler and Zeiser (830) report the preparation of 2-(β-phenylethyl)pyridine from the lithium salt of 2-picoline (*cf.* 48a).

(*b*) Sodium 2-picolyl reacts with benzophenone to form an addition product which, after hydrolysis, gives diphenyl-α-picolylcarbinol.

$$C_5H_4N{-}CH_2Na + (C_6H_5)_2C{=}O \longrightarrow$$

$$(C_6H_5)_2C(ONa)(CH_2{-}C_5H_4N(2)) \xrightarrow{H_2O} (C_6H_5)_2C(OH)(CH_2{-}C_5H_4N(2)) \qquad (26)$$

Here, sodium picolyl behaves like a Grignard reagent (133).

In a similar fashion, lithium 2-picolyl reacts with benzaldehyde to form phenyl(pyridylmethyl)carbinol, $C_6H_5CHOHCH_2C_5H_4N$ (48, 133), and with acetaldehyde to give methyl(2-picolyl)carbinol (805). 2-Phenacylpyridine is the product of condensation of benzoyl chloride with lithium 2-picolyl (48). Lithium picolyl reacts with acetic anhydride or with ethyl acetate to form, among other compounds, 2-acetonylpyridine (43; this is called "dehydroisopelletierine" in the abstracts).

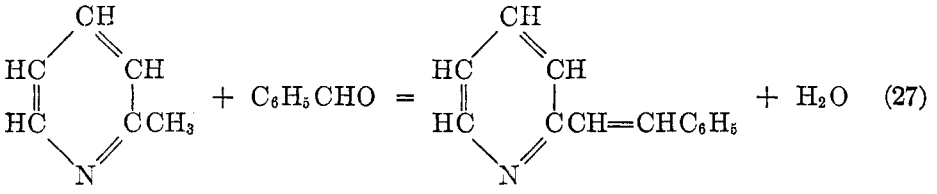
(*c*) Chichibabin (117b) treated α- and γ-picolines with sodium amide and β-chloroethyl ethyl ether, $ClCH_2CH_2OC_2H_5$, and obtained pyridylpropyl ethyl ethers of the general formula $C_5H_4NCH_2CH_2CH_2OC_2H_5$. Similarly, it was

found that γ-picoline, chloroacetal, and sodium amide react to form 1,1-diethoxy-3-(4′-pyridyl)propane, $C_5H_4NCH_2CH_2CH(OC_2H_5)_2$. Wibaut and Beets (813) were unable to prepare the corresponding derivative of α-picoline by Chichibabin's method, but were successful in carrying out the reaction between the lithium salt of α-picoline and bromoacetal in ether.

(*d*) Dirstine (250) and Seibert (752b) have catalytically phenylated the potassium salts of 2- and 4-methylpyridines in liquid ammonia, and have obtained yields of benzylpyridine, benzohydrylpyridine, and triphenylmethylpyridine that total as high as 80 per cent of the theoretical. Potassium amide, dissolved in liquid ammonia, was added to a solution of potassium picolyl and chlorobenzene in the same solvent. The peculiar activation of the aromatically bound halogen has not yet been satisfactorily explained, but is thought possibly to be due to the formation of *o*- or *p*-potassium salts of the type, $K^+ (C_6H_4Cl)^-$, from which halogen is more readily removed as an ion.

(*2*) The methyl group in 2- and 4-methylpyridines (but not in 3-methylpyridine; see reference 493) reacts with many aldehydes to undergo an aldol condensation, or an aldol condensation followed by loss of water (Claisen reaction). As expected, the corresponding reactions of open-chain aquo methyl ketones, such as acetone or acetophenone, are much more rapid. A few examples are listed below:

(*a*) 2-Picoline reacts with benzaldehyde and other aromatic aldehydes to form styryl or substituted styryl derivatives in the manner of the following equation:



α-Stilbazole

The corresponding reaction with 4-picoline is not as rapid. It is often necessary to heat in the neighborhood of 200°C. to bring about these condensations, even in the presence of an added catalyst, such as zinc chloride.

Shaw and Wagstaff (759; *cf.* 44) claim that better yields of α-stilbazoles (see equation 27) are formed by refluxing 2-methylated pyridines with aromatic aldehydes in the presence of acetic anhydride, and without the addition of zinc chloride. Parallel reactions without a condensing agent (zinc chloride or acetic anhydride) gave mixtures of alkines (I) and stilbazoles (II), the former being produced by an aldol-like condensation, and passing by loss of water into the latter, as shown by equation 28:

$$C_5H_4NCH_3 + RCHO = \underset{\text{I}}{C_5H_4NCH_2CH(OH)R} = \underset{\text{II}}{C_5H_4NCH{=}CHR} + H_2O \quad (28)$$

The alkines are converted to stilbazoles by boiling for an hour with acetic anhydride, and to the aldehyde and 2-picoline (to some extent) by heating with water (140°C.; 10 hr.). The formation of alkines is therefore reversible, just as is the

ordinary aldol condensation. The function of the condensing agent seems therefore to convert intermediates of the general formula I to stilbazoles, as well as to increase the velocity of the over-all reaction. However, Roth (731) reports his inability to dehydrate with zinc chloride the alkine formed by condensing *o*-nitrobenzaldehyde and 2-picoline.

The preparation of the pure alkines (I) from 2-methylpyridine and aromatic aldehydes is accomplished by heating the two in the presence of a little water at temperatures in the neighborhood of 140–160°C. (21a, 566, 731) for 10 hr. or more.

Feist, Awe, and Kuklinski (288a) find that substituted styryl derivatives are not formed by heating benzaldehydes with 2-amino-6-methylpyridine, 2-dimethylamino-6-methylpyridine, 2-methylamino-6-methylpyridine, or 2-acetamido-6-methylpyridine. 2-Amino-6-methylpyridine condenses with these aldehydes to give Schiff bases instead.

2-Picoline (and 4-picoline as well) reacts with aqueous formaldehyde at temperatures of about 130–150°C. and over a period of 10–15 hr. to form monomethylolpicoline, dimethylolpicoline, and trimethylolpicoline (501a, 565d, 567, 567a, 590; *cf.* 798). The formation of the latter two is of course favored by an excess of formaldehyde. The reactions follow the equations below:

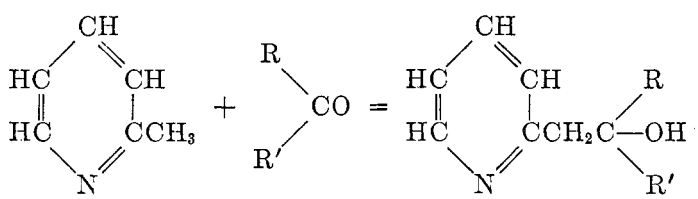
$$C_5H_4NCH_3 \xrightarrow{HCHO} C_5H_4NCH_2CH_2OH \xrightarrow{HCHO}$$

$$C_5H_4NCH(CH_2OH)_2 \xrightarrow{HCHO} C_5H_4NC(CH_2OH)_3 \qquad (29)$$

Methyl(2-pyridyl)carbinol and ethyl(2-pyridyl)carbinol are similarly obtained from 2-picoline and aqueous acetaldehyde or propionaldehyde, respectively, though in comparatively poor yields (550, 552; see also 805 and 797).

Chloral and 2-(or 4-)picoline react when heated to form picolyltrichloromethylcarbinols, $C_5H_4NCH_2CH(OH)CCl_3$ (276, 798).

McElvain and Johnson (568) have heated 2-picoline and quinaldine with active carbonyl compounds at 140°C., and have obtained condensations in the sense of equation 30:



(30)

Some of their results are listed below:

TIME AT 140°C.	R	R′	YIELD OF PURE PRODUCT
hours			*per cent*
2.0	$COOC_2H_5$	$COOC_2H_5$	33
1.5	C_6H_5CO	C_6H_5CO	16
1.0	C_6H_5CO	$COOC_2H_5$	74
4.0	C_6H_5	C_6H_5CO	54

Condensations of polymethylated pyridines

2,6-Dimethylpyridine reacts with benzaldehyde in the presence of zinc chloride at elevated temperatures to form a distyryl derivative (751), indicating that both methyl groups are equally reactive, as might be expected because of the ring resonance.

Clemo and Gourlay (170) heated 2,4-dimethylpyridine (α,γ-lutidine) with benzaldehyde and acetic anhydride (reflux for 16 hr.) and obtained 2-styryl-4-methylpyridine and 2,4-distyrylpyridine in the approximate ratio of two to one. Bachér (22), who previously carried out this reaction in the presence of zinc chloride (7 hr. at 225°C.), reported only 2-styryl-4-methylpyridine. Similarly, Langer (554) found that *p*-tolualdehyde condenses with 2,4-dimethylpyridine in the 2-position, forming both the styryl derivative and its corresponding alkine, the latter in smaller quantity.

It is therefore apparent that a methyl group in the 2-position of the pyridine nucleus is more reactive than when it is in the 4-position, pointing to the fact that there is some damping in the transmission of the effect of the —C=N— to the methyl along the conjugated chain (for discussion of damping, see reference 87).

(*3*) The 2- and 4-picolines react with heated sodium amide under an inert hydrocarbon oil to give, respectively, 6-amino-2-methylpyridine and 2-amino-4-methylpyridine (158, 753, 754), therefore behaving as unsubstituted pyridine would under the same conditions. 2,6-Dimethylpyridine is harder to convert to an amino derivative (NH_2 in position 4) than are the 2- and 4-picolines (128), perhaps largely because of the lower reactivity of the 4-hydrogen. If sodium amide and the dimethylpyridine react under the conditions of the experiment to form a sodium salt, the negative charge on the side-chain carbon should hinder a reaction which depends upon the attack of the pyridine nucleus by an active anion, NH_2^-.

(*4*) 2-Picoline reacts with selenium dioxide, when heated, to give the corresponding pyridinecarboxylic acid, together with a small amount of pyridine-2-aldehyde (81, 420, 422). The use of selenium dioxide to convert a methyl attached to carbonyl to an aldehyde group is well known (704). A typical example is the preparation of phenylglyoxal in accordance with the following equation:

$$C_6H_5COCH_3 + SeO_2 = C_6H_5COCHO + Se + H_2O \qquad (31)$$

I. QUATERNARY PYRIDINIUM SALTS

Pyridine and many other substances containing tertiary nitrogen react with alkyl iodides, alkyl sulfates, and alkyl *p*-toluenesulfonates to form quaternary ammonium salts in the manner of the representative equation below:

$$C_5H_5N + CH_3I = [C_5H_5\overset{+}{N}CH_3]I^- \text{ or } [C_5H_5NCH_3]^+I^- \qquad (32)$$

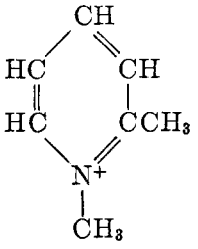
In the quaternary ammonium salt above, the nitrogen of the pyridine bears a positive charge; supposedly this charge is distributed by resonance, in small measure at least, to the 2- and 4-carbon atoms. The formula on the right of equation 32 is therefore to be preferred.

The charged nitrogen atom has not affected the essential character of the double bond between carbon and nitrogen. For this reason, pyridine methiodide —or rather the *N*-methylpyridinium ion—is still a cyclic ammono aldehyde ether, and 2-methylpyridine is a cyclic ammono ketone ether, although of somewhat more active types than hitherto encountered in this review. The distributed positive charge on the cation will markedly accelerate reactions involving active anions (i.e., bases) either directly or as catalysts. The close resemblance of pyridinium and pyrylium salts has previously been commented upon, and will be elaborated in detail later (Section III).

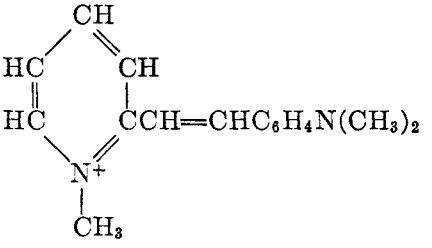
There follows a list of some characteristic reactions of the quaternary pyridinium salts:

1. Formation of styryl derivatives

2-Methylpyridine methiodide and *p*-dimethylaminobenzaldehyde are refluxed in alcoholic solution for 5 hr., with the addition of a small amount of piperidine as a catalyst. There is obtained 2-*p*-dimethylaminostyrylpyridine methiodide, a sensitizer of photographic plates for green light (616).



$$I^- + (CH_3)_2NC_6H_4CHO =$$

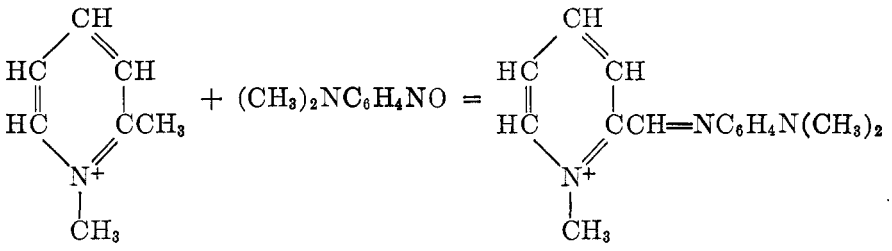


$$H_2O + \qquad I^- \qquad (33)$$

Picoline methiodide thus condenses more rapidly with aldehydes and in the presence of a more mildly acting catalyst than does picoline itself, showing clearly the accelerating effect of quaternary salt formation on reactivity. Many other condensations of this type have been described recently (171, 172, 183, 259, 260, 604).

2. Reaction with nitrosodimethylaniline

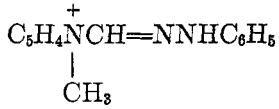
p-Nitrosodimethylaniline (I) resembles the ketones to some extent in its reactivity, but it fails to condense with 2-picoline under any conditions that have been tried. Nevertheless, it reacts without difficulty with 2-picoline methiodide or ethiodide in the presence of piperidine to form an alkiodide of the *p*-dimethylamino anil of pyridine-2-aldehyde (II) (462).



(cation only) I II

+ H_2O (34)

When II is heated with phenylhydrazine the dimethylaminophenyl group is replaced by $—NHC_6H_5$ to give



which splits off methyl iodide in a high vacuum to give the phenylhydrazone of pyridine-2-aldehyde. This can be hydrolyzed by heating with dilute hydrochloric acid to pyridine-2-aldehyde.

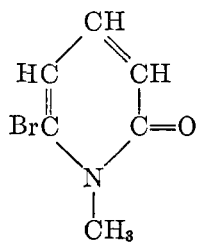
3. Cyanine dyes

Cyanine dyes may be prepared from the alkiodides of 2- and 4-methylpyridines by reactions that are dependent upon the activity of the methyl group. A brief discussion of this important class of compounds is given in Section IV, N, 9. A partial list of references to the preparation of cyanine dyes containing the pyridine nucleus is appended (88, 92, 93, 94, 259, 260, 402, 645, 719, 773).

4. 2-Halogenopyridine alkiodides

In a later section (II, M) it will be shown that 2-chloropyridine is a cyclic ammono acid chloride ester, and therefore contains a reactive chlorine atom. The activity of a halogen in the 2-position is enhanced by quaternary salt formation. Fischer (297) has thus prepared 2-anilinopyridine iodomethylate by heating 2-iodopyridine iodomethylate with aniline in alcoholic solution at 100°C., at the same time remarking that the 2-iodine atom in the quaternary salt is exchanged much more easily for the phenylamino group than is the chlorine in 2-chloropyridine. Pseudocyanines and cyanines may readily be prepared from the 2- or 4-iodopyridine alkiodides (92, 93, 94, 402; see Section II, I, 3).

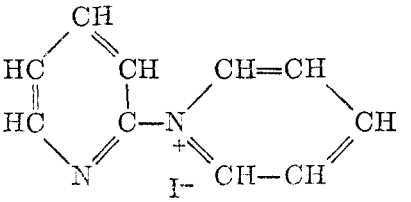
Wibaut, Speekman, and Wagtendonk (814i) have prepared the methosulfate of 2,6-dibromopyridine, and find that it is converted by sodium hydroxide at room temperatures to 1-methyl-6-bromo-2-pyridone,



rather than to 1-methyl-6-bromo-2-hydroxypyridinium hydroxide.

5. Pyridylpyridinium salts

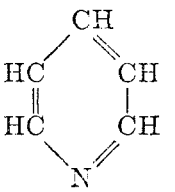
The formation of 2- and 3-pyridylpyridinium salts by the oxidation of pyridine with persulfate or with atmospheric oxygen has been described previously (Section II, E). Rodewald and Plazek (715d, 715e) prepared 2-pyridylpyridinium iodide (I) by heating pyridine hydrochloride with iodine or iodine chloride for about 5 hr. at 280°C. The primary reaction product, 2-iodopyridine, adds to unchanged pyridine to give the quaternary salt (I).



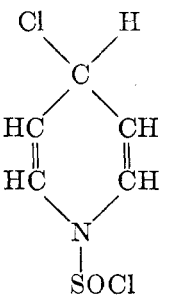
I

Iodinated pyridines are also formed in the reaction (see Section II, M, 1). 2-Aminopyridine may be made by the action of ammonia on the 2-pyridylpyridinium iodide, much in the manner of equation 17. (See reference 814f, pp. 709 and 717, for the corresponding chlorine compound.)

4-Pyridylpyridinium salts are among the products of the self-condensation of 4-chloro- and 4-bromopyridine (Section II, M, 2). Koenigs and Greiner (497a and b) prepared the best-known representative of this class of compounds, the hydrochloride of 4-pyridylpyridinium chloride (II of equation 35) by allowing dry pyridine (100 g.) and thionyl chloride (300 g.) to stand for 3 days at ordinary temperatures or by heating for 5 hr. on the water bath. The reaction is expressed by the equation below:

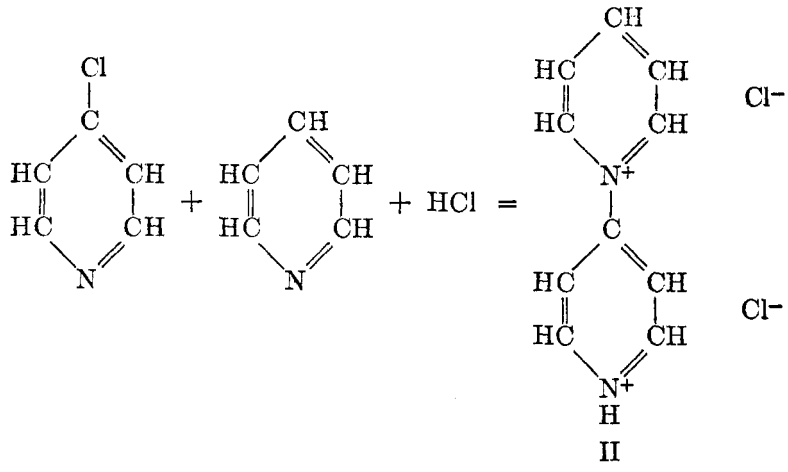
 + $SOCl_2$ = addition compound

which rearranges to



(35)

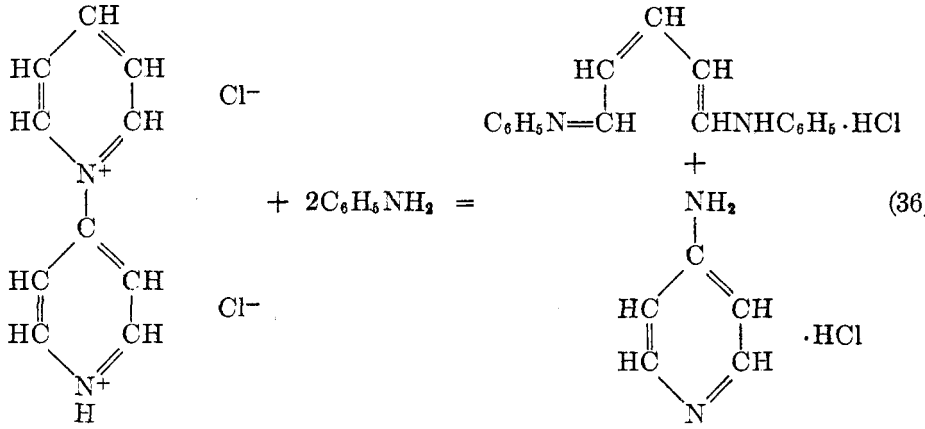
or perhaps to 4-chloropyridine itself; this reacts with unchanged pyridine to form the quaternary salt, 4-pyridylpyridinium dichloride (II).



II

The above mechanism of Koenigs is probable in view of the fact that picolinic acid chloride (pyridine-2-carboxylic acid chloride) reacts with thionyl chloride to form 4-chloropicolinic acid chloride (601a). The exact fate of the thionyl chloride is unknown.

4-Pyridylpyridinium dichloride may be converted to a number of 4-substituted pyridines that are not otherwise readily available; at the same time, one of the pyridine rings is opened to form glutacondialdehyde, or a derivative. One typical reaction is the following:



(36)

The action of aniline on 4-pyridylpyridinium dichloride has given 4-aminopyridine hydrochloride and the hydrochloride of the anil anilide of glutacondialdehyde.

4-Aminopyridine is, however, better made by heating 4-pyridylpyridinium dichloride with concentrated ammonia for 8 hr. in an autoclave at 150°C. 4-Hydroxypyridine is obtained by heating the quaternary salt with water for 8 hr. at 150°C. (70 g. from 200 g. of starting material).

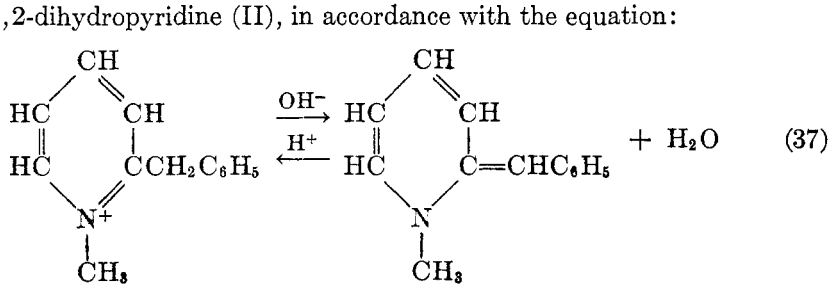
The similarity between the reactions of 4-pyridylpyridinium dichloride and of

2,4-dinitrophenylpyridinium chloride (see Section II, C,1) is rather close. In both cases, a pyridine ring is opened to form glutacondialdehyde or a derivative. Accompanying this are the aminated compounds, 4-aminopyridine and 2,4-dinitroaniline, respectively.

The effect of the 2,4-dinitrophenyl group is promoting scission of the pyridine ring of 2,4-dinitrophenylpyridinium chloride was ascribed (Section II, C, 1) to the electron attraction of the two nitro groups ($-I$ $-T$ effects). The strong $-I$ effect of the positively charged nitrogen of the lower ring of pyridylpyridinium dichloride (equation 36) is of course not as great as the combined $-I$ $-T$ effects of the two nitro groups of dinitrophenylpyridinium chloride; therefore it is more difficult to open a pyridine ring in the former case.

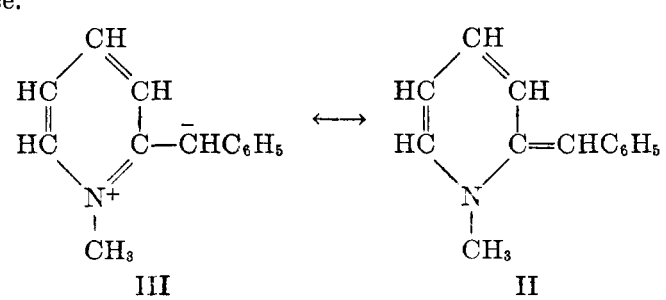
6. Methylene bases (ammono enol ethers) or pyridone methides

Decker (192) treated 2-benzylpyridine methiodide (cation = I) with strong sodium hydroxide solution and obtained the orange-colored 2-benzylidene-1-methyl-1,2-dihydropyridine (II), in accordance with the equation:



I II

The mechanism of this change is not definitely known. If the hydroxyl ion adds to the 2-carbon atom, a pseudo base will result and II will be formed by removal of the elements of water. The suggestion has also been made that a hydrogen of the side-chain methylene ionizes to a slight extent under the influence of the electron attraction ($-I$ effect) of the positively charged nitrogen. Combination of the hydrogen ion so produced with the hydroxyl of the base will give III, a polar or "zwitter ion" form of the methylene base (II), with which it is doubtless in resonance.



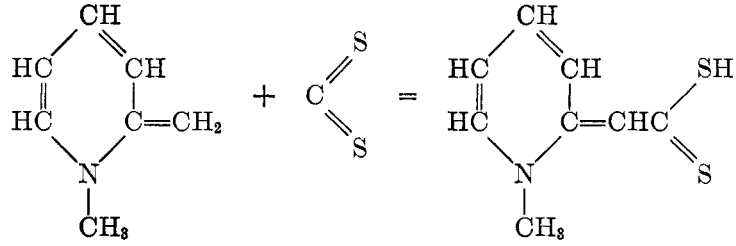
III II

Benzene extracts the methylene base, II or III, from the product of the action of a base on the quaternary salt (I), while water in turn extracts the strong base,

1-methyl-2-benzylpyridinium hydroxide, from the benzene solution. This indicates an equilibrium between the two forms dependent not only upon hydrogen-ion concentration, but also upon the solvent (193a, 224a). Every methylene base examined by Decker (193a, 224a) behaves in a similar manner.

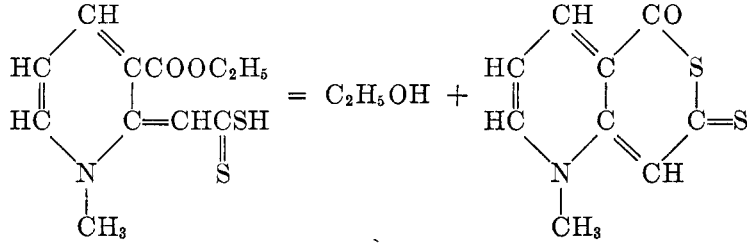
The related enamine, 1-methyl-2-methylene-1,2-dihydropyridine (formula II, $=CHC_6H_5$ replaced by $=CH_2$) is similarly prepared from 2-picoline methiodide and strong sodium hydroxide (748; *cf.* 633, 634). It is rather unstable, but it may be isolated in the form of addition compounds with phenyl isocyanate or carbon disulfide (635, 746a).

According to Mumm (635), the reaction with carbon bisulfide follows the equation:



III IV (38)

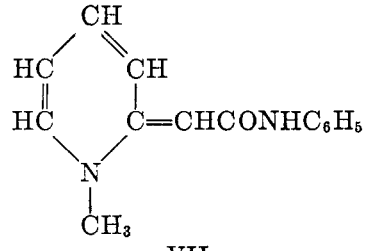
Evidence for formula IV is afforded by the conversion of its 3-carboethoxy derivative (V) into a cylic compound (VI), in accordance with the equation:



V VI (39)

Earlier formulas (746; *cf.* 720) are regarded as improbable.

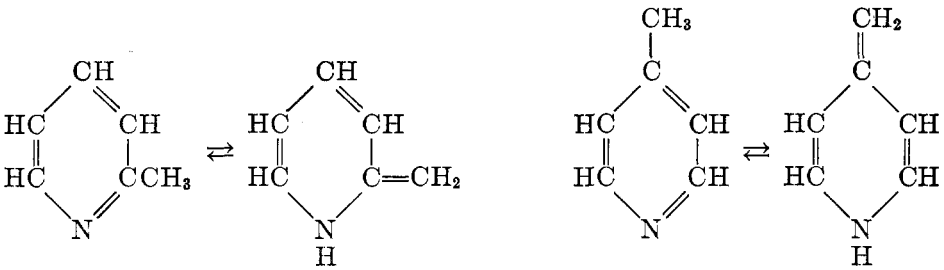
The phenyl isocyanate addition compound has formula VII (635, 747).



VII

Many related methylene bases (= pyridone methides) have been prepared; a number of them are derived from 4-picoline (135, 143, 499, 633, 634, 748).

It has been known for a long time from the work of Chichibabin (115, 117a) that 2- and 4-picolines (VIII, IX) are tautomeric with the enamic, or ammono enolic, forms (X, XI) shown below:

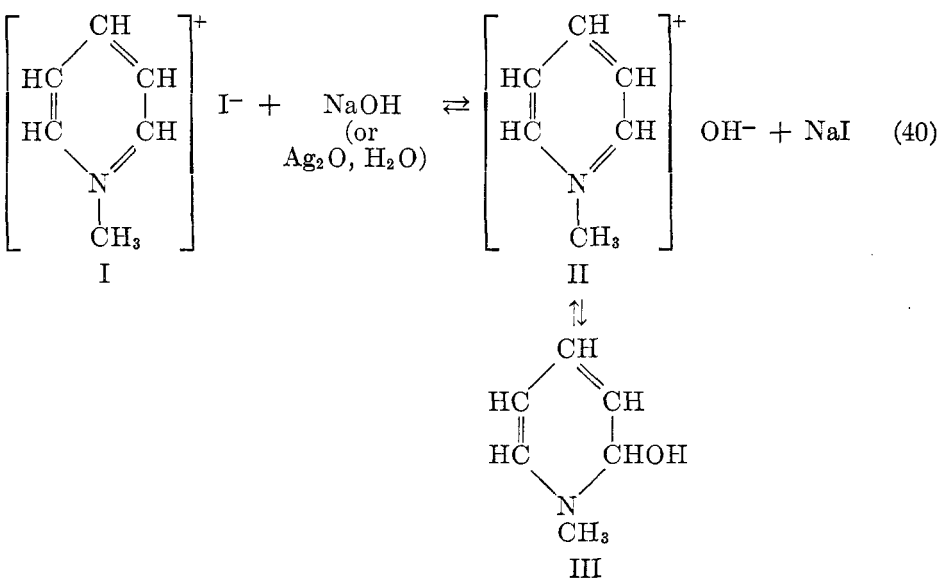


VIII X IX XI

The methylene bases, or pyridone methides, are the *N*-ethers of X and XI and are therefore to be compared with the ethers of the aquo enols (e.g., with $CH_2{=}CHOC_2H_5$) that were discussed briefly in Section II, C, (a). The occurrence of methylene bases as intermediates in the condensations of the picoline and quinaldine alkiodides which lead to the formation of cyanine dyes will be dealt with in section IV, N, 5, (a).

7. Pseudo bases, carbinol bases, or 1-alkyl-2-hydroxy-1,2-dihydropyridines

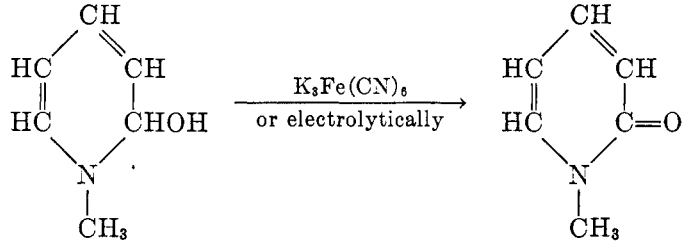
Pyridine halogen alkylates or pyridine methosulfates (I below) when treated with silver oxide and water, or with aqueous alkali, give first the strongly basic *N*-alkylpyridinium hydroxides (II), which undergo partial isomerization to the 1-alkyl-2-hydroxy-1,2-dihydropyridines (III), as expressed by equation 40 (267, 409, 427; *cf.* 28):



I II III (40)

Hantzsch and Kalb (409) and Aston and Lasselle (18) consider the point of equilibrium in the reaction, II $\rightleftarrows$ III, to be far over on the left, because formation of the pseudo base, III, involves partial destruction of the completely conjugated system of the pyridine ring in II.

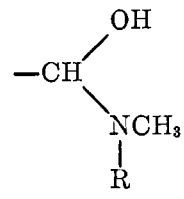
Even though large quantities of III may not be present, oxidation of pyridine methiodide in alkaline solution results in a good yield of 1-methyl-2-pyridone (IV), as shown by the equation:



III IV (41)

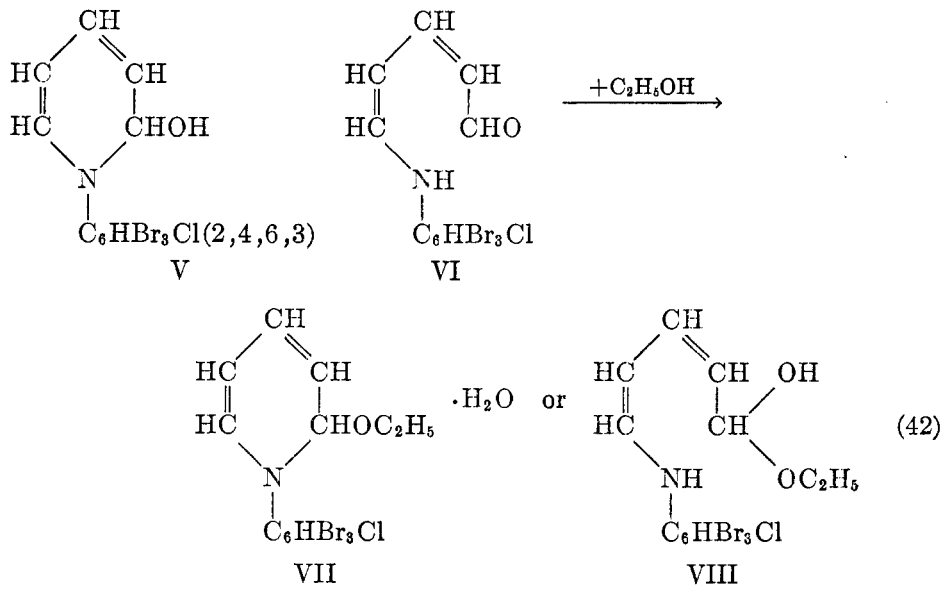
Generally, the pyridine alkiodide or methosulfate is dissolved in aqueous alkali, benzene added, and then an aqueous solution of potassium ferricyanide introduced with stirring. The *N*-methylpyridone (IV) dissolves in the benzene layer (188, 196, 223, 286, 295, 697). Oxidation can also be accomplished electrolytically (302, 309, 639).

The 1-alkyl-2-hydroxy-1,2-dihydropyridines (III) are cyclic ammono aquo meroacetals (see Section I, E) because of the grouping



Like other meroacetals, they have as high a reactivity as the corresponding aquo aldehyde, and a much greater aldehydic reactivity than pyridine itself because of the decreased resonance in a ring that now contains only two double bonds instead of three. Related substances are treated somewhat more completely in the sections on quinoline (IV, N, 2) and isoquinoline (V, I; cotarnine).

In the past years there has been much discussion as to whether these pseudo bases have the closed-chain "carbinol" (V) or the open-chain "aldehyde" (VI) formula (371a and 458, where earlier references are given; 512). A related situation in the water system is afforded by glucose and other monosaccharides which are regarded as existing for the most part in the cyclic hemiacetal modification, in equilibrium, probably, with very small quantities of the open-chain aldehyde.

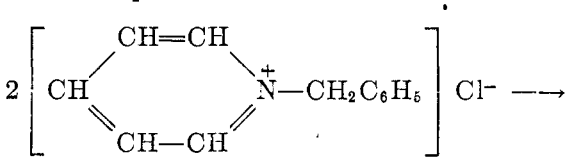


(42)

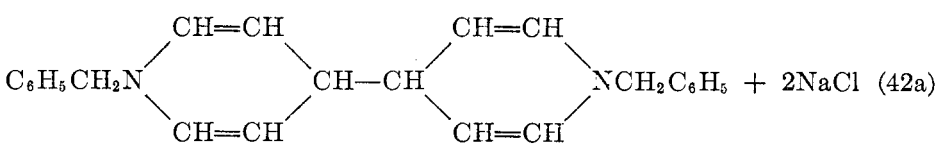
The above equation represents a reaction carried out by König (513). 2,4,6-Tribromo-3-chlorophenylpyridinium bromide was treated with alkali to give the pseudo base (V), which König considers to exist in the open-chain form, VI. Attempted crystallization from alcohol gave an "alcoholate" of the structure VII or VIII, which passed into the corresponding methoxy compound when heated with methanol. Analogous reactions of chloral alcoholate, $CCl_3CH(OH)OC_2H_5$, are mentioned in Section IV, N, 2, (a).

8. Reduction: N,N-dialkyldihydrodipyridyls, dipyridinium subhalides (tetraalkyl dipyridyl violet halides)

Reduction of *N*-benzylpyridinium chloride (I) with sodium amalgam gives *N,N'*-dibenzyltetrahydro-γ,γ'-dipyridyl (II) (*cf.* 280, 636, 809), in accordance with the equation:



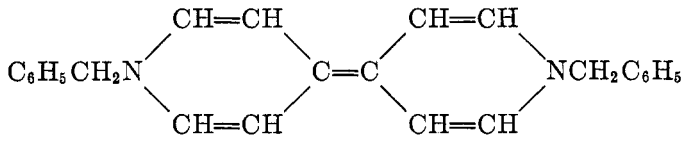
I



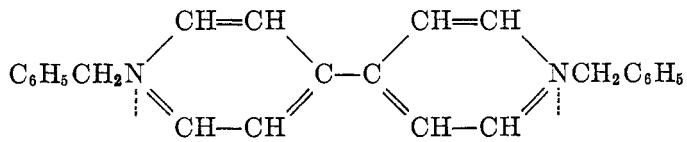
(42a)

II

When alcoholic solutions of II are heated in the presence of a limited supply of air, there is formed a deep blue solution from which reddish crystals may be made to separate. Weitz (809) believes that this compound is a mixture of the quinoid dihydro-γ,γ'-dipyridyl derivative (III) with the diradical (IV) which contains two atoms of tetravalent nitrogen; recent physicochemical work indicates the correctness of the first formula, III (631, 752).

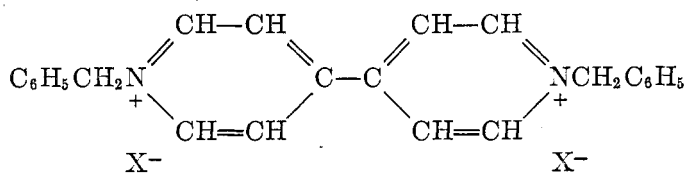


III



IV

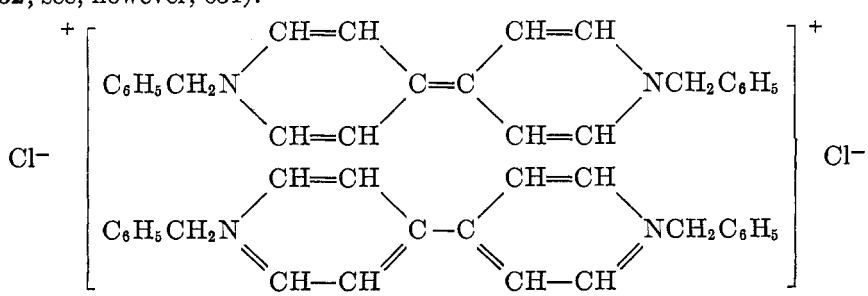
Halogens react with III to form dialkyl halogenides of γ,γ'-dipyridyl (V). These may also be formed by oxidation of III with silver nitrate, or, less favorably, with atmospheric oxygen, followed by treatment with hydrochloric acid.



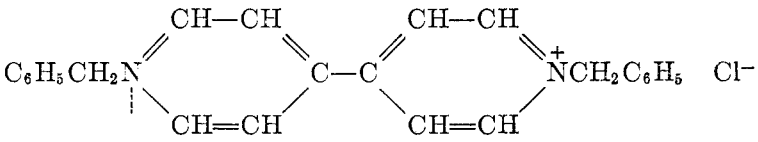
V

Reduction of V with sodium amalgam, or with zinc dust and glacial acetic acid, gives the blue dibenzyldihydro-γ,γ'-dipyridyl (III).

Emmert (280) heated alcoholic solutions of N,N'-dibenzyltetrahydro-γ,γ'-dipyridyl (II) with γ,γ'-dipyridyldichlorobenzylate (V, X = Cl) and obtained a deep blue or violet salt which he considers to be a quinhydrone-like compound of the constitution below (VI), and calls "tetrabenzyldipyridyl violet chloride", following suggestions of Dimroth and Frister (249). Weitz is of the opinion that it is best regarded as a free radical (VII) with one tetravalent nitrogen atom, and indeed this formula is in agreement with its behavior towards para-hydrogen (752; see, however, 631).



VI



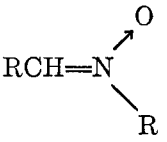
VII

The dibenzyldipyridinium subhalide (VII) may also be prepared by the action of dibenzyldihydrodipyridyl (III) on an equimolar quantity of γ,γ'-dipyridyl dichlorobenzylate (V, X = Cl). Many other compounds of similar structure have been prepared and studied (280, 631, 636, 752, 809).

The mother substance of VI or VII, with hydrogen replacing the benzyl groups, was prepared by Dimroth and Frister (249) by reducing γ,γ'-dipyridyl in dilute acetic acid solution with chromous chloride.

J. PYRIDINE *N*-OXIDE

Colonna (174) has pointed out that the known analogy between the Schiff bases and pyridine exists also between the *N*-oxides of these compounds, that is to say, between the aldonitrones,



and the pyridine *N*-oxides:

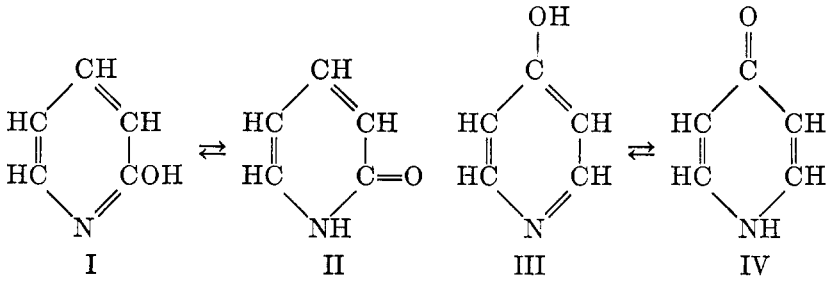
$$C_5H_5N\rightarrow O$$

Because of the coördinate bond between nitrogen and oxygen, the former atom is positively charged, and the aldehydic properties should be enhanced in the same manner as are those of the quaternary pyridinium salts (Section II, I). This hope appears only to have been partly realized at the present time. It is reported that 2-phenylpyridine is formed by the action of phenylmagnesium bromide on pyridine *N*-oxide, though conditions under which this occurs are not to be found in the abstract that was available.

K. HYDROXY- AND ALKOXY-PYRIDINES, *N*-ALKYLPYRIDONES

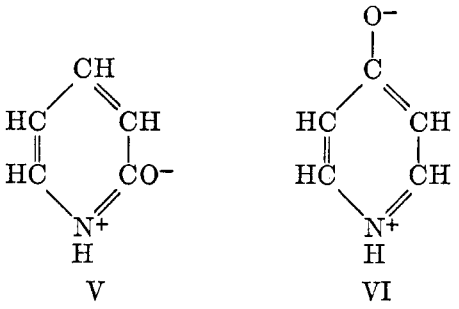
2-Hydroxypyridine (1) and 2-pyridone (II) are to be considered tautomeric forms of a cyclic aquo ammono acid ester; 4-hydroxypyridine (III) and 4-pyridone (IV) are their vinylogues (*cf.* 71, 138, 675). 2-Hydroxypyridine is made by diazotizing 2-aminopyridine in sulfuric acid solution (108a, 156), by hydrolysis of 2-chloropyridine under acid or alkaline conditions (Section II, M, 4), by heating pyridine with dry potassium hydroxide (Section II, G), and by decarboxylating various 2-pyridonecarboxylic acids (see Beilstein, Vol. XXI, p. 43 for references). 4-Hydroxypyridine is made by heating 4-pyridonecarboxylic acids or

their salts (see Beilstein, Vol. XXI, p. 48 for references), by ammonolysis of 4-pyrone (Section II, B, 2; *cf.* 473a), and also from 4-pyridylpyridinium dichloride (497a and 497b).



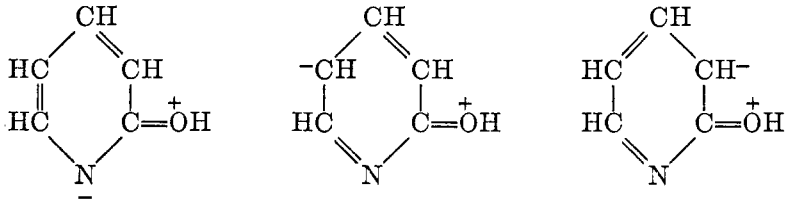
I II III IV

The ultraviolet absorption spectra of the *N*-alkylpyridones (see below) indicate that the aromatic ring structure of pyridine is still present (15a, 711a, 767c; *cf.* 14a, 20b, 596b, 760a).



V VI

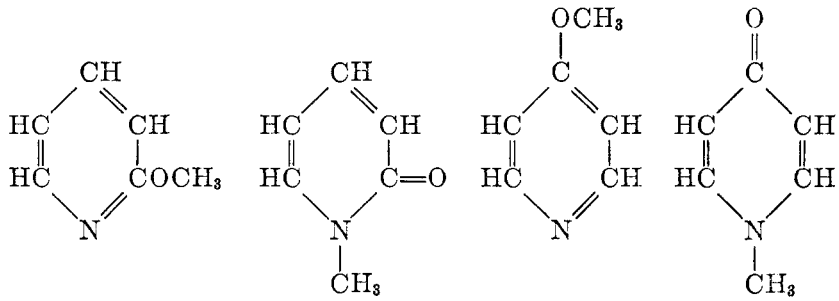
It is probable that the pyridones or hydroxypyridines are resonance hybrids of II and V or of IV and VI, in admixture with the tautomeric hydroxypyridines, I and III, and their resonant forms (VII, VIII, IX, for example).



VII VIII IX

The three structures above have been patterned after the known resonant forms of phenol (83c).

While it has proven impossible to separate the chemical individuals (I and II) or (III and IV), alkyl derivatives of both are known, and are shown below:



X XI XII XIII

The absorption-spectra measurements referred to previously (15a, 711a, 767c) indicate that the *N*-alkylpyridones (XI and XIII) still retain the aromatic ring structure of pyridine and are accordingly best considered as *N*-methyl derivatives of the dipolar forms, V and VI.

2-Hydroxypyridine reacts with diazomethane to give 2-methoxypyridine as the sole product (596b, 597, 673a), but a mixture of 4-methoxypyridine and 1-methyl-4-pyridone is similarly obtained from 4-hydroxypyridine (597). Pure 2- and 4-alkoxypyridines are formed by the action of sodium alkoxides on the 2- or 4-chloropyridines (see Section II, M, 4). 2-Methoxypyridine (X) may also be made by shaking the silver salt of 2-hydroxypyridine with ethereal methyl iodide solution, but an almost equal amount of the isomeric *N*-methylpyridone (XI) is formed at the same time. 2-Ethoxypyridine is obtained, either by the reaction just described (680), or by the addition of sodium nitrite to a boiling solution of 2-aminopyridine and sulfuric acid in absolute ethanol (156).

A reasonably pure *N*-methylpyridone (XI) may be prepared by shaking 2-hydroxypyridine with methyl iodide at 100°C. (678), by boiling a methyl alcoholic solution of its potassium salt with dimethyl sulfate (701), or by oxidation of pyridine iodomethylate in alkaline solution (Section II, I, 7).

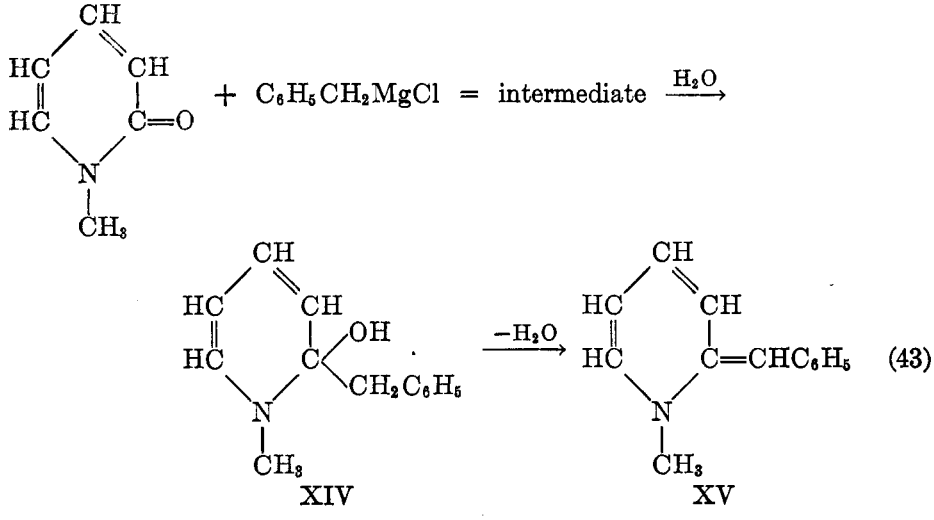
The conclusion might be drawn that 2-alkoxypyridines are always formed when the silver salts of the pyridones are heated with alkyl halides, while the isomeric *N*-alkylpyridones are obtained by the alkylation of the potassium salts of the pyridones. Räth (697a) has, however, shown that this is not the case, since the proportion of the two forms is dependent upon other groups present in the molecule. Negative groups in the 5-position of 2-hydroxypyridine favor the production of *N*-alkyl derivatives. Thus, the silver salt of 2-hydroxy-5-nitropyridine, when heated with methyl iodide in methanol (8 hr. reflux) gave 15.6 per cent of 2-methoxy-5-nitropyridine (volatile with steam) and 60 per cent of *N*-methyl-5-nitro-2-pyridone (not volatile with steam). An 80 per cent yield of 5-iodo-*N*-methyl-2-pyridone may be obtained by boiling 5-iodo-2-hydroxypyridine, methyl iodide, and potassium hydroxide in absolute alcohol for 2 hr. The potassium salt of 2-hydroxy-5-nitropyridine, on the other hand, when methylated with methyl iodide in alcohol (boiled for 1.5 hr.) gives 0.8 per cent of 2-methoxy-5-nitropyridine and 83 per cent of 1-methyl-5-nitro-2-pyridone. The prepara-

tion of the 2-methoxy compound is best accomplished by heating 2-chloro-5-nitropyridine with methyl alcoholic sodium methylate.

2-Methoxypyridine is partially rearranged to the isomeric 1-methyl-2-pyridone when heated at 290°C. (600; *cf.* 600a). Presumably, both 2- and 4-alkoxypyridines should have labile alkoxy groups, since these substances are cyclic ammono aquo esters, but there is almost no evidence on this point. Their low reactivity is again to be ascribed to the effect of the high resonance energy of the pyridine ring.

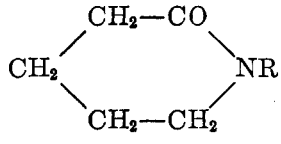
2-Methoxypyridine, when heated with concentrated hydrogen iodide (d = 1.8) for 48 hr. at 100°C., gives methyl iodide and 2-hydroxypyridine—a hydrolysis of a cylic ammono aquo ester to a cyclic ammono aquo acid. However, the reaction is slower than the scission of a methyl ether in the Zeisel determination (389). It is reported in a patent (381a) that 2-alkoxy-5-aminopyridines are converted to 2-hydroxy-5-aminopyridine salts by heating with the hydrogen halides. Reduction of 2-methoxypyridine gives piperidine, apparently without the intermediate formation of pyridine (379) that was observed in the hydrogenation of 2-chloropyridine.

The isomeric *N*-alkylpyridones are also cylic ammono aquo esters, but they show practically no ketonic or ester reactivity. Thus, *N*-methyl-α-pyridone is not affected by hydrogen iodide at 165°C. (385). Decker (193) does, however, report that a poor yield of 1-methyl-2-benzylidene-1,2-dihydropyridine (XV) is formed by the action of benzylmagnesium chloride on 1-methyl-2-pyridone.



The intermediate XIV has not been isolated.

Räth (702; *cf.* 379) reduced 1-methyl-2-pyridone and related substances with hydrogen in the presence of a catalyst, and obtained *N*-alkylpiperidones of the general formula:



2-Pyridone (2-hydroxypyridine) was reduced with somewhat greater difficulty (200–235°C., 40 atmospheres of hydrogen) to 2-piperidone.

The *N*-alkylpiperidones are saturated cyclic ammono aquo esters; they may be further reduced to the corresponding cyclic ammono ether, a substituted piperidine, by heating with sodium in rigidly dried butanol (489a).

2-Phenoxypyridine, another cyclic ammono aquo ester, is prepared by heating pyridine 2-diazotate with phenol. It isomerizes at a dull red heat to 1-phenyl-2-pyridone, and is hydrolyzed to phenol and 2-hydroxypyridine by hot concentrated hydrochloric acid (138), a reaction that may be compared to the hydrolysis of an ester to the corresponding alcohol and acid.

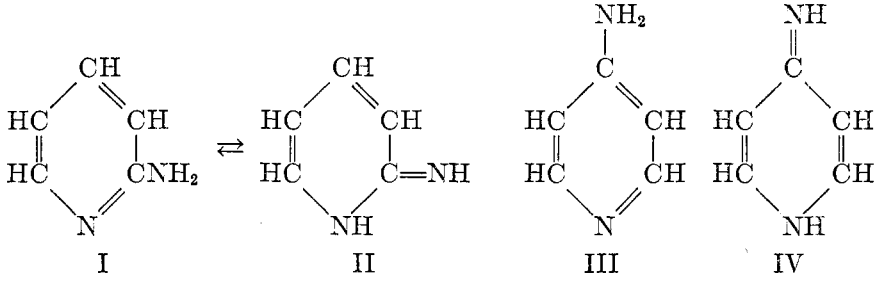
2,5-Dihydroxypyridine, boiled with acetic anhydride and sodium acetate, gives 2-hydroxy-5-acetoxypyridine (547a), indicating that the hydroxyl attached to the —C=N— group is less readily acetylated or, perhaps, that it is more readily removed from the 2-position when once in place. Chichibabin and Szokow (159) have thus prepared 2-acetoxypyridine, a mixed anhydride of aquo-acetic acid and the cyclic ammono aquo acid, 2-hydroxypyridine, and find that it is readily hydrolyzed by water.

L. AMINOPYRIDINES

2-Aminopyridine is best prepared by heating pyridine with sodium amide under an inert solvent (see Section II, G), although it can also be made by the ammonolysis of 2-chloropyridine (Section II, M, 4) or by decomposition of the 2-pyridylpyridinium salts (Section II, E).

4-Aminopyridines are made in small amounts by the sodium amide method but in better yields by the ammonolysis of the 4-pyridylpyridinium salts (Section II, I, 5) or the 4-halogenopyridines (Section II, M, 7).

2-Aminopyridine (I) is a cyclic ammono acid ester, while 4-aminopyridine (III) is a vinylogue.



I II III IV

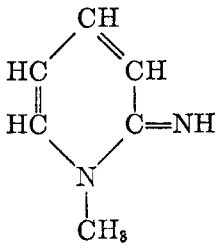
Tautomerism, in the sense of I ⇄ II and III ⇄ IV, was recognized at an early date by Chichibabin (114a, 115, 141, 142), since derivatives of all of the above are known, and particularly since bicyclic compounds including both of the two nitrogens of II in the new ring can be obtained. Perhaps the structure of the aminopyridines will be somewhat modified in the future in accordance with suggestions that have been made with regard to the hydroxypyridines and the pyridones (Section II, K).

3-Aminopyridine (for preparation see Section II, M, 6 and reference 699a) is

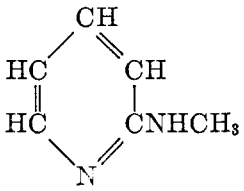
related to the ammonia system much as is pyridine itself; that is to say, the amino group is not particularly influenced by the double bond between the cyclic nitrogen and an adjacent carbon. The properties of an amino group in the 3-position are for this reason more like those of the amino group in aniline or other primary aromatic amines (182a; *cf.* 596a, 691a). While 3-aminopyridine forms a dihydrochloride, 2- and 4-aminopyridines form only monohydrochlorides (596a, 692), indicating that they are less basic. Although 3-aminopyridine can be diazotized in the usual manner, the formation of a diazo derivative of 2-aminopyridine is accomplished only by treating the sodium salt of 2-aminopyridine with amyl nitrite in ethereal solution. Direct diazotization of 2-aminopyridine in sulfuric acid solution, and also under other conditions, gives 2-hydroxypyridine (108a, 156); diazotization in hydrofluoric acid (156), in hydrochloric acid (156), or in hydrobromic acid (156, 182) gives, respectively, 2-fluoropyridine (25 per cent yield), 2-chloropyridine (not over 50 per cent), and 2-bromopyridine (87 per cent yield). Careful acidification of a solution of the diazo oxide prepared from 2-aminopyridine and mixed with potassium iodide gives 2-iodopyridine (156).

Nitration of 2-aminopyridine first gives the mixed anhydride of the ammono aquo acid ester, 2-aminopyridine, and aquonitric acid, $C_5H_4N \cdot NHNO_2$ (154). When warmed in concentrated sulfuric acid solution, isomerization to 3- and 5-nitro-2-aminopyridine occurs (139). At the same time, some 2-hydroxypyridine is formed by a process which amounts to the hydrolysis of a cylic ammono acid ester (2-aminopyridine) to a cyclic ammono aquo acid ester (2-hydroxypyridine (139). Better yields of 2-hydroxypyridine (about 60 per cent) are obtained by boiling 2-nitraminopyridine, $C_5H_4N \cdot NHNO_2$, with acetic anhydride and glacial acetic acid, the other product being nitrous oxide, an anhydride of ammonoaquonitric acid (324).

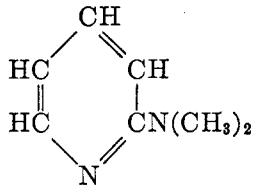
Methylation of 2-aminopyridine by heating with methyl iodide alone gives 1-methyl-2-pyridone imide (V) (141b, 141c, 142),



V



VI



VII

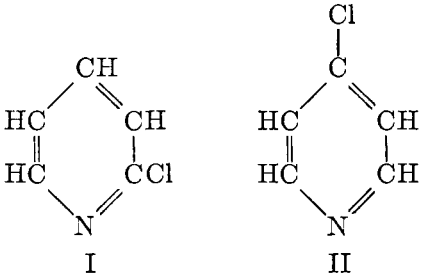
while methylation of sodium 2-aminopyridine gives monomethylaminopyridine (VI) and dimethylaminopyridine (VII). The two methylated aminopyridines can be separated by fractional distillation, after acetylation of the mixture. There is little in the literature concerning the mobility of the methylamino or dimethylamino group of the above compounds, VI and VII, but it is apparently rather low in spite of the fact that VI is a cyclic ammono acid ester, and VII is a cyclic ammono ester (140, 141, 141d, 142, 153, 158). Chichibabin and Knunianz

(140) heated 2-dimethylaminopyridine (VII) with sodium amide for some hours at 190°C. and prepared 2,6-diaminopyridine. In this process, a dimethylamino group was split off, albeit somewhat reluctantly, and 2-aminopyridine formed. Introduction of a second amino group gives 2,6-diaminopyridine. Of course, 2-dimethylamino-6-aminopyridine could be the first reaction product, for the order of the steps is unknown. The replacement of dimethylamino by amino is to be compared to the saponification of an ester.

Like 2-aminopyridine, 2,6-diaminopyridine and 2-amino-6-hydroxypyridine are mono acid bases (754a). When 2,6-diaminopyridine is heated with 70 per cent sulfuric acid on the water bath for 2 hr., one amino group is almost quantitatively replaced by hydroxyl (754a). Seide and Titov (754a) believe that the mobile amino group is attached to doubly bonded carbon, thereby making the assumption that the bonds of 2- or 2,6-substituted pyridines are sensibly static.

M. HALOGEN SUBSTITUTION PRODUCTS OF PYRIDINE

It has been previously shown that 2-chloropyridine (I) is a cyclic ammono acid chloride ester, while 4-chloropyridine (II) is its vinylogue.

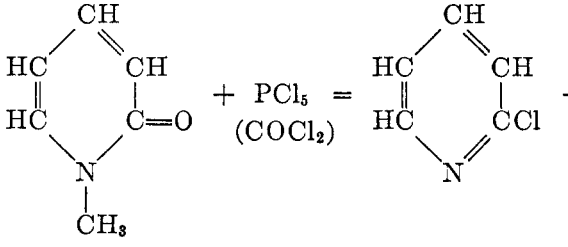


I II

Activation of halogen in the 2- or 4-position is therefore to be expected. The reactivity of the halogen in the 3-halogenopyridines will be of the same order as in the phenyl halides.

1. Preparation

2-Chloropyridine may be made from 2-aminopyridine through pyridine 2-diazotate (see Section II, L), as well as by the action of phosgene or phosphorus pentachloride on the *N*-alkyl-2-pyridones (295, 672, 682, 699) or on 2-hydroxypyridine (386), in accordance with equations 44 and 45:



$$+ PCl_5 \ (COCl_2) = + POCl_3 + CH_3Cl \quad (44)$$

$$C_5H_4NOH + PCl_5 = C_5H_4NCl + HCl + POCl_3 \quad (45)$$

The reaction of equation 45 is the conversion of an ammono aquo acid ester to an ammono acid chloride ester. In the reaction of equation 44, a cyclic ammono aquo ester is changed to an ammono acid chloride ester, just as acetyl chloride and ethyl chloride are formed when ethyl acetate is heated at 140–150°C. with phosphorus pentachloride (602), or as benzoyl chloride is similarly prepared from methyl benzoate (21).

Direct chlorination of pyridine in the vapor phase at 270°C. results in a fairly good (31–46 per cent) yield of 2-chloropyridine, together with a smaller amount of 2,6-dichloropyridine (814f). Chlorination at the lower temperature of 200°C. gives 3,5-dichloro-, 3,4,5-trichloro-, and pentachloro-pyridines; the first named is also formed by chlorinating fused pyridine hydrochloride (715f, 814g).

3-Chloropyridine may be made from 3-aminopyridine through the diazonium salt (71a). 4-Chloropyridine is best prepared by the methods of equation 44 or 45 (303, 383a, 813b), but it may also be obtained, mixed with an isomer, by treating pyridine *N*-oxide with sulfuryl chloride (77a) or by the action of hydrochloric acid on 4-nitraminopyridine (500a).

2-Bromopyridine has been prepared from 2-aminopyridine through the isodiazotate (Section II, L), or from the *N*-alkylpyridones in the manner of equation 44 (298). It may be made, together with 2,6-dibromopyridine, by the vapor-phase bromination of pyridine at 500°C., according to den Hertog and Wibaut (424). McElvain and Goese (567b) have modified this synthesis by preheating the bromine and pyridine vapors before they reach the reaction chamber.

Vapor-phase bromination at 300–350°C. gives 3-bromo- and 3,5-dibromopyridines (424; *cf.* 567b), but the preparation of large quantities of both of these compounds seems most readily accomplished by heating the perbromide of pyridine hydrobromide (or hydrochloride), $(C_5H_5NH)^+Br \cdot Br_2^-$, for 6 to 8 hr. at 230–250°C. (280a, 567b, 570a; *cf.* 106c). 3-Bromopyridine is also readily made from 3-aminopyridine through the diazonium salt (71a).

4-Bromopyridine is obtained by the action of phosphorus pentabromide and phosphorus oxybromide on 4-hydroxypyridine (813b, 814c) and by a series of reactions that start with 4-aminopyridine (814e).

The direct iodination of pyridine in the vapor phase has been accomplished (715c), though better results are obtained in the presence of an oxidizing agent, fuming sulfuric acid (715c), but even in this case the yield of 3-iodopyridine is only 18 per cent. Pentaiodopyridine may be formed in yields as high as 37 per cent by heating iodine and pyridine hydrochloride (567b, 715d). Baumgarten (41a) treated the open-chain glutacondialdehyde derivative,

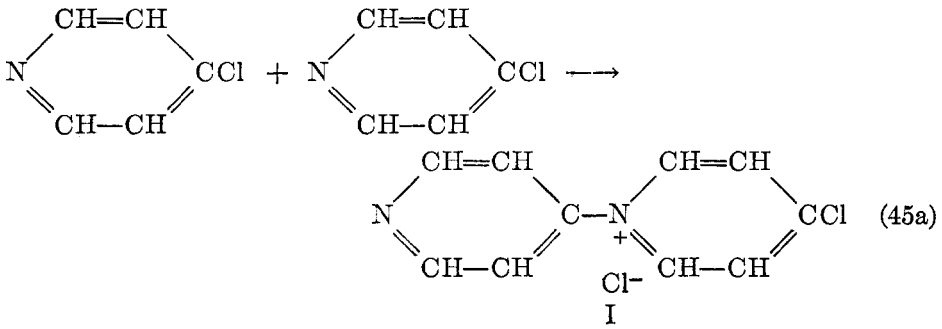
$$NaOCH{=}CH{-}CH{=}CH{-}CH{=}N{-}SO_3Na$$

with iodine and potassium acetate, to prepare a mixture of 3-iodo- and 3,5-diiodo-pyridines, with the latter predominating. 3-Iodopyridine can of course be made from 3-aminopyridine by the usual methods (71a, 699a).

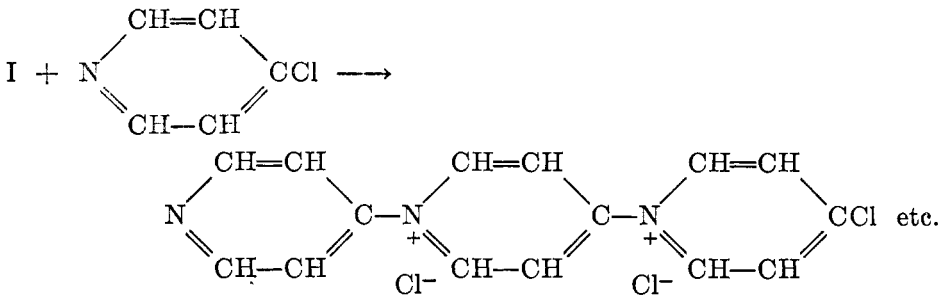
2. Instability of the 4-halogenopyridines

While the 2-halogenopyridines are stable and may be stored for some time without serious decomposition, 4-chloro- and 4-bromo-pyridines are very re-

active and therefore difficult to keep. Haitinger and Lieben (383a) commented on this instability many years ago. Wibaut and coworkers (813a, 814c) find that 4-bromopyridine turns to a solid if kept in a sealed tube overnight, and decomposes violently when an attempt is made to analyze it by the usual combustion method. 4-Chloropyridine is a little more stable, but it will slowly solidify over a period of days, perhaps in the manner of the following equations (813a):

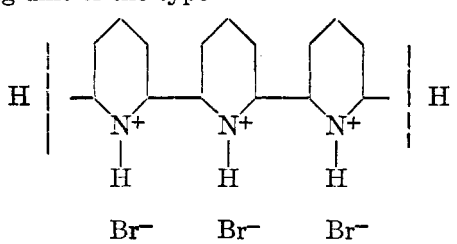


(45a)



Steric factors appear to prevent the similar intermolecular condensations of the 2-halogenopyridines.

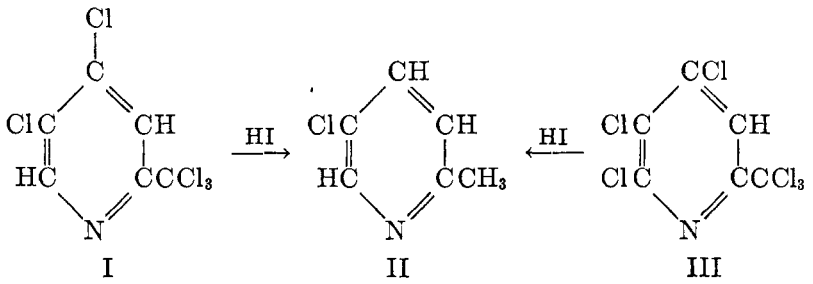
McElvain and Goese (567b), in attempting to prepare 3-bromopyridine by the method of den Hertog and Wibaut (424), found that their reaction tube became plugged periodically with a black solid, particularly if pyridine was in excess. The same solid was obtained when excess pyridine and pyridine hydrobromide perbromide were heated together (567b). Analysis of the free base obtained by adding alkali to an aqueous solution of the black mass indicated that this latter contained a repeating unit of the type



The nuclei may, of course, be united in the 2,4′- or in the 4,4′-positions. The average polymer is believed to contain four pyridine rings, indicating a possible relationship with the 2,2′,2″-tripyridyl of Morgan and Burstall (627).

3. Comparison of reactivity of halogen in the 2-, 3- and 4-positions

A pentachloro-2-picoline (I) and hexachloro-2-picoline (III) mixture is partially reduced when heated with hydrogen iodide with the formation of 5-chloro-2-methylpyridine (II). The reduction has therefore affected all of the chlorine atoms except the one in the 5-position, which is the most inert (648a).



I II III

2-Chloro-5-iodopyridine is converted to 2-methoxy-5-iodopyridine by heating for 4 hr. with methyl alcoholic sodium methylate on the water bath (571b). Räth (700a) has prepared 5-halogenopyridine-2-thiols by heating 2-chloro-5-(chloro, bromo, iodo)pyridine with alcoholic potassium hydrosulfide.

It is clear that, as expected, a halogen in the 3-position is the least reactive. A definite comparison of the mobility of chlorine or bromine in the 2- or 4-position of the pyridine ring does not seem possible at the present time, since the self-condensation of the 4-(but not of the 2-)halogenopyridines may be partially explained by steric considerations. Wibaut, Bickel, and Brandon (814j) report that a poor yield of 2,6-diamino-4-bromopyridine is obtained by high-temperature ammonolysis of 2,4,6-tribromopyridine, but it is unsafe to draw conclusions from this evidence alone.

4. Reactivity of chlorine or bromine in the 2-position

2-Chloropyridine reacts with aqueous ammonia in the presence of a copper sulfate catalyst (6 hr. at 250°C.) to form 2-aminopyridine (653b). The latter may also be prepared by heating 2-chloropyridine with zinc chloride–ammonia at 220°C. (297), or by the ammonolysis of 2-bromopyridine at elevated temperatures (423a, 424a). 2-Amino-6-bromopyridine and 2,6-dibromopyridine are similarly made from 2,6-dibromopyridine (423a, 424a; *cf.* 814g), and the latter also reacts with piperidine with replacement of one or both bromines by piperidino residues (424a; *cf.* 814h).

2-Anilinopyridine, $C_5H_4NNHC_6H_5$, may be prepared by heating 2-chloropyridine with zinc chloride–aniline at 200°C. (298, 307); other aromatic amines react similarly (307). Somewhat better yields of 2-anilinopyridine are obtained by refluxing 2-chloropyridine with aniline (1.5 hr.; 93 per cent yield) (814h).

Gray (379a) prepared 4-(2′-pyridylamino)benzenesulfonamide

$$C_5H_4NNHC_6H_4SO_2NH_2\text{-}p$$

by heating *p*-aminobenzenesulfonamide with 2-chloropyridine for 15 hr. at 140°C., while Phillips (686a) made the isomeric 2-(4′-aminobenzenesulfonamido)-pyridine

$$C_5H_4NNHSO_2C_6H_4NH_2\text{-}p$$

by heating 2-bromopyridine and sulfanilamide with anhydrous potassium carbonate and a trace of copper powder (180°C., 3 hr.). A potassium salt of sulfanilamide, $NH_2C_6H_4SO_2NHK$, appears to be an intermediate in this second reaction.

Replacement of the 2-chlorine is readily accomplished by heating with acid or with alkali (653a, 671). 2,6-Dibromopyridine is partly hydrolyzed to 2-bromo-6-hydroxypyridine by heating for 3 hr. with 80 per cent phosphoric acid in a sealed tube (813c); the same result may be accomplished by an aqueous alcoholic solution of alkali at 90°C. (813c). Wibaut and his coworkers (813c) point out that the rate of the acid hydrolysis is doubtless increased by the positive charge on the nitrogen of the dibromopyridine phosphate.

2-Methoxypyridine has been made by heating 2-chloropyridine with methyl alcoholic sodium methylate solution (379, 384) (see Section II, M, 4), while 2-benzyloxypyridine and many 2-aryloxypyridines have been prepared by heating the corresponding sodium alcoholate or sodium phenolate with 2-bromopyridine (710a). The 2- and 6-alkoxynicotines and 2- and 6-aryloxynicotines are similarly formed from the 2- or 6-halogenonicotines (106a).

den Hertog and Wibaut (424a) prepared 2-ethoxy-6-bromopyridine by heating 2,6-dibromopyridine with sodium hydroxide in alcohol for 4–5 hr. The 2,6-diethoxypyridine was formed only at higher temperatures (6 hr. at 160°C.).

Pyridine-2-thiol is the product of the action of an alcoholic solution of potassium hydrosulfide on 2-chloropyridine (586) or 2-iodopyridine (372a). 2-Chloropyridine can be successfully used in a modified Grignard reaction (650a; *cf.* 129, 413a, 424a). Picolinonitrile (2-cyanopyridine) is readily obtained by heating 2-chloropyridine with cuprous cyanide (182). It is tentatively reported that 2,6-dibromopyridine is catalytically reduced to pyridine in alkaline solution in the presence of nickel (814j). 2-Chloropyridine may be hydrogenated to pyridine and then to piperidine (379).

5. 2-Chloro-5-nitropyridine: activating effect of the —C=N— linkage

2-Chloro-5-nitropyridine is made by the general methods of equations 44 and 45 from the *N*-alkyl-5-nitro-2-pyridones or from 2-hydroxy-5-nitropyridine (106d, 572, 686a, 699). The chlorine is activated, not only by the cyclic —C=N— group, but also by the nitro group in the para position with respect to it. As the result of comparative experiments, Mangini and Frenguelli (572) have concluded that chlorine in 2,5-dinitrochlorobenzene is the more reactive, indicating that the halogen is affected more by an ortho nitro group than by —C=N— in the same position.

The high mobility of the chlorine in 2-chloro-5-nitropyridine makes it a

valuable intermediate in the synthesis of pyridine derivatives. Catalytic hydrogenation, best with a palladium–calcium carbonate catalyst, not only reduces the nitro group but also replaces the chlorine with hydrogen to give 3-aminopyridine, (72a, 72b), which is otherwise not readily available. Reduction in a similar manner in alcoholic sodium hydroxide solution yields 2-alkoxy-5-aminopyridines (72a).

2-Hydrazino-5-nitropyridine is formed quantitatively from 2-chloro-5-nitropyridine and hydrazine in aqueous solution (572, 698a). It is converted by catalytic oxidation to 3-nitropyridine (702d), which is obtained in very poor yield by direct nitration of pyridine. Short boiling with alcoholic solutions of primary aromatic amines or with piperidine replaces the 2-chlorine with substituted amino groups (572; *cf.* 742a). *p*-(5′-Nitro-2′-pyridylamino)benzenesulfonamide may be made by heating sulfanilamide with 2-chloro-5-nitropyridine for 15 min. at 170°C. (686a).

5,5′-Dinitro-2,2′-dipyridyl sulfide (788a; *cf.* 788) and 5-nitropyridine-2-thiol (106d) have been prepared individually by the action of thiourea on 2-chloro-5-nitropyridine under different conditions.

6. Reactivity of halogen in the 3-position

3-Bromo- and 3,5-dibromopyridines are found to be much less reactive than the 2- and 2,6-halogenated pyridines described in the preceding paragraphs. Reduction of 3-bromopyridine with hydrazine hydrate, in the presence of palladized calcium carbonate, gives 3,3′-dipyridyl (106c) and high-temperature ammonolysis with aqueous ammonia and copper sulfate yields 3-aminopyridine (424a, 570a). 3-Methoxypyridine is formed by heating 3-bromopyridine for 2 days with alcoholic potash at 150°C. (496, 807). 3-Cyanopyridine (nicotinonitrile) may be prepared by heating 3-bromopyridine with cuprous cyanide at 165–170°C. (1 hr.; 567c).

High-temperature ammonolysis of 3,5-dibromopyridine by concentrated aqueous ammonia in the presence of copper sulfate (30 hr., 200°C.) gives 3-amino-5-bromopyridine (424a, 585b) or 3,5-diaminopyridine (424a, 570a).

Attempted formation of the Grignard reagent from 3-bromo- or 3,5-dibromopyridine was unsuccessful (413a), though 3-pyridyllithium was prepared from 3-bromopyridine and butyllithium in ether (373b, 772b).

7. Reactivity of 4-chloro- and 4-bromopyridines

Reactions with the above-named compounds should be carried out shortly after their preparation, to avoid the self-condensations that have been previously described (see II, M, 2).

4-Aminopyridine is obtained either by heating 4-chloropyridine with zinc chloride–ammonia (4–5 hr. at 220–230°C.) (279) or by heating 4-bromopyridine with concentrated aqueous ammonia for 8 hr. at 200°C. (814d). 4-Amino- and 4-anilinopyridines can be prepared from 4-pyridylpyridinium dichloride (497a, 497b).

Renshaw and Conn (710a) have made 4-butoxy-, 4-phenoxy-, 4-cresoxy-

pyridines and related "ethers" by heating 4-pyridylpyridinium dichloride with alcohol or phenol, in accordance with the original method of Koenigs and Greiner (497a, 497b).

4-Methoxypyridine has been prepared by heating 4-chloropyridine with methyl alcoholic sodium methylate at 100°C. (388; *cf.* 710a), and pyridine-4-thiol is similarly obtained, but at higher temperature (140°C.), from 4-chloropyridine and alcholic potassium hydrosulfide (500).

3,4,5-Trihalogenopyridines, when heated with alkali hydrosulfides, give 3,5-dihalogenopyridine-4-thiols (260c), which may be oxidized to the corresponding 4-sulfonic acids (260a, 260c). The latter may also be prepared by heating the 3,4,5-trihalogenopyridines with alkali bisulfite (260a). The sulfonic acid group in the 4-position is mobile, and may be replaced by an amino or phenylamino group when heated with ammonia or aniline, respectively (260b).

When 4-chloropyridine is heated in a sealed tube for a long time with concentrated hydrogen iodide solution, 4-iodopyridine hydroiodide and pyridine hydroiodide are formed successively, the latter requiring the higher temperature (383a). Catalytic hydrogenation of 2,6-diamino-4-bromopyridine with nickel in alkaline solution gives 2,6-diaminopyridine (814j).

N. PYRIDINECARBOXYLIC ACIDS

The effect of the —C=N— group in activating a substituent in the 2- or 4-position of the pyridine ring is generally rather pronounced, as has been shown in the preceding section. Pyridine-2-carboxylic acid (picolinic acid) is analogous to an α-keto acid of the water system, while pyridine-4-carboxylic acid (isonicotinic acid) may be regarded as a vinylogue. The literature does not allow us to differentiate between their stabilities toward heat, since the melting points increase uniformly with distance from the nitrogen, that of picolinic acid being 138°C., of nicotinic acid 232°C., and of isonicotinic acid 317°C. While picolinic acid is a water–ammonia analogue of an α-ketonic acid, and nicotinic acid is similarly related to a β-keto acid, their stability is of course greater than expected because of the pyridine ring resonance.

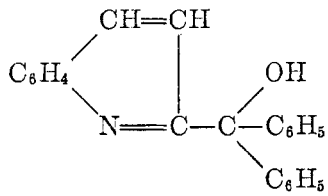
However, pyridine-2,3-dicarboxylic acid (quinolinic acid), when heated to 180–190°C., melts with gas evolution, and passes into pyridine-3-carboxylic acid (nicotinic acid) (108, 429). All pyridine di- or poly-carboxylic acids with one carboxyl in the 3-position similarly lose a 2- or 4-carboxyl to form nicotinic acid; the 2-carboxyl is the most readily lost (108, 571a, 647). The double bond between carbon and nitrogen in the pyridine ring therefore has some influence, particularly on carboxyl in the 2-position, and to a lesser degree on carboxyl in 4.

2-Pyridylacetic acid, $C_5H_4NCH_2COOH$, is analogous to a β-keto acid, such as acetoacetic acid, CH_3COCH_2COOH, since the —C=N— of the ring is analogous to carbonyl. Like acetoacetic acid, carbon dioxide is lost rather readily on heating, in this case only to 50–60°C. in aqueous solution. The methyl ester, like acetoacetic ester, is stable (646).

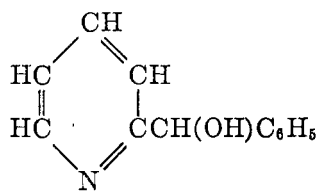
A rather peculiar reaction, dependent upon the proximity of carboxyl to the —C=N— of the ring, is reported by Ashworth, Daffern, and Hammick (16,

264). When 2-picolinic acid, and also quinoline-2-carboxylic acid or isoquinoline-1-carboxylic acid, are decarboxylated thermally in the presence of aldehydes or ketones, 2-pyridyl(2-quinolyl, 1-isoquinolyl)carbinols are formed. Typical reactions are the following:

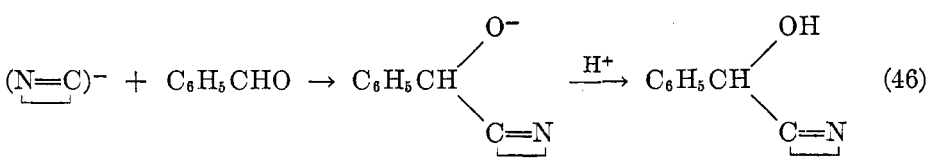
Quinoline-2-carboxylic acid (quinaldic acid) (2.5 g.) and benzophenone (25 g.) are heated for 2 hr. at 175°C., giving 3 g. of diphenyl(2-quinolyl)carbinol:



Picolinic acid (5 g.) and benzaldehyde (30 g.), heated for 1¼ hr. at 140°C., gave 3 cc. of phenyl(2-pyridyl)carbinol:

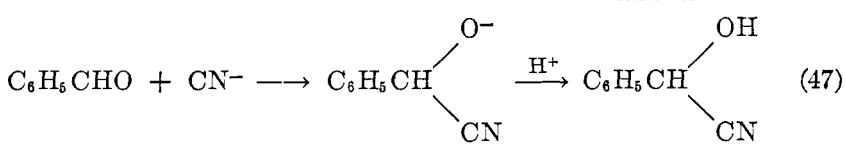


These reactions are specific for α-imino acids such as the two above. The suggestion is made that the anion radicals produced when these acids lose carbon dioxide contain a modified "cyanide ion" structure, $(\overline{N{=}C})^-$, which adds to the carbonyl group as does the cyanide ion in the familiar cyanohydrin reaction. The parallel equations are the following:



(46)

Phenyl(2-pyridyl) carbinol

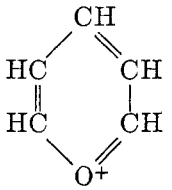


(47)

III. Some Cyclic Oxygen Compounds Related to Pyridine and Quinoline

Cyclic oxonium salts are known in considerable numbers, but it is impossible adequately to review their chemistry in an article devoted to heterocyclic nitro-

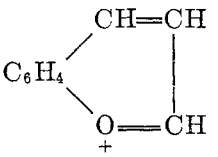
gen compounds. Representatives of a few of the principal types are shown below, together with their nitrogen analogues:



Cl⁻

I

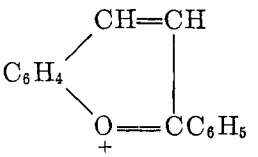
Pyrylium chloride



Cl⁻

II

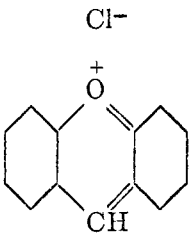
Benzopyrylium chloride



Cl⁻

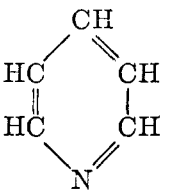
III

Flavylium chloride



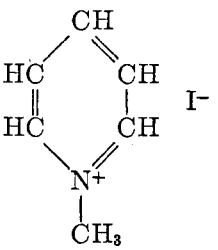
IV

Xanthylium chloride



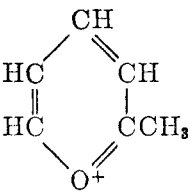
V

Pyridine



VI

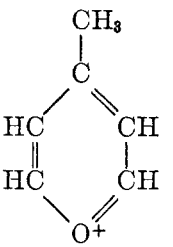
Methylpyridinium iodide



Cl⁻

VII

Methylpyrylium salts



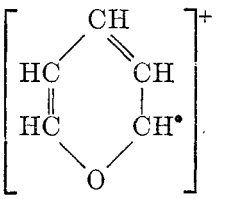
Cl⁻

VIII

Each of the oxygen compounds listed contains a —CH=$\overset{+}{O}$— or CH_3—$\overset{|}{C}$=$\overset{+}{O}$— group and so can be regarded as a type of cyclic aquo aldehyde (I, II, III, IV) or ketone (VII, VIII). It is true that the cyclic structure is possible only if the oxygen is positively charged; one may accordingly speak of the positive ions of (I–IV) or of (VII, VIII) as aldehydic or ketonic cations, respectively. The positive charge, which must be redistributed in some measure to the *o*- and *p*-positions of the ring by resonance, should result in an increase of the carbonyl re-

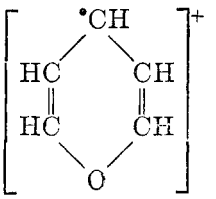
activity in transformations which concern basic reagents, as has proven to be the case with the related pyridinium (VI), quinolinium, and isoquinolinium salts (see Sections II, I; IV, N; V, G). The structural and chemical resemblance between oxonium salts and quaternary ammonium salts related to methylpyridinium iodide (VI) has been very clearly pointed out by Dilthey, Decker, and their coworkers (212, 247).

The formulas of the pyrylium, benzopyrylium, and xanthylium salts given above are not universally accepted, but are believed by some (*cf.* 425) to be the following (carbonium and carbenium theories):



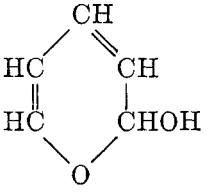
IX

or



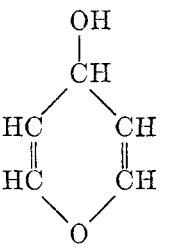
X

The anionic charge is localized for the most part on the ortho or para position, as indicated by the dots. The corresponding bases (XI and XII) should have the structures:



XI

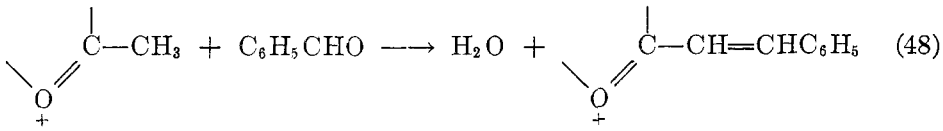
or



XII

The former, XI, is merely a cyclic hemiacetal; the latter, XII, its vinylogue. The salt (IX) might be compared with monochloromethyl methyl ether, $ClCH_2OCH_3$, or with dichloromethyl ether, $ClCH_2OCH_2Cl$, which contains chlorine intermediate in reactivity between that of an alkyl halide, RCH_2X, and an acid halide, RCOX. Both of the halogen-substituted methyl ethers can easily be converted to formaldehyde or its derivatives by the action of water, alcohol, or ammonia, and therefore can be said to act as a source of formaldehyde. Otherwise stated, the compounds that are obtained by replacing the hydroxyl group of a hemiacetal, RCH(OH)OR′, with halogen still have aldehydic reactivity.

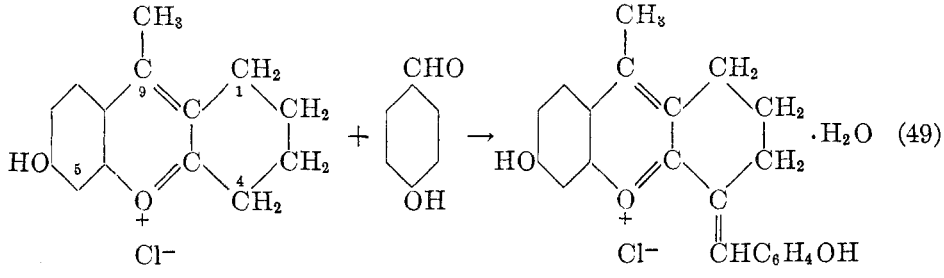
A methyl group in the 2-, 4-, or 6-position of a pyrylium salt and in the 2- or 4-position of a benzopyrylium salt resembles the same group in a methyl ketone in that styryl derivatives are readily formed by the action of aromatic aldehydes (82, 106, 246, 401, 415, 416, 744, 804, 804a; *cf.* 79). A partial equation is the following:



(48)

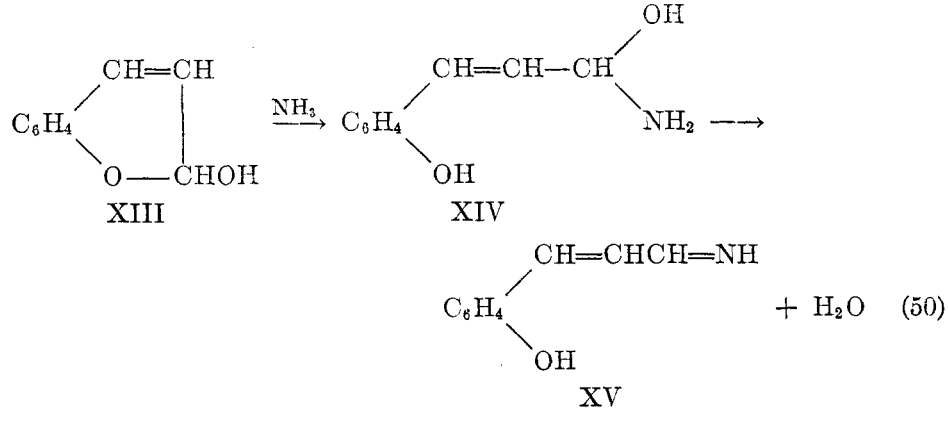
Styrylpyrylium and styrylxanthylium salts can of course also be made by ring closure reactions (*cf.* 80).

Methylene in the 4-position of a tetrahydroxanthylium salt appears more reactive than a 9-methyl group, since Borsche and Wunder (82a) report the following condensation:



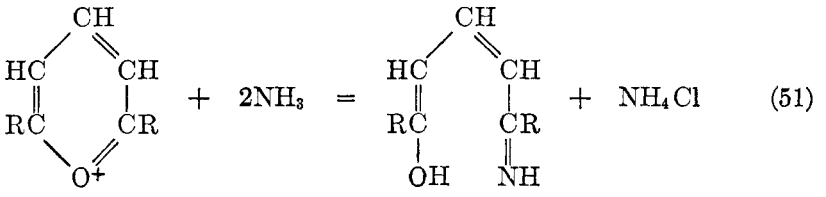
(49)

The reviewer was unable to find record of the ammonolysis of a simple benzopyrylium (II) or flavylium (III) salt to the corresponding quinoline. Perhaps in the very voluminous literature on these salts, such transformations have been described. Ammonia in aqueous solution supposedly first precipitates a pseudo base or pyranol (XIII):

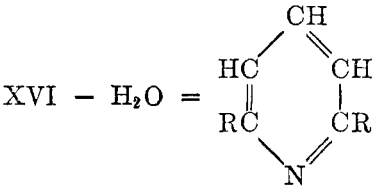


XIII XIV XV

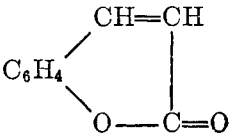
If ammonolysis occurs at this stage and the ring opens to form the hypothetical substance XIV, which will lose water to give XV, ring closure will give a quinoline derivative only if the phenolic hydroxyl is lost, a reaction that would be difficult. On the other hand, ammonolysis of a pyrylium salt will be much easier, since the loss of water from the (not isolated) intermediate (XVI), with resulting ring closure, involves a much more mobile enolic hydroxyl.



Cl⁻ XVI (51)



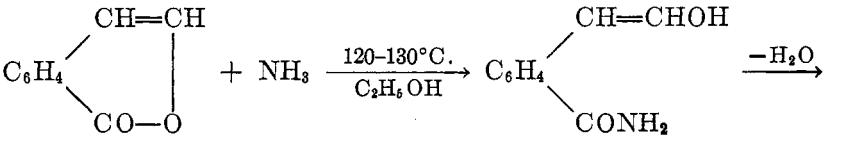
For similar reasons, the γ-pyrones are easily ammonolyzed to γ-pyridones Section II, B, 2), while quinolones or carbostyryls apparently cannot be made in a like manner from the related coumarins:



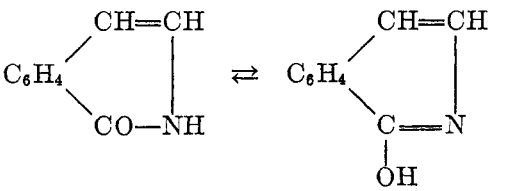
XVII

Ring opening with ammonia probably would give *o*-hydroxycinnamamide, $C_6H_4(OH)CH{=}CHCONH_2$, rather than *o*-aminocinnamic acid, $C_6H_4(NH_2)CH{=}CHCOOH$, although neither transformation seems to be on record. Coumarin (XVII) is an internal ester, and ammonolysis of esters usually gives an acid amide. While *o*-aminocinnamic acid can be converted to 2-hydroxyquinoline (carbostyryl), though not too readily (see Section IV, G), *o*-hydroxycinnamic acid apparently cannot be by the action of ammonia.

Isoquinoline derivatives can, on the other hand, be made without difficulty by the ammonolysis of isocoumarin or isocoumarincarboxylic acids (equations 145, 147; Section V, A, 4).



XVIII

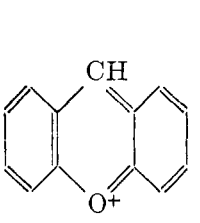


(52)

The enolic hydroxyl of the assumed intermediate (XVIII) will be more readily replaced by a substituted amino group (ammonolysis) than is the phenolic hydroxyl of *o*-hydroxycinnamamide.

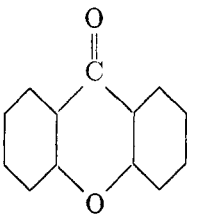
Expanded cyclic aquo acetals: xanthydrol

As many investigators have pointed out, xanthydrol (IV) is the pseudo base corresponding to the xanthylium salts (I); it is best made by reducing xanthone (II).

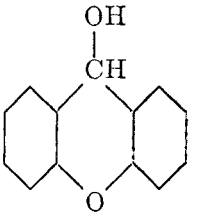


Cl^-

I



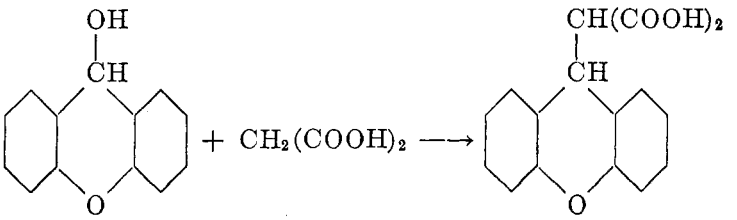
II



III

Since the grouping, —CH(OH)—C=COR, of xanthydrol (III) is equivalent to —CH(OH)OR by the principle of vinylogy (see Section I, I), xanthydrol is a vinylogue of an aquo hemiacetal, or, perhaps more simply, an expanded hemiacetal, if one uses the terminology of Ingold. Xanthone (II) is an expanded aquo ester.

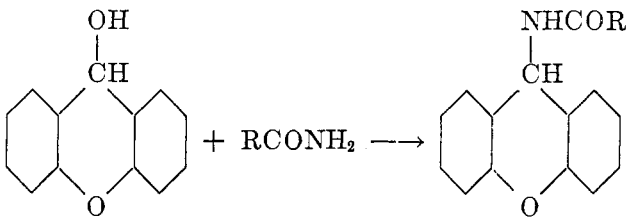
A large number of compounds with reactive methylene, or even with active hydrogen, condense readily with xanthydrol, as in the illustrative equation:



(52a)

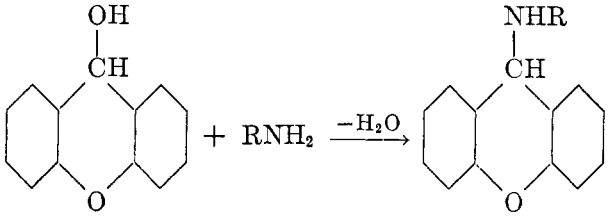
Among the substances that react in accordance with equations similar to 52a are the following: malonic acid (318a), malonic ester, acetylacetone, cyanoacetic esters, benzoylacetic esters, acetoacetic ester (318a, 318b, 318i), α- and β-substituted indoles (441c), thiophene and thionaphthene (8b), and pyrrole (441b).

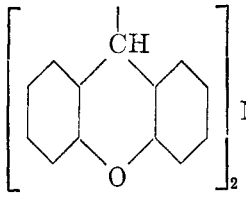
Aromatic amines and acid amides readily form xanthyl derivatives when treated with xanthydrol, in the manner of the following equations:



(52b)

Primary aromatic amines thus form mono- or di-xanthyl derivatives, depending upon conditions.





(52c)

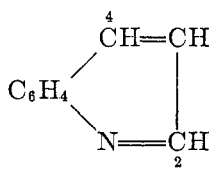
Among the nitrogenous compounds that react with xanthydrol are the following: fatty acid amides (318h), urea (8a, 318h; a dixanthyl derivative is formed), substituted ureas (2a), thiourea (318h), hydroxylamine (318a, 318g), semicarbazide (261a, 318a, 318g), indole and α- and β-substituted indoles (318f, 441c), isatin (441c), saccharin (285a), antipyrine (285a), veronal and other barbiturates (285a), aniline, toluidine, *o*-nitroaniline, diphenylamine, acetanilide, naphthylamine, etc. (2a, 318a), sulfamide and sulfonamides (819a).

Xanthydrol is used in the quantitative analysis of urea (8a, 318f) and many other compounds.

Dinaphthopyranol (*sym*-dibenzoxanthydrol) behaves chemically in the same manner as xanthydrol (318a, 318b, 318i).

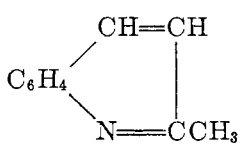
IV. Quinoline

Quinoline (I) is best regarded as a cyclic ammono aldehyde ether, whose reactivity should be somewhat greater than that of pyridine because of the activating influence of the fused benzene ring. Substituents in the 4- and 2-positions will have approximately the same function (principle of vinylogy, transmission of effects along a conjugated chain; Section I, I).

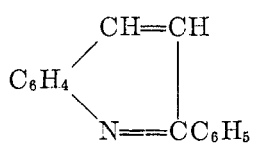


I

Cyclic aldehyde ether

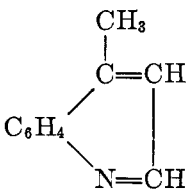


II

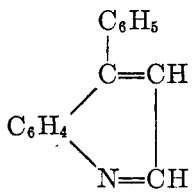


III

Cyclic ketone ethers

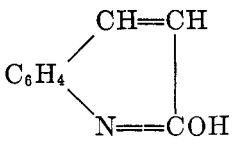


IV



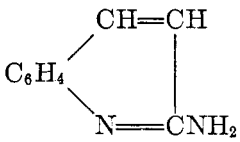
V

Vinylogues of ketone ethers



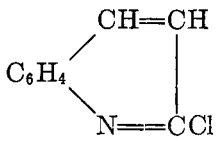
VI

Cyclic ammono aquo acid ester



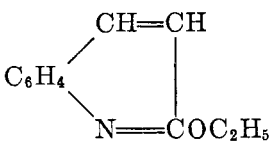
VII

Cyclic ammono acid ester



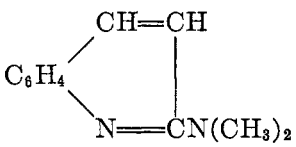
VIII

Cyclic ammono acid chloride ester



IX

Cyclic ammono aquo ester



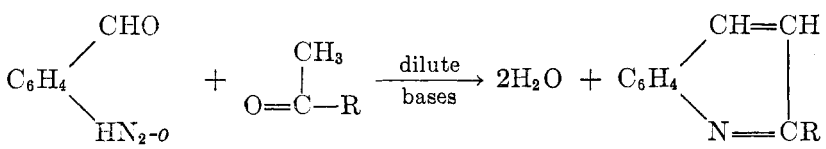
X

Cyclic ammono ester

A. SYNTHESIS OF QUINOLINE AND ITS DERIVATIVES

Since there is available a recent review concerning quinoline (584), the discussion of the methods of synthesis may be limited to the reactions that are the most readily interpreted in accordance with the point of view of the present article.

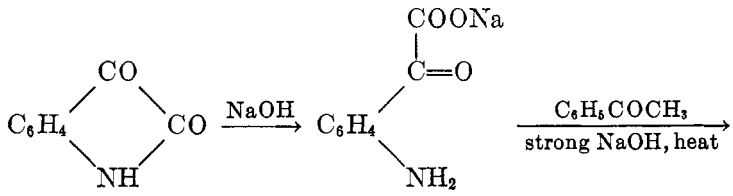
1. The Friedländer synthesis



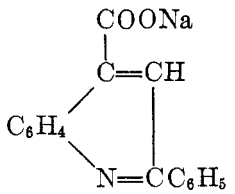
(53)

There are two distinct reactions involved: a Claisen reaction between the aldehyde group and the active methyl of the ketone, and an ammonolysis of the carbonyl group of the ketone by a substituted ammonia. The type of ammonolysis represented above is familiar as the method by which Schiff bases (ammono aldehyde ethers) are formed, and the Friedländer synthesis therefore indicates quinoline to be a cyclic Schiff base. Open-chain Schiff bases, RCH=NR′, have long been known to have aldehydic properties (321, 608, 609, 780, 782); in fact, the anils of *o*-aminobenzaldehyde, $C_6H_4(NH_2)CH{=}NR$, have recently been used by Borsche and Ried (81d) in a modification of the Friedländer synthesis.

2. The Pfitzinger synthesis



Isatin Sodium isatinate



(54)

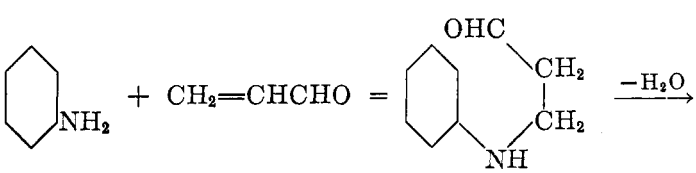
Sodium salt of cinchophen

This reaction is very similar to the Friedländer synthesis, but uses the more readily available isatin as a starting material instead of the comparatively unstable *o*-aminobenzaldehyde.

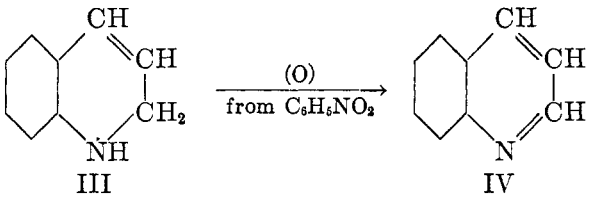
3. The Skraup synthesis

Quinoline and its derivatives are formed by heating a primary aromatic amine, the corresponding nitro compound (or arsenic acid, etc.), glycerol, and concentrated sulfuric acid, with the occasional addition of ferrous sulfate or boric acid to prevent too violent a reaction at the beginning. Clarke and Davis (162) with the latter modification have prepared quinoline in 84–91 per cent yields. Catalysts, such as thorium oxide, metavanadic acid, or vanadium pentoxide (184b, 234) and copper sulfate (474b), have been recommended, and the use of acetylated amines is believed by Manske (582, 583) to offer distinct advantages in some cases. 2-Ethylquinoline and several 3-alkyl- and -arylquinolines have been made by using substituted glycerol ethers in a modification of the Skraup synthesis (184a, 234, 799f, 806).

It is generally assumed that acrolein (I) is an intermediate in the Skraup synthesis as generally carried out (*cf.* 73a, 288b, 584). The inability to obtain significant yields of quinoline (IV) from the product of reaction of acrolein and aniline (109, 490, 573) may be construed as evidence of a negative character for some other intermediate, or it may only mean that acrolein must be generated *in situ* to avoid side reactions.



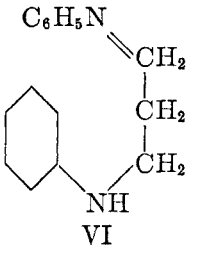
I II



(55)

$$CH_2{=}CHCHO + C_6H_5NH_2 \rightarrow CH_2{=}CHCH{=}NC_6H_5 \xrightarrow{C_6H_5NH_2}$$

V



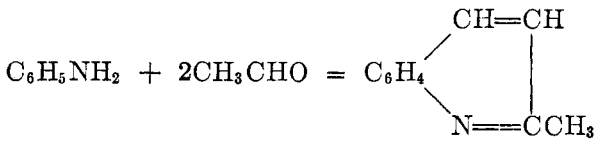
$\xrightarrow{-C_6H_5NH_2}$ III $\xrightarrow[C_6H_5NO_2]{(O)}$ IV (56)

In equation 56 the Schiff base, acrolein aniline (V), adds aniline to form VI, which by loss of aniline is cyclized to dihydroquinoline (III), The addition of aniline to a carbon-to-carbon double bond conjugated with —CH=N— is reasonable, since Bruson and Riener (102, where earlier references are given; 105c, 656) have carried out many related reactions with acrylonitrile, $CH_2{=}CHC{\equiv}N$. Whether II or VI or some other compound (73, 506a, 584) is the true intermediate in the Skraup synthesis will depend upon whether or not it is formed in sufficient concentration under the conditions of the experiment. The fact that Schiff bases may be hydrolyzed by heating with dilute acids might argue against V or VI (702c).

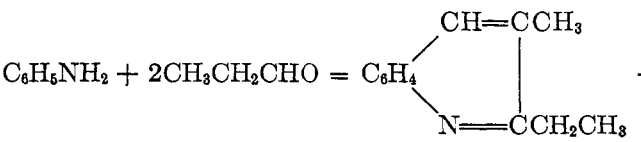
Regardless of the mechanism assumed, the cyclization is the result of the loss of water or of aniline by attack of the aldehydic terminal of a side chain on a ring hydrogen in the ortho position. Whether this is preceded by isomerization of II or V to an enol or to the related enamine is not known (*cf.* 775).

4. The Döbner–(von) Miller synthesis

When aldehydes or polymerized aldehydes, such as paraldehyde, are refluxed for several hours with concentrated hydrochloric acid, quinoline derivatives are formed in accordance with the over-all equations:



(57)



(58)

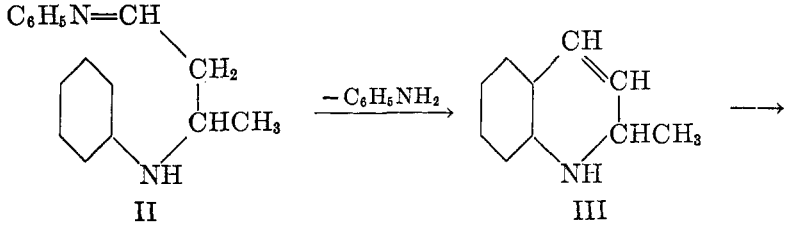
The alkyl in position 2 always has one more carbon than the one in position 3.

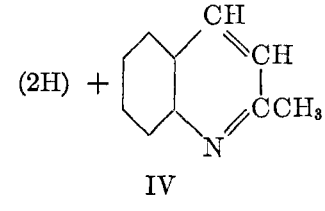
As will be seen further on, a dihydroquinoline is usually believed to be intermediate in the reaction. It is generally thought that this is reduced by the hydrogen (=2H) to a tetrahydroquinoline (*cf.* 445), but Mills and coworkers (614) were unable to isolate any compound of this type in a Döbner–Miller synthesis of quinaldine from acetaldehyde, aniline, hydrochloric acid, and zinc chloride. They obtained instead a mixture of ethylaniline and butylaniline, in approximately equal amounts, apparently as the result of a reduction of ethylideneaniline, $CH_3CH{=}NC_6H_5$, and crotonylideneaniline, $CH_3CH{=}CHCH{=}NC_6H_5$, respectively. The latter is probably obtained from the former by the action of acetaldehyde. At the same time there was isolated a smaller amount of 6-ethylquinaldine.

One mechanism proposed long ago by Döbner and von Miller is the following (255a; *cf.* 73, 288b, 607, 608, 609a):

$$CH_3CHO + C_6H_5NH_2 = \underset{\text{I}}{CH_3CH{=}NC_6H_5} + H_2O \qquad (57)$$

$$2CH_3CH{=}NC_6H_5 = \underset{\text{I}}{} \quad \underset{\text{II}}{CH_3CHNHC_6H_5 \text{ with } CH_2CH{=}NC_6H_5}$$

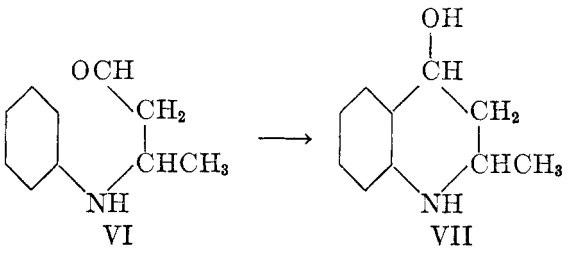




(57)

Ethylideneaniline (I), a Schiff base, is an ammono aldehyde ether. It undergoes an aldol condensation to give II, whose relationship to ordinary aldol is made apparent by replacing OH with NHC_6H_5 and =O with $=NC_6H_5$ in the formula $CH_3CH(OH)CH_2CHO$. Cyclization is effected by loss of aniline to give dihydroquinaldine (III), which has not been isolated since it gives quinaldine and tetrahydroquinaldine by dismutation, or else it loses two hydrogens to the Schiff base (I) to form ethylaniline, $CH_3CH_2NHC_6H_5$, as in the experiments of Mills (614). More recently, Jones and collaborators (268, 372, 446) and Mills, Harris, and Lambourne (614) have given evidence for believing that the "aldol bases" of Miller and Plöchl (609b) are intermediates in the Döbner–Miller synthesis.

These compounds (VII) may be regarded as formed from open-chain amino-aldehydes (VI) in accordance with the equation:



(58)

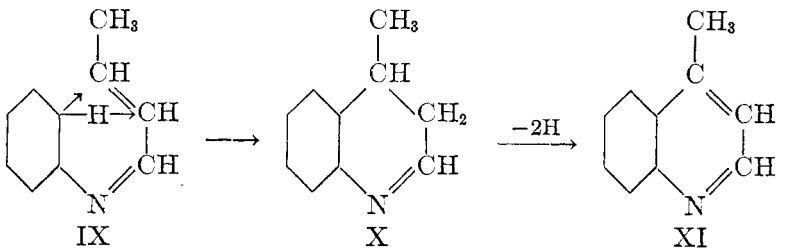
The similarity to the last step of the Skraup reaction is apparent, since cyclization takes place because of the attack of the terminal aldehydic group of a side chain upon an ortho hydrogen of the ring. This is also true of the reaction of equation 57. An intermediate similar to the "aldol base" (VII) is of course possible in the Skraup synthesis, and it is unnecessary to say that enolization precedes ring closure.

The precursor of the aldol base, possibly VI, may be formed by the hydrolysis of the ammono aldol (II), with replacement of $=NC_6H_5$ by $=O$, or by the aldol condensation of ethylideneaniline (I) with aquoacetaldehyde in accordance with the equation:

$$CH_3CHO + CH_3CH{=}NC_6H_5 \longrightarrow \underset{\text{VIII}}{CH_3CH(OH)CH_2CH{=}NC_6H_5}$$

$$\text{or } \underset{\text{VI}}{CH_3CH(CH_2CHO)NHC_6H_5} \qquad (58a)$$

By loss of water, VIII passes into crotonylideneaniline (IX), $CH_3CH{=}CHCH{=}NC_6H_5$, the reduction of which gives the butylaniline obtained by Mills and his students (614). Cyclization of IX should proceed in accordance with equation 58b to give 4-methyl-3,4-dihydroquinoline (X).



(58b)

Dehydrogenation of X will give lepidine (XI), but no 4-substituted quinolines appear ever to have been isolated in the Döbner–Miller synthesis. This is an excellent indication that ring closure goes most readily if the end of the side chain is a group of aldehydic or ketonic function, such as —CHO, —CH=NC_6H_5, —$CH(OC_2H_5)_2$, —COR, or —$CH(NR_2)_2$ (*cf.* equations 57, 58).

It is reasonable to say that the actual intermediate in any quinoline synthesis must be capable of formation in concentration sufficiently great to account for the speed of the overall reaction. Therefore, reactivities being approximately equal, the intermediate is the one that is most likely to be present under the prevailing conditions of acidity and temperature. It is possible that both II and VI or VII will contribute toward the formation of quinaldine, though doubtless to unequal extents, since Schiff bases may be hydrolyzed in acid solution (702c).

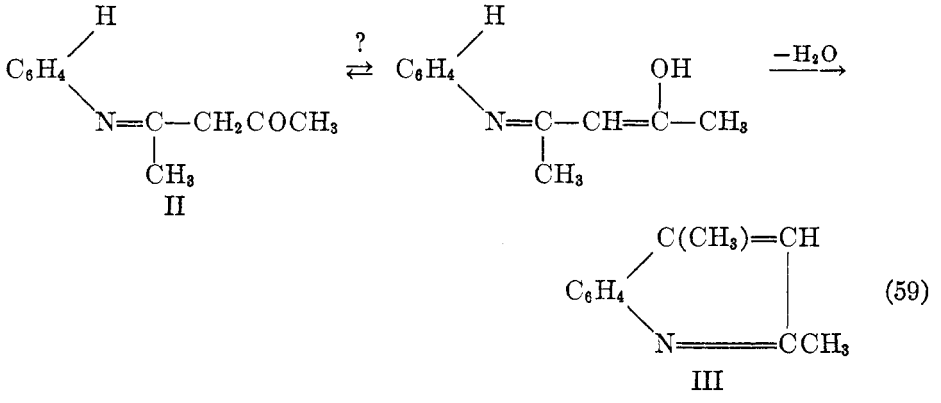
Roberts and Turner (713) have given a good discussion of the effect of substituents upon the ring closure of the Döbner–Miller and related syntheses.

5. The Combes synthesis

The fundamental Combes synthesis (175) is best illustrated by the formation of 2, 4-dimethylquinoline in the manner of the following equation:

$$C_6H_5NH_2 + CH_3COCH_2COCH_3 = H_2O + CH_3COCH_2C(=NC_6H_5)CH_3$$

I: Acetylacetone — II: Monoanil of acetylacetone

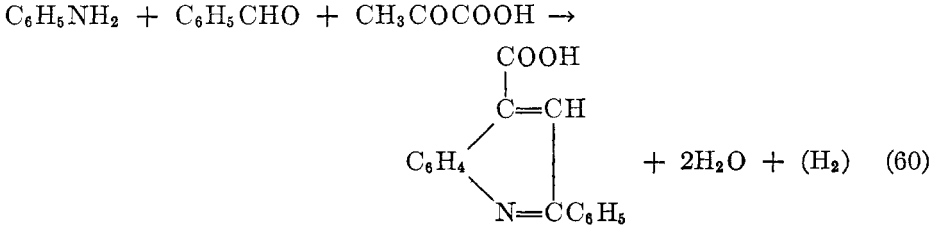


(59)

Factors that influence this synthesis have been discussed by Roberts and Turner (712).

6. The Döbner reaction (Döbner's cinchoninic acid synthesis)

A substituted cinchoninic acid (quinoline-4-carboxylic acid) is formed by heating an aromatic amine with pyruvic acid and an aldehyde (253, 254), generally in alcoholic solution. The preparation of cinchophen (2-phenylquinoline-4-carboxylic acid) proceeds in accordance with the following equation:



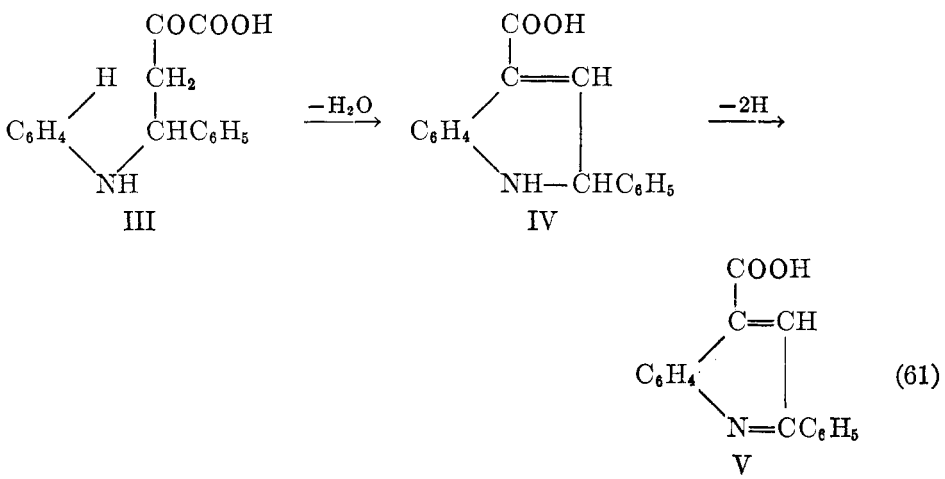
(60)

The hydrogen is not liberated as gas, but reduces the cinchoninic acids to their tetrahydrides, or the Schiff base formed from the amine and aldehyde to the corresponding secondary amine. Perhaps the most satisfactory mechanism is the one proposed by Ciusa and Musajo (161a), and shown below:

$$C_6H_5CHO + C_6H_5NH_2 = H_2O + \underset{\text{I}}{C_6H_5CH{=}NC_6H_5}$$

$$C_6H_5N{=}CHC_6H_5 + CH_3COCOOH = \underset{\text{III}}{C_6H_5NHCHCH_2COCOOH}$$

$$\underset{\text{I}}{\text{Schiff base}} \qquad \underset{\text{II}}{\text{pyruvic acid}} \qquad \underset{\text{III}}{\text{aldol}}$$



(61)

The first step represents the formation of a Schiff base, benzylideneaniline which, as an ammono aldehyde ether, undergoes an aldol condensation with pyruvic acid (II) to give the intermediate, III. This is cyclized by loss of water to the dihydrocinchophen (IV), which is oxidized at its own expense to form cinchophen (V) and its tetrahydride. Since the amount of the latter is always less than that of the unreduced V, some of the Schiff base (I) is reduced to the corresponding secondary amine, benzylaniline. Written in this manner, the Döbner reaction bears rather close relationship to the Skraup, Döbner–Miller, and Combes syntheses.

Carrara (110) formulates the Döbner reaction in a somewhat more complex fashion, to take account of the large yields of resin and of reduced Schiff base. In one experiment, pyruvic acid (40 g.) was added dropwise to a boiling solution of aniline (67 g.) and benzaldehyde (76 g.) in 1200 cc. of alcohol. From the approximately 100 g. of resin was isolated 80–90 g. of benzylaniline. The yield of cinchophen was only 6–7 g.

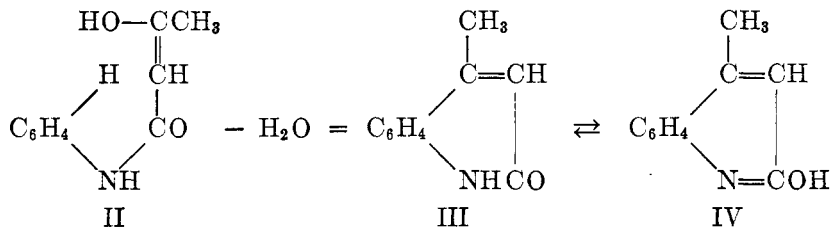
7. The synthesis of lepidones

Acetoacetic ester and aniline react to form acetoacetanilide (I, II), which is readily cyclized to lepidone (III, IV) by warming with concentrated sulfuric

acid on the water bath (483a, 657). Lepidone may readily be converted to 2-chlorolepidine by the action of phosphorus halides, and this in turn may be reduced to lepidine (540, 606; *cf.* 51). Some modifications and improvements of the original Knorr method have been described (6, 606, 606a, 629). Equations follow.

$$CH_3COCH_2COOC_2H_5 + C_6H_5NH_2 \xrightarrow[130\text{–}140°C.]{3\text{–}4\ hr.} CH_3COCH_2CONHC_6H_5 \rightleftarrows CH_3C(OH)=CHCONHC_6H_5$$

I II



II III IV (62)

It is to be noted again that cyclization occurs as a result of the attack of the ketonic end of a side chain upon an ortho ring hydrogen.

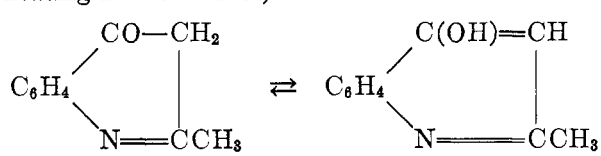
8. The synthesis of quinaldones

The isomeric quinaldones (such as 2-methyl-4-hydroxyquinoline) are made by heating β-phenyliminobutyric acid esters, or their derivatives, to about 240°C. (176a, 176b, 485, 774), in the manner expressed by the following equations:

$$CH_3COCH_2COOCH_3 + C_6H_5NH_2 \xrightarrow[\text{in cold}]{\text{about 2 days}} CH_3C(=NC_6H_5)CH_2COOCH_3 \quad (176b)$$

I

$$I - CH_3OH \text{ (short heating at 240–250°C.)} \rightarrow$$



(63)

Lions, Hughes, and Ritchie (373a, 441a) have recently modified the original method of Conrad and Limpach in several details.

9. The synthesis of quinolines by the action of acetylene on aromatic amines

Acetylene and ammonia gas react over a heated contact catalyst to form pyridine derivatives, as well as acetonitrile and other substances, in a reaction discovered by Chichibabin (126) and later elaborated in the patent literature (see Section II, B, 7). It has been found in recent years that acetylene similarly reacts with aniline and other aromatic amines when warmed in the presence of

catalysts to give substituted quinolines. Kozlov and coworkers thus report that quinaldine may be made in accordance with the equations (523, 527, 528, 534):

$$C_6H_5NH_2 + CH{\equiv}CH \xrightarrow[50°C.]{Cu_2Cl_2} \underset{\text{I}}{CH_3CH{=}NC_6H_5}$$

$$2CH_3CH{=}NC_6H_5 = \underset{\text{I}}{CH_3CH{=}NC_6H_5} \quad \underset{\text{II}}{\begin{matrix} CH_3CHNHC_6H_5 \\ | \\ CH_2CH{=}NC_6H_5 \end{matrix}} \tag{64}$$

$$\text{II} - C_6H_5NH_2 - (2H) \xrightarrow{\text{heat}} \underset{\text{III}}{C_6H_4\begin{matrix} CH{=}CH \\ | \\ N{=}{=}CCH_3 \end{matrix}} \quad \text{(see equation 57)}$$

Aniline adds catalytically to acetylene to form the ammono aldehyde ether, ethylideneaniline (I), much as water reacts with acetylene in the presence of mercuric salts to give acetaldehyde. The ethylideneaniline then dimerizes by a process related to the ordinary aldol condensation, and cyclization occurs as in the Döbner–Miller synthesis of equation 57. Hydrogen is, of course, not liberated as a gas, but appears in the form of various reduced organic compounds, such as tetrahydroquinaldine. Silver nitrate, mercuric chloride, mercuric bromide, and mercuric iodide may be used as catalysts in place of the cuprous chloride. The dimeric alkylideneanilines (II) may be isolated as intermediates, but presumably require higher temperatures for conversion to quinaldines than are used in the initial condensation of acetylene with aniline.

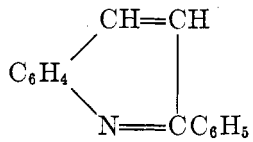
N-Ethylaniline and acetylene react similarly to give quinaldine, indole, ethane, and hydrogen or, rather, products of reduction of the organic matter that is available (546). Kozlov and Golod (529) greatly lowered the amount of tetrahydroquinaldine formed along with the quinaldine of the reaction of equation 64 by the use of nitrobenzene. A number of other references to this synthesis are listed (287, 521–534 inclusive, 654, 659a).

A variant of the above has been described by Kozlov (521, 523), who heated aniline, benzaldehyde, and acetylene for some hours and obtained 2-phenylquinoline in accordance with the following equations:

$$C_6H_5NH_2 + C_6H_5CHO = C_6H_5CH{=}NC_6H_5 + H_2O$$

$$C_6H_5NH_2 + CH{\equiv}CH = CH_3CH{=}NC_6H_5$$

$$\underset{\text{I}}{C_6H_5CH{=}NC_6H_5} + \underset{\text{II}}{CH_3CH{=}NC_6H_5} \rightarrow \underset{\text{III}}{C_6H_4\begin{matrix} H \\ | \\ NHCHCH_2CH{=}NC_6H_5 \\ | \\ C_6H_5 \end{matrix}} \rightarrow$$



$$+ C_6H_5NH_2 + (2H) \quad (65)$$

IV

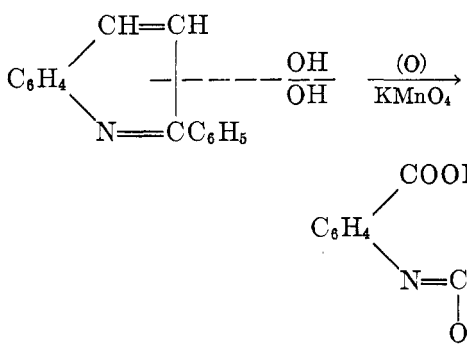
The ammono aldehyde ethers, benzylideneaniline (I) and ethylideneaniline (II), react with each other in the sense of the aldol condensation to give III, just as in Ciusa's mechanism for the Döbner cinchoninic acid synthesis (Section IV, A, 6).

Some years previous to the work described above, Chichibabin and Oparina condensed acetaldehyde and paraldehyde with aniline in the presence of aluminum oxide at elevated temperatures, and obtained a mixture of quinoline bases whose chief constituent was lepidine, 4-methylquinoline (122, 147).

B. RING OPENINGS OF QUINOLINE AND ITS RELATIVES; OXIDATIONS

From the quinoline ring openings that have been published, there are selected the following examples:

(*a*) 2-Aryl- or 2-alkyl-quinolines, when oxidized by potassium permanganate, give acyl derivatives of anthranilic acid, in accordance with the scheme below, which represents the formation of benzoylanthranilic acid from 2-phenylquinoline (257; *cf.* 177, 799d):



$$\rightleftarrows \quad (66)$$

The yield of the acid was 1.5 g. from 5 g. of 2-phenylquinoline. Quinaldine similarly yields *N*-acetylanthranilic acid, but anthranilic acid and oxalic acid are obtained at the same time (255).

When an aquo ketone is oxidized the bond between the carbonyl and an adjacent group is broken, and a mixture of acids (or of acids and ketones) is formed, as in the following example:

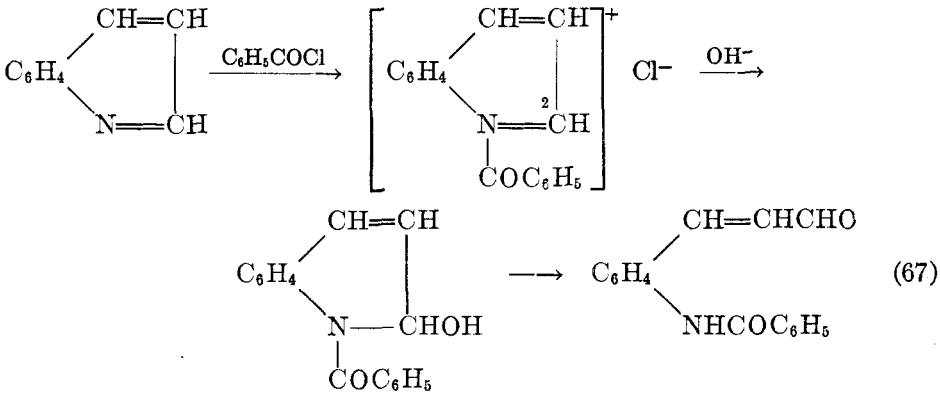
$$RCH_2COCH_2R \rightarrow RCOOH + RCH_2COOH \quad (66a)$$

The bond that is ruptured in the case of 2-phenylquinoline is similarly attached to the ammonia analogue of the carbonyl group, that is, to —C=N— (S. Skraup (763) calls this a carbimide group).

When quinoline itself is oxidized with dichromic acid, the pyridine ring is not much affected, since pyridine-2, 3-dicarboxylic acid (quinolinic acid) is formed.

The stability of the pyridine nucleus may well have been increased by the positive charge on the nitrogen of the salt that is present in the acid solution. Quinolinic acid may be prepared in 65 per cent yield by oxidizing quinoline with hydrogen peroxide in the presence of cupric sulfate (779).

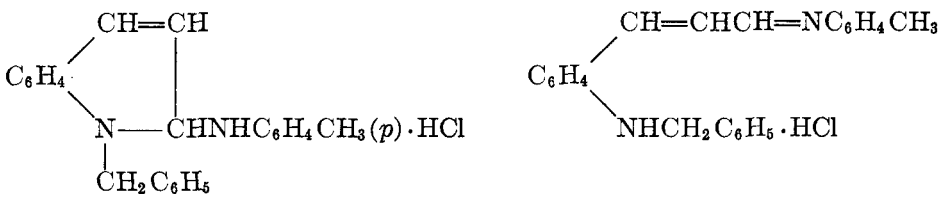
(*b*) Benzoyl chloride and quinoline react in 10 per cent aqueous sodium hydroxide to form *o*-benzoylaminocinnamaldehyde, as shown by the following equations:



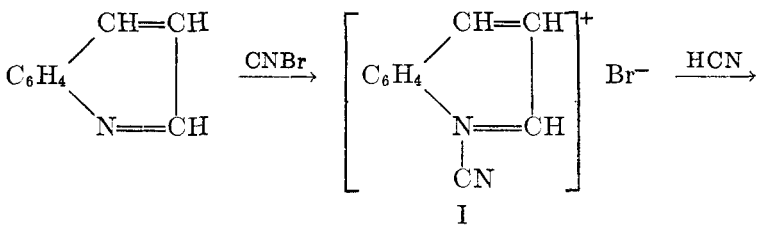
(67)

The hydroxyl ion of the sodium hydroxide adds to the carbon atom No. 2 to give 1-benzoyl-2-hydroxy-1, 2-dihydroquinoline, which supposedly exists as the open-chain *o*-benzoylcinnamaldehyde (706, 707).

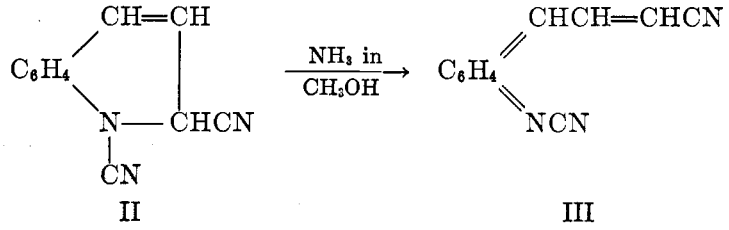
(*c*) A possible ring opening was obseved by Mikhailenko and Minof'ev (605), who treated benzylquinolinium chloride with a number of aromatic and aliphatic amines (*p*-toluidine, piperidine, aniline, diphenylamine, etc.) and obtained red compounds which probably had one of the structures given below (*cf.* 509, and Section II, C, (a)):



(*d*) Mumm and Herrendörfer (632) treated quinoline with cyanogen bromide to obtain the addition compound (I) below, which reacts with anhydrous hydrogen cyanide to give a dicyanide (II). Methyl alcoholic ammonia changes this to an isomer, for which the open-chain structure (III) has been suggested.



I



(68)

II III

(*e*) The pseudo bases which are obtained by the action of alkali on the quinaldine alkiodides are so reactive that they have often been assigned open-chain structures, although the bulk of the evidence seems to support the ring formulas.

C. REDUCTION OF QUINOLINE

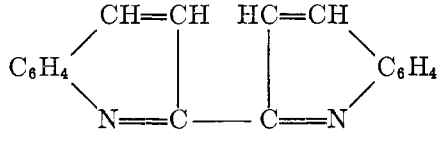
Quinoline may easily be reduced catalytically or with tin and concentrated hydrochloric acid to 1,2,3,4-tetrahydroquinoline (85, 428, 520a, 652, 652a, 737a, 737b, 762). The reduction to the decahydro stage is somewhat more difficult (32a, 32b, 441, 652a, 762). Ahrens (5) reports that the electrolytic reduction of quinoline in sulfuric acid solution with a lead cathode gives tetrahydroquinoline, together with dimeric and trimeric dihydroquinolines. Electrolysis of quinoline in potassium hydroxide with a platinum anode and mercury cathode in a divided cell (558) gives monomeric and polymeric 1,4-dihydroquinolines. Tetrahydroquinoline (43 per cent) and amorphous dihydroquinoline polymer (38 per cent) are formed by reducing quinoline with sodium in absolute alcohol; poor results are obtained by using ordinary 95 per cent alcohol (32a, 32b).

Addition of 1 mole of hydrogen to quinoline should give either 1,2-dihydroquinoline, the corresponding unsaturated cyclic ammono alcohol, or 1,4-dihydroquinoline. Attempts to prepare either of these have generally given their polymers (*cf.* 5, 32a, 32b, 558). Knowles and Watt (488) have recently reduced quinoline and some of its derivatives with sodium in liquid ammonia, obtaining, apparently, 1,4-dihydroquinoline, which was isolated as the diacetylated dimer. Attempts to reduce quinaldine to a dihydroquinaldine with hydrochloric acid and zinc dust have given the dimer instead (419).

Dialkyl derivatives of 1,2-dihydroquinoline, however, do exist (Section IV, N, 4). The parent compounds are intermediates in many of the quinoline ring syntheses.

D. BIQUINOLINES (BIQUINOLYLS, DIQUINOLYLS)

2,2'-Diquinolyl,



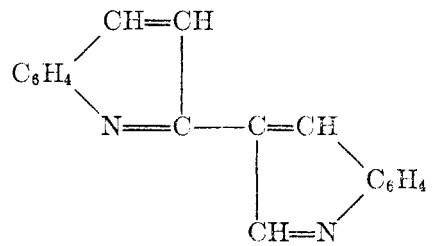
is a cyclic ammono diketone diether, an analogue of benzil, $C_6H_5COCOC_6H_5$. It may be made by the following methods:

(*a*) By heating quinoline at 325–335° C. with nickel–alumina in a sealed glass tube in 15 per cent yield (814b).

(*b*) By reducing a mixture of 2- and 7-bromoquinolines with hydrazine hydrochloride in alcoholic potassium hydroxide solution, in the presence of palladium on calcium carbonate (799a); 7,7′- and 2,7′-biquinolyls are also formed.

(*c*) By a Friedländer synthesis from methyl 2-quinolyl ketone and *o*-aminobenzaldehyde, or from 2 moles of the latter and 1 mole of diacetyl (767b).

2,3′-Diquinolyl,



is a cyclic ammono ketone aldehyde diether, analogous to water system compounds of the type CH_3COCH_2CHO or $C_6H_5COCH(C_6H_5)CHO$. The dihydro compound (see equation 79) is to be regarded as formed by the "aldol" condensation of quinoline.

2,3′-Diquinolyl may be prepared:

(*a*) By the action of sodium on quinoline, in 30–40 per cent yield (807b). Weidel and coworkers (807c) believed that they had obtained 2,2′-diquinolyl, but Einhorn and Sherman (273a) showed it to be the 2,3′-isomer by synthesizing it from *o*-aminobenzaldehyde and 2-quinolylacetaldehyde.

(*b*) By heating quinoline with sodium amide in an inert solvent; 2-aminoquinoline is also obtained (Section IV, H, 4). Dihydro-2,3′-diquinolyl is formed; it may readily be oxidized to 2,3′-diquinolyl.

(*c*) By the action of selenium on quinoline at 280–300°C. (799b). One gram of product was obtained from 10 g. of quinoline and 15 g. of selenium. Mills and Ordish (615a) decarboxylated 2,3′-diquinolylcarboxylic acid, which they prepared from 2-quinolylpyruvic acid ester and *o*-aminobenzaldehyde by a Friedländer synthesis.

(*d*) By the action of *o*-aminobenzaldehyde on methyl 3-quinolyl ketone (519a).

Most of the remaining diquinolyls can be prepared by the Skraup reaction from diaminodiphenyls or by the method of Ueda, which consists in the reduction of bromoquinolines, or a mixture of two bromoquinolines, with hydrazine hydrate or hydrochloride in alcoholic potassium hydroxide solution and in the presence of palladized calcium carbonate (see method (*b*) under 2,2′-diquinolyl). An example of the Skraup synthesis is the formation of 6,6′-diquinolyl from benzidine

(648b). References to the preparation of some individual diquinolyls are given below:

DIQUINOLYL	REFERENCE	DIQUINOLYL	REFERENCE
2,6′–	(806a)	5,5′–	(799a)
2,7′–	(799a)	6,6′–	(648b)
3,3′–	(702b, 799c)	7,7′–	(106b, 799a)
3,4′–	(615a)	8,8′–	(639a)
4,4′–	(170a)	3,7′ or 4,7′–	(443a)

All of the diquinolyls listed, with the exception of the 2,2′-and 2,3′-isomers, are cyclic ammono dialdehyde diethers.

E. THE ACTION OF ALKALI BISULFITES ON QUINOLINE

Quinoline reacts with sodium bisulfite and potassium bisulfite to form water-soluble addition compounds, which decompose into their constituents at 60–70°C. in aqueous solution (101). Voroshzov and Kogan (803) warmed quinoline with sulfur dioxide in water and obtained the addition compound $C_9H_7N \cdot SO_2$, which they consider to be identical with the one prepared by Brunck and Gräbe (101). It is not known whether the aldehydic —CH=N— linkage of quinoline is involved in the reaction; it seems certain that this is not the case, however, with some azo dyes derived from 8-hydroxyquinoline, which appear to add sodium bisulfite in the 5,8-positions (803).

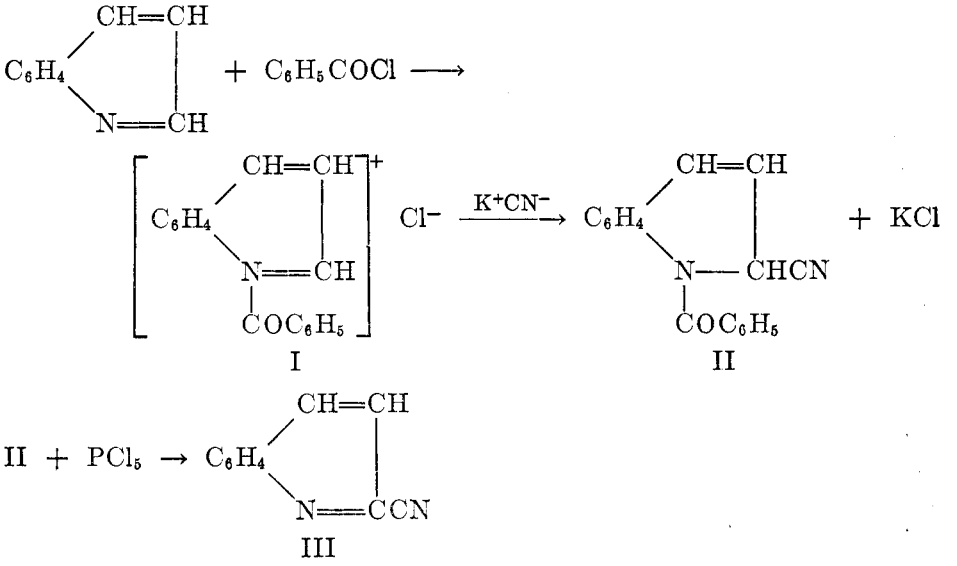
The related ammono aldehyde ether, benzalaniline, reacts with aqueous sulfur dioxide to give a compound that is considered to have the formula (269, 479, 776; *cf.* 650):

$$\begin{array}{l} C_6H_5CHNHC_6H_5 \\ \quad\quad | \\ \quad SO_3H \cdot C_6H_5NH_2 \end{array}$$

It may be regarded as the aniline salt of a sulfurous acid addition compound of the ammono aldehyde ether.

F. THE ACTION OF BENZOYL CHLORIDE AND ALKALI ON QUINOLINE

Benzoyl chloride (2 moles), quinoline, and potassium cyanide react to give 1-benzoyl-2-cyano-1,2-dihydroquinoline in almost quantitative yield (Reissert's reaction; 455, 705). When treated with hydrochloric acid, quinoline-2-carboxylic acid (quinaldic acid) and benzaldehyde are formed, among other substances. It is better to mix the benzoylcyanodihydroquinoline with phosphorus pentachloride in chloroform, whereupon 2-cyanoquinoline may be obtained in yields as high as 55 to 70 per cent of the theoretical (455). Sugasawa and Tsuda (787) hoped to use Reissert's reaction to prepare aromatic aldehydes, but their expectations were only partly fulfilled. The probable equations follow:

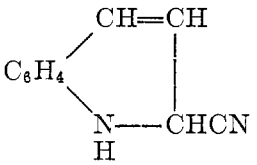


+ C_6H_5CHO (perhaps also C_6H_5COCl) (69)

When hydrochloric acid is used in place of the phosphorus pentachloride, the 2-cyanoquinoline is hydrolyzed to quinaldic acid.

The addition compound (I) reacts with cyanide ion to form 1-benzoyl-2-cyano-1,2-dihydroquinoline (II), from which benzaldehyde may be abstracted to give quinaldonitrile (III). The second step of the reaction may be regarded as an indirect addition of hydrocyanic acid to quinoline, an ammono aldehyde ether, to give a cyanohydrin, which is isolated as its benzoyl derivative. There is some analogy in the use of benzoyl chloride to form a quinoline cyanohydrin, and in the use of the bisulfite addition compound of benzaldehyde to form mandelonitrile, or benzaldehyde cyanohydrin. The addition of the cyanide ion to the 2-carbon of quinoline (equation 69) is doubtless accelerated by the positive charge on the cation of I; in fact, it will not occur without this activation.

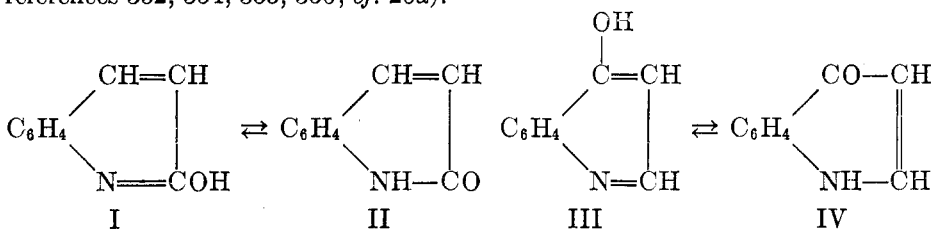
Benzoyl mandelonitrile, $C_6H_5CH(CN)OCOC_6H_5$, is an approximate water system analogue of II, the benzoyl derivative of the hypothetical quinoline cyanohydrin:



The former may be made, in a manner paralleling equation 69, by allowing benzoyl chloride, benzaldehyde, and potassium cyanide to react (319). It is interesting that the product is not decomposed by prolonged boiling with dilute acids.

G. QUINOLINES HYDROXYLATED IN THE PYRIDINE NUCLEUS

2-Hydroxyquinoline (I) and 4-hydroxyquinoline (III) are tautomeric, respectively, with 2-quinolone (II) and 4-quinolone (IV); it is possible that the isomerism is as complicated as that of the hydroxypyridines (see Section II, K; references 352, 354, 355, 356; *cf.* 20a).

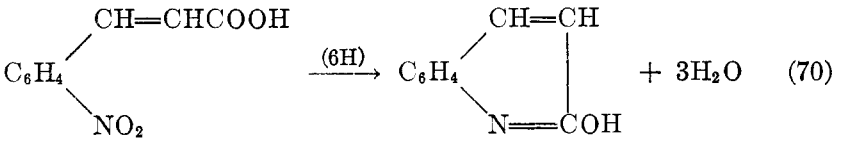


2-Hydroxyquinoline (carbostyryl) in either of its tautomeric forms is a cyclic ammono aquo acid ester, while 4-hydroxyquinoline is its vinylogue. In neither of these is the hydroxyl group as phenolic as it is in 3-hydroxyquinoline.

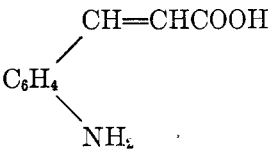
2-Hydroxyquinoline may be prepared by the following methods: (*a*) Oxidation of quinoline by means of bleaching powder solution at 100°C. (2–3 hr.) (275, 284, 716, 795). In this reaction, a cyclic ammono aldehyde ether has been oxidized to the corresponding cyclic ammono aquo acid ester.

(*b*) Ring-closure reactions, such as the two already mentioned (Section IV, A, 7–8), and the following:

(*1*) *o*-Nitrocinnamic acid or its esters when reduced give carbostyryl (27, 288, 353, 695, 791). The assumed intermediate, *o*-aminocinnamic acid, is by itself changed only slowly to carbostyryl; its acetyl derivative is changed readily (27).

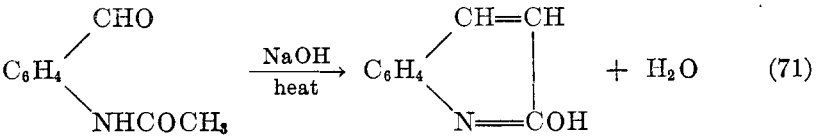


Carbostyryl can therefore be regarded as formed by the intramolecular esterification of the aquo acid-ammono phenol, *o*-aminocinnamic acid,



and the correctness of its assumed relationship to the ammonia system is shown.

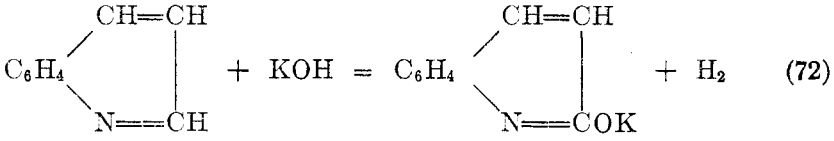
(*2*) *o*-Acetaminobenzaldehyde, when boiled with aqueous alcoholic potassium hydroxide, gives carbostyryl in 80 per cent yield (107).



It will be noted that the $—C_6H_4NHCOCH_3$ portion of the molecule represents a monosubstituted acetamide and therefore an ammono aquo acid ester, as acetamide is an ammono aquo acid. The ring closure is merely a Claisen reaction between the ortho —CHO and an active methyl group, which is analogous to the methyl group in an ester of acetic acid, CH_3COOR.

(*3*) 2-Chloroquinoline—a cyclic ammono acid chloride ester (Section IV)—is hydrolyzed to carbostyryl when heated to 120°C. with water containing a little hydrochloric acid (764; *cf.* 179). 4-Hydroxyquinoline is similarly prepared from 4-chloroquinoline (76).

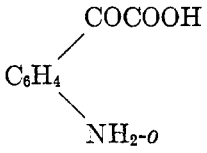
(*4*) Chichibabin (114, 131, 143a) prepared carbostyryl in yields of 80 per cent and better by heating quinoline with dry potassium hydroxide or barium hydroxide for a few hours at about 225°C. Small quantities of indole may be formed in the reaction, but this is not unexpected, since indole may be made, along with other compounds, by melting carbostyryl with potassium hydroxide (628). The reaction of Chichibabin follows the equation:



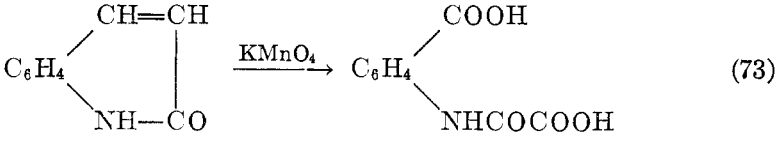
(72)

Carbostyryl itself is obtained by acidifying an aqueous solution of its potassium salt. Many substituted quinolines react similarly (114, 143a, 243).

Properties of carbostyryl: When carbostyryl is ozidized with cold potassium permanganate, isatinic acid,



(→ isatin) is formed by ring scission and loss of one atom of carbon; at the same time, oxalylanthranilic acid is obtained, by the oxidation of the double bond in the 3,4-position (349).



(73)

Cinnamic acid is similarly oxidized by dilute dichromic acid or by alkaline boiling permanganate to benzaldehyde (603, 761). Crotonic acid, $CH_3CH=CHCOOH$, is oxidized by concentrated nitric acid to acetic and oxalic acids, or by chromic acid mixture to acetaldehyde and acetic acid (470).

Arndt, Eistert, and Ender (15) have concluded that the 3-hydroxyl group is more acidic than the 2-hydroxyl, as the result of an experiment in which they methylated isatin with diazomethane and obtained 2,3-dihydroxyquinoline, together with 2-hydroxy-3-methoxyquinoline.

H. 2-, 3-, AND 4-HALOGENATED QUINOLINES

2-Chloroquinoline, a cyclic ammono acid chloride ester, is made, as are the aquo acid chlorides, by the action of phosphorus pentachloride and phosphorus oxychloride on 2-hydroxyquinoline, but at the higher temperature of 130–140°C. (350). It may also be made by treating *N*-methyl-α-quinolone, a cyclic ammono aquo ester, with the same mixture of reagents (293, 304) or with phosgene (698). 2-Bromoquinoline is similarly prepared (167, 299, 304, 778). Quinoline may be brominated in the gaseous phase over a pumice catalyst at 300°C. to give a 25 per cent yield of 3-bromoquinoline (442b; *cf.* 163a), and at 450°C. to give a 24 per cent yield of 2-bromoquinoline (442b). The yield of the latter may be increased to 53 per cent by passing the quinoline and bromine through an empty tube at 500°C., with a carrier of nitrogen gas. 4-Chloroquinoline is prepared, along with some 2-chloroquinoline, by the action of sulfuryl chloride on quinoline *N*-oxide (77, 591a) and, free from isomers, by heating 4-hydroxyquinoline (kynurine) with phosphorus halides (23a, 542, 764) or with benzyol chloride (277), or by diazotizing-4-aminoquinoline in concentrated hydrochloric acid solution (165, 810). 4-Bromoquinoline may be made either from kynurine or from 4-aminoquinoline (166a). Treatment of 3-acetoxymercuriquinoline with potassium bromide gives 3-bromoquinoline (799e).

Of the 2-, 3-, and 4-halogenoquinolines, the 2- and 4-isomers are the most reactive, though much less so than a typical open-chain acid chloride of the water system. The fused benzene ring of quinoline seems to be responsible for increasing the mobility of a 2- or 4-substituted chlorine over that of the 2- and 4-chloropyridines (296). A number of examples follow.

1. Preparation of alkoxyquinolines

2-Chloroquinoline is readily converted to 2-methoxyquinoline (a cyclic ammono aquo ester) by short heating with sodium methylate in methanol, or into 2-ethoxyquinoline by heating with ethyl alcoholic potassium hydroxide (78, 351). In one case, at least, partial isomerization has been reported, since Bogert and May (78) find that a mixture of 80 per cent of 2-isoamyloxyquinoline and 20 per cent of 1-isoamyl-2-quinolone is formed by heating 2-chloroquinoline with sodium isoamylate. 4-Chloroquinoline may similarly be converted to 4-alkoxyquinolines (811).

A phenyl group in the 2-position does not appear greatly to influence the reactivity of a 4-chlorine atom, since it is necessary to heat 2-phenyl-4-chloroquinoline with alcoholic potassium hydroxide for 8 hr. at 145–165°C. to prepare 2-phenyl-4-ethoxyquinoline (444b).

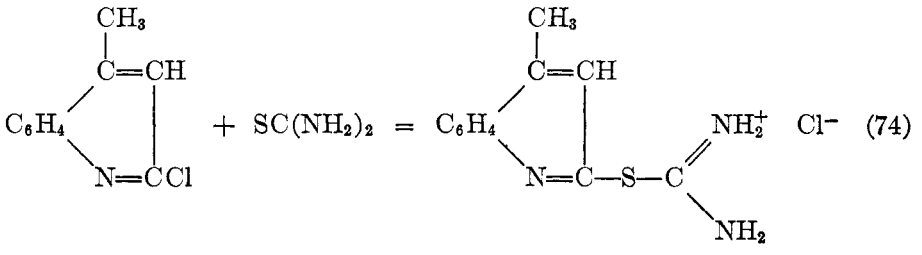
2. Preparation of phenoxyquinolines

2-Phenoxyquinoline is made by heating 2-chloroquinoline with sodium phenoxide dissolved in phenol (351). Backeberg and Marais (26) found that the chief product of the action of ammonia gas on a heated phenol solution of 2-chloro-4-methylquinoline was 2-phenoxy-4-methylquinoline. The latter can be prepared somewhat more conveniently by heating the reactants for about 5 hr. at 180°C.,

with omission of the ammonia. 2-Phenyl-4-phenoxyquinoline is formed, apparently with some difficulty, by heating 2-phenyl-4-chloroquinoline with potassium phenoxide in phenol for 10 hr. at 180°C. (444c). Turner and coworkers have prepared a number of 2- and 4-phenoxyquinolines in connection with the synthesis of compounds of possible therapeutic value (565a, 637).

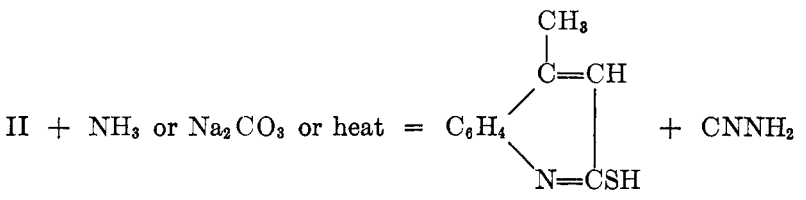
3. Preparation of thiolquinolines and arylquinolyl sulfones

2-Chloroquinoline is converted to 2-thiolquinoline (III) or 2-mercaptoquinoline (a cyclic thio ammono acid ester) by heating with potassium hydrosulfide in alcohol for a few hours at 150°C. (300). 2-Phenylquinoline-4-thiol is similarly formed from 4-chloro-2-phenylquinoline but seemingly less readily (444a). It is better to heat 2-chloroquinolines with thiourea on the water bath for about 15 min., whereupon the following series of reactions occur (721):



(74)

I II



III IV

An addition compound of the possible structure II is first formed, but this can be isolated only by working in the cold. When treated with ammonia or sodium carbonate or heated, a thiolquinoline (III) is obtained, together with cyanamide (IV) or its polymerization product, dicyanodiamide. Thiourea is a thioammonocarbonic acid, while cyanamide and dicyanodiamide are ammonocarbonic acids. Under the above conditions, 4-chloroquinaldine is largely converted to (2,2′-dimethyldiquinolyl-4,4′) sulfide.

Aryl quinolyl sulfones, $C_9H_6NSO_2Ar$, may be made by heating 2-chloroquinoline with sodium aryl sulfinates for several days at 100°C. (794).

4. Preparation of amino- and substituted amino-quinolines

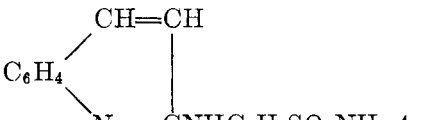
2-Aminoquinoline and 2-hydroxyquinoline are formed when 2-chloroquinoline is heated with aqueous ammonia and ammonium carbonate at 200–210°C. (168). 2-Aminoquinoline may be prepared in 50 per cent yield by heating 2-bromoquinoline with liquid ammonia in the presence of copper powder (6 hr. at 70°C.

(443)). (For the preparation of substituted 2-aminoquinolines, see reference 318.) 3-Aminoquinoline is made by the ammonolysis of 3-bromoquinoline in liquid ammonia, with added copper powder, or in aqueous ammonia with copper sulfate as a catalyst (711). Halogen in position 3 is less reactive than in position 2 or 4.

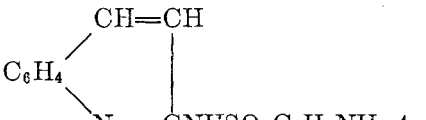
2-Chloroquinoline (or 4-chloroquinaldine) and aniline react at about 200°C. to give 2-anilinoquinoline (23, 24, 357). Backeberg and Marais (26) have obtained 4-amino-2-methylquinolines in almost quantitative yield by passing ammonia into a hot phenol solution of the corresponding 4-chloro-2-methylquinoline (2 hr. at 180°C.), but the 2-chloro-4-methylquinolines give only small yields (about 10 per cent) of amines, the main product being a 2-phenoxy-4-methylquinoline. To prepare the 2-amino-4-alkylquinolines, it is best to heat the 2-chloro-4-alkylquinolines with ammoniated zinc chloride in a sealed tube.

Substituted 4-chloroquinolines react with arylamines at elevated temperatures to give 4-arylaminoquinolines (23, 283, 595).

Bobranski (75a) and Gray (379a) heated sulfanilamide with 2-chloroquinoline and obtained 4-(2′-quinolylamino)benzenesulfonamide (I), while Phillips (686a) prepared the isomeric 2′-(4-aminobenzenesulfonamido)quinoline (II) by carrying out the reaction in the presence of potassium carbonate and a trace of copper (*cf.* Section II, M, 4).



I



II

5. Preparation of hydrazino- and phenylhydrazino-quinolines

2-Hydrazinoquinoline is best made by refluxing 2-chloroquinoline with hydrazine hydrate for 1 hr. (684a). If carried out in sealed tubes at higher temperatures, this reaction is not only less convenient, but also gives some *sym*-di-2-quinolylhydrazine, Qu·NHNH·Qu (587a). 2-Hydrazino-4-methylquinoline and 4-hydrazino-2-methylquinoline have been prepared by heating the corresponding chlorine compound with hydrazine hydrate for 5 hr. at 150°C. (585a; see reference 501 for structure).

Koenigs and von Loesch (501; *cf.* 102a) report that two products are formed by the action of hydrazine hydrate on 4-chloroquinaldine: one was the expected 4-hydrazinoquinaldine, while the other was a diaminoquinaldine of unknown structure.

2-Phenylhydrazinoquinoline (281a) and 2-phenylhydrazino-4-methylquinoline (281b) are easily made by heating the respective chloroquinolines with phenylhydrazine. Backeberg (25) finds that phenylhydrazine reacts with derivatives of 4-chloroquinoline to give two isomeric products under slightly different experimental conditions. At 200°C., in an inert solvent, there is formed the ex-

pected 4-phenylhydrazinoquinoline, while at 200°C. in a sealed tube there is obtained an isomer, which is considered to be a 3-anilino-4-aminoquinoline. Ephraim (282) has prepared 4-phenylhydrazinoquinaldine by heating 4-chloroquinaldine and phenylhydrazine at 115°C.

The hydrazino- and phenylhydrazino-quinolines may in general be reduced to the corresponding aminoquinolines by zinc dust and acid, or by hydrogen iodide and red phosphorus (281, 501b, 587).

6. Preparation of hydroxyquinolines

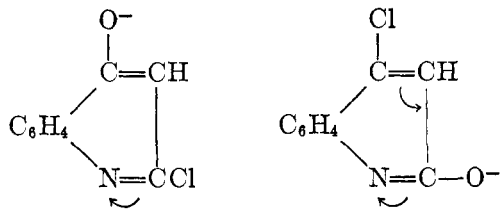
The replacement of a 2- or 4-chlorine by hydroxyl has in general been fully covered elsewhere (Section IV, G, 3; IV, H, 7). Some carbostyryl is obtained when 2-chloroquinoline is heated with ammonium carbonate and aqueous ammonia at 200°C. (168), or with aqueous alcoholic potassium cyanide at 200°C. (443).

7. Reactivity of 2- and 4-halogen as influenced by other groups

There seems to be little definite evidence concerning the relative reactivities of chlorine in the 2- and 4-positions. Buchmann and Hamilton (104) refluxed 2,4-dichloroquinoline with a solution of potassium hydroxide in methanol and obtained a mixture of 2-chloro-4-ethoxyquinoline (31 per cent), 4-chloro-2-ethoxyquinoline (32 per cent), and 4-chloro-2-hydroxyquinoline (5.5 per cent). These results might be interpreted as indicating a slightly greater reactivity of a 2-chlorine, in accordance with expectation because of greater proximity to the —C=N— group.

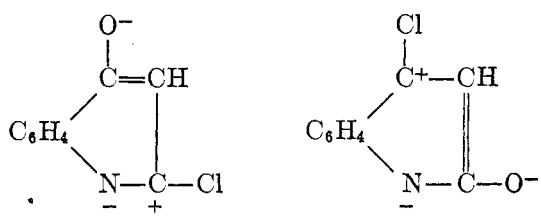
There is, however, a very marked difference in the reactivity of chlorine provided a hydroxyl group is present in the same ring. Thus, Friedländer and Müller (348) state that 4-chloro-2-hydroxyquinoline does not react with boiling sodium alkoxide solutions, and gives 2,4-dihydroxyquinoline only when melted with alkalies. Ephraim (283) finds that while aniline and 4-chloroquinoline react at 120°C. to give 4-anilinoquinoline, the halogen in 4-chloro-2-hydroxyquinoline cannot be similarly replaced. On the other hand, 2,4-dichloroquinoline is converted to 2,4-dianilinoquinoline when heated with aniline, and 2-ethoxy-4-anilinoquinoline may similarly be prepared from 2-ethoxy-4-chloroquinoline. According to Buchmann and Hamilton (104), the halogen in 4-chloro-2-hydroxyquinoline is quite inactive, while the chlorine in 2-chloro-4-hydroxyquinoline and both halogens in 2,4-dichloroquinoline are active. The halogen in 2-chloro-4-ethoxyquinoline is fairly active, while that in 4-chloro-2-ethoxyquinoline is much more inert. Therefore, hydroxyl in the 2-position will make a 4-chlorine atom much more inert, and groups of the type of ethoxyl or phenylamino (C_6H_5NH—) will have less influence, wherever they may be. A possible explanation, based on interference with the normal activation of the chlorine, is given below.

When either of the hydroxychloroquinolines reacts with a basic reagent, such as sodium ethoxide, the ions shown below will be formed:



I II

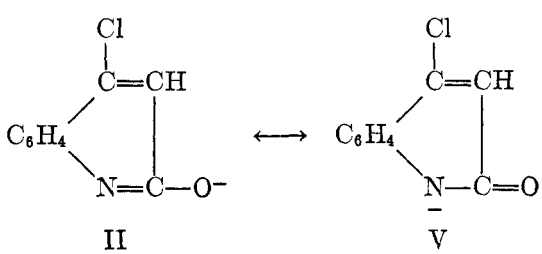
According to recent electronic theories, replacement of chlorine by ethoxyl or a similar group is preceded by an activation in the sense of the arrows in I and II, which places a (temporary) positive charge on the 2- or 4-carbon atom, respectively. These changes, if completed, will give the (unperturbed) forms, III and IV.



III IV

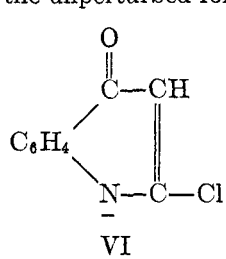
An ethoxyl, $C_2H_5O^-$, or related ion unites with the positively charged carbon of III or IV, and this is followed by elimination of chlorine.

The activation of the 4-carbon atom in IV will be greatly hindered by a resonance involving the negatively charged oxygen, in the manner shown below:



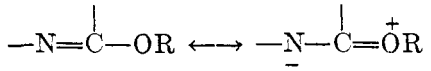
II V

Essentially, of course, this is the 2-hydroxyquinoline–2-quinolone tautomerism. The related resonance, giving the unperturbed form,

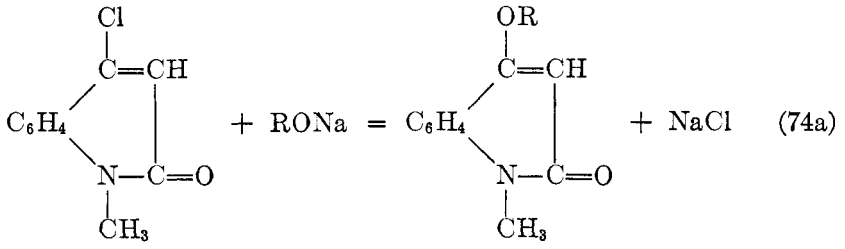


VI

apparently will not prevent the activation of the 2-chlorine, as in III, though there may well be some hindrance. With an alkoxy or phenylamino group in the 2- or 4-position, resonance of the type shown below will be of less importance, and will accordingly not influence the reactivity of a 2- or 4-halogen as much as will a hydroxyl group.



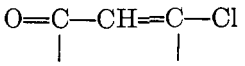
4-Chloro-1-methyl-2-quinolone (VII) reacts with alcoholic metal alkoxides on short heating to give 4-alkoxy derivatives, in accordance with the following equation (348):



VII

(74a)

The effect of the carbonyl upon the mobility of the chlorine has therefore been damped but little in transmission across the conjugated system,



partly because ring resonance does not interfere as much where there are only two cyclic double bonds.

I. ALKOXYQUINOLINES, *N*-ALKYLQUINOLONES

It has been previously shown that these compounds are cyclic ammono aquo esters (Section I, G); their preparation has been adequately discussed elsewhere (Section IV, H, 1, Section IV, N, 2, (c) and (d)).

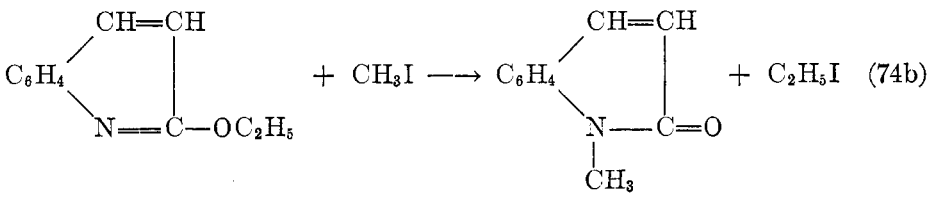
2- or 4-Alkoxyquinolines may generally also be made by heating the silver salts of the corresponding hydroxyquinolines (carbostyryl or kynurine, respectively) with an alkyl halide (346a, 356; *cf.* 811a). Alkylation of carbostyryl or kynurine with alkyl halides and alkali usually gives a preponderating amount of the isomeric *N*-alkylquinolone (346a, 353, 356; *cf.* 811a), though Meyer (598, 601) reports that 2-methoxyquinoline is formed by methylating carbostyryl with dimethyl sulfate (no experimental details are given).

Diazomethane in ethereal solution converts both 2- and 4-hydroxyquinolines into their *O*-methyl ethers (=alkoxyquinolines) (598, 599b). 2-Ethoxyquinoline has also been made by cyclizing ethyl 2-aminocinnamate with concentrated zinc chloride in alcohol at 80–90°C. (355).

The reactivity of an alkoxy group in the 2- or 4-position of the quinoline nu-

cleus is somewhat more than that of the same group in an ordinary ether, though less than that of the group in an open-chain ester. A few examples follow:

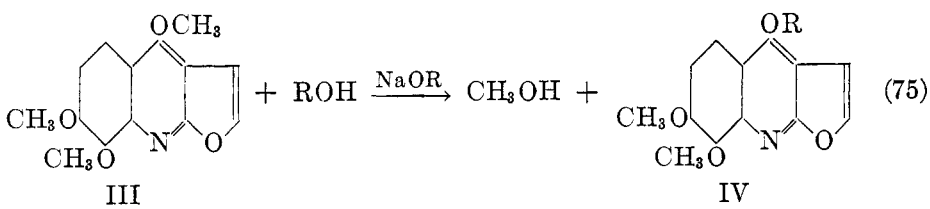
(*1*) 2-Ethoxyquinoline (I), when heated with methyl iodide for 2 days at 100° C., gives 1-methyl-2-quinolone (II) in good yield (487). Perhaps there is formed first a methiodide of the ethoxyquinoline, which loses ethyl iodide to give II.



I II (74b)

Whatever the mechanism may be, comparison may be made with a *trans*-esterification, or interchange of the alkyl groups attached to the oxygen of an ester. The analogy is not quite exact, since the reaction of equation 74b involves also a rearrangement. The same type of isomerization will take place on simple heating, since the 2-alkoxyquinolines rearrange to the 1-alkyl-2-quinolones (601) at 100°C. and the 4-alkoxyquinolines similarly rearrange to the 1-alkyl-4-quinolones at temperatures in the neighborhood of 280–290°C. (484).

A clearer cut example of a *trans*-esterification has recently been reported by Berinzaghi and coworkers (66). Under the influence of alcoholic alkali, a methoxyl group in the 4-position (with relation to nitrogen) of the alkaloid skimmianine (III) is replaced by the alkoxyl group of the particular alcohol used. The reaction is expressed by the equation:



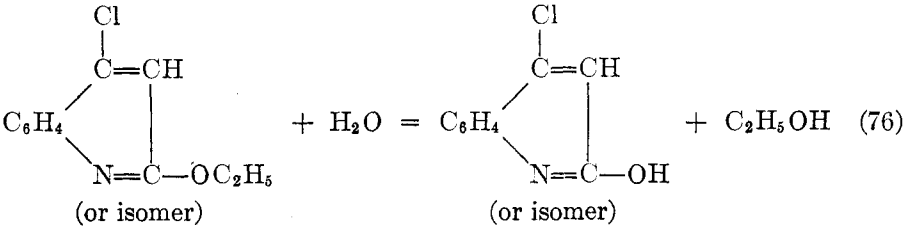
III IV (75)

The change is interpreted as involving, first, a 1, 4-addition of the alcohol to the pyridine nucleus, followed by a loss of methanol. The authors correctly consider 4-methoxyquinoline as a vinylogue of an "imino ether", RC(=NH)OR′, an ammono aquo acid ester. It will be seen later that related *trans*-esterifications are known in the quinazoline series.

(*2*) 2-Ethoxyquinoline is stable towards boiling dilute potassium hydroxide (351, 353a, 457), though it is converted to ethyl chloride and 2-hydroxyquinoline when heated with dilute hydrochloric acid at 120°C.; the latter may be slowly formed even at room temperatures (351, 353a, 457). The behavior of an acetal is very similar, since it may be hydrolyzed readily by acids but is comparatively unaffected by alkalies.

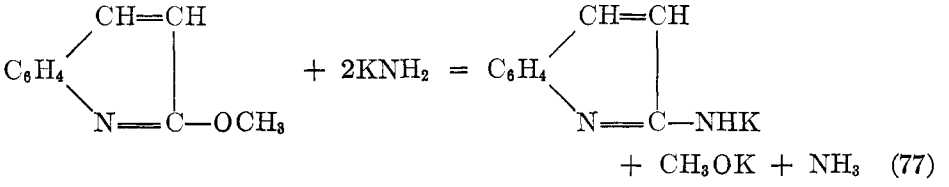
(*3*) Buchmann and Hamilton (104) found that there is a considerable differ-

ence in the ease of replacement of the alkoxyl groups of 2-chloro-4-ethoxyquinoline and 4-chloro-2-ethoxyquinoline by hydroxyl. Thus, the 4-chloro isomer required only 20–30 min. of reflux with 6 *N* hydrochloric acid, while the 2-chloro compound had to be boiled for 10 hr. with 70 per cent hydrogen iodide before the alkoxyl was replaced by hydroxyl. Furthermore, the yield in the former case was almost quantitative, in the latter about 40 per cent, as calculated from the equation:



It is interesting that in both cases the alkoxyl group is replaced rather than the chlorine. As expected, the alkoxyl in the 4-position is the less reactive.

(4) 2-Methoxyquinoline readily reacts with potassium amide in liquid ammonia solution to form the potassium salt of 2-aminoquinoline in 51 per cent yield, in accordance with the equation:



A cyclic ammono aquo ester has been saponified by the strong base, potassium amide, to the potassium salt of a cyclic ammono aquo acid ester, 2-aminoquinoline (58).

The 4-alkoxyquinolines, when heated with ammonium salts either alone or in the presence of ammonia or of alkylamines, give 4-amino- or 4-alkylaminoquinolines (670).

Many 2-alkoxyquinoline-4-carboxylic acids have a local anesthetic activity that is supposed to be due in part to the alkoxyl groups (819).

The 1-alkyl-2-quinolones seem to be less reactive than the isomeric 2-alkoxyquinolines, as one might expect because ester-like reactions would generally involve a rupture of the ring. The ketonic reactivity of the carbonyl group is low (*cf.* 347).

J. QUINOLINE-2-SULFONIC ACID

The sodium salts of quinoline 2-sulfonic acid and related compounds are made by heating 2-chloroquinolines with sodium sulfite solution (67). The sulfonic acid group is attached to the same carbon as is the doubly bonded nitrogen, and so is mobile, presumably for that reason. When heated with aqueous ammonia in the presence of zinc chloride at 135°C., 2-aminoquinoline is formed (667), while

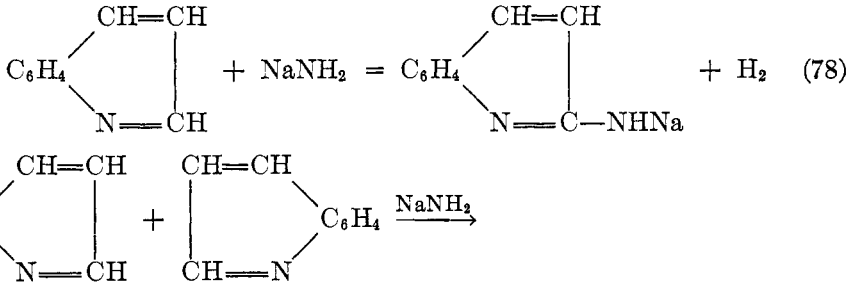
with alkylamines it is possible to prepare compounds of the type of 2-dimethylaminoquinoline (667).

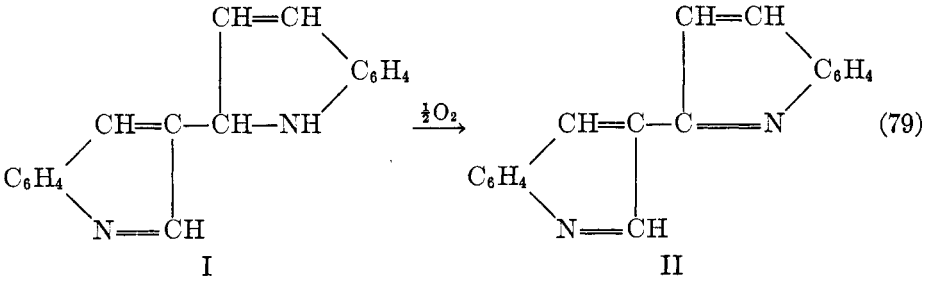
Quinoline-2-sulfonic acid reacts readily with potassium amide in liquid ammonia at room temperatures to give the potassium salt of 2-aminoquinoline in 74 per cent yield, together with potassium sulfite (59).

A water system analogue of quinoline-2-sulfonic acid will have the formula $C_6H_5COSO_2OH$, but it apparently does not exist. Its reduction product, benzaldehyde sodium bisulfite, $C_6H_5CH(OH)SO_2ONa$, has an easily replaceable sulfonic acid salt group, since mandelonitrile, $C_6H_5CH(OH)CN$, is obtained from it without trouble by the action of sodium cyanide.

K. 2-, 3-, AND 4-AMINOQUINOLINES

2-Aminoquinoline was prepared by Chichibabin and Zatzepina (160) by heating quinoline and sodium amide in the presence of an inert hydrocarbon. The yield is rather low (about 25 per cent), since there is formed at the same time some 2,3-diquinoline (I), which readily reacts with the oxygen of the air to form 2,3-diquinolyl (II). The reactions are expressed by the following equations:

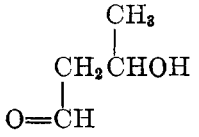




I II

The diquinoline (I) is doubtless present as a sodium salt.

Equation 78 represents the nitridation of quinoline to a salt of a cyclic ammono acid ester, while equation 79 is in its first phase similar to an aldol condensation, since I is a somewhat complex ammonia analogue of aldol (III).



III

Better yields of 2-aminoquinoline (up to about 80 per cent) are obtained by treating a solution of quinoline in liquid ammonia at room temperatures with barium amide; hydrogen is also formed, much in the manner of equation 78. The reaction is markedly catalyzed by soluble barium salts (52, 55). Quinoline reacts with an excess of potassium amide in liquid ammonia to give resins and oils of indefinite characteristics, but in the presence of potassium nitrate or of mercury there is formed a mixture of 2-aminoquinoline (50–55 per cent) and 4-aminoquinoline (about 10 per cent). The equations are the following (55):

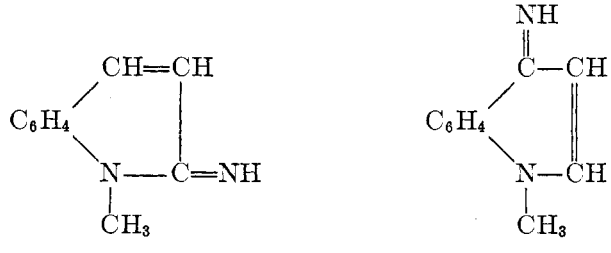
$$C_9H_7N + 2KNH_2 + KNO_3 \rightarrow C_9H_6N{-}NHK + KNO_2 + KOH + NH_3 \quad (80)$$

$$C_9H_7N + 3KNH_2 + xHg \rightarrow K_2Hg_x + 2NH_3 + C_9H_6N{-}NHK \quad (81)$$

4-Amino-2-phenylquinoline may be obtained in yields as high as 99 per cent of the theoretical by treating 2-phenylquinoline with potassium amide and potassium nitrate in liquid ammonia, in the manner of equation 80 (59a). Here it will be noticed that the 4-hydrogen has the function of the 2-hydrogen of quinoline. Several related liquid ammonia reactions have been described (57). 2-Aminoquinoline may also be made by the ammonolysis of 2-chloroquinoline (Section IV, H, 4), by the action of potassium amide on 2-methoxyquinoline or quinoline-2-sulfonic acid (Sections IV, I, 4; IV, J), and by the reduction of *sym*-di(2-quinolyl)hydrazine (587) or 2-phenylhydrazinoquinoline (281), as well as by other methods.

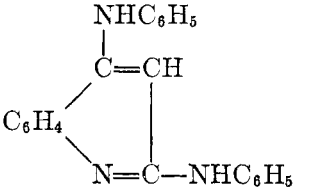
3-Aminoquinoline may be prepared by the ammonolysis of 3-bromoquinoline (Section IV, H, 4) or of 3-hydroxyquinoline (666a).

2-Cyclohexylaminoquinoline, a cyclic ammono acid ester, is made in 60 per cent yield by heating quinoline with the eutectic of sodium amide and potassium amide (541) in cyclohexylamine (786, 793); the mechanism of the reaction has been discussed previously (Section II, G). 2-Methylaminoquinoline is obtained by treating quinoline with a liquid methylamine solution of sodium methylamide (CH_3NHNa), potassium methylamide, and potassium nitrate, in a manner similar to that of equation 80 (789). Attempts to form mono- and di-methylaminoquinolines by heating 2- and 4-aminoquinolines with methyl iodide have given instead the isomeric *N*-methylquinoloneimides, of the type (113b) shown below:



3-Aminoquinoline behaves generally as a typical aromatic amine, while 2- and 4-aminoquinolines, like the corresponding pyridine derivatives, are somewhat anomalous (*cf.* Section II, L).

2-Aminoquinoline can be hydrolyzed to the corresponding mixed ammono aquo acid ester, carbostyryl, by heating with alkali or acid (168). 2,4-Dianilinoquinoline,



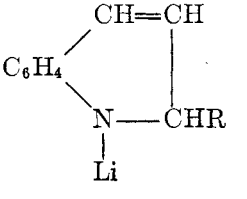
was changed successively to a mixture of phenylaminohydroxyquinolines and to 2,4-dihydroxyquinoline by heating with alcoholic potassium hydroxide at 220°C. (265). The mobility of the phenylamino groups is therefore not very high under alkaline conditions.

L. THE ACTION OF METALLOÖRGANIC COMPOUNDS ON QUINOLINE

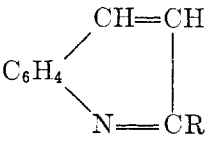
The reactivity of the aldehydic —CH=N— group in quinoline is comparatively low because of the resonance energy associated with the six-membered ring. Nevertheless, quinoline does react with the Grignard reagent and with lithium alkyls and aryls.

(1) Sachs and Sachs (735) added quinoline to an ethereal solution of phenylmagnesium bromide and of ethylmagnesium bromide, and obtained addition compounds of the type, $C_9H_7N \cdot RMgX$, from which quinoline was regenerated on hydrolysis. The analyses were not too well in agreement with the formulas given. Oddo (642) reports also the compounds, $2C_9H_7N \cdot C_6H_5MgBr$ and $3C_9H_7N \cdot C_6H_5MgBr$, from which he prepared some 2-phenylquinoline by heating in benzene solution (641a). At a later date, this reaction was extended and 2-phenylquinoline was formed in somewhat better yield by heating an excess of phenylmagnesium bromide with quinoline in diethyl ether at 150°C. (62). Bergmann and Rosenthal (47) shook quinoline with benzylmagnesium chloride in an ether–dioxane mixture for 2 days at room temperatures, and obtained both 2-benzylquinoline and 2,4-dibenzylquinoline. The reaction mechanism has been discussed previously (Section II, F).

(2) Lithium alkyls and aryls react rapidly with quinoline to give compounds of the type



which are converted by hydrolysis into 1, 2-dihydroquinolines (Li replaced by H). These can either be isolated and purified by vacuum distillation, or they may be heated with nitrobenzene and thus be oxidized to the corresponding quinoline (825a):



Specifically, quinoline, when treated with a 1.32 *N* solution of butyllithium in benzene, forms an addition product which may be hydrolyzed to give a 90 per cent yield of 2-butyl-1, 2-dihydroquinoline. Thermal decomposition of the addition compound gives 50–60 per cent of 2-butylquinoline, with elimination of lithium hydride. Phenyllithium gives principally 2-phenyl-1, 2-dihydroquinoline, with a little of the 4-phenyl derivative (825b).

Gilman and Spatz (374) treated quinoline with a slight excess of *n*-butyllithium in ether at −35°C. for 15 min. On hydrolysis, 2-butylquinoline was formed in 93.5 per cent yield, apparently without the formation of the expected intermediate, 2-butyl-1,2-dihydroquinoline. Subsequently (374a) it was shown that 6-methoxy-2-(4′-chlorophenyl)quinoline and related compounds could be made by the same method, but again the temperature and the time of reaction are of great importance. The lithium chlorophenyls were prepared by the action of butyllithium in ether on the chlorobromobenzenes.

M. 2- AND 4-ALKYLATED QUINOLINES

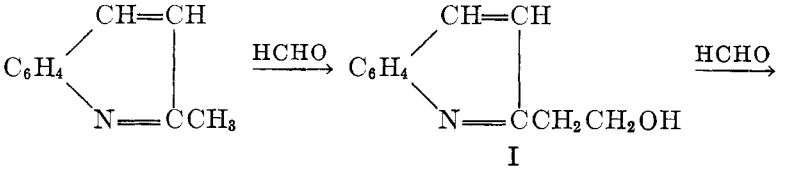
2-Alkylated quinolines are cyclic ammono ketone ethers, while the 4-alkylated quinolines are their vinylogues. From the numerous published reactions of quinaldine (2-methylquinoline, a "methyl ketone" of the ammonia system) and lepidine (4-methylquinoline) the following selection has been made, in order to show how closely they approach the aquo ketones in chemical behavior:

1. Deuterium interchange

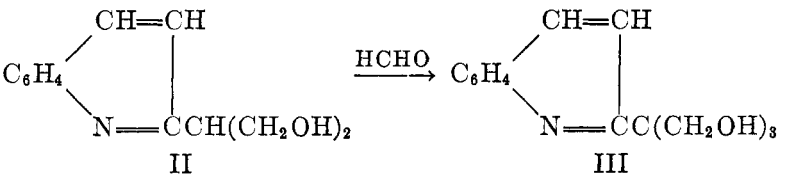
Quinaldine, when heated for 60 hr. with heavy water (D_2O) at 110°C., exchanges approximately two of its side-chain hydrogens for deuterium. Benzo-[*h*]-quinaldine exchanges one hydrogen after 104 hr. at 110°C. but two hydrogens after 108 hr. at the same temperature in 0.02 *N* sodium hydroxide. Alkali therefore catalyzes the interchange, indicating that the α-hydrogen atoms of quinaldine are mobile, though of course not to the extent of the α-hydrogens of an aquo ketone (99, 473).

2. Formation of carbinols (aldol condensation)

Quinaldine condenses with 40 per cent aqueous formaldehyde at 100°C. to give 2-quinolylethanol (I) in an aldol-type condensation. By using a larger amount of formaldehyde solution, and prolonging the time of action, bis(hydroxymethyl)-quinaldine (II) and tris(hydroxymethyl)quinaldine (III) may be prepared (491, 493, 594). The reactions follow the equations below:



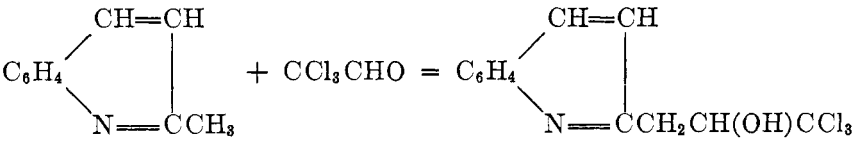
I



(82)

II III

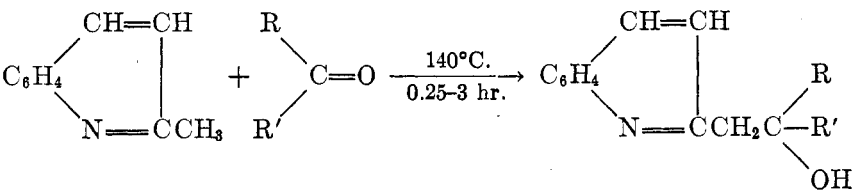
When quinaldine and chloral are heated together on the water bath, there is formed quinaldyltrichloromethylcarbinol, in accordance with the equation (274, 373, 610):



(83)

Benzaldehyde and quinaldine react in the sunlight over a period of several months to give a fair yield of phenyl(2-quinaldyl)carbinol, $C_9H_6NCH_2CH(OH)C_6H_5$ (44a). The *o*-nitro derivative of the latter may be made by heating *o*-nitrobenzaldehyde, quinaldine, and water for 10 hr. at 85–90°C. (565b), but only a nitrostyrylquinaldine is obtained from *m*-nitrobenzaldehyde (790).

McElvain and Johnson (568) have condensed several ketones containing reactive carbonyl groups with quinaldine and have prepared aldol-like condensation products in the manner of the equation:



(84)

R may be $—COOC_2H_5$ or $C_6H_5—$, while R′ is $C_6H_5CO—$; or both R and R′ may be $C_6H_5CO—$ or $—COOC_2H_5$.

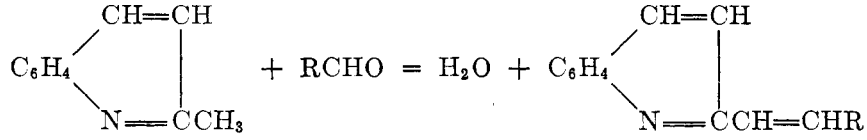
Kaplan and Lindwall (449) have recently condensed quinoline-2- and -4-aldehydes (= RCHO) with quinaldine and lepidine to form the corresponding carbinols, $RCH(OH)CH_2C_9H_6N$, by an aldol-like condensation. The reaction is brought about by refluxing the components in a solvent, ethanol, for about 6 hr. with or without the addition of a catalyst, diethylamine. It is interesting that quinoline-4-aldehyde condenses with quinaldine, but not with the less reactive lepidine.

3. Formation of styryl derivatives ("Claisen reaction")

In the preceding section, quinaldine has undergone an aldol condensation with aldehydes or ketones under comparatively mild conditions. If the reactants are heated for a longer time at higher temperatures, either alone or in the presence of a catalyst such as zinc chloride or potassium acid sulfate, water is eliminated in the manner of the familiar Claisen reaction. The parallel equations are the following:

$$C_6H_5COCH_3 + C_6H_5CHO = H_2O + C_6H_5COCH{=}CHC_6H_5 \qquad (85)$$

Sodium hydroxide, sodium alkoxides, acetic anhydride, or hydrochloric acid are suitable condensing agents.



(86)

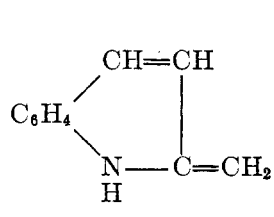
R is generally aryl.

Although zinc chloride is often used as a catalyst, as in the earlier preparations of 2-styrylquinoline (442c, 804b), it is sometimes replaced by acetic anhydride (43b, 81a, 421a; *cf.* 759), potassium acid sulfate (425a, 804b), or even by concentrated hydrochloric acid (640, 733). Since the 2- and 4-methylquinolines boil at a higher temperature and also are more reactive than the corresponding pyridines, it may be satisfactory to reflux the components for several hours without the use of a condensing agent, as in the preparation of the following: 2-*p*-dimethylaminostyryl)quinoline (640), 2-(*m*-nitrostyryl)quinoline (790), and 2-(2,4-dinitrostyryl)quinoline (43a). 2-Methyl-4-phenylquinoline, when heated for 4–5 hr. at 130°C. with benzaldehyde gives 2-styryl-4-phenylquinoline (306), but aldol-like condensation products (carbinols) are formed with *o*- and *p*-nitrobenzaldehydes.

Benzylidenediquinaldine, $C_6H_5CH(CH_2C_9H_6N)_2$, is a by-product of the action of benzaldehyde on quinaldine at elevated temperatures, or the main product, if 2 moles of the latter are used (392b, 421a, 491a).

In two cases, at least, it has been recorded that zinc chloride is harmful in the reaction of equation 86. John (444) finds that 2-phenyl-4-methylquinoline and benzaldehyde, when heated at 200–210°C., give 2-phenyl-4-styrylquinoline, but in the presence of zinc chloride, potassium acid sulfate, or an equimolar mixture of the two no condensation occurs. The use of a zinc chloride catalyst leads to the formation of troublesome by-products in the reaction between aldehydes and 2,4-dimethylquinoline (772a).

It has been suggested many times (115, 625, 760b) that quinaldine and lepidine react with aldehydes and other reagents in their isomeric enamic forms, I and II, respectively.



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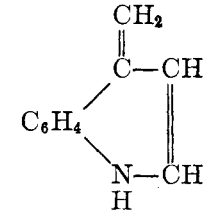
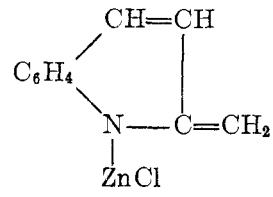


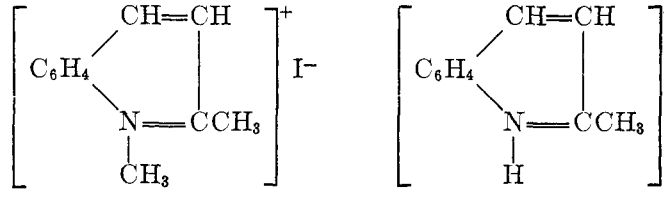
II

Such forms would certainly be favored by a basic environment, but many styrylquinolines are made under acid conditions. Sidgwick, Taylor, and Baker (760b) believe that zinc chloride and quinaldine react when heated to give an enamine derivative (III) that is active in the condensations.



III

Since quaternary salts of the type of methylquinaldinium iodide (IV) are more reactive than quinaldine itself with respect to carbonyl group condensations (see Section II, I), it is possible that formation of a quinaldinium ion (V) may increase the velocity of the condensations where potassium acid sulfate or hydrochloric acid are used as catalysts.



IV V

A related reaction in the water system is the hydrogen-ion (or positive-ion) catalyzed aldol condensation or Claisen reaction between an aquo aldehyde or ketone and a compound which contains reactive methylene (see Knoevenagel reaction, Section VI, A; reference 403a).

4. Reactions of lepidine and of 2,4-dimethylquinoline: comparison of reactivity of 2- and 4-methyl

Lepidine undergoes essentially the same reactions with aldehydes that have been described for quinaldine. It reacts with formalin solution to give mono- and di-methylol derivatives (493, 518), with benzaldehyde and zinc chloride at 180°C. to form 4-styrylquinoline (256, 271; *cf.* 498), with chloral to give an aldol-like condensation product (*cf.* equation 83) (610), and with quinoline-2-aldehyde, likewise to give a carbinol (449; see Section IV, M, 7).

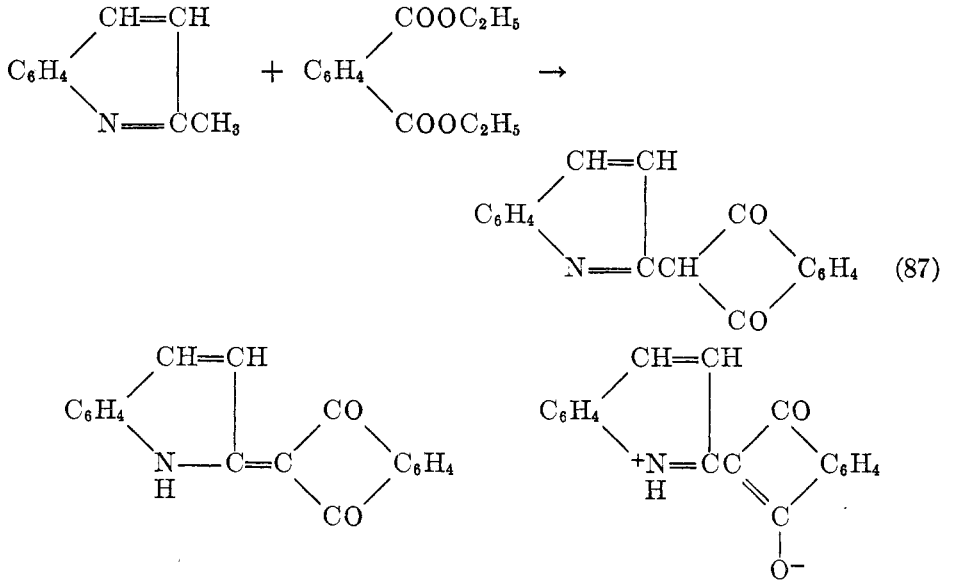
Eibner (271), in parallel experiments, heated quinaldine and lepidine (5 g. of each) with an equal weight of benzaldehyde for 3 hr. at the boiling point; there was obtained 7.95 g. of 2-styrylquinoline and only 1 g. of the hydrochloride of 4-styrylquinoline. When an excess of formaldehyde is heated with quinaldine or lepidine, there is obtained a trimethylol derivative of the former, but only a dimethylol derivative of the latter (490a, 491; *cf.* 519). 2,4-Dimethylquinoline, heated with 1 mole of formaldehyde, gives 4-methyl-2-(β-hydroxyethyl)-quinoline, and with 2 moles of formaldehyde, 4-methyl-2(β,β-dihydroxyisopropyl)quinoline (504). Chloral and 2,4-dimethylquinoline condense to form 4-methyl-2-(γ,γ,γ-trichloro-β-hydroxypropyl)quinoline or 4-methyl-2-(γ,γ,γ-trichloropropenyl)quinoline, depending upon the conditions (503, 772). 2-Styryl-4-methylquinoline may be prepared by heating equimolar parts of 2,4-dimethylquinoline and benzaldehyde (311b), while similarly the 2-methyl alone

is reactive in phthalone formation (69, 271). 2,4-Dinitrobenzaldehyde and 2,4-dimethylquinoline, when heated for 0.5 to 1 hr., give 2-dinitrostyryl-4-methylquinoline, while 6 to 8 hr. are required to form a 2,4-di(2,4-dinitrostyryl) derivative (44). In all of these experiments the 2-methyl has consistently proved to be more reactive than the 4-methyl, which is more distant from the activating —C=N— group. It is, however, reported that 2,4-dimethylquinoline may be oxidized by chromic acid and sulfuric acid to 2-methylquinoline-4-carboxylic acid, contrary to expectations (70). Oxidation by means of alkaline permanganate gives 4-methylpyridine-2,3,6-tricarboxylic acid, with destruction of the 2-methyl group (608a).

5. Claisen condensations

A Claisen condensation of two molecules of an aquo ester or of one molecule each of an aquo ester and and aquo ketone may be brought about by means of sodium, sodium ethoxide, and related alkoxides, or sodium amide. Claisen condensations that involve quinaldine or lepidine are effected by the same reagents.

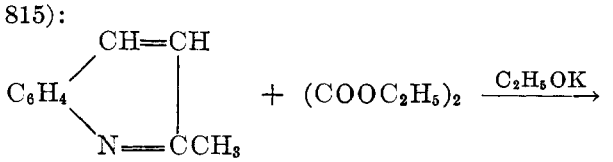
(*a*) Quinophthalone is formed in almost theoretical yield by heating quinaldine and diethyl phthalate with metallic sodium (272; *cf.* 548). The reaction follows the equation:

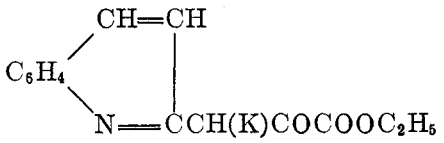


(87)

Kuhn and Bär (548) prefer one or the other of the last two formulas.

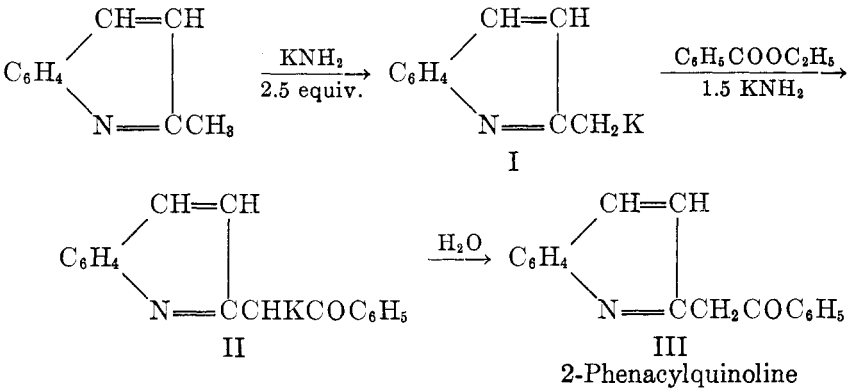
(*b*) Quinaldine was refluxed with potassium ethoxide and diethyl oxalate in ether or in ether–alcohol solution for about a day. The potassium salt of quinaldine oxalic ester was formed in accordance with the equation (81a, 81b, 815):





The free ester is obtained by decomposing the potassium salt with dilute sulfuric acid. A similar reaction takes place with lepidine (815).

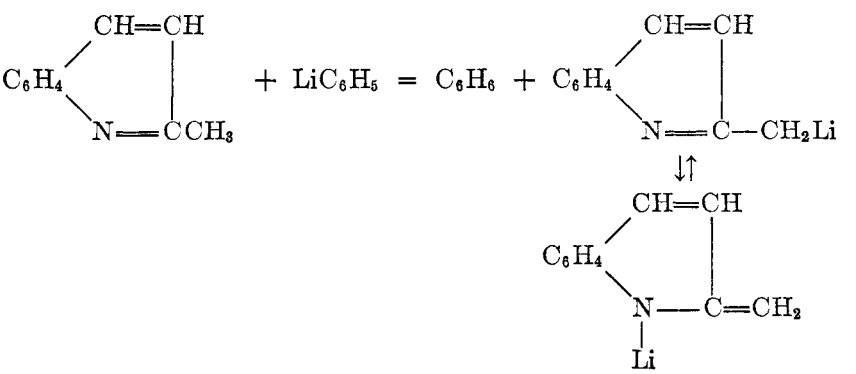
(*c*) The potassium salt of quinaldine (I) reacts with an ethereal solution of an aromatic ester, in the presence of an excess of potassium amide, to give yellow ketones, as shown in the following equations (64):

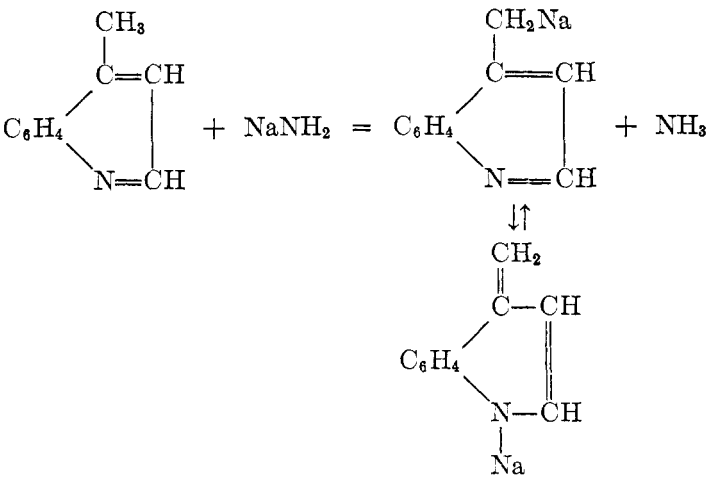


This method does not succeed with lepidine, since potassium lepidyl has too low a solubility in ether; good yields of aryl lepidyl ketones can be obtained by carrying this reaction out in liquid ammonia (317). Aliphatic esters appear to undergo metal-exchange reactions with potassium quinaldyl and potassium lepidyl, and so are unsuited for the synthesis represented by equation 89.

6. Metallic salts of quinaldine and lepidine

Quinaldine may be converted to an alkali-metal salt by treatment with phenyllithium in ether (826) (equation 90), and by the action of an alkali amide, either without solvent (118, 133) or in liquid ammonia (53, 54). Sodium and potassium salts of lepidine have similarly been made in liquid ammonia (54a).



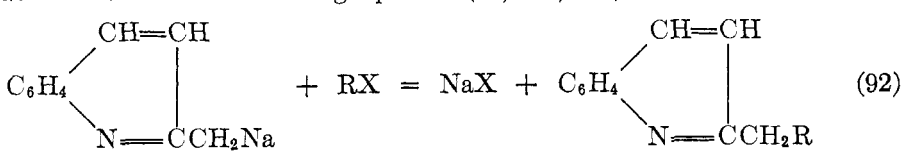


(91)

It may be presumed that the salts of quinaldine and lepidine resemble sodium acetoacetic ester in being tautomeric.

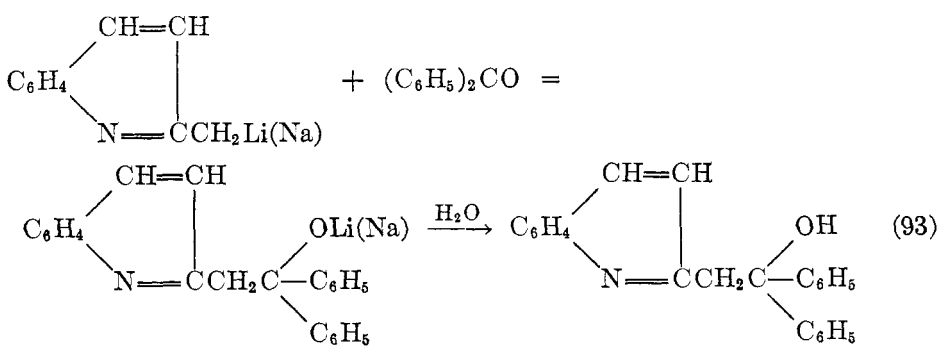
Among the reactions that have been carried out with these compounds are the following (see also section 5, just above).

Alkyl or aralkyl halides convert them to homologous quinaldines and lepidines, in accordance with the following equation (53, 118, 826):



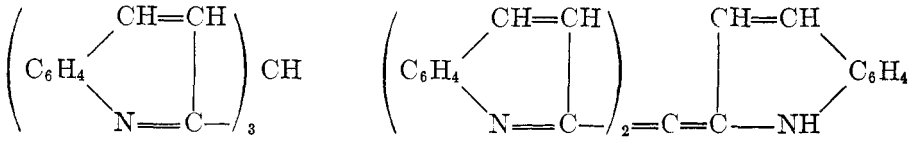
(92)

The sodium and lithium salts of quinaldine behave like a Grignard reagent in many respects, as may be seen from equation 93, which represents the formation of diphenylquinaldylcarbinol (134, 829).



(93)

While the enamic forms of quinaldine and lepidine, corresponding to the alternate structures of the metallic salts given in equations 90 and 91, have never been isolated, both di- and tri-quinolylmethanes exist in two modifications, one of which is red, and the other colorless (740a, 741, 742).



(colorless) (red)

Tri-2-quinolylmethane

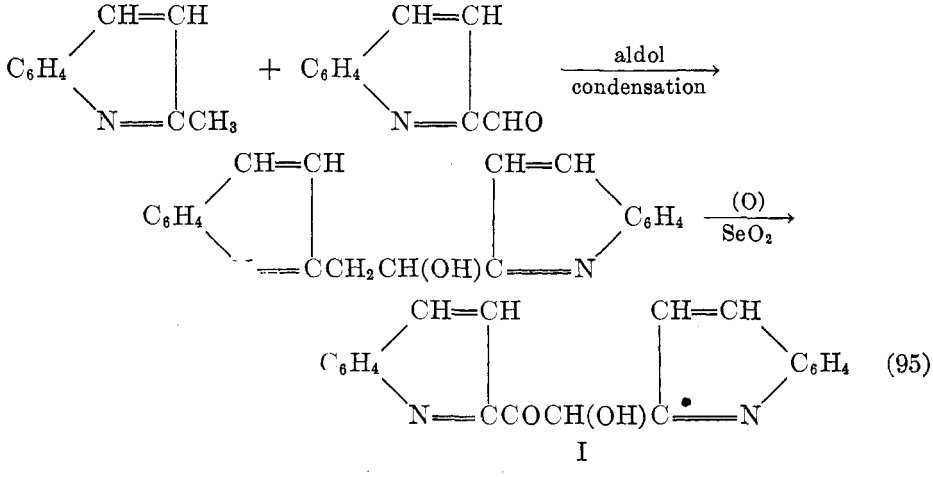
7. Oxidation with selenium dioxide

Methyl ketones of the oxygen system react with selenium dioxide when heated to form α-ketoaldehydes, in the manner of the following equation (704):

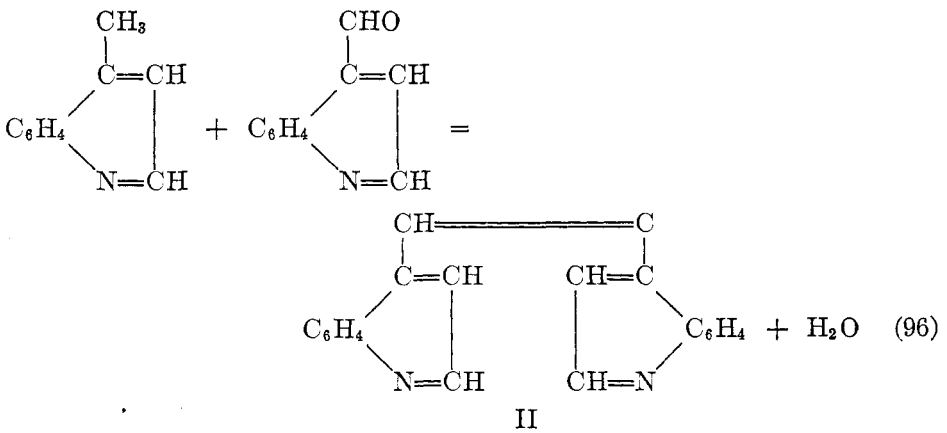
$$SeO_2 + C_6H_5COCH_3 = C_6H_5COCHO + H_2O + Se \qquad (94)$$

Henze (420), in an attempt to extend these reactions to the pyridine and quinoline series, refluxed 2-picoline, quinaldine, and a number of related compounds with selenium dioxide, and obtained the corresponding carboxylic acid ($CH_3 \rightarrow COOH$), together with smaller quantities of the aldehyde. In this fashion, 2-ethyl-3-methylquinoline is oxidized by selenium dioxide to 3-methylquinoline-2-carboxylic acid, with the destruction of the alkyl group directly attached to —C=N—.

Other workers have had better success with the selenium dioxide method for the preparation of quinoline-2- and -4-aldehydes. Kaplan (448), in repeating earlier work of Kwartler and Lindwall (549) along similar lines, found that the selenium dioxide should be freshly prepared just prior to use as an oxidant; if this is done, the yields of aldehyde will reach 58 per cent of the theoretical. If, on the other hand, the selenium dioxide had been stored unsublimed for several months, it converted quinaldine into a benzoin-type compound, quinaldoin (I), and lepidine into the ethylenic derivative (II). Possible equations are the following:



I (95)



II

2,3,8-Trimethylquinoline has similarly been oxidized to 3,8-dimethylquinoline-2-aldehyde, in 82 per cent yield (105b).

8. Quinaldine and bromine

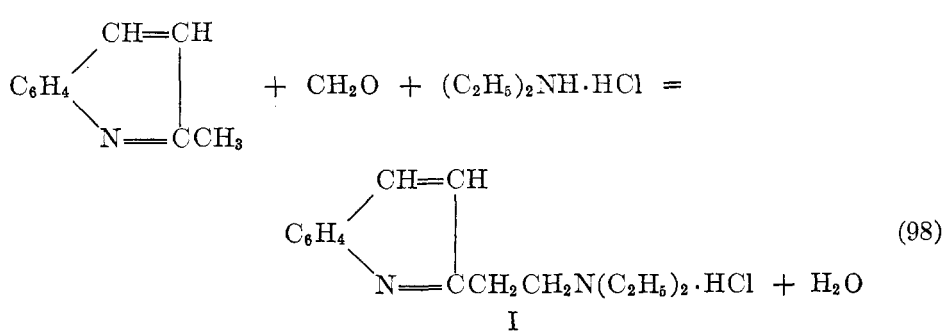
Quinaldine reacts with bromine to form ω,ω,ω-tribromoquinaldine, $C_9H_6NCBr_3$, which is converted to quinaldic acid, C_9H_6NCOOH-2, when heated with 1:10 sulfuric acid (404). The analogous replacement of the α-hydrogen atoms of an aquo ketone by halogen generally takes place readily.

9. The Mannich reaction

An aquo ketone containing a reactive methyl or methylene group reacts with formaldehyde and a primary or secondary amine in accordance with the representative equation (74, 578):

$$C_6H_5COCH_3 + HCHO + (CH_3)_2NH\cdot HCl = C_6H_5COCH_2CH_2N(CH_3)_2\cdot HCl + H_2O \quad (97)$$

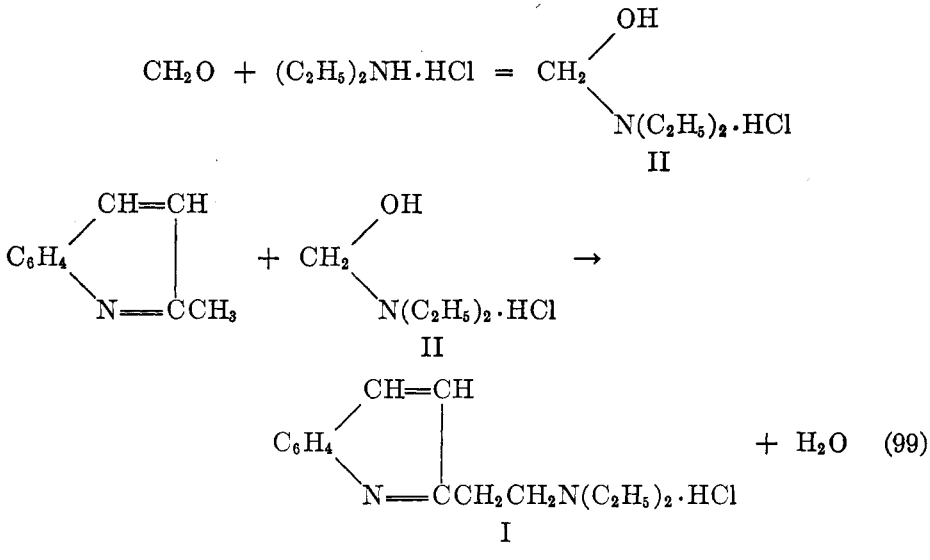
Quinaldine, 2-picoline, 2-ethoxy-4-methylquinoline, and a few related compounds have been similarly condensed with formaldehyde and primary or secondary amine hydrochlorides (288c, 289, 472, 663) in the manner of the equation below:



I

Formaldehyde (9 g. of 37.5 per cent solution) was added slowly to a mixture of diethylamine hydrochloride (10.9 g.), water (9 g.), alcohol (8 g.), and quinaldine (14.5 g.), and the mixture heated for about 2 hr. at 60°C. The reaction product colored in the air and soon resinified, but the related compound obtained from formaldehyde, lepidine, and diethylamine hydrochloride is more stable (288c).

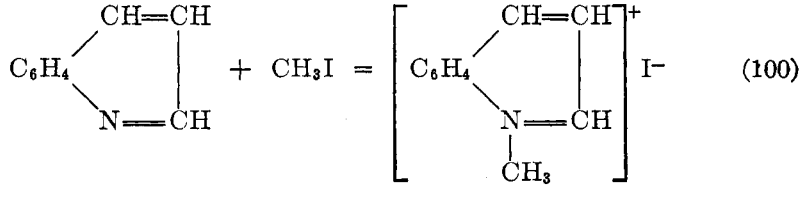
Tseou Heou-Feo (288c) has shown that the most probable mechanism is the following:



Formaldehyde and diethylamine hydrochloride condense to form the hydrochloride of diethylaminomethyl alcohol (II), which has a very readily replaceable hydroxyl group since it is an ammono aquo meroacetal (*cf.* Sections I, E and VI). Hydrochloric acid is a necessary catalyst in the reaction, suggesting that the ions, $CH_2{=}\overset{+}{O}H$ or $CH_2{=}\overset{+}{N}(C_2H_5)_2$, might be intermediates.

N. QUATERNARY QUINOLINIUM SALTS

Quinoline adds alkyl iodides, alkyl bromides, and some alkyl chlorides and esters of the type of methyl sulfate or methyl *p*-toluenesulfonate to form quaternary ammonium salts, as is shown in the equation below:

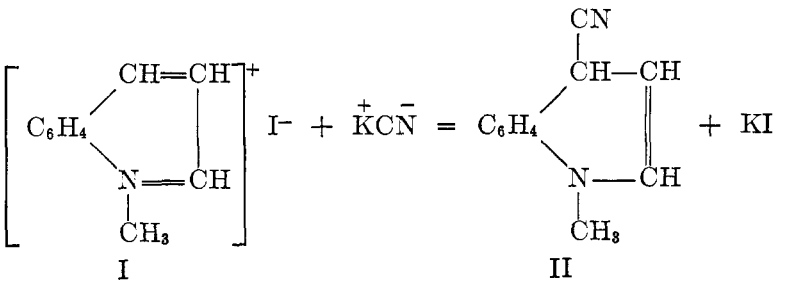


It has been pointed out previously in connection with the quaternary pyridinium salts (Section II, I) that the positive charge on the cation, while chiefly on the

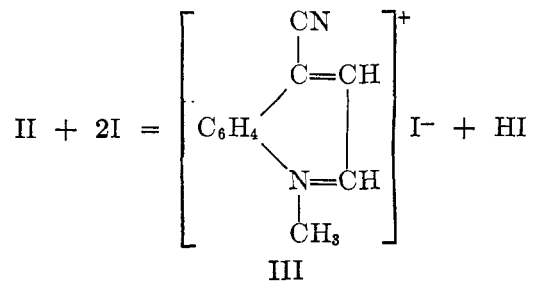
nitrogen, may resonate to the 2- and 4-positions, and increase the aldehydic or ketonic reactivity of the molecule as a whole. Therefore in many respects the study of these salts as representatives of a nitrogen system of compounds is of particular interest, as will be seen from the numerous examples that are given below.

1. Quinoline alkiodides and potassium cyanide

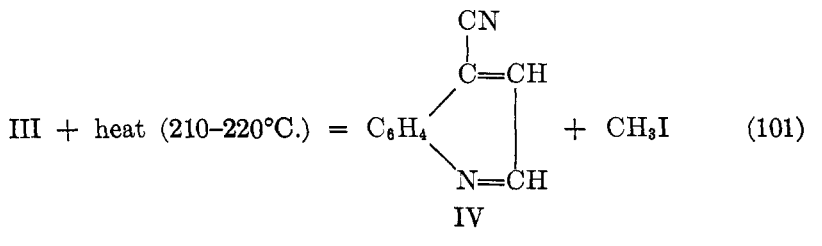
Quinoline methiodide and related salts when treated with an aqueous solution of potassium cyanide give 1-alkyl-4-cyano-1,4-dihydroquinolines in good yield. These are oxidized by iodine in methanol containing pyridine to 4-cyanoquinoline alkiodides, and the latter, when heated, are converted to 4-cyanoquinoline and an alkyl iodide. The reactions are expressed by the following equations:



I II



III

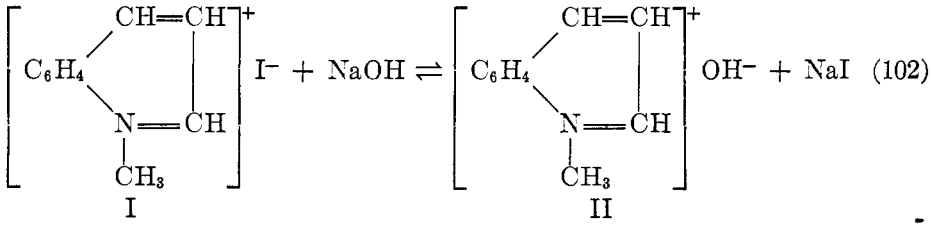


IV (101)

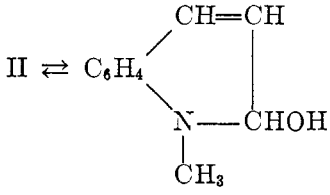
Just why the cyanogen group is attached to the 4-carbon in this reaction, and to the 2-carbon in the product obtained by treating quinoline and benzoyl chloride with potassium cyanide, is not known, but it may be connected with the difference in the polar character of the methyl and benzoyl groups (451, 454, 468, 520) (see also Section IV, F; *cf.* Section IV, N, 9, b, (1)).

2. Formation of pseudo bases

The reaction of quaternary quinolinium salts with the strongly basic hydroxyl ion follows the course of equation 102 below:



I II (102)

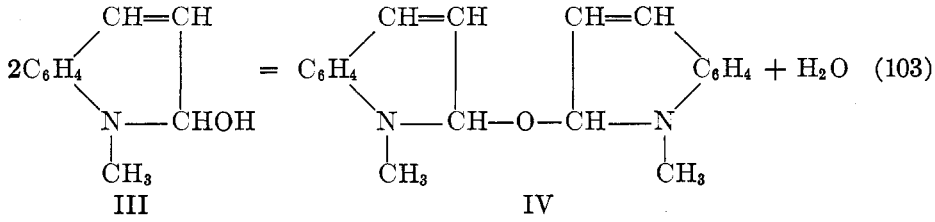


III

When alkali is added to an aqueous solution of quinoline methiodide, there results an equilibrium mixture of *N*-methylquinolinium ion, sodium ion, hydroxyl ion, and iodide ion. The solution can be said to contain the true (strong) quaternary ammonium base (II), but this is in equilibrium with the pseudo base (III), in which the hydroxyl has become attached to the 2-carbon atom.

In connection with pseudo bases of the pyridine series (Section II, I, 7), it was shown that substances of the type of III are cyclic ammono aquo meroacetals, comparable with an aldehyde alcoholate of the water system, $CCl_3CH(OH)OC_2H_5$. The relationship of the pseudo bases to the aldehyde hydrates and to aldehyde ammonias of the constitution $RCHOHNH_2$, has been clearly pointed out by Decker and Kaufmann (220; *cf.* 63), who also call attention to the fact that the change II → III is analogous to the decomposition of ammonium hydroxide into ammonia and water (215).

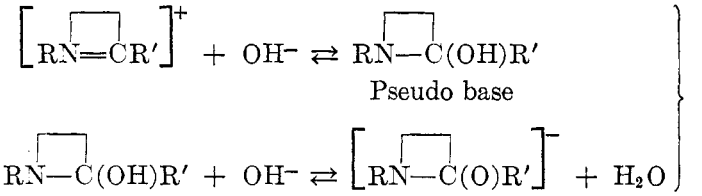
Hantzsch and Kalb (407) were the first to investigate with any thoroughness the reactions expressed by equation 102. An aqueous solution of methylquinolinium iodide was digested with an excess of silver oxide (409a) and the changes followed titrimetrically. The titre of the filtrate from the silver iodide–silver oxide precipitate, while high at first, steadily fell because of the precipitation of an insoluble ether of the composition IV (see also 200, 218, 459).



III IV (103)

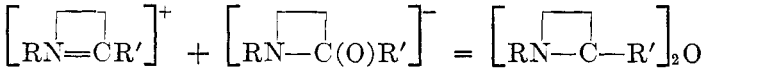
Therefore, it is this ether that is the cause of the slowly developing cloudiness when alkali is added to a solution of quinoline methiodide in water at room temperatures (409a). In benzene or alcohol solution, IV is easily decomposed with the formation of reddish "smears" and resins, while hydrochloric acid in water converts it to *N*-methylquinolinium chloride, a salt of the true base (II). If the same reaction is carried out in benzene under anhydrous conditions, there is obtained a reddish precipitate containing more chlorine than the salt, into which it passes when treated with water.

Aston and coworkers (17, 18) consider that the point of equilibrium in the reaction, II → III, lies far over on the left, in favor of the true base, since pseudo bases appear to form in quantity only when the conjugation of an aromatic six-membered ring is not broken. The mechanism of ether formation from the pseudo base is regarded as the following:



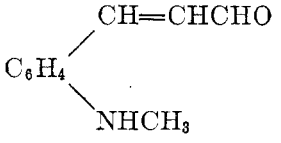
(104)

Both of the above equilibria are established rapidly. The quaternary ammonium cation and the negative alkoxide ion then react more slowly to form the ether, as shown in the equation:



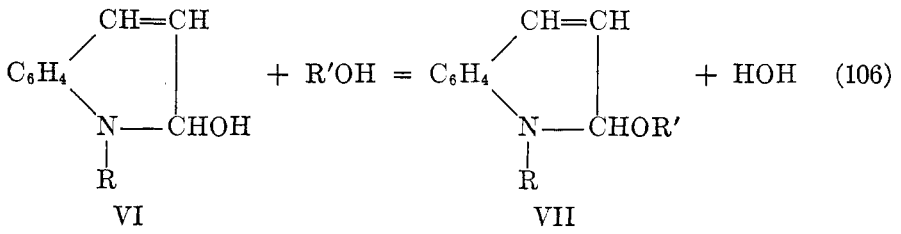
(105)

The hydroxyl group in the pseudo bases, or 1-alkyl-2-hydroxy-1,2-dihydroquinolines, is very mobile (220, 460) and may be readily replaced by other groups, as will be seen from the examples listed below (*cf.* also cotarnine and hydrastinine in Sections V, I and J). Many investigators (216, 371a, 371b, 458, 707, 729) believe that the high reactivity of this class of compounds is best explained on the basis of an open-chain amino aldehyde formula,



although the evidence seems to point to the correctness of the cyclic form (216). An equilibrium between the two is not excluded, since the related meroacetal (hemiacetal), glucose, appears to exist as an open-chain aldehyde in an amount not exceeding a few tenths of 1 per cent.

(*a*) When the pseudo bases are crystallized from alcohol, they react to form the corresponding alcoholate, or "oxygen ether", in accordance with the equation:

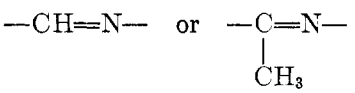


VI VII

A cyclic ammono aquo meroacetal has been converted to a cyclic ammono aquo acetal (VII). Crystallization of the latter from another alcohol will replace R′ by the group derived from that alcohol (188a, 201, 371d, 458).

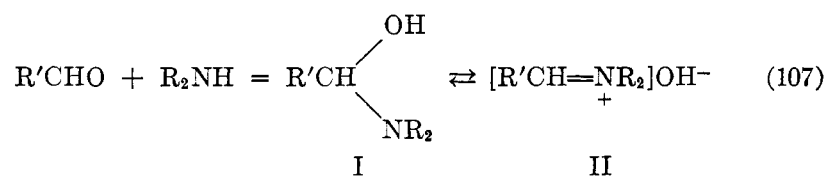
Related changes of the water system are known, since chloral alcoholate, $CCl_3CH(OH)OC_2H_5$ reacts reversibly with alcohols to form ethanol and another chloral alcoholate (371e, 548a). Aquo acetals probably would require acid catalysts to effect such an interchange reaction under mild conditions.

(*b*) Decker and Kaufmann (219) believe that the cyanines owe their formation to the reactivity of these carbinols or pseudo bases, in a manner more fully developed in Section IV, N, 9. It may be said in passing that some of the reactions are related rather closely to the aldol condensation between an aldehyde and a ketone, the ketones in question being the quaternary quinaldinium or lepidinium salts. In view of the earlier discussion of pyridine alkiodides (Section II, I), it is clear that the positive charge on the cation of a quaternary quinolinium salt will increase the aldehydic or ketonic reactivity of the linkages, respectively,



particularly in those reactions which concern a basic anion. The question as to whether the positive quinaldinium ion or the pseudo base is involved in a particular condensation is somewhat akin to a decision as to whether or not an aldehyde in water solution reacts as the free aldehyde, or as the aldehyde hydrate, or in alcoholic solution as the hemiacetal. It is possible that both forms are reactive but under different experimental conditions. Decker and Kaufmann (221) have already speculated upon this possibility.

Open-chain equivalents of a pseudo base, or ammono aquo meroacetal, may sometimes be prepared by the addition of an amine to an aldehyde, in the manner of the following equation (290, 570, 777):



I II

The high reactivity of the known representatives of this class of compounds has led many investigators to assume that they are intermediates in amine-catalyzed

condensations of the type of Knoevenagel reaction. Within recent years, there has been a tendency to consider that other mechanisms are the more probable (see Section VI, A, 1).

At the time of the appearance of the paper of Decker and Kaufmann (221), Hope and Robinson (436; *cf.* 715a) explained the function of the secondary amine as a catalyst in the following manner: The addition compound (I) formed by the action of a secondary amine on an aldehyde or ketone is an open-chain pseudo base, which is believed to be in equilibrium with the true base (II), at least in an ionizing solvent such as water. The cation of II may be considered a specialized type of ammono aldehyde ether, of very high reactivity toward basic anions, such as are derived from compounds with reactive methylene. Related cyclic compounds are the quaternary pyridinium and quinolinium hydroxides (*cf.* Section IV, N, 9, b, (1)). The positive ion of II can unite with the negative residue of HX, where X is CN, $-CH_2NO_2$, $-CH_2C_6H_3(NO_2)_2$, etc., to give

$$[R'CH{=}\overset{+}{N}R_2]X^-$$

which is unstable and soon becomes $R'CH\underset{X}{|}NR_2$. The latter is stable if X is CN, but if X contains a reactive methylene group, dialkylamine may be lost (i.e., the catalyst is regenerated) to form a condensation product, such as $R'CH{=}CHNO_2$ or $R'CH{=}CHC_6H_3(NO_2)_2$.

It is possible for a system of the structure $R\overset{\alpha}{C}H_2CH{=}\overset{+}{N}R_2$ to add to a carbonyl group or to its ammonia system equivalent, —C=N—, since the ionization of a hydrogen in the α-position will be favored by the positive charge on the nitrogen ($-I$ effect).

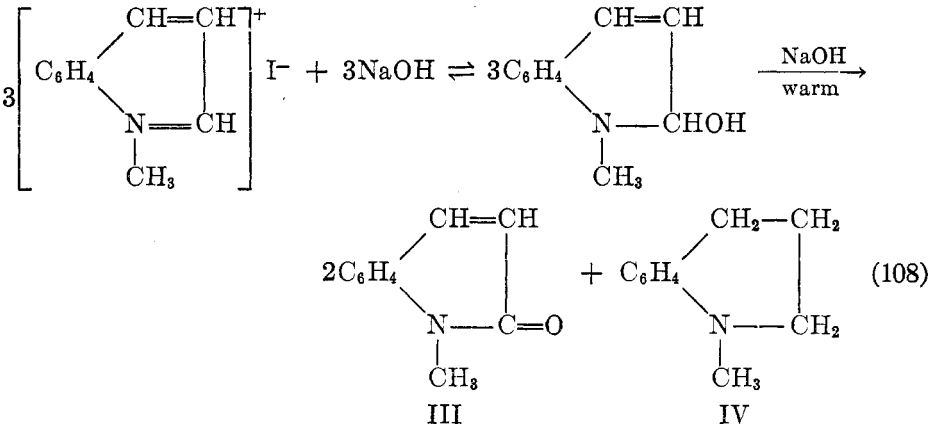
In summarizing, it may be said that the chemistry of the pseudo bases can be explained on the basis of either the carbinol or the quaternary ammonium hydroxide formulas.

Many reactions of an aquo aldehyde or ketone, including the aldol condensation, are catalyzed by the hydrogen ion, which is generally assumed to add to the carbonyl oxygen to form an oxonium ion, as shown in the equation below (*cf.* 83a, 403a):

$$R_2C{=}O + H^+ \rightarrow R_2C{=}\overset{+}{O}H \qquad (110a)$$

The positive charge on the oxygen will function as does the positive charge on the nitrogen in the cases just discussed and will increase carbonyl reactivity, as with the oxonium salts that are mentioned in Section III. It is possible that quinoline ring closures that depend upon the reaction between an aldehydic terminal of a side chain and an ortho hydrogen of the ring are catalyzed in this manner (see Section IV, A; compare the formation of triphenylmethane dyes from phenols or dialkylanilines and aromatic aldehydes or ketones in the presence of zinc chloride or phosphorus oxychloride).

(*c*) Quinoline methiodide is converted by an excess of warm alkali into a mixture of 1-methyl-2-quinolone (III) and 1-methyl-1,2,3,4-tetrahydroquinoline (IV), in accordance with the equation (191):



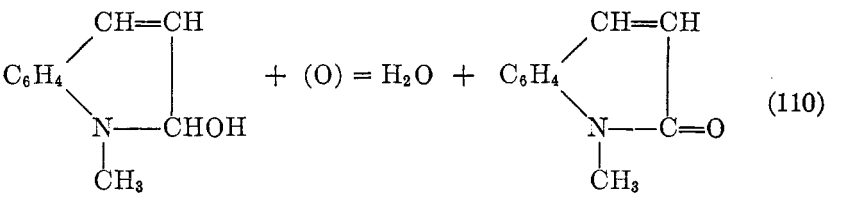
(108)

III IV

The yields do not appear to be very good. Since 1-methyl-2-quinolone (III) is a cyclic ammono aquo ester, and since 1-methyl-1,2,3,4-tetrahydroquinoline (IV) is a cyclic ammono ether, the reaction of equation 108 is related to the Cannizzaro reaction below, though not strictly comparable.

$$2C_6H_5CHO + NaOH(conc.) = C_6H_5COONa + C_6H_5CH_2OH \quad (109)$$

(*d*) Oxidation of an alkaline solution of a quinolinium salt—which contains a small amount of pseudo base—leads to the formation of a 1-alkyl-2-quinolone, as shown in the equation below:

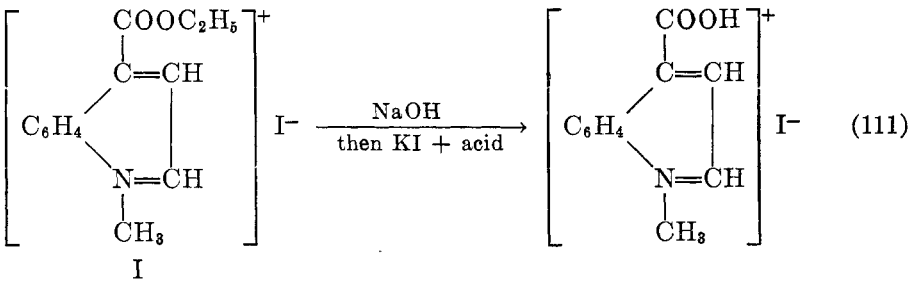


(110)

The oxidation is accomplished by potassium ferricyanide in alkaline solution, or electrolytically (188, 197, 202, 210, 294, 308, 684). A cyclic ammono aquo meroacetal (the pseudo base) is oxidized to a cylic ammono aquo ester.

3. Quaternary salt of cinchoninic acid ester

The iodomethylate of the ethyl ester of cinchoninic acid (I) when treated with alkali or ammonia gives a thick dirty white precipitate, probably of the pseudo or carbinol base. This dissolves slowly in excess of alkali at ordinary temperatures. When treated with potassium iodide and acid, there is obtained the methiodide of cinchoninic acid, indicating that quaternary salt formation has increased the rate of saponification of the ester (232).

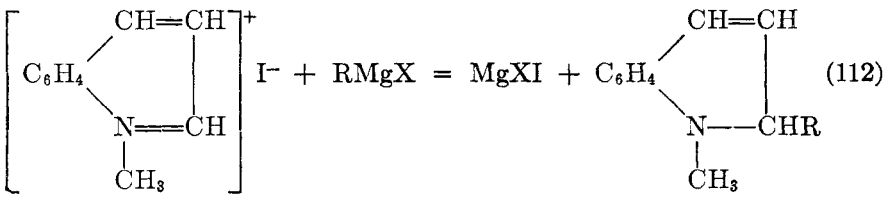


(111)

I

4. Quinoline alkiodides and the Grignard reagent

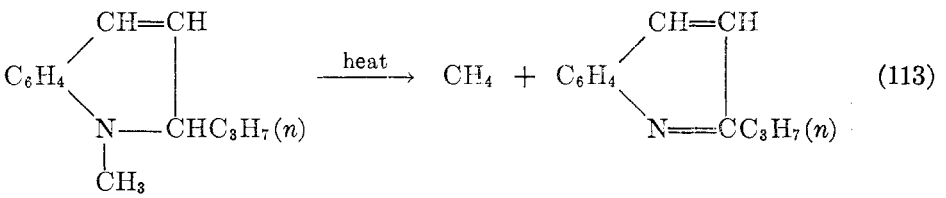
The Grignard reagent reacts with quinoline alkyl halides in ether to form 1,2-dialkyl-1,2-dihydroquinolines in good yields in accordance with the equation (84, 332, 338, 341, 592, 593):



(112)

I II

Quinoline methiodide (I), here regarded as a specialized type of aldehyde (see Sections II, I; IV, N), has been converted by the Grignard reagent to a cyclic ammono ether (II). The latter may often be thermally decomposed to a hydrocarbon and a 2-substituted quinoline, as in the specific example below (592a; *cf.* 338):

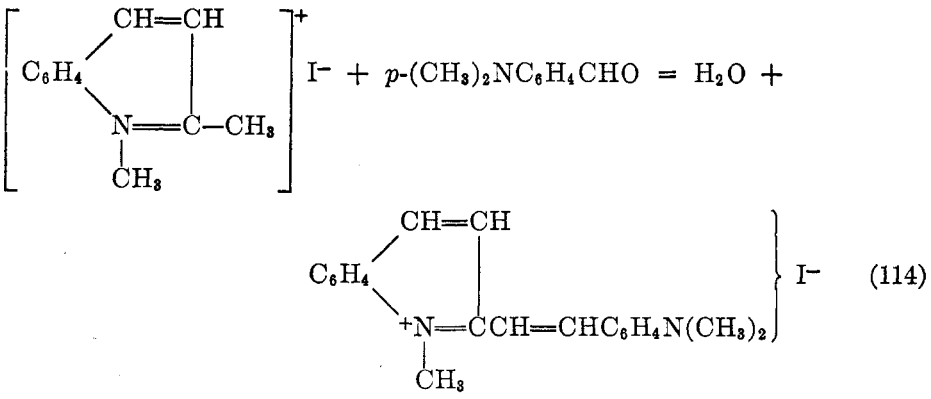


(113)

5. The alkiodides of quinaldine and lepidine

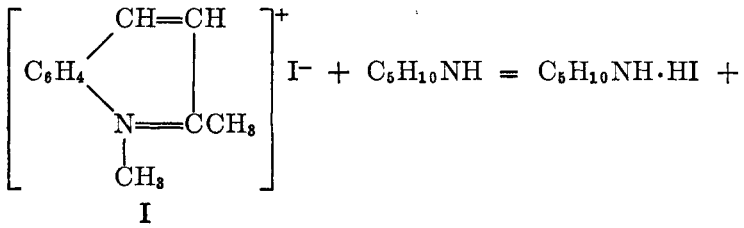
Quaternary salt formation not only increases the aldehydic reactivity of quinoline, but also the ketonic reactivity of quinaldine and lepidine, as the following illustrations will show:

(*a*) Quinaldine methiodide is mixed with the theoretical quantity of *p*-dimethylaminobenzaldehyde and dissolved in alcohol by short warming. A few drops of piperidine are added, and the mixture refluxed for 2–3 hr., whereupon the methiodide of *p*-dimethylaminostyrylquinoline is formed (514, 734; *cf.* 620):

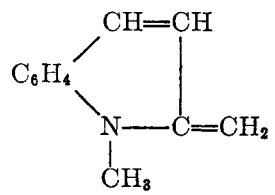


König and Treichel (516) remark that this condensation goes especially readily with *p*-aminobenzaldehyde, but less readily with the ortho isomer. Quinaldinium salts in general react sensibly faster than lepidinium salts, and both are much more reactive than the free heterocycles, showing the great activating influence of the positive charge on the cation. Within comparatively recent years there have been prepared a large number of substituted styrylquinoline alkiodides (19, 35, 95, 173, 184, 184c, 399, 400, 474, 516, 596, 655a, 711b).

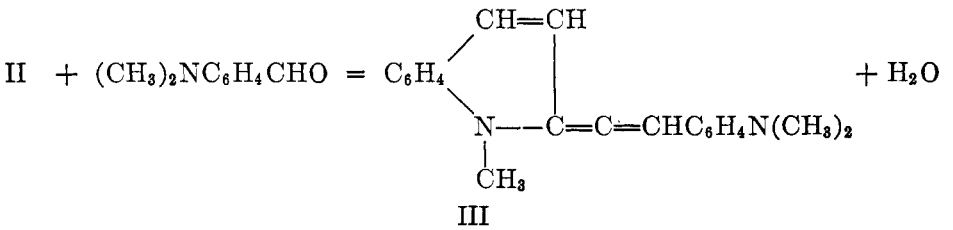
According to Mills, Smith, and Raper (617, 625; *cf.* 760b) the mechanism of the reaction of equation 114 is the following: Quinaldine methiodide, to take a specific example, reacts with the small amount of piperidine or other secondary amine used as a catalyst to form some 1-methyl-2-methylene-1,2-dihydroquinoline (II) (a "methylene base"), which condenses with dimethylaminobenzaldehyde to give an allenic compound (III). This abstracts hydrogen iodide from piperidine hydroiodide to form the final product, 2-(*p*-dimethylaminostyryl)-quinoline methiodide (IV), with regeneration of the catalyst, piperidine. The equations are the following:



I

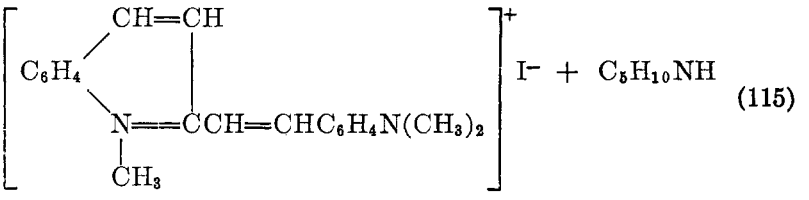


II



III

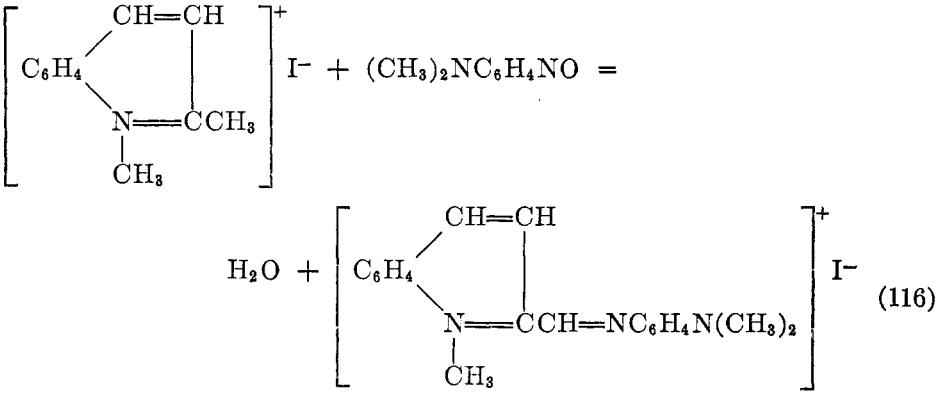
III + $C_5H_{10}NH \cdot HI$ =



(115)

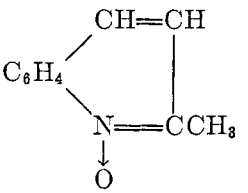
IV

(*b*) Quinaldine alkiodides react with *p*-nitrosodimethylaniline in the manner of equation 116, but quinaldine itself (75, 463) does not.



(116)

(*c*) Henze (421) has carried out reactions with quinoline *N*-oxide and quinaldine *N*-oxide



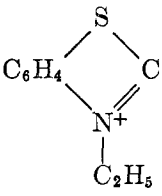
hoping that the reactivity would be enhanced by the positively charged nitrogen, just as it is with the quaternary quinaldinium salts. Definite conclusions cannot be drawn at the present time.

(*d*) Ammono aldehyde ethers and ammono esters or ammono aquo esters react

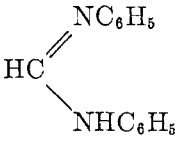
with quaternary salts containing a reactive methyl group. It has thus been found that the alkiodides of 2-methylbenzothiazole (V), quinaldine, lepidine, and related substances react not only with aquo aldehydes, but also with the ammono dialdehyde ether, β-anilinoacrolein anil,

$$C_6H_5NHCH{=}CHCH{=}NC_6H_5 \rightleftarrows C_6H_5N{=}CHCH_2CH{=}NC_6H_5$$

which may be considered to be a derivative of malondialdehyde (98). Diphenylformamidine (VI) is a diphenyl ester of ammonoformic acid (formamidine), $HC(=NH)NH_2$, and resembles aquoformic acid or its esters in having aldehydic characteristics. Glutacondialdehyde dianil (VII) is an ammono dialdehyde ether.



V

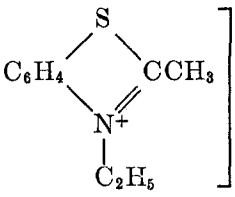


VI

$$C_6H_5N{=}CHCH_2CH{=}CHCH{=}NC_6H_5 \rightleftarrows C_6H_5NHCH{=}CHCH{=}CHCH{=}NC_6H_5$$

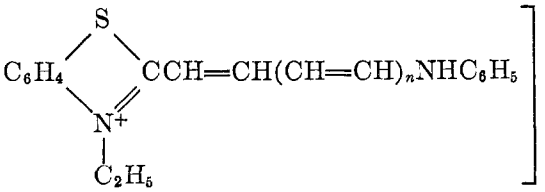
VII

Diphenylformamidine ($n=0$), β-anilinoacrolein anil ($n=1$), and glutacondialdehyde dianil ($n=2$) may all be represented by the general formula VIII below, and the reaction with a typical quaternary salt, 2-methylbenzothiazole ethiodide (V), may be written in the following manner:



$I^- + C_6H_5N{=}CH(CH{=}CH)_nNHC_6H_5 =$

V VIII



$I^- + C_6H_5NH_2$ (117)

IX

The anils are used as hydrochlorides, and when the condensation takes place in acetic anhydride solution, the terminal $—NHC_6H_5$ becomes $—N(COCH_3)C_6H_5$. The formation of these compounds affords a further example of the similarities of

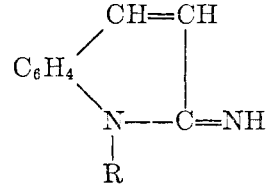
the ammono aldehyde ethers (Schiff bases) and the aquo aldehydes (98, 655, 823a). The condensation products (IX) are useful in the preparation of cyanine dyes (see Section IV, N, 9, b, (1) to (3)).

6. The alkiodides of 2-alkylthio-, 2-alkylseleno-, and 2-aryloxy-quinolines

The alkiodides of 2-alkylthio- or 2-alkylseleno-quinolines may be prepared by heating 2-iodoquinoline alkiodides with a mercaptan or with an alkyl hydrogen selenide, respectively (91a). Together with the 2-aryloxyquinoline alkiodides, they have been of value in the preparation of some monomethine cyanine dyes that otherwise are not readily obtainable (Section IV, N, 9, b, (1)).

7. The alkiodides of 2- and 4-halogenated and 2- and 4-aminated quinolines

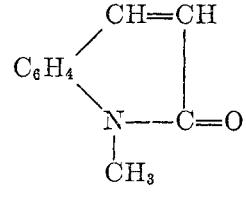
The reactivity of halogen in the 2- or 4-position of quinoline is increased by quaternary salt formation. 2-Iodoquinoline methiodide (394) thus reacts with boiling sodium hydroxide solution to form *N*-methylquinolone, and with alcoholic ammonia, dimethylamine, aniline, or phenylhydrazine to give 2-amino- or substituted 2-amino-quinoline methiodides (730b). Patents have recently been granted for the preparation of *N*-alkyl-2-quinolonimine derivatives by the action



of ammonia or of amines on quaternary salts of 2-chloro- or 2-bromo-quinoline (666).

Brydowna (102a) prepared 4-iodoquinoline methiodide by heating 4-chloroquinoline with methyl iodide, and found that it reacts readily with aniline, alcoholic ammonia, hydrazine, and phenylhydrazine to form 4-amino- or substituted 4-amino-quinoline methiodides. Alekseeva (8) heated 4-chloro-2-methylquinoline methiodide and aniline for 2 hr. at 120°C. and obtained the methiodide of 4-phenylamino-2-methylquinoline.

The 2- and 4-aminoquinoline alkiodides are often considered the hydroiodides of 1-alkyl-2-(or 4-)quinolonimine (see formula above) (113b, 169). Both 2-aminoquinoline methiodide (730a) and 2-dimethylaminoquinoline methiodide (730) are converted to 1-methyl-2-quinolone



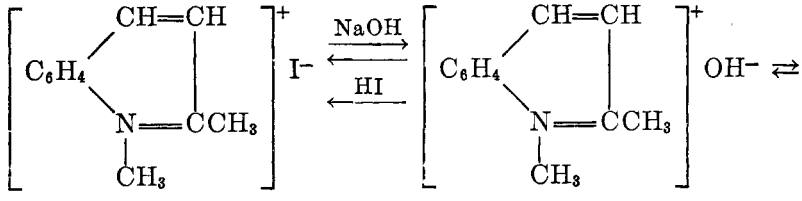
by boiling with an aqueous solution of sodium hydroxide. The methiodides of a cyclic ammono acid ester and of a cyclic ammono ester, respectively, have been

hydrolyzed to a cyclic ammono aquo ester and ammonia or dimethylamine. Since 2-aminoquinoline appears to be converted to 2-hydroxyquinoline with somewhat more difficulty (168), the hydrolyses under discussion have been accelerated by the positive charge on the nitrogen.

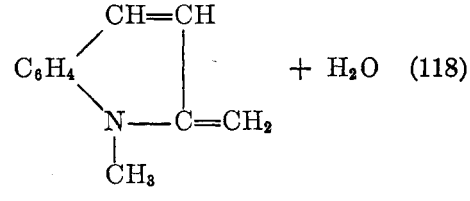
Advantage is taken of the reactivity of the nuclear halogen of 2- or 4-iodoquinoline or -pyridine alkiodides in the formation of cyanine dyes (see Section IV, N, 9, b, (1)).

8. Methylene bases from 2- and 4-alkylquinolines

The alkiodides of quinaldine, lepidine, and related compounds are converted by alkali to "methylene" bases, in the manner of the equations:

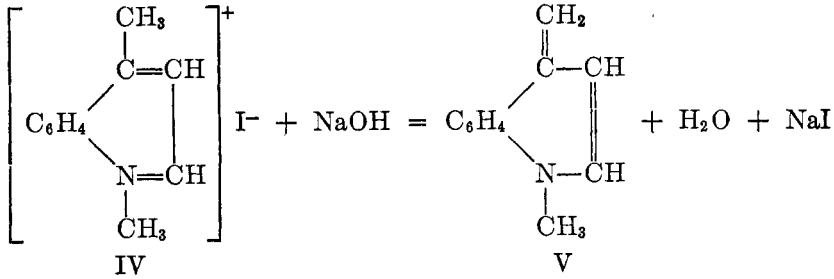


I II



III (118)

Similarly,

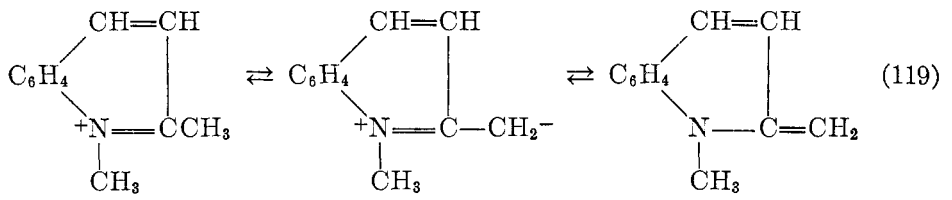


IV V

The mechanism of the formation of the methylene base (III or V) is not definitely known. Perhaps the pseudo base, with hydroxyl attached to either the 2- or the 4-carbon atom, is an intermediate which passes by loss of water into III or V.

It has been suggested that the first step in the reaction is the ionization of a hydrogen of the methyl group of the quaternary salt, a process that will be

favored by the positive charge on the nitrogen and also by an alkaline environment.



VI VII III (119)

In this way there is formed the dipolar ion VII, which is in its non-polar form the methylene base itself (III). The two are doubtless in resonance. Some references to the methylene bases of the quinoline series are the following: 194, 505, 506, 507, 618, 720, 721a, 745, 746.

Decker (193a, 224a) has shown very clearly that there is an equilibrium between the methylene base (III) and the strong quaternary base (II) of equation 118. Non-aqueous and non-polar solvents extract the methylene base from water solution, while, conversely, water extracts the quaternary ammonium hydroxide (II) from the non-polar solvent.

The methylene bases are as a class difficult to isolate in an analytically pure condition and to keep because of their high chemical reactivity (*cf.* 618), which is comparable to that of the enolic form of an aquo ketone. 1-Methyl-2-methylene-1,2-dihydroquinoline (III) of equations 118 or 119 is the *N*-ether of the enamic or ammono enolic form of quinaldine, while 1-methyl-4-methylene-1,4-dihydroquinoline (V of equation 118) is a vinylogue.

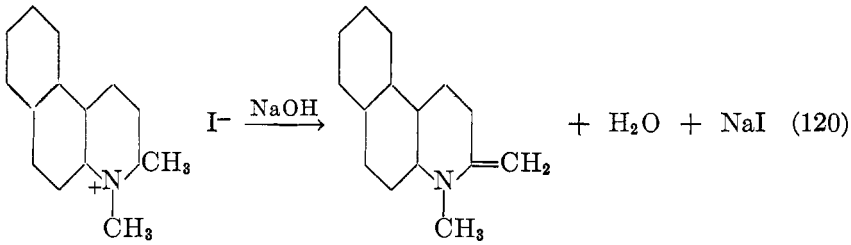
Some of the reactions which are characteristic of the methylene bases are given below:

(*a*) The function of methylene bases as intermediates in the synthesis of styrylquinoline alkiodides and of the cyanine dyes is discussed elsewhere (see Sections IV, N, 5; IV, N, 9, b, (1)).

(*b*) Rosenhauer, Hofmann, and Unger (721a) prepared 1-methyl-2-methylene-1,2-dihydroquinoline (III) in the following manner: The quaternary salt formed by heating quinaldine and dimethyl sulfate was dissolved in a little water and dilute sodium hydroxide slowly added. The oily liquid separating was at once extracted with ether, and the latter then dried and concentrated in a vacuum desiccator to obtain yellow prisms (m.p. 71–72°C.) of the methylene base. This shortly turns reddish in air and resinifies, so an analysis must be carried out as rapidly as possible. If the ether extraction is delayed, or if the methylene base precipitates out in a solid form, it has a lower solubility, indicating that some polymerization has occured. Needless to say, most of the reactions of this compound have been carried out either with an ethereal solution (*cf.* 746) or with the unpurified material shortly after precipitation.

A more stable methylene base (VIII) has been prepared by Mills and Raper

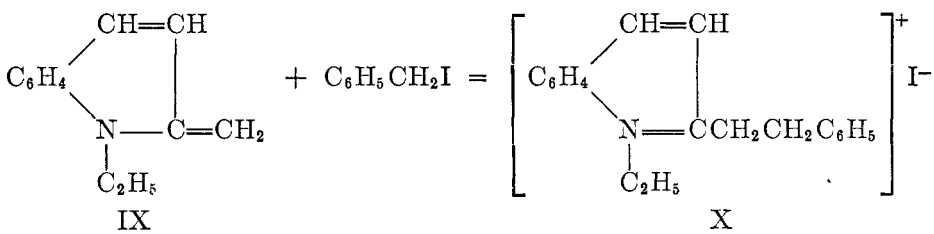
(618) from the iodomethylate of 3,4-dimethyl-3,4-dihydrobenzo[*f*]quinoline, in accordance with the equation:



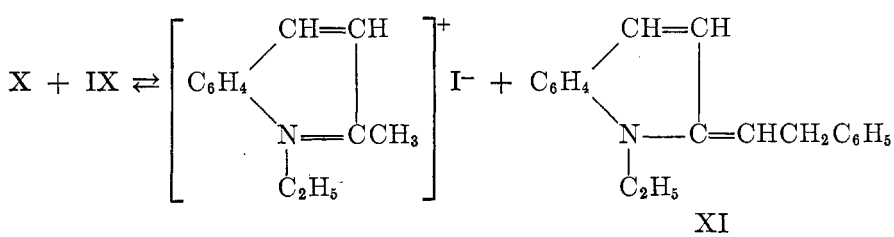
VIII

Mills (619a, 625), Robinson (13, 413, 714), Decker (194a), Sidgwick, Taylor, and Baker (760b), and others have adequately discussed the mechanism of the condensations undergone by the methylene bases.

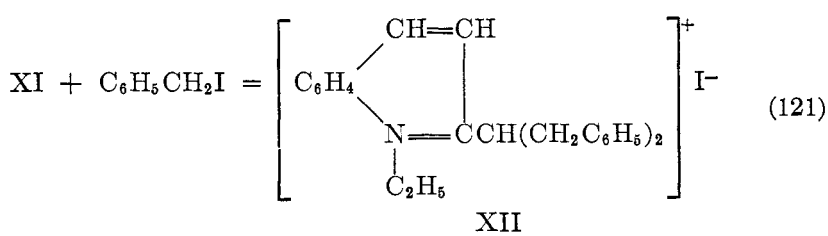
(*c*) The methylene base from quinaldine ethiodide (IX), when heated for 0.5 hr. with benzyl iodide in benzene, gave a mixture of quinaldine ethiodide, dibenzylquinaldine ethiodide (X), and some isocyanine (619), in accordance with the equation below:



IX X

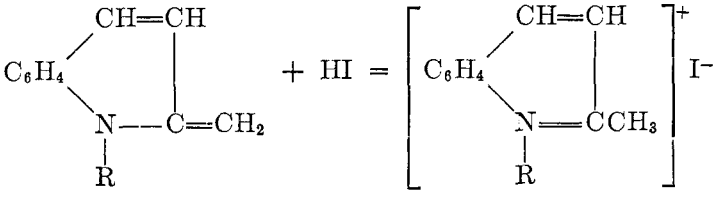


XI



XII (121)

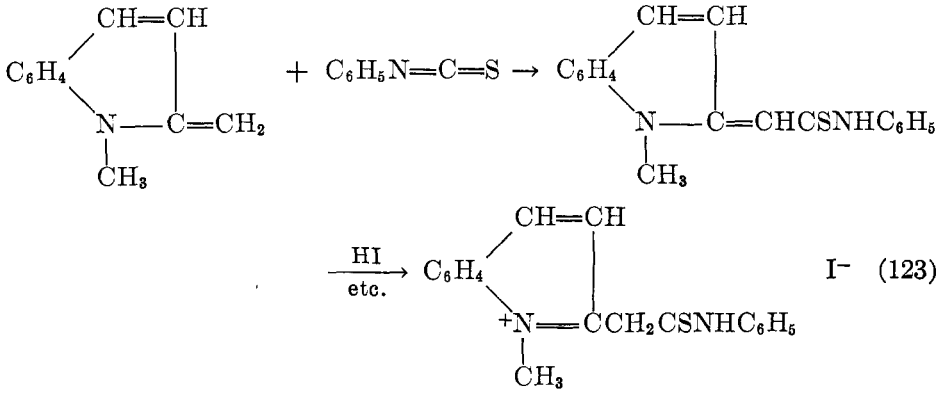
The first step of the reaction, IX → X, may be compared with the more rapid addition of hydrogen iodide to the methylene base to give a quaternary salt, as shown in the following equation:



(122)

(*cf.* equation 118).

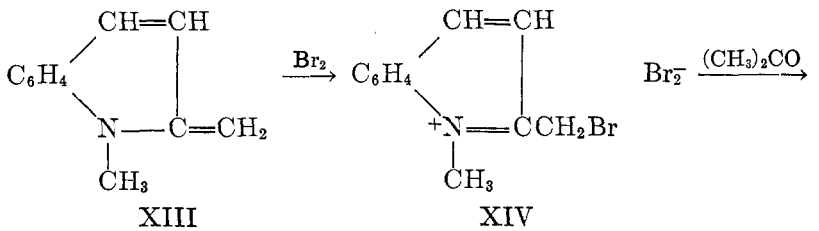
(*d*) 1-Methyl-2-methylene-1,2-dihydroquinoline and related compounds react readily with phenyl isothiocyanate or with phenyl isocyanate to form addition compounds, in the manner of the following equation (747):



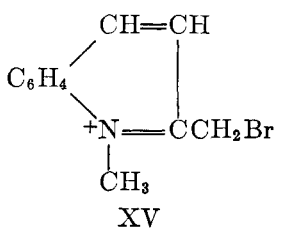
(123)

The methylene base has added to the C=N linkage of phenyl isothiocyanate to form an intermediate, which halogen acid changes to the quaternary salt shown in the last formula above.

(*e*) Rosenhauer (718) treated 1-methyl-2-methylene-1,2-dihydroquinoline (XIII) in ether or benzene solution with bromine and obtained a yellow perbromide (XIV), which lost one atom of bromine when acetone was added, giving the highly reactive ω-bromoquinaldine methobromide (XV).



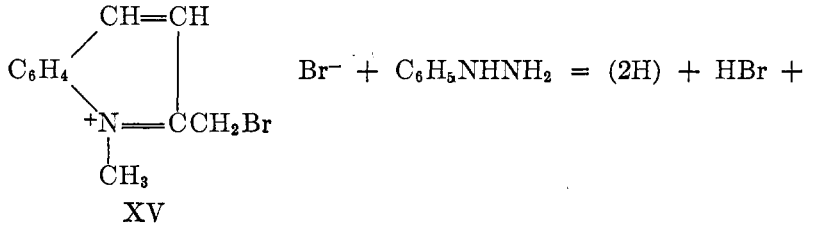
XIII XIV



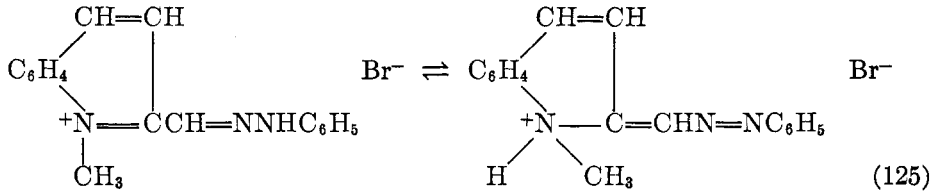
XV

(124)

The bromine atom in the side chain of XV has an enhanced reactivity, at least toward amines and basic reagents, because of the effect of the positively charged nitrogen. Thus, when phenylhydrazine and XV are warmed for a short time on the water bath, the bromine is replaced in accordance with the following equation:



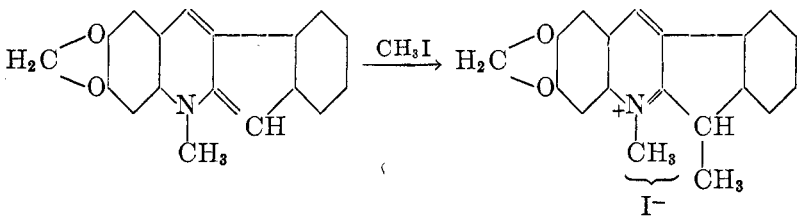
XV



XVI XVII (125)

The expected reaction product has lost two hydrogens to form the dye, XVI or XVII.

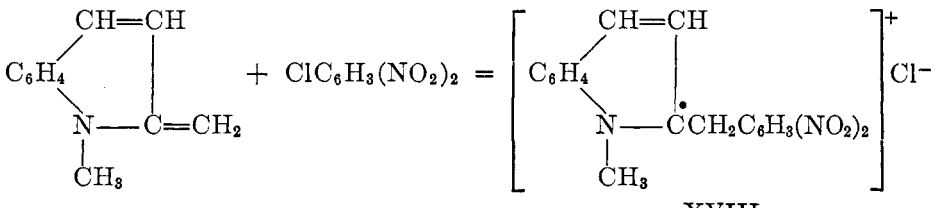
(*f*) Armit and Robinson (13; *cf.* 413, 714) have added methyl iodide to an anhydro (methylene) base, in the manner of the equation:



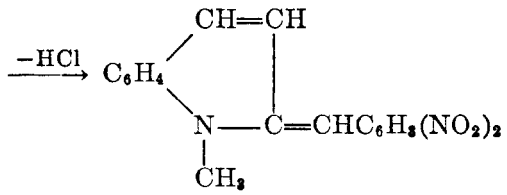
(126)

The resemblance to the reaction of Mills and Raper (Section (c) above; see reference 619) is evident.

(*g*) 2,4-Dinitrochlorobenzene and picryl chloride add to 1-methyl-2-methylene-1,2-dihydroquinoline to form addition compounds of the type of XVIII, which are considered to be carbenium salts (817) since hydrochloric acid is readily lost to give side-chain unsaturated substances similar to XIX.



XVIII

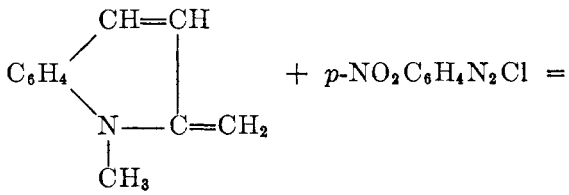


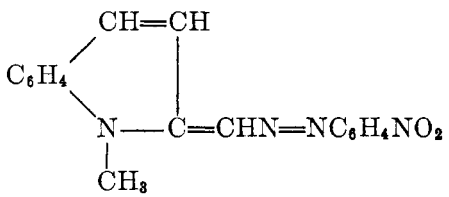
(127)

XIX

The positive charge is assumed to be localized on the 2-carbon atom of XVIII, but the reaction can be explained equally well by saying that it is on the nitrogen.

(*h*) 1-Methyl-2-methylene-1,2-dihydroquinoline, in resemblance to acetoacetic ester and other enolizable ketones, reacts with diazonium salts in the sense of the following equation (495, 506, 507, 720):





(128)

9. The cyanine dyes

Cyanine dyes have been prepared in very large numbers because of their action in sensitizing a photographic emulsion to wave lengths greater than the blue. It is far beyond the scope of this article to attempt an adequate description of the reactions involved in their preparation, or to make a complete survey of even limited portions of the field. Fortunately, the older work (before 1932) has been well covered by a review by Doja (258), and an excellent up-to-date general summary is to be found in Mees' new book (589).

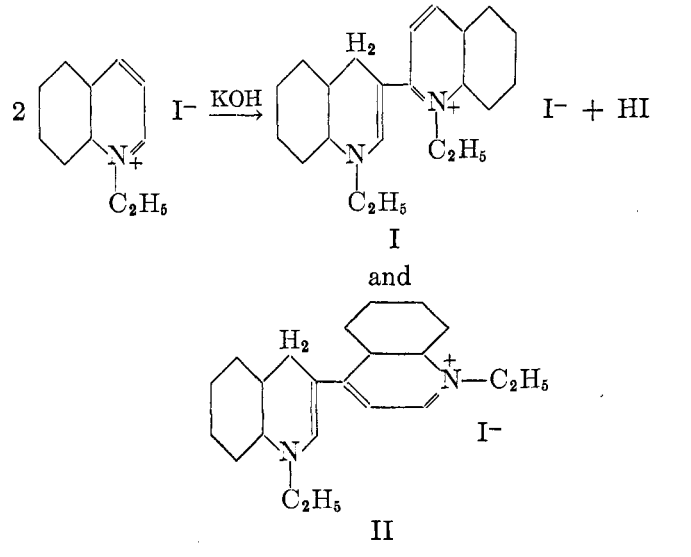
In the formation of cyanines, advantage is almost always taken of the high reactivity of a methyl group in the α- or γ-position with respect to the nitrogen of quaternary salts of 2- and 4-methylpyridines, 2- and 4-methylquinolines, 2-methylbenzothiazole, and related compounds. The effect of the positively charged nitrogen in increasing the ketonic reactivity of the side-chain methyl group has been commented upon previously (see Sections II, I, 1 and IV, N, 5).

In the paragraphs that follow will be recognized close relatives of the aldol condensation (formation of apocyanines), the Michael reaction (2,4′- and 4,4′-cyanines), the Claisen ester condensation (formation of cyanines from quaternary salts of thio ethers or *O*-aryl ethers, formation of carbocyanines), the Claisen reaction (aldol condensation followed by loss of water; mono-, di-, and tri-carbocy-

anines, styrylquinolinium salts), and the alkylation (or acylation) of a ketone containing a reactive methylene group (2,2′-, 2,4′- and 4,4′-cyanines).

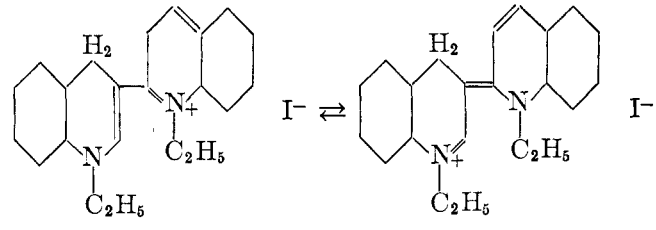
a. Cyanines with two nuclei directly connected: apocyanines

When a solution of quinoline ethiodide and potassium hydroxide in methyl alcohol is refluxed, two compounds are formed: xanthoapocyanine (I; yellow) and erythroapocyanine (II; red) (461, 615). The equation is given below:



(129)

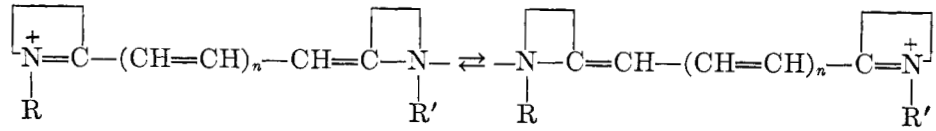
The apocyanines are resonance hybrids in the sense shown below:



The formation of xanthoapocyanine may be regarded essentially as an aldol condensation of the activated cyclic aldehyde ether, quinoline ethiodide; comparison may be made with the related condensation of quinoline itself to dihydro-2,3′-diquinolyl (Section IV,K) under the influence of the strong base, sodium amide. The erythroapocyanine condensation concerns the related 4-position of one of the molecules of the quinolinium salt (615).

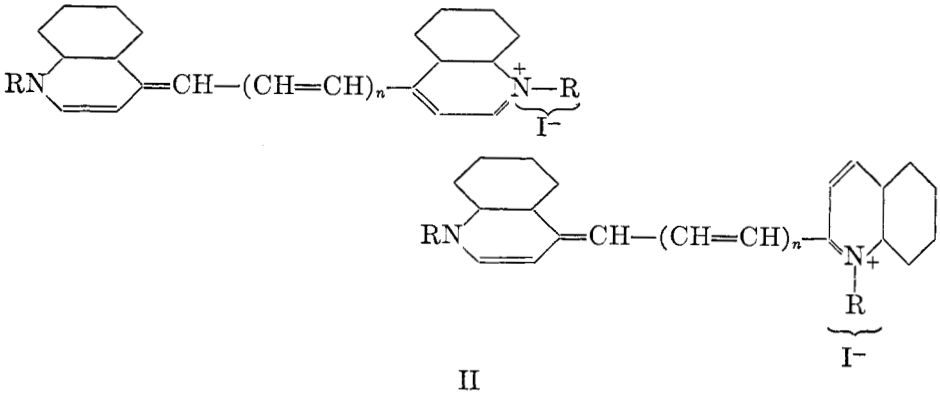
b. Cyanines with two heterocyclic nuclei separated by an unsaturated carbon chain

If —N=C— represents a heterocyclic nucleus, such as is found in pyridine, quinoline, benzoquinoline, or benzothiazole, one may represent the constitution of many cyanine dyes by the general formula:



I

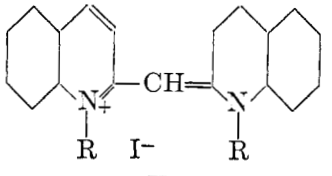
If lepidine or other compound having a reactive methyl in the γ-position is one of the reactants, the resulting dye will have one of the forms:



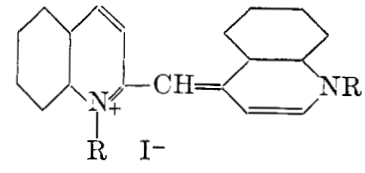
II

One nitrogen is always quaternary and the other tertiary, and the conjugation between the rings is unbroken. The color of the dyes and their stability is adequately explained by saying that the positive charge resonates between the two nitrogen atoms (96).

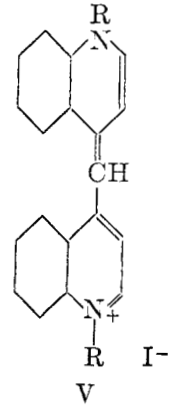
(*1*) *The monomethine cyanines* ($n=0$):



III

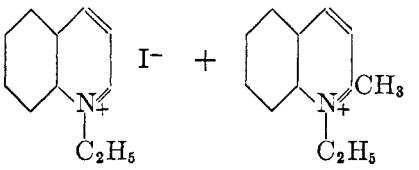


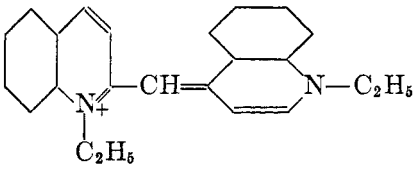
IV



V

The monomethine cyanines consist of two nitrogenous rings united in the α- or γ-positions through a methine (=CH—) bridge. The true cyanines (V) were first made by treating a mixture of the alkiodides of quinoline and of lepidine with an alkali (*cf.* 604a); the isocyanines (IV) (*cf.* 625a) were later prepared by the substitution of quinaldine alkiodides for the lepidine alkiodide. A typical dye (Ethyl red) is formed in accordance with the equation below (465a, 800):



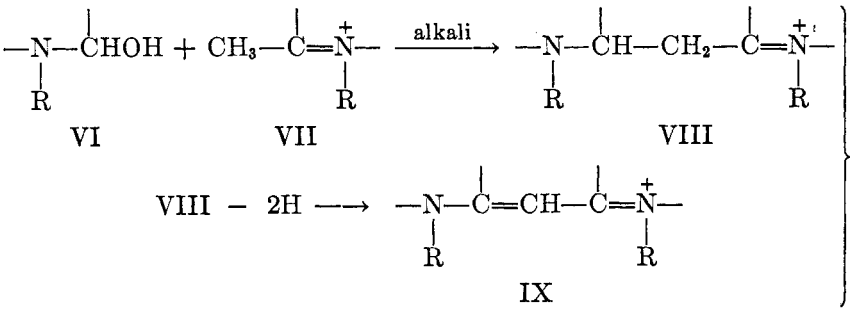


$$I^- + HI + (2H) \qquad (130)$$

$$(HI + KOH \rightarrow KI + H_2O)$$

Quinaldine ethiodide (17.5 g.) and 33 g. (2 moles) of quinoline iodoethylate are dissolved in 1 liter of alcohol and treated with 33 cc. of 10 per cent alcoholic potassium hydroxide. After 2 days' standing at room temperatures, there had separated a mixture of crystals of Ethyl red and diethyl erythroapocyanine hydroiodide, which were obtained in pure condition by crystallization from alcohol (the latter is the more soluble). The yield of Ethyl red was 7.5 g., and of the erythroapocyanine, 14 g.

Decker and Kaufmann (219) say, "The formation of the cyanine dyes is due to the aldehydic function of the oxyhydro base (carbinol, or pseudo base) and the acid nature of the quinaldine methyl". In its barest details, the reaction can be expressed by the equation:

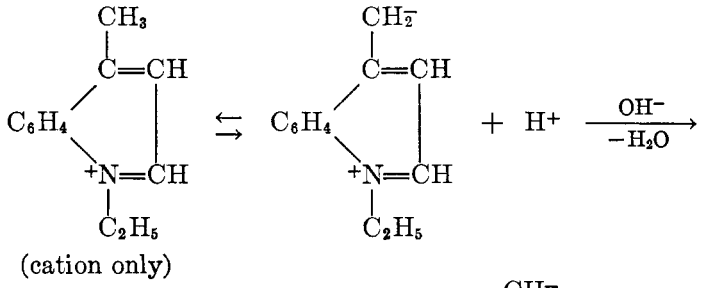


(131)

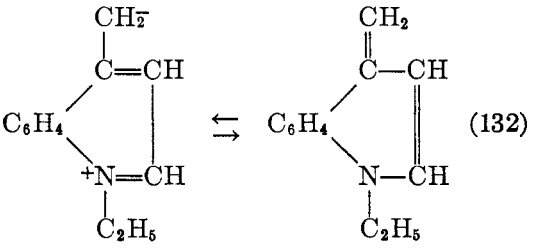
Unfortunately for this otherwise plausible theory, it was later shown that in this condensation, the quinoline alkiodide was attacked in the 4-position, rather than in the 2-, so that the pseudo base, which contains the grouping VI, cannot be an intermediate.

Vongerichten and Höfchen (800a) believe that the "isobase" or "methylene base" (XI) is the true carrier of the cyanine reaction, and Kaufmann and Vonderwahl (465) have suggested that this adds in the 1,4-position to the pseudo base of

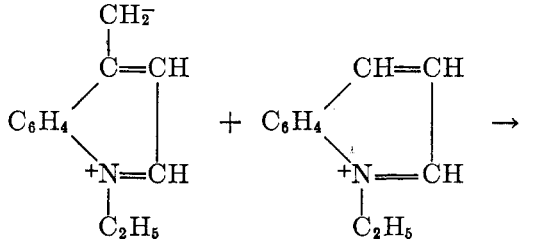
the lepidinium salt, which they write in an open-chain form. An extension of their theory is presented below (*cf.* 715a):



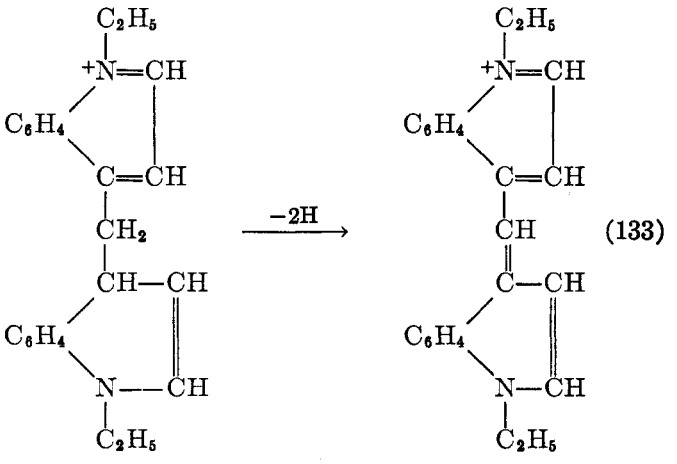
(cation only)



X XI (132)



X XII



XIII XIV (133)

Cation of 4,4′-diethyl cyanine iodide

The positive charge will resonate between the two nitrogens of formula XIV.

Very little of the pseudo base is formed by treating quaternary quinolinium salts with alkali (17, 18). Perhaps it is more plausible to say that the cation (XII) of ethylquinolinium iodide or hydroxide is involved in the reaction rather than the pseudo base. The otherwise low aldehydic reactivity of quinoline itself has been greatly intensified by the positive charge on this ion. Ionization of a hydrogen from the ketonic methyl group of the quaternary lepidinium salt is facilitated by the charge on the nitrogen; there will result the dipolar ion (X), particularly in the presence of a base that can react with the proton. The non polar form of X is the familiar "methylene base" (XI) (*cf.* Section IV, N, 8), which is known to be formed when lepidine (or quinaldine) alkiodides are treated with alkali.

When the lepidinium (or a related) ion (X) is added to the 1,4-positions of the ethylquinolinium ion (XII), there results the leuco base (XIII), which is not isolated because organic matter present robs it of two hydrogens to give the cyanine (XIV). A counterpart of this reaction in the water system is the well-known addition of substances with reactive methyl or methylene groups to a double bond conjugated with carbonyl (the Michael reaction (603a)). In the following example, malonic ester adds to benzalacetophenone (XV) in the presence of piperidine to form ethyl (2-carbethoxy-3-phenyl-4-benzoyl)butyrate (XVI) (175a).

$$C_6H_5CH{=}CHC(C_6H_5){=}O \quad + \quad CH_2(COOC_2H_5)_2 \xrightarrow[\text{reflux 72 hr.}]{\text{piperidine}}$$

XV

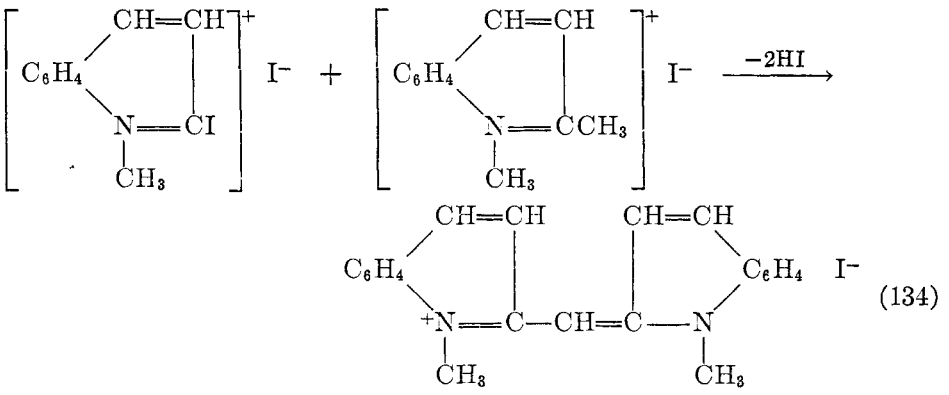
$$C_6H_5CH(CH(COOC_2H_5)_2)CH_2COC_6H_5$$

XVI

The Michael reaction is generally interpreted as involving the anion formed by the action of the basic catalyst upon the compound with the reactive methyl or methylene group. This anion probably adds in the 1,4-position to the conjugated system, $-CH{=}CH{-}\overset{|}{C}{=}O$, giving a product which rearranges to XVI upon hydrolysis. The related 1,4-addition of the Grignard reagent to a carbonyl conjugated with a double bond is well known from the work of Kohler (519b).

Monomethine cyanines are prepared more readily and in better yields by condensing a quaternary salt of an α- or γ-methylpyridine or -quinoline or of an α-methylbenzothiazole, etc., with an α- or γ-iodo-pyridine or -quinoline alkyl halide (394), in the presence, preferably, of potassium carbonate or of triethylamine (43b, 43c, 87d, 87f, 87i, 88, 92, 93, 94, 94b, 310, 313, 393, 395, 396a, 397, 402).

The preparation of a typical 2,2′- or pseudo-cyanine follows the equation:

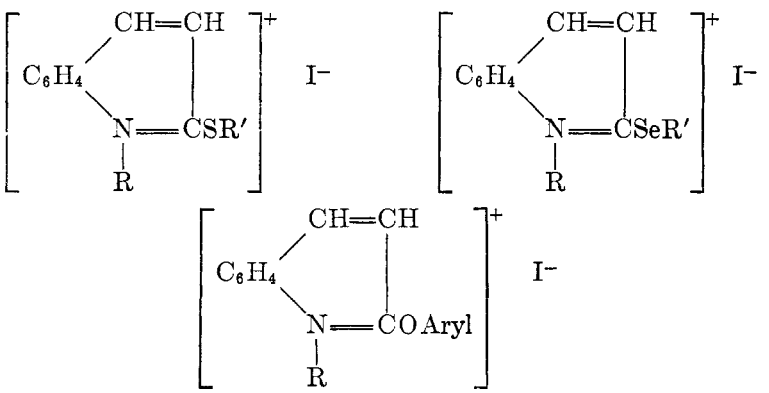


(134)

XVII

2-Iodoquinoline is a cyclic ammono acid iodide ester. The increased reactivity of the 2-halogen in the salt, 2-iodoquinoline methiodide, is undoubtedly not due to ionization of the iodine, for this will be greatly hindered by the positive charge on the cation. It seems more probable that the methylene base related to the quinaldine methiodide, perhaps in its dipolar resonant form (*cf.* X of equation 132), attacks the α-carbon atom directly. The cyanine is formed by loss of hydrogen iodide from this unstable intermediate. Another possibility is that the 2-iodoquinoline methiodide adds to the methylene base to form an addition compound that loses hydrogen iodide to give the cyanine.

Within recent years, the monomethine cyanines have been synthesized by methods which take advantage of the reactivity of an —SR, —SeR, or —OAryl group in compounds of the general types shown below (43c, 90a, 90b, 91a, 470b, 470c):

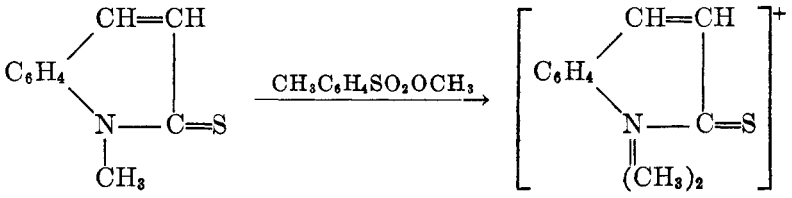


The thio and seleno ethers above are cyclic thio or seleno ammono esters, activated by quaternary salt formation. The formation from them of a cyanine dye is analogous in its first stage to the preparation of a β-diketone by the Claisen condensation, as in the following equation:

$$C_6H_5COOC_2H_5 + CH_3COC_6H_5 \xrightarrow{C_2H_5ONa} C_6H_5COCH_2COC_6H_5 + C_2H_5OH \quad (135)$$

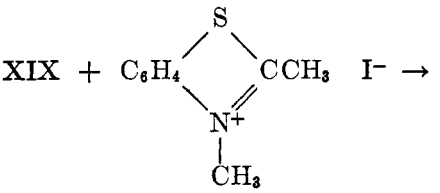
The cyanine is, of course, formed by loss of hydrogen iodide from the hypothetical intermediate.

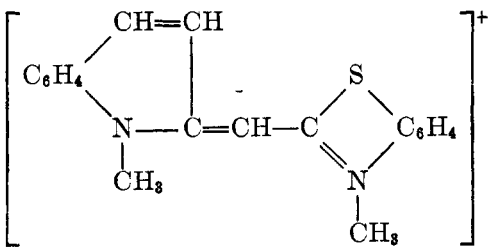
Beilenson and Hamer (43c), following preliminary work of Kendall (470c, 470e), heated 2-thio-1-methyl-1,2-dihydroquinoline (XVIII) (a cyclic thio ammono ester) with methyl *p*-toluenesulfonate and obtained a quaternary salt (cation = XIX). When this was boiled for 3 min. with 2-methylbenzothiazole methiodide and anhydrous potassium carbonate, there was obtained an 84 per cent yield of crude 3,1′-dimethylthia-2′-cyanine iodide (XX). The same goal was reached more simply by fusing XVIII and 1-methylbenzothiazole with methyl *p*-toluenesulfonate (150°C., 2 hr.) without the isolation of the quaternary salt.



XVIII XIX

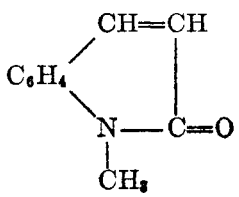
$[CH_3C_6H_4SO_2O]^-$





XX

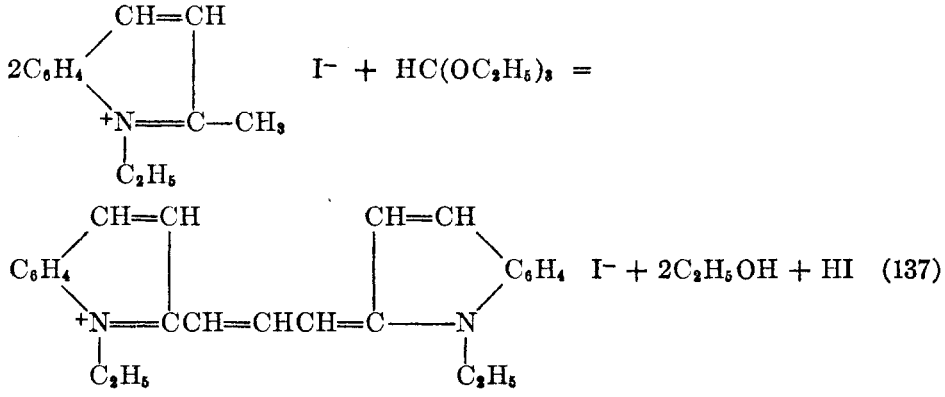
Attempts to prepare the same dye from 1-methyl-2-keto-1,2-dihydroquinoline (*N*-methyl-α-quinolone)



under the same conditions failed, doubtless because the quinolone does not form a quaternary salt, and is therefore not sufficiently reactive. The formation of the

thiacyanine of equation 136 resembles a Claisen condensation as well as a Claisen reaction (aldol condensation followed by loss of water).

(*2*) *Carbocyanines* (*n*=*1*): The best-known carbocyanine is pinacyanole (I), a panchromatic sensitizer. It may be made by refluxing quinaldine ethiodide with formaldehyde, paraformaldehyde, ethyl orthoformate (this is recommended), or even with iodoform (722) in the presence of a base, such as pyridine (301, 392a, 555, 613, 643a (cryptocyanines), 644, 658, 722; for mechanism see 392, 505, 505a, 613). The reaction is expressed by the equation:

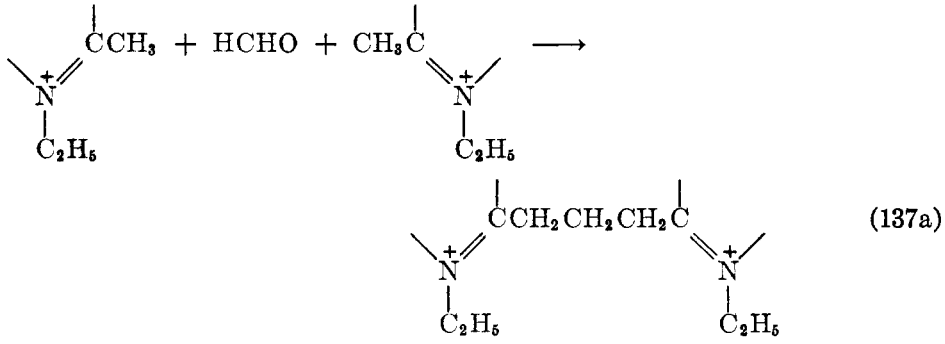


(137)

I

The hydrogen iodide of course reacts with the base used as a condensing agent, while the positive charge resonates between the two nitrogens (*cf.* 92, 94a, 96, 548b, 610b, 625b, 644a).

Mills and Hamer (613) believe that formaldehyde first condenses with quinaldine methiodide in the manner of the equation:



(137a)

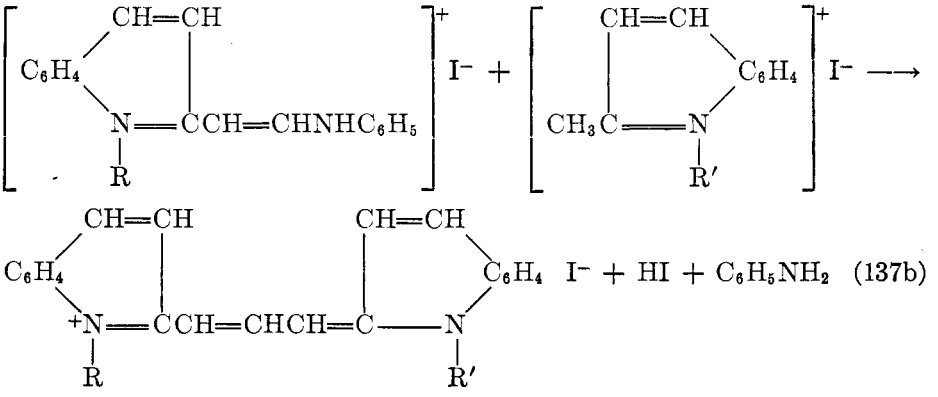
(Diethiodide of methylene diquinaldine)

Related reactions between formaldehyde and acetoacetic ester (697b) or malonic ester (477a) in the presence of piperidine or diethylamine as a catalyst give methylene bisacetoacetic ester or methylene bismalonic ester, respectively. The trimethylene intermediate of formula 137a loses a proton in the alkaline medium in which the reaction takes place and is oxidized to give the cyanine dye, pinacyanol.

Miss Hamer succeeded in preparing the dimethiodide of methylene diquinaldine by the action of formaldehyde on quinaldine methiodide in the presence of piperidine (392); the diethiodide was prepared by a somewhat more roundabout method. When either of these compounds was heated with alkali under the conditions of the carbocyanine condensation, less than 4 per cent of the latter was formed. The yield was increased tenfold by the addition of an alkiodide of quinoline, though much less effect was observed when a quaternary salt of quinaldine was used. Perhaps this is a case of positive-ion catalysis (see Section VI, A, 1 and reference 740a for related work).

The use of esters of orthoacetic acid, orthobenzoic acid and their homologues makes it possible to synthesize carbocyanines with a substituent in the three-carbon-atom bridge (87b, 97). Ammono aquo esters (imino esters, imino "ethers") of the general formula, $RC(=NH)OR'$, in which R and R′ are alkyl, aralkyl, or aryl residues, and certain acid anhydrides (470f) may also serve as intermediates in the formation of cyanines (470a). The esters are made by the addition of alcohol to a nitrile in the presence of hydrochloric acid (compare the formation of diethyl malonate by heating cyanoacetic acid with alcohol and sulfuric acid).

In the action of *N*,*N*′-diphenylformamidine on a quaternary salt of quinaldine or a similar compound with reactive methyl, a β- phenylaminovinyl derivative is first formed in accordance with equation 117. Further action with another molecule of the same or of a different quaternary salt with reactive methyl will give a carbocyanine dye, as shown below (43b, 87c, 90c, 94a, 98, 470d, 470g, 470h, 643a, 644a, 655):



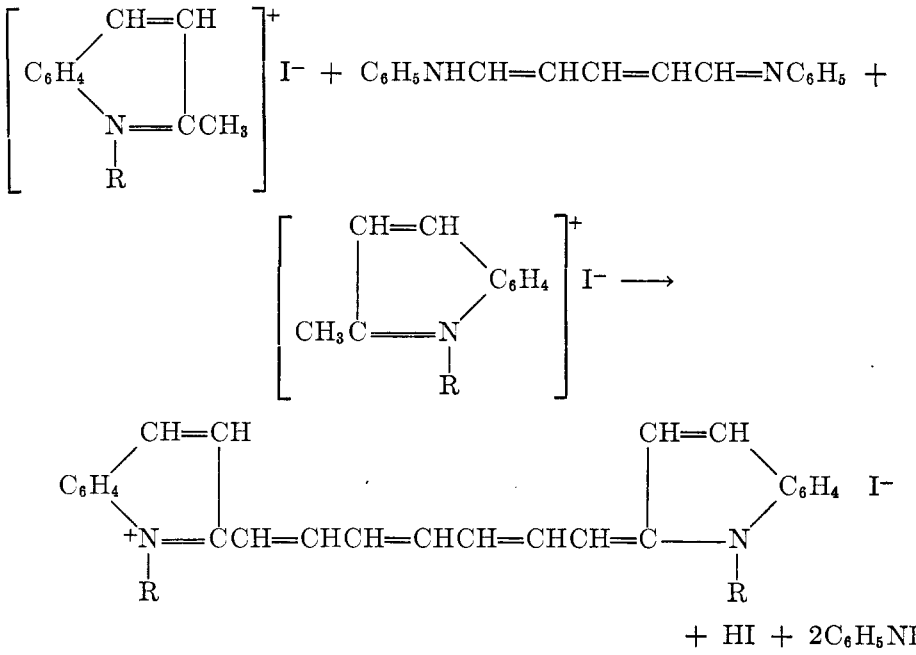
Insofar as the side chain is concerned, the quinaldine derivative on the upper left-hand side of the equation is a monophenyl ether of an ename, or ammono enol, $RCH{=}CHNH_2$. In its tautomeric form, $RCH_2CH{=}NC_6H_5$, it is an ammono aldehyde ether. The replacement of $-NHC_6H_5$ in the one case or of $=NC_6H_5$ in the other case is analogous to the replacement of the oxygen of an enolizable aldehyde with the residue of a compound with reactive methylene. It will be noted that here, as in most cyanine dye syntheses, the conjugated chain separating the two nuclei is formed by elimination of hydrogen iodide from a

possible intermediate, resulting in a considerable stabilization of the molecule by the added resonance.

Lepidine alkiodides can of course be used in the preparation of 4,4′-cyanines by methods that are similar to the above (see earlier references on carbocyanines and also 392a and 645). For the preparation of the related neocyanines, see reference 396.

(3) *Dicarbocyanines (n = 2) and tricarbocyanines (n = 3)*: Beattie, Heilbron, and Irving (41b) prepared a dicarbocyanine dye by heating α-bromo- and β-anilinoacryaldehyde anil, $C_6H_5NHCH{=}CBrCH{=}NC_6H_5$, with quinaldine ethiodide in a pyridine solution that contained some piperidine. Piggott and Rodd (655) and Brooker (98) have recently prepared many dicarbocyanines with the use of β-anilinoacrolein anil itself. It will be noted that this compound is, in its tautomeric form, the dianil of malondialdehyde, that is to say, an ammono dialdehyde diether.

Tricarbocyanines are obtained by heating a quaternary salt of quinaldine, lepidine, or a related substance, with the dianil of glutacondialdehyde (87e, 90, 91, 312, 401a, 823a) in the manner of the equation:



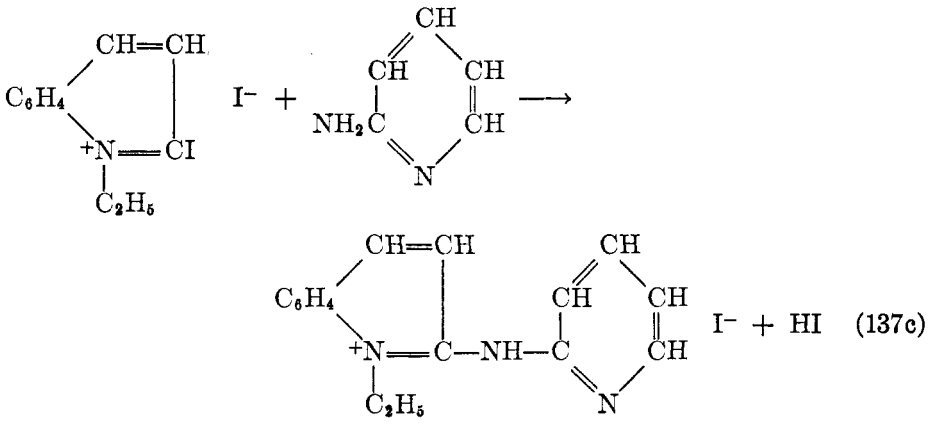
The relationship of glutacondialdehyde dianil to the ammonia system has been given in Section IV, N, 5, d; its preparation has been described in Section II, C, (a). The quaternary salt formed by adding 2-iodoquinoline to pyridine may also be used as a source of glutacondialdehyde (87 g.). Polymethine dyes have been made by the ammonolysis of an unsymmetrical dye of the pyrylium series by ammonia or a primary amine (654a).

c. Styrylquinolinium salts

Styrylquinolinium salts, which have some action as photographic sensitizers, have been dealt with in an earlier section (IV, N, 5, (a)).

d. Azacyanines

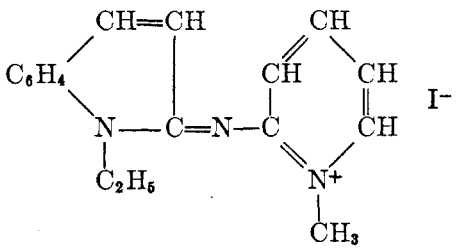
2,2′-Pyridylaminoquinoline ethiodide (I) is formed by short boiling of 2-iodoquinoline ethiodide with an excess of 2-aminopyridine in absolute alcohol (316), the reaction proceeding in accordance with the equation:



(137c)

I

The pyridylaminoquinoline ethiodide (I) is boiled with sodium carbonate solution, and the resulting unsaturated compound then converted to a quaternary salt, the azacyanine (II), by heating with methyl iodide.



II

Here again is an illustration of the ease with which the nuclear halogen in 2-iodoquinoline ethiodide may be replaced.

e. Anhydronium bases

The anhydronium bases corresponding to a number of cyanine dyes have been made, either by heating the dye in a high vacuum (467) or with dimethylaniline (96, 398, 752a) or by synthesis (610a).

O. QUINOLINECARBOXYLIC ACIDS

Pyridine-2-acetic acid (Section II, N) resembles β-keto acids in that it loses carbon dioxide readily when gently heated. The related quinoline-2-acetic acid is on the other hand much more stable, as it melts at 274–275°C. (273, 471). It is interesting that quinoline-2-carboxylic acid (quinaldic acid) melts at 156°C. when anhydrous, and quinoline-2-propionic acid melts at 122–123°C. (273), so that quinoline-2-acetic acid is out of line in this regard also.

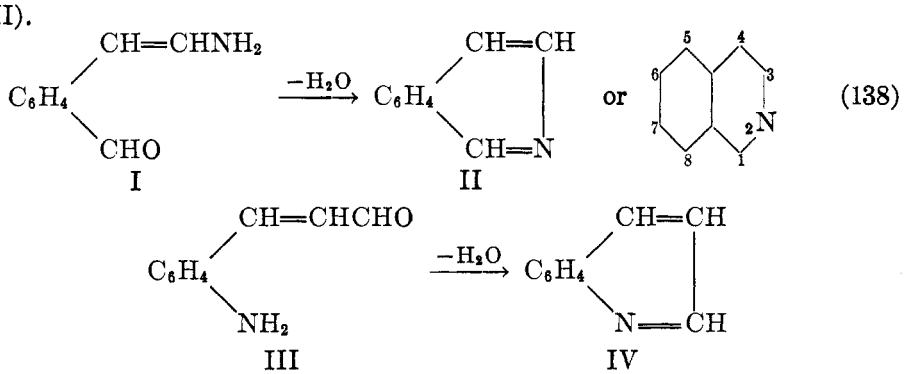
Decarboxylation of quinoline-2,4-dicarboxylic acid in boiling nitrobenzene for 10 min. gives a 90 per cent yield of quinoline-4-carboxylic acid (cinchoninic acid) (711; *cf.* 819c). The removal of carbon dioxide can also be effected by heating alone at 240°C. (686; *cf.* 81c) or in phenol at its boiling point (502).

Quinoline-2,3-dicarboxylic acid (acridinic acid) loses carbon dioxide at 120–130°C. to form quinoline-3-carboxylic acid (377), showing that the —C=N— group affects the carboxyl directly attached to it. The literature does not permit a decision as to the relative stability of quinoline-3- and 4-carboxylic acids.

(For the mechanism of the decarboxylation of quinaldinic acid, see reference 264 and Section II,N.)

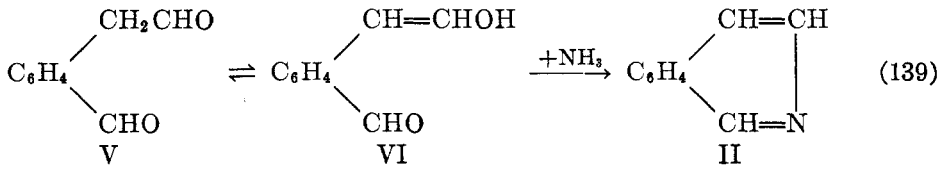
V. ISOQUINOLINE

Isoquinoline (II) resembles quinoline (IV) in most respects. The properties of the two, while generally similar, are not identical, because the former is a cyclic Schiff base (ammono aldehyde ether) derived from a substituted benzaldehyde (I), while the latter is a cyclic Schiff base related to *o*-aminocinnamaldehyde (III).



The differences between quinoline and isoquinoline are reflections of the dissimilarity of benzaldehyde and cinnamaldehyde.

More exactly, one should perhaps regard isoquinoline as formed by the ammonolysis of the dialdehyde (V):



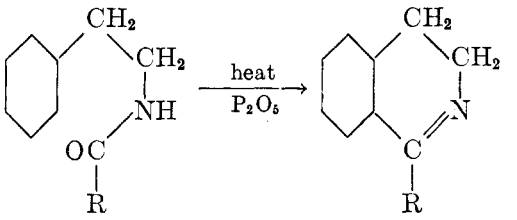
A similar situation exists with regard to pyridine, but here, as there, it is considered better to adopt the simpler but generally adequate viewpoint that isoquinoline is a cyclic ammono aldehyde ether. On this basis, it follows that 1-methylisoquinoline and 1-phenylisoquinoline are cyclic ammono ketone ethers, that 1-hydroxyisoquinoline (isocarbostyryl) is a cyclic ammono aquo acid ester, that 1-chloroiosoquinoline is a cyclic ammono acid chloride ester, and that 1-aminoisoquinoline is a cyclic ammono acid ester. It will be seen on inspection of formula II of equation 138 that the 1-carbon and attached groups will be unique in that no other position in the ring will have their function. Thus, while the alkyl groups of 2- and 4-methylquinolines are similar chemically, the same situation cannot exist in the isoquinoline series. Although ring resonance might make the 1- and 3-methyls equivalent, in that, at separate intervals, each will be attached to a —C=N— group, this is not the case, since the 3-methyl has been shown to be inactive (621).

A. SYNTHESES OF ISOQUINOLINE

The discussion of the syntheses of isoquinoline and its derivatives will be abbreviated, because of the existence of a previous review covering this field (585). A few of the methods are listed below.

1. Bischler–Napieralski synthesis

Acyl derivatives of β-phenethylamine, when heated with phosphorus pentoxide or certain other dehydrating agents, give 1-substituted 3,4-dihydroisoquinolines, in accordance with the scheme:

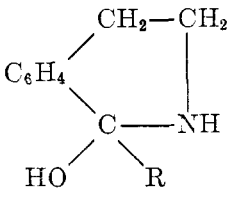


VII VIII (140)

Isoquinoline itself is not advantageously made in this manner, although many substitution products are, since they may be obtained by oxidizing or dehydrogenating the intermediate 3,4-dihydride (VIII; 195, 227, 228, 688, 768, 770).

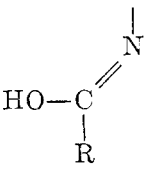
The *N*-acyl derivatives of β-phenethylamine (VII) are substituted acid amides and therefore ammono aquo acid esters (see Section I, G). For this reason, the "ketonic reactivity" of the carbonyl group should be greater than in an acid amide (ammono aquo acid) and perhaps somewhat less than in a neutral ester. The ring closure can be said to follow the general pattern of the Skraup and Döbner–von Miller syntheses (Sections IV, A, 3 and 4) and to result from a reaction between a carbonyl of a side chain and a ring hydrogen. The synthesis of phenanthridines from acyl derivatives of *o*-aminobiphenyl is closely related (see forthcoming review).

It is not known whether an intermediate addition compound (IX) similar to the aldol base of Döbner and von Miller (Section IV, A, 4) is formed



IX

or whether ring closure is the result of loss of water between the imidol modification of VII



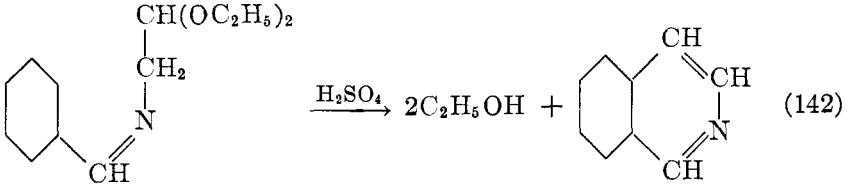
and a ring hydrogen; if this is the case, there is a relationship to the conversion of *o*-benzoylbenzoic acid to anthraquinone or to the reaction of Groggins (381) below:

$$C_6H_6 + CH_3COOH + 2AlCl_3 = C_6H_5COCH_3 + AlOCl + 2HCl + AlCl_3 \quad (141)$$

2. Aminoacetal synthesis

Arylidene amino acetals, when warmed with concentrated sulfuric acid, or with sulfuric and arsenic acids, give isoquinoline or substituted isoquinolines, as shown by the representative equation below (693, 732; *cf.* 775):

$$C_6H_5CHO + NH_2CH_2CH(OC_2H_5)_2 \rightarrow \underset{\text{I}}{C_6H_5CH{=}NCH_2CH(OC_2H_5)_2} + H_2O$$



I II

This method is of limited application, although recently it has been utilized to prepare a number of bromoisoquinolines, which have been converted successively to the cyanides and to the carboxylic acids (799).

The first step in the reaction is the familiar ammonolysis of an aquo aldehyde to a substituted ammono aldehyde ether, or Schiff base (I). The ring closure is brought about by attack of the terminal —$CH(COOC_2H_5)$ of the side chain,

which is aldehydic in character, on a hydrogen in the ortho position in the benzene ring. It has been shown by Staub (775) that cyclization occurs most readily when this condition is fulfilled, and we find numerous other examples among the quinoline syntheses previously discussed (see Section IV, A). The formation of triphenylmethane derivatives by the action of dialkyl-anilines or -phenols upon aromatic aldehydes may be regarded as a related type of reaction.

3. The Pictet-Gams synthesis

Acylated aminomethylphenyl carbinols of the type formula, $C_6H_5CH(OH)CH_2NHCOR$ (100, 687), or the corresponding aminophenylcarbinol ethers (723, 724) give isoquinolines directly when heated with phosphorus pentoxide in toluene or in xylene. The equations are the following:

$$C_6H_5COCH_3 \xrightarrow[NaOC_2H_5]{C_5H_{11}ONO} C_6H_5COCH{=}NOH \xrightarrow[HCl]{SnCl_2}$$

$$C_6H_5COCH_2NH_2 \cdot HCl \xrightarrow{RCOCl} C_6H_5COCH_2NHCOR \xrightarrow[\text{absolute alcohol}]{\text{Na amalgam}}$$

$$C_6H_5CH(OH)NHCOR \xrightarrow[\text{heat}]{P_2O_5} C_6H_4\begin{cases} CH{=}CH \\ C{=}N \\ \quad | \\ \quad R \end{cases} \qquad (143)$$

$$C_6H_5CHO \xrightarrow[\text{alkali}]{CH_3NO_2} C_6H_5CH{=}CHNO_2 \xrightarrow{CH_3ONa}$$

$$C_6H_5CH(OCH_3)CH_2NO_2 \xrightarrow{(6H)} C_6H_5CH(OCH_3)CH_2NH_2 \xrightarrow{RCOCl}$$

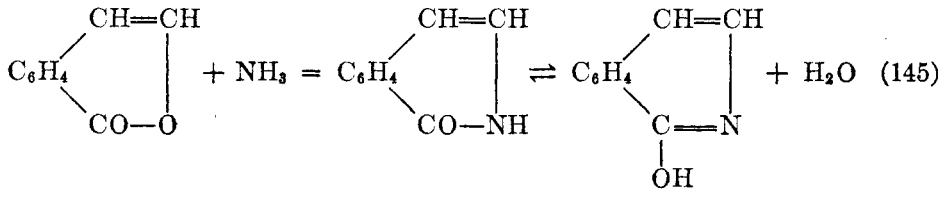
$$C_6H_5CH(OCH_3)CH_2NHCOR \xrightarrow[\text{heat}]{P_2O_5} C_6H_4\begin{cases} CH{=}CH \\ C{=}N \\ \quad | \\ \quad R \end{cases} \qquad (144)$$

The interpretation of the reaction is essentially the same as given for the Bischler–Napieralski synthesis.

Krabbe and coworkers (535–539) have shown that the *N*-acylvinylamines of the type $R_2C{=}C(R')NHCOR''$ (a specific example is $C_6H_5CH{=}CHNHCOR$) are intermediates in this synthesis. They represent the first step in the conversion of the acylated aminophenylcarbinol (see equation 143) or of the methyl ether (see equation 144) to the isoquinoline derivative. It is recommended (539) that the carbinol be dehydrated first to the vinyl compound by means of an alkaline dehydrating agent, say RMgX, and the ring then closed in the usual manner with phosphorus pentoxide. Otherwise, oxazolines may be formed as by-products.

4. Isocarbostyryl syntheses

Hydroxyisoquinolines are prepared by heating isocoumarins with ammonia, just as the pyridones or hydroxypyridines are made by the ammonolysis of pyrones. Thus, 1-hydroxyisoquinoline, or isocarbostyryl, is formed in almost quantitative yield by heating isocoumarin with alcoholic ammonia at 120–130°C., in accordance with the equation (105):

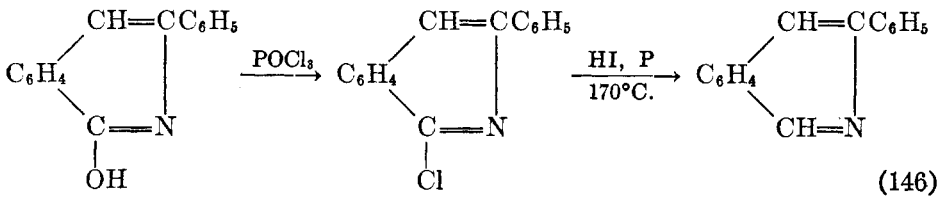


(145)

I II

The isocoumarincarboxylic acids are readily converted into the corresponding isocarbostyrylcarboxylic acids, generally by short contact with ammonia at ordinary temperatures (29, 30, 32, 244). It will be noted that isocoumarin (I), a cyclic aquo ester, is ammonolyzed to isocarbostyryl (II), a cyclic ammono aquo acid ester.

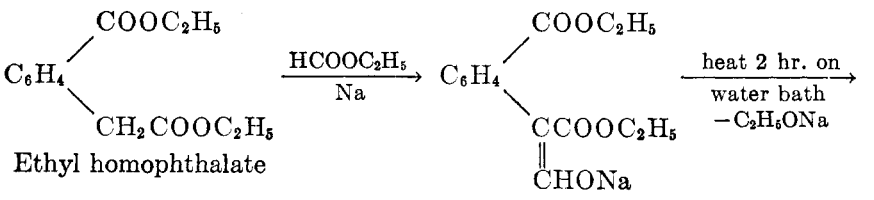
The isocarbostyryls may be distilled with zinc dust and so converted to isoquinolines, or they may be heated, generally under pressure, with phosphorus oxychloride to give chloroisoquinolines. These latter are then reduced to the corresponding isoquinoline by heating with hydrogen iodide and red phosphorus. A typical preparation of 3-phenylisoquinoline is shown in the equation that follows (361):



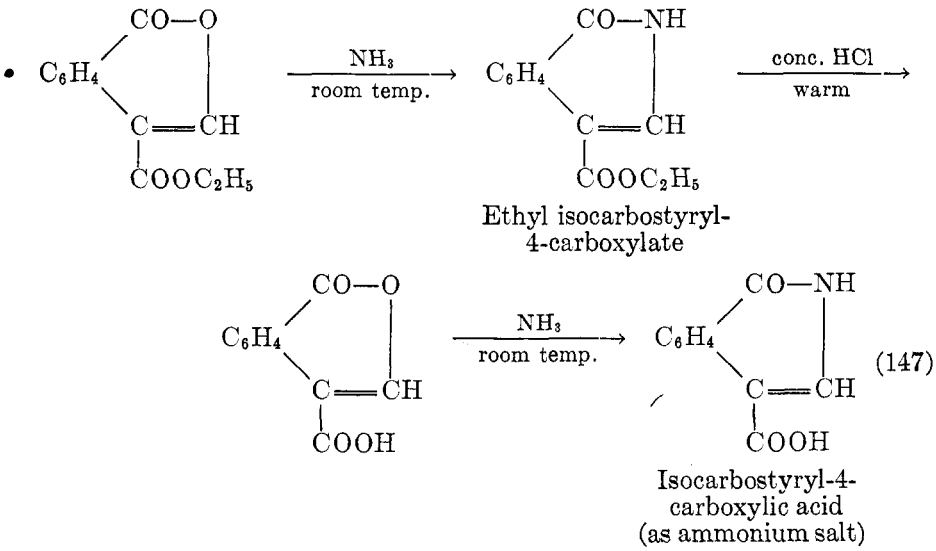
(146)

1,4-Dichloro-3-phenylisoquinoline is reduced by refluxing with hydrogen iodide solution and red phosphorus to 4-chloro-3-phenylisoquinoline, showing the greater mobility of the chlorine in the 1-position (361).

Dieckmann and Meiser (244) report the preparation of isocarbostyryl-4-carboxylic acid and its esters by the following series of reactions.

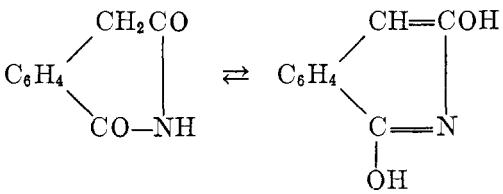


Ethyl homophthalate



(147)

Homophthalimide (III) is tautomeric with 1,3-dihydroxyisoquinoline (IV) and is made (364, 365, 685) from homophthalic acid (696), which can be prepared from the commercially available phthalide.



III IV

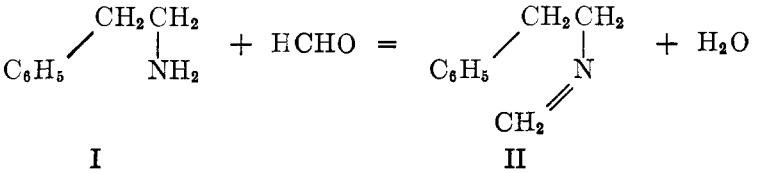
Other methods for preparing isocarbostyryl will be discussed later (see Section V, D).

5. Tetrahydroisoquinoline syntheses

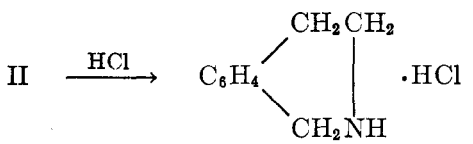
1,2,3,4-Tetrahydroisoquinolines may be formed by reducing the 3,4-dihydroisoquinolines, or the isoquinolines themselves, with tin and concentrated hydrochloric acid on a water bath (292a, 358, 431) or with sodium and absolute alcohol (31, 564a). The *N*-alkyl-1,2,3,4-tetrahydroisoquinolines are prepared by reducing the isoquinoline iodoalkylates (or halogenoalkylates), generally with tin and concentrated or fuming hydrochloric acid (105a, 807d). Isoquinoline may also be hydrogenated to 1,2,3,4-tetrahydroisoquinoline in the presence of platinum oxide (702a).

Of greater interest in connection with this review is the synthesis of tetrahydroisoquinolines by the action of formaldehyde or methylal on substituted β-

phenethylamines in strong hydrochloric acid (105, 195a, 206, 208, 520b, 689, 690, 703), The reactions follow the equations below:

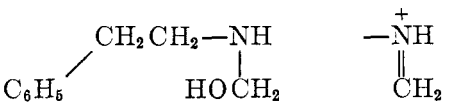


I II



III (148)

The Schiff base, such as the formal-β-phenethylamine (II) in the equation above, may often be isolated and then cyclized with hydrochloric acid, sulfuric acid, hydrobromic acid, or phosphorus oxychloride as catalysts. It is possible that the agent active in the condensation is the carbinol amine, or ammono aquo mero-acetal, of the formula (IV) below:



IV V

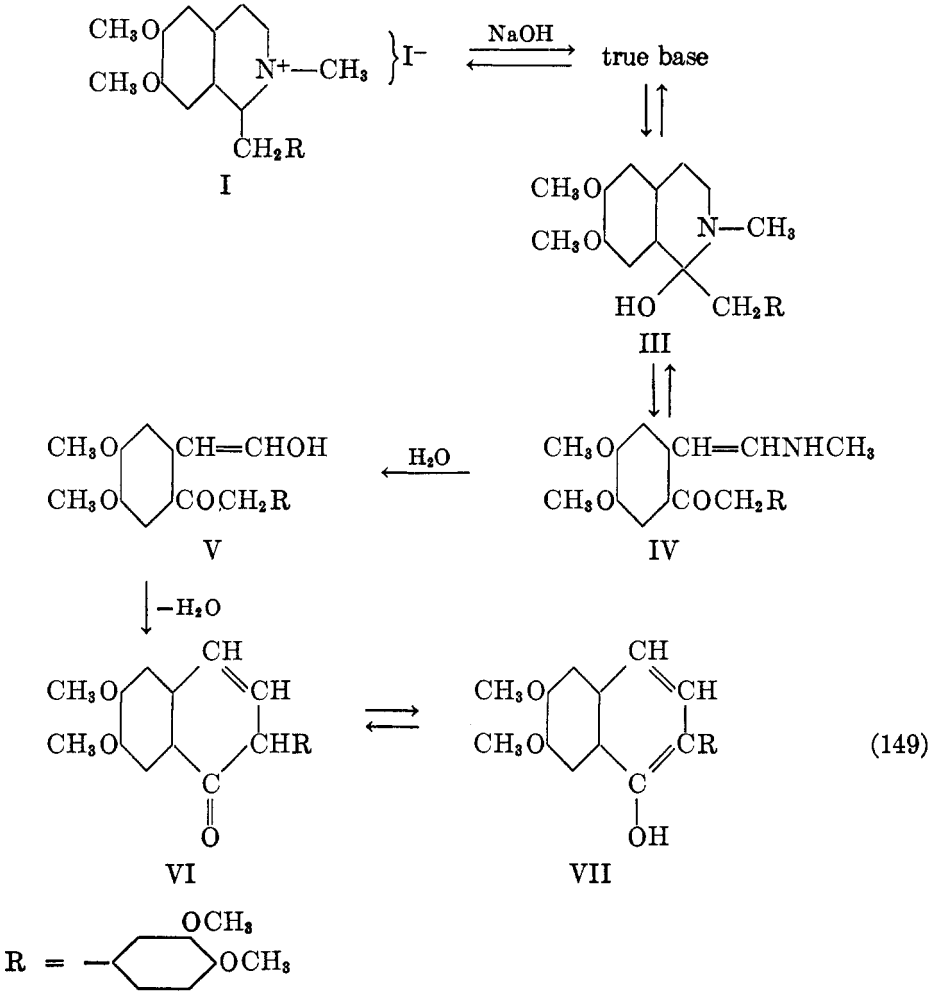
the product of addition of β-phenethylamine to formaldehyde. Ring closure in any event has been effected by attack of the aldehydic terminal of a side chain upon an ortho position of the ring, according to the conditions laid down by Staub (775). The aldehydic cation, V, of a salt of II is a more likely intermediate.

It is reported by Cooke and Gulland (181) that good yields of isoquinolines are formed by catalytic dehydrogenation of the corresponding tetrahydroisoquinoline with palladous chloride, though they remark that the method probably will not find general use.

B. ISOQUINOLINE RING OPENINGS

Very few openings of the isoquinoline ring appear to have been described; some are listed below.

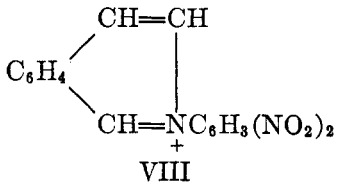
(*1*) Papaverine halogen alkylates (I), when treated with alkalies, give a nitrogen-free phenolic compound (VII), probably in accordance with the equations below (185, 209, 214):



(149)

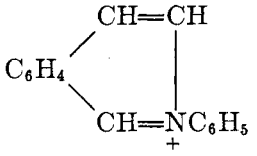
Here it is assumed that the pseudo base (III) is in equilibrium with the open-chain aldehyde form (IV) which is to be considered an ammono enol ether insofar as the grouping —CH=CHNHCH$_3$ is concerned. All substances of this class are readily hydrolyzed to the water system equivalent, —CH=CHOH or —CH$_2$CHO. Ring closure, V → VI, is the result of a Claisen reaction. 1-Benzylisoquinoline methiodide is similarly converted to 2-phenyl-1-naphthol (186).

(*2*) Attempts to open the isoquinoline ring by the action of benzoyl chloride and alkali failed (708; see Section IV, F). Quaternary salts are formed when isoquinoline is heated with 2,4-dinitrochlorobenzene or with 1-chloro-2,4-dinitronaphthalene, but neither could be changed to glutacondialdehyde derivatives, as in the case of the corresponding pyridines. The reaction instead follows the rather unusual course below:



VIII

$$Cl^- + C_6H_5NH_2 \longrightarrow$$

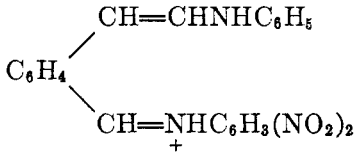


X

$$Cl^- + C_6H_3(NO_2)_2NH_2 \quad (150)$$

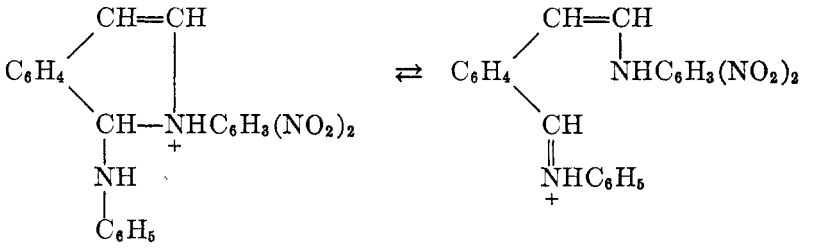
IX

Zincke and Weisspfenning (839b) believe that the dinitrophenyl group is directly replaced by phenyl without ring opening, though this latter alternative seems much more probable. Aniline could react with the quaternary salt (VIII) to give an intermediate (XI), from which phenylisoquinolinium chloride (X) might be formed by a subsequent ring closure with loss of dinitroaniline.



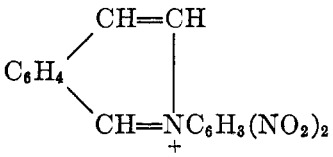
XI

The single bond between the nitrogen and the 3-carbon atom of the dinitrophenylisoquinolinium chloride has been opened by adding the elements of aniline to the molecule. It is perhaps more reasonable to assume that aniline adds to the aldehydic —CH=N— group to give XII, the tautomeric form of which can lose dinitroaniline to form phenylisoquinolinium chloride (X).



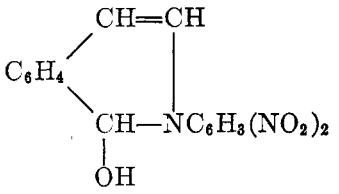
XII XIII

2,4-Dinitrophenylisoquinolinium chloride (VIII) reacts with warm alcoholic phenylhydrazine to give a well-crystallized black phenylhydrazone, apparently through an intermediate reddish brown solid (XIV) that may be isolated by working at lower temperatures. Zincke and Weisspfenning (839) interpret the reaction in the following manner:

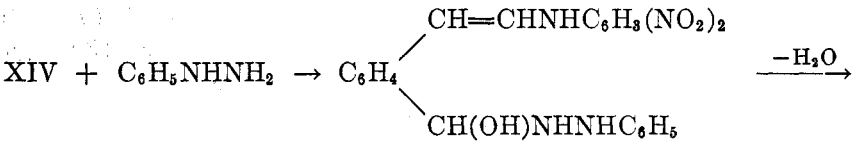


VIII

$$Cl^- \xrightarrow[C_2H_5OH + H_2O]{C_6H_5NHNH_2}$$



XIV



(150a)

XVI

The phenylhydrazone (XVI) is believed to have the open-chain formula shown, though the evidence does not seem to be too conclusive. The reddish pseudo base (XIV) is also formed by the action of alkali, or of water solutions of aniline and aliphatic amines on dinitrophenylisoquinolinium chloride (VIII).

Similar reactions have been recorded for 2,4-dinitronaphthylisoquinolinium chloride (837).

(*3*) Cotarnine and hydrastinine, pseudo bases of the isoquinoline series (see Section V, I–J), have sometimes been given the structures of open-chain methylamino aldehydes because of their high aldehydic reactivity, even though the majority of observers seem to prefer the cyclic formula. Nevertheless, it appears that several of the compounds formed chemically from cotarnine and hydrastinine have open-chain configurations.

(*4*) Oxidation of isoquinoline and its substitution products often leads to the partial disruption of the pyridine nucleus, but these reactions are of little interest here, though they are, in a sense, ring openings. As an example, about equal parts of phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid) are formed when isoquinoline is oxidized with alkaline permanganate (430; *cf.* 376).

(*5*) When 2,4-dinitrophenyl-6,7-dimethoxyisoquinolinium chloride is re-

fluxed for 5–6 hr. with 2 moles of aniline, there results a quantitative yield of 2,4-dinitrodiphenylamine with the simultaneous formation of 6,7-dimethoxyisoquinoline (447). Here dinitrochlorobenzene, formed by slight dissociation of the quaternary salt, was continually removed by the aniline, with which it reacted to give the dinitrodiphenylamine. Under similar conditions, the pyridine ring would have been opened.

C. REACTION OF ISOQUINOLINE WITH METALS AND WITH METALLOÖRGANIC COMPOUNDS

Isoquinoline adds two atoms of sodium in liquid ammonia at −33°C. (60) in either the 1,2- or the 1,4-positions. If the nitrogen atom has sodium attached to it, the addition can only have been in the 1,2-position. When isoquinoline and potassium are heated together at about 100°C., and then finally at 170–180°C. and allowed to cool in air, isocarbostyryl is formed in yields that do not exceed about 10 per cent of the theoretical (291). The action of sodium on isoquinoline gave only a very small amount of diisoquinolyl (291a).

The synthesis of isocarbostyryl in the above reaction can be explained by saying that potassium adds to isoquinoline to give a 1,2-addition product, which is oxidized by air to the potassium salt of 1-hydroxyisoquinoline and, presumably, also to some oxide of potassium. The over-all process amounts to the oxidation of a cylic ammono aldehyde ether, isoquinoline, to a cylic ammono aquo acid ester, isocarbostyryl.

Ethylmagnesium bromide reacts with isoquinoline in diethyl ether at 140–160°C. to form 1-ethylisoquinoline (62), while phenylmagnesium bromide and benzylmagnesium chloride (the latter in dioxane) give 1-phenylisoquinoline and 1-benzylisoquinoline, respectively (46).

Isoquinoline reacts somewhat more readily with the lithium alkyls than with the Grignard reagent (828). Thus, hydrolysis of the product of the reaction of butyllithium with isoquinoline in benzene gives 1-butyl-1,2-dihydroisoquinoline, which is easily oxidized to 1-butylisoquinoline by heating with nitrobenzene.

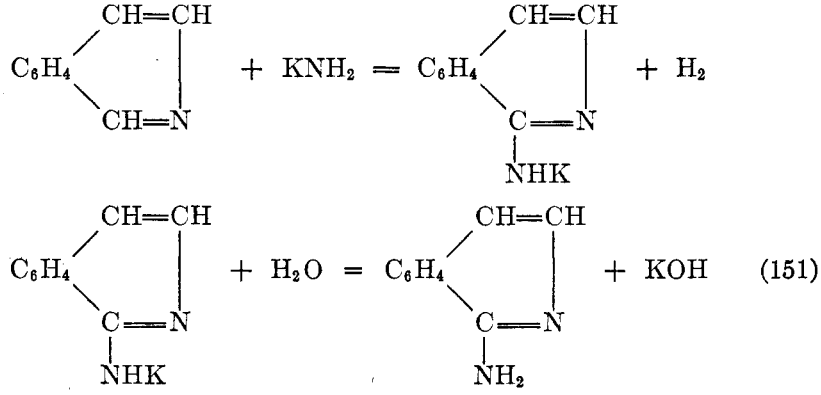
D. 1-HYDROXYISOQUINOLINE AND 1-AMINOISOQUINOLINE

Chichibabin (143a) prepared 1-hydroxyisoquinoline (isocarbostyryl) by heating isoquinoline with dry potassium hydroxide at 220°C. for about 3.5 hr. This type of reaction, an oxidation of a cyclic ammono aldehyde ether to a cyclic ammono aquo acid ester, has been discussed in Sections II, G and IV, G (*cf.* 808).

There is at least one statement on record to the effect that hydroxyl in position 1 is more readily replaced by chlorine than in position 4. Gabriel and Colman (366) heated 1,4-dihydroxyisoquinoline with phosphorus oxychloride at 160–170°C. and obtained 1-chloro-4-hydroxyisoquinoline, together with a small amount of 1,4-dichloroisoquinoline. However, it is reported (368) that 1,4-dihydroxy-3-methylisoquinoline is reduced by hydrogen iodide and red phosphorus at 180°C. to 3-methylisocarbostyryl, indicating the higher mobility of the 4-hydroxyl group.

1-Aminoisoquinoline may be prepared by heating isoquinoline with sodium

amide under neutral solvents, though the yields are not very good (149). There is some improvement (to about 65 per cent of the theoretical) if the fused eutectic of sodium amide and potassium amide (541) is used in place of sodium amide (793). In liquid ammonia, isoquinoline reacts with an excess of potassium amide to form aminoisoquinoline in yields of 70 per cent or over, together with an equivalent quantity of hydrogen gas (49, 56).



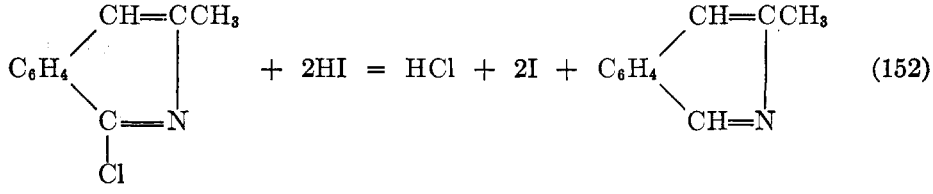
(151)

Isoquinoline has therefore been nitridized to a cylic ammono acid ester.

E. 1-CHLOROISOQUINOLINE, 4-BROMOISOQUINOLINE, 1-ALKOXYISOQUINOLINES, *N*-ALKYLISOQUINOLONES

1-Chloroisoquinoline is made by the action of the oxychloride and pentachloride of phosphorus on *N*-methylisoquinolone (314, 315) (*cf.* Section IV, H), or of the former on isocarbostyryl (367a). 4-Bromoisoquinoline may be prepared by heating the hydrobromide perbromide of isoquinoline for about 7 hr. at 180–190°C. (65c, 181a, 267b).

Isoquinolines with a chlorine in the 1-position are reduced by hydrogen iodide (b.p. 127°C.) and red phosphorus at 170-180°C. to the corresponding isoquinoline, in accordance with the equation (361, 367, 370):

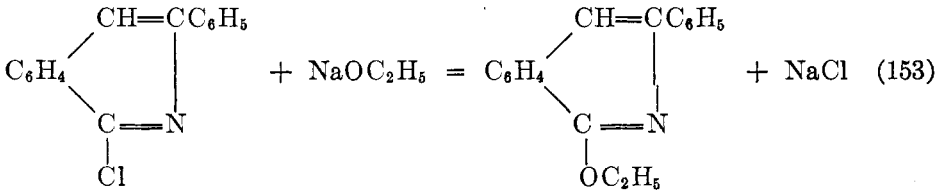


(152)

A comparison of the reactivity of chlorine in the 1- and 3-positions was made by heating 1,3-dichloroisoquinoline with hydrogen iodide and red phosphorus at 150–170°C., or by warming with tin and hydrochloric acid in glacial acetic acid solution. 3-Chloroisoquinoline is formed in both cases, indicating the higher mobility of halogen in the 1-position, in accordance with expectations (*cf.* Section IV, H). (1-Chloroisoquinoline is a cyclic ammono acid chloride ester.) Similarly, 1,4-dichloro-3-phenylisoquinoline may be reduced to 3-phenyl-4-chloroisoquinoline (362a).

When 1-chloroisoquinolines are warmed with alcoholic solutions of potassium

hydroxide, or of the alkali-metal alkoxides, the halogen is replaced by an alkoxyl group, as in the following example (363):

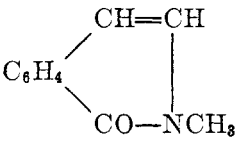


(153)

1,4-Dichloro-3-methylisoquinoline, when heated for 0.75 hr. with sodium methoxide in methanol at 100°C., similarly gives 4-chloro-1-methoxymethylisoquinoline, showing that the 1-chlorine is most readily replaced (369). 1-Alkoxyl-3-propyl (or isopropyl)isoquinolines have been made in the same way (7,557), while 1-methoxyisoquinoline has also been prepared by heating the silver salt of isocarbostyryl with methyl iodide at 100°C. (292). 1-Chloro-3-phenylisoquinoline and aniline react when heated to give anilinophenylisoquinoline (281c).

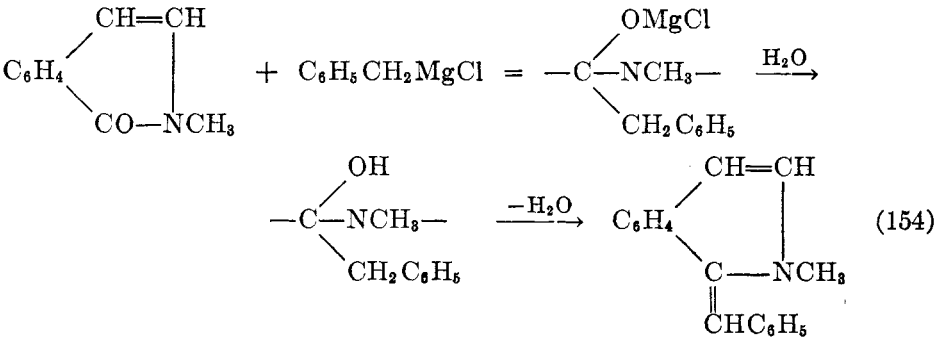
4-Bromoisoquinoline is converted to 4-cyanoisoquinoline (799) or to 4-aminoisoquinoline (181a) by heating with cuprous cyanide (0.75 hour at 250°C.) or with concentrated aqueous ammonia and copper sulfate (16 hr. at 165–170°C.), respectively. When heated with sodium methylate in methanol (7 hr. at 235°C.), 4-bromoisoquinoline is reduced to isoquinoline in about 50 per cent yield (65c).

2-Methyl-1-isoquinolone, a cyclic ammono aquo ester,



is formed by heating isocarbostyryl for several hours with methyl alcoholic potassium hydroxide (292), by oxidizing methylisoquinolinium iodide with alkaline potassium ferricyanide (198, 314), or by the action of a primary amine (CH_3NH_2) on isocoumarin (32).

The carbonyl group in 2-methyl-1-isoquinolone should resemble that in an ester, though its reactivity appears to be somewhat less. Decker and Pschorr (230) have thus prepared 1-benzylidene-2-methyl-1,2-dihydroisoquinoline by the following reaction:



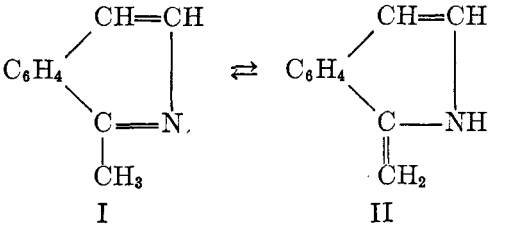
(154)

None of the intermediates was isolated (see also 229a).

A mixture of phosphorus pentachloride and phosphorus oxychloride reacts with 2-methyl-1-isoquinolone to form 1-chloroisoquinoline (314–315).

F. 1-ALKYLISOQUINOLINES

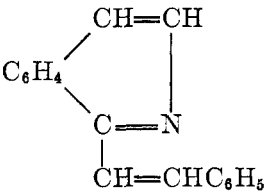
Mills and Smith (625; *cf.* 760b) showed many years ago that the methyl in 1-methylisoquinoline (I) had ketonic reactivity, while a methyl in the 3-position was inactive, presumably because of the impossibility of a tautomerism of the latter in the sense of the following equation:



I ⇄ II (155)

The characteristic behavior of the 1-alkylisoquinolines is considered to be due, at least in part, to the enamic or ammono enolic, form (II).

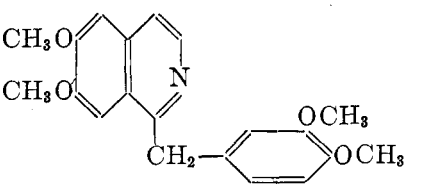
1-Styrylisoquinoline (III) may be prepared by heating 1-methylisoquinoline with an equimolar quantity of benzaldehyde and a small quantity of zinc chloride at 100°C. (623).



III

The preparation of the styryl derivatives of a number of substituted isoquinolines has been patented (665).

Papaverine (IV) reacts with alkali-metal amides in liquid ammonia to form red salts (60), and with aqueous formaldehyde at 100°C. (20 hr.) to give methylene papaverine (=CH_2 → =C=CH_2) (492, 769; *cf.* 337). Furthermore, papaverine is readily oxidized by mercuric acetate in acetic acid solution to papaverinol (=CH_2 → =CHOH) (371c) and with cold dilute acid permanganate to papaveraldine (=CH_2 → =C=O) (375b), indicating again that the methylene group is reactive.



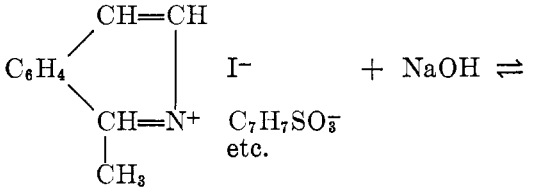
IV

G. ISOQUINOLINE ALKYL HALIDES

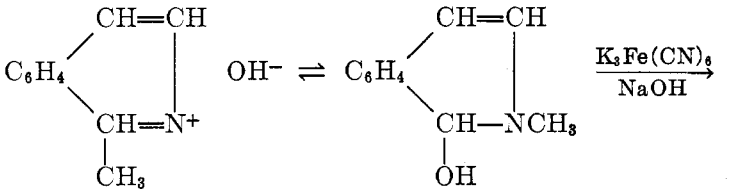
1. Pseudo bases and methylene bases

Quaternary isoquinolinium salts (I) react with alkali to form a strongly basic solution which contains a small amount of the pseudo base (III), together with a larger quantity of the true base (II). Benzene extracts the pseudo base from this mixture, and water will in turn extract the true base from the benzene, indicating clearly the influence of solvent upon the point of equilibrium (222a; see also 163, 164, 166, 193a, 224a, 792).

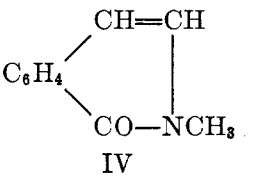
Oxidation of a mixture of a quaternary quinolinium salt and alkali by means of potassium ferricyanide gives 2-methyl-1-isoquinolone (IV), an ammono aquo ester, in accordance with the equation (198a, 314):



I

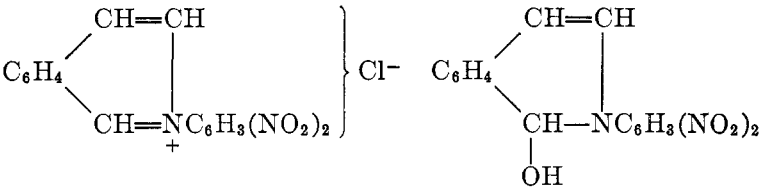


II III



IV (156)

2,4-Dinitrophenylisoquinolinium chloride (V)

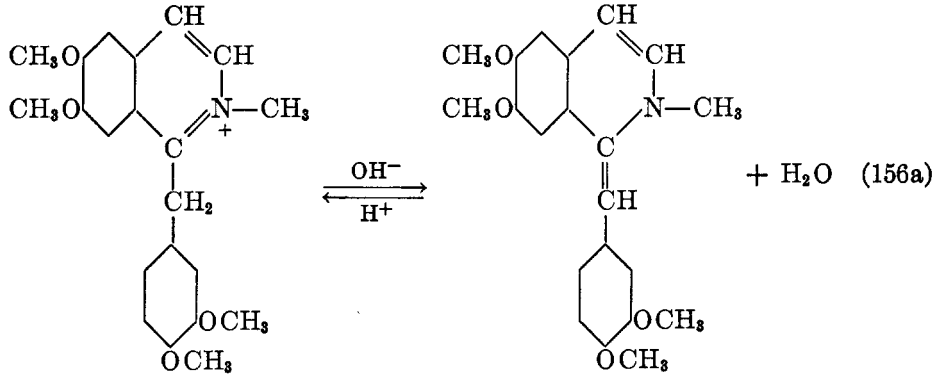


V VI

may be prepared by heating 2,4-dinitrochlorobenzene with isoquinoline. When treated with alkalies, soda, ammonia or primary amines in aqueous solution, a red pseudo base (VI) is formed, and this may readily be converted to red crystal-

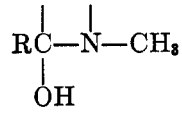
line oxygen ethers (OH of formula VI → OR) by boiling with methyl alcohol or ethyl alcohol. The pseudo base, a cyclic ammono aquo meroacetal, has been changed to a cyclic ammono aquo acetal. The alkoxy groups can be interchanged by boiling the oxygen ether with another alcohol, showing their high mobility (839a). Similar results have been recorded for dinitronaphthylisoquinolinium chloride (837).

By the action of alkalies on quaternary salts of papaverine (VII) Claus and his students (for references see 224a) obtained compounds which were subsequently called "isopapaverines" by Decker and Klauser (224a). A typical preparation is the following (224a; *cf.* 224, 231, 226):



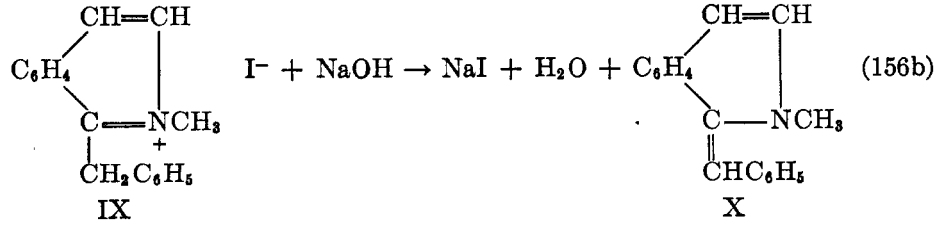
VII VIII

The cation (VII) of methylpapaverinium iodide is attacked by hydroxyl ion to give VIII, a "methylene base", either through the intermediate pseudo base,



or by removal of an ionizable hydrogen from the methylene group between the two nuclei. The isopapaverine (VIII), when shaken with water or when treated with acids, reverts to the strong base, *N*-methylpapaverinium hydroxide, or to its salts, respectively (cation = VII). The methylene base (VIII) precipitates when an aqueous solution of the quaternary ammonium base is concentrated.

The iodomethylate of 1-benzylisoquinoline (IX) reacts with sodium hydroxide to give the methylene base, 2-methyl-1-benzylidene-1,2-dihydroisoquinoline (X), as shown by the following equation:



IX X

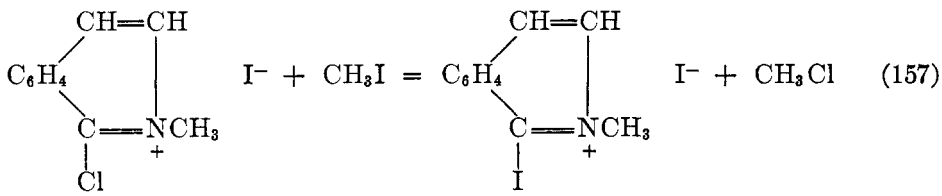
The same product is obtained by the action of benzylmagnesium chloride on 2-methyl-1-isoquinolone (230; equation 154). It is converted by hydrogen iodide to 1-benzylisoquinoline iodomethylate.

2. 1-p-Dimethylaminostyrylisoquinoline methiodide

This compound is made by boiling 1-methylisoquinoline methiodide with *p*-dimethylaminobenzaldehyde for 3 hr. in absolute alcohol solution with the addition of a little piperidine as a catalyst (622). 1-Methylisoquinoline reacts less readily with aldehydes.

3. 1-Iodoisoquinoline methiodide

This compound (XI) is prepared by heating 1-chloroisoquinoline methiodide with methyl iodide in a sealed tube for 2 days at 100°C. (315). The reaction is expressed by the equation:



(157)

XI

The activity of the iodine is so great that XI cannot be crystallized from water or alcohol without large losses, owing to the replacement of the iodine in the 1-position by hydroxyl or ethoxyl, respectively (313).

1-Aminoisoquinoline alkiodides are made readily by refluxing the 1-iodoisoquinoline alkiodides for about 10 min. with ammonia (315).

4. Isoquinoline alkiodides and the Grignard reagent

Isoquinoline alkiodides react with the Grignard reagent to form 1,2-dialkyl-1,2-dihydroisoquinolines in a manner similar to that of equation 112 (45, 335).

5. Isoquinoline, benzoyl chloride, and potassium cyanide

When these three substances are heated together, 1-cyano-2-benzoyl-1,2-dihydroisoquinoline is obtained (*cf.* Section IV, F and equation 69) (708). When hydrolyzed with 36 per cent hydrochloric acid for about a day at room temperature, there is formed a mixture of isoquinoline-1-carboxamide and isoquinoline-1-carboxylic acid, together with benzaldehyde. It was found somewhat better to heat the 2-benzoyl-1-cyano-1,2-dihydroisoquinoline with phosphorus pentachloride at 125–130°C. to obtain 1-cyanoisoquinoline, which acid hydrolysis converts to isoquinoline-1-carboxylic acid (375a, 453, 456).

6. Cyanine dyes containing the isoquinoline nucleus

The formation of cyanine dyes is dependent in large measure upon the aldehydic or ketonic reactivity of quaternary salts containing pyridine, quinoline, isoquinoline, benzothiazole, or related nuclei (see Section IV, N, 9). Fisher and

Hamer (313) have described the preparation of 2,1′- and 4,1′-cyanines derived from isoquinoline by condensing 1-iodoquinoline alkiodides with quinaldine alkiodides or lepidine alkiodides under alkaline conditions (see Section IV, N, 9, b, (1) and equation 134). The 2,1′-cyanines may also be made, though in much poorer yield, by heating the alkiodides of quinaldine and of isoquinoline in the presence of a base (*cf.* equations 130, 133). Isoquinoline red, a somewhat more complex cyanine, is obtained when isoquinoline and quinaldine are heated with benzotrichloride at 150°C. (802; *cf.* 739, 740).

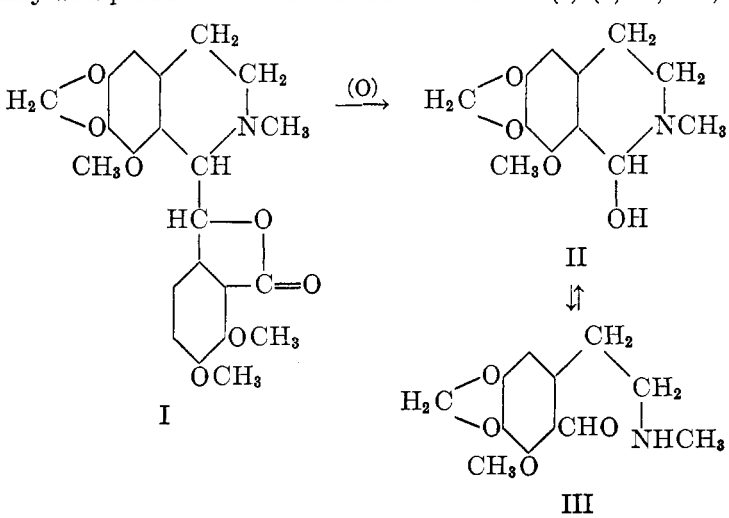
H. DIHYDROISOQUINOLINES

The comparatively low aldehydic and ketonic reactivity of isoquinoline and its 1-alkyl and 1-aryl derivatives, respectively, has been explained as due to the effect of the resonance of the six-membered ring with three double bonds. The 3,4-dihydroisoquinolines are intermediates in the Bischler–Napieralski synthesis (Section V, A, 1), but the literature concerning their chemical properties is too scanty to permit of comparisons with the corresponding isoquinolines. It is expected that the former will behave more like open-chain compounds which contain the groupings —CH=N— or RC=M—.

Pseudo bases and methylene bases are derivatives of 1,2-dihydroisoquinoline, but they have been described a few pages before. Hamilton and Robinson (413) heated 1-benzyl-3,4-dihydroisoquinoline with methyl sulfate in benzene and prepared a methosulfate, whose aqueous solution reacted with potassium hydroxide to give 1-benzylidene-2-methyl-1,2,3,4-tetrahydroisoquinoline. Apparently the chemistry of the dihydroisoquinolines and of the isoquinolines will be similar.

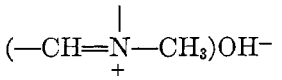
I. COTARNINE

Cotarnine (II or III) has probably been more intensively investigated than any other single pseudo base, both because of its high reactivity, and because of its availability as a product of the oxidation of narcotine (I) (9, 42, 818).



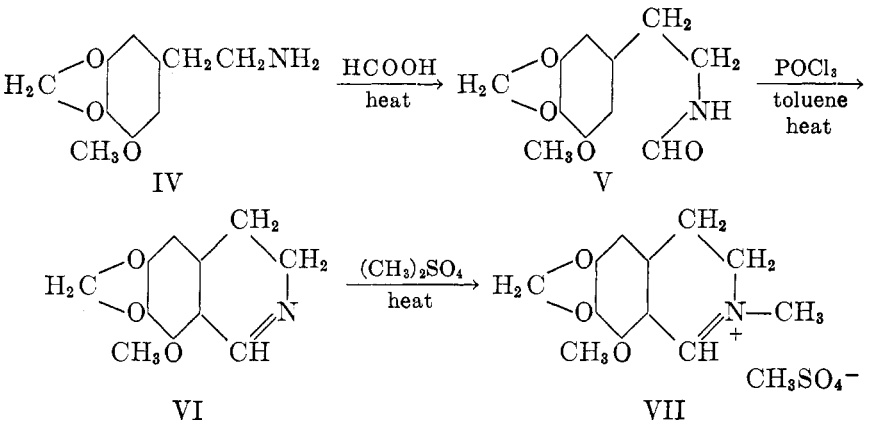
I (158)

Narcotine (I) is an ammono ether, since the nitrogen has three indifferent groups attached to it; cotarnine, its oxidation product, is variously represented in the cyclic form of an ammono aquo meroacetal (II), (199; *cf.* 435) or as an open-chain aminoaldehyde (III) (237, 725; *cf.* 407). An analogous case of tautomerism of an open-chain aldehyde with a cyclic hemiacetal of the water system is encountered in glucose and other monosaccharides. Dobbie, Lander, and Tinkler (251) conclude as a result of an examination of the absorption spectra of cotarnine and its derivatives that the former in the solid state, in ether, or in chloroform has the structure shown in formula II above. The aqueous solution of cotarnine is yellow, and is believed to contain the strong ammonium base



and no evidence was found for the existence of any forms other than the two that have been mentioned. A good discussion of the question of the constitution of this important alkaloidal derivative is given by Small and Lutz (767).

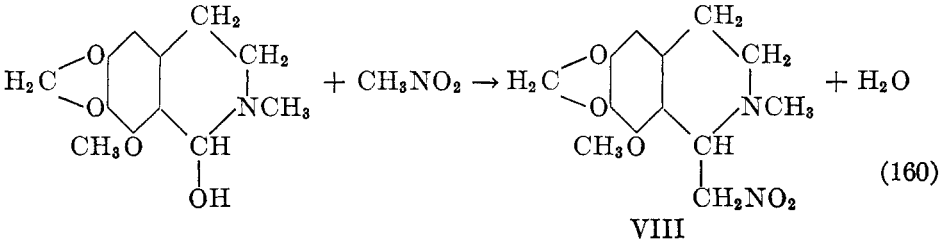
Decker and Becker (203) have synthesized cotarnine methosulfate by the following series of reactions:



(159)

The quaternary salts of cotarnine (VII) are derivatives of 3,4-dihydroisoquinoline, while cotarnine itself is related to 1,2,3,4-tetrahydroisoquinoline. The iodide corresponding to VII is identical with cotarnine iodide.

The substances formed chemically by condensations involving cotarnine are generally given cyclic structures, though this is not always the case (*cf.* 237, 725). Hope and Robinson (434) have prepared anhydrocotarnine nitromethane (VIII) by the action of cotarnine on nitromethane at room temperatures, in accordance with the equation:

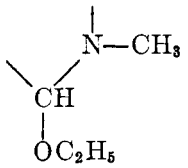


(160)

Anhydrocotarnine nitromethane forms two methiodides; the one produced in the smaller amount is probably the open-chain derivative, while the major product has the closed-chain structure. Along similar lines, it has been reported that glucose gives two phenylhydrazones (325), one of which is a cyclic, the other an open-chain, derivative.

A few of the condensations of cotarnine are listed below. It seems probable that the quaternary ammonium hydroxide form (formula VII above, $CH_3SO_4^-$ replaced by OH^-) is the true carrier of the reactions involved, rather than the pseudo, or carbinol, base (formula II above, equation 158; Robinson and Robinson (715a)).

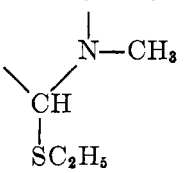
(*1*) Cotarnine and absolute ethyl alcohol give in the cold an ethoxy derivative (IX) which is to be considered a cyclic ammono aquo acetal (333, 727, 728).



IX

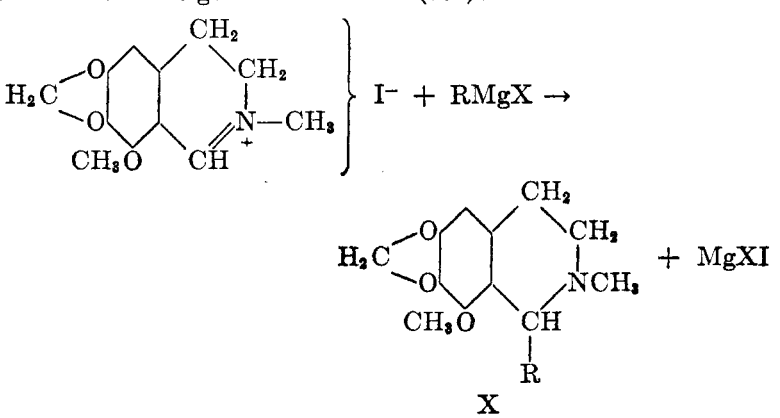
It is readily hydrolyzed by water into its components, and unexpectedly so, since acetals are as a class more stable. However, if it is converted to a methiodide, hydrolysis cannot be affected even by hot concentrated hydrochloric acid, apparently as a result of the additional stabilization given by the positively charged nitrogen (727; *cf.* 333).

Ethyl mercaptan, a thioalcohol, and cotarnine react (333a) to form a readily hydrolyzable thiol derivative containing the grouping,



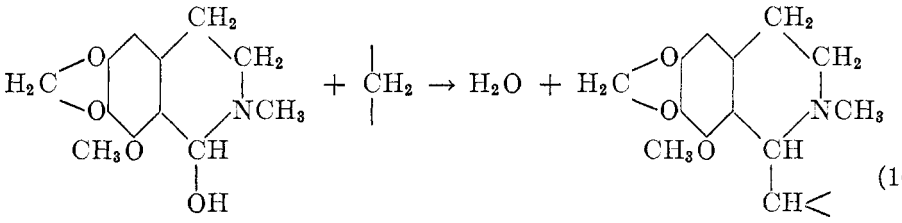
which is to be regarded as a cyclic thio ammono acetal.

(*2*) Cotarnine and its salts react with the Grignard reagent to give substituted hydrocotarnines of the general formula X (331):



X

(*3*) Cotarnine condenses with a large number of compounds containing reactive hydrogen, or a reactive methyl or methylene group, to give products that have generally been considered cyclic, though some believe otherwise and think that the structure is dependent upon the nature of the reagent (238, 543, 562; *cf.* 240). The reactions are represented by the equation:

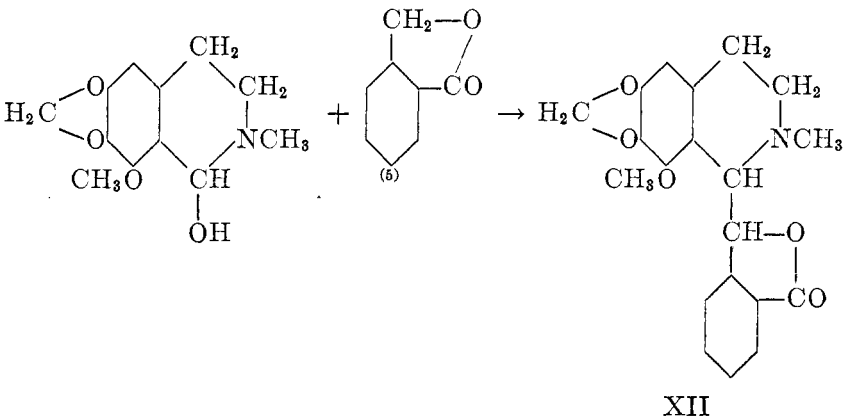


(161)

XI

A partial list of substances that have been condensed with cotarnine is the following: The methyl ketones (240, 439, 559), resorcinol, pyrogallol, and other phenols (4, 564), acetoacetic esters (545, 561), amides and imides, including isatin (438, 440), nitrotoluenes and nitromethane (433), nitroveratrole and nitropiperonal (714a), nitroaldehydes of the aromatic series (3, 238, 450), *p*-aminoacetophenone and various aromatic amines (241, 334), hippuric acid, oxalacetic ester, phenylacetic acid, benzyl cyanide, and even fluorene and indene (438, 755), methyloxindole (694), phenyl isocyanate, phenyl isothiocyanate (239) and many others.

(*4*) Cotarnine reacts with phthalide, or better with 5-nitrophthalide (432), to yield narcotine-like compounds, as shown by the equation:

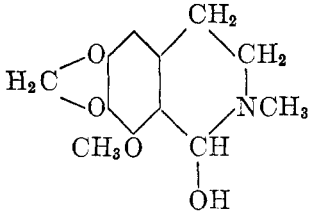


(162)

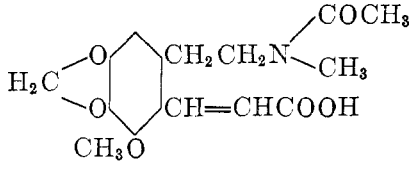
XII

Anhydrocotarnine phthalide (XII) is an alkaloid, dedimethoxygnoscopine.

(*5*) One of the first condensations with cotarnine was carried out in 1887 by Bowman (83), who refluxed it with acetic anhydride to form an open-chain compound (V), by a Perkin-type reaction combined with an acetylation.



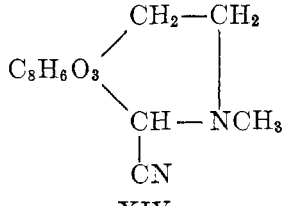
$+ (CH_3CO)_2O \rightarrow$



$+ H_2O$ (163)

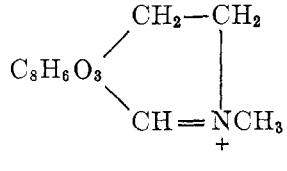
XIII

(*6*) With anhydrous hydrogen cyanide, cotarnine gives cyanohydro cotarnine (XIV), which exists in the equilibrium forms shown (189, 330, 410, 411):



XIV

$\leftrightarrows$

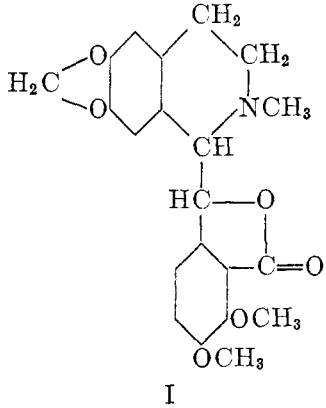


CN^-

XV

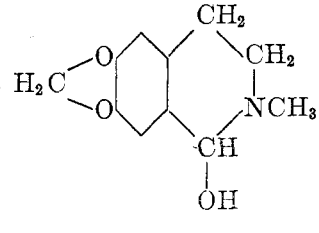
J. HYDRASTININE

Hydrastinine (II) (for constitution, see reference 252) bears the same relation to hydrastine (I) that cotarnine bears to narcotine.



I

$\xrightarrow{(O)}$

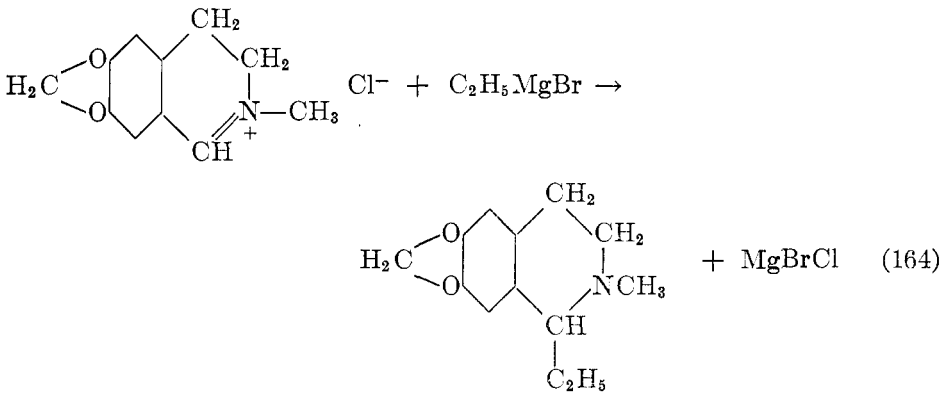


II

Hydrastinine may be formed by oxidizing hydrastine (344a, 344b, 749), by the action of alkali on its salts (187; *cf.* formula VII in equation 159), or by ring-closure methods (187, 205). The chemical similarity to cotarnine is very marked, as will be seen in the following examples:

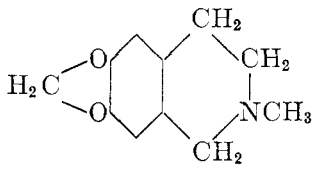
(*1*) Hydrastinine reacts with nitromethane in boiling methanol to give anhydrohydrastinine nitromethane; a similar reaction occurs with 2,4-dinitrotoluene (437; *cf.* equation 160).

(*2*) Hydrastinine chloride reacts with ethylmagnesium bromide in ether to form 1-ethylhydrohydrastinine, in accordance with the equation (340):

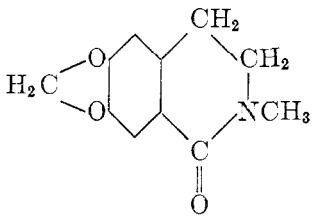


(164)

(*3*) Hydrastinine may be oxidized to oxyhydrastinine (IV), a cyclic ammono aquo ester (hydrastinic acid is also formed) (329, 339), and reduced to hydrohydrastinine (III), a cyclic ammono ether (34, 326, 336, 342, 344b). Simultaneous oxidation and reduction can be brought about by heating with alkali, in the sense of the Cannizzaro reaction (327, 343, 569; *cf.* 726), to give hydrohydrastinine and oxyhydrastinine.



III
Hydrohydrastinine



IV
Oxyhydrastinine

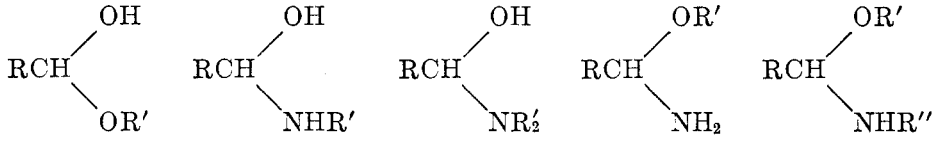
(*4*) Hydrastinine condenses with acetone or with acetophenone in the presence of sodium carbonate to form anhydrohydrastinine-acetone or -acetophenone, respectively (560). Similar reactions occur with cumaron, malonic ester, and phenylacetic ester (563).

(*5*) Hydrastinine, boiled for 2 hr. with acetic anhydride under reflux, gives an open-chain compound (328), in a reaction of the type shown in equation 163.

(*6*) 3-Methylhydrastinine is reported to undergo condensations with greater facility than hydrastinine itself (640b).

VI. Appendix: The Reactivity of Ammono Aquo Acetals and of Ammono Aquo Meroacetals

Aquo hemiacetals or their vinylogues (see xanthydrol, Section III), and the ammono aquo meroacetals, or "partial acetals" of the general formulas



all have a reactivity comparable to or perhaps even exceeding that of typical open-chain aldehydes. The cyclic ammono aquo meroacetals, which include the pseudo bases of the pyridine, quinoline, and isoquinoline series, have been described in some detail previously (see Sections II, I, 7; IV, N, 2; V, G, 1). The following brief account of the properties of some of the open-chain compounds whose formulas are given above is for purposes of comparison.

A. Meroacetals and Acetals as Possible Intermediates in the Knoevenagel and Mannich Reactions

1. The Knoevenagel reaction

The Knoevenagel reaction is the name applied to the ammonia- or amine-catalyzed condensation of an aldehyde with a compound having a reactive methylene group. Typical examples are given in the equations that follow:

$$C_6H_5CHO + CH_2(COOH)_2 \xrightarrow[50\text{-}70°C.]{NH_3} \underset{\text{I}}{C_6H_5CH{=}C(COOH)_2} + H_2O \quad (165)$$

$$C_6H_5CHO + CH_2(COOH)_2 \xrightarrow[100°C.]{NH_3 \text{ or amines}} \underset{\text{II}}{C_6H_5CH{=}CHCOOH} + CO_2 + H_2O \quad (166)$$

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow[\text{heat}]{NH_3 \text{ or amines}} C_6H_5CH{=}C(COOC_2H_5)_2 + H_2O \quad (167)$$

(References: equation 165, (478d); equation 166, (478b, 478d); equation 167, (478c)). The mechanism of this synthesis is not yet clear in all of its details, in spite of the large number of papers that have appeared upon this subject within recent years (14, 73c, 83b, 181b, 243a, 404a, 478a, 478b, 519c, 547b, 565c, 715b, 723a, 766a, 819b).

According to an earlier view of Knoevenagel (478a, 478b), the amine or ammonia used as a catalyst reacts with the aldehyde to form highly active inter-

mediate compounds (ammono acetals), as shown in the equations below, and these are responsible for the condensations observed.

$$C_6H_5CHO + 2C_5H_{10}NH \text{ (piperidine)} = H_2O + \underset{\text{III}}{C_6H_5CH(NC_5H_{10})_2} \quad (168)$$

$$C_6H_5CHO + C_6H_5NH_2 = \underset{\text{IV}}{C_6H_5CH{=}NC_6H_5} + H_2O \quad (169)$$

$$C_6H_5CH(NC_5H_{10})_2 + CH_2(COOH)_2 =$$
$$C_6H_5CH{=}CHCOOH + CO_2 + 2C_5H_{10}NH \quad (170)$$

$$C_6H_5CH{=}NC_6H_5 + CH_2(COOH)_2 =$$
$$C_6H_5CH{=}CHCOOH + CO_2 + C_6H_5NH_2 \quad (171)$$

Knoevenagel (478b) has, in fact, carried out many reactions similar to those of equations 170 and 171, and has even found that hydrobenzamide condenses with malonic acid when heated in alcoholic solution, in the manner shown below:

$$(C_6H_5CH{=}N)_2CHC_6H_5 + 3CH_2(COOH)_2 =$$
$$3CO_2 + 2NH_3 + 3C_6H_5CH{=}CHCOOH \quad (172)$$

This method for preparing benzalmalonic acid (I) has recently been recommended by Boehm and Grohnwald (77b).

The Knoevenagel reaction is considered by Rodionov and his coworkers (715b; *cf.* 723a) to proceed in accordance with the following equations:

$$RCHO + NH_3 \rightarrow \underset{\text{V}}{RCH(OH)(NH_2)}$$

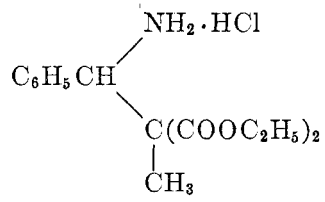
$$\underset{\text{V}}{RCH(OH)(NH_2)} + \underset{\text{VI}}{CH_2(COOH)_2} \rightarrow \underset{\text{VII}}{RCH(NH_2)CH(COOH)_2} + H_2O \quad (173)$$

Subsequently the following reactions may occur:

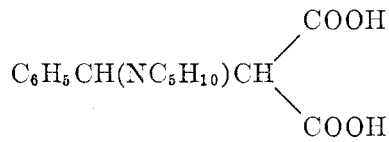
$$\text{VII} \rightarrow RCH(NH_2)CH_2COOH + CO_2$$
$$\text{VII} \rightarrow RCH{=}CHCOOH + CO_2 + NH_3$$

The ammonia may be replaced by a primary amine (e.g., CH_3NH_2) or by a secondary amine (such as piperidine) and malonic ester, $CH_2(COOC_2H_5)_2$, or a substituted malonic ester, $RCH(COOC_2H_5)_2$, may be used in place of the malonic

acid. It is accordingly possible to prepare compounds similar to those whose formulas are given below:



VIII

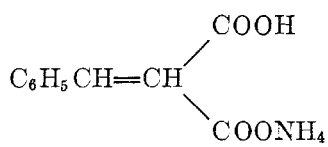


IX

($C_5H_{10}N$— is the *N*-piperidyl radical).

An ammono aquo aldehyde solvate, $C_6H_5CH(OH)NH_2$, or the ammono aquo meroacetals, $C_6H_5CH(OH)NHCH_3$ and $C_6H_5CH(OH)NC_5H_{10}$, have therefore been regarded as intermediates in the reactions of equation 173 ($R=C_6H_5$).

The bearing of this work upon the mechanism of the Knoevenagel reaction must, however, await an answer to the objections that have been raised by Boehm and Grohnwald (77b). It is claimed that the compound prepared by the action of alcoholic ammonia on a mixture of malonic acid and benzaldehyde is the monoammonium salt of benzalmalonic acid,



and not the aminobenzylmalonic acid (equation 173, formula VII, $R=C_6H_5$) that Rodionov thought he had prepared. Phenylaminopropionic acid, $C_6H_5CH(NH_2)CH_2COOH$, may be obtained by heating monoammonium benzalmalonate with dilute alcohol, evaporating the solvent, and treating the residue with hydrochloric acid, making it unnecessary to assume that the aldehyde derivative (V of equation 173) is an intermediate in its formation. Boehm and Grohnwald accordingly are of the opinion that the ammonia or amine is merely an enolization catalyst, but they do not seem to have explained satisfactorily the formation of the aminomalonic esters represented by formula VIII.

Hope and Robinson (435) believe that an addition compound of a secondary amine and an aldehyde, $R'CH(OH)NR_2$ (*cf.* equation 173), in the form of the true base $(R'CH=NR_2)OH$, is the effective intermediate in the Knoevenagel reaction (see Section IV, N, 2, b and reference 715a).

Because of the fact that tertiary amines are often very good catalysts (*cf.* 83b), the theory of an intermediate compound has been discarded by many investigators (73c, 83b, 181b, 404a, 519c, 547b, 819b), who believe that the function of the catalyst is to promote the enolization of the substance with reactive methylene. There follows an aldol-type condensation, with subsequent loss of water to give the unsaturated compound characteristic of the Knoevenagel reaction (*cf.* equation 173). It is assumed by some that the nitrogenous products so often isolated

are formed by the reaction of the amine catalyst with the intermediate aldol, but this view is not yet adequately supported experimentally.

Kuhn and coworkers (547b) have made the observation that piperidine will not catalyze the self-condensation of crotonaldehyde, though a small quantity of a salt of piperidine, such as the crotonate or acetate, will. They are therefore in agreement with the suggestion of Blanchard, Klein, and MacDonald (73c) that the Knoevenagel reaction is an example of positive-ion catalysis. Cope (181b) has recently found that acetamide, urea, piperidine, and ethylenediamine (but not sodium acetate) are good catalysts in acetic acid solution, and the results have been interpreted from the point of view of the extended Brönsted theory. It is considered that the function of the catalyst is to promote the enolization of the compound containing the reactive methylene group.

Even though an amine and an aldehyde may unite reversibly to give a reactive addition compound, $RCH(OH)NR'_2$ (equation 173), free aldehyde is still present and may well be the true intermediate in the Knoevenagel reaction (766a).

When primary amines are used as catalysts, it is probable that Schiff bases (X) are formed in the manner of the equation:

$$C_6H_5CHO + C_6H_5NH_2 \rightarrow \underset{\text{X}}{C_6H_5CH{=}NC_6H_5} + H_2O \qquad (174)$$

Worrall (819b) is of the opinion that the function of the Schiff base is to furnish, by hydrolytic reversal of the above reaction, a small amount of the primary amine which will then act as a catalyst in the usual way. The Schiff base, benzalaniline (X), is assumed to behave as shown below in the reaction of benzaldehyde, aniline, and nitromethane.

$$\underset{\text{X}}{C_6H_5CH{=}NC_6H_5} + CH_3NO_2 \rightarrow \underset{\text{XI}}{C_6H_5CH(CH_2NO_2)NHC_6H_5} + H_2O$$

$$\text{XI} + C_6H_5CHO \rightarrow \underset{\text{XII}}{C_6H_5CH{=}CHNO_2} + \underset{\text{X}}{C_6H_5CH{=}NC_6H_5} + H_2O \qquad (174a)$$

The first step is an aldol-like condensation of nitromethane with the ammono aldehyde ether, benzalaniline; presumably this must be catalyzed in the same manner as the corresponding reaction with benzaldehyde itself. The phenylaminonitroethylbenzene (XI) probably loses aniline to give the nitrostyrene (XII), and the former reacts with benzaldehyde to regenerate the Schiff base.

It is difficult to account satisfactorily for the observations of Boxer and Linstead (83b) that a β,γ-unsaturated acid is apparently the normal product of the condensation of butyraldehyde and malonic acid in the presence of tertiary amines.

$$CH_3CH_2CH_2CHO + CH_2(COOH)_2 \rightarrow CH_3CH_2CH{=}CHCH_2COOH + CO_2 + H_2O \qquad (175)$$

2-Hexenoic acid, $CH_3CH_2CH_2CH{=}CHCOOH$, is formed when a sufficient quantity of pyridine is used as a catalyst.

2. The Mannich reaction

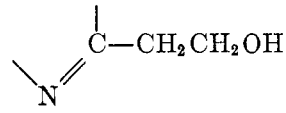
The Mannich reaction consists in the condensation of formaldehyde and ammonia, a primary or secondary amine (usually as the hydrochloride) with a compound containing at least one reactive hydrogen (74). A typical preparation is the following (576a):

$$(CH_3)_2NH + CH_2O + CH_2(COOH)_2 \xrightarrow{0°C.} (CH_3)_2NCH_2CH(COOH)_2 + H_2O$$

$$(CH_3)_2NCH_2CH(COOH)_2 \xrightarrow{\text{heat}} (CH_3)_2NH + CH_2{=}CHCOOH + CO_2 \quad (176)$$

The products formed in a Mannich reaction are often of comparative instability and pass into unsaturated compounds, particularly when heated. The Knoevenagel synthesis (compare equation 173) is closely related, and the reaction under consideration here may likewise involve an intermediate product of addition of the amine to formaldehyde, $CH_2(OH)NR_2$. Doubt has been expressed as to whether this is the case, since antipyrine and dimethylaminomethanol, $(CH_3)_2NCH_2OH$, give a poorer yield of condensation product than antipyrine, formaldehyde, and the amine or amine hydrochloride (74a).

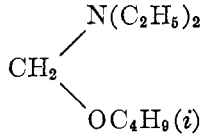
Heou-Feo Tseou (288c) is of the opinion that the dialkylaminomethanol, $CH_2(OH)NR_2$, or ammono aquo meroacetal, is an intermediate in the reaction between formaldehyde, a secondary amine, and quinaldine (see equation 99). An alternate possibility that the methylols,



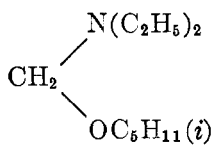
have a function in the synthesis has been disproved (288c; *cf.* 74a). It is believed that the instability of the dialkylaminomethanols is responsible for the failure to duplicate the yields of product that are obtained when an amine and formaldehyde react with quinaldine or other compound with reactive methyl or methylene.

B. REACTIVITY OF THE ISOLATED AMMONO AQUO MEROACETALS OR ACETALS

(*1*) McLeod and Robinson seem to have been the first to describe a reaction between an ammono aquo acetal and a compound with reactive hydrogen (570); two are given below:



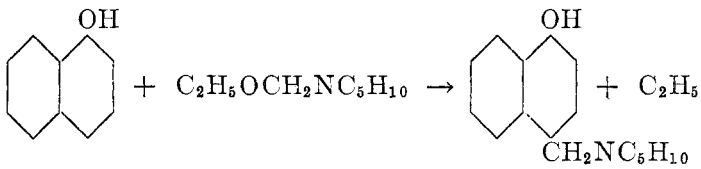
$$+ CH_3COC_6H_5 \rightarrow i\text{-}C_4H_9OH + (C_2H_5)_2NCH_2CH_2COC_6H_5 \quad (177)$$



$$+ CH_3C_6H_3(NO_2)_2\text{-}1,2,4 \rightarrow$$

$$i\text{-}C_5H_{11}OH + (C_2H_5)_2NCH_2CH_2C_6H_3(NO_2)_2 \quad (178)$$

Tseou Heou-Feo and Yang (290) report reactions of the following type. No heating is required.



$$+ C_2H_5OCH_2NC_5H_{10} \rightarrow$$

$$+ C_2H_5OH \quad (182)$$

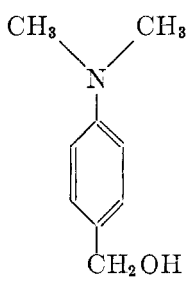
$C_5H_{10}N$— is *N*-piperidyl.

(*2*) Stewart and Bradley (777; *cf.* 570) have found that the dialkylaminomethanols, R_2NCH_2OH, are very readily hydrolyzed under acid conditions.

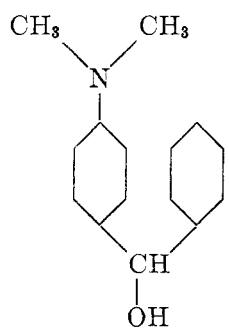
(3) Phenols react with formaldehyde in the presence of ammonia or various amines to form bakelite-type resins. Ammono aquo meroacetals, $CH_2(OH)NR_2$, may possibly be intermediates, since formaldehyde, phenol, and dimethylamine are reported to react to give *o*-hydroxybenzyldimethylamine, *o*-$HOC_6H_4CH_2N(CH_3)_2$ (233).

C. VINYLOGUES OF AMMONO AQUO ACETALS OR MEROACETALS

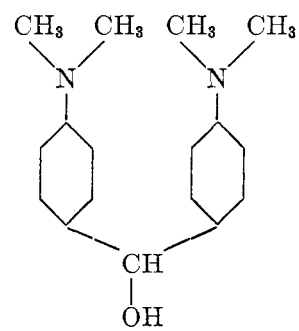
The high reactivity of these compounds often persists when two portions of the molecule are separated by one or more vinylene groups, as in the following examples:



XIII



XIV



XV

Smith and Welch (766a) have prepared *p*-dimethylaminobenzyl alcohol (XIII) by condensing formaldehyde with dimethylaniline in the presence of concentrated hydrochloric acid. When phenol is heated with the dimethylaminobenzyl alcohol at 155–170°C., with the addition of a small quantity of triethylamine, 4-hydroxy-4′dimethylaminodiphenylmethane is formed in accordance with the equation:

$$(CH_3)_2NC_6H_4CH_2OH + C_6H_5OH = H_2O + (CH_2)_2NC_6H_4CH_2C_6H_4OH \quad (180)$$

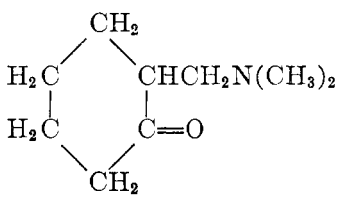
p-Dimethylaminobenzohydrol (XIV) and bis(*p*-dimethylaminophenyl)carbinol (XV; Michler's hydrol) both condense with compounds having active hydrogen, in the sense of equation 180; many of these reactions have been patented. It must be admitted that benzohydrol, $(C_6H_5)_2CHOH$, will behave similarly, so no proper estimate can be made of the activating effect of the *p*-dialkylamino group on the hydroxyl, particularly since much of the earlier literature in this field is practically devoid of experimental data (318a, 318b, 318c, 318d, 318e).

It is interesting that the dimethylamino group of 1-dimethylamino-3-butanone (XVI) and the cyclohexanone derivative (XVII) can be replaced by residues of acetoacetic and malonic esters in the presence of sodium ethylate (576, 581; *cf.* 574).

$$CH_3COCH_2CH_2N(CH_3)_2 + CH_2(COOC_2H_5)_2 \xrightarrow{NaOC_2H_5}$$

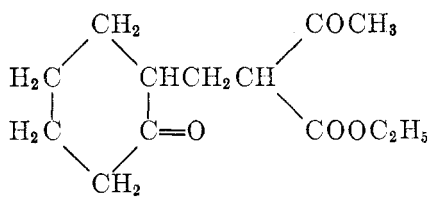
XVI

$$CH_3COCH_2CH_2CH(COOC_2H_5)_2 + (CH_3)_2NH$$



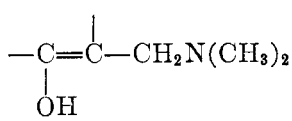
XVII

$$+ CH_3COCH_2COOC_2H_5 = (CH_3)_2NH +$$



(181)

Both of the dimethylamino ketones above, in their tautomeric forms, contain the system,



and so may be regarded as vinylogues of the ammono aquo meroacetal, $CH_2OHN(CH_3)_2$.

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