THE NAPHTHYRIDINES[1]

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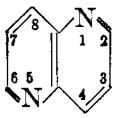
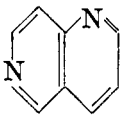
I. Introduction

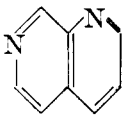
Naphthyridine is the name commonly given to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring thus containing only one nitrogen atom. This name was suggested by Reissert (57), who, in 1893, made the first representative of the series, since 1,8-naphthyridine was considered to be the naphthalene analog of pyridine. Six naphthyridines are possible:



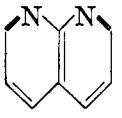
1,5-Naphthyridine



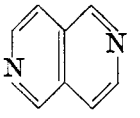
1,6-Naphthyridine



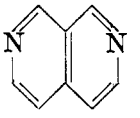
1,7-Naphthyridine



1,8-Naphthyridine



2,6-Naphthyridine



2,7-Naphthyridine

[1] Communication No. 1319 from the Kodak Research Laboratories.

These ring systems have received various names, such as "pyridinopyridines" and "benzodiazines" (see *The Ring Index*, Nos. 1004–1008, inclusive) (51). They may also be named by the "aza" system; i.e., "1,5-diazanaphthalene" may be used instead of "1,5-naphthyridine." However, since all these compounds have been indexed in *Chemical Abstracts* since 1936 under the heading "naphthyridine," this system of nomenclature will be followed in the present review.

The naphthyridine ring systems are usually built up from aminopyridines, by utilizing various cyclization reactions, essentially the same as those employed in quinoline chemistry (Skraup, Doebner–Miller, Doebner, Knorr). In a few instances they have resulted from the degradation of polynuclear compounds or from the ring enlargement of appropriately constituted phthalimides. The literature is scanty, for naphthyridines are not numerous. No 2,6-naphthyridines are known, and only one compound in the 1,7-series has been described (see page 285).

Naphthyridines (pyridinopyridines) undergo some of the reactions characteristic of pyridines. Among these may be mentioned the activity of halogen atoms ortho or para to the ring nitrogen, the ready hydrolysis of an ortho or para amino group to hydroxyl, replacement of ortho or para hydroxyl by chlorine by means of phosphorus pentachloride at an elevated temperature, and easy decarboxylation of acids. No instances of halogenation or sulfonation have been described, and there is but one instance of nitration.

Little is known about the physiological activity and therapeutic value of naphthyridines, only a few having been examined (75).

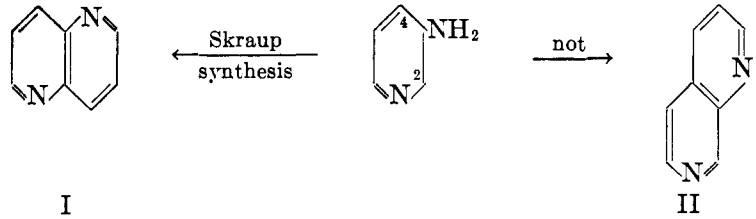
II. 1,5-Naphthyridines

This ring system is listed under 1,5-pyridopyridine in the 1936 *Decennial Index* of *Chemical Abstracts* and is called isonaphthyridine in some patents, but in the German literature it is usually given as 1,5-naphthyridine; the latter name is also used by *Chemical Abstracts* after 1936 and in the 1946 *Decennial Index*.

A. Preparation

1. Ring closure

Palazzo and Marogna (49) were the first to note that 3-aminopyridine, in contrast to the 2- and 4-aminopyridines, has aromatic characteristics, and they expressed the hope that in the Skraup synthesis it would give 1,5-naphthyridine (I). Fourteen years later it was found that 1,5-naphthyridines are, indeed, obtainable by application of this reaction; thus, 3-aminopyridine gives the base itself (6, 7, 69), as does 3-amino-2-chloropyridine, the halogen being eliminated.



I
1,5-Naphthyridine

3-Aminopyridine

II
1,7-Naphthyridine

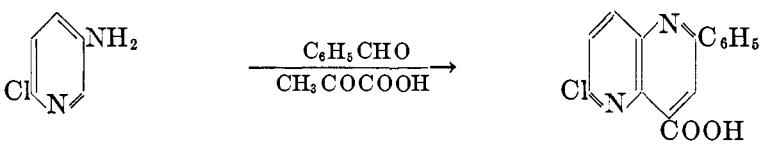
The cyclization takes place through the 2-position, giving 1,5-naphthyridine (I). None of the 1,7-isomer (II), which would result from a ring closure through the 4-position, is obtained.

Even when the 2-position is blocked, as in 3-amino-2,6-dimethylpyridine, no cyclization to the 1,7-naphthyridine ring system occurs. Evidently cyclization of a 3-aminopyridine to the 4-position is difficult. This may be due (*a*) to failure to achieve the optimum experimental conditions, (*b*) to side reactions involving the reactive methyl groups, or (*c*) to a preferred bond position such as shown by the resonance structure B.

A B

Many years ago Marckwald (37, 39) showed that in the Skraup reaction the new ring is always closed on the other end of the double bond bearing the amino group, and that the presence of a methyl group in that position prevents ring closure. Fieser (15) states that "apparently there is a general disposition for cyclization to occur in such a way that the new ring includes the double bond of the original ring system."

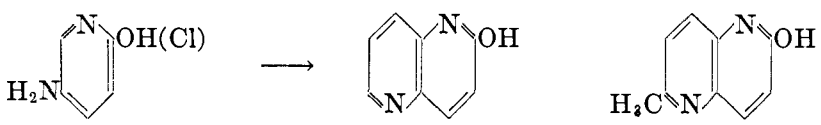
When Doebner's modification of the Skraup synthesis is used, 5-amino-2-chloropyridine, benzaldehyde, and pyruvic acid are said to give 6-chloro-2-phenyl-1,5-naphthyridine-4-carboxylic acid (54, 56, 69), but this statement has been questioned (73).



5-Amino-2-chloropyridine

6-Chloro-2-phenyl-1,5-naphthyridine-4-carboxylic acid

In the Skraup reaction both 5-amino-2-hydroxypyridine and 5-amino-2-chloropyridine give 2-hydroxy-1,5-naphthyridine (III), the chlorine atom undergoing hydrolysis (69).



III

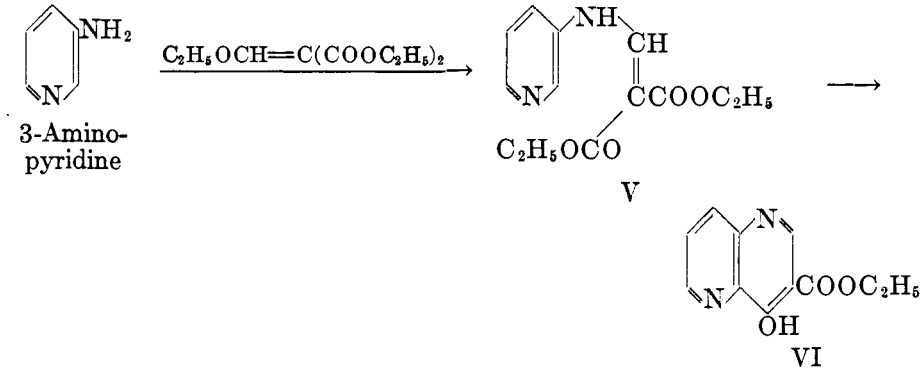
2-Hydroxy-1,5-naphthyridine

IV

The 2-hydroxy-6-methyl-1,5-naphthyridine homolog (IV) results when paraldehyde reacts with 5-amino-2-hydroxypyridine (69).

Adaptation of the excellent quinoline synthesis of Price and Roberts (54) is the most practical preparative method. In this reaction, 3-aminopyridine is first

condensed with ethoxymethylenemalonic ester, and the resulting ester (V) is then cyclized to 4-hydroxy-1,5-naphthyridine-3-carboxylic acid ethyl ester (VI) (1,54a) by heating in Dowtherm A.[2]

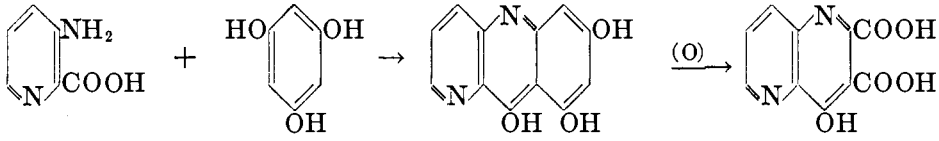


3-Amino-pyridine

V

VI

Another synthesis, not of preparative value but used as proof of structure, is the condensation of 3-amino-2-picolinic acid and phloroglucinol, followed by oxidation of the product, 7,9,10-trihydroxy-1,5-diazanthracene (VII) (6, 22), to 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (VIII).



3-Amino-2-picolinic acid

Phloroglucinol

VII

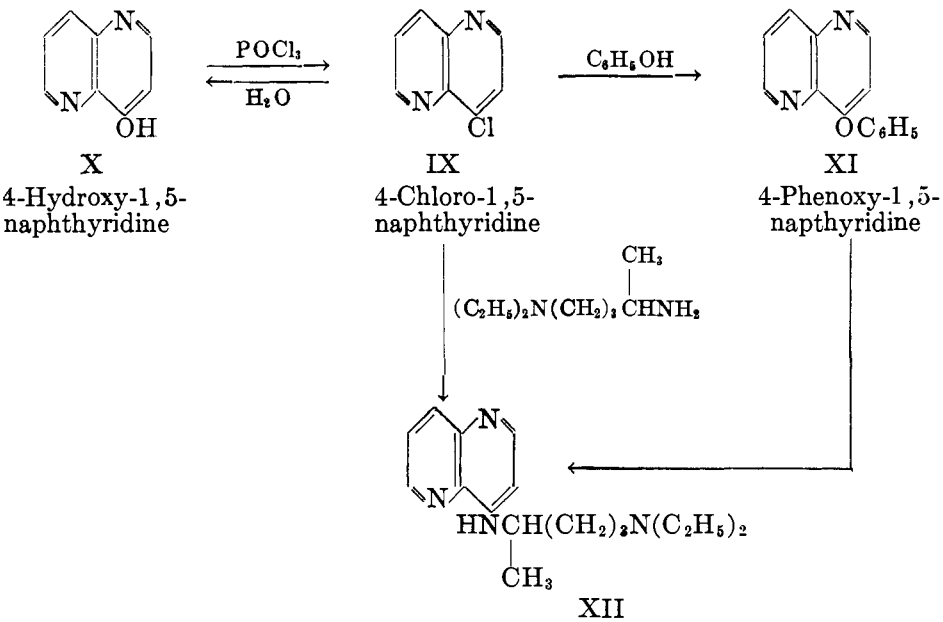
VIII

4-Hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid

2. Replacement reactions

Once the naphthyridine ring system has been formed by ring closure, derivatives can be prepared by the usual reactions of double decomposition, or by elimination of a group present. The hydroxyl groups ortho or para to the nitrogen atoms are easily replaced by chlorine, using phosphoryl chloride. The chlorine atom, in turn, is available for other reactions of double decomposition, including hydrolysis; the latter was mentioned in one of the preparative procedures just described (page 277). When the 4-chloro derivative (IX) is treated with a large excess of 4-amino-1-diethylaminopentane at 100°C., 4-(4′-diethylamino-1′-methylbutylamino)-1,5-naphthyridine (XII) is obtained in a yield of 90 per cent (1). When the foregoing reaction was carried out in phenol as a solvent, the 4-phenoxy compound (XI) was isolated; it gave the same product (XII) when heated with the aminopentane derivative (1).

[2] Dowtherm A, a eutectic mixture of diphenyl ether and biphenyl, is used as the solvent, and the reaction temperature is 250°C. The ester concentration is set at 0.25 mole per liter, in order to favor intramolecular ring closure as against polymer formation.



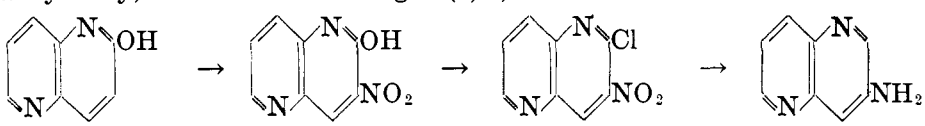
X
4-Hydroxy-1,5-naphthyridine

IX
4-Chloro-1,5-naphthyridine

XI
4-Phenoxy-1,5-napthyridine

XII

3-Amino-1,5-naphthyridine (XIV) can be obtained by the following series of reactions: 2-hydroxy-1,5-naphthyridine (III) is readily nitrated, the NO_2 group entering in the 3-position (XIII). The hydroxyl group is then replaced by chlorine in the usual way, and the 2-chloro-3-nitro derivative (XV) is reduced catalytically, with loss of the halogen (4, 5).



III
2-Hydroxy-1,5-naphthyridine

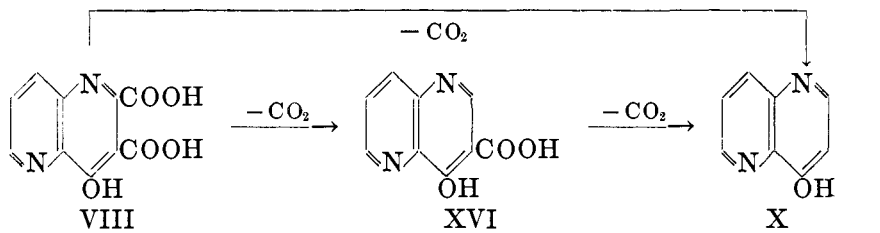
XIII
2-Hydroxy-3-nitro-1,5-naphthyridine

XV
2-Chloro-3-nitro-1,5-naphthyridine

XVI
3-Amino-1,5-naphthyridine

3. Elimination reactions

The most useful elimination reaction is decarboxylation. 4-Hydroxy-1,5-naphthyridine-3-carboxylic acid (XVI), whether obtained by hydrolysis of the



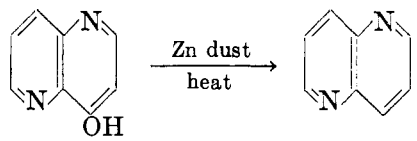
VIII
4-Hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid

XVI
4-Hydroxy-1,5-naphthyridine-3-carboxylic acid

X
4-Hydroxy-1,5-naphthyridine

ester (VI) or from 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid (VIII) by partial decomposition, is readily decarboxylated by heating to give 4-hydroxy-1,5-naphthyridine (X) (6, 22, 54); the latter can also be obtained directly from the dibasic acid (VIII) (6, 22).

Hydroxyl groups can be eliminated by the usual zinc dust distillation (6, 22); in this way the free base 1,5-naphthyridine (I) was first obtained. The Skraup reaction is now employed to prepare this substance (page 276).



X — 4-Hydroxy-1,5-naphthyridine

I — 1,5-Naphthyridine

B. PROPERTIES

1,5-Naphthyridine is a white solid (m.p. 75°C., b.p. 112°C./12 mm.) with a strong tendency to sublime. It turns yellowish in the air. It is soluble in all solvents, including water, and is best recrystallized from petroleum ether or carbon disulfide. The aqueous solution has a bitter, burning taste and a neutral reaction.

The hydroxynaphthyridines have high melting points and often sublime without melting. They are insoluble or sparingly soluble in hot water or hot alcohol, but dissolve in solvents such as chloroform. They have both acidic and basic properties, dissolving in both mineral acids and inorganic alkaline solutions.

While usually slightly colored, the pure naphthyridine derivatives so far described are undoubtedly colorless if protected from aerial oxidation.

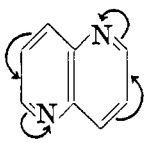
1,5-Naphthyridine forms salts, usually in a 1:1 ratio; among these are a sulfate, picrate, and chloroplatinate. Salts of certain derivatives are oils, but the picrates are usually crystalline.

As pyridinopyridines, naphthyridines might be expected to exhibit the basic properties of pyridine twice. However, salts with one equivalent of acid for each pyridine nucleus have been mentioned only in isolated cases, *viz.*, the dihydrochloride of 1,5-naphthyridine (6) and the trihydrochloride of 3-amino-1,5-naphthyridine (5). It appears possible that neutral salts composed of one mole of base and two equivalents of acid have not been isolated more often because they are more soluble than the basic salts. The observation that the monohydrochloride of 7-carbomethoxy-4-hydroxy-1,6-naphthyridine (page 285) dissolves in excess hydrochloric acid would agree with this suggestion.

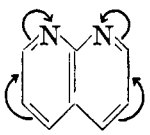
However, there is another possible cause for the failure to observe the formation of neutral salts. In the salt formation of tertiary bases a coördinative link is formed between the nitrogen and the proton of the acid, i.e., a pair of electrons from the nitrogen is shared with the proton. Thus the nitrogen acquires a positive charge and might polarize the remainder of the molecule so that the "lone" pair of electrons on the other nitrogen is now drawn closer into the mole-

cule, with the result that the ability of this nitrogen to form a coördinate link is restricted, i.e., its tendency to salt formation is decreased (36).

A shift of electrons to the nitrogen atoms by resonance of the molecule, however, can increase the tendency to salt formation (opposing the polarization effect). Assuming that the structures with symmetrical distribution of the double bonds are most important, and indicating the resonance by curved arrows, 1,5-naphthyridine can be designated by formula XVII and 1,8-naphthyridine by formula XVIII.



XVII
1,5-Naphthyridine



XVIII
1,8-Naphthyridine

It is evident from the structural formulas on page 275 that a two-step mesomeric shift of electrons to both nitrogen atoms can take place only with these two isomers. With 1,8-naphthyridine, however, the shift would cause an accumulation of electrons on neighboring nitrogen atoms, resulting in a high electric moment for the molecule. Electrostatic interactions, therefore, would tend to counteract the resonance effect. In 1,5-naphthyridine, on the other hand, resonance is unhindered and is strong enough to overcome the polarization effect by salt formation. The fact that salts with two equivalents of acid are reported only for the 1,5-naphthyridines agrees with this electronic explanation.

Substituents which polarize the molecule by attracting electrons diminish the tendency to salt formation. Thus, 2,4-dichloro-1,8-naphthyridine can be separated from the parent compound by extracting the ether solution of the mixture with aqueous picric acid; only the unchlorinated compound goes into the acidic solution (24) (see page 295).

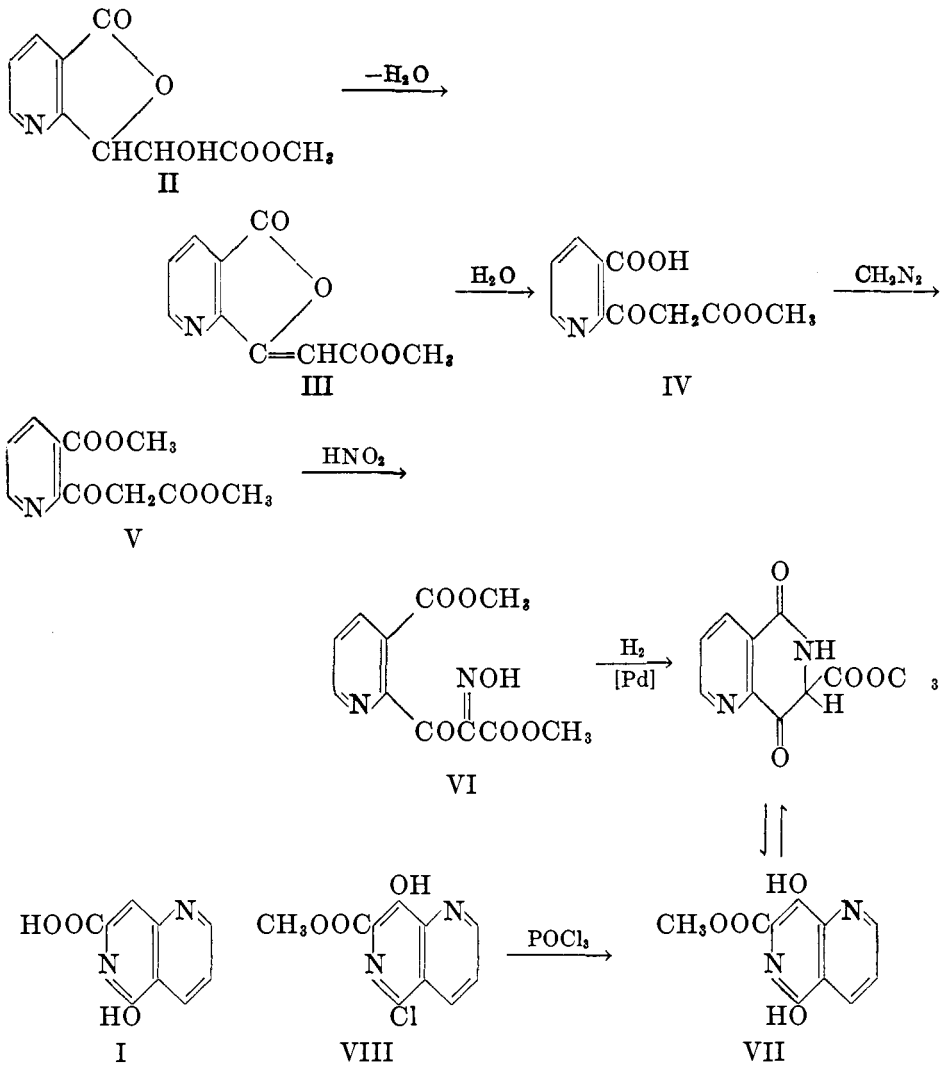
Measurements of electrolytic dissociation in solution and of dipole moments of naphthyridines should furnish valuable information on these compounds.

III. 1,6-Naphthyridines

1,6-Naphthyridines cannot be said to be readily accessible substances. The few compounds known have been prepared by reactions involving several steps and have required relatively complex starting materials. In the literature this ring system has been given an alternate, less-favored numbering, and most of the derivatives are listed under 2,5-naphthyridines.

The base itself has not yet been described. Only hydroxy-1,6-naphthyridines, their simple derivatives, and related compounds are known. Rosenheim and Tafel (60) treated the lactone of "pyridylglycerincarboxylic acid" with ammonia, and obtained 5-hydroxy-1,6-naphthyridine-7-carboxylic acid (I), which they called "1-oxo-3-carboxy-2,5-naphthyridine." The reaction is complex; the various steps and proof that the lactone is a γ-lactone were given by Ochiai and

his collaborators (48). Their synthesis is as follows: The methyl ester (II) of the lactone of β-(3-carboxypyridyl-2)glyceric acid is dehydrated to the unsaturated lactone (III); the latter easily adds a molecule of water to give the keto ester (IV), the free carboxyl group of which is then methylated using diazomethane. The resulting methyl ester (V) gives an isonitroso derivative (VI) when treated with acetic acid and sodium nitrite, and upon hydrogenation in the

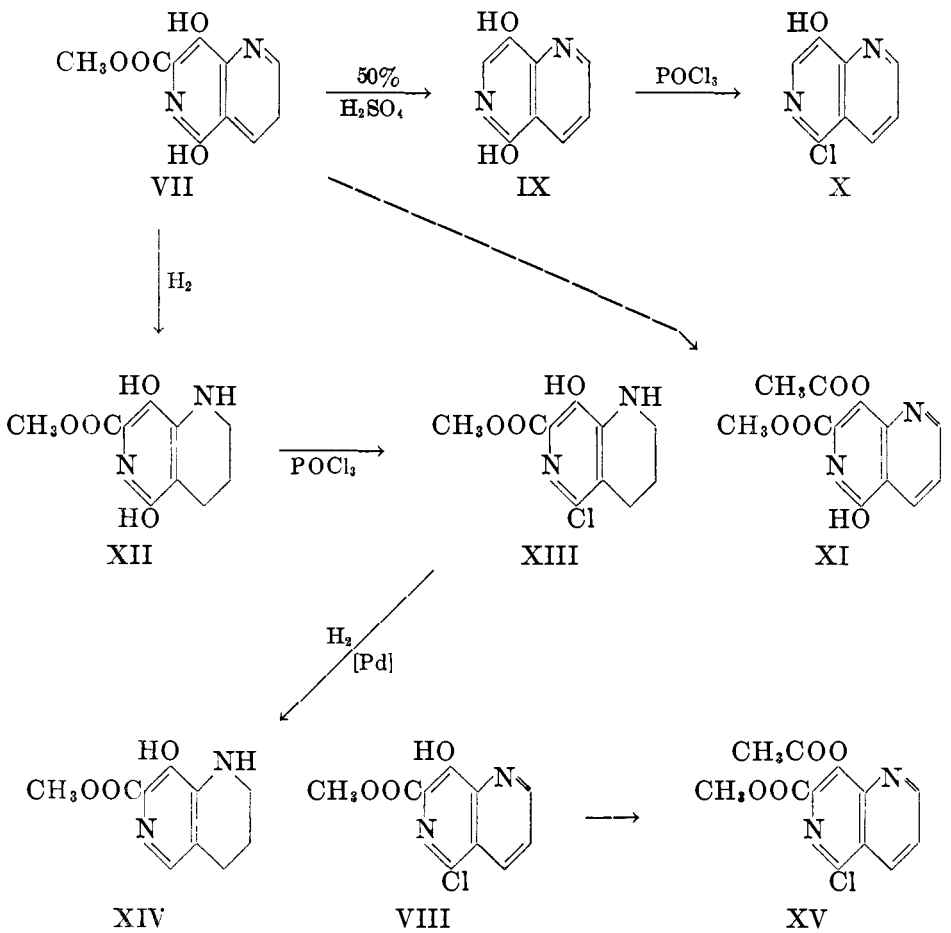


presence of palladium on charcoal the methyl ester of 5,8-dihydroxy-1,6-naphthyridine-7-carboxylic acid (VII) is obtained. Ochiai and coworkers assigned the name "1,4-dioxy-2,5-naphthyridine carbonic acid-(3) methyl ester" to VII. As a lactam it gives a monochloro derivative, 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (VIII) on treatment with phos-

phoryl chloride. The phenolic hydroxyl was detected by the formation of the monoacetate, 8-acetoxy-5-hydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (XI).

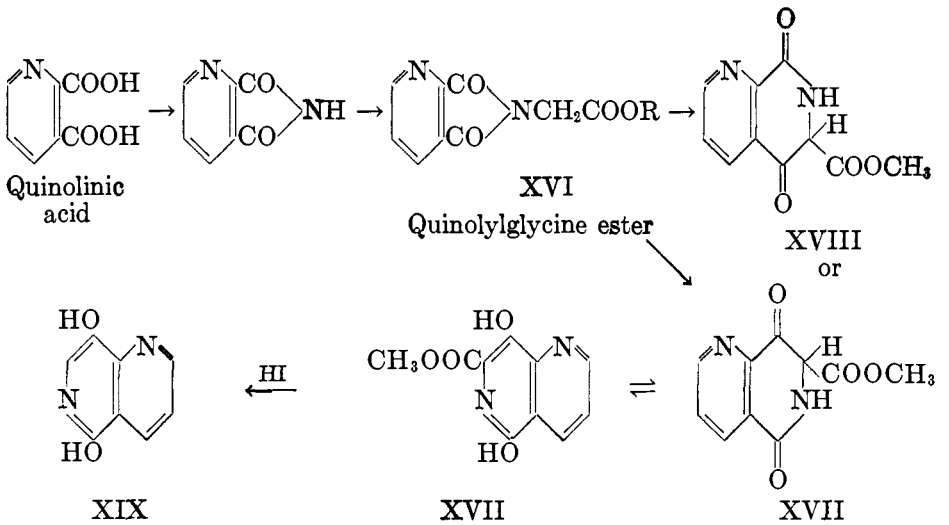
Subsequently (46) the ester VII was both hydrolyzed and decarboxylated with 50 per cent sulfuric acid; 5,8-dihydroxy-1,6-naphthyridine (IX) resulted instead of the anticipated acid (I) of Rosenheim and Tafel (60).

The lactam group in IX was confirmed (48) by preparation of the chloro derivative, 5-chloro-8-hydroxy-1,6-naphthyridine (X), whereas the hydroxyl group in position 8 was detected by formation of an ester, 8-acetoxy-5-hydroxy-1,6-naphthyridine. Upon catalytic reduction four atoms of hydrogen were taken up (46); the tetrahydro derivative, 5,8-dihydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XII), likewise gave a 5-chloro derivative, 5-chloro-8-hydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XIII). In the latter, the chlorine was replaced by hydrogen upon catalytic reduction, with consequent formation of 8-hydroxy-1,2,3,4-tetrahydro-1,6-naphthyridine-7-carboxylic acid methyl ester (XIV).



Acetylation of the chloro ester (VIII) gave 8-acetoxy-5-chloro-1,6-naphthyridine-7-carboxylic acid methyl ester (XV) (46); this ester (VIII) was also converted to the corresponding amide, 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxamide.

In 1904 Fels (14) studied the rearrangement of quinolylglycine ester (XVI) in the presence of sodium methoxide; Gabriel and Coleman had previously applied this reagent to phthalimidoacetic ester (16) and to cinchomeronylglycine ester (I, page 287).

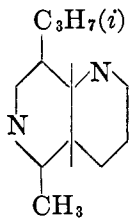


The rearrangement is ambiguous, in that the product may be a derivative of either 1,6-naphthyridine (XVII) or 1,7-naphthyridine (XVIII). Fels attempted to prove the structure of the ester by treatment with hydrogen iodide and red phosphorus, a reaction successfully employed by Gabriel and Coleman with their quinolinic compound, and also by Fels in the 2,7-naphthyridine series (page 286). Fels concluded that the substance was a derivative of the expected naphthyridine ring system because, upon oxidation, the dihydroxy derivative gave a colored product (dimer?) resembling those obtained from analogous compounds both by Fels in the 2,7-series and by Gabriel and Coleman. However, with this ester only hydrolysis and decarboxylation to the dihydroxy derivative, 5,8-dihydroxy-1,6-naphthyridine (XIX) took place. Fels also suggested the name "chinopyrin" for the new ring system. Since his structures are written throughout his paper as 1,7-naphthyridines, it would seem that this was his preference; however, he was careful to note that the alternative 1,6-structures were not excluded.

Ochiai and coworkers (45) proved recently that the product was a 1,6-naphthy-

ridine. They prepared the methyl ester by Fels's procedure and showed that it was identical with a specimen obtained by their own procedure (page 283) (i.e., XVII = VII). Hence the two dihydroxynaphthyridines shown in formulas IX and XIX also are identical.

The Japanese authors carried out these reactions with the ultimate aim of synthesizing a substance, $C_{12}H_{24}N_2$, which they had obtained by degradation of an alkaloid, matrin, and which they concluded was either 8-isopropyl-5-methyldecahydro-1,6-naphthyridine (XX) or the 7-methyl isomer (48).



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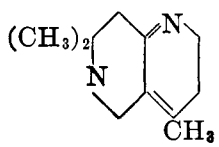


XXI

A 1,6-naphthyridine structure has been assigned to one other substance. When β-ethoxyethyl β′,β′-dimethylvinyl ketone was shaken with 25 per cent ammonium hydroxide, a base, $C_{11}H_{18}N_2$, was found among the products; the authors (44) represented it as 4,7,7-trimethylhexahydro-1,6-naphthyridine (XXI). No proof of structure has been given for either base (XX or XXI).

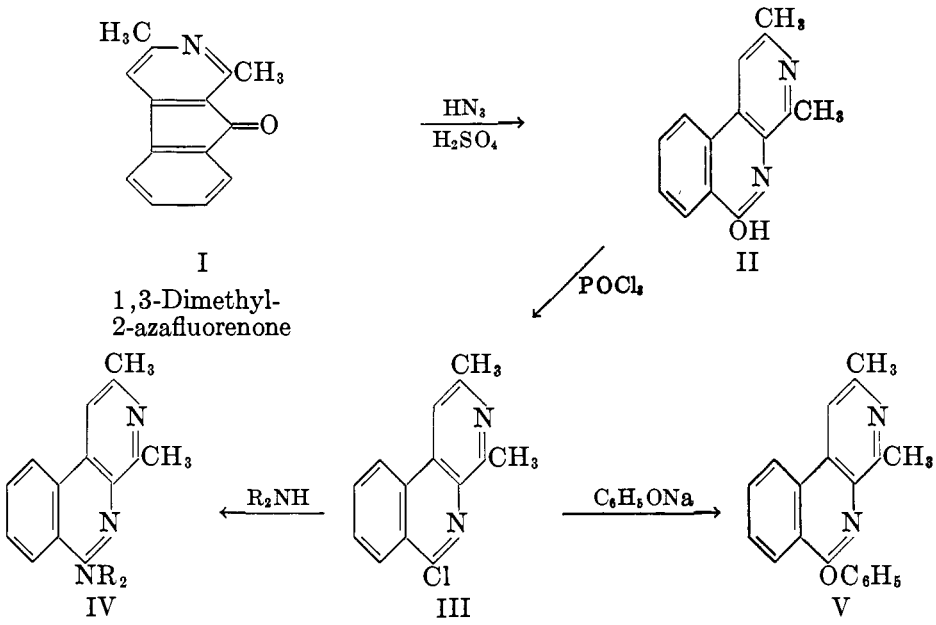
5,8-Dihydroxy-1,6-naphthyridine-7-carboxylic acid methyl ester (VII) forms highly colored salts with mineral acids, platinic and gold chlorides, and picric acid. The monohydrochloride that first separates when the ester is treated with hydrochloric acid dissolves in an excess of the latter. The ester is acidic enough to dissolve in ammonium hydroxide but, as might be expected, the ammonium salt is readily hydrolyzed, and the ester is precipitated when the ammonia is boiled off. 5,8-Dihydroxy-1,6-naphthyridine (IX) likewise forms colored salts. It gives yellow solutions in acids and alkalies, including sodium carbonate solution. It is soluble in hot water, but it cannot be recovered; the aqueous solution turns brown in the air. A monohydrochloride of the reduction product (XII) has also been described.

IV. 1,7-Naphthyridine

No simple 1,7-naphthyridine is known. A brief description of a benzo derivative may be given at this point.

1,3-Dimethyl-2-azafluorenone (I) undergoes a ring enlargement when submitted to the Schmidt reaction (hydrazoic acid and a catalyst) (19, 20, 63, 64, 71, 72). Phosphoryl chloride converts the resulting lactam, 3,4-benzo-2-hydroxy-6,8-dimethyl-1,7-naphthyridine or 6-hydroxy-2,4-dimethyl-3,5-diazaphenanthrene (II), to a 2-chloro derivative (III); the chlorine atom can be replaced by NH_2, NR_2, and OR. The 2-amino (IV: R = H), 2-piperidino (IV: R = C_5H_{10}), and 2-

phenoxy (V) derivatives have been prepared (52). The 1-carbethoxy derivative of II has also been mentioned (71).



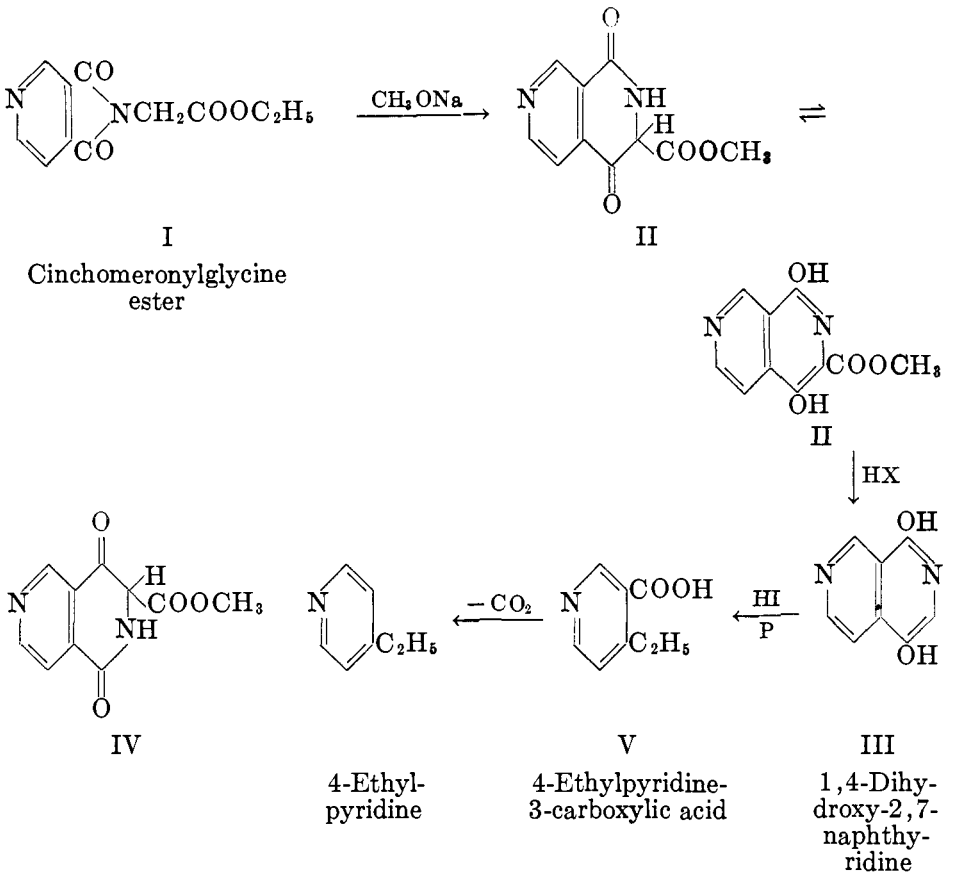
V. 2,7-Naphthyridines

The 2,7-diazanaphthalene ring system was given the name "copyrin" by its discoverers, Gabriel and Coleman (16). The base itself is unknown, and but few derivatives have been described.

Gabriel and Coleman adapted their ring enlargement of phthalimidoacetic ester to cinchomeronylglycine ester (I). This reaction, already mentioned (page 284), consists in heating the ester in absolute methanol in the presence of sodium methoxide. A rearrangement takes place, and 1,4-dihydroxy-3-methoxycarbonyl-2,7-naphthyridine (II) is formed; the ethyl ester undergoes transmethylation at the same time. The ester is hydrolyzed and decarboxylated, upon treatment with hydrogen bromide or iodide, to 1,4-dihydroxy-2,7-naphthyridine (III).

The rearrangement is ambiguous, in that the new ring system could have the two nitrogen atoms in either the 2,7- (II) or the 2,6-position (IV). That the former is correct was shown by degrading the ester, using hydrogen iodide and red phosphorus, in a sealed tube; 4-ethylpyridine-3-carboxylic acid is formed. Upon decarboxylation the latter gives 4-ethylpyridine; hence the acid is V and the starting ester must have structure II.

Both of the 2,7-naphthyridine derivatives shown in formulas II and III are yellow. They are sparingly soluble in water, but the aqueous solutions rapidly become yellow brown. The dihydroxy compound (III) is soluble in hot alcohol but insoluble in acetone and ethyl acetate. Its suspension in pseudocumene turns brown when heated.



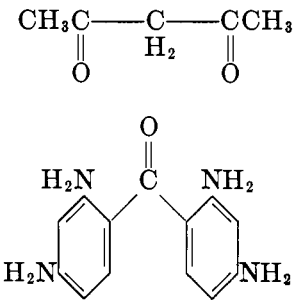
Both substances are soluble in dilute mineral acids and bases, including carbonates. The ester dissolves in ammonium hydroxide, but separates when the solution is heated to expel the ammonia.

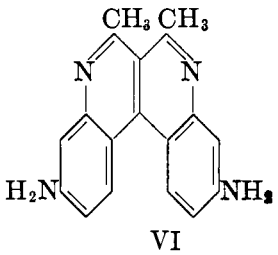
They form highly colored salts which have decomposition points above 200°C. A picrate was prepared from 1,4-dihydroxy-2,7-naphthyridine (III). The latter was oxidized to a colored base (dimer?) according to the equation:

$$2C_8H_6N_2O_2 + O = C_{16}H_{10}N_4O_4 + H_2O$$

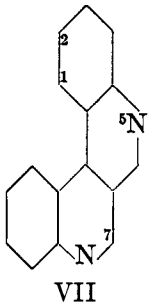
Nothing is known about this new base, except that it was isolated as a dihydrochloride.

A "dibenzocopyrin" (VI) has been obtained from 2,4,2′,4′-tetraaminobenzophenone and acetylacetone (17) (see page 288). A few other derivatives of this system are known, being obtained from 2,2′-diaminobenzophenones and 1,3-diketones (30); they are not included here since they really belong to the tetracyclic system, 5,8-diazabenzo[*c*]phenanthrene (VII), shown as Ring Index No. 2710 (51).





VI



VII

5,8-Diazabenzo[*c*]-phenanthrene

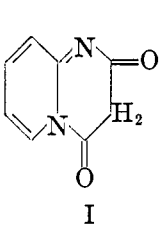
VI. 1,8-Naphthyridines

More is known about the 1,8-naphthyridines than about all the other naphthyridines combined. Most of the work dates from the discovery that 2-aminopyridines can be easily and cheaply prepared by the action of sodium amide on pyridine bases. However, it has been shown that many of the heterocyclic compounds prepared from 2-aminopyridine are not naphthyridines (Section VI, C). 2,6-Diaminopyridine, however, is readily cyclized to derivatives of 1,8-naphthyridine; this ring closure takes place through the 3-position, whereas with 2-aminopyridine the ring closes through the 1-position.

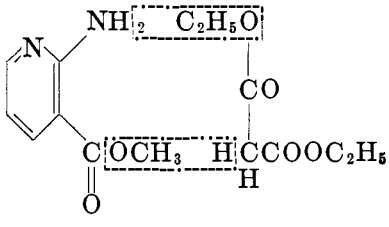
A. Preparation

1. Ring closure

(*a*) Most attempts to prepare the 1,8-naphthyridine ring system from 2-aminopyridines have been unsuccessful, because the ring closure takes place through the ring nitrogen. Among these may be mentioned the Skraup (38, 40), Doebner–Miller (38, 61, 62), Knorr (12), and Price–Roberts (54) syntheses (see Section VI, C). Likewise, ethyl malonate and 2-aminopyridine give a 1,4a-diazanaphthalene derivative (I) (8), but, with methyl 2-aminonicotinate, ring closure takes place through the carboxyl group and 2,4-dihydroxy-1,8-naphthyridine-3-carboxylic acid methyl ester (II) is obtained (it should be noted that there has also been an ester interchange) (23).

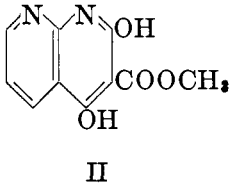


I



Methyl 2-aminonicotinate

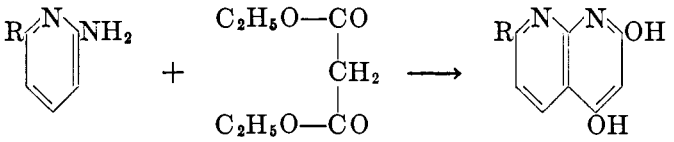
Ethyl malonate



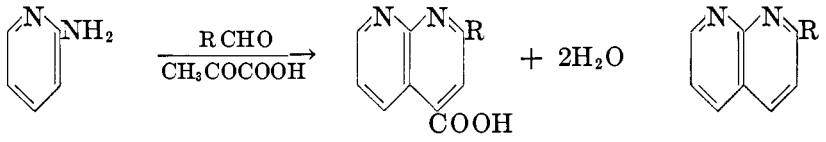
II

2,4-Dihydroxy-1,8-naphthyridine-3-carboxylic acid methyl ester

A recent study (29) of the reaction between 2-aminopyridine and malonic ester has shown that 1,8-naphthyridines are formed in a few instances only. The essential feature is the presence of a methyl (5 per cent), acetamido (85 per cent), ethoxy (92 per cent), or amino (100 per cent) group (the yields are given in parentheses).



It has been stated that the Doebner reaction, when applied to 2-aminopyridine, gave 2-substituted 1,8-naphthyridine-4-carboxylic acids (III), from which the parent bases (IV) were obtained upon decarboxylation (41, 42).

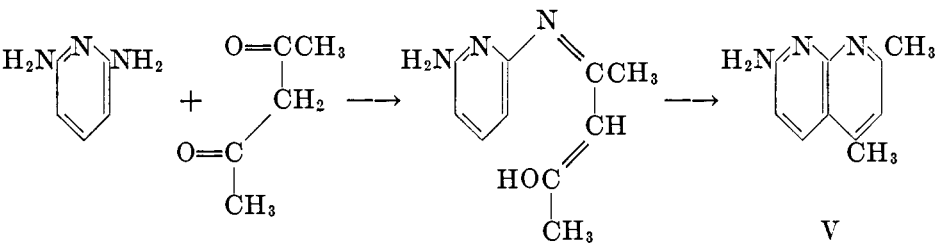


2-Aminopyridine III IV

R = C_6H_5—, *o*-HOC_6H_4—, *p*-$CH_3OC_6H_4$—, *p*-$(CH_3)_2NC_6H_4$—, $C_6H_5CH_2CH_2$—, $C_6H_5CH{=}CH$—.

This reaction needs confirmation, for in all other ring-forming reactions 2-aminopyridine gives rise to 1,4a-diazanaphthalene derivatives having a nitrogen atom common to both rings ("shared N"), and not 1,8-naphthyridines (see Section VI, C, pages 299 and 301).

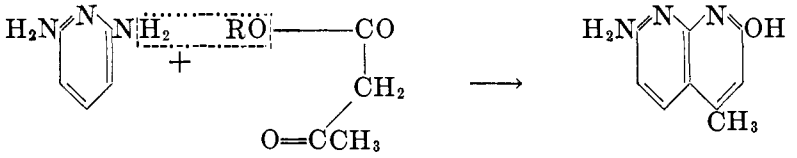
(*b*) Although the Skraup reaction is of no value with 2,6-diaminopyridine, its various modifications have been very useful in obtaining 1,8-naphthyridine derivatives; all of the latter have an amino group in the 7-position. By Knorr's procedure, for example, acetylacetone and 2,6-diaminopyridine give 7-amino-2,4-dimethyl-1,8-naphthyridine (V) (31, 35, 47). Benzoylacetone gives the corresponding phenyl analog (53). The yield, which is only 15–25 per cent when zinc chloride is used as condensing agent, or 60–70 per cent with concentrated sulfuric acid (53), is raised to 85 per cent when phosphoric acid is employed (3). The intermediate anil has been isolated and cyclized (3).



V

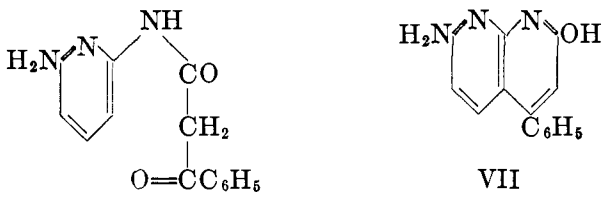
7-Amino-2,4-dimethyl-1,8-naphthyridine

Acetoacetic ester and ethyl β-aminocrotonate (or 2,6-diaminopyridine) react easily to give 7-amino-2-hydroxy-4-methyl-1,8-naphthyridine (VI) (18, 53, 68), while ethyl α-ethoxalylpropionate gives 7-amino-4-hydroxy-3-methyl-1,8-naphthyridine-2-carboxylic acid ethyl ester (18).



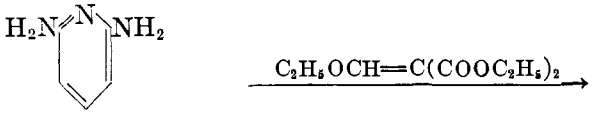
2,6-Diaminopyridine Acetoacetic ester 7-Amino-2-hydroxy-4-methyl-1,8-naphthyridine

The phenyl homolog (VII) is obtained by the use of benzoylacetic ester; in this case it is possible to isolate the intermediate open-chain acetamide (32, 33).

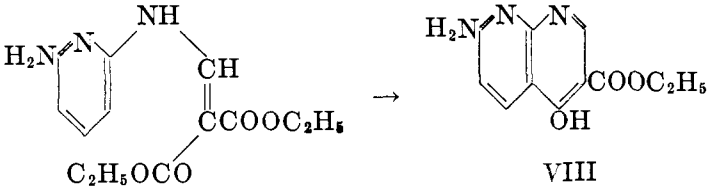


VII
7-Amino-2-hydroxy-4-phenyl-1,8-naphthyridine

7-Amino-4-hydroxy-1,8-naphthyridine-3-carboxylic acid ethyl ester (VIII) is prepared by the Price–Roberts reaction, using 2,6-diaminopyridine and ethoxymethylenemalonic ester (54).

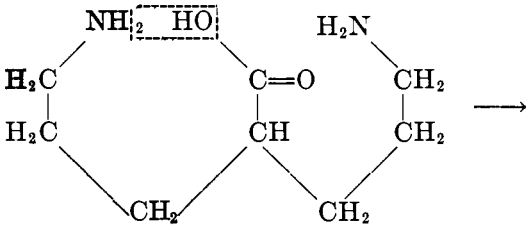


2,6-Diaminopyridine

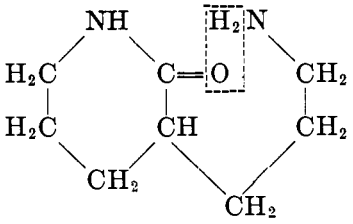


VIII

(*c*) Reissert (57) heated di(γ-aminopropyl)acetic acid and obtained a very small amount of the base, octahydro-1,8-naphthyridine (IX). Subsequently (58) the yield was improved and the intermediate product, γ-aminopropylpiperidone (X), was isolated.

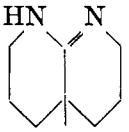


Di(γ-aminopropyl)acetic acid



X

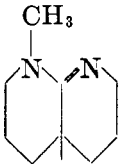
γ-Aminopropylpiperidone



IX

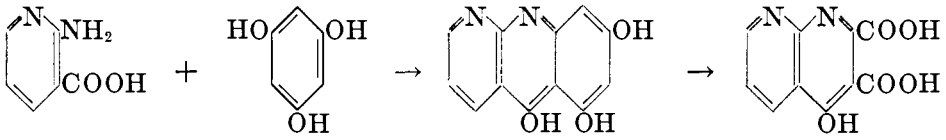
Octahydro-1,8-naphthyridine

Methylation of the base with methyl iodide yielded the 8-methyl homolog (XI).



XI

(*d*) 4-Hydroxy-1,8-naphthyridine (XII) has been obtained from 2-aminonicotinic acid and phloroglucinol, by oxidizing the primary condensation product (XIII) and decarboxylating the resulting acids, 4-hydroxy-1,8-naphthyridine-2,3-dicarboxylic acid (XIV) and 4-hydroxy-1,8-naphthyridine-2-carboxylic acid (XV) (70).

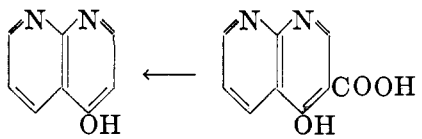


2-Aminonicotinic acid

Phloroglucinol

XIII

XIV



XII

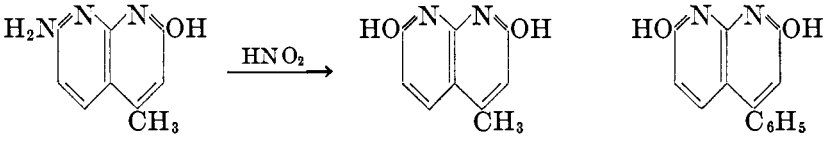
4-Hydroxy-1,8-naphthyridine

XV

This series of reactions has its analogy in the 1,5-naphthyridines (page 278).

2. Replacement reactions

As was noted with the 1,5-naphthyridines, once the ring has been closed, the substituent groups can be replaced by others or eliminated. The 7-amino-1,8-naphthyridines undergo some of the reactions of the analogous 2-aminopyridine. Thus, the amino group in VI is converted to a hydroxyl group by treatment with nitrous acid, giving 2,7-dihydroxy-4-methyl-1,8-naphthyridine (XVI) (31, 32, 33, 68). 2,7-Dihydroxy-4-phenyl-1,8-naphthyridine (XVII) is similarly ob-

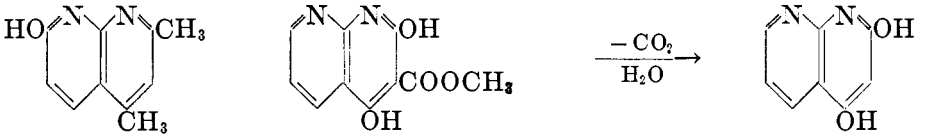


VI — 7-Amino-2-hydroxy-4-methyl-1,8-naphthyridine

XVI — 2,7-Dihydroxy-4-methyl-1,8-naphthyridine

XVII — 2,7-Dihydroxy-4-phenyl-1,8-naphthyridine

tained from the corresponding aryl derivative (VII) (32), whereas 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) arises from the amine (V). 2,4-Dihydroxy-1,8-naphthyridine (XIX), however, is obtained (23) by the hydrolysis and decarboxylation of the ester (II).

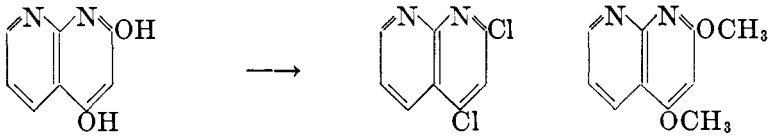


XVIII — 7-Hydroxy-2,4-dimethyl-1,8-naphthyridine

II — 2,4-Dihydroxy-1,8-naphthyridine-3-carboxylic acid methyl ester

XIX — 2,4-Dihydroxy-1,8-naphthyridine

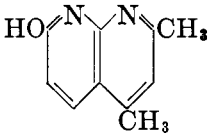
In hydroxy-1,8-naphthyridines, treatment with phosphoryl chloride and/or phosphorus pentachloride brings about a replacement of the hydroxyl group by chlorine in the 2-, 4-, 5-, and 7-positions.



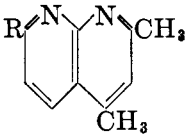
XIX XX XXI

This is a most useful reaction, for the chlorine atoms are available for reactions of double decomposition; in this way substituted amines, hydrazines, and ethers can be obtained (23, 31, 34). For instance, 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) has been transformed into the 7-chloro, 7-ethoxy, 7-benzyloxy, 7-benzylamino, and 7-hydrazino derivatives (XXII) (35), while the 4-phenyl

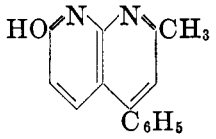
analog (XXIII) has given 7-chloro, 7-anilino, 7-piperidino, and 7-phenoxy derivatives (53).



XVIII



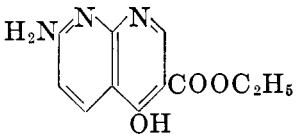
XXII



XXIII

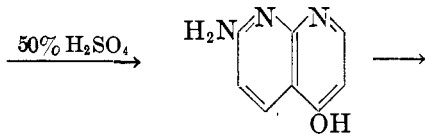
The amino group in 7-amino-2-hydroxy-1,8-naphthyridine is acetylated preferentially (53), but attempts to acylate it with *p*-acetaminobenzenesulfonyl chloride were unsuccessful (53). 7-Acetamino-2-hydroxy-4-methyl-1,8-naphthyridine has been transformed, by reactions similar to those just described, into 2-chloro, 2-arylamino,[3] 2-piperidino,[3] and 2-phenoxy derivatives (53).

The preparation of an antimalarial drug (XXVIII) illustrates the combination of several of these reactions (1). 2-Amino-5-hydroxy-1,8-naphthyridine-6-carboxylic acid ethyl ester (VIII) is hydrolyzed and decarboxylated with 50 per cent sulfuric acid to give 2-amino-5-hydroxy-1,8-naphthyridine (XXV). After the amino group has been protected by acetylation, the amide (XXVI) is heated with phosphoryl chloride, and the chloro derivative (XXVII) is then converted to the drug, 4-(4′-diethylamino-1′-methylbutylamino)-7-acetamido-1,8-naphthyridine (XXVIII) by a double decomposition with 1-diethylamino-4-aminopentane.



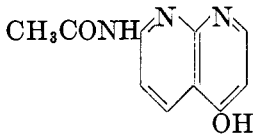
VIII

2-Amino-5-hydroxy-1,8-naphthyridine-6-carboxylic acid ethyl ester

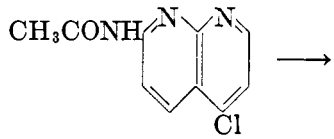


XXV

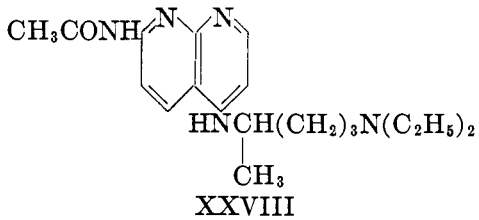
2-Amino-5-hydroxy-1,8-naphthyridine



XXVI



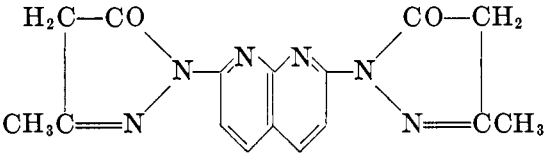
XXVII



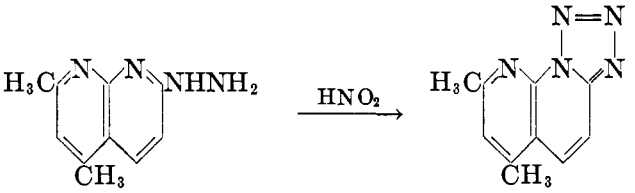
XXVIII

[3] The acetyl group is removed by hydrolysis in these instances.

The hydrazines (XXIV) react with aldehydes and ketones to give hydrazones (35); with ethyl acetoacetate, the dihydrazine (XLVI) (page 298) forms a dipyrazolone (XXIVa) (3). Tetrazoles (XXIVb) result when the hydrazines are treated with nitrous acid (35, 68); this reaction is used in proving structures (page 298).

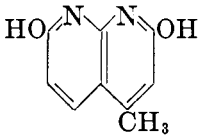


XXIVa

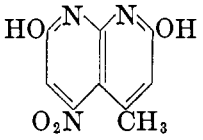


XXIV XXIVb

A single instance of nitration has been reported (31); 2,7-dihydroxy-4-methyl-1,8-naphthyridine (XVI) gives a mononitro derivative (XXIX). The location of the nitro group was not determined, but since the statement was made that it could not be ortho to either hydroxyl group, only the 5-position remains.

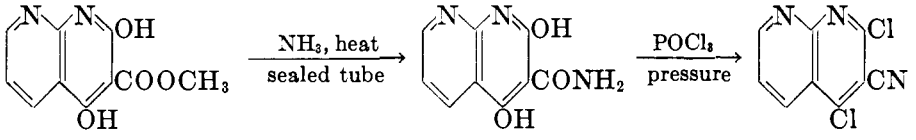


XVI
2,7-Dihydroxy-4-methyl-1,8-naphthyridine



XXIX
2,7-Dihydroxy-4-methyl-5-nitro-1,8-naphthyridine

One cyano-1,8-naphthyridine is known (24). The dihydroxy ester (II) was converted to the amide by heating with ammonia in a sealed tube. The 2,4-dihydroxy-1,8-naphthyridine-3-carboxamide (XXX) was then treated with phosphoryl chloride under pressure, with consequent formation of 2,4-dichloro-3-cyano-1,8-naphthyridine (XXXI).



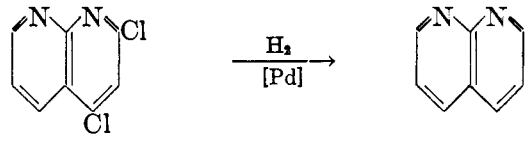
II
2,4-Dihydroxy-1,8-naphthyridine-3-carboxylic acid methyl ester

XXX
2,4-Dihydroxy-1,8-naphthyridine-3-carboxamide

XXXI
2,4-Dichloro-3-cyano-1,8-naphthyridine

The naphthyridine bases themselves have nearly all been obtained from the chloro compounds by catalytic hydrogenation. Since the reaction is seldom restricted to replacement of the chlorine atom, mixtures result from which the pure bases can be isolated only after tedious manipulation.

1,8-Naphthyridine itself (XXXII) has been obtained by this procedure from 2,4-dichloro-1,8-naphthyridine (24, 25). It is interesting to note that the use of iron and acid, zinc dust and aqueous alcohol, hydrogen and phosphonium iodides,



XX — 2,4-Dichloro-1,8-naphthyridine

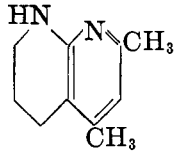
XXXII — 1,8-Naphthyridine

and zinc dust distillation did not give the base. In one instance, hydrogen iodide brought about hydrolysis, the chlorine being replaced by a hydroxyl group (68) 4-Methyl- and 2,4-dimethyl-1,8-naphthyridines are also known (43, 47).

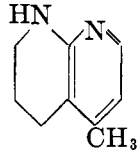
3. Addition reactions

(a) Hydrogenation

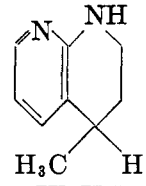
By an appropriate choice of catalysts and conditions, hydrogenation can be carried beyond the simple replacement of chlorine by hydrogen; di- and tetrahydronaphthyridines can thus be obtained (47, 68). 2,4-Dimethyl-1,8-naphthyridine gives a single tetrahydro derivative (XXXIII), whereas the 4-methyl analog gives two (XXXIV and XXXV) in a ratio of 4:1 (47). While it has not been conclusively proved, the available evidence indicates that the hydrogen is on the rings, as shown in the structural formulas. The difference in the behavior of the mono- and dimethylated 1,8-naphthyridines on partial reduction is attributed, by Mangini and Colonna (35), to their nuclear configuration. In the dimethyl derivative an aromatic-centered bond is stabilized by the two methyl groups; hence reduction occurs only in the unsubstituted pyridine ring.



XXXIII
2,4-Dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine

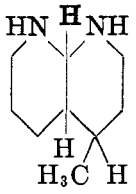


XXXIV



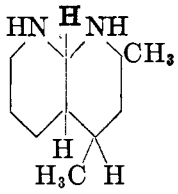
XXXV

Catalytic hydrogenation stops at the tetrahydro stage, but by means of sodium and amyl alcohol the 4-methyl- and 2,4-dimethyldecahydro-1,8-naphthyridines (XXXVI and XXXVII) are obtained (47).



XXXVI

4-Methyldecahydro-1,8-naphthyridine



XXXVII

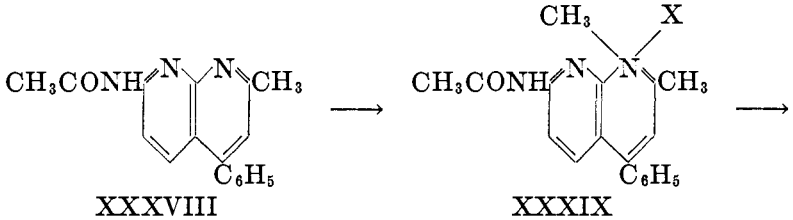
2,4-Dimethyldecahydro-1,8-naphthyridine

Hydrogenation of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVIII) gives a dihydro derivative in which the location of the hydrogen has not been determined (47); likewise, the reduction of 2,7-dichloro-4-methylnaphthyridine results in the formation of an intermediate monochloro derivative in which the position of the chlorine atoms is unknown (47).

(b) Quaternary salts

Four instances have been recorded in which 1,8-naphthyridines form salts; in all of these the addends have combined in a 1:1 proportion.

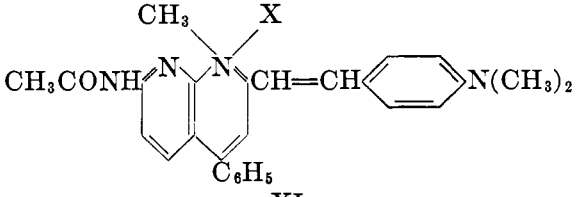
7-Acetamino-2-methyl-4-phenyl-1,8-naphthyridine (XXXVIII) adds methyl sulfate to give a salt (XXXIX), which, it was subsequently shown, could be converted to a methiodide and methoperchlorate. The nitrogen in the 1-position is quaternarized, for, when the salt was heated with *p*-dimethylaminobenzaldehyde (and a trace of piperidine), a styryl dye (XL) resulted; the authors were unable to isolate the pure dye, however (53).



XXXVIII

7-Acetamino-2-methyl-4-phenyl-1,8-naphthyridine

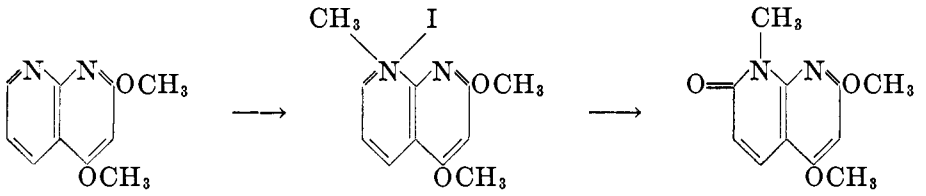
XXXIX



XL

1,8-Naphthyridine adds one equivalent of methyl iodide. The methiodide, when heated, is decomposed, and the 1,8-naphthyridine is regenerated (24) in unstated yield. This is an unexpected result, for the usual behavior of such salts on heating is to give rise to nuclear-alkylated bases and hydrogen iodide.

2,4-Dimethoxy-1,8-naphthyridine (XXI) also forms a monomethiodide (XLII). In this case, the nitrogen in the 8-position is quaternarized, because oxidation with alkaline ferricyanide gives 2,4-dimethoxy-8-methyl-1,8-naphthyridone-7 (XLIII) (26).



XXI XLII XLIII

2,4-Dimethoxy-1,8-naphthyridine

4-Methyl-5,6,7,8-tetrahydronaphthyridine (XXXIV) adds one equivalent of chloroacetone; when heated with dilute sodium carbonate, the addition product is changed into a noncrystalline material. The latter gives a blue color in the Ehrlich reaction with *p*-dimethylaminobenzaldehyde. The authors consider this characteristic of the indolizine ring, and tentatively suggest an indolizine structure (XLIV) (47).

XXXIV XLIV

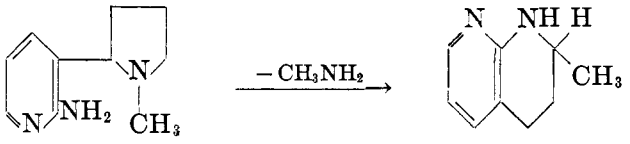
4-Methyl-5,6,7,8-tetrahydro-1,8-naphthyridine

4. Miscellaneous

Clemo and Swan (11) obtained a base, $C_9H_{12}N_2$, formed during a dehydrogenation of 2-aminonicotine. The properties of this base are as follows: It has one secondary and one tertiary nitrogen, for it gives a nitroso derivative, and an amide, insoluble in sodium hydroxide, with *m*-nitrobenzenesulfonyl chloride. It gave monoacetyl and monobenzoyl derivatives, a monomethiodide, a picrate, and a picrolonate. It could not be catalytically reduced further nor be dehydrogenated[4] by selenium at 280°C. or 330°C., and was unchanged by fusion with potassium hydroxide at 280°C. Upon oxidation by alkaline permanganate, 2-aminonicotinic acid resulted.

[4] These authors cite an inaccessible communication by Koller and Kandler (27) in which it is shown that dehydrogenation over palladium at 220°C. of decahydro-1,8-naphthyridine only goes as far as the tetrahydro derivative and then stops.

On the basis of this evidence the authors ascribe the structure 2-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (XLI) to the base, and suggest that its formation has taken place by a ring opening and closure, with elimination of methylamine.

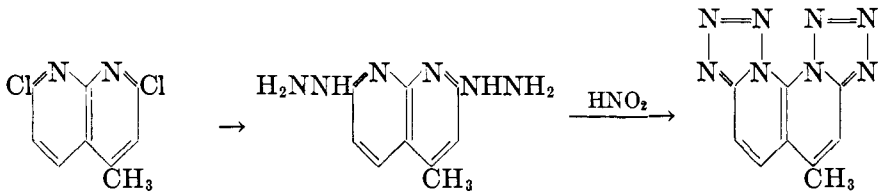


XLI

2-Methyl-1,2,3,4-tetrahydro-1,8-naphthyridine

B. PROOF OF STRUCTURE

The methods of synthesis by ring closure in some cases leave little doubt as to the presence of the 1,8-naphthyridine ring, but the derivatives obtained from 2,6-diaminopyridine might have other structures. The presence of the naphthyridine nucleus was shown in two cases by the formation of a tetracyclic system containing tetrazole rings (32, 34). Thus, 2,7-dichloro-4-methyl-1,8-naphthyridine (XLV) was converted to 2,7-dihydrazino-4-methyl-1,8-naphthyridine (XLVI) by a double decomposition reaction; with nitrous acid, the dihydrazine gave the tetracyclic base XLVII, which was oxidized to tetrazole (68).



XLV

2,7-Dichloro-4-methyl-1,8-naphthyridine

XLVI

XLVII

Tetrazole

The phenyl analog of XLVII has also been prepared (32, 34).

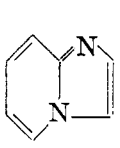
Lappin (28) has recently made a study of the cyclization of certain 2-aminopyridine derivatives. There were two different types of products: the one commonly formed (the "normal" reaction) was a 1,4a-diazanaphthalene derivative (XLIX), whereas in two instances only, derivatives of 1,8-naphthyridine resulted. He was able to relate mode of ring closure to nature of substituent, and demonstrated that the presence of electron-releasing groups in position 6 of the pyridine ring was essential for naphthyridine formation. The groups so far found to be effective in this way are amino, ethoxy, and methyl. Lappin states: "It seems most probable, therefore, that the formation of 1,8-naphthyridines is due to prevention of ring closure at the 1-position by the ortho effect of the 6-substitu-

ent, since the steric requirements of closure at a nitrogen atom might well differ considerably from those at a carbon atom. Activation of the 3-position is in all probability also required."

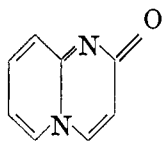
To differentiate between the two ring structures, Lappin used great differences in melting points, relative solubilities, and basic hydrolysis. The 1,4a-diazanaphthalenes have relatively low melting points, are soluble in most of the common solvents, and are easily hydrolyzed to the corresponding 2-aminopyridine derivatives, while the converse is true of the naphthyridines.

C. SUBSTANCES ERRONEOUSLY DESCRIBED AS 1,8-NAPHTHYRIDINES

As already mentioned (page 289), it appears that when 2-aminopyridine and its derivatives react with other substances to form bicyclic systems, ring closure nearly always takes place through the ring nitrogen rather than in the 3-position. Russian chemists, especially Chichibabin (8, 9, 10), have shown that the products are derivatives of pyrimidazole (XLVIII) or 2-keto-1,4a-diazanaphthalene (XLIX). Before these facts were established, some investigators had represented



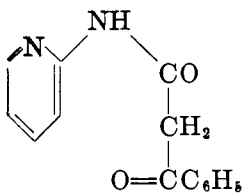
XLVIII
Pyrimidazole



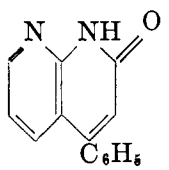
XLIX
2-Keto-1,4a-diazanaphthalene

their reaction products as derivatives of 1,8-naphthyridine. All such instances are collected in this section, and the corrected explanations are given in some detail. It has been pointed out (53) that "2-aminopyridine behaves as a cyclic amidine in these reactions, and on electrochemical grounds alone, its conversion into a 1,8-naphthyridine appears highly improbable."

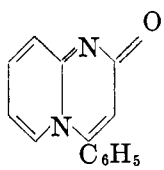
The first instance of this kind was recorded in 1911 by Palazzo and Tamburini (50), who dehydrated the benzoylacetamide (L) formed from 2-aminopyridine and benzoylacetic ester and represented the product as the naphthyridone shown in formula LI.



L

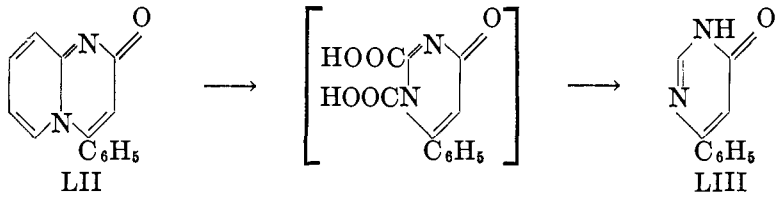


LI



LII

Seide (67) showed that the so-called naphthyridone (LI) is really a diazanaphthalene (LII), having one nitrogen atom common to both rings, by oxidizing it to the known 4-hydroxy-6-phenylpyrimidine (LIII).



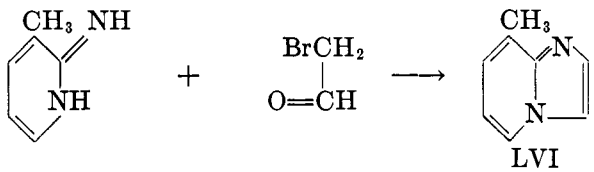
LII LIII

4-Hydroxy-6-phenylpyrimidine

Khitrik (21) examined the reaction products obtained by the interaction of 2-aminopyridine and acetoacetic ester with great care, in view of the contradictory claims in the literature (12, 50), and showed that the base, $C_9H_8N_2O$, is not a methylnaphthyridine (LIV) but a diazanaphthalene (LV).

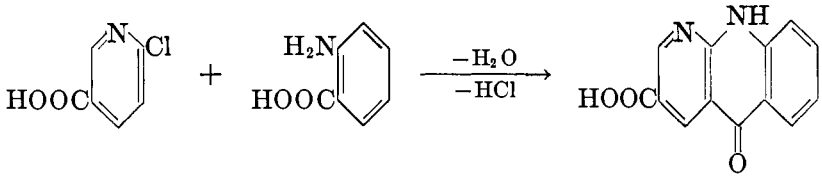
LIV LV

As evidence for the synthesis of 2-amino-3-methylpyridine, Räth (55) heated the substance in a sealed tube with bromoacetaldehyde (as bromoacetal) and obtained an oily product that was stated to be "1,2-dihydronaphthyridine." Both Chichibabin (10) and Seide (68) disputed this, and the former was able to show that the product was a pyramidazole base (LVI).



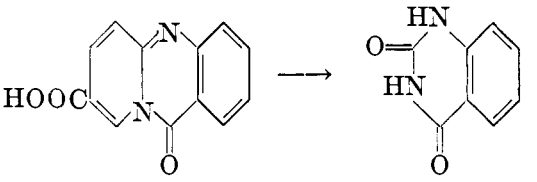
Bromoacetaldehyde LVI

Reissert (59) ascribed a naphthyridine structure (LVII) to a substance obtained by the interaction of 6-chloronicotinic and anthranilic acids.



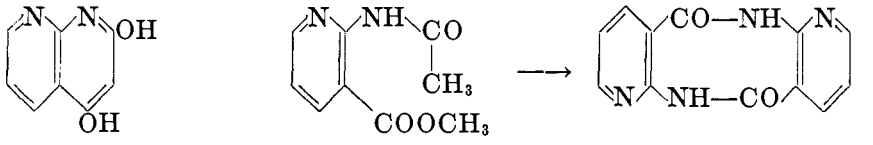
6-Chloronicotinic acid Anthranilic acid LVII

Seide (65, 66) corrected this also; he oxidized the product (LVII), obtaining the quinazolone LIX, from which it was obvious that the acid has the structure shown in formula LVIII.



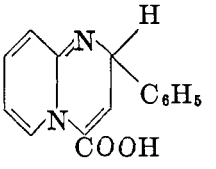
LVIII LIX

Seide further attempted to prepare 2,4-dihydroxy-1,8-naphthyridine (XIX) by an intramolecular ring closure with methyl 2-acetaminonicotinate, but obtained only the dilactam LX.



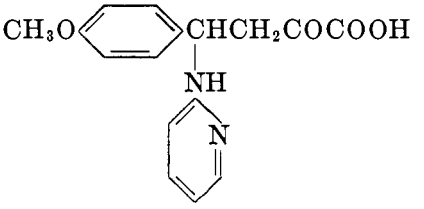
XIX Methyl 2-acetaminonicotinate LX

In view of these numerous instances, it is somewhat surprising to find in recent publications (41, 42) that 2-aminopyridine is stated to give derivatives of 1,8-naphthyridine in the Doebner reaction (page 289). One would have expected that the product would be a 1,4a-diazanaphthalene (LXI) (2, 53).



LXI

Attempts to repeat this work have been unsuccessful (2). Although the substances which were obtained had decomposition points in the ranges stated, they proved to be the 2-aminopyridine addition products of the benzalpyruvic acids; e.g.,



from anisaldehyde.

D. MECHANISM OF RING CLOSURE[5]

It is noteworthy that the condensation products of 2-aminopyridine close the ring through the nuclear nitrogen and form a 1,4a-diazanaphthalene (pyrido-

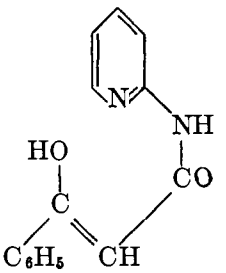
[5] This section was written by A. Weissberger of the Kodak Research Laboratories.

pyrimidine), while the condensation products of 2,6-diaminopyridine close the ring through the carbon atom in position 3 and form 7-amino-1,8-naphthyridine. This behavior may be explained as follows:

The reactivity of the 2-, 3-, and 4-positions of pyridine with electrophilic reagents is lowered by a shift of electrons towards the nitrogen, owing to the inductive effect of the latter. Moreover, positions 2 and 4 suffer further in reactivity with electrophilic reagents by the mesomeric shift of electrons (resonance) indicated in formula LXII (74). Both effects increase the electron density at the nitrogen

LXII

and accordingly the reactivity of the latter with electrophilic reagents. In the ring closure of 2-benzoylacetaminopyridine (LXIII), to choose a definite example, it may be assumed that the enolic hydroxyl group splits off a hydroxyl



LXIII

2-Benzoylacetaminopyridine

ion, and that the proton is released from the nitrogen, while the electrophilic atom links with the nuclear nitrogen. This bonding is facilitated by the high electron density at the nuclear nitrogen atom. The electron density in position 3, although higher than in positions 2 and 4, appears to be too low to effect a ring closure in position 3.

By analogy with aniline, a free amino group in position 6 should cause an increase in electron density in positions 1, 3, and 5. The last position is of no interest at present, but the course of the ring closure of 2-acetoacetamino-6-aminopyridine seems to indicate that the relative gain in position 3 is greater than that in position 1. This is plausible because the electron density at 1 is already high in the absence of the amino group in 6, while some depletion prevails at 3. A shift of electrons with equal force into both positions will therefore benefit position 3 more than it will position 1. This would explain the effect of the 6-amino group on the course of the ring closure. These conclusions are like those reached independently by Lappin (28) and Hauser (18).

TABLE I

Properties of 1,8-naphthyridine bases

SUBSTANCES	FORMULA NO.	MELTING POINT	BOILING POINT	ACETYL AND BENZOYL DERIVATIVES	MELTING POINT OF PICRATE	REFERENCES
		°C.	°C.		°C.	
1,8-Naphthyridine	XXXII	98–99			207–208	(24, 25)
4-Methyl-1,8-naphthyridine			147–148/0.05 mm.		204–205	(43, 47)
2,4-Dimethyl-1,8-naphthyridine		85–86			204–206	(47)
4-Methyl-1,2,3,4-tetrahydro-1,8-naphthyridine	XXXV	62–63		Benzoyl, m.p. 86–87°C.		(47)
4-Methyl-5,6,7,8-tetrahydro-1,8-naphthyridine	XXXIV	102–103		Acetyl, m.p. 94°C. Benzoyl,m.p.105–106°C.	248	(47) (68)
2,4-Dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine	XXXIII	118		Acetyl, m.p. 42–43°C.	207	(47)
Octahydro-1,8-naphthyridine	IX	67	248/754 mm.	Acetyl, oil	208–209	(57, 58)
4-Methyldecahydro-1,8-naphthyridine	XXXVI	87	70–80/0.1 mm.		210	(47)
2,4-Dimethyldecahydro-1,8-naphthyridine	XXXVII	92–93		Acetyl, b.p. 135–145°C. /0.02 mm.		(47)
8-Methyloctahydro-1,8-naphthyridine	XI	Oil; not isolated			209	(58)

E. PROPERTIES

The 1,8-naphthyridine bases are liquids or low-melting solids, but most of the derivatives have relatively high melting points; the latter are really decomposition points when hydroxyl groups are present in the molecule. They form salts, as usual, with mineral acids and picric acid, as well as double salts with platinum and gold chlorides. One perchlorate has been recorded (47). The salts likewise have decomposition points rather than true melting points; those of the picrates are too close together to be very useful. The properties of the bases are listed in table 1.

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