[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

CYCLIZATION OF 2-AMINOPYRIDINE DERIVATIVES TO FORM 1,8-NAPHTHYRIDINES

CHARLES R. HAUSER AND MARTIN J. WEISS[1]

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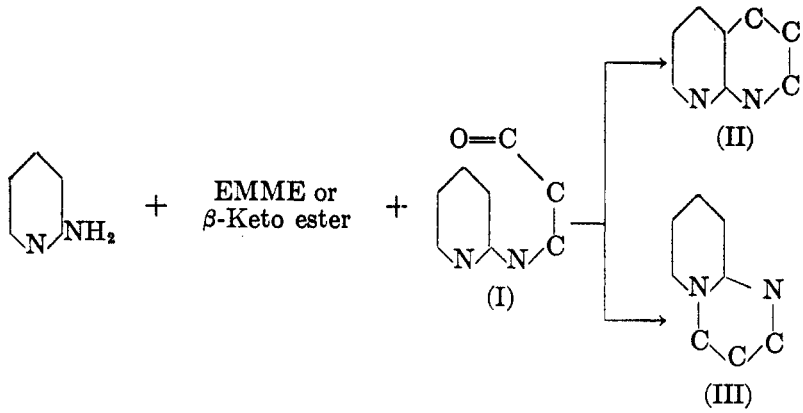
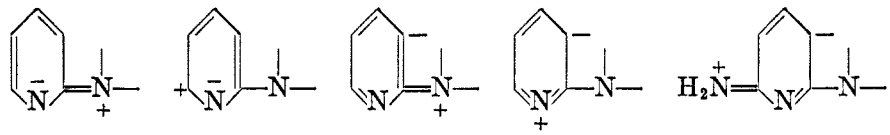
The EMME, Conrad-Limpach, and Knorr methods have been particularly successful for the synthesis of certain 2- or 4-hydroxyquinolines (1). The reactions involve the condensation of an aniline with EMME (ethoxymethylenemalonic ester) or a β-keto ester, and the cyclization of the resulting anil, crotonate, or anilide. The adaptation of these reactions to the synthesis of the corresponding 1,8-naphthyridines (II) by employing 2-aminopyridines instead of anilines should furnish convenient methods for the preparation of these types of compounds since 2-aminopyridines are readily available. However, these methods have not been as satisfactory for the preparation of 1,8-naphthyridines as for the preparation of quinolines. In contrast to anilino derivatives, 2-aminopyridine derivatives (I) may cyclize in two ways, one leading to the formation of 1,8-naphthyridines (II) and the other to the formation of pyrimidines (III). Actually the latter course of reaction often occurs. The two courses of reaction may be indicated schematically as follows:



In both types of cyclization, the pyridine ring functions as the electron donor and the carbonyl group in the side chain serves as the electron acceptor. The mechanism is presumably analogous to that of other electrophilic substitutions into aromatic rings such as the Friedel-Crafts type of reaction. The formation of pyrimidines is not surprising since resonance structure (IV), which may be considered an activated form leading to pyrimidines, probably contributes considerably to the structure of the 2-aminopyridine derivative (I). There is evidence (2) that this resonance structure makes the main contribution to the structure of 2-aminopyridine itself. The electron donating capacity of the

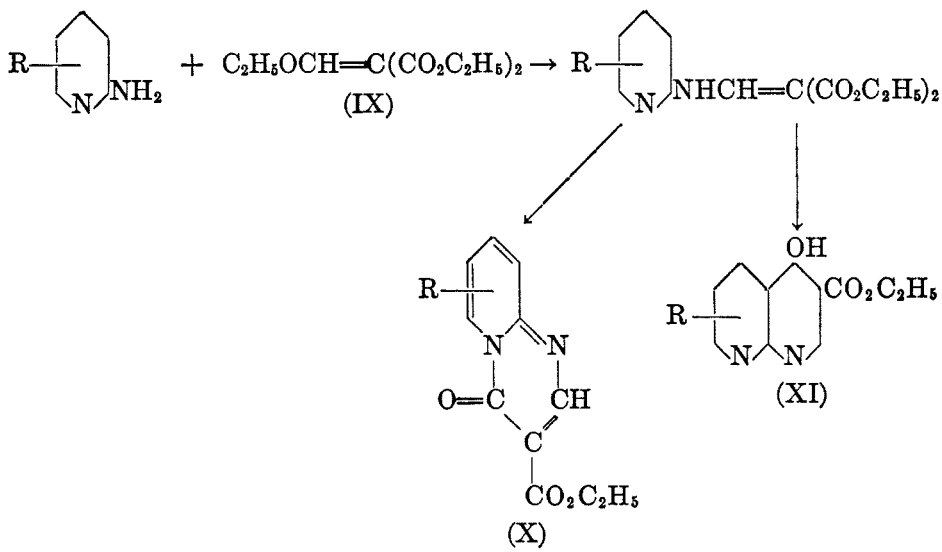
[1] Eli Lilly Fellow, 1947–1948.

heterocyclic nitrogen may be further enhanced by contributions of the resonance structures such as (V) which have been considered characteristic of the pyridine ring (3). Resonance structures (VI) or (VII) (4), which may be considered activated forms leading to 1,8-naphthyridines, might also make important contributions but usually further activation at the 3-position or deactivation at the heterocyclic nitrogen appears to be required for this cyclization to be realized. Thus, although the formation of the pyrimidine often occurs, the naphthyridine is formed with the 6-amino derivative in which resonance structure (VIII) may make an important contribution to the structure of the molecule. The 6-amino group might also activate the heterocyclic nitrogen but, in this instance, cyclization at this position appears to be hindered sterically (5).



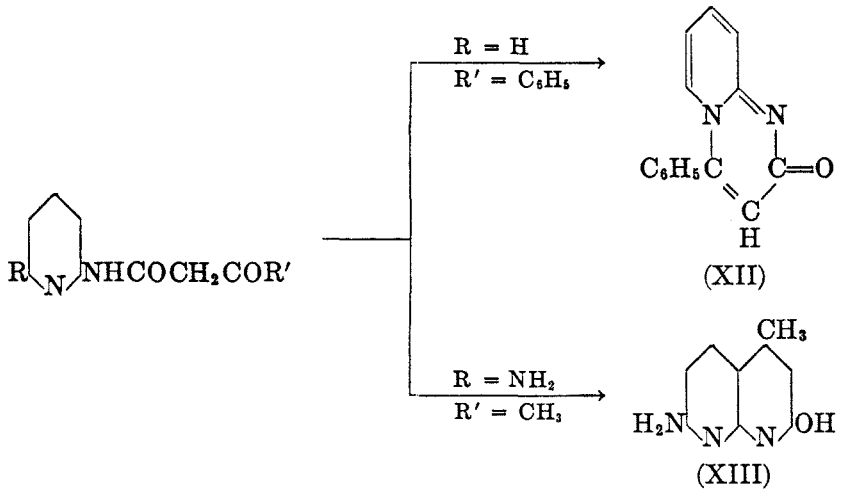
(IV) (V) (VI) (VII) (VIII)

In agreement with these considerations, Lappin (5) has shown that, in the reaction with EMME (IX), the pyrimidine (X) is normally formed. However, the corresponding 1,8-naphthyridines (XI) are produced when R is 6-amino (6), 6-ethoxy (5) or 6-methyl (5).



Similarly, the amide from 2-aminopyridine and ethyl benzoylacetate cyclizes to form the pyrimidine (XII) (7). However the Knorr type of reaction to form a 1,8-naphthyridine (XIII) has been realized with the amide of 2,6-diaminopyridine and ethyl acetoacetate (8).

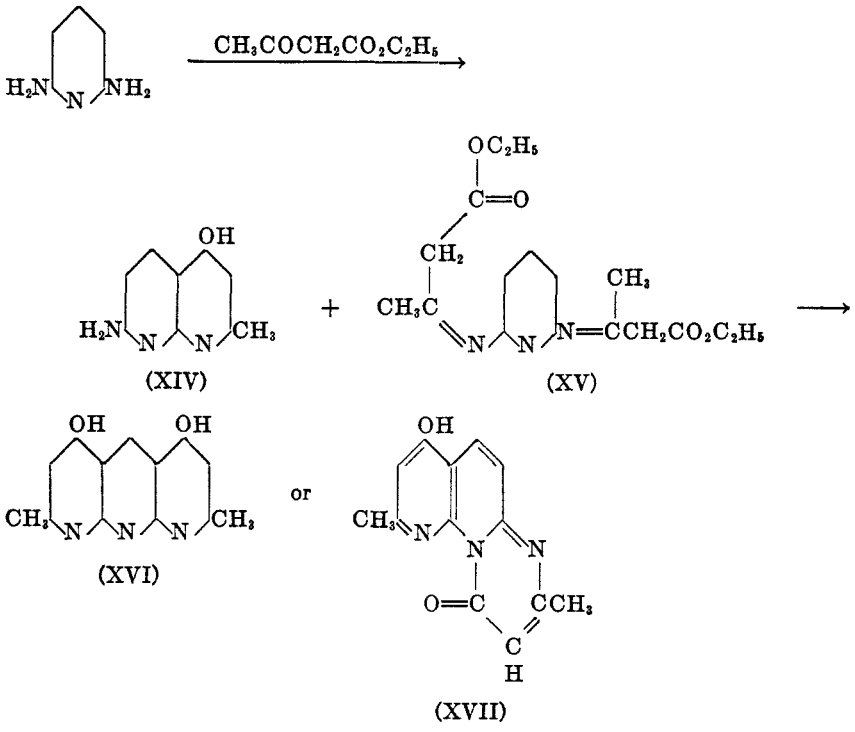
In the present investigation similar results have been obtained in the Conrad-Limpach reaction, which involves the cyclization of an anil or a crotonate formed from the condensation of a β-keto ester with an aromatic amine. With 2-amino-



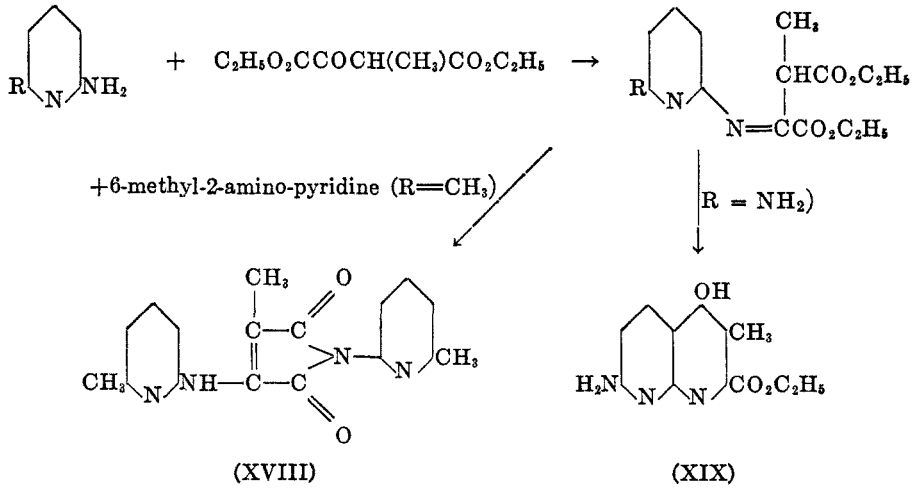
pyridine and ethyl acetoacetate, a product was obtained which appeared to be the pyrimidine although it did not analyze very satisfactorily. It had a relatively low melting point, was soluble in various organic solvents and was hydrolyzed by alkali to 2-aminopyridine. Lappin (5) has found that somewhat similar pyrimidines, obtained with EMME, also exhibited these characteristics. However, with 2,6-diaminopyridine and ethyl acetoacetate, the Conrad-Limpach type of cyclization was evidently realized. Rather surprisingly, this cyclization to form the naphthyridine (XIV) appeared to occur at room temperature under the conditions generally employed for the preparation of the anil or crotonate, except that the time of reaction was considerably longer. That the product is a naphthyridine rather than a pyrimidine, was indicated by its high melting point and its insolubility in most organic solvents. Lappin (5) has shown that the naphthyridines obtained from EMME exhibit similar properties.

In addition to the naphthyridine (XIV), there was obtained a product which was evidently the dianil (XV). This substance was readily separated from the naphthyridine by extraction of the mixture with hot ligroin in which the dianil was soluble. That this substance is the dianil (XV) was shown not only by its analysis but also by its cyclization to a product which analyzed either for a pyridonaphthyridine (XVI) or a pyrimidonaphthyridine (XVII). The cyclized product gave a positive enol test with ferric chloride.

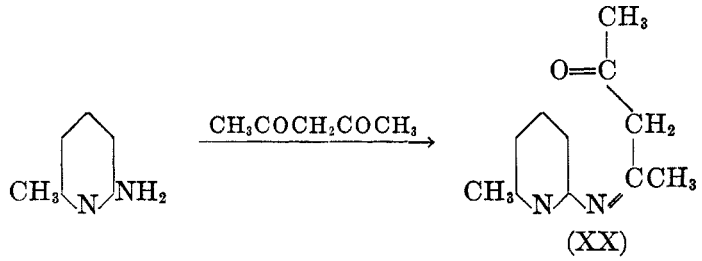
Similarly with 2,6-diaminopyridine and ethyl α-ethoxalylpropionate, which may be regarded as a β-keto ester, the Conrad-Limpach reaction appeared to occur to form (XIX), although the pure product has not been isolated. In this case also, the cyclized product was obtained under conditions which generally give only the anil (refluxing in ethanol over Drierite) (9). That the product was the naphthyridine (XIX) was indicated by its high melting point and by its solubility in sodium hydroxide solution but not in sodium bicarbonate solution. With 2-aminopyridine or 6-methyl-2-aminopyridine and ethyl α-ethoxalylpropionate, neither a naphthyridine nor a pyrimidine appeared to be formed. A pure product was isolated with the 6-methyl derivative but this was evidently



the maleimide (XVIII), which could have resulted from the reaction of the anil with a second molecule of 6-methyl-2-aminopyridine. The formation of a similar maleimide has been reported by Surrey and Cutler (10) from the reaction of *m*-chloroaniline with the anil from this amine and ethyl α-ethoxalylpropionate. It seems likely that the yield of maleimide (XVIII), could be improved by using two molecular equivalents of the 2-aminopyridine instead of the one equivalent employed in this investigation.



Although Mangini and Colonna (11) have reported the formation of 2,4-dimethyl-7-amino-1,8-naphthyridine from 2,6-diaminopyridine and acetylacetone, we have been unable to effect the analogous reaction of 6-methyl-2-aminopyridine and acetylacetone even after first isolating the corresponding anil (XX). It is of interest that an attempt to prepare the picrate of this anil led to hydrolysis of the compound, the picrate of 6-methyl-2-aminopyridine being obtained.



(XX)

EXPERIMENTAL[2]

Ethyl acetoacetate with 2-aminopyridine. To a solution of 9.4 g. (0.10 mole) of 2-aminopyridine in 13.0 g. (0.10 mole) of ethyl acetoacetate was added four drops of concentrated hydrochloric acid solution and the solution placed in an evacuated desiccator over concentrated sulfuric acid. After seven days, the solution was distilled through an 11 cm. Vigreux column yielding, after a forerun of starting materials, 7.4 g. of product boiling at approximately 143° at 3.5 mm., the product solidifying on cooling. After one recrystallization from benzene-Skellysolve B, the product (white crystals) melted at 115–117°, and, after four additional recrystallizations it melted at 120–120.5° with some shrinking at 80°. This substance was apparently 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one.

Anal.[3] Calc'd for $C_9H_8N_2O$: C, 67.49; H, 5.04; N, 17.49.
Found: C, 66.88; H, 5.14; N, 17.02.

This substance was soluble in benzene, ethanol, methanol, acetone, and water. It was recovered unchanged after refluxing in 10% hydrochloric acid solution for two hours, but it was hydrolyzed by hot 10% sodium hydroxide solution to form *2-aminopyridine*, m.p. 48–53°; reported m.p. 56° (12). The *picrate* melted at 222–223°; reported m.p. 217° (13). A mixed melting point with an authentic sample of the picrate (m.p. 221–222°) showed no depression.

Ethyl acetoacetate with 2,6-diaminopyridine. To a partial solution of 25.0 g. (0.217 mole) of 2,6-diaminopyridine in 28.2 g. (0.217 mole) of ethyl acetoacetate was added eight drops of concentrated hydrochloric acid solution and the mixture was kept in an evacuated desiccator over concentrated sulfuric acid for thirty-three days. The product was thoroughly washed with water, dried in air, and refluxed with 100 ml. of ligroin (b.p. 70–90°). The suspension was filtered and the solid washed once with ligroin. The solid (3.0 g., 8%) was 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine (XIV), melting above 360°, which was insoluble in hot 10% sodium hydroxide solution, was unaffected by several hours boiling in a 6 *N* hydrochloric acid solution and was insoluble in ethanol, ispropyl ether, dioxane, butanol, ethyl acetate, pyridine, Methyl Cellosolve and chloroform. One recrystallization from quinoline yielded a white powder, m.p. > 360°, which was thoroughly washed with acetone and ether.

Anal.[5] Calc'd for $C_9H_9N_3O$: C, 61.71; H, 5.18; N, 23.99.
Found: C, 61.63, 61.59; H, 5.02, 4.91; N, 23.86.

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[2] Boiling points and melting points are uncorrected.

[3] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

[4] Analysis by the University of Pittsburgh Microchemical Laboratory.

[5] Analysis by Oakwold Laboratories, Alexandria, Virginia.

The solvent was evaporated from the filtrate obtained from the treatment of the reaction mixture with ligroin, leaving 6.6 g. (13%) of crude *dianil* (XV), m.p. 61–67°. Several recrystallizations from ligroin (b.p. 70–90° gave crystals of (XV) melting at 76°.

Anal.[3,4] Calc'd for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95; N, 12.60.
Found: C, 61.16, 61.47; H, 6.82, 6.66; N, 12.75.

The crude *dianil* (1.0 g., m.p. 61–67°) was dissolved in 5 ml. of warm Dowtherm A and the solution was refluxed for ten minutes. After cooling, 25 ml. of ligroin was added. The brown solid was filtered off and washed with ligroin yielding 0.6 g. of material which was extracted with ether in a Soxhlet extractor. Evaporation of the solvent from the ether extracts yielded 0.45 g. of a product, melting at 210–220° dec., which, after several recrystallizations from ethanol-water and from ethanol-isopropyl ether, gave white crystals melting at 230–231°. This substance analyzed either for compound (XVI) or compound (XVII), both of which have the same empirical formula.

Anal.[3,4] Calc'd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42.
Found: C, 64.36; H, 4.91; N, 17.42, 17.43.

Ethyl α-ethoxalylpropionate with 6-methyl-2-aminopyridine. A solution of 21.2 g. (0.10 mole) of ethyl α-ethoxalylpropionate, 10.8 g. (0.10 mole) of 6-methyl-2-aminopyridine and six drops of glacial acetic acid in 50 ml. of commercial absolute ethanol was refluxed on the steam-bath for 18 hours with 30 g. of Drierite. The hot mixture was filtered and most of the solvent was removed with a water aspirator. The residue, which partly solidified on standing overnight, appeared to contain some of the maleimide (XVIII) but attempts to isolate the product at this stage were unsuccessful. A solution of the residue in xylene was refluxed for thirty minutes. The solution was poured into a large excess of Skellysolve B. The oil which separated became, after several hours, a waxy semi-solid from which was decanted the xylene-Skellysolve B solution. An ethanol solution of the semi-solid was treated with Norit and, after evaporating the solution to approximately 40 ml., an equal volume of water was added. After chilling, the yellow crystals were filtered off and recrystallized from ethanol-water yielding 1.6 g. (10%) of *α-(6-methyl-2-pyridoamino)-N-(6-methyl-2-pyridyl)-β-methylmaleimide* (XVIII), melting at 195–197°. Several additional recrystallizations from ethanol-water gave yellow crystals melting at 198.5–200°.

Anal.[3] Calc'd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.22; N, 18.17.
Found: C, 66.02, 65.89; H, 5.34, 5.35; N, 18.20, 18.12.

Ethyl α-ethoxalylpropionate with 2,6-diaminopyridine. To a solution of 10.6 g. (0.05 mole) of ethyl α-ethoxalylpropionate and 5.8 g. (0.05 mole) of 2,6-diaminopyridine in 50 ml. of commercial absolute ethanol was added three drops of glacial acetic acid and 15 g. of Drierite. The mixture was refluxed twelve hours, then filtered. The filtrate was poured into 400 ml. of water yielding 5.0 g. (40%) of a yellow-brown solid, melting at about 300–305° dec., which was apparently *2-carbethoxy-3-methyl-4-hydroxy-7-amino-1,8-naphthyridine* (XIX). Several recrystallizations from ethanol-water did not produce a pure substance. The product readily dissolved in 10% sodium hydroxide solution and was reprecipitated by carbon dioxide. On refluxing in a 10% sodium hydroxide solution, followed by acidification, an acid was obtained; however, the pure acid was not isolated.

Acetylacetone with 6-methyl-2-aminopyridine. A solution of 9.4 g. (0.10 mole) of 6-methyl-2-aminopyridine and 10.0 g. (0.10 mole) of acetylacetone was refluxed for five hours and then distilled through an 11 cm. Vigreux column yielding, after a forerun of starting material, 5.8 g. (31%) of *anil* (XX) boiling at 138–139° at 5 mm. On redistillation and after several recrystallizations of the resulting solid from Skellysolve B, white crystals were obtained melting at 74.5–75.5°.

Anal.[3] Calc'd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73.
Found: C, 69.06; H, 7.26; N, 14.34.

In an attempt to prepare the picrate of the anil in ethanol in the usual manner, the *picrate* of *6-methyl-2-aminopyridine* was obtained instead. The picrate of the amine melted

at 202–203° [reported m.p. 202° (14)]. A mixed melting point with an authentic sample (m.p. 202–204°) showed no depression.

SUMMARY

Certain of the theoretical aspects of some of the synthetic methods used for the preparation of 1,8-naphthyridines from 2-aminopyridine derivatives have been considered.

An investigation of the synthesis of certain 1,8-naphthyridines from 2-aminopyridines with ethyl acetoacetate or ethyl α-ethoxalylpropionate by the Conrad-Limpach reaction has been made.

DURHAM, NORTH CAROLINA

REFERENCES

(1) REITSEMA, *Chem. Rev.*, **43**, 43 (1948).
(2) STECK AND EWING, *J. Am. Chem. Soc.*, **70**, 3397 (1948).
(3) SCHOMAKER AND PAULING, *J. Am. Chem. Soc.*, **61**, 1769 (1939).
(4) See REMICK, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., (1943), p. 105.
(5) LAPPIN, *J. Am. Chem. Soc.*, **70**, 3348 (1948).
(6) ADAMS, BRADSHER, BRESLOW, AMORE, AND HAUSER, *J. Am. Chem. Soc.*, **68**, 1317 (1946).
(7) SEIDE, *Ber.*, **58**, 352 (1925).
(8) SEIDE, *Ber.*, **59**, 2465 (1926).
(9) HAUSER AND REYNOLDS, *J. Am. Chem. Soc.*, **70**, 2402 (1948).
(10) SURREY AND CUTLER, *J. Am. Chem. Soc.*, **68**, 514 (1946).
(11) MANGINI AND COLONNA, *Gazz. chim. ital.*, **73**, 329 (1943); *Chem. Abstr.*, **41**, 1225 (1947).
(12) LANGE, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, (3rd edition, 1939), p. 278.
(13) MARCKWALD, *Ber.*, **27**, 1321 (1894).
(14) SEIDE, *J. Russ. Phys.-Chem. Soc.*, **50**, 543 (1918); *Chem. Zentr.*, **94**, (III) 1022 (1923).