[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

RELATIVE EASE OF CYCLIZATION OF 2-, 3-, AND 4-AMINOPYRIDINE DERIVATIVES. SYNTHESIS OF NAPHTHYRIDINES[1]

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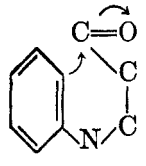
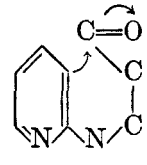
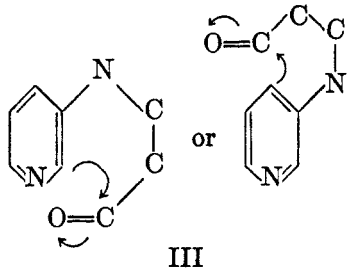
Successful methods for the synthesis of quinolines include the cyclizations of intermediates produced by the reactions of aniline with the ketone group of acetoacetic ester (Conrad-Limpach method), with the ester group of acetoacetic ester (Knorr method), with acetylacetone (Combes method), with ethoxymethylenemalonic ester (EMME method), with glycerine or acrolein (Skraup method), and with benzaldehyde and pyruvic acid (Doebner method). These cyclizations involve carbon-carbon condensations of the ionic type in which a benzene ring serves as the electron-donor and a carbonyl group as the electron-acceptor as indicated in I. By employing 2-, 3-, or 4-aminopyridine instead of aniline, these methods would lead to the formation of naphthyridines. In these cases, a pyridine ring would serve as the electron-donor and the carbonyl group as the electron-acceptor as indicated in II, III, and IV, respectively.



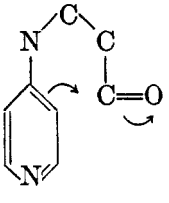
I



II



III

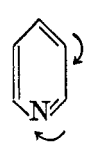


IV

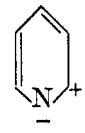
However, these methods have generally not been as successful for the synthesis of naphthyridines as for the synthesis of quinolines. This is not surprising because the pyridine nitrogen tends to withdraw electrons from the remainder of the ring thereby making the pyridine ring a poorer electron-donor in cyclizations II, III, or IV than the benzene ring in I. The pyridine nitrogen tends to withdraw electrons particularly from the 2- and 4-positions as indicated in V; indeed resonance forms such as VI and VII, having positive charges at the 2- and 4-positions,

[1] This work was supported by the Office of Naval Research and by the Duke University Research Council.

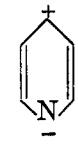
have been considered to make important contributions to the structure of pyridine itself (1).



V

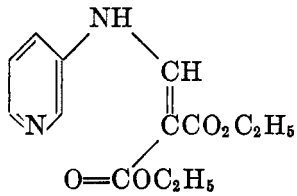


VI

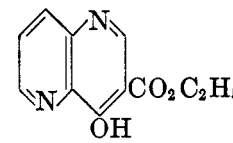


VII

Since 3-aminopyridine derivatives III would have to cyclize at the 2- or 4-position, they might be expected to do so with the greatest difficulty. Actually only one such 3-aminopyridine derivative, that (VIII) obtained with ethoxymethylenemalonic ester, appears to have been cyclized satisfactorily, the 1,5-naphthyridine (IX) being obtained in 70–80% yields (2); even in this case, special conditions (high dilution) were required.

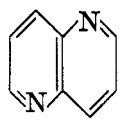


VIII

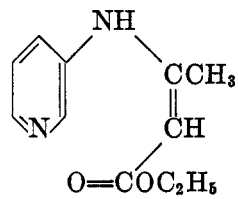


IX

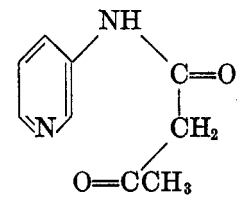
The Skraup reaction with 3-aminopyridine has been reported to form 1,5-naphthyridine (X), but no yield was given (3). We have obtained only a 28% yield of X under the usual Skraup conditions. We have found that, although 3-aminopyridine readily forms the anil or crotonate (XI) and the amide (XII) with acetoacetic ester, these intermediates fail to undergo the Conrad-Limpach and Knorr types of cyclization under the usual conditions.



X



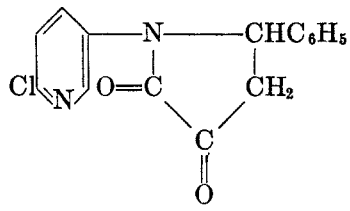
XI



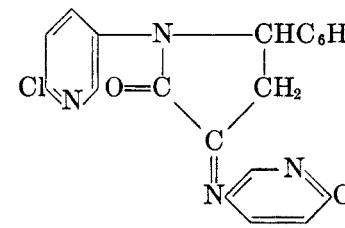
XII

The Combes reaction has been reported to fail with 2,6-dimethyl-3-aminopyridine (4) with which cyclization would have had to occur at the 4-position. Apparently this type of reaction has not been attempted with 3-aminopyridine itself. The Doebner reaction has been reported to fail with 3-aminopyridine and with 6-chloro-3-aminopyridine (5); in the latter case, cyclization occurred out-

side of the pyridine ring to form the pyrrolidine (XIII) which was isolated as its 6-chloro-3-aminopyridine derivative (XIV).



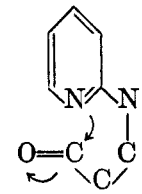
XIII



XIV

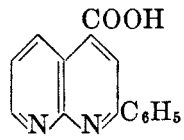
Of course it is possible that some of these cyclizations that fail with 3-aminopyridine might be effected with certain substituted 3-aminopyridines such as 3,5-diaminopyridine in which the 2- and 4-positions would be relatively more reactive.

In contrast to 3-aminopyridine derivatives, 2- and 4-aminopyridine derivatives (II and IV) may cyclize at the least deactivated position, the 3-position, to form 1,8- and 1,6-naphthyridines, respectively. 2-Aminopyridine derivatives may also cyclize at the pyridine nitrogen to form pyrimidines as indicated in XV (6); this course of reaction should be favored by important contributions of resonance structures like VI and VII having negative charges on the pyridine nitrogen.

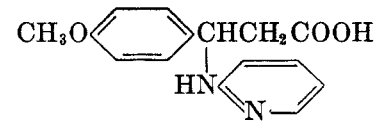


XV

Therefore, it is not surprising that 2- and 4-aminopyridine derivatives generally undergo cyclizations more readily than the corresponding 3-aminopyridine derivatives. 2-Aminopyridine or substituted 2-aminopyridine derivatives usually form pyrimidines under the conditions of the Conrad-Limpach (6), Knorr (7), and EMME (8) methods. 1,8-Naphthyridines appear to be produced only with such substituted 2-aminopyridines as 2,6-diaminopyridine in which the 3-position is activated and the pyridine nitrogen apparently hindered sterically (6, 8). The Doebner reaction with 2-aminopyridine has been reported to form the 1,8-naphthyridine (XVI) (9) but later workers (10, 11) have concluded that the product is not the naphthyridine. Using anisaldehyde in the reaction, Allen and



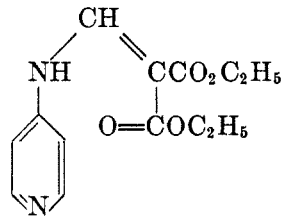
XVI



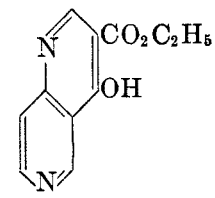
XVII

co-workers (10) obtained compound XVII which is the addition product of 2-aminopyridine and anisalpyruvic acid.

The 4-aminopyridine derivative (XVIII) obtained with ethoxymethylenemalonic ester was found to cyclize to form the 1,6-naphthyridine (XIX) in high yield (82%) under the usual conditions, whereas cyclization of the corresponding 3-aminopyridine derivative has previously been reported to require special conditions (2). Unfortunately we have been unable to prepare the crotonate or amide from 4-aminopyridine and ethyl acetoacetate or the anil from this amine and acetylacetone even though relatively drastic conditions were employed. In this respect, 4-aminopyridine resembles *o*-nitroaniline which has failed to form the crotonate (12) or the amide[2] with acetoacetic ester. These failures appear to be ascribable to the relatively weakly basic nature of the amine. Earlier workers (3) reported that 4-aminopyridine did not undergo the Skraup reaction, and they similarly ascribed this failure to the weakly basic properties of the amine.

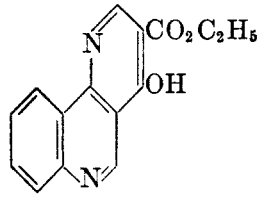


XVIII

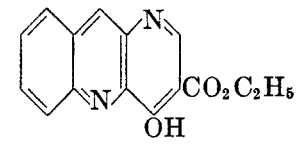


XIX

Although only the intermediate in the EMME method was formed with 4-aminopyridine, intermediates in the EMME, Conrad-Limpach, and Knorr methods were readily produced with 4-aminoquinoline. In agreement with theory, these intermediates cyclized more readily or in better yield than the corresponding intermediates from 3-aminoquinoline. Thus, 4-aminoquinoline and ethoxymethylenemalonic ester formed the 1,6-naphthyridine (XX) in 93% yield whereas 3-aminoquinoline gave the 1,5-naphthyridine (XXI) in only 22% yield. In these cases the intermediate crotonates were not isolated.



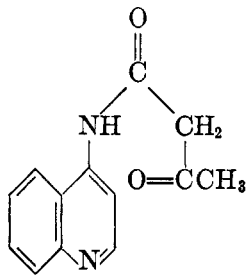
XX



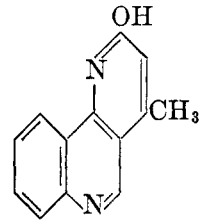
XXI

The amide (XXII) from 4-aminoquinoline and ethyl acetoacetate gave the 1,6-naphthyridine (XXIII) in 58% yield whereas the corresponding amide (XXIV) from 3-aminoquinoline failed to cyclize under similar conditions.

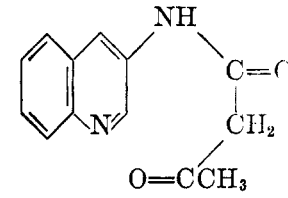
[2] We recovered starting material after refluxing a mixture of *o*-nitroaniline and ethyl acetoacetate for an hour.



XXII

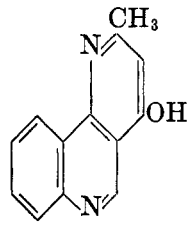


XXIII

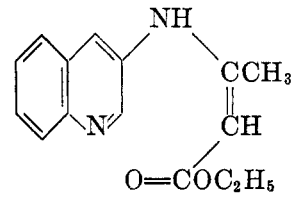


XXIV

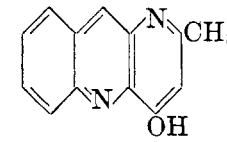
4-Aminoquinoline and ethyl acetoacetate, in the presence of a catalytic amount of acid, reacted at room temperature to form the 1,6-naphthyridine (XXV) whereas 3-aminoquinoline and this β-keto ester yielded only the intermediate crotonate (XXVI) under these conditions, subsequent heating being required to convert the crotonate to the 1,5-naphthyridine (XXVII). The formation of the cyclized product at room temperature is not without precedent; another example is the reaction of 2,6-diaminopyridine with acetoacetic ester to form the corresponding 1,8-naphthyridine (6).



XXV



XXVI



XXVII

EXPERIMENTAL[3]

2-Aminopyridine (m.p. 58–60°) and 3-aminoquinoline (m.p. 92–94°) were Eastman Kodak products.

3-Aminopyridine. This amine was prepared by a modification[4] of the method of Maier-Bode (13). In an iron bomb, having a capacity of one liter, was placed a mixture of 172 g. (1.09 moles) of 3-bromopyridine (b.p. 169–170°),[5] 340 ml. of concentrated ammonium hydroxide (sp. gr. 0.9), and 10 g. of copper sulfate pentahydrate. The bomb was sealed and heated in an oven at 140° for 20 hours. After cooling, the reaction mixture was transferred to a flask, and the bomb washed with hot water. The combined reaction mixture and wash solution was heated on the steam-bath until most of the ammonia had evaporated. The mixture was made strongly alkaline by the slow addition of about 75 g. of solid sodium hydroxide and then saturated with anhydrous potassium carbonate. After filtering, the solid residue was transferred to a beaker and washed with ether. The filtrate was extracted

[3] Boiling points are uncorrected; melting points are corrected. Microanalyses are by Clark Microanalytical Laboratory, Urbana, Illinois.

[4] The procedure described here was developed in this laboratory by Dr. S. T. Amore.

[5] We are indebted to the Dow Chemical Company for a generous supply of this chemical.

with ether until the ether solution was no longer colored. The ether was dried over sodium sulfate, decanted, and concentrated. The residue was distilled *in vacuo*, yielding 24 g. (15%) of recovered 3-bromopyridine, b.p. 60–63° at 15 mm. and 61 g. (60%) of 3-aminopyridine, b.p. 107–109° at 3 mm., m.p. 60–61°.

4-Aminopyridine. This amine was prepared by three methods. In the method of Koenig and Greiner (14), 100 g. (1.76 moles) of pyridine and 300 g. (2.54 moles) of thionyl chloride were reacted to form yellow pyridyl pyridinium dichloride (m.p. 170–173°) in 70% (175 g.) yield. To this dichloride was added 500 ml. of concentrated ammonium hydroxide and the mixture was refluxed for eight hours. After removal of the water, 25 ml. of a concentrated solution of potassium hydroxide was added and the mixture steam-distilled with superheated steam (180°). The distillate was evaporated *in vacuo* and the residue recrystallized from chloroform yielding 4-aminopyridine, m.p. 158–159°. Koenig and Greiner reported a 62% yield from the dichloride, but the best yield obtained by us was 40%. In several runs the yields were much lower.

In the method of Camps (15), 100 g. of 95% γ-picoline (1.02 moles) was oxidized by 170 g. of potassium permanganate in 3 liters of water to isonicotinic acid (m.p. 310°) in 50–58% (65 g.) yield; this acid was esterified to the ethyl ester (b.p. 97° at 9 mm.) in 65–70% (56 g.) yield; this ester was ammoniated to isonicotinamide (m.p. 152–154°) in 98% (44 g.) yield; and finally the amide (21 g., 0.172 mole) was converted to 4-aminopyridine (m.p. 158–159°) by bromine and potassium hydroxide in 1.5 liters of water (Hofmann) in 74% yield. This yield of 4-aminopyridine was obtained only after many ether extractions of the aqueous solution.

In the third method, 96 g. (0.577 mole) of chelidamic acid (m.p. 248° dec.) (16) was decarboxylated to 4-hydroxypyridine (m.p. 149°) (16) in 45% yield and the hydroxy compound (25 g., 0.26 mole) refluxed with 75 ml. of phosphorus oxychloride to form 4-chloropyridine hydrochloride. A mixture of the salt and 125 g. of phenol was heated to 170° and dry ammonia gas passed into the solution for three hours. The cooled mixture was poured into aqueous concentrated sodium hydroxide and the resulting solution thoroughly extracted with ether. The solvent was evaporated and the residue recrystallized from chloroform yielding 7.5 g. (30%) of 4-aminopyridine (m.p. 158–159°).

4-Aminoquinoline. 4-Hydroxyquinoline (m.p. 200°) was prepared in 60% (43 g.) yield from 46.5 g. (0.5 mole) of aniline and 108 g. (0.5 mole) of ethoxymethylenemalonic ester by the method of Price and Roberts (17) for the preparation of 7-chloro-4-hydroxyquinoline. The hydroxy compound was heated for two hours at 110° with 90 ml. of phosphorus oxychloride to give 4-chloroquinoline (m.p. 34–35°) in 86% (41 g.) yield. A mixture of the chloro compound (0.36 mole) and 130 g. (1.38 moles) of phenol was heated to 180° and dry ammonia gas passed in for three hours yielding 25 g. (70%) of the 4-aminoquinoline, m.p. 153–154°; reported m.p. 153–154° (18).

Skraup reaction with 3-aminopyridine. A mixture of 5 g. (0.064 mole) of 3-aminopyridine, 23.6 g. (0.256 mole) of glycerine, 32 g. of concentrated sulfuric acid, and 6 g. of arsenic pentoxide was heated at 170° for six hours. The reaction mixture was poured into 100 ml. of water, excess solid sodium hydroxide added, and the mixture steam-distilled until one liter of distillate was collected. After saturation with solid potassium carbonate, the distillate was extracted with ether. The ethereal solution was dried over Drierite and the solvent removed. The oily residue (3 g.) solidified after standing in the refrigerator overnight. Recrystallization from ligroin (b.p. 90–120°) gave 2.4 g. (28%) of 1,5-naphthyridine (X), m.p. 70–72°; reported m.p. 72–73° (3).

Conrad-Limpach intermediate with 3-aminopyridine. A mixture of 7.1 g. (0.076 mole) of 3-aminopyridine, 9.8 g. (0.076 mole) of ethyl acetoacetate, 10 g. of Drierite, 25 ml. of commercial absolute ethanol, and about four drops of glacial acetic acid were refluxed for twelve hours (see 19). After filtering and removing the ethanol under reduced pressure, the residue was distilled *in vacuo* yielding 9.8 g. (63%) of light yellow *ethyl 2-methyl-2-(3'-aminopyridyl)crotonate* (XI), b.p. 158–160° at 2 mm.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: N, 13.59. Found: N, 13.43.

Attempts to cyclize the crotonate in refluxing Dowtherm[5] for the usual 15 minutes (19) or for an hour were unsuccessful. After 15 minutes, most of the crotonate was recovered unchanged; after an hour, crotonate and decomposition products were obtained.

Knorr intermediate with 3-aminopyridine. A mixture of 6 g. (0.064 mole) of 3-aminopyridine and 8.7 g. (0.064 mole) of ethyl acetoacetate was refluxed for 20 minutes. On cooling to room temperature, the reaction mixture solidified. The solid was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) yielding 7.5 g. (66%) of the *N-(3-aminopyridyl)acetoacetamide* (XII) melting at 125–129°. After three recrystallizations from the same solvents, white needles, m.p. 137–138° were obtained.

Anal. Calc'd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.65.
Found: C, 61.07; H, 5.75.

Attempts to cyclize the amide by heating in concentrated sulfuric acid on a steam-bath for one-half hour, essentially according to the usual procedure (19), or for five hours were unsuccessful. Some of the amide was recovered along with 3-aminopyridine which was formed presumably by hydrolysis of the amide.

EMME reaction with 4-aminopyridine. A mixture of 5 g. (0.053 mole) of 4-aminopyridine and 11.5 g. (0.053 mole) of ethoxymethylenemalonic ester was heated in an oil-bath at 110° for one hour and allowed to stand overnight. The solid was recrystallized from ligroin (b.p. 90–120°) yielding 11.5 g. (83%) of *ethyl 1-carbethoxy-2-(4'-aminopyridyl)crotonate* (XVIII) melting at 71–74°. After two more recrystallizations from the same solvent, it had m.p. 74–75°.

Anal. Calc'd for $C_{13}H_{16}N_2O_2$: C, 59.07; H, 6.10; N, 10.60.
Found: C, 59.31; H, 6.26; N, 10.55.

To 25 ml. of refluxing Dowtherm[5] was added 7.5 g. (0.028 mole) of the crotonate and the resulting solution was refluxed for 15 minutes. On cooling, a light tan solid separated. Recrystallization from ethanol gave 5 g. (82%) of the *3-hydroxy-4-carbethoxy-1,6-naphthyridine* (XIX) (m.p. 292–293°).

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: C, 60.54; H, 4.61; N, 12.83.
Found: C, 60.21; H, 4.57; N, 12.92.

Attempts to prepare other intermediates with 4-aminopyridine. This amine (0.043 mole) failed to form the crotonate with ethyl acetoacetate (0.043 mole) on standing in the presence of a catalytic amount of concentrated hydrochloric acid in an evacuated desiccator over sulfuric acid (see 19) for a week or on refluxing in ethanol in the presence of Drierite (19) for 24 hours. Most of the 4-aminopyridine and ethyl acetoacetate were recovered.

4-Aminopyridine (0.053 mole) failed to form the amide with ethyl acetoacetate (0.053 mole) on refluxing the mixture for a few minutes (19) or for three hours. Most of the starting materials were recovered.

4-Aminopyridine (0.043 mole) failed to react with acetylacetone (0.043 mole) on heating the mixture for 24 hours on the steam-bath. Most of the starting materials were recovered.

EMME reaction with 3- and 4-aminoquinoline. A solution of 5 g. (0.035 mole) of 3-aminoquinoline and 7.5 g. (0.035 mole) of ethoxymethylenemalonic ester in 100 ml. of Dowtherm[5] was boiled in an open beaker for 30 minutes. The brown solid which separated on cooling was washed with Skellysolve B. Recrystallization of the solid from a mixture of pyridine and water gave 2 g. (22%) of *3-carbethoxy-4-hydroxy-6,7-benzo-1,5-naphthyridine* (XXI), m.p. 264–265° dec.

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.11; H, 4.50; N, 10.44.
Found: C, 66.91; H, 4.38; N, 10.20.

In a similar manner were reacted 5 g. (0.035 mole) of 4-aminoquinoline and 7.5 g. (0.035 mole) of ethoxymethylenemalonic ester. After washing with Skellysolve, the brown solid was recrystallized from ethanol yielding 7 g. (93%) of *3-carbethoxy-4-hydroxy-7,8-benzo-1,6-naphthyridine* (XX) (m.p. above 300°).

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.11; H, 4.50; N, 10.44.
Found: C, 67.25; H, 4.64; N, 10.23.

Conrad-Limpach reaction with 3- and 4-aminoquinoline. A mixture of 5 g. (0.035 mole)

of 3-aminoquinoline, 5.2 g. (0.035 mole) of ethyl acetoacetate, and three drops of concentrated hydrochloric acid was allowed to stand in an evacuated desiccator over sulfuric acid for three days. The oily product solidified on scratching. Recrystallization of the solid from a mixture of benzene and ligroin (b.p. 90–120°) gave 5.2 g. (58%) of *ethyl 2-methyl-2-(3'-aminoquinolyl)crotonate* (XXVI), m.p. 44–45°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.92. Found: N, 10.73.

Cyclization of 1 g. (0.004 mole) of the crotonate in 25 ml. of refluxing Dowtherm by the usual procedure (19) gave, after washing with Skellysolve B and recrystallization from a mixture of ethanol and water, 0.6 g. (71%) of *2-hydroxy-4-methyl-7,8-benzo-1,5-naphthyridine* (XXVII) (m.p. above 300°).

Anal. Calc'd for $C_{13}H_{10}N_2O$: N, 13.33. Found: N, 12.98.

When a mixture of 5 g. (0.035 mole) of 4-aminoquinoline, 5.2 g. (0.035 mole) of ethyl acetoacetate, and a catalytic amount of hydrochloric acid was reacted in a similar manner there was obtained directly *2-methyl-4-hydroxy-7,8-benzo-1,6-naphthyridine* (XXV) which, after recrystallization from a mixture of benzene and ligroin (b.p. 90–120°), melted at 310°; the yield was 5 g. (70%).

Anal. Calc'd for $C_{12}H_{10}N_2O_2$: N, 13.33. Found: N, 13.20.

Knorr reaction with 3- and 4-aminoquinoline. A mixture of 5 g. (0.035 mole) of 3-aminoquinoline and 5.2 g. (0.035 mole) of ethyl acetoacetate was refluxed for 30 minutes. On cooling, the mixture solidified. Recrystallization of the solid from water yielded 5.95 g. (75%) of *N-(3-quinolyl)acetoacetamide* (XXIV), m.p. 112–113°.

Anal. Calc'd for $C_{13}H_{12}N_2O_2$: C, 68.20; H, 5.31; N, 12.26.
Found: C, 68.39; H, 5.31; N, 12.28.

A solution of the amide (1 g., 0.004 mole) in 5 ml. of concentrated sulfuric acid was heated on the steam-bath for 30 minutes and, after cooling, poured onto ice. Since no solid separated, the solution was neutralized with ammonia and evaporated to dryness. The residue was extracted with hot ethanol. To the ethanolic extract was added an alcoholic solution of picric acid yielding the *picrate* of *3-aminoquinoline* melting at 112–113°, which was identified by mixed melting point. No naphthyridine was obtained.

In a similar manner were reacted 5 g. (0.035 mole) of 4-aminoquinoline and 5.2 g. (0.035 mole) of ethyl acetoacetate. The solid was recrystallized three times from a mixture of benzene and ligroin (b.p. 90–120°) yielding 3.8 g. (50%) of *N-(3-quinolyl)acetoacetamide* (XXIII) melting at 210°. When this amide (1 g., 0.004 mole) was treated with sulfuric acid as described above for the amide from 3-aminoquinoline, there was obtained, after neutralization with ammonia and recrystallization from ethanol and water, 0.47 g. (58%) of *2-hydroxy-4-methyl-7,8-benzo-1,6-naphthyridine* melting above 300°.

Anal. Calc'd for $C_{13}H_{10}N_2O$: N, 13.33. Found: N, 13.53.

SUMMARY

The relative ease of cyclization of corresponding carbonyl derivatives of 2-, 3-, and 4-aminopyridine have been considered.

In general, 2- or 4-aminopyridine intermediates cyclize more readily than the corresponding 3-aminopyridine intermediates; in fact, only one of the latter has been cyclized satisfactorily. Most 2-aminopyridine intermediates cyclize to form pyrimidines. 4-Aminopyridine intermediates cyclize to form 1,6-naphthyridines, but only one such intermediate could be prepared.

Several 4-aminoquinoline intermediates were produced and these were found to cyclize to form 1,6-naphthyridines more readily than the corresponding 3-aminoquinoline intermediates which cyclized to form 1,5-naphthyridines.

Several new naphthyridines were synthesized.

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