[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

CYCLIZATION OF 3-AMINOPYRIDINE 1-OXIDE WITH ETHOXYMETHYLENEMALONIC ESTER TO FORM 4-HYDROXY-1,7-NAPHTHYRIDINE AND ITS 4-CHLORO DERIVATIVE

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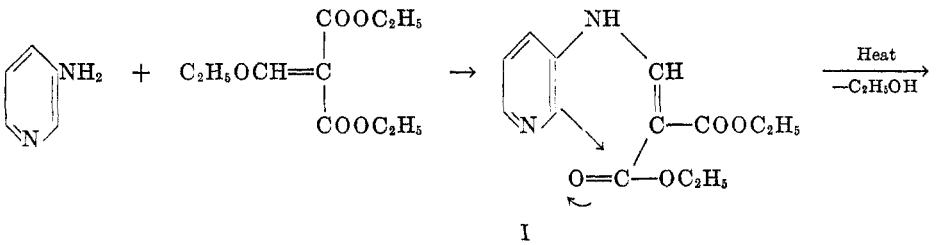
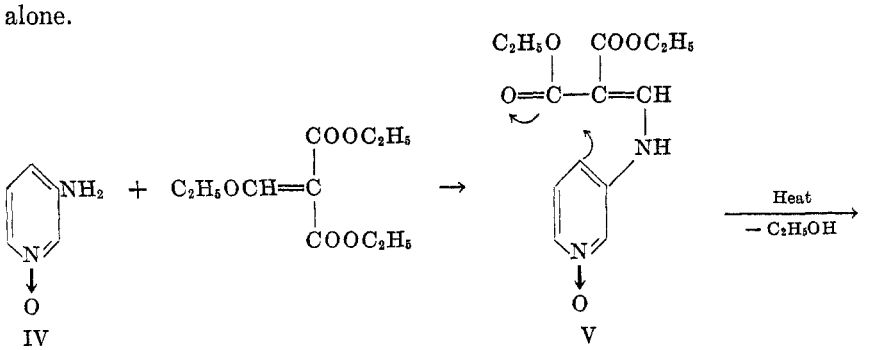
3-Aminopyridine has previously been cyclized with ethoxymethylenemalonic ester through intermediate I to form, after hydrolysis and decarboxylation, 4-hydroxy-1,5-naphthyridine (II) and, after further treatment with phosphorus oxychloride, the 4-chloro derivative (III) (1).



3-Aminopyridine 1-oxide (IV) has now similarly been cyclized with ethoxymethylenemalonic ester through intermediate V to give after reduction, hydrolysis, and decarboxylation, 4-hydroxy-1,7-naphthyridine (VI) and, after further treatment with phosphorus oxychloride, the 4-chloro derivative (VII). These two products were shown to be different from, but isomeric with, the two corresponding products from 3-aminopyridine. Thus, each of the 4-hydroxy derivatives (II and VI) and each of the 4-chloro derivatives (III and VII) had different melting points, and mixtures of the two isomers melted lower than either alone.



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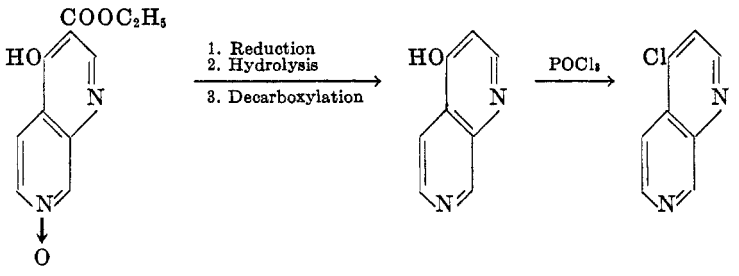


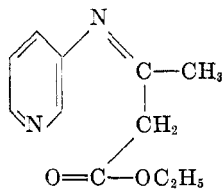
VI VII

It is obvious that these two modes of cyclizations, involving the 2- and 4-positions of the pyridine ring, are the only ones possible with such intermediates as I and V. Thus, one series of products must have the 1,5-naphthyridine structure, and the other, the 1,7-naphthyridine structure. The assignment of the 1,5-naphthyridine structure to the series from 3-aminopyridine was originally based on two pieces of evidence neither of which was conclusive. One was the observation that the 4-hydroxy derivative had the physical properties reported for 4-hydroxy-1,5-naphthyridine (II) prepared by an unequivocal method (2). The other was the fact that the corresponding Skraup reaction with 3-aminopyridine had been shown to involve the 2-position of the pyridine ring to form 1,5-naphthyridine (3). Now that the second possible mode of cyclization has been realized and the 4-hydroxy derivative found to have a different melting point from II, the 1,5-naphthyridine structure for the products from 3-aminopyridine may be regarded as established. Also, the 1,7-naphthyridine structure for the products from the amine oxide (IV) may be considered as established. Actually the formation of the 1,7-naphthyridine structure from the amine oxide was anticipated since pyridine 1-oxide has been shown to undergo substitution at the 4-position with nitric acid and other electrophilic reagents (4).

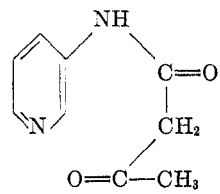
Evidently intermediate V from the oxide underwent cyclization somewhat more readily than intermediate I from 3-aminopyridine. Thus, the former intermediate exhibited maximum cyclization within about 15 minutes in refluxing Dowtherm, whereas the latter appeared to undergo only about half as much cyclization during this time as that reported previously after one hour (1). This is in line with the fact that pyridine 1-oxide is more reactive than pyridine towards nitric acid (4). However, the difference in the ease of the thermal cyclizations of intermediates V and I appears to be much less pronounced than the difference in the reactivity of pyridine 1-oxide and pyridine with nitric acid.

Although 3-aminopyridine reacts with the ketone and ester groups of acetoacetic ester to form the anil (VIII) (or crotonate) and the amide (IX) (5), 3-aminopyridine 1-oxide has failed to undergo corresponding reactions to give X and XI respectively. Thus, only starting materials were recovered after refluxing the β-keto ester and amine oxide in ethanol over Drierite, which was the method employed in the preparation of anil VIII (5). A water-soluble compound (m.p. 234°) was obtained on heating the β-keto ester with the amine oxide at 140° for four hours, which is one of the methods employed for the preparation of amide

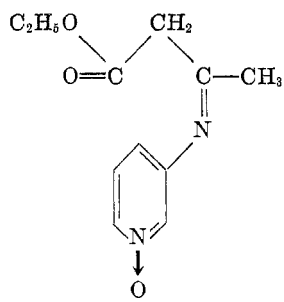
IX (5), but the product did not analyze for amide XI. Also, 3-aminopyridine 1-oxide failed to form the anil (or crotonate) with acetylacetone.



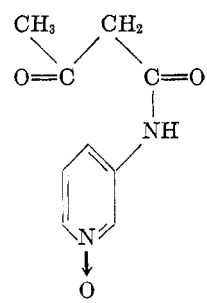
VIII



IX



X



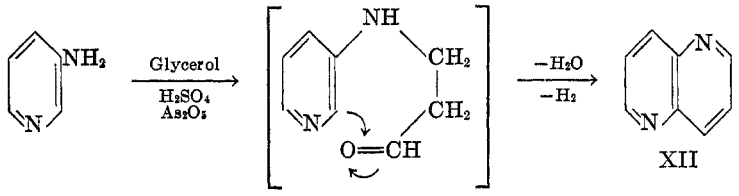
XI

The failure of 3-aminopyridine 1-oxide (IV) to form the anil with the β-keto ester or β-diketone under the conditions that produced the corresponding anil from 3-aminopyridine appears to be due to the relatively weakly basic nature of the primary amino group of the oxide. Nitroanilines and 4-aminopyridine, which are known to have relatively weakly basic primary amino groups (6, 7), similarly have failed to form such intermediates (8, 5). In agreement with this, the pK_a values for 3-aminopyridine and 3-aminopyridine 1-oxide hydrochlorides (assuming a mono basic acid) were found to be 6.1 and 1.8, respectively. Although these values have not been shown to represent a measure of the relative basicities of the primary amino electron pairs, it appears likely that the nitrogen oxide function decreases, through an inductive effect, the availability of this electron pair in the oxide. In line with this, 3-hydroxypyridine 1-oxide is a stronger acid than 3-hydroxypyridine, the pK_a values being 6.4 and 8.6 respectively (9).

It should be pointed out that anil VIII and amide IX from 3-aminopyridine have failed to cyclize under the conditions generally employed for effecting such Conrad-Limpach and Knorr types of cyclizations of corresponding anilino derivatives (5). Even the cyclization of intermediate I required special conditions (1). This is not surprising since the pyridine ring is known to undergo electrophilic reactions less readily than the benzene ring. However, it is possible that intermediates X and XI (if they could be prepared) might undergo cyclization since their aromatic rings should be more reactive than those of intermediates VIII and IX.

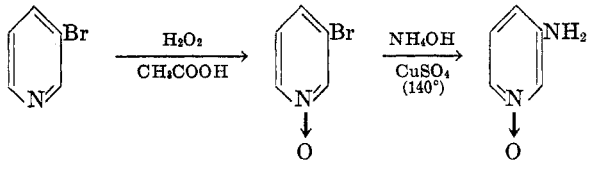
As mentioned above, the Skraup reaction with 3-aminopyridine has previously been shown to involve the 2-position of the pyridine ring to form 1,5-naphthy-

ridine (XII), although the yields have been only fair (1, 10). The structure of the product (XII) was established by two independent syntheses involving unequivocal methods (2, 3, 10).

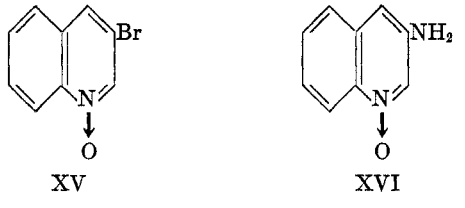


We attempted to prepare 1,7-naphthyridine by the Skraup reaction with 3-aminopyridine 1-oxide (IV) but the only product isolated was 1,5-naphthyridine (XII). Apparently the amine oxide was first deoxygenated to form 3-aminopyridine which then underwent the Skraup reaction. Such deoxygenation of pyridine oxides in the presence of acid and oxidizing agents has been reported (11).

The 3-aminopyridine 1-oxide used in this investigation was prepared from 3-bromopyridine (XIII) which was converted to its oxide (XIV) by an adaptation of Ochiai's method for preparing pyridine 1-oxide (4). The halogen of oxide XIV was then replaced by the amino group to form oxide IV by an adaptation of the usual method employing a sealed glass tube or an iron bomb (5). Like pyridine 1-oxide, 3-aminopyridine 1-oxide was readily reduced by iron and acetic acid to form 3-aminopyridine.



In connection with this work, 3-bromoquinoline has similarly been converted to its oxide (XV), which was then converted to 3-aminoquinoline 1-oxide (XVI).



EXPERIMENTAL[2]

3-Bromopyridine 1-oxide. This amine oxide was prepared by a modification of the method of Ochiai (4). 3-Bromopyridine[3] (79 g., 0.5 mole) was heated with 85 ml. of hydrogen

[2] Melting and boiling points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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

peroxide in 300 ml. of glacial acetic acid at 70–80° for 12 hours. Most of the acetic acid was removed under reduced pressure on the steam-bath, and the residue (about 100 ml.) was distilled *in vacuo* to give some material, b.p. 50–54° at 13 mm., and 59.1 g. (68%) of 3-bromopyridine 1-oxide, b.p. 143–148° at 4 mm. A sample of the product was identified as its *hydrochloride*, m.p. 181–183°; reported m.p. 181–182° (12).

The material, b.p. 50–54° at 13 mm., was taken up in chloroform, washed with sodium bicarbonate solution, dried, and the solvent was removed. The residue was distilled yielding 13.9 g. (17%) of recovered 3-bromopyridine, b.p. 169–171°.

3-Aminopyridine 1-oxide (IV). A mixture of 17.4 g. (0.1 mole) of 3-bromopyridine 1-oxide, 33 ml. of ammonium hydroxide (*sp. gr.* 0.90), and 1 g. of copper sulfate pentahydrate was heated in a sealed iron or glass tube for 20 hours at 130–140° essentially as described for the conversion of 3-bromopyridine to 3-aminopyridine (5). The resulting solution was evaporated under reduced pressure on the steam-bath, and the residue was extracted with chloroform in a Soxhlet extractor during 24 hours. After removing the solvent on the steam-bath, the residue was taken up in ethanol, and the colored solution was passed through a short column of alumina, followed by more ethanol. The slightly colored ethanolic solution was evaporated on the steam-bath, and the residue was recrystallized from a mixture of ethanol, chloroform, and water. The solution was cooled with Dry Ice to precipitate needles of a hydrate of 3-aminopyridine 1-oxide. The mixture was filtered, and the needles were dried in a vacuum desiccator to give 5.5 g. of slightly yellow anhydrous 3-aminopyridine 1-oxide, m.p. 123–124°. From the filtrate there was obtained an additional 0.93 g. of product, m.p. 121–123° (Total yield 58.6%). A sample was recrystallized several times from the mixture of chloroform, ethanol, and water, to give colorless product which melted, after drying, at 124–125°.

Anal. Calc'd for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44.
Found: C, 54.52; H, 5.67; N, 25.48.

The pK_a values of 3-aminopyridine and 3-aminopyridine 1-oxide hydrochlorides were determined by measuring the *p*H (with a Beckman *p*H meter) of a solution prepared from 0.1 *N* hydrochloric acid using the calculated amount of acid needed to half neutralize the amine, taking the measured *p*H as equal to the pK_a value of the amine hydrochloride. The value found for 3-aminopyridine was 6.1, and that of 3-aminopyridine 1-oxide was 1.8.

A sample of 3-aminopyridine 1-oxide (1.0 g.) was reduced with iron in acetic acid in the usual manner (3) to give 0.58 g. of 3-aminopyridine, m.p. 58–62° (reported 64–65°) (13). The *monoacetyl* derivative melted at 133–134°; reported 133° (13).

Intermediate V *from* IV *and ethoxymethylenemalonic ester*. 3-Aminopyridine 1-oxide (IV) (6.6 g., 0.06 mole) was heated with 18.3 g. of ethoxymethylenemalonic ester for two hours on the steam-bath. The resulting solid was recrystallized once from ethanol yielding 13.5 g. (80%) of slightly yellow cubes of intermediate V, m.p. 174–176°. A sample after several recrystallizations from ethanol, gave colorless cubes, m.p. 177–178°.

Anal. Calc'd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00.
Found: C, 55.59; H, 5.71; N, 10.02.

Cyclization of intermediate V, *4-hydroxy-1,7-naphthyridine* (VI). To 180 ml. of refluxing Dowtherm[3] in a 300-ml. flask equipped with a stirrer and reflux condenser was added 3.0 g. of intermediate V (m.p. 174–176°). After stirring and refluxing for 15 minutes, the solution was cooled, and 100 ml. of petroleum ether was added. The solid was removed by filtration and washed with 100 ml. of petroleum ether followed by 10 ml. of hot ethanol. After drying there was obtained 1.40 g. of crude 3-carbethoxy-4-hydroxy-1,7-naphthyridine 7-oxide, m.p. 272° dec.

The crude oxide was reduced by stirring it with 1.0 g. of iron powder (100 mesh) in a mixture of 25 ml. of acetic acid and 5 ml. of pyridine for 1.5 hours. The excess solvent was evaporated under reduced pressure on the steam-bath. The residue was stirred with 30 ml. of water, and then with sufficient 40% sodium hydroxide to make the solution slightly alkaline, 3 ml. excess of the alkali finally being added. The mixture was refluxed one hour and filtered. The filtrate was made slightly acid with concentrated hydrochloric acid to

precipitate crude 3-carboxy-4-hydroxy-1,7-naphthyridine. This acid was removed by filtration and dried; yield 0.95 g.

The crude acid (1.50 g., obtained from several experiments) was decarboxylated by refluxing it in 15 ml. of quinoline for one hour. After filtering the hot solution, 15 ml. of acetone was added, the solution was cooled, and the precipitate was removed by filtration, dried, and sublimed at 220° (1 mm.), yielding 0.55 g. of slightly yellow 4-hydroxy-1,7-naphthyridine (VI), m.p. 297–298° dec. The over-all yield from intermediate V was 22%.

Anal. Calc'd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17.

Found: C, 65.49; H, 4.45; N, 18.89.

Admixture of a sample of this compound (VI) with a sample of 4-hydroxy-1,5-naphthyridine (II) (m.p. 338–340° dec.) depressed the melting point to 246–273°. The sample of II which had been prepared several years before (1), was purified by sublimation at 190° (1 mm.). This compound has been reported both to melt at 340° (9) and to sublime at this temperature (2).

4-Chloro-1,7-naphthyridine (VII). 4-Hydroxy-1,7-naphthyridine (0.3 g.) was heated with 3 ml. of phosphorus oxychloride on the steam-bath for 1.5 hours, and the mixture was allowed to stand overnight. After removing the excess phosphorus oxychloride, the residue was cooled and ice was added. The solution was neutralized with concentrated ammonium hydroxide and then extracted with chloroform. The chloroform solution was dried over Drierite, and the solvent was distilled on the steam-bath. The residue was sublimed under slightly reduced pressure at 100° yielding 0.186 g. of colorless needles of 4-chloro-1,7-naphthyridine (VII), m.p. 121–122°.

Anal. Calc'd for $C_8H_5ClN_2$: C, 58.37; H, 3.06; N, 17.02.

Found: C, 58.37; H, 2.77; N, 17.21.

Admixture of a sample of VII with 4-chloro-1,5-naphthyridine (III) (m.p. 102°) depressed the melting point to 78–100°. The sample of III was prepared from the corresponding hydroxy compound (II) in the usual manner.

3-Bromoquinoline 1-oxide (XV). 3-Bromoquinoline (104 g., 0.5 mole) was heated with 85 ml. of hydrogen peroxide in 300 ml. of glacial acetic acid at 75° for 12 hours. After removing most of the acetic acid under reduced pressure on the steam-bath, 200 ml. of chloroform was added and the resulting mixture was shaken vigorously with sodium carbonate paste. The chloroform was distilled and the residue was cooled. Ether (200 ml.) was added to precipitate, after cooling overnight in the refrigerator, 34.7 g. (30%) of crude 3-bromoquinoline 1-oxide, m.p. 96–101°, reported m.p. 102–103° (14). 3-Bromoquinoline was recovered from the filtrate.

3-Aminoquinoline 1-oxide (XVI). A mixture of 22.4 g. (0.1 mole) of 3-bromoquinoline 1-oxide, 35 ml. of ammonium hydroxide (*sp. gr.* 0.90), 20 ml. of 95% ethanol, and 1.0 g. of copper sulfate pentahydrate was heated in a sealed tube at 165° for 22 hours. The solvent was removed under reduced pressure on the steam-bath, and the residue was extracted with chloroform in a Soxhlet extractor. After removing the chloroform, the residue was dissolved in the minimum amount of hot 95% ethanol. The ethanolic solution was poured through an alumina column, and the column was washed with chloroform. The product was eluted with 95% ethanol and the solvent removed by distillation. The residue was recrystallized from a mixture of acetone and ethanol yielding 3.81 g. of red needles of 3-aminoquinoline 1-oxide, m.p. 187–189°, and a second crop of 1.33 g. of needles, m.p. 185–187°; total yield 5.14 g. (32%). A sample was sublimed at 160° (0.4 mm.) giving a bright yellow solid, m.p. 190–191°.

Anal. Calc'd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49.

Found: C, 67.63; H, 4.92; N, 17.69.

SUMMARY

1. 3-Aminopyridine 1-oxide was cyclized with ethoxymethylenemalonic ester to give, after reduction, hydrolysis, and decarboxylation, 4-hydroxy-1,7-naphthyridine. This product and its 4-chloro derivative were shown to be isomeric

with corresponding compounds obtained previously from the cyclization of 3-aminopyridine and ethoxymethylenemalonic ester.

2. 3-Aminopyridine 1-oxide failed to form intermediate anils or amide with ethyl acetoacetate and acetylacetone, and failed to undergo the Skraup reaction under the usual conditions.

3. The syntheses of 3-aminopyridine 1-oxide and of 3-aminoquinoline 1-oxide are described.

DURHAM, NORTH CAROLINA

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