[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

SOME DERIVATIVES OF 3-METHYLISOQUINOLINE

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3-Methylisoquinoline, previously prepared only on a small scale, has recently become available in quantity and at a reasonable cost.[1] Unfortunately, studies of the properties of this compound have been indefinitely interrupted; the work already accomplished is described below.

3-Methylisoquinoline dissolves readily in a solution of potassium amide in liquid ammonia, with evolution of some hydrogen and the formation of a small amount of 1-amino-3-methylisoquinoline. In the presence of potassium nitrate at room temperatures, the yield is increased to 70% of the theoretical. 1-Amino-3-methylisoquinoline forms only a monohydrochloride in 1:3 hydrochloric acid, as do also 2-aminopyridine, 2-aminoquinoline, and 1-aminoisoquinoline (1). All of these compounds contain the grouping, (a), below and react with a proton to form a salt which probably has the constitution, (b), rather than (d) because of the increased resonance between the nearly equivalent forms, (b) and (c). Such a resonance is impossible in the case of (d). Furthermore, the union with a second proton will be greatly hindered because each nitrogen is positively charged about half of the time.

$$\underset{\text{(a)}}{\text{--C(NH}_2\text{)=N--}} \quad \underset{\text{(b)}}{\text{—C(NH}_2\text{)=}\overset{+}{\text{N}}\text{H—}} \quad \underset{\text{(c)}}{\text{—C(=}\overset{+}{\text{N}}\text{H}_2\text{)—NH—}} \quad \underset{\text{(d)}}{\text{—C(}\overset{+}{\text{N}}\text{H}_3\text{)=N—}}$$

Since isoquinoline and sodium amide give 1-aminoisoquinoline (1 b), it is very probable that a 1-amino derivative is formed in the present case.

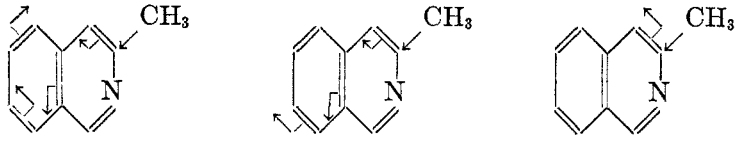
All attempts to diazotize 1-amino-3-methylisoquinoline, either in sulfuric acid or in hydrochloric acid, have failed; it was hoped thereby to prepare 1-hydroxy-3-methylisoquinoline or 1-chloro-3-methylisoquinoline, respectively. The amino group is stable toward hydrolysis by boiling 1 *N* sulfuric acid, over a period of five hours.

Nitration of 3-methylisoquinoline gives a good yield of a mononitro derivative melting at 109–110°, together with a smaller quantity of material that melts at 90–91°. The two may be isomeric compounds or possibly different crystalline modifications of the same substance, since amines of the same melting point are formed on reduction. The possibility that the low-melting product is a mixture has not been excluded.

The higher-melting material may be 5-nitro-3-methylisoquinoline, since 5-nitroisoquinoline appears to be the chief product of the nitration of isoquinoline (2). A methyl group in position 3 would increase the electron density at carbon atoms 4, 5, and 7 more than at other positions, and accordingly would accelerate the substitution of an electrophilic group, such as NO_2, at these places. In the

[1] Obtained from the Reilly Tar and Chemical Corporation, Indianapolis, Indiana.

following diagrams, the curved arrows indicate the mode of transmission of the weak electron repulsion of the methyl group.



EXPERIMENTAL PART

3-Methylisoquinoline[1] was crystallized once from ligroin (b.p. 55–85°) before use; it then melted at 64.5–66.5°. All melting points in this article are uncorrected.

3-Methylisoquinoline methiodide. 3-Methylisoquinoline (14.3 g.) and methyl iodide (15 g.) were gently refluxed in 30 cc. of ethanol for about one and one-half hours. From the cooled solution was filtered 24.2 g. (82%) of a yellow methiodide, which melted at 218–220°, and at 221–222° after three recrystallizations from ethyl alcohol. This compound was previously prepared by Mills and Smith (3), who give 219° as the melting point.

Anal.[2] Calc'd for $C_{11}H_{12}IN$: C, 46.33; H, 4.25.

Found: C, 46.32, 46.41; H, 4.43, 4.29.

1-Amino-3-methylisoquinoline. 3-Methylisoquinoline is moderately soluble in liquid ammonia at 25°, but much less so at 0°.

In a two-legged reaction tube (4), the potassium amide prepared from 18 milliatoms of potassium with the aid of a ferric oxide catalyst, was brought into reaction with 5.6 millimoles of 3-methylisoquinoline in the other leg. The solution rapidly became opaque green, and then, in the course of time, an opaque red, with the slow evolution of 2.03 millimoles (36%) of hydrogen. The red solid left after evaporating the ammonia was hydrolyzed with a mixture of benzene and a little water. The benzene left on evaporation a plastic yellow solid, from which boiling ligroin extracted a small amount of impure aminomethylisoquinoline. It is better to proceed as follows.

In one of the compartments of a steel bomb[3] was placed 8.3 g. (0.21 atom) of potassium metal and a tenth of a gram of ferric oxide; the other compartment contained 14.3 g. (0.1 mole) of 3-methylisoquinoline and 12.7 g. (0.13 mole) of dry powdered potassium nitrate. Liquid ammonia was distilled in and the contents of the chambers mixed after formation of the potassium amide (hydrogen no longer evolved). The autoclave was rocked for 20 hours at room temperatures, after which the solvent ammonia was evaporated into a carboy of water. The reaction vessel was evacuated with a water-pump, and 100 cc. of benzene drawn in, followed by 100 cc. of water in small portions at a time (shake). The water and benzene were removed, the latter layer separated, dried over sodium hydroxide pellets, and concentrated. Two crops of light tan crystals were obtained, a total of 11 g. melting at 127.5–129.5° (70%). The melting point was raised to 130.5–131° by several crystallizations from benzene. Similar yields were obtained in glass reaction tubes, in smaller scale experiments (4).

Anal. Calc'd for $C_{10}H_{10}N_2$: C, 75.90; H, 6.37; N, 17.71.

Found: C, 76.00, 76.05; H, 6.27, 6.33; N, 17.76, 17.71.

Aminomethylisoquinoline dissolves readily in the following solvents at room temperature: Chloroform, ethyl acetate, dilute formic acid, dilute acetic acid, methanol, ethanol, cellosolve. It can best be crystallized from benzene, xylene, chlorobenzene, dilute methanol, or dilute ethanol. An excess of the following acids, in aqueous solution, dissolve it when hot: Nitric acid, hydrochloric acid, sulfuric acid, *d*-tartaric acid, malonic acid,

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[2] All microanalyses reported in this paper were carried out by the Huffman Microanalytical Laboratories of Denver.

[3] The type of bomb closure described by Bergstrom (5) is very unsatisfactory, and has been replaced by one similar to that of Adkins (6).

hydrobromic acid. Well formed colorless crystals separate abundantly on cooling in each case, though often very sluggishly. The tartrate was obtained largely as a clear transparent jelly in which a white solid slowly formed.

Monohydrochloride of 1-amino-3-methylisoquinoline. Aminomethylisoquinoline was dissolved in hot 1:3 hydrochloric acid; the crystals separating on cooling were twice recrystallized from acid of the same strength, and dried *in vacuo* at 80°. The melting behavior (m.p. 272–278°) indicates possibly the presence of two forms of the hydrochloride.

Anal. Calc'd for $C_{10}H_{10}N_2 \cdot HCl$: C, 61.69; H, 5.70.
Found: C, 61.75, 61.81; H, 5.76, 5.71.

Aminomethylisoquinoline is not affected by boiling for five hours with 1 *N* sulfuric acid.

x-(5?)-Nitro-3-methylisoquinoline. A solution of 3-methylisoquinoline (21.5 g., 0.15 mole) in 100 cc. of concentrated sulfuric acid at 25° was placed in a 500-cc. three-necked flask with thermometer, dropping-funnel, and mechanical stirrer. Fuming nitric acid (7.2 cc., *d* 1.5) dissolved in concentrated sulfuric acid (40 cc.) was added dropwise over a period of fifteen minutes, with stirring, the temperature being maintained at 25° by external cooling. After fifteen minutes more the solution was poured over 200 cc. of cracked ice and made basic with sodium hydroxide, resulting in a yellow precipitate, which was collected by filtration and dried (24.9 g., m.p. 85–98°). Five crystallizations from 50% ethanol gave 15.5 g. (55%) of material melting at 108–110°. The combined filtrates were evaporated and the residue crystallized several times from 50% ethanol to give 4 g. of pale yellow needles, melting at 90–91°.

Anal. Calc'd for $C_{10}H_8N_2O_2$: C, 63.80; H, 4.28; N, 14.90.
Found (m.p. 90–91°): C, 63.87; H, 4.30; N, 14.93.
(m.p. 109–110°): C, 63.81; H, 4.30; N, 14.94.

x-Amino-3-methylisoquinoline. The higher-melting nitromethylisoquinoline (13.3 g.) was dissolved in concentrated hydrochloric acid (60 cc.) and added over a period of about 15 minutes to a solution of 64 g. of stannous chloride in 100 cc. of 2 *N* hydrochloric acid at 60°. The temperature was then increased to 80° and held at this point for an hour. After cooling, the reaction mixture was poured into a solution of 80 g. of sodium hydroxide in 2.5 liters of water, and allowed to stand about a day before filtering the product (white plates, melting at 216–218°; 10.7 g. or 95.5%). Recrystallization from 40% ethanol raised the melting point to 219.5–221°.

Anal. Calc'd for $C_{10}H_{10}N_2$: C, 75.90; H, 6.37; N, 17.83.
Found: C, 75.90; H, 6.30; N, 17.83.

The reduction of the low-melting x-nitro-3-methylisoquinoline by the same method gave a product melting at 206–212°, in 90% yield. Several recrystallizations from 50% ethanol raised the melting point to 217–220°, and the mixed melting point with the amine prepared above was the same. This may signify that the two nitromethylisoquinolines are different modifications of the same substance, or that the lower-melting isomer is perhaps a mixture that was not resolved by continued crystallization.

SUMMARY

3-Methylisoquinoline reacts with potassium amide and potassium nitrate in liquid ammonia to form 1(?)-amino-3-methylisoquinoline, which may be converted to a monohydrochloride. Nitration of 3-methylisoquinoline gives a (5?) mononitro compound, together with a lower-melting isomer. An aminomethylisoquinoline is formed on reduction.

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