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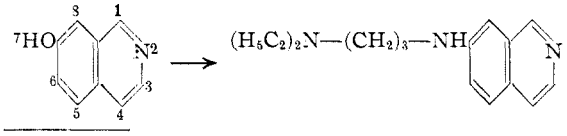
7-(γ-Diethylaminopropylamino)-isoquinoline[1]

BY RICHARD A. ROBINSON

In continuation of the study of basically alkylated aminoisoquinolines[2,3] we have prepared 7-(γ-diethylaminopropylamino)-isoquinoline. In the second paper of this series it was shown that 5-(γ-diethylaminopropylamino)-isoquinoline could be prepared by the application of the Bucherer reaction to 5-hydroxyisoquinoline. The 7-hydroxyisoquinoline, under similar conditions, was found to react with even greater ease than the 5-isomer, yielding 65% of 7-(γ-diethylaminopropylamino)-isoquinoline. With ammonium sulfite practically quantitative yields of 7-aminoisoquinoline[3] were obtained.



(1) Presented before the Organic Section of the American Chemical Society, Sept., 1946.

(2) This work was undertaken in coöperation with the Survey of Antimalarial Drugs of the National Research Council. The results of antimalarial screening tests on the compounds here reported will be found in "Antimalarial Drugs 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(3) Robinson, THIS JOURNAL, paper 2, **69**, 1942 (1947).

Experimental

7-(γ-Diethylaminopropylamino)-isoquinoline.—Fourteen and five-tenths grams of 7-hydroxyisoquinoline, 45 g. of γ-diethylaminopropylamine, 100 ml. of water and 12.8 g. of sulfur dioxide were refluxed under a pressure of 3 in. for thirty-six hours. The product was isolated by ether extraction and purified by distillation at 3 mm. The dihydrochloride, yellow needles of m. p. 145°, was purified by recrystallization from isopropanol. By desiccation at 100°, 1 mm., for twelve hours a weight loss of 4.54% occurred. The analysis is reported on a dry basis.

Anal. Calcd. for $C_{16}H_{25}Cl_2N_3$: C, 58.18; H, 7.63; Cl, 21.47. Found: C, 58.1; H, 8.17; Cl, 21.62.

Summary

The preparation of 7-(γ-diethylaminopropylamino)-isoquinoline is described.

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[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

8-(γ-Diethylaminopropylamino)-isoquinoline[1]

BY RICHARD A. ROBINSON

In preceding papers[2,3] we have described the synthesis of 5- and 7-(γ-diethylaminopropylamino)-isoquinoline by application of the Bucherer reaction to 5- and 7-hydroxyisoquinoline. In view of the difficulties encountered with other methods tried for this type of substitution[3a] the Bucherer reaction seemed to present the most hopeful means for introducing a dialkylaminoalkylamino group at position 8. Although the 8-hydroxyisoquinoline required for this reaction had never been described a suggestion for a possible method of preparation was found in Claus'[4] work on isoquinolinesulfonic acids. He obtained by sulfonation of isoquinoline at 115° two isoquinolinesulfonic acids which he designated as Acids I and II. Acid I, the chief product, has now been established as isoquinoline-5-sulfonic acid.[5] By sulfonation at 300° acid II was the chief product. This acid on caustic fusion yielded a hydroxyisoquinoline of m. p. 184° whose structure was not known. We repeated the preparation of this hydroxyisoquinoline with the hope that it would be the 8-hydroxyisoquinoline. The sulfonation of isoquinoline (A), carried out at 300° as suggested by Claus, produced about 35% of isoquinoline-5-sulfonic acid which could be separated by means of a difficultly soluble calcium salt. The residue of soluble calcium salts which was evidently a mixture could not be resolved into its pure components. By converting this mixture to the sodium salts and fusing with 60% sodium hydroxide a new hydroxyisoquinoline was obtained in an over-all yield of 15%. This new hydroxyisoquinoline melted at 213°; it was entirely pure and showed no tendency to be unstable as suggested by Claus. It was different from the known 5- and 7-hydroxyisoquinoline and from 6-hydroxyisoquinoline which was prepared by demethylation of 6-methoxyisoquinoline.[6] It reacted with ammonium sulfite yielding 85% of an

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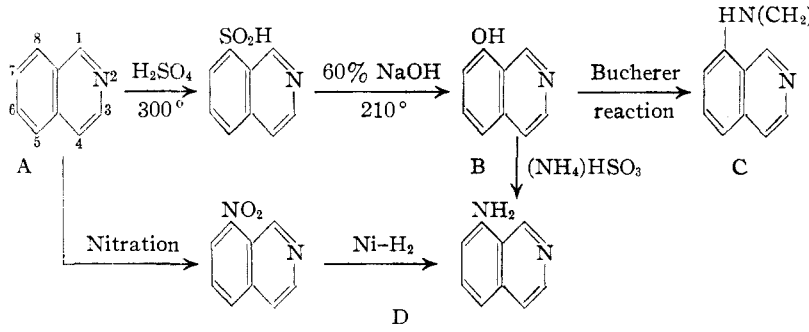
(3) (a) Robinson, THIS JOURNAL, paper 2, **69**, 1942 (1947); (b) paper 3, **69**, 1944 (1947).

(4) Claus and Raps, *J. prakt. Chem.*, (2) **45**, 241 (1892); Claus and Seeleman, *ibid.*, **52**, 1 (1895).

(5) Tyson, THIS JOURNAL, **61**, 183 (1939); Andersag, *Med. Chem. Abhandl. a. med. chem.*, **2**, 377 (1934); Claus and Gutzeit, *J. prakt Chem.*, [2] **52**, 9 (1895).

(6) Robinson, *ibid.*, paper 1, **69**, 1939 (1947).



aminoisoquinoline of m. p. 174°. This same aminoisoquinoline was also obtained in small yields from the nitration product of isoquinoline. Andersag[5] isolated two isomeric aminoisoquinolines from the reduction product of nitroisoquinoline. The chief product, an aminoisoquinoline of m. p. 132°, was shown by him to be the 5-aminoisoquinoline. The other aminoisoquinoline melted at 171°. Its structure was established as the 8-aminoisoquinoline (D). In view of this evidence it seems reasonable to assume that the new hydroxyisoquinoline is 8-hyroxyisoquinoline (B). It reacted with γ-diethylaminopropylamine sulfite according to Chelintsev and Dubinin[7] to give 45% of the theory of 8-(γ-diethylaminopropylamino)-isoquinoline (C).

Experimental

8-Hydroxyisoquinoline (B).—To seventy-eight grams of isoquinoline sulfate (m. p. 206°), (0.34 mole), preheated to 300° was added 60 g. of 60% oleum during five minutes. The mixture was heated five minutes longer at 300°. A solution of the calcium salts in a volume of 1500 ml. was prepared in the usual way. The volume was reduced to 175 ml. and then allowed to cool. Thirty grams of calcium salt crystallized at this volume. The filtrate was treated with sodium carbonate until alkaline to phenolphthalein. The calcium carbonate was removed and the filtrate evaporated to dryness. Fifty-five grams of isoquinoline sodium sulfonate was obtained. This sodium salt was mixed with 160 g. of sodium hydroxide and 50 ml. of water and fused at 210° for ten minutes (the mixture was stirred during the fusion). The mixture was dissolved in one liter of water and treated with concentrated hydrochloric acid until just alkaline to litmus. The precipitated hydroxyisoquinoline was filtered and washed with 50 ml. of hot water. The yield, after drying, was 11 g. The crude material was dissolved in hot dilute hydrochloric acid and filtered from a small quantity of insoluble material. Ten grams of the hydrochloride, m. p. unsharp at 240°, crystallized from 60 ml. of dilute hydrochloric acid containing 15 ml. of concentrated hydrochloric acid. The hydrochloride was recrystallized from 28 ml. dilute hydrochloric acid containing 5 ml. concentrated hydrochloric acid, yield 9.5 g., m. p. 244°. The base obtained from this salt melted at 210°. Purification by sublimation and recrystallization from ethanol yielded the pure base, m. p. 213°. The picrate melted at 285°. A mixture of the base with 6-hydroxyisoquinoline of m. p. 220° melted at 165°.

Anal. Calcd. for C_9H_7NO: C, 74.46; H, 4.86; N, 9.65. Found: C, 74.6; H, 4.76; N, 10.01.

8-Aminoisoquinoline (D).—Ten grams of 8-hydroxyisoquinoline, 60 ml. of concentrated ammonium hydroxide and 14 g. of sulfur dioxide were heated under pressure at 150–160° for six hours. On working up by the customary method 8.5 g. of aminoisoquinoline of m. p. 173° was obtained. The pure substance, from benzene, melted at 174°.

Anal. Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.44. Found: C, 75.0, 75.1; H, 5.62; N, 19.85, 19.51.

A sample of 8-aminoisoquinoline prepared according to Andersag[5] melted at 174° and was identical in appearance with the aminoisoquinoline described above. No depression of the melting point was observed when the two were mixed.

8-(γ-Diethylaminopropylamino)-isoquinoline (C).—Twenty grams of 8-hydroxyisoquinoline m. p. 213°, 120 g. of γ-diethylaminopropylamine, 150 ml. of water and 30 g. of sulfur dioxide were heated to reflux temperature under a pressure of 3 in. of mercury for thirty-six hours. The product was isolated by ether extraction and heated at low pressure to expel any low boiling bases. Seventeen and one-half grams of oily residue was converted to the dihydrochloride which was purified by recrystallization from ethanol. The yield was 18 g. The product, yellow crystals of m. p. 231°, was difficultly soluble in alcohols or acetone.

Anal. Calcd. for $C_{16}H_{23}N_3$: C, 74.66; H, 9.01; N, 16.33. Found: C, 74.2, 74.6, 74.8; H, 8.88, 9.17, 8.68; N, 16.64, 16.82.

6-Hydroxyisoquinoline.—Three-tenths gram of 6-methoxyisoquinoline was heated with 20 ml. of 48% hydrobromic acid at reflux temperature for two hours. The mixture was then evaporated to dryness on the steam-bath. The residue was dissolved in 5 ml. of water and neutralized with sodium carbonate. The precipitated hydroxyisoquinoline was filtered and washed with hot water. The crude material, m. p. 210°, was purified by sublimation followed by recrystallization from isopropanol. The product consisted of colorless crystals of m. p. 220°.

Anal. Calcd. for C_9H_7NO: C, 74.46; H, 4.86. Found: C, 74.4, 74.7; H, 4.6, 5.08.

The hydrochloride, from isopropanol–ether, melted at 175°.

Anal. Calcd. for C_9H_8ClNO: Cl, 19.52. Found: Cl, 19.18.

Summary

The preparation of 6- and 8-hydroxyisoquinoline is described.

The preparation of 8-aminoisoquinoline and 8-(γ-diethylaminopropylamino)-isoquinoline is described.

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(7) Chelintsev and Dubinin, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1395 1940); Hartshorn, THIS JOURNAL, **68**, 1562 (1946).