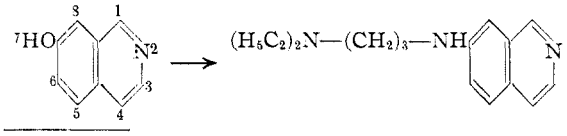
[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

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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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).