5-Aminoisoquinoline.—One and eight-tenths grams of amino-1-chloroisoquinoline (prepared from 1-chloroisoquinoline by nitration and reduction), 0.9 g. of sodium hydroxide, 1 g. of Raney nickel and 0.05 g. of chloroplatinic acid in 150 cc. of ethanol was hydrogenated at forty pounds pressure. One mole of hydrogen was absorbed in four hours. One and one-half grams of aminoisoquinoline which melted unsharply at 125° was obtained. After recrystallization from benzene, the product melted at 132°. When it was mixed with 5-aminoisoquinoline there was no depression of the melting point.

Summary

Several 1-dialkylaminoalkylaminoisoquinolines are described.

Several chloro and methoxy derivatives of 1-(γ-diethylaminopropylamino)-isoquinoline are described.

Several methoxy and chloro derivatives of 1-chloroisoquinoline are described.

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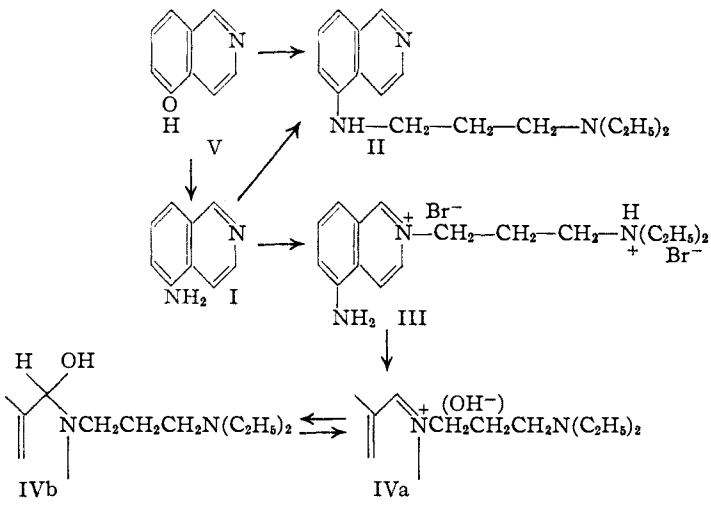
5-(γ-Diethylaminopropylamino)-isoquinoline[1]

BY RICHARD A. ROBINSON

As outlined in the preceding paper[2,3] we have undertaken the synthesis of basically alkylated aminoisoquinolines as a contribution to the search for new antimalarial drugs. The synthesis of the 1-dialkylaminoalkylaminoisoquinolines was readily accomplished through the reaction of 1-chloroisoquinoline derivatives with dialkylaminoalkyl amines. Such a simple synthesis was not effective for the introduction of a dialkylaminoalkylamino side chain at position 5. In this connection various attempts to bring about a transformation between 5-iodoisoquinoline and dialkylaminoalkylamines were made without success. The problem of preparing a 5-(γ-diethylaminopropylamino)-isoquinoline was therefore approached by other methods. The most obvious method, the aminoalkylation of 5-aminoisoquinoline (I)



was tried under a broad range of conditions. Despite numerous modifications of the known alkylation procedures, no condition was ever found which would produce a 5-(dialkylaminoalkylamino)-isoquinoline in satisfactory yield. Under neutral or slightly acid conditions (*p*H 4–5) alkylation by means of γ-diethylaminopropyl bromide attacks preferentially the ring nitrogen thereby producing an isoquinolinium salt (III). The isoquinolinium compound was characterized through the strongly basic properties of its base form (IVa) (an aqueous solution is alkaline to phenolphthalein) and by the demonstration of the presence of a primary amino group by a diazotization and coupling reaction.

The *p*H value of a tenth normal solution of 5-aminoisoquinoline hydrochloride (*p*H = 2.4) indicated that aminoalkylation might take place under more acidic conditions. A trial was accordingly made in the *p*H range 2.8 to 3.2. The 5-aminoisoquinoline was chiefly unattacked, but in this case 6% of the 5-(γ-diethylaminopropylamino)-isoquinoline (II) was obtained. This indicates that aminoalkylation of the 5-amino group could probably be accomplished under very strictly defined conditions. However, the desired product was obtained by another method and further study of the aminoalkylation procedure was not deemed necessary.

Other unsuccessful attempts at aminoalkylation included the reaction of 5-aminoisoquinoline with dialkylaminoalkanols and dialkylaminoalkylamines at elevated temperatures with the hope that alkylation would take place through the elimination of water and ammonia, respectively. Such was not the case. The reaction of 5-formylaminoisoquinoline with γ-diethylaminopropyl-sodium oxide according to German Patent 650,491 also failed to yield the desired product. Various attempts to condense 5-diethylaminopentanone-2 and 5-aminoisoquinoline were unsuccessful. It was hoped that a 5-(δ-diethylaminoisobutylamino)-isoquinoline could be obtained in this way. An indirect ap-

(1) Presented before the organic division of the Am. Chem. Soc., 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) Paper I, THIS JOURNAL, **69**, 1939 (1947).

proach consisted in the reaction of 1-chloro-5-aminoisoquinoline with γ-diethylaminopropyl bromide with subsequent reduction to remove the 1-chloro atom. The desired product could not be isolated.

Chelintsev and Dubinin[4] introduced dialkylaminoalkylamino groups into the 8-position of the quinoline nucleus through the application of the Bucherer reaction to 8-hydroxyquinoline. A similar reaction with the known 5-hydroxyisoquinoline (V) and γ-diethylaminopropylamine sulfite produced 25% of 5-(γ-diethylaminopropylamino)-isoquinoline (II) which could be readily isolated in a pure state. For the purpose of comparison 5-hydroxyisoquinoline was treated with ammonium sulfite thereby producing 65% of 5-aminoisoquinoline.

Experimental

5-Hydroxyisoquinoline.—Seventy grams of isoquinoline-5-sodium sulfonate, 200 g. of potassium hydroxide and 60 ml. of water were heated to 210–220° for ten minutes. The mass was stirred well during the fusion. The hydroxyisoquinoline was then isolated in the usual way. Twenty-eight grams of crude material was obtained which was purified by dissolving in hydrochloric acid, filtering from insoluble material and again precipitating the free hydroxyisoquinoline. The yield was 21 g. (48%), m. p. 230°.

5-(γ-Diethylaminopropylamino)-isoquinoline.—Fifty-nine grams of 5-hydroxyisoquinoline, m. p. 230°, 179 g. of γ-diethylaminopropylamine, 300 g. of water and 39 g. of sulfur dioxide were refluxed under a pressure of 12 in. of mercury for fifty-five hours. The 5-(γ-diethylaminopropylamino)-isoquinoline which separated slowly as an oily layer was isolated in the usual way and converted to the dihydrochloride. The dihydrochloride was hygroscopic but on standing a stable crystalline substance was formed which was evidently a hydrate. This substance, m. p. 85°, was recrystallized three times from isopropanol without change in the melting point. By desiccation at 62°, 3 mm., for twelve hours a weight loss of 9.11% 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, 57.5; H, 7.28; Cl, 21.83.

On recrystallization of the dihydrochloride of m. p. 85° from isopropanol containing excess hydrogen chloride a substance of similar appearance but of m. p. 185° separated.

Anal. Calcd. for $C_{16}H_{25}Cl_2N_3$: Cl, 21.47. Found: Cl, 20.63.

A dihydrobromide and picrate, prepared in the usual way, both melted at 195°.

5-Aminoisoquinoline.—Seven and one-half grams of 5-hydroxyisoquinoline, m. p. 230°, 50 ml. of concentrated ammonium hydroxide, 20 ml. of water and 7 g. of sulfur dioxide were heated at 150° under pressure for thirteen hours and then at 160° for four hours. The crystalline product obtained was washed well with dilute sodium hydroxide. Six grams of a crystalline base was obtained. The product was purified by sublimation, yielding thereby 5 g. of 5-aminoisoquinoline, m. p. 132°. The product was identical with 5-aminoisoquinoline prepared from nitroisoquinoline.

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

Aminoalkylation of 5-Aminoisoquinoline.—Seven and two-tenths grams of 5-aminoisoquinoline, m. p. 130°, 15 g. of γ-diethylaminopropyl bromide hydrobromide (purity 93%) and 18 cc. of anhydrous isopropanol were heated under reflux for fifteen hours. The mixture, at first an orange-red solution, changed after thirty minutes to a mass of orange colored crystals (a duplicate preparation terminated after thirty minutes indicated the reaction was complete in this time). The orange crystals were filtered and washed with isopropanol and acetone (difficultly soluble in isopropanol or acetone), yield 13 g. The filtrate yielded 1 g. of unchanged 5-aminoisoquinoline and an additional 4 g. of the alkylated product. The orange crystals, m. p. 230°, were recrystallized twice from methanol with no change in the melting point. When this substance was mixed with 5-(γ-diethylaminopropylamino)-isoquinoline dihydrobromide of m. p. 195° the melting point was 185°.

Anal. Calcd. for $C_{16}H_{25}Br_2N_3$: Br, 38.03; N, 10.02. Found: Br, 38.35, 38.31; N, 9.72.

The salt was easily soluble in water and did not precipitate as the base when the solution was made strongly alkaline to phenolphthalein. When a large excess of sodium hydroxide was added or when the dilute solution was permitted to stand the base precipitated as an oil which in some instances crystallized. The base was almost completely soluble in ether. It could be slowly extracted from ether solution by water. Its yellow aqueous solution was alkaline to phenolphthalein. If the ether solution was dried and treated with hydrogen chloride a dihydrochloride was obtained. This substance was solid but could not be obtained in a crystalline state.

Anal. Calcd. for $C_{16}H_{25}Cl_2N_3$: Cl, 21.4. Found: Cl, 21.56.

A picrate prepared from the base melted at 185°. The dihydrochloride diazotizes in hydrochloric acid solution and couples with β-naphthol to give a red dye. The product is therefore an isoquinolinium salt. The solubility of the base in ether can be attributed to a carbinol base form, IVb.

A repetition of the aminoalkylation procedure, adding this time one equivalant of acetic acid, produced the same result. No change in the course of the reaction was obtained when water was substituted for isopropanol. The *p*H of this mixture at the start and finish of the reaction was 5 and 4, respectively.

A test run in 2 molar monosodium phosphate using hydrochloric acid and disodium phosphate to maintain a *p*H of 3 ± 0.2 gave 80% of unchanged 5-aminoisoquinoline which was removed at *p*H 5–6 by ether extraction and 6% of 5-(γ-diethylaminopropylamino)-isoquinoline (II) which was extracted by ether at *p*H 7.5. The latter fraction was purified by distillation. Its dihydrochloride melted at 183° and was identical with the dihydrochloride of the product obtained by the Bucherer reaction.

Summary

Aminoalkylation of the primary amino group of 5-aminoisoquinoline could not be accomplished in satisfactory yield.

Aminoalkylation by γ-diethylaminopropyl bromide attacks the ring nitrogen.

5-(γ-Diethylaminopropylamino)-isoquinoline was prepared from 5-hydroxyisoquinoline by the Bucherer reaction.

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