[CONTRIBUTION FROM THE NICHOLS CHEMISTRY LABORATORY OF NEW YORK UNIVERSITY]

Derivatives of Aminoisoquinolines[1]

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The purpose of the present work was the preparation of compounds of possible therapeutic interest from isoquinoline.[3] To this end, acetyl, benzoyl and sulfanilyl derivatives were prepared from the 1-, 4- and 5-amino-isoquinolines.

The method of Bergstrom[4] was used for the preparation of 1-aminoisoquinoline. 4-Aminoisoquinoline was obtained from 4-bromoisoquinoline, using a modification of the procedure of Bergstrom and Rodda.[5] The reduction of 5-nitroisoquinoline[6] to 5-aminoisoquinoline was carried out by catalytic hydrogenation over Raney nickel.

The acetyl, benzoyl, acetylsulfanilyl and sulfanilyl derivatives of the aminoisoquinolines were obtained in the usual manner. Benzoylation of 1-aminoisoquinoline resulted in the formation of a di-benzoyl derivative, as was found to be the case for the benzoylation of the analogous 2-aminopyridine by Chichibabin and Bylinkin.[7] The 5- and 4-(N^4-acetylsulfanilamido)-isoquinolines were hydrolyzed to sulfanilamido derivatives with dilute hydrochloric acid. This treatment was found to rupture the sulfonamide linkage in 1-(N^4-acetylsulfanilamido)-isoquinoline; however, by treatment with dilute aqueous sodium hydroxide the acetyl group was removed from the latter compound with the formation of 1-sulfanilamidoisoquinoline.[8]

Preliminary pharmacological tests on 1-, 4- and 5-sulfanilamidoisoquinolines have been carried out by the Merck Institute for Therapeutic Research, Rahway, New Jersey. Only the 5-sulfanilamido derivative exhibited toxic symptoms in mice in dose levels of 5, 10 and 20 mg. per 20 g. of animal body weight. In tests for antistreptococcal efficacy in mice, protection was obtained with 1-sulfanilamidoisoquinoline comparable with a sulfadiazine standard; protection afforded by the 4-derivative was somewhat less; the 5-derivative was ineffective.

(1) Constructed, in part, from the B.A. research paper of John J. Craig, New York University, University College, June, 1941.

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(3) The authors wish to express their appreciation to the research laboratory of the Barrett Company, Edgewater, New Jersey, for the gift of the isoquinoline used in this work.

(4) Bergstrom, *Ann.*, **515**, 34 (1935).

(5) Bergstrom and Rodda, THIS JOURNAL, **62**, 3030 (1940).

(6) See Tyson, THIS JOURNAL, **61**, 183 (1939), for a proof of the structure of the "5- or 8-nitroisoquinoline" of Claus and Hoffman, *J. prakt. Chem.*, **47**, 252 (1893).

(7) Chichibabin and Bylinkin, *Ber.*, **55**, 998 (1922).

(8) The preparation of 1-sulfanilamidoisoquinoline has been reported previously by other workers: (a) Crossley, Northey and Hultquist, unpublished work (see Northey, *Chem. Rev.*, **27**, 107 (1940)); (b) Ewins and Phillips, British Patent 512,145 (see *Brit. Abs.*, **B59**, 405 (1940)).

Experimental

All melting points are corrected.

4-Bromoisoquinoline.—The hydrobromide of 4-bromoisoquinoline was prepared, as described by Bergstrom and Rodda[5] from 63 g. of isoquinoline. Free 4-bromoisoquinoline, however, was obtained by a different procedure. The solid reaction mixture was treated with excess 20% sodium hydroxide solution and the resulting dark oil extracted with three 100-cc. portions of benzene. The benzene extracts were dried with anhydrous potassium carbonate and distilled. After the removal of the benzene, two fractions were obtained. The first fraction of 16 g. boiled at 125–141° (16 mm.) and was mostly isoquinoline (25% recovery); this material was re-used in subsequent brominations. The second fraction of 67 g. boiled at 142–154° (16 mm.) and consisted chiefly of 4-bromoisoquinoline. Redistillation of the second fraction at 147–152° (13 mm.) yielded 54 g. (53%) of fairly pure 4-bromoisoquinoline. A sample of the redistilled oil, dissolved in warm ether and ligroin, precipitated on cooling as white crystals of m. p. 38–39°.[5]

Picrate.—Recrystallized from 50% alcohol as fine yellow needles; m. p. 195.5–197°,

Anal. Calcd. for $C_{15}H_9O_7N_4Br$: N, 12.81. Found: N, 12.9.

4-Aminoisoquinoline.—By modification of the conditions used by Bergstrom and Rodda[5] for the ammonolysis of 4-bromoisoquinoline, the yield of product was materially increased. Fifty grams of 4-bromoisoquinoline, 160 cc. of concentrated ammonium hydroxide and 3 g. of hydrated copper sulfate were heated sixteen hours at 165–170° in a shaking autoclave. The reaction mixture, to which dilute sodium hydroxide was first added, was extracted with five 100-cc. portions of benzene. The benzene extracts were dried with anhydrous potassium carbonate, treated with decolorizing charcoal and then concentrated by distillation to about 70 cc. volume. On cooling, clumps of tan microcrystals precipitated. There was obtained 24 g. (70%) of 4-aminoisoquinoline of m. p. 107–107.5°. Recrystallized twice from benzene, the substance melted at 108.5°.[5]

Picrate.—Recrystallized from 70% alcohol as fine yellow needles; m. p. 231–232.5° (dec.).

Anal. Calcd. for $C_{15}H_{11}O_7N_5$: N, 18.76. Found: N, 18.5.

5-Aminoisoquinoline.—5-Nitroisoquinoline[9] (8.7 g.) in 150 cc. of absolute ethanol was hydrogenated over 3 g. of Raney nickel under 3 atm. of hydrogen in three hours. After filtration of the catalyst, the alcohol was evaporated under reduced pressure. The residue was taken up in

(9) Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1470 (1935).

warm chloroform and treated with decolorizing charcoal. The chloroform solution was evaporated to incipient precipitation and poured into ligroin. There was obtained 5.8 g. (80%) of 5-aminoisoquinoline as slightly yellowish crystals of m. p. 128–129° (Claus and Hoffman[5] reported m. p. 128°).

Acetylaminoisoquinolines.—Acetylation of the aminoisoquinolines was carried out in acetic acid solution by warming with a slight excess of acetic anhydride. The crude derivatives were precipitated with ammonium hydroxide in 80–90% yields.

TABLE I

Isoquinoline	M. p., °C.	*Anal.*[a] Found N, %
1-Acetylamino-[b]	148–148.5	15.1
4-Acetylamino-[c]	167–168	15.0
5-Acetylamino-[b]	166	15.0

[a] Calcd. for $C_{11}H_{10}ON_2$: N, 15.05. [b] Recrystallized from water. [c] Recrystallized from benzene plus a small amount of absolute ethanol.

Benzoylaminoisoquinolines.—1- and 4-aminoisoquinolines were benzoylated in pyridine solution with benzoyl chloride, the products being precipitated by the addition of water. 5-Aminoisoquinoline was benzoylated in 10% sodium carbonate solution with benzoyl chloride; on standing the oily product crystallized. The crude yields were 60–90%.

TABLE II

Isoquinoline	M. p., °C.	*Anal.*[a] Found N, %
Dibenzoyl-1-amino-[b,c]	223.5–224.5	8.16
4-Benzoylamino-[d]	188–189	11.3
5-Benzoylamino-[e]	158–159	11.3

[a] Calcd. for $C_{23}H_{16}O_2N_2$: N, 7.95; calcd. for $C_{16}H_{12}ON_2$: N, 11.28. [b] Insoluble in dilute hydrochloric acid, possibly indicating the 1,2-dibenzoyl configuration. [c] Recrystallized from alcohol. [d] Recrystallized from benzene. [e] Recrystallized from dilute alcohol.

N⁴-Acetylsulfanilamidoisoquinolines.—4- and 5-(N⁴-acetylsulfanilamido)-isoquinolines were prepared by adding 4.67 g. (0.02 mole) of finely-powdered acetylsulfanilyl chloride to a solution of 2.88 g. (0.02 mole) of the aminoisoquinoline in 30 cc. of acetone plus 3 cc. of pyridine. After heating to the boiling point the reaction mixture was let stand overnight. In the case of the 5-substituted derivative, 200–300 cc. of water was added to precipitate the product. The crude yields were 80–90%.

Treatment of 1-aminoisoquinoline with acetylsulfanilyl chloride in acetone solution containing a small amount of pyridine, as above, resulted in the formation of a substance of anomalous properties, melting, after recrystallization from alcohol or water, at 262°. This substance was not readily soluble in dilute alkali and it was transformed by warm 20% sodium hydroxide solution into 1-aminoisoquinoline. The compound was not investigated further.

When 1-aminoisoquinoline in pyridine solution was treated with acetylsulfanilyl chloride, the desired 1-(N⁴-acetylsulfanilamido)-isoquinoline was obtained. To a solution of 2.75 g. (0.019 mole) of 1-aminoisoquinoline in 12 cc. of dry pyridine was added 4.45 g. (0.019 mole) of finely-powdered acetylsulfanilyl chloride. The reaction mixture was let stand overnight and then 300 cc. of cold water was added. The crude yield was 4.1 g. or 63%.

TABLE III

Isoquinoline	M. p., °C.	*Anal.*[a] Found N, %
1-(N⁴-Acetylsulfanilamido)-[b,c]	246–247	12.1
4-(N⁴-Acetylsulfanilamido)-[d]	304–306 (dec.)	12.1
5-(N⁴-Acetylsulfanilamido)-[d]	284–288 (dec.)	12.2

[a] Calcd. for $C_{17}H_{15}O_3N_3S$: N, 12.31. [b] Melting points reported for this substance are: 245.3–247° by Crossley, Northey and Hultquist[8a] (private communication from Dr. E. H. Northey): 225° by Ewins and Phillips.[8b] [c] Recrystallized from absolute ethanol. [d] Recrystallized by the addition of water to the pyridine–acetone–alcohol solution of the substance.

Sulfanilamidoisoquinolines.—The crude 4- and 5-(N⁴-acetylsulfanilamido)-isoquinolines were hydrolyzed by refluxing for thirty minutes with six to twelve times their weight of 12% hydrochloric acid. Cooling and neutralization with ammonium hydroxide yielded the corresponding crude sulfanilamido derivatives in 60–80% yields.

Alkaline hydrolysis of crude 1-(N⁴-acetylsulfanilamido)-isoquinoline was effected by refluxing the substance with five to ten times its weight of 10% sodium hydroxide solution for two hours. Neutralization of the solution with acetic acid resulted in the precipitation of the crude 1-sulfanilamido derivative in 80–90% yields.

TABLE IV

Isoquinoline	M. p., °C.	*Anal.*[a] Found, % C	H	N
1-Sulfanilamido-[b,c]	264–267 (dec.)	60.4	4.24	14.2
4-Sulfanilamido-[d]	211.5–212.5	60.1	4.76	14.3
5-Sulfanilamido-[e]	223–224.5 (dec.)	60.2	4.32	14.1

[a] Calcd. for $C_{15}H_{13}O_2N_3S$: C, 60.18; H, 4.38; N, 14.04. [b] The melting points reported for this substance are: 268–270° (dec.) by Crossley, Northey and Hultquist[8a] (private communication from Dr. E. H. Northey); 263° by Ewins and Phillips.[8b] [c] Recrystallized by adding an equal volume of hot water to a hot acetone solution of the substance. [d] Recrystallized from 50% alcohol plus a small amount of acetic acid. [e] Recrystallized from 50% alcohol.

Summary

1. Modified procedures for the preparation of 4-bromo-, 4-amino- and 5-aminoisoquinolines have been described.

2. Acetyl, benzoyl, acetylsulfanilyl and sulfanilyl derivatives of 1-, 4- and 5-aminoisoquinolines have been prepared.

3. Preliminary pharmacological tests on the sulfanilyl derivatives have been reported.

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