evidenced by a brisk evolution of bubbles and a rise in temperature to 50°; the reaction was complete in 20 minutes, leaving a gummy red tar suspended in the benzene. The benzene was evaporated in a stream of air, and the residue treated in the cold with 100 ml. of cold 10% sodium hydroxide solution, which liberated a dark oil and some red solid. The basic solution was extracted with five 75-ml. portions of ether, the ether extract dried overnight over potassium carbonate, and the ether evaporated. Distillation of the residue gave 1.4 g. (49%) of iridescent pale yellow 3-fluoroisoquinoline; the material gave a strong positive test for fluorine and a negative test for hydroxyl groups.

4-Fluoroisoquinoline.—A beaker containing 50 ml. of 42% fluoroboric acid and 15 g. of 4-aminoisoquinoline was cooled in a Dry Ice–ether-bath until the solution was almost solid; 7 g. of powdered sodium nitrite was added with stirring in small portions during the course of an hour, during which time the original reddish color of the suspension changed to a light yellow. A filter stick was inserted into the slurry and as much liquid as possible was removed; ether was added and the filter stick filtration repeated. The addition and removal of ether was repeated several times to remove as much water as possible. The ether in its turn was drawn off and replaced with 100 ml. of dry xylene and the beaker removed from the cooling bath and allowed to come to room temperature. As no decomposition was noted, gentle heat was applied; when the temperature of the solution reached 25° decomposition of the diazonium fluoborate commenced, as evidenced by gas evolution and a sudden rise in temperature. The source of heat was withdrawn, and the decomposition allowed to runs its course; the temperature of the solution reached 75° after about 2 hours of slow decomposition. The xylene was decanted from the lower red layer, the decanted xylene solution extracted with dilute hydrochloric acid, and the acid extract added to the red layer. The resulting mixture was diluted with water and steam distilled to remove any xylene, cooled, neutralized with sodium carbonate and extracted with ether. After drying over sodium carbonate and removing the ether the residue was distilled to give 5.5 g. (36%) of 4-fluoroisoquinoline. The compound gave a strong positive test for fluorine and a negative test for hydroxyl groups.

5-Fluoroisoquinoline.—The fluoborate of 5-aminoisoquinoline was prepared by dissolving 15 g. of the amine in 200 ml. of 42% fluoboric acid; on cooling to 0° the salt precipitated. The addition of 200 ml. of cold 95% ethanol redissolved the precipitate. A saturated aqueous solution of 8 g. of sodium nitrite was added slowly with stirring; a heavy precipitate of 5-isoquinolinediazonium fluoborate formed. When diazotization was complete, 100 ml. of ether was added, the precipitate filtered, washed with cold ethanol–ether and dried; 42 g. of salt was obtained; m.p. 190° (dec.). The dried diazonium fluoborate was thermally decomposed in the usual manner[4]; the decomposition was mild and heat was occasionally necessary to keep the reaction going. Water was added when the decomposition was complete, the solution made alkaline with 30% sodium hydroxide solution, the mixture steam distilled and the distillate extracted with ether. After drying overnight with sodium carbonate the ether was removed and the 5-fluoroisoquinoline distilled; 10.3 g. (67%) was obtained. The compound gave a strong qualitative fluorine test and a negative test for hydroxyl groups.

Hydroxyisoquinolines.—Isocarbostyril,[11] 4-hydroxyisoquinoline[12] and 5-hydroxyisoquinoline[13] were isolated from the residue after distillation of the corresponding fluorine compounds, and were in each case identified by melting point. In the case of 3-fluoroisoquinoline, traces of a solid thought to be the unknown 3-hydroxyisoquinoline were isolated, but the amount was too small for positive identification; the solid gave a strong positive ferric chloride test.

Attempted Preparation of 6-Fluoroisoquinoline.—*p*-Fluorobenzalaminoacetal (formed by the condensation of *p*-fluorobenzaldehyde and aminoacetal) was treated with sulfuric acid in an attempt to prepare 6-fluoroisoquinoline by the method used for 6-bromoisoquinoline[7]; no 6-fluoroisoquinoline was isolated.

Summary

The preparation and properties of 1-, 3-, 4- and 5-fluoroisoquinoline and the attempted preparation of 6-fluoroisoquinoline are reported.

(11) Bain, Perkin and Robinson, *J. Chem. Soc.*, **105**, 2397 (1914).
(12) Gilman and Gainer, THIS JOURNAL, **69**, 1946 (1947).
(13) Woodward and Doering, *ibid.*, **67**, 860 (1945).

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of 3-Aminoisoquinoline and Related Compounds[1]

BY CLAUDE E. TEAGUE, JR.[2], AND ARTHUR ROE

3-Aminoisoquinoline has been prepared in about 30% yield from 3-methylisoquinoline; new intermediates characterized in the synthesis are isoquinoline-3-carboxaldehyde, isoquinoline-3-percarboxylic acid, isoquinoline-3-carboxylic acid and isoquinoline-3-carboxamide.

An investigation of the methods of preparation and properties of heterocyclic fluorine compounds is under way in this Laboratory.[3,4] Some of the unknown 3-aminoisoquinoline was desired for the preparation of 3-fluoroisoquinoline[4] by the Schiemann reaction[5]; a method of synthesis of it and several other 3-isoquinoline derivatives is reported in this paper.

3-Methylisoquinoline, the only readily available isoquinoline with a substituent in the 3-position, was converted to 3-aminoisoquinoline as shown in the accompanying equations, where R represents the 3-isoquinolyl radical. 3-Methylisoquinoline (I) was

$$\underset{\text{I}}{\text{R—CH}_3} \xrightarrow[48\%]{SeO_2} \underset{\text{II}}{\text{RCHO}} \xrightarrow[98\%]{H_2O_2} \underset{\text{III}}{\text{RCO}_3\text{H}} \xrightarrow[\text{Boil}\ 98\%]{H_2O} \underset{\text{IV}}{\text{RCOOH}} \xrightarrow[2.\ CH_3OH,\ NH_3\ 97\%]{1.\ CH_2N_2} \underset{\text{V}}{\text{RCONH}_2} \xrightarrow[64\%]{NaOBr} \underset{\text{VI}}{\text{RNH}_2}$$

oxidized by means of selenium dioxide to isoquinoline-3-carboxaldehyde (II) in 48% yield. An acetone solution of the aldehyde was treated with 30% hydrogen peroxide forming a 96% yield of isoquinoline-3-percarboxylic acid (III); the structure of this compound was indicated by its acidic reaction, analysis, reaction with starch iodide paper, and easy quantitative conversion in boiling water to

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(2) American Viscose Corporation, Marcus Hook, Pa. The work reported in this paper was taken from the Ph.D. thesis of Claude E. Teague, Jr., June, 1950.

(3) A. Roe and G. F. Hawkins, THIS JOURNAL, **71**, 1785 (1949); **69**, 2443 (1947).

(4) A. Roe and C. E. Teague, Jr., *ibid.*, **73**, 687 (1951).

(5) A. Roe, in R. Adams, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, Chap. 4.

isoquinoline-3-carboxylic acid (IV). The acid was converted to the methyl ester using diazomethane; the liquid ester was not isolated but converted to the amide (V) in 97% yield (crude from the acid) using methanolic ammonia at −33°. The amide was transformed into 3-aminoisoquinoline (VI) in 64% yield with sodium hypobromite.

Several other reactions were tried before the successful approach reported above was found. First, an attempt was made to oxidize 3-methylisoquinoline to isoquinoline-3-carboxylic acid with nitric acid, chromic acid, and with potassium permanganate, alkaline and acid; no isoquinoline-3-carboxylic acid was obtained in any case, the isoquinoline nucleus apparently being destroyed by these oxidizing agents under the variety of conditions used. Oxidation of 3-methyl-5-nitroisoquinoline[6] likewise gave no heterocyclic acid.

In an attempt to form 3-tribromomethylisoquinoline it was rather surprisingly found that ring substitution occurs along with side chain substitution. An apparently pure compound containing three bromine atoms and melting at 230° (dec.) was isolated, but hydrolysis of it gave a compound tentatively characterized as *x*-bromoisoquinoline-3-carboxylic acid (melting at 210°) instead of the expected isoquinoline-3-carboxylic acid. Further work on the bromination of 3-methylisoquinoline and its derivatives is under way and will be reported later.

Experimental

Isoquinoline-3-carboxaldehyde.—3-Methylisoquinoline (64.5 g., 0.45 mole) was placed in a 500-ml. three-neck flask fitted with a heating mantle, mechanical stirrer, and thermometer. The 3-methylisoquinoline was heated to 180°; 50 g. of purified selenium dioxide was added in small portions with stirring, during the course of an hour, the rate of addition being adjusted to keep the temperature below 220°. When all the selenium dioxide had been added the mixture was kept at 220° for 10 minutes, then cooled; a button of selenium formed in the bottom of the flask. The oily reaction mixture was extracted with three 200-ml. portions of boiling ether, the ether extract dried over anhydrous sodium sulfate, and the solvent evaporated. The residual oily liquid was distilled at reduced pressure through a 10" Vigreux column; 7 g. of 3-methylisoquinoline was obtained first, then 30.2 g. of isoquinoline-3-carboxaldehyde, b.p. 151° (10 mm.); m.p. 47°. This represents a yield of 48%, taking the unchanged starting material into account. *Anal.* Calcd. for $C_{10}H_7NO$: N, 8.91. Found: N, 8.92.

(6) F. W. Bergstrom and R. E. Patterson, *J. Org. Chem.*, **10**, 479 (1945).

Isoquinoline-3-percarboxylic Acid.—An acetone solution containing 12 g. of isoquinoline-3-carboxaldehyde and 10 ml. of 30% hydrogen peroxide was prepared and allowed to stand; the temperature rose to 36°, remained there several hours, then slowly fell to room temperature. An additional 15 ml. of 30% hydrogen peroxide was then added, and the solution allowed to stand overnight. A copious white precipitate formed in the beaker; the solution was evaporated to near dryness in a stream of nitrogen, and the solid filtered and dried in the air; yield 14 g. (96%) of the per-acid, m.p. 134° (dec.). The acid liberated iodine from starch–iodide paper, and showed a *p*H of about 5 using *p*H paper. *Anal.* Calcd. for $C_{10}H_7O_3N$: N, 7.41. Found: N, 7.42.

Isoquinoline-3-carboxylic Acid.—A solution of isoquinoline-3-percarboxylic acid (14 g.) was boiled in water for an hour; on evaporation of the solution to half its volume and cooling, long white needles of the acid formed. The precipitate was dried at 100°; 12.5 g. (98%) of isoquinoline-3-carboxylic acid was obtained; m.p. 134° (dec.). The acid may also be isolated using the copper salt. *Anal.* Calcd. for $C_{10}H_7NO_2$: N, 8.08. Found: N, 8.11.

Isoquinoline-3-carboxamide.—Thirty grams of isoquinoline-3-carboxylic acid was treated with 100 ml. of methanol; most of the solid dissolved. An ether solution of diazomethane[7] was added until no further effervescence on mixing was noted. The solution containing the ester was evaporated on the steam-bath leaving the oily ester. Without further purification the ester was dissolved in 200 ml. of absolute methanol in a Dewar flask, an equal volume of liquid ammonia was added, and the flask closed with a stopper fitted with a drying tube. The solution was allowed to stand 4 days, replenishing the ammonia as it evaporated; it was then poured into a large evaporating dish and evaporated to dryness, yielding 29 g. (97%) of the crude amide melting at 206–207°. Recrystallization from dilute methanol raised the melting point of the isoquinoline-3-carboxamide to 213°. *Anal.* Calcd. for $C_{10}H_8N_2O$: N, 16.3. Found: N, 16.3.

3-Aminoisoquinoline.—A solution of 85 g. of potassium hydroxide in 600 ml. of water was cooled to 0°, and 15 g. of bromine was added slowly with stirring. The solution was kept between 0 and 10° while 18 g. of isoquinoline-3-carboxamide was added slowly with stirring over a period of half an hour; the mixture was then heated to 80° for 1 hour, then boiled 2 minutes. After dissolving 100 g. of potassium hydroxide in the solution, it was allowed to stand overnight at room temperature. On chilling to 0° a yellow precipitate settled out; recrystallization from benzene gave 8.3 g. (64%) of pure yellow 3-aminoisoquinoline, m.p. 178°.

Anal. Calcd. for $C_9H_8N_2$: N, 19.4. Found: N, 19.4.

A picrate was prepared in the usual manner; recrystallization from 95% ethanol gave a bright yellow picrate, m.p. 261° (dec.). *Anal.* Calcd. for $C_{15}H_{11}N_5O_7$: N, 18.8. Found: N, 18.9.

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(7) F. Arndt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.