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

The Preparation of Heterocyclic Fluorine Compounds by the Schiemann Reaction. III. Some Monofluoroisoquinolines[1]

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

The preparation of some fluoroisoquinolines was undertaken as part of a continuing study of the preparation and properties of heterocyclic fluorine compounds.[3] The synthesis of 1-, 3-, 4- and 5-fluoroisoquinoline and the attempted synthesis of 6-fluoroisoquinoline is reported in this paper.

The diazonium fluoborates, intermediates in the Schiemann reaction,[4] are usually stable enough to be isolated, and are thermally decomposed to give the corresponding fluorine compounds. Many of the heterocyclic diazonium fluoborates, however, are not stable enough to be isolated, although they do decompose to form heterocyclic fluorine compounds; thus all three of the pyridinediazonium fluoroborates and 2- and 4-quinolinediazonium fluoborate decompose at room temperature or below. In contrast, the stability of 3-quinolinediazonium fluoborate (m.p. 95°) is noteworthy; it resembles in this respect the 5-, 6-, 7- and 8-quinolinediazonium fluoborates, all of which are relatively stable.

A comparison of the behavior of the isoquinolinediazonium fluoborates with the pyridine and quinoline derivatives brings out several interesting points. It is worth noting that the isolation of the isoquinoline derivatives was achieved only after considerable modification of the usual Schiemann techniques; details are given in the experimental section. Of the four isoquinolinediazonium fluoborates, only the 1- and 5-isomers were stable; the 3- and 4-isomers decomposed at room temperature. The stability of 1-isoquinolinediazonium fluoborate was somewhat unexpected in view of the marked instability of the roughly analogous 2-quinolinediazonium fluoborate. The instability of 4-isoquinolinediazonium fluoborate was also unexpected in view of the stability of 3-quinolinediazonium fluoborate (with which it is roughly comparable with respect to the hetero-N atom), and the stability of α-naphthalenediazonium fluoborate.[4]

Neither 1- nor 3-fluoroisoquinoline forms a hydrochloride in dilute acid; the other isomers do. Ultraviolet absorption studies[5] show that 1-fluoroisoquinoline is readily hydrolyzed in dilute acid, while the other isomers are not. In the quinoline series, 2-fluoroquinoline alone did not form a hydrochloride, and it was the only isomer hydrolyzed in dilute acid.[3,6]

The fluoroisoquinolines are all high-boiling stable compounds, whose properties and analyses are shown in Table I.

The hydroxyisoquinolines, expected by-products in the Schiemann reaction, were isolated in every case from the reaction mixtures.

Attempted preparation of 6-fluoroisoquinoline by cyclization of *p*-fluorobenzalaminoacetal failed, although the preparation of 6-bromoisoquinoline by this method has been reported.[7]

The preparation of other heterocyclic fluorine compounds in this Laboratory is continuing.

TABLE I

FLUOROISOQUINOLINES

Compound	Overall % yield	B. p., °C.	$n^{30}D$	Nitrogen, % Calcd.	Nitrogen, % Found	RN_2BF_4 M. p., °C.
1-Fluoro-	13	208 (micro)	1.5861	9.52	9.56	68
3-Fluoro-	49	251 (micro)	1.5875	9.52	9.51	15–25
4-Fluoro-	36	236 (micro)	1.5914	9.52	9.64	20–25
5-Fluoro-	67	145 (62 mm.) m. p. 43°	solid	9.52	9.56	190

Experimental

Starting Materials.—1-Aminoisoquinoline was prepared essentially as reported by Bergstrom.[8] 3-Aminoisoquinoline was prepared as described elsewhere.[9] 4-Aminoisoquinoline was prepared by the method of Craig and Cass,[10] as was 5-aminoisoquinoline, except that a palladium catalyst instead of Raney nickel was used to reduce 5-nitroisoquinoline.

1-Fluoroisoquinoline.—Fifteen grams of 1-aminoisoquinoline was dissolved in 120 ml. of 42% fluoboric acid by warming; on cooling to −5° the amine fluoborate precipitated. The salt was filtered, dried in air, and suspended in 150 ml. of freshly distilled 30–40° petroleum ether. At room temperature, with stirring, 7.2 g. of finely powdered sodium nitrite was added in small portions over the course of an hour; to ensure complete diazotization ethyl nitrite was bubbled into the solution for 30 minutes. The suspension was allowed to stand with occasional stirring for 2 hours, after which the tan solid was filtered and dried; the impure isoquinoline-1-diazonium fluoborate weighed 36 g. and decomposed at 68°.

Eighteen grams of 1-isoquinolinediazonium fluoborate was placed in a 300-ml. flask fitted with a 36″ reflux condenser. Heat was applied cautiously, and a typical mild thermal decomposition of the salt ensued, with liberation of nitrogen and boron trifluoride; heat had to be applied intermittently to keep the reaction going. A second 18-g. batch was decomposed in exactly the same manner. The residues were treated with water, neutralized with sodium carbonate, then made distinctly basic by the addition of 10 g. of sodium hydroxide; the combined solutions were then extracted continuously with ether for an extended period. The ether extract was dried over anhydrous sodium carbonate and the ether evaporated, leaving a viscous red oil which was distilled to give a 13% over-all yield of 1-fluoroisoquinoline. The compound gave a strong positive qualitative test for fluorine and a negative test for hydroxyl groups.

3-Fluoroisoquinoline.—The fluoborate of 3-aminoisoquinoline was prepared by dissolving 2.8 g. of the amine in 8 ml. of 42% fluoboric acid; on cooling the salt precipitated and was filtered and dried. The dried salt was suspended in 25 ml. of dry benzene and 1.4 g. of dry powdered sodium nitrite was added with stirring at room temperature. The addition of the nitrite took 15 minutes; at the end of that time decomposition of the diazonium fluoborate set in, as

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(2) American Viscose Corporation, Marcus Hook, Pa. The work here reported is taken from the Ph.D. Thesis of Dr. Teague.

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

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

(5) Soon to be published.

(6) Miller, Knight and Roe, THIS JOURNAL, **72**, 4765 (1950).

(7) Tyson and Boyd, *ibid.*, **61**, 183 (1945).

(8) Bergstrom, *Ann.*, **515**, 34 (1934).

(9) Teague and Roe, THIS JOURNAL, **73**, 688 (1950).

(10) Craig and Cass, *ibid.*, **64**, 783 (1942).

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

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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.