[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

SYNTHESIS OF MEDICINALS DERIVED FROM 5-FLUORO-8-HYDROXYQUINOLINE

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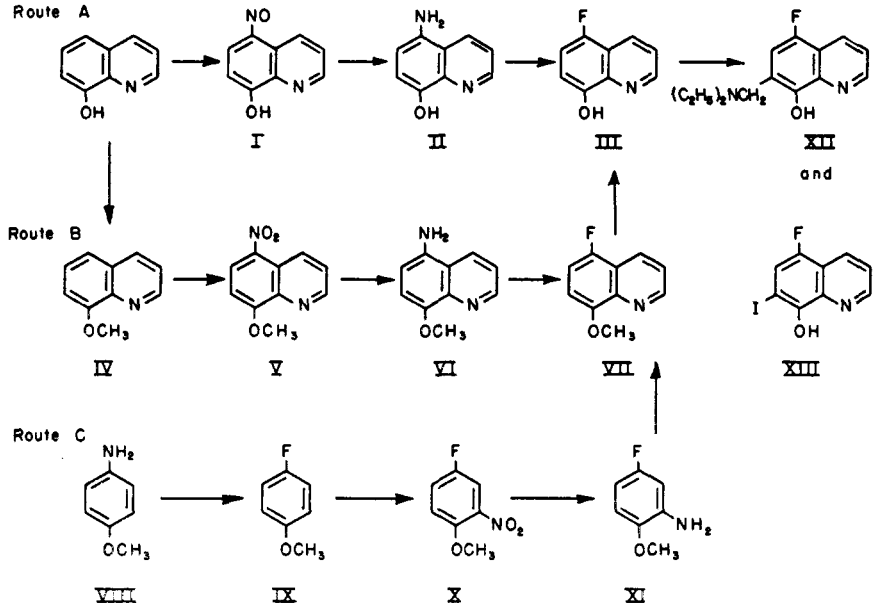
In continuation of our studies on the pharmacological activity of fluorine-substituted medicinals, we have synthesized two derivatives of 5-fluoro-8-hydroxyquinoline of pharmaceutical interest, 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline (XII), and 5-fluoro-7-iodo-8-hydroxyquinoline (XIII). The former is an isostere of 5-amino-7-diethylaminomethyl-8-hydroxyquinoline, which possesses an interesting type of antimalarial activity (1), and the latter of vioform, 5-chloro-7-iodo-8-hydroxyquinoline. The positions of the diethylaminomethyl and iodo groups were not established by absolute methods, but from a consideration of similar reactions (2, 3, 4) it is reasonably certain that the assigned structures are correct.

Three projected synthetic routes leading to 5-fluoro-8-hydroxyquinoline (III) were carefully explored. In the first of these (Route A), 5-amino-8-hydroxyquinoline (II), prepared by the reduction of 5-nitroso-8-hydroxyquinoline (I), was converted to III *via* the Schiemann reaction. In the second proposed sequence (Route B), the attempted reduction of 5-nitro-8-methoxyquinoline (V) was unsuccessful.



In the third method (Route C) the fluorine atom was introduced into the benzene nucleus, which was later converted into a quinoline ring. *p*-Fluoroanisole

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(IX), obtained from *p*-anisidine (VIII) by means of the Schiemann reaction, was nitrated with ethyl nitrate, and the resulting 2-nitro-4-fluoroanisole (X) was reduced catalytically to 2-amino-4-fluoroanisole (XI). This was converted to 5-fluoro-8-methoxyquinoline (VII) which, upon ether cleavage with hydriodic acid, gave III. 5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline (XII) was prepared from III by means of the Mannich reaction, and 5-fluoro-7-iodo-8-hydroxyquinoline (XIII) by direct iodination.

EXPERIMENTAL[2]

Intermediates. 5-Nitroso-8-hydroxyquinoline (I) was prepared in 78% yield by the nitrosation of 8-hydroxyquinoline according to the method of Kostanecki (5). *5-Amino-8-hydroxyquinoline* (II) was obtained in 41% yield by reduction of II with tin and hydrochloric acid and quantitatively by catalytic hydrogenation with platinum oxide as the catalyst. *8-Methoxyquinoline* (IV) was prepared by methylation of 8-hydroxyquinoline in yields of 10–18%, much lower than those reported by Kaufman and Rothlin (6). Nitration of IV by the method of Balaban (7) gave 5-nitro-8-methoxyquinoline (V) in 56% yield, but attempted reduction of V to 5-amino-8-methoxyquinoline (VI), both catalytically and with iron and hydrochloric acid, produced only a tarry material from which no pure product could be isolated.

p-Fluoroanisole (IX) was obtained from *p*-anisidine (VIII) in 69% yield through the Schiemann reaction (8). Nitration of IX with nitric acid according to the method of Swarts (9) gave 2-nitro-4-fluoroanisole (X) in 38% (71% based on unrecovered starting material) yield; with ethyl nitrate as the nitrating agent, the yield was increased to 56%.

5-Fluoro-8-hydroxyquinoline (III). *From 5-amino-8-hydroxyquinoline* (II). The fluorinated compound was prepared by the general method of Roe and Hawkins (10) for introducing fluorine into heterocyclic nuclei. To a solution of 67 ml. (0.47 mole) of 45% fluoboric acid diluted with 20 ml. of water, 20 g. (0.086 mole) of the hydrochloride of II was added. The solution was cooled to 60° and diazotized by the addition of a solution of 6.0 g. (0.086 mole) of sodium nitrite in 20 ml. of water. The precipitate was allowed to stand for 90 minutes and was then removed and washed, first with 30 ml. of a cold 1:1 mixture of ethanol and ether and then three times with 30 ml. of cold ether. The dried 8-hydroxyquinolyl-5-diazonium fluoborate hydrofluoborate weighed 16 g. (55%). A 10.5 g. (0.030 mole) portion of the dry salt was sprinkled into a beaker heated in a bath at 130°. The tarry residue which remained after the decomposition was dissolved in hot water, filtered hot, and the filtrate neutralized with sodium acetate. The resulting precipitate was removed, dried, and sublimed at 105°/5 mm. to give 1.3 g. (26% based on fluoroborate) of colorless, crystalline 5-fluoro-8-hydroxyquinoline (III), m.p. 110.0–110.5°.

Anal. Calc'd for C_9H_6FNO: C, 66.3; H, 3.7; N, 8.6.
Found: C, 66.5; H, 3.8; N, 8.5.

From 5-fluoro-8-methoxyquinoline (VII). A mixture of 10.8 g. (0.058 mole) of VII was refluxed with 150 g. (0.58 mole) of 50% hydriodic acid for 24 hours. The cooled solution was diluted with 150 ml. of water and neutralized with sodium bicarbonate, and the resulting precipitate removed, washed with cold water, dried, and finally sublimed at 105°/5 mm. The sublimed product was purified by extraction, first of an acid solution, then of a strongly basic solution, with ether. The aqueous layer was then re-acidified, neutralized with sodium bicarbonate, and the precipitate dried and sublimed to yield 6.9 g. (70%) of III, m.p. 109.8–110.4°.

2-Amino-4-fluoroanisole (XI). This compound was prepared by reduction of X both chemically and catalytically. In the chemical reduction, a mixture of 12 g. (0.07 mole) of X, 60 ml. (0.72 mole) of concentrated hydrochloric acid, and 50 g. (0.27 mole) of stannous chloride was heated on a steam-bath. After the reaction mixture became homogeneous (about 20

[2] Melting points are corrected, boiling points uncorrected.

minutes), it was cooled in ice. The gray precipitate which formed was removed, dissolved in water, and neutralized with 10% sodium carbonate solution under a layer of ether. The mixture was shaken thoroughly, and the ether layer separated and dried over sodium sulfate. The ether was removed and the residue distilled to yield 5.5 g. (56%) of XI, b.p. 105–106°/8 mm.

Catalytic reduction of X in a Parr hydrogenator in the presence of Raney nickel and a trace of platinum chloride gave XI in 86% yield; with platinum oxide, the yield was 88%.

Anal. Calc'd for C_7H_8FNO: C, 59.5; H, 5.7.

Found: C, 59.5; H, 5.7.

The *hydrochloride* was prepared by passing dry hydrogen chloride into a solution of the free base in anhydrous ether.

Anal. Calc'd for C_7H_8ClFNO: C, 47.3; H, 5.1; N, 7.9.

Found: C, 47.5; H, 5.2; N, 7.7.

5-Fluoro-8-methoxyquinoline (VII). This compound was prepared from XI by three variations of Cohn's (11) modification of the Skraup reaction. In the first of these, a solution prepared by dissolving 36.0 g. (0.59 mole) of boric acid in 196 g. (1.75 mole) of hot glycerol was added at room temperature to a mixture of 82 g. (0.58 mole) of XI, 20 g. of ferrous sulfate, and 43 g. (0.35 mole) of nitrobenzene. Concentrated sulfuric acid (100 ml.) was added slowly with cooling, and the mixture was refluxed for 24 hours at a bath temperature of 150°. The cooled mixture was made basic by the cautious addition of 450 g. of a 50% solution of sodium hydroxide, and then extracted several times with ether. The combined ether extracts were filtered through activated charcoal, dried over sodium sulfate, and the ether removed. The residue was distilled, the fraction boiling at 140–150°/9 mm. being retained. In order to remove any starting material which may have been present, the distillate was shaken thoroughly with 30 ml. of a 20% solution of sodium hydroxide and 20 g. of benzoyl chloride; the mixture was then cooled, made acid with hydrochloric acid, and extracted with ether, the ether extract being discarded. The aqueous layer was made basic with sodium hydroxide solution and extracted with ether. The ether extract was dried, the ether removed, and the residue distilled to yield 38 g. (37%) of VII, b.p. 145–147°/9 mm., m.p. 34.0–36.5°.

The second procedure was similar to that just described, except that 2-nitro-4-fluoroanisole was substituted for the nitrobenzene. At the conclusion of the reaction period, the cooled mixture was made almost neutral with 50% sodium hydroxide solution, and then basic with sodium bicarbonate. The basic mixture was then extracted continuously with benzene for 36 hours. The yield of VII by this method was only 9.0%.

The third procedure, which was identical with the second except that nitroethane was substituted for the 2-nitro-4-fluoroanisole, gave VII in 29% yield.

Anal. Calc'd for $C_{10}H_8FNO$: C, 67.8; H, 4.6; N, 7.9.

Found: C, 67.5, 67.4; H, 4.6, 4.7; N, 7.8.

5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline (XII). To a solution of 1.2 g. (0.013 mole) of paraformaldehyde and 3.1 g. (0.042 mole) of diethylamine in 25 ml. of ethanol there was added dropwise a solution of 5.5 g. (0.034 mole) of III in 100 ml. of 1:1 ether-ethanol. After the mixture had stood for 30 minutes, the solvent was removed under reduced pressure. There remained a dark amber oil which solidified partially upon cooling. The solid was removed and washed with cold ether. The combined filtrate and washings were evaporated to dryness, the remaining oil dissolved in dilute hydrochloric acid, and the solution extracted with ether. The aqueous layer was neutralized with sodium acetate. A colorless precipitate which consisted of 0.5 g. of recovered III was removed. Addition of sodium hydroxide to the filtrate threw down a yellow precipitate which was added to the dark amber oil previously isolated. This combined product was sublimed under reduced pressure, twice recrystallized from ligroin, and sublimed again to give 3.5 g. (42%) of pure XII, m.p. 80.0–80.6°.

Anal. Calc'd for $C_{14}H_{17}FN_2O$: C, 67.7; H, 6.8; N, 11.3.

Found: C, 67.7; H, 6.8; N, 11.1.

5-Fluoro-7-iodo-8-hydroxyquinoline (XIII). To 32 g. (0.13 mole) of iodine dissolved in

200 ml. of a 5% solution of sodium hydroxide, there was added 17 g. (0.092 mole) of the sodium salt of III. The mixture was diluted to 500 ml., heated on a steam-bath for 5 hours, and finally allowed to stand for 12 hours at room temperature. It was then filtered and the filtrate acidified with dilute hydrochloric acid and extracted with ether. The ether layer was washed with 4 100-ml. portions of 6 *M* hydrochloric acid, which were combined with the previous aqueous layer. The acid solution was made just neutral with ammonium hydroxide. The light yellow precipitate which formed was removed, dried, sublimed under reduced pressure, and recrystallized from ligroin to give 12 g. (46%) of XIII, pale yellow needles, m.p. 147.7–148.5°.

Anal. Calc'd for C_9H_5FINO: C, 37.4; H, 1.7; I, 43.9; N, 4.8.
Found: C, 37.4; H, 1.9; I, 43.7; N, 4.9.

Pharmacological data.[3] *In vitro* tests of 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline as an antimalarial showed it to be only 0.075 times as active as quinine. As an amebicidal agent, it was as effective in dilutions of 1:150,000 as emetine is in dilutions of 1:1,000,000. 5-Fluoro-7-iodo-8-hydroxyquinoline was not amebicidal in dilutions of 1:50,000 and was essentially inactive as an antimalarial.

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SUMMARY

1. Three synthetic routes leading to 5-fluoro-8-hydroxyquinoline have been explored.

2. Synthesis and pharmacological activity of 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline and 5-fluoro-7-iodo-8-hydroxyquinoline are reported.

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