Notes

Synthetic Schistosomicides. VII. 5-Azo-6-Alkoxy-8-(Aminoalkylamino)quinolines[1]

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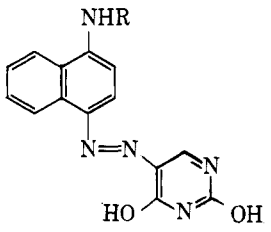
5-(4-Amino-1-naphthylazo)uracil (Ia) is highly active against experimental *Schistosoma mansoni* infections in the mouse, hamster, and monkey.[2] In contrast, 5-(8-amino-5-quinolylazo)uracil and related 8-amino-6-methoxy-5-heterocyclicazo compounds are devoid of antischistosome activity.[2] Since the antischistosome

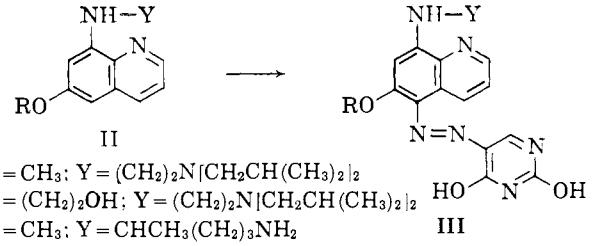


Ia, R = H
b, R = $(CH_2)_2N(C_2H_5)_2$

activity of Ia and related compounds is markedly enhanced by the introduction of a basic side chain as in Ib,[3,4] and since 8-(2-diisobutylaminoethylamino)-6-methoxyquinoline[5] (IIa) and 2-[8-(2-diisobutylamino-ethylamino)-6-quinolyloxy]ethanol (IIb)[6] exhibit good antischistosome activity *per se*,[6,7] we have prepared representative 5-azo-6-alkoxy-8-(aminoalkylamino)quinolines for test against schistosomiasis.

5-[8-(2-Diisobutylaminoethylamino)-6-methoxy-5-quinolylazo]uracil (IIIa), 5-[8-(2-diisobutylamino-ethylamino)-6-(2-hydroxyethoxy)-5-quinolylazo]uracil (IIIb), and 5-[8-(4-amino-1-methylbutylamino)-6-methoxy-5-quinolylazo]uracil (IIIc) were synthesized by allowing diazotized 5-aminouracil to couple with IIa, IIb, and primaquine, respectively, in aqueous ethanol.[3,4,8] 5-[4-(2-Diethylaminoethylamino)-1-naphthylazo]-8-(2-diisobutylaminoethylamino)-6-methoxyquinoline (V), which incorporates the active moieties of both Ib and II, was prepared by coupling diazotized N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide hydrochloride[3,4] with IIa, followed by alkaline hydrolysis of the intermediate trifluoroacetamide (IV).

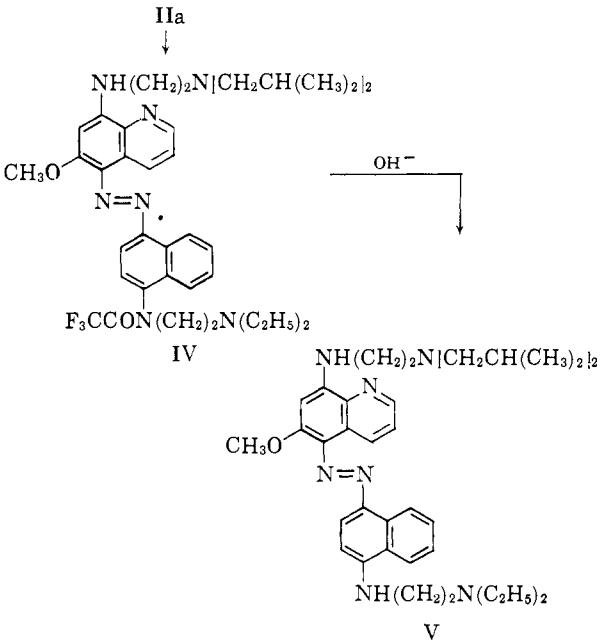
The 5-azo-6-alkoxy-8-(aminoalkylamino)quinolines



II

a, R = CH_3; Y = $(CH_2)_2N[CH_2CH(CH_3)_2]_2$
b, R = $(CH_2)_2OH$; Y = $(CH_2)_2N[CH_2CH(CH_3)_2]_2$
c, R = CH_3; Y = $CHCH_3(CH_2)_3NH_2$

III



IV

V

(IIIa–c and V) were tested against a Puerto Rican strain of *Schistosoma mansoni* in mice by Thompson and coworkers.[9] When administered in the diet to infected mice in doses ranging from 139 to 240 mg./kg./day for 14 days, compounds IIIa, IIb, and V effected a moderate reduction in live worms, but none was as promising as 5-[4-(2-diethylaminoethylamino)-1-naphthylazo]-uracil (Ib).

Experimental[10]

5-[8-(2-Diisobutylaminoethylamino)-6-methoxy-5-quinolylazo]uracil (IIIa).—A solution of 6.4 g. (0.05 mole) of 5-aminouracil in 100 ml. of 50% aqueous ethanol and 10 ml. of concentrated hydrochloric acid was cooled to −5° and diazotized by the addition of a cold solution of 3.5 g. (0.05 mole) of sodium nitrite in 20 ml. of water. The temperature was maintained below 5° during the addition. The diazonium salt mixture was stirred for 15 min. at 0°, then added over a period of 15 min. to a cold solution of 21.0 g. (0.05 mole) of 8-(2-diisobutylaminoethylamino)-6-methoxyquinoline dihydrochloride monohydrate in 200 ml. of water and 3 ml. of concentrated hydrochloric acid. The mixture was stirred for 1 hr. at 0–5°, then at room temperature for 24 hr. A mixture of 150 g. of sodium acetate and 300 ml. of water was added and the crude dye was collected by filtration, washed successively with water and ether, and dried *in vacuo* at 45° for 48 hr. Crystallization of the crude product from a dimethylacetamide–water mixture gave 15 g. (62%) of red crystals with a golden luster, m.p. 209–211°.

Anal. Calcd. for $C_{24}H_{33}N_7O_3 \cdot H_2O$: C, 59.36; H, 7.27; N, 20.19; H_2O, 3.71. Found: C, 59.79; H, 7.56; N, 20.17; H_2O (Karl Fischer), 3.50.

(1) Previous paper: E. F. Elslager, D. B. Capps, and L. M. Werbel, *J. Med. Chem.*, **7**, 658 (1964).

(2) E. F. Elslager and D. F. Worth, *ibid.*, **6**, 444 (1963).

(3) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *ibid.*, **6**, 217 (1963).

(4) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(5) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. T. Edwards, Ann Arbor, Mich., 1946, p. 1195.

(6) M. S. Morgan, U. S. Patent 2,852,518 (Sept. 16, 1958).

(7) R. N. Bieter, E. M. Cranston, W. Chadbourn, A. C. Cuckler, D. DeGuisti, W. W. Becklund, and H. N. Wright, *Federation Proc.*, **8**, 275 (1949).

(8) K. N. Campbell, J. F. Kerwin, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, **68**, 1559 (1946).

(9) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).

(10) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

5-[8-(2-Diisobutylaminoethylamino)-6-(2-hydroxyethoxy)-5-quinolylazo]uracil Dihydrochloride (IIIb).—5-Aminouracil (4.1 g., 0.0324 mole) was diazotized and coupled with 14.3 g. (0.0324 mole) of 2-[8-(2-diisobutylaminoethylamino)-6-quinolyloxy]-ethanol dihydrochloride hemihydrate[6] according to the procedure described for IIIa. The crude hydrochloride salt was filtered from the reaction mixture and was crystallized from 0.5 *N* hydrochloric acid. The dark blue needles thus obtained weighed 6.7 g. (33%), m.p. 258–260°.

Anal. Calcd. for $C_{25}H_{38}N_7O_4 \cdot 2HCl \cdot 3.33H_2O$: C, 47.62; H, 6.98; Cl, 11.25; N, 15.55; H_2O, 9.51. Found: C, 47.72; H, 7.08; Cl, 11.80; N, 15.53; H_2O, 9.58.

5-[8-(4-Amino-1-methylbutylamino)-6-methoxy-5-quinolylazo]-uracil (IIIc).—5-Aminouracil (12.7 g., 0.1 mole) was diazotized and coupled with 45.5 g. (0.1 mole) of primaquine diphosphate utilizing the procedure described for IIIa. The crude dye was crystallized from dimethylacetamide–water to give 6.9 g. (15%) of reddish brown crystals, m.p. 254–256°.

Anal. Calcd. for $C_{19}H_{23}N_7O_3$: C, 57.42; H, 5.83; N, 24.67. Found: C, 57.05; H, 5.67; N, 24.16.

5-[4-(2-Diethylaminoethylamino)-1-naphthylazo]-8-(2-diisobutylaminoethylamino)-6-methoxyquinoline (V).—To a solution of 9.8 g. (0.025 mole) of N-(4-amino-1-naphthyl)-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide hydrochloride[3,4] in 100 ml. of ice–water and 4.5 ml. of concentrated hydrochloric acid was added 25 ml. of a 1 *M* sodium nitrite solution over a period of 2 min. The resulting red solution was stirred for 4 min. and added in one portion at 0–5° to a solution of 10.5 g. (0.025 mole) of 8-(2-diisobutylaminoethylamino)-6-methoxyquinoline dihydrochloride monohydrate in a mixture of 100 ml. of water, 10 ml. of concentrated hydrochloric acid, and 100 g. of ice. The reaction mixture was stirred at 0–5° for 2 hr., 15 ml. of concentrated ammonium hydroxide was added, and the crude intermediate trifluoroacetamide IV that separated was collected by filtration, washed with water, and dried *in vacuo*. The maroon solid weighed 16.7 g. (96%), m.p. 50–70°.

The crude amide was dissolved in 400 ml. of methanol, 15 ml. of 6 *N* aqueous sodium hydroxide was added, and the mixture was stirred at 40° under nitrogen for 5 days. The mixture was cooled and the deep maroon crystals that separated were collected by filtration and washed successively with cold methanol and water. Crystallization from 95% ethanol gave 7.9 g. (53% over-all) of maroon crystals, m.p. 92–94° dec.

Anal. Calcd. for $C_{36}H_{51}N_7O$: C, 72.32; H, 8.60; N, 16.40. Found: C, 72.54; H, 8.60; N, 16.80.

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Hypocholesteremic Agents. II. The Hydrogenation of Some Pyridinesulfonic and Pyridinealkanesulfonic Acids

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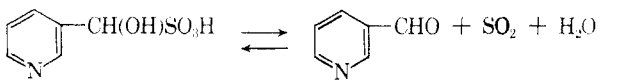
Our interest in some aminosulfonic acids as cholesterol-lowering agents prompted us to attempt hydrogenation of available pyridine and pyridinealkanesulfonic acids and test the activity of the resultant products in this program.

2-(2-Pyridine)ethanesulfonic acid (I) and the corresponding 4-pyridine derivative (III) were readily converted to the piperidine acids II and IV by a method used for the reduction of pyridinealkanoic acids.[1] It is of interest that this method failed in attempting to convert pyridine-3-sulfonic acid (V) to piperidine-3-sulfonic acid (VI). However, in the absence of ammonia, VI was obtained when enough platinum catalyst was used.[2] 3-Pyridinehydroxymethanesulfonic acid (VII) could not be reduced under any conditions. The compound can be viewed as an aldehyde addition product. It apparently undergoes reversal during attempted reduction with the release of sulfur dioxide. This is reduced to hydrogen sulfide, poisoning the catalyst immediately.



Pharmacology.—The test method used was described by Wright.[3] Compounds I, II, and V were found inactive. The general lack of activity discouraged further testing among this group. The toxicity of IV and VI, however, was determined. One delayed death (48 hr.) was noted in a dose of 1500 mg./kg. and none at 2000 mg./kg. when IV was administered orally as a 5% solution in water (pH 5.0). Intermittent convulsions were noted at the higher doses. Compound VI, administered as a 5% solution in water (pH 7.0), was well tolerated intraperitoneally and orally in doses up to 1500 mg./kg., but appeared to have no physiological activity.

Experimental

All melting points taken on a Thomas–Hoover apparatus are corrected.

2-(2-Piperidine)ethanesulfonic Acid (II).—A solution of 18.7 g. (0.1 mole) of I[4] in 150 ml. of water and 9 ml. of concentrated ammonium hydroxide was hydrogenated in the presence of 5.0 g. of 5% rhodium on alumina[5] under 2 atm. pressure. Uptake was complete in less than 2 hr. The solution was filtered from the catalyst and concentrated to dryness. It was ground to a fine powder, dried to constant weight, and analyzed without further purification; yield, 18.5 g. (95.8%); m.p. 315°.

Anal. Calcd. for $C_7H_{15}NO_3S$: C, 43.50; H, 7.82; N, 7.25. Found: C, 43.60; H, 7.92; N, 7.10.[6]

The isomeric 2-(4-piperidine)ethanesulfonic acid, melting at 355°, was prepared in 96.8% yield by the same method.[7] The carbon, hydrogen, and nitrogen found, 43.43, 7.84, and 7.47%, respectively, are in excellent agreement with the calculated values shown for II.

II could also be obtained by reduction of I with platinum oxide[5] in the absence of ammonia. Colloid formation occurred which required large amounts of filter aids to remove the catalyst. As a result, much material was adsorbed and the yield was low.

Piperidine-3-sulfonic Acid (VI).—The described method[2] calls for a small quantity of catalyst. When 7.95 g. (0.05 mole) of pyridine-3-sulfonic acid[4] (m.p. 331°) in 50 ml. of water was hydrogenated in the presence of 0.5 g. of platinum oxide at 60° under 2.7 atm. pressure, uptake of hydrogen was about 50% in 18–20 hr. The solution was filtered and rehydrogenated with an additional 1.0 g. of catalyst. When uptake was complete the reduction solution was filtered from the catalyst and concentrated under reduced pressure to dryness. The solid material was treated with absolute alcohol, filtered, washed, and dried

(1) M. Freifelder, *J. Org. Chem.*, **28**, 602 (1963).
(2) O. Nicodemus and O. Wolff, U. S. Patent 2,008,292 (1935).
(3) H. B. Wright, *J. Med. Chem.*, **7**, 113 (1964).
(4) Available from Aldrich Chemical Company, Milwaukee, Wis.
(5) The catalyst was purchased from Engelhard Industries, Newark, N. J.
(6) Microanalyses were carried out by Mr. O. F. Kolsto and his group at this laboratory.
(7) The starting material, 2-(4-pyridine)ethanesulfonic acid was supplied by Reilly Tar and Chemical Co., Indianapolis, Ind.