4-(6′-Diethylaminohexylamino)-6-methoxybenzothiazole (SN 15,295)[1,2]

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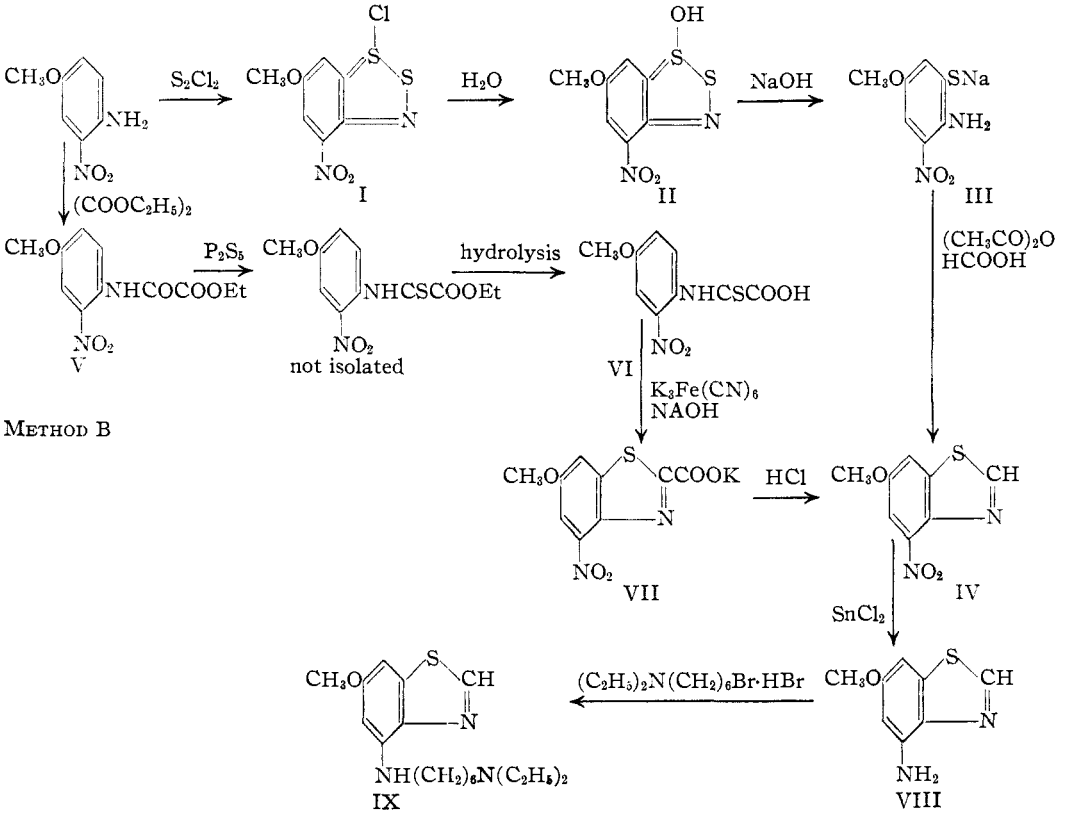
The investigation of 4-(6′-diethylaminohexylamino)-6-methoxybenzothiazole (IX) as potential antimalarial was deemed advisable, although the corresponding diethylaminoethylamino-[3] and diethylaminopropylamino-[4] derivatives had been prepared. The latter compound was reported as having no antimalarial activity.

For comparison the intermediate 6-methoxy-4-nitrobenzothiazole (IV) has been made from 4-amino-3-nitroanisole by the two methods[3,4] and the over-all yield in each case has been increased over that of the previous investigator. The reduction of (IV) gave 4-amino-6-methoxybenzothiazole (VIII) and this was condensed[5] with the hydrobromide of 6-diethylaminohexyl bromide to give IX.

METHOD A



Experimental

Method A

6-Methoxy-4-nitrobenzo-2,3-thiaza-1-thionium Chloride (I).—This was prepared[3] from 150 g. (0.9 mole) of 4-amino-3-nitroanisole. A yield of 174 g. (73.8%) of a product (m. p. 186° dec.) was obtained. The reported yield[3] was 170 g. (m. p. 220° (cor.) dec. with previous darkening).

6-Methoxy-4-nitrobenzo-2,3-thiaza-1-thionium Hydroxide (II).—Twenty grams (0.075 mole) of (I) was stirred vigorously with 200 ml. of ice cold water, the orange solution quickly decanted through a Büchner funnel and the process repeated until practically all the chloride was dissolved. Approximately eight liters of water were required. A flocculent yellow precipitate (II) separated very rapidly in the filtrate. The major portion of the solution was decanted and the solid suspension used directly for III.

For identification some of the hydroxide (II) was filtered, dried and recrystallized from absolute ethanol. The long yellow needles melted at 162–164°, dec. (reported m. p. 162.5°, dec.).[3]

Sodium 2-Amino-3-nitro-5-methoxyphenyl Mercaptide (III).—The product II treated with 20 ml. of sodium hydroxide (20% solution) gave a blood red solution of the mercaptide (III).

Method B

Ethyl 4-Methoxy-2-nitro-oxanilate (V).[4]—From 70 g. (0.42 mole) of 4-amino-3-nitroanisole and 184 g. (1.26 mole) of diethyl oxalate, 88 g. (79% yield) of (V), m. p. 156–157°, was obtained. The reported yield[4] was 70%, m. p. 157°.

4-Methoxy-2-nitrothio-oxanilic Acid (VI).[4]—To thirty grams (0.11 mole) of (V), dissolved in 600 ml. of boiling xylene, 14 g. (0.06 mole) of phosphorus pentasulfide was added with stirring and the mixture refluxed. After alkaline hydrolysis of the thio-oxanilic ester, the acid (VI) was precipitated in 76% yield, 21.5 g., m. p. 131–132° (reported value 132°).[4] No yield of the acid was reported but

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Mount Holyoke College.

(2) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(3) Fox and Bogert, THIS JOURNAL, **61**, 2012 (1939).

(4) Knunyants and Benevolenskaya, *J. Gen. Chem. U. S. S. R.*, **7**, 2471 (1937).

(5) Acknowledgment is hereby given to James D. Head, Columbia University, for this condensation.

a 70% yield of the ester was indicated.[4] The increased yield of (VI) may be due to the larger proportion of sulfide and solvent used in this Laboratory.

Potassium 6-Methoxy-4-nitrobenzothiazole-2-carboxylate (VII).—This salt was precipitated by adding a solution of 15 g. (0.058 mole) of (VI) in 10% sodium hydroxide (45 g. in 400 ml. of water) to a solution of 104 g. of potassium ferricyanide in 240 g. of water.[4]

6-Methoxy-4-nitrobenzothiazole. (IV). Method A.—To a freshly prepared solution of the sodium mercaptide (III) was added all at once[3] 16–20 ml. of the crude formic-acetic anhydride mixture.[6] The solution became orange colored and (IV) precipitated within half an hour. If, as indicated by Fox and Bogert,[4] sodium hydrosulfite[7] was added to the solution (III) prior to the addition of the anhydride mixture, no benzothiazole precipitated.

The 6-methoxy-4-nitrobenzothiazole (IV), crystallized from ethanol, formed glistening yellow needles, m. p. 154–155° (cor.), reported value 150–151°.[3,4] The yield was 6.8 g. (43.3% from 20 g. of (I)) or 31.7% yield based on the nitroanisidine as compared with the reported 21% yield.

Method B.—After refluxing the freshly prepared potassium salt (VII) with 5% hydrochloric acid (175 ml.), the benzothiazole (IV) crystallized on cooling. Recrystallization from alcohol gave 3.7 g. (30% yield from 15 g. of VI), m. p. 153–154.5° (cor.), reported value m. p. 151°, 30% yield.[4] This corresponds to an 18% yield from the nitroanisidine as compared with 14.7% previously obtained.[4] This compound was identical with that obtained in method A but was somewhat darker in color.

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88. Found: C, 45.70, 45.63; H, 2.85, 2.78.[8]

(6) Behal, *Ann. chim.*, (7) **20**, 417 (1900).

(7) Ast and Bogert, *Rec. trav. chim.*, **54**, 917 (1935).

(8) Microanalyses made by Barbara Ripley, Mount Holyoke College. Acknowledgment for them and for other experimental work is hereby given.

4-Amino-6-methoxybenzothiazole (VIII).—Four grams (0.019 mole) of nitrobenzothiazole (IV) (either A or B) was reduced with stannous chloride.[4] The amine recrystallized from dilute ethanol, was obtained in 81.6% yield (2.8 g.), m. p. 145–146° (cor.), which did not change on repeated crystallization. The yield was identical with that previously obtained but the reported melting point was 151°. Fox and Bogert[3] obtained the amine (m. p. 145.5–146°, cor.) by reduction with iron and hydrochloric acid, no yield given.

Anal. Calcd. for $C_8H_8N_2OS$: C, 53.3; H, 4.47. Found: C, 52.35, 52.91; H, 4.27, 4.53.[8]

4-(6′-Diethylaminohexylamino)-6-methoxybenzothiazole. IX. SN 15,295.—The procedure as outlined by Head[5] is as follows: A mixture of 25 g. (0.14 mole) of (VIII), 45 g. (0.14 mole) of 6-diethylaminohexylbromide hydrobromide, 21 g. of sodium acetate trihydrate and 100 ml. of absolute ethanol, was refluxed for sixty hours. The mixture was then diluted to one liter, made strongly alkaline, and extracted with ether. After drying over magnesium sulfate, the product was distilled at reduced pressure, yielding the following fractions: a forerun consisting of 14 g. of nearly pure 4-amino-6-methoxybenzothiazole, followed by a fraction of 14 g. (30% yield) of (IX) boiling at 195–200° at 0.4 mm.

Oxalate.—The solution of the distilled base (IX) in 300 ml. of ether was treated with a solution of 5.3 g. of oxalic acid in 20 ml. of absolute alcohol. The oxalate separated as a white solid, melting at 72–76°. After recrystallization from isopropanol and washing with anhydrous ether it melted at 73–76°.

Anal. Calcd. for $C_{18}H_{29}ON_3S \cdot C_2H_2O_4$: C, 56.47; H, 7.29. Found: C, 55.94; H, 7.28.[9]

(9) Analyses made at Columbia University.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Bucherer Reaction on 5-Hydroxybenzo(f)quinoline[1]

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The investigation of additional derivatives of 5-aminobenzo(f)quinoline in the search for new antimalarial drugs has necessitated a reinvestigation of the work of Barnum and Hamilton.[3] Several modifications have been made and some exceptions noted.

The Skraup reaction for the preparation of 5-carboxybenzo(f)quinoline (I) was modified by the use of sulfonated nitrobenzene[4] as the oxidant and borated glycerol[5] to moderate the reaction. No significant improvement in yield was obtained.

The synthesis of 5,6-dihydro-(5,6)-dichloro-5-carbomethoxybenzo(f)quinoline reported by Barnum[3] is assumed to have resulted from the use of thionyl chloride containing free chlorine, since a repetition of his procedure with purified thionyl chloride (Eastman Kodak Co. white label) gave only 5-carbomethoxybenzo(f)quinoline (II), m. p. 83–85°.

By slight modification of Barnum's[3] procedure, II was converted to 5-carboxylazidebenzo(f)quinoline (IV) which was used immediately without drying to prepare 5-acetaminobenzo(f)quinoline (V) in 98% yields. The hydrolysis and replacement of the amino group by an hydroxyl group was effected by refluxing V with 14 *N* sulfuric acid. The condensation of 4-diethylamino-1-methylbutylamine with 5-hydroxybenzo(f)quinoline (VI) was accomplished by the Bucherer reaction.[6,7]

Experimental

5-Carboxybenzo(f)quinoline (I).—3-Amino-2-naphthoic acid (180 g., 0.96 mole) was added portionwise with stirring to "sulfomix"[4] (378 g.) in a 5-liter three-necked flask. Borated glycerol[8] (540 g.) was added in one portion, the

(1) The work described in this paper was done under contracts OEMsr-85 and OEMcmr-566, recommended by the National Defense Research Committee and the Committee on Medical Research, between the Office of Scientific Research and Development and the Board of Regents of the University of Nebraska.

(2) Responsible investigator.

(3) Barnum and Hamilton, THIS JOURNAL, **64**, 540 (1942).

(4) Utermohlen, *J. Org. Chem.*, **8**, 544 (1943).

(5) Cohn, THIS JOURNAL, **52**, 3685 (1930).

(6) Chelintsev and Dubienen, *J. Gen. Chem. U. S. S. R.*, **10**, 1395 (1940); *C. A.*, **35**, 3641 (1941).

(7) Hartshorn and Baird, THIS JOURNAL, **68**, 1562 (1946).

(8) A mixture of boric acid (3 lb.) and glycerol (1 gal.) was heated to 150° under reduced pressure until the distillation of water became very slow.