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]

BY ROBERT F. COLES AND CLIFF S. HAMILTON[2]

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.

temperature raised to 135° over a period of three to four hours and maintained at 135° for six hours. The water was allowed to escape as formed. The mixture was then poured into 2 liters of water, filtered, the filtrate made basic with ammonium hydroxide, and the refiltered solution acidified with acetic acid. The tar which separated was treated in a similar manner and the dilute acetic acid solution finally concentrated to yield 84 g. (39%) of product crystallized from ethanol; m. p. 205°.

5-Carbonylhydrazidebenzo(f)quinoline (III).—A mixture of II (169 g., 0.71 mole) in methanol (1250 ml.) and 85% hydrazine hydrate (105 g., 1.78 moles) was warmed for fifteen minutes until solid started to separate. The mixture was allowed to stand overnight, the product collected on a filter; yield 160 g. (95%).

5-Hydroxybenzo(f)quinoline (VI).—Crude V (39 g., 0.165 mole) was refluxed for six hours with 200 ml. of 14 *N* sulfuric acid. The mixture was cooled and the orange sulfate salt collected on a filter. The product was dissolved in 300 ml. of hot water, charcoaled and the cooled filtrate made basic with ammonium hydroxide. The yield of crystallized product was 17 g. (53%); m. p. 104–106°. No depression in melting point was observed when mixed with an authentic sample of VI.

5-(4-Diethylamino-1-methylbutylamino)-benzo(f)quinoline (VII).—An amino sulfite solution consisting of 4-diethylamino-1-methylbutylamine (44.3 g., 0.28 mole) in water (100 ml.) containing sulfur dioxide (13 g., 0.2 mole) was refluxed for 216 hours with V (19.6 g., 0.1 mole) under a pressure greater than atmospheric by 20 cm. of mercury. The mixture was poured into 500 ml. of water and the aqueous solution decanted from the separated oil which was then washed with 50 ml. of water. The oil was taken up in 400 ml. of water by the addition of concentrated hydrochloric acid. The solution was made slightly basic to litmus paper with 10% sodium hydroxide solution and the unreacted starting material removed by filtration. The filtrate was made strongly basic to litmus paper with 10% sodium hydroxide solution, and the oil which separated was taken up in ether. The dried ether solution was fractionally distilled at reduced pressure to yield 10 g. (23%) of yellow viscous oil; b. p. 172–173° (0.04 mm.).

Anal. Calcd.[9] for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71. Found: C, 78.70, 78.81; H, 8.70, 8.78.

Summary

1. 5-Carboxybenzo(f)quinoline was prepared by a new modification of the Skraup reaction.

2. 5-Hydroxybenzo(f)quinoline was prepared in 52% yield by the hydrolytic replacement of the 5-amino group in 5-acetaminobenzo(f)quinoline.

3. 4-Diethylamino-1-methylbutylamine was condensed with 5-hydroxybenzo(f)quinoline by the Bucherer reaction.

(9) Analyses by R. E. Benson of this Laboratory.

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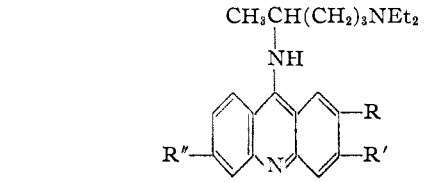
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. IX. 3,6-Dichloro-9-(1-methyl-4-diethylaminobutyl)-aminoacridine

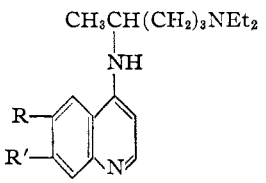
BY DAVID P. SPALDING,[1] GEORGE W. MOERSCH,[1,2] HARRY S. MOSHER AND F. C. WHITMORE

The effect of various nuclear substituents upon the antimalarial activity of acridine derivatives such as Atabrine (I) has been extensively investigated. Apparently the 6-chloro substituent is a greater contributing factor to the activity of this nucleus than the 2-methoxy group; for although "demethoxyatabrine" (II)[3] is reported to be almost as active as Atabrine itself, "dechloroatabrine" (III)[4] is reported to have only slight activity against avian malarial infections. The importance of the 6-chloro substituent in Atabrine is substantiated by a consideration of the corresponding quinoline compounds V and VI in which the 7-chloro-4-aminoquinoline derivative V is reported to be a very potent antimalarial[5] while the 6-methoxy-4-aminoquinoline derivative, VI,[6] possesses only moderate activity in similar tests.

This correlation between the activities of the quinoline and acridine antimalarials is not surprising when we consider "demethoxyatabrine" (II) as the benzo[*b*]quinoline derivative of V and "dechloroatabrine" (III) as the benzo[*b*]quinoline derivative of VI.



I R = —OCH_3, R′ = —H, R″ = —Cl
II R and R′ = —H, R″ = —Cl
III R′ and R″ = —H, R = —OCH_3
IV R′ and R″ = —Cl, R = —H



V R = —H, R′ = —Cl
VI R = —OCH_3, R′ = —H

Thus Atabrine itself may be considered a hypothetical fusion product between the two quinoline compounds V and VI.

The above evidence prompted us to attempt the synthesis of 3,6-dichloro-9-(1-methyl-4-diethylaminobutyl)-amino-acridine (IV) which may similarly be considered a hypothetical fusion product

(1) Parke, Davis and Co. fellow, 1945–1946.

(2) Present address, Parke, Davis and Co., Detroit, Michigan.

(3) Mauss and Mietzsch, British Patent 363,392 (Dec. 18, 1931).

(4) Cherntsov and Drozdov, *J. Gen. Chem. U. S. S. R.*, **9**, 1435–1440 (1939); *C. A.*, **34**, 1667 (1940).

(5) Andersag, Breitner and Jung, U. S. Patent 2,233,970 (March 4, 1941); *C. A.*, **35**, 3771 (1941).

(6) Magidson and Rubtsov, *J. Gen. Chem. U. S. S. R.*, **7**, 1896–1908 (1937); *C. A.*, **32**, 564 (1938); Hal'perin, *Med. Parasitol. Parasitic Disease, U. S. S. R.*, **9**, No. 1-2, 44-53 (1940); *C. A.*, **36**, **1674** (1942).