[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Dialkylaminoalkylamino Derivatives of Dibenzothiophene

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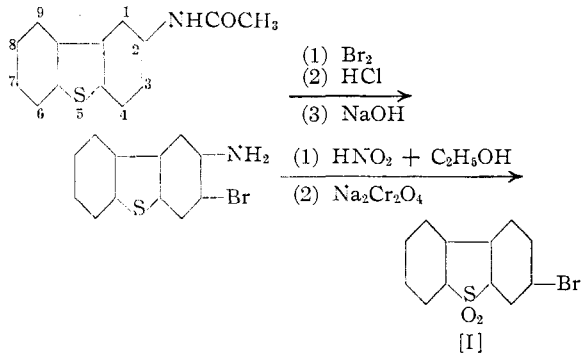
The marked similarities between dibenzothiophene and dibenzofuran suggested an examination of some simple dialkylaminoalkylamino derivatives for antimalarial action. One of the mono-substituted aminodibenzothiophenes used in this study was prepared by the direct bromination of 2-acetaminodibenzothiophene, and the following reactions were used to establish the position of the bromine.



[I]

A mixed melting point of [I] with an authentic specimen of 3-bromodibenzothiophene-5-dioxide showed no depression. Admittedly, a 2-acetamino-7-bromodibenzothiophene would give the same 5-dioxide. However, the possibility of heteronuclear substitution can be confidently excluded on the basis of the known homonuclear directive influence of the acetamino group.

None of the several compounds tested in experimental avian malaria was found active. Also, none of the compounds had more than one nuclear substituent in addition to the γ-diethylaminopropylamino group. On the basis of a related study with dibenzofuran derivatives,[1] it is highly probable that a compound like 1-bromo-4-methoxy-3-diethylaminopropylaminodibenzothiophene will be active. A contributing factor to such activity would be the presence of sulfur.[2]

Apropos the effect of nuclear substituents other than the dialkylaminoalkylamino group, it is interesting to note that the activity of the "open models" patterned after atebrin[3] was continued when the chlorine in 6-methoxy-2-(3′-chlorophenyl) - 4 - [(δ - methyl - δ - diethylaminobutyl)-amino]-quinoline was replaced by hydrogen.

Experimental

2-γ-Diethylaminopropylaminodibenzothiophene.—First 2-aminodibenzothiophene was prepared by warming on a steam-bath for one-half hour, a mixture obtained by adding a solution of 85 g. (0.38 mole) of hydrated stannous chloride in 100 cc. of concentrated hydrochloric acid to a solution of 22.5 g. (0.1 mole) of 2-nitrodibenzothiophene[4] in 300 cc. of glacial acetic acid. After digesting the precipitate with an excess of 10% sodium hydroxide solution, washing, and filtering, crystallization from dilute ethanol gave 17 g. (87%) of the pure amino compound melting at 133°.

A mixture of 6 g. (0.03 mole) of 2-aminodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 145–150° for three hours. The reaction mixture was digested in hot water, cooled and filtered free from a small amount of insoluble material. The solution was made basic with concentrated ammonium hydroxide, extracted with ether, and the ether extract dried and distilled. The yield of yellow oil distilling at 280–282° (2 mm.) was 8 g. (85.2%).

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 9.00. Found: N, 9.16.

2-Acetamino-3-bromodibenzothiophene.—To a solution of 10 g. (0.042 mole) of 2-acetaminodibenzothiophene in 200 cc. of glacial acetic acid was added, over a thirty-minute period, 44 cc. of a 0.1 molar solution of bromine in acetic acid. After stirring for an additional hour, the mixture was poured into 500 cc. of water to which a little sodium bisulfite had been added. The precipitated solid, melting at 197–198°, weighed 10 g. (74%). Two crystallizations from ethanol gave a product melting at 199–200°.

Anal. Calcd. for $C_{14}H_{10}ONSBr$: N, 4.38. Found: N, 4.41.

2-Amino-3-bromodibenzothiophene.—Hydrolysis of 6.4 g. (0.02 mole) of 2-acetamino-3-bromodibenzothiophene in 300 cc. of 95% ethanol, by refluxing on a steam-bath with 300 cc. of concd. hydrochloric acid, gave the hydrochloride. From this, by treatment with ammonium hydroxide followed by crystallization from ethanol, was obtained 5 g. (90%) of compound melting at 135–135.5°.

Anal. Calcd. for $C_{12}H_8NSBr$: N, 5.04. Found: N, 5.11.

3-Bromodibenzothiophene-5-dioxide.—The de-amination was effected by a procedure like that used by Cullinane[5] for another compound. To a solution of 0.5 g. (0.0018 mole) of 2-acetamino-3-bromodibenzothiophene in 15 cc. of ethanol was added cautiously a mixture of 4 cc. of concd. sulfuric acid in 2 cc. of water. While the resulting solution was kept at 80°, 1.2 g. of sodium nitrite was added slowly. The reaction was then completed by refluxing for twenty minutes. Dilution of the reaction mixture with water, and cooling, gave a red solid. This crude product was added to a cold solution of 14 cc. of glacial acetic acid, 5 drops of concd. sulfuric acid, 5 drops of water and 0.1 g. of sodium dichromate to give (after recrystallization from ethanol) 3-bromodibenzothiophene-5-dioxide which melted at 224–225° and showed no depression in a mixed melting point determination with an authentic specimen.[6]

2-γ-Diethylaminopropylamino-3-bromodibenzothiophene.—From 4.5 g. (0.0163 mole) of 2-amino-3-bromodibenzothiophene and 6 g. (0.0322 mole) of γ-diethylaminopropyl chloride hydrochloride, heated at 155–160° for three hours, was obtained 2.8 g. (44%) of a reddish oil distilling at 275–280° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{23}N_2SBr$: N, 7.16. Found: N, 6.93.

2-Acetamino-3-chlorodibenzothiophene.—To 17 g. (0.0708 mole) of 2-acetaminodibenzothiophene in 300 cc.

(1) Gilman and Avakian, THIS JOURNAL, **68**, 580 (1946).

(2) Gilman and Woods, *ibid.*, **67**, 1843 (1945). Activity is, of course, to be expected with the 5-dioxides of 2,8-diaminodibenzothiophene derivatives currently examined by John Nobis, because of their relationship to derivatives of *p,p′*-diaminodiphenyl sulfone.

(3) Gilman and Spatz, *ibid.*, **66**, 621 (1944).

(4) Cullinane, Davies and Davies, *J. Chem. Soc.*, 1435 (1936).

(5) Cullinane, *ibid.*, 2365 (1932).

(6) Gilman, Jacoby and Pacevitz, *J. Org. Chem.*, **3**, 120 (1938).

of chloroform was added dropwise over a thirty-minute period, at room temperature and with stirring, 71 cc. of a 0.1 molar solution of sulfuryl chloride in chloroform. When about one-third of the sulfuryl chloride had been added, a crystalline precipitate started to form. The precipitated material weighed 17 g. (87%) and melted at 194–196°. One crystallization from ethanol gave a product melting at 199.5–200°.

Anal. Calcd. for $C_{14}H_{10}ONSCl$: N, 5.08. Found: N, 5.12.

The position of the chlorine was assumed to be as indicated by analogy with the bromination of 2-acetaminodibenzothiophene.

2-Amino-3-chlorodibenzothiophene.—A mixture of 13.8 g. (0.05 mole) of 2-acetamino-3-chlorodibenzothiophene, 150 cc. of concd. hydrochloric acid and 150 cc. of 95% ethanol was refluxed for two hours, a heavy precipitate forming after one-half hour. From the precipitated hydrochloride, after treatment with ammonium hydroxide, was obtained 10.5 g. (98%) of plates melting at 117–118°. One crystallization from methanol gave a product melting at 118–119°.

Anal. Calcd. for $C_{12}H_8NSCl$: N, 5.99. Found: N, 6.03.

2-γ-Diethylaminopropylamino-3-chlorodibenzothiophene.—From a mixture of 7 g. (0.03 mole) of 2-amino-3-chlorodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride which was heated at 135–140° for four hours was obtained 5.5 g. (53%) of a yellow oil distilling at 215–220° at a pressure less than 0.1 mm.

Anal. Calcd. for $C_{19}H_{23}N_2SCl$: N, 8.08. Found: N, 7.97.

4-Aminodibenzothiophene.—This compound has been prepared in 25% yield by the Bücherer reaction, and in 35% yield by amination of 4-bromodibenzothiophene.[7] The following directions describe its preparation in a 64% yield by reaction of 4-dibenzothienyllithium and α-methylhydroxylamine.

A mixture of 78 g. (0.424 mole) of dibenzothiophene and *n*-butyllithium [prepared from 137 g. (1.0 mole) of *n*-butyl bromide in 150 cc. of ether and 17.5 g. (2.5 g. atoms) of lithium in 500 cc. of ether] was stirred and refluxed for twenty hours. An aliquot was then withdrawn and titrated for RLi compound.[8] Since the solution was found to be 0.64 molar in RLi compounds, 10 g. (0.21 mole) of α-methylhydroxylamine in 60 cc. of ether was added slowly with stirring to the solution cooled in an ice–salt-bath. Subsequent to hydrolysis by the slow addition of dilute hydrochloric acid, the ether layer was separated and the aqueous solution extracted twice with 100-cc. portions of ether. The admission of hydrogen chloride to the dried ether solutions precipitated the amine-hydrochloride. The free amine, obtained by adding cold, dilute ammonium hydroxide to the hydrochloride, was crystallized from methanol to yield 26 g. (64%, based on the α-methylhydroxylamine) of pure 4-aminodibenzothiophene melting at 110°. In addition, there was recovered 30 g. of dibenzothiophene.

4-γ-Diethylaminopropylaminodibenzothiophene.—From 6.5 g. (0.032 mole) of 4-aminodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride, after heating in an atmosphere of nitrogen at 150–155° for four hours, was obtained 7.5 g. (73.5%) of a light yellow oil distilling at 210–213° at a pressure of less than 0.1 mm.

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 9.00. Found: N, 9.12.

1-Bromo-4-γ-diethylaminopropylaminodibenzothiophene.—After heating a mixture of 5 g. (0.018 mole) of 1-bromo-4-aminodibenzothiophene[7] and 6 g. (0.0322 mole) of γ-diethylaminopropyl chloride hydrochloride in a nitrogen atmosphere at 145–150° for three and one-half hours, there was isolated 5.4 g. (76.7%) of a yellow oil which distilled at 263–266° (0.3 mm.).

Anal. Calcd. for $C_{19}H_{23}N_2SBr$: N, 7.16. Found: N, 7.23.

1-Nitro-4-methoxydibenzothiophene.—First, 4-methoxydibenzothiophene was prepared by oxidizing 4-dibenzothienyllithium and then methylating the resulting 4-hydroxydibenzothiophene.

To a solution of 25 g. (0.116 mole) of 4-methoxydibenzothiophene in 400 cc. of glacial acetic acid, cooled to 15°, was added with stirring and over a ten-minute period 20 cc. of fuming nitric acid (sp. g., 1.49). The mixture was kept at 18–20° for ten minutes and then filtered to give 20 g. (66.6%) of product melting at 159–161°. Crystallization from ethanol gave the pure compound melting at 161–162°.

Anal. Calcd. for $C_{13}H_9O_3NS$: N, 5.45. Found: N, 5.58.

1-Amino-4-methoxydibenzothiophene.—A solution of 60 g. (0.267 mole) of hydrated stannous chloride in 70 cc. of concd. hydrochloric acid was added to a suspension of 18 g. (0.071 mole) of the crude 1-nitro-4-methoxydibenzothiophene in 350 cc. of acetic acid. The mixture was heated on a water-bath, and after twenty minutes a precipitate separated. Heating was continued for thirty minutes; the solution was cooled; and the precipitate was then separated and treated with an excess of 25% sodium hydroxide solution. The yield of product, melting at 101–102° after crystallization from ethanol, was 12.7 g. (81%).

Anal. Calcd. for $C_{13}H_{11}ONS$: N, 6.11. Found: N, 6.16.

In addition, one gram of a less soluble amino product, melting at 132–133°, separated first from the ethanol. By analogy with the nitration of 4-methoxydibenzofuran with fuming nitric acid at 18–20°, which gives only 1-nitro-4-methoxydibenzofuran, it is assumed that the main product (m. p. 101–102°) is 1-amino-4-methoxydibenzothiophene and the small fraction (m. p. 132–133°) is 3-amino-4-methoxydibenzothiophene.

Anal. Calcd. for $C_{13}H_{11}ONS$: N, 6.11. Found: N, 6.21.

1-γ-Diethylaminopropylamino-4-methoxydibenzothiophene.—From 5 g. (0.022 mole) of 1-amino-4-methoxydibenzothiophene and 7.5 g. (0.04 mole) of γ-diethylaminopropyl chloride hydrochloride, after heating at 150–155° for four hours, was obtained 3.7 g. (49%) of a yellow oil distilling at 251–254° (0.15 mm.).

Anal. Calcd. for $C_{20}H_{26}ON_2S$: N, 8.12. Found: N, 7.94.

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Summary

Several γ-diethylaminopropylaminodibenzothiophenes have been prepared and found to be inactive in experimental avian malaria. None of these contained more than one nuclear substituent in addition to the diethylaminopropylamino group. The structure of 3-bromo-2-aminodibenzothiophene, prepared by bromination of 2-acetaminodibenzothiophene, was established by a series of reactions leading to the known 3-bromodibenzothiophene-5-dioxide.

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(7) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(8) Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).