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[x] To whom inquiries should be directed.

Antimalarials V: Aminobenzothiazoles

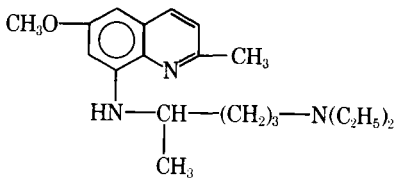
EDWARD R. ATKINSON [x] and FELIX E. GRANCHELLI

Abstract □ Four mono- and dialkylated 4-aminobenzothiazoles (VII–X) were prepared as analogs of potent causal prophylactic drugs in the 8-aminoquinoline series. Compounds VII and VIII were toxic at 80 mg/kg in the chick; IX was inactive at 640 mg/kg. In a sporozoite-induced mouse test system, X was inactive at 30 mg/kg and toxic at 480 mg/kg. None of the compounds was active as a suppressive drug.

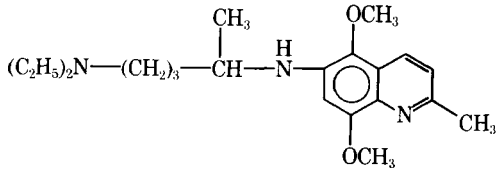
Keyphrases □ 4-Aminobenzothiazoles, mono- and dialkylated—synthesis, antimalarial activity screened □ Antimalarial agents, potential—mono- and dialkylated 4-aminobenzothiazoles screened □ Structure–activity relationships—mono- and dialkylated 4-aminobenzothiazoles, antimalarial activity

The history of the development of causal prophylactic antimalarials in the 6- and 8-aminoquinoline series, such as I and II, is well known; convenient summaries are available (1, 2). More recently developed additions to the series (III) are among its more potent members (3, 4).

The pharmacological analogy between quinolines and benzothiazoles was drawn first by Bogert and Abrahamson (5), who prepared 2-phenylbenzothiazole-6-carboxylic acid as an analog of cinchophen. Benzothiazole amino alcohols, having the side chain at the 6-position, were later found not to be curative



I



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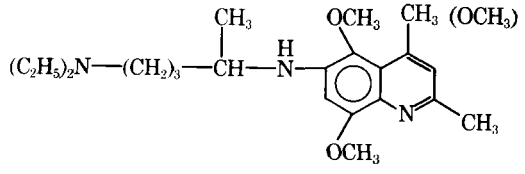
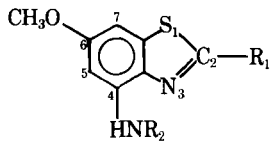


III



IV: $R_1 = CH_3$, $R_2 = (CH_2)_3N(C_2H_5)_2$

V: $R_1 = H$, $R_2 = NH(CH_2)_2N(C_2H_5)_2$

VI: $R_1 = CH_3$, $R_2 = NH(CH_2)_6N(C_2H_5)_2$

and to be highly toxic in mice at 160–640 mg/kg (6). A few other inactive benzothiazoles derived from 2-amino- or 2-mercaptobenzothiazole were reported (7). Compound IV was reported to be inactive (test system unreported) (8) and V was synthesized but not evaluated (9). Compound VI was found to be inactive (10) in the test system then in vogue (7).

Benzothiazoloquinones, as analogs of quinolinequinones, have been found to have effective prophylactic activity against *Plasmodium gallinaceum* in the chick (11).

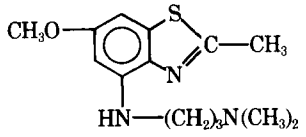
The purposes of the present work were to prepare additional members of the 4-aminobenzothiazole series and to determine their prophylactic activity in a standard animal test system.

DISCUSSION

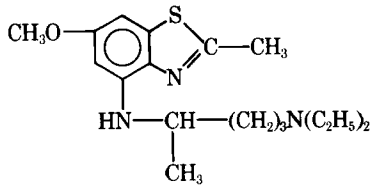
A general literature procedure (9) was used for the sequence 4-methoxy-2-nitroaniline → 1-chloro-6-methoxy-4-nitrobenzodithiazole (55%) → 1-hydroxy-6-methoxy-4-nitrobenzodithiazole (21%, but not isolated in most runs) → 6-methoxy-2-methyl-4-nitrobenzothiazole (43% overall from 1-chloro precursor) → 4-amino-6-methoxy-2-methylbenzothiazole (57%). The amine was alkylated by 3-dimethylaminopropyl chloride to give 4-(3-dimethylaminopropyl)amino-6-methoxy-2-methylbenzothiazole (VII·2HCl·H_2O, 24%).

The alkylation of 4-amino-6-methoxy-2-methylbenzothiazole by 2-bromo-5-diethylaminopentane (12) to VIII gave an unacceptable poor yield. An alternative procedure, recently used for the analogous alkylation of 1,4-dimethoxy-2-naphthylamine (13), involved the condensation of the amine with 5-diethylamino-2,2-dimethoxypentane followed by reduction of the intermediate anil by sodium borohydride. 4-(4-Diethylamino-2-methylbutyl)amino-6-methoxy-2-methylbenzothiazole (VIII·HCl·H_2O) was obtained in 21% yield.

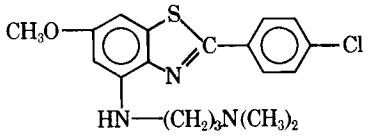
The precursor for both IX and X was prepared from 1-hydroxy-6-methoxy-4-nitrobenzodithiazole (an intermediate in the 2-methyl series described previously) by the sequence 2-mercapto-4-methoxy-6-nitroaniline (9) (65%) → 2-(4-chlorophenyl)-6-methoxy-4-nitrobenzothiazole (85%) → 4-amino-2-(4-chlorophenyl)-6-methoxybenzothiazole (71%). Alkylation of the amine by 3-dimethylaminopropyl chloride gave 2-(4-chlorophenyl)-4-(3-dimethyl-



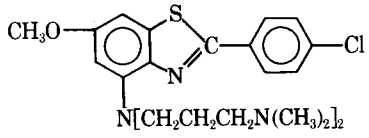
VII



VIII



IX



X

aminopropyl)amino-6-methoxybenzothiazole (IX, 50%). When an excess of alkylating agent was used, 4-[bis(3-dimethylaminopropyl)amino]-2-(4-chlorophenyl)-6-methoxybenzothiazole (X, 73%) was obtained.

Attempts to prepare an analog of VIII in the 2-(4-chlorophenyl) series failed when the reductive alkylation of the amine precursor could not be achieved as in the synthesis of VIII.

Compounds VII–X were examined in tests[1] designed to detect true causal prophylactic drugs (those that affect primary exoerythrocytic parasites). Against *P. gallinaceum* in a sporozoite-induced chick test (14), both VII and VIII caused toxic deaths at or above 80 mg/kg; IX caused no increase in mean survival time at 640 mg/kg, the highest dose tested. Compound X was examined in a sporozoite-induced mouse test system against *P. berghei yoelii* (15); it was inactive at 30 mg/kg and caused toxic deaths at 480 mg/kg. Primaquine prevents parasitemia at 30 mg/kg in this test.

Compounds VII, IX, and X were also tested for suppressive antimalarial activity in mice (16) and were found to be inactive at 640 mg/kg. The 4-amino precursors of VII and IX were also inactive in this test.

EXPERIMENTAL[2]

4-(3-Dimethylaminopropyl)amino-6-methoxy-2-methylbenzothiazole Dihydrochloride Monohydrate (VII·2HCl·H_2O)—A mixture of 5.6 g (0.0288 mole) of 3-dimethylaminopropyl chloride hydrochloride[3] and 30 ml of absolute ethyl alcohol was refluxed for 3 days, an alkylation procedure used successfully in the quinoline series (2). The mixture was allowed to stand at room temperature until separation of the hydrochloride salt of unreacted aminobenzothiazole stopped; 3.5 g was recovered. The filtrate then was diluted with 200 ml of water and extracted with ether to remove a small additional amount of unreacted amine.

The aqueous phase was made basic by addition of excess solid potassium carbonate and then extracted with ether. The ether extract was washed with saturated aqueous sodium chloride until neutral, dried over sodium sulfate, and evaporated to dryness to give 2.2 g of a green oil. Bulb-to-bulb distillation at 175–180°/0.01 mm gave 1.9 g (24%) of an almost colorless oil, which was converted in the usual way to a colorless dihydrochloride salt, mp 188–195° dec. (sealed capillary).

Anal.—Calc. for $C_{14}H_{21}N_3OS·2HCl·H_2O$: C, 45.41; H, 6.80; Cl, 19.15; N, 11.35. Found: C, 45.64; H, 6.29; Cl, 19.43; N, 11.33.

The hydrate character was assigned on the basis of the analysis and the NMR spectrum.

4-(4-Diethylamino-1-methylbutyl)amino-6-methoxy-2-methylbenzothiazole Dihydrochloride Monohydrate (VIII·2HCl·H_2O)—The general procedure was that described previously (13) for the alkylation of 1,4-dimethoxy-2-naphthylamine.

A mixture of 3 g (0.0155 mole) of 4-amino-6-methoxy-2-methylbenzothiazole, 3.55 g (0.0175 mole) of 5-diethylamino-2,2-dimethoxypentane, and 175 mg of *p*-toluenesulfonic acid was heated under nitrogen to 140° and held at that temperature for 24 hr. The methyl alcohol that formed during the reaction was collected and not allowed to return to the reaction mixture.

The dark-red viscous oil was dissolved in ether. The solution was washed with saturated aqueous sodium carbonate, dried over potassium carbonate, and evaporated to give 4.85 g (93%) of crude anil, whose spectrum showed strong absorption at 1665 cm^{-1}.

A solution of 1.45 g (0.037 mole) of sodium borohydride in 40 ml of absolute ethyl alcohol was added in one lot to a stirred solution of the crude anil in 100 ml of absolute ethyl alcohol at 0°. Stirring was continued under nitrogen for 24 hr at room temperature. The solution then was poured into 500 ml of water, and the mixture was extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried over potassium carbonate, and evaporated to give 4.55 g of an oil. Distillation of the oil in a bulb-to-bulb apparatus gave a forecut of unalkylated aminobenzothiazole followed by 1.1 g of crude VII (base), bp 165–175°/0.01 mm, whose spectrum showed no absorption at 1665 cm^{-1}. However, NMR and elemental analyses clearly showed that a significant amount of unalkylated aminobenzothiazole still remained.

The crude oil was dissolved in chloroform–benzene (1:1), and the solution was passed through a 2 × 25-cm magnesium silicate[4] column, on which the unalkylated amine was not absorbed significantly. Elution of the column with the solvent mixture containing 5–10% methyl alcohol gave an oil; this oil was converted in the usual way to a hygroscopic dihydrochloride salt (VIII·2HCl·H_2O), mp 110° dec. (shrinks at 84°).

Anal.—Calc. for $C_{18}H_{29}N_3OS·2HCl·H_2O$: C, 50.69; H, 7.79; Cl, 16.63: N, 9.85; S, 7.52. Found: C, 50.64; H, 7.73; Cl, 16.53; N, 9.79; S, 7.67.

The hydrate character was assigned on the basis of the analysis and the NMR spectrum.

2-(4-Chlorophenyl)-6-methoxy-4-nitrobenzothiazole—The procedure was based on earlier preparations of 2-phenylbenzothiazoles (17, 18).

A mixture of 21 g (0.12 mole) of *p*-chlorobenzoyl chloride and 70 ml of *N,N*-dimethylaniline was purged with nitrogen, and then 14 g (0.07 mole) of freshly prepared 2-mercapto-4-methoxy-6-nitroaniline (9) was stirred in rapidly. The mixture warmed spontaneously to 50° and became very stiff. The temperature was then raised during 2 hr to 190° and held there for an additional hour; when the mixture was held at this temperature for longer times or when it was heated to reflux, yields were inferior.

The mixture was cooled and then stirred for 30 min with a mixture of 525 ml of 6 *N* HCl and 525 ml of chloroform. The aqueous phase was additionally extracted with chloroform. The combined chloroform phases were washed with 6 *N* HCl, water, aqueous sodium bicarbonate, saturated aqueous sodium chloride, and water. After drying over magnesium sulfate, they were evaporated under vacuum. The residual pasty solid was triturated with alcohol and filtered to give 19.1 g (85%), mp 167–171°. A sample for analysis, mp 170–171°, was obtained by recrystallization from ethyl alcohol–dimethoxyethane.

Anal.—Calc. for $C_{14}H_9ClN_2O_3S$: C, 52.43; H, 2.83; Cl, 11.05; N, 8.73. Found: C, 52.52; H, 2.88; Cl, 10.93; N, 8.68.

4-Amino-2-(4-chlorophenyl)-6-methoxybenzothiazole—A mixture of 20 g (0.061 mole) of the nitro compound, 70 g (0.31 mole) of stannous chloride dihydrate, 350 ml of 12 *N* HCl, and 5 g

[1] Test results were obtained by the Rane Laboratory, Miami, Fla., and by the Illinois Institute of Technology, Chicago, Ill., and were provided by the Walter Reed Army Institute of Research.

[2] Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and by the late Dr. S. M. Nagy (Belmont, Mass.). Satisfactory IR and NMR spectra were recorded for all new compounds and for all important intermediates.

[3] Aldrich.

[4] Florisil.

of tin (30 mesh) was stirred at 70–90° and diluted with about 850 ml of acetic acid until the nitro compound dissolved. Heating at 90–95° was continued for 4 hr, and the mixture was allowed to cool overnight. A tin complex (18 g, mp 195°) separated. It was stirred with 20% NaOH for several hours, washed with water until neutral, and dried to give 12.5 g (71%), mp 160–164°. A sample for analysis, mp 169–174°, was obtained by recrystallization from acetic acid.

Anal.—Calc. for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81; Cl, 12.19; N, 9.63; S, 11.03. Found: C, 57.69; H, 3.69; Cl, 12.26; N, 9.60; S, 11.10.

2-(4-Chlorophenyl)-4- (3-dimethylaminopropyl)amino -6-methoxybenzothiazole (IX)—A mixture of 2.32 g (0.008 mole) of 4-amino-2-(4-chlorophenyl)-6-methoxybenzothiazole, 0.34 g (0.008 mole) of sodium hydride (as a 57% suspension in mineral oil[5]), 1.0 g (0.008 mole) of 3-dimethylaminopropyl chloride, and 100 ml of dry toluene was stirred under nitrogen at 110–120° for 64 hr. The mixture was cooled to 0°, and 5 ml of water was added dropwise. The small aqueous layer was separated and extracted with toluene. The combined toluene solutions were dried over magnesium sulfate and taken to dryness under vacuum to give 2.9 g of a brown pasty solid. A thin-layer chromatogram [silica, benzene–hexane–methanol (5:3:2)] showed that a significant amount of unalkylated amine was present.

From a number of alternative purification procedures examined with the products or previous runs, the following was chosen. The solid was extracted with 60 ml of boiling hexane, and a small amount of insoluble gum was discarded. The hexane solution was cooled to 0° and deposited 1.5 g (50%) of yellow crystals, mp 93–96°. Recrystallization from boiling hexane gave a good recovery of material, mp 97–100°.

Anal.—Calc. for $C_{19}H_{22}ClN_3OS$: C, 60.71; H, 5.89; Cl, 9.43; N, 11.18; S, 8.53. Found: C, 60.68; H, 6.17; Cl, 9.16; N, 11.05; S, 8.28.

Unsuccessful alkylation reactions were attempted in refluxing ethyl alcohol, dimethylformamide at 70°, and diethylene glycol at 175°, in which reaction times of 3–4 days were used.

4-[Bis(3-dimethylaminopropyl)amino]-2-(4-chlorophenyl)-6-methoxybenzothiazole (X)—A solution of 4.35 g (0.036 mole) of 3-dimethylaminopropyl chloride in 20 ml of dry toluene was added dropwise to a stirred mixture of 2.63 g (0.009 mole) of 4-amino-2-(4-chlorophenyl)-6-methoxybenzothiazole, 1.65 g (0.039 mole) of sodium hydride (as a 57% dispersion in mineral oil[5], and 150 ml of dry toluene. Additional dry toluene was added to bring the mixture to a total volume of 250 ml, and the mixture was refluxed for 54 hr. When TLC showed that much unalkylated material remained, an additional 1.6 g of sodium hydride, 4.3 g of 3-dimethylaminopropyl chloride, and 20 ml of toluene were added.

After an additional 24-hr reaction time, unalkylated material was no longer present. The reaction mixture was treated with 40 ml of water, and the aqueous phase was extracted with toluene. The combined toluene phases were dried over magnesium sulfate and taken to dryness under vacuum. The pasty residue was triturated with cold petroleum ether, and the filterable solid (mp 85–89°; 3 g, 73%) was recrystallized from boiling hexane to give yellow needles, mp 89–90°.

Anal.—Calc. for $C_{24}H_{33}ClN_4OS$: C, 62.52; H, 7.21; Cl, 7.69; N, 12.15; S, 6.95. Found: C, 62.29; H, 7.27; Cl, 7.51; N, 11.88; S, 7.10.

[5] Alfa.

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[x] To whom inquiries should be directed.