Antimalarial Phenothiazine Amino Alcohols (1)

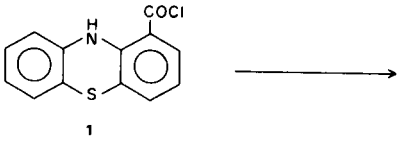
Edward A. Nodiff, Werner Müller, and Takahiro Yabuuchi

Germantown Laboratories, Inc., Affiliated with The Franklin Institute,
4150 Henry Avenue, Philadelphia, Pennsylvania 19144

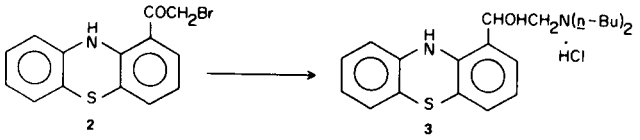
Received May 14, 1973

The antimalarial activity of the phenothiazine, methylene blue, was claimed by Ehrlich as early as 1891 (2). Little work on phenothiazine antimalarials has emerged since then (3-6). The enhancement of the antimalarial activity of various ring systems by introduction of an amino alcohol side chain has been well documented (4,5). It, therefore, seemed worthwhile, in this connection, to evaluate some phenothiazine amino alcohols. These compounds were prepared as indicated in Schemes 1 and 2.

Scheme 1

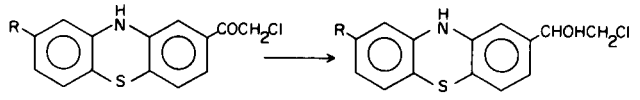


1



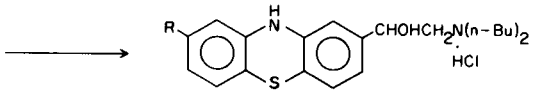
2 3

Scheme 2



4a R = H
4b R = Cl

5a R = H
5b R = Cl



6a R = H
6b R = Cl

The 2-phenothiazinemethanols (**6a** and **6b**) were ineffective but the 1-phenothiazinemethanol (**3**) was almost twice as active as quinine (Table I). All three compounds were non-toxic over the entire dosage range.

TABLE I

Antimalarial Data (a)

No.	ΔMST (b) Dose, mg./kg. 40	160	640
3	1.0	5.8	13.0
6a	0.4	0.4	0.8
6b	0.2	0.2	3.4
quinine sulfate	1.0	3.6	7.1

(a) Tests were carried out in five mice, infected with a lethal dose of *P. berghei*, by Dr. L. Rane and coworkers, Malaria Screening Laboratory, University of Miami, Miami, Florida. For details of test procedure, see Osdene *et al.* (11). (b) ΔMST, mean survival time over controls (6.2 ± 0.49 days); a compound is considered to be active when the MST of the treated group is more than twice that of the control group.

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware.

1-Bromoacetylphenothiazine (**2**).

To a stirred solution of diazomethane (from 24 g. of *N*-methyl-*N*-nitrosourea) in 300 ml. of ether at 0°, was added 3.7 g. (0.014 mole) of powdered phenothiazine-1-carboxylic acid chloride (**1**) (7) during 30 minutes. The orange solution was allowed to stand at room temperature for 4 hours and concentrated *in vacuo*. The remaining red crystalline diazoketone was dissolved in 300 ml. of ether and treated dropwise with 4.3 ml. of 48% hydrobromic acid during 20 minutes at 5-10°. After 10 more minutes at 5-10°, the solution was diluted with 300 ml. of ether and washed with saturated sodium bicarbonate and water. The dried (magnesium sulfate) solution was concentrated almost to dryness and the semisolid was washed with hot petroleum ether (b.p. 30-60°) to give 3.7 g. (81%) of **2**, m.p. 88-89°. Recrystallization from petroleum ether (b.p. 60-90°) provided an analytical sample as orange needles with the same m.p.

Anal. Calcd. for $C_{14}H_{10}BrNOS$: Br, 24.96; N, 4.37; S, 10.00. Found: Br, 25.25; N, 4.15; S, 10.03.

α-(Di-*n*-butylaminomethyl)-1-phenothiazinemethanol Hydrochloride (**3**).

A mixture of 3 g. (0.009 mole) of **2**, 5 ml. (0.05 mole) of dibutylamine and 40 ml. of benzene was stirred under nitrogen for 24 hours, concentrated and diluted with ether. The precipitated dibutylamine hydrobromide was filtered and the filtrate was concentrated. The residual amino ketone was dissolved in 60 ml. of methanol and treated with a solution of 0.4 g. (0.01 mole) of sodium borohydride in 3.5 ml. of water containing 1 drop of 2*N* sodium hydroxide. The red mixture was stirred at room temperature for 6 hours, gradually becoming colorless. The mixture was diluted with water and the amino alcohol was extracted with ether. The dried (magnesium sulfate) extract was treated dropwise with ethereal hydrogen chloride. The resulting dibutylamine hydrochloride was removed and the filtrate was allowed to stand in a stoppered flask over a weekend. The yellow solid (2.5 g.), which separated, was washed with water and crystallized several times from ethyl acetate (carbon) to give 0.8 g. (21%) of **3** as off-white solid, m.p. 148-149°.

Anal. Calcd. for $C_{22}H_{31}ClN_2OS$: C, 64.92; H, 7.68; Cl, 8.71; N, 6.88. Found: C, 65.09; H, 7.61; Cl, 8.97; N, 6.97.

Concentration of the ether solution, prior to treatment with hydrogen chloride gas, provided the free amino alcohol, m.p. 66-67° (methanol).

Anal. Calcd. for $C_{22}H_{30}N_2OS$: C, 71.31; H, 8.16; N, 7.56; S, 8.65. Found: C, 71.30; H, 8.20; N, 7.84; S, 8.64.

2-Phenothiazinylchlorohydrine (**5a** and **5b**).

Reduction of the chloroacetyl derivatives **4a** (8) and **4b** (9) with aluminum isopropoxide as described by Hromatka *et al.* (10) gave 70% of **5a**, m.p. 173° [lit. (8) m.p. 171-172°] and 89% of **5b**, m.p. 154-156° (dioxane-water).

Anal. Calcd. for $C_{14}H_{11}Cl_2NOS$: C, 53.86; H, 3.55; Cl, 22.71; N, 4.49; S, 10.27. Found: C, 53.69; H, 3.71; Cl, 22.63; N, 4.39; S, 10.26.

α-(Di-*n*-butylaminomethyl)-2-phenothiazinemethanol Hydrochloride (**6a**).

A mixture of 5.6 g. (0.02 mole) of **5a**, 12.9 g. (0.1 mole) of dibutylamine and 50 ml. of dioxane was heated under reflux for 24 hours and concentrated *in vacuo*. The residue was extracted with ether and the extract was washed with water, dried (magnesium sulfate), cooled and adjusted to *p*H 4 with ethereal hydrogen chloride. Repeated crystallization of the resulting solid from chloroform-ethyl acetate gave 1 g. (12%) of **6a** as pale yellow prisms, m.p. 190° (sealed evacuated tube).

Anal. Calcd. for $C_{22}H_{31}ClN_2OS$: C, 64.92; H, 7.68; Cl, 8.71; N, 6.88. Found: C, 64.52; H, 7.55; Cl, 8.66; N, 7.02.

8-Chloro-α-(di-*n*-butylaminomethyl)-2-phenothiazinemethanol Hydrochloride (**6b**).

A mixture of 6.2 g. (0.02 mole) of **5b**, 21 ml. of dibutylamine, 8 g. of anhydrous potassium carbonate and 120 ml. of dioxane was heated under reflux for 65 hours and filtered. The filtrate was concentrated and the residue was diluted with 100 ml. of 6*N* hydrochloric acid. Ether was added and the mixture was stirred and rubbed with a glass rod until the initially formed yellow oil crystallized. The solid was washed with ether, dried *in vacuo* and crystallized from chloroform-ether (carbon) to give 2.5 g. (28%) of **6b** as white needles, m.p. 185-186° (sealed, evacuated tube).

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2OS$: C, 59.85; H, 6.85; Cl, 16.06; N, 6.35; S, 7.26. Found: C, 60.24; H, 7.07; Cl, 15.86; N, 6.50; S, 7.25.

Acknowledgement.

We are grateful to Drs. T. R. Sweeney and R. E. Strube, Walter Reed Army Institute of Research, for antimalarial screening data and for helpful discussions during the course of this work.

REFERENCES

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DADA17-67-C-7067 and is Contribution No. 1163 from the Army Research Program on Malaria.

(2) P. Guttman and P. Ehrlich, *Berlin Klin. Wochschr.*, **28**, 953 (1891).

(3) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944) and references therein.

(4) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenburg, "Survey of Antimalarial Agents", Public Health Monograph No. 9, 1953.

(5) F. Y. Wiselogle, "A Survey of Antimalarial Drugs 1941-1945", J. W. Edwards, Ann Arbor, Michigan, 1946.

(6) P. Chien and C. C. Cheng, *J. Med. Chem.*, **9**, 960 (1966).

(7) N. V. Savitskaya and M. N. Shchukina, *Zh. Obshch. Khim.*, **24**, 152 (1954); *Chem. Abstr.*, **49**, 3202i (1955).

(8) A. Burger and J. B. Clements, *J. Org. Chem.*, **19**, 113 (1954).

(9) P. K. Kadaba, *J. Heterocyclic Chem.*, **3**, 345 (1966).

(10) O. Hromatka, G. Stehlik, and F. Sauter, *Monatsh. Chem.*, **91**, 583 (1960).

(11) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).