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# SYMMETRICAL 1,3-BIS-DIALKYLAMINO-2-PROPANOLS

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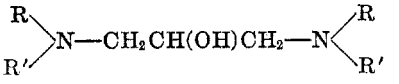
*Received March 9, 1953*

In the course of a systematic study of the action of a wide variety of organic compounds on avian malaria (*P. gallinaceum*), it was observed that an occasional $\alpha,\omega$-diaminoalkane was moderately effective in reducing parasitemia. Because of the apparent importance of the grouping $—CHOHCH_2NR_2$ in the Cinchona alkaloids, as well as in other series of drugs having antimalarial action (1), it seemed logical to extend this observation to compounds of the type $R_2NCH_2CH(OH)CH_2NR_2$. This idea gained further support in the work of Magidson and Rubtsov (2), who found that decreased toxicity and increased therapeutic index resulted from the introduction of the side-chain $—NHCH_2CH(OH)CH_2NR_2$ at the 4-position of the quinoline nucleus. Further, Eisleb (3) has described the outstanding bactericidal power of an acridine having the 9-side-chain $—NHCH_2CH(OH)CH_2NEt_2$.

We have prepared a series of tetraalkylated 1,3-diamino-2-propanols (I) in which R = R′ = methyl (SN 464), ethyl (SN 3606), propyl (SN 5938), butyl



I

(SN 5939), amyl (SN 5769), hexyl (SN 5925),[1] octyl (SN 2675), and decyl (SN 10,149), and also one member in which R = benzyl and R′ = methyl (SN 10,224). Of these, the first two have been prepared previously (5). Tests conducted with our compounds indicate no promise of obtaining an effective antimalarial agent in this series (4).

The synthesis of these compounds was accomplished by heating the appropriate secondary amine with glycerol-$\alpha,\gamma$-dichlorohydrin. In general, an excess of the secondary amine was employed to bind the hydrogen chloride liberated in the reaction. The bis-dioctylamino derivative is an exception, for here sodium bicarbonate gave superior results (6), although in general the use of bicarbonate was inferior to the use of secondary amine[2] as a hydrogen chloride acceptor. In the case of the bis-dimethylamino derivative, heating 2 moles of dimethylamine with 1 mole of glycerol-$\alpha,\gamma$-dichlorohydrin in a sealed tube at 100° resulted in

[1] Due to an error originating in this laboratory the bis di-*n*-hexylamino-2-propanol (SN 5925) is incorrectly reported (1, 4) as being 1,3-bis-di*cyclo*hexylamino-2-propanol.

[2] The course of the reaction between glycerol-$\alpha,\gamma$-dihalohydrins and basic reactants has been studied previously (7, 8), and probably goes through a propylene oxide type intermediate for each halogen reaction, rather than by direct replacement of halogen by amine. Since carbonate apparently inhibits the formation of oxide rings (9), this may explain the generally unfavorable results obtained with bicarbonate.

## TABLE I

BIS-1,3-DIALKYLAMINO-2-PROPANOLS

| $R_1$ | $R_2$ | REACTANTS | | TIME, hrs. | TEMP., °C. | YIELD | | B.P., °C. | MM. | ANALYSES | | | | MOL. WT.[h] | | SOLUBILITY | | $n_D^{20}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Amine, g. | Chlorohydrin, g. | | | g. | % | | | C | | H | | Calc'd | Found | $H_2O$ | HCl | |
| | | | | | | | | | | Calc'd | Found | Calc'd | Found | | | | | |
| Me | Me | 18.5 | 12.9 | 1/12 | 150[a] | — | — | 89–96 | 25 | 38.4[c] | 38.2[c] | 9.2[c] | 9.2[c] | 146 | — | + | + | — |
| Et | Et | 80 | 25.8 | 20 | Reflux. | — | — | 117–119.5 | 15 | — | — | — | — | 202 | 191 | [g] | + | — |
| Pr | Pr | 30 | 9.6 | 4 | 140–150[a] | 14.1 | 73 | 98–103 | 0.3 | 69.7 | 69.7 | 13.3 | 13.3 | 258 | 262 | — | + | 1.4482 |
| Bu | Bu | 30 | 7.5 | 4 | 140–150[a] | 15.2 | 83 | 134–135 | 0.4 | 72.6 | 72.3 | 13.5 | 13.7 | 314 | 300 | — | + | 1.4502 |
| Am | Am | 30 | 6.1 | 4 | 140–140[a] | 10.2 | 58 | 147–151 | 0.1 | 74.5 | 74.5 | 13.6 | 14.3 | 370 | 377 | — | [f] | 1.4547 |
| Hex[1] | Hex | 30 | 5.2 | 4 | 140–150[a] | 10.2 | 59 | 173–178 | 0.1 | 76.0 | 75.7 | 13.7 | 13.5 | 426 | 435 | — | [f] | 1.4576 |
| Oct | Oct | 50 | 12.9 | 5 | [b] | — | — | 150 | $10^{-5}$ | 78.0 | 77.5 | 13.9 | 13.6 | 538 | 577 | — | [f] | 1.4606 |
| Dec | Dec | 46 | 5.0 | 8 | Xylene reflux | 14.8[c] | — | m.p. 105–150°[c] | | 71.3[c] | 72.0[c,e] | 12.8[c] | 13.2[c,e] | 724[c,d] | 750[c,d] | — | — | — |
| Me | Benzyl | 32.6 | 8.2 | 4 | 140–150 | 16.1 | 85 | 60 | $10^{-4}$ | 76.5 | 75.6 | 8.8 | 9.0 | — | — | — | + | 1.5452 |

[a] The reaction was conducted in a sealed tube. [b] 200 ml. of toluene and 20 g. $NaHCO_3$ were added, and the mixture was refluxed with removal of water with a moisture trap. [c] These figures are for the dihydrochloride. [d] By titration. [e] It is fortuitous that this analysis is consistent with the theory for didecylamine hydrochloride. Didecylamine is soluble in methanol, and the hydrochloride can be crystallized from methanol; it is insoluble in ether and petroleum ether. It melts at 225°. Bis-1,3-didecylamino-propanol-2 is insoluble in methanol, and the dihydrochloride is too soluble in this solvent for recrystallization. The dihydrochloride is readily soluble in ether, can be recrystallized from petroleum ether, and has m.p. 105–150°. [f] Slightly soluble. [g] Moderately soluble. [h] By freezing point method in benzene.

a violent explosion, whereas if 4 or 5 moles of dimethylamine were used the reaction proceeded smoothly at 150°.

The effect of the length of the alkyl group, R, on the physical properties of these compounds is regular, as may be seen from Table I and Figure 1. The decreasing hydrophyllic character is strikingly illustrated in the solubility of the hydrochloride of the decyl homolog in petroleum ether. A regularity is also observed in the effect of alkyl chain length on toxicity, as illustrated in Figure 2.[3]

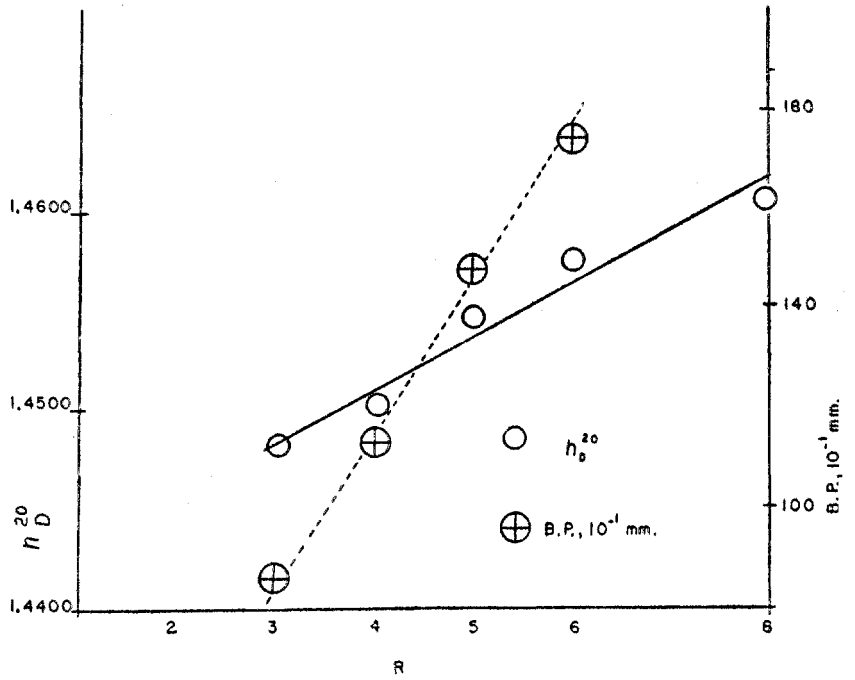



FIG. 1. EFFECT OF LENGTH OF ALKYL GROUP, R, ON BOILING POINT AND REFRACTIVE INDEX OF SYMMETRICAL 1,3-BIS-DIALKYLAMINO-2-PROPANOLS

## EXPERIMENTAL

All melting points are uncorrected.

The dialkylamines used in this work were commercial materials which were used without further purification.

*Bis-1,3-dimethylaminopropanol-2.* Liquid dimethylamine (4 moles) and 1 mole of glycerol-$\alpha,\gamma$-dichlorohydrin were sealed in a glass tube and heated to 150° for about 5 minutes. After basification with NaOH, the reaction mixture was extracted with ether. The product obtained from the ether was distilled *in vacuo*, b.p. 89–96°/25 mm.; lit. b.p., 170–185°. The base was converted to the *hydrochloride*, m.p. 260–260.5°.

*Bis-1,3-diethylaminopropanol-2 picrate.* This compound had m.p. 163°; lit. (10), 163°.

*Bis-1,3-dihexylaminopropanol-2. A. Bicarbonate method.* A mixture of 37 g. of dihexylamine and 12.9 g. of glycerol-$\alpha,\gamma$-dichlorohydrin in 200 ml. of toluene was refluxed for 5

[3] The term "molar toxicity" is here used to indicate the reciprocal of the maximum tolerated dose in *moles* per kilogram of body weight. These tests were made in chicks.

hours in the presence of 20 g. of $NaHCO_3$. The evolved water was collected in a Dean and Stark moisture trap, 3.1 ml. being obtained in 5 hours. On distillation of the product, a considerable amount of dihexylamine was recovered, and all fractions contained halogen. It was not possible to effect satisfactory purification of this material.

*B. Excess amine method.* A mixture of 30 g. of dihexylamine and 5.2 g. of glycerol-$\alpha,\gamma$-dichlorohydrin, heated in a sealed tube at 140–150° for 4 hours gave 10.25 g. of material, b.p. 173–178°/0.1 mm. This product was free of halogen.

*Bis-1,3-didecylaminopropanol-2.* A solution of 46 g. of didecylamine and 5.0 g. of glycerol-$\alpha,\gamma$-dichlorohydrin in 55 ml. of xylene was refluxed for 8 hours. After adding 250 ml. of ether, the didecylamine hydrochloride was filtered off. Yield: 23.1 g. (theory, 25.6 g.).

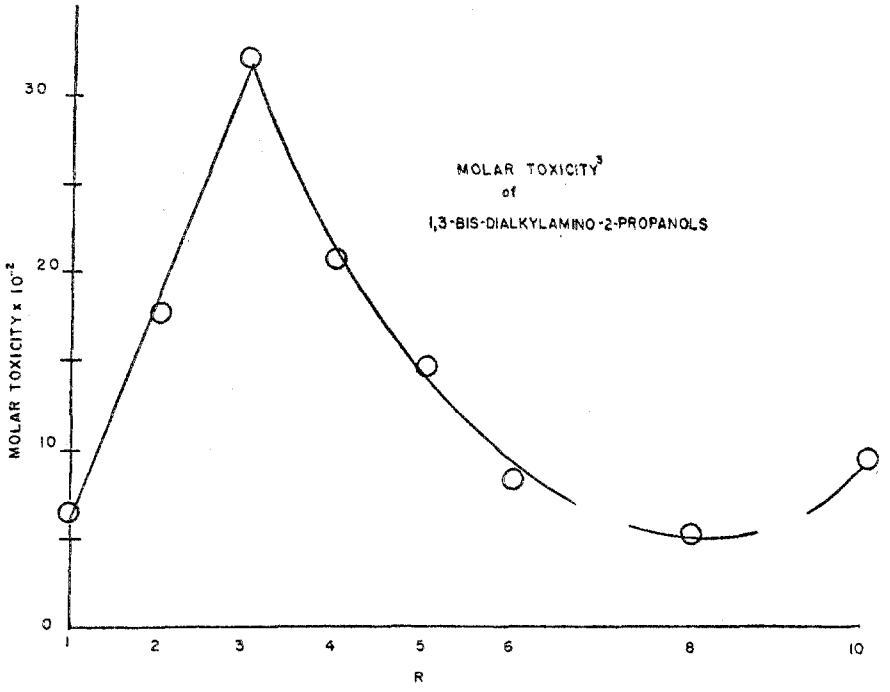



FIG. 2.

After removal of the ether from the filtrate, it was dissolved in petroleum ether, (b.p. 85–100°), and the dihydrochloride of the diamino alcohol was precipitated by the addition of anhydrous HCl. Purification was effected by recrystallization from *petroleum ether*, (b.p. 85–100°); m.p. 105–150°.

Titration of the dihydrochloride with standard alkali indicated a molecular weight of 750 (theory, 724). (The molecular weight of the hydrochloride, determined cryoscopically by the f.p. depression of benzene was 2400, probably indicating association in this solvent.)

The base is insoluble in water and methanol, and soluble in other organic solvents. The dihydrochloride is insoluble in water, and soluble in methanol and other organic solvents, including ether and petroleum ether. The dihydrochloride does not appear to hydrolyze in the presence of water.

*Acknowledgment.* The toxicity studies were by Dr. N. B. Eddy, and the antimalarial screening by Dr. G. Robert Coatney, both of the National Institutes of Health. The microanalyses were by Mr. E. A. Garlock, formerly of this Institute.

SUMMARY

A series of 1,3-bis-dialkylamino-2-propanols has been prepared, screened for antimalarial activity, and found wanting. Some physical and toxicological properties of these compounds are briefly discussed.

BETHESDA, 14, MD.

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