approximately 0.9 of an equivalent of oxygen in two hours. Ethyl ether alone under similar conditions absorbed no oxygen; phenacyl bromide in ether absorbed at a very slow rate. The hydrochloride of (IIIa) in 50% aqueous ethanol absorbed no oxygen when shaken for two hours.

Phenyl-di-*n*-butylaminomethylcarbinol (IVa). An *i*-propanol solution of 5.0 g. (0.0203 mole) of (IIIa) was reduced[14] with aluminum *i*-propoxide (eight hours). After removal of solvent *in vacuo*, the residue was decomposed by treatment with 3 *N* aqueous sodium hydroxide and extracted with ether. Distillation *in vacuo* gave 3.5 g. (69%) of nearly constant boiling light yellow oil; a cut, b.p. 119–121° (1 mm.)[15], was analyzed.

Anal. Calcd. for $C_{16}H_{37}NO$: C, 77.07; H, 10.92; N, 5.62. Found: C, 77.36; H, 11.15; N, 5.86.

(IVa) remained unaltered on standing (and gave no test for ketone with 2,4-dinitrophenylhydrazine reagent); the 3,5-dinitrobenzoate crystallized in prisms from isopropyl ether–ethanol, m.p. 103–105°; the picrate was an oil.

6-Methoxy-4'-(α-di-*n*-hexylaminomethyl)quinolinemethanol (IVb).[4a]—Di-*n*-hexylamine[16] (28.6 g. = 0.154 mole) was dissolved in 65 ml. of ether and 18.6 g. (0.0515 mole) of 6-methoxy-4-bromoacetylquinoline hydrobromide[17] was added during three minutes (system under nitrogen). A crystalline precipitate began to form immediately and the mixture rapidly thickened to a paste; this was stirred for two hours and forty-five minutes and quickly filtered; the precipitate was washed with ether, and the ether removed from the filtrate and washings under reduced pressure. To the residue were added 350 ml. of anhydrous isopropanol and 69 g. (0.296 mole) of aluminum *i*-propoxide and the solution was refluxed for fifty-two hours (until the distillate no longer gave a precipitate with 2,4-dinitrophenylhydrazine reagent). After removing 200 ml. of solvent *in vacuo*, ice was added, then 75 ml. of 12 *N* hydrochloric acid and the aqueous phase was next made strongly alkaline (to *p*H 10) with sodium hydroxide solution and the phases separated. The organic phase was dried, the solvent removed *in vacuo* and the residue was taken up in ether. Ethereal picric acid was added slowly; the solution was decanted from the tarry material which precipitated first. After excess of picric acid had been added, the dipicrate of (IVb) was filtered off and washed with cold acetonitrile, yield 10.7 g., m. p. 160–165°; an additional 2.0 g. was recovered from washings and mother liquors (total yield 29% from (Ib)). A sample was recrystallized from acetonitrile, m.p. 169° (lit.[4a] m.p. 173°).

The dihydrochloride of (IVb) was prepared from the dipicrate by treating with excess of 6 *N* hydrochloric acid, extracting the picric acid with ethyl acetate, then making the aqueous phase strongly alkaline, extracting the free base with ether and gradually adding ethereal hydrochloric acid which precipitated the dihydrochloride, m.p. 155° dec.

Anal. Calcd. for $C_{24}H_{38}N_2O_2 \cdot 2HCl$: N, 6.10. Found: N, 5.90.

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(14) *Cf.*, for example, Jacobs, Winstein, *et al.*, ref. 6.

(15) The boiling point, lower than that of (IIIa), is noteworthy.

(16) Prepared according to the directions of King and Work[4a]; intermediates[4] and final product[4a] were characterized as follows: di-*n*-hexylbenzylamine, b.p. 183° at 14 mm., b.p. 137° at *ca.* 1 mm., dilituratе m.p. 165–166°, 3,5-dinitrobenzoate and picrate oils; *n*-hexylbenzylamine, b.p. 100° at 1 mm., 3,5-dinitrobenzoate m.p. 141–142°, picrate oil; di-*n*-hexylamine, b.p. 98° at 5 mm., picrate m.p. 58.0–59.8°, 3,5-dinitrobenzoate m.p. 98.0–99.5°, hydrobromide m.p. 263–268° (prior softening). This series of compounds and derivatives illustrates the superiority in some cases of 3,5-dinitrobenzoates [Buehler, Currier and Lawrence, *Ind. Eng. Chem., Anal. Ed.*, **5**, 277 (1933)] over picrates, and the usefulness of dilituric (5-nitrobarbituric) acid [Redemann and Niemann, THIS JOURNAL, **62**, 590 (1940) when both picric and dinitrobenzoic acids fail to give crystalline derivatives.

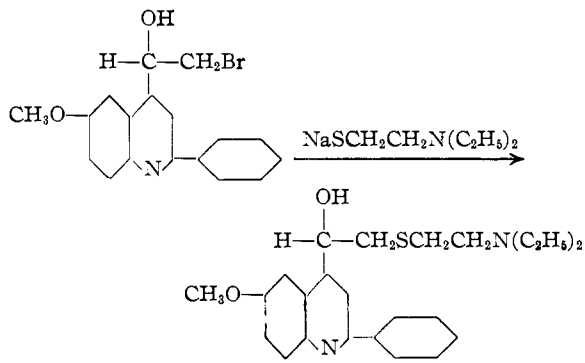
(17) Prepared by the method of Rabe, Pasternack and Kindler, *Ber.*, **50**, 150 (1917); yield 75%, m.p. 195–196° dec.

α-(2-Diethylaminoethylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol and a Homolog[1]

BY HENRY GILMAN, ROBERT A. BENKESER AND LEO TOLMAN

The recent availability of β-diethylaminoethyl mercaptan and γ-diethylaminopropyl mercaptan[2] suggested their application in the synthesis of some appropriately substituted 4-quinolinemethanols.[3] The use of some sulfur side-chains in other quinolines examined for avian malaria has been reported.[4a]

We are now describing the synthesis of the dihydrochlorides of α-(2-diethylaminoethylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol,[4b] and the homolog[4c] having 3-diethylaminopropylmercaptomethyl in the side-chain. The syntheses were effected by reaction of α-bromomethyl-6-methoxy-2-phenyl-4-quinolinemethanol with the sodium salt of the appropriate diethylaminoalkyl mercaptan.



Experimental

α-(2-Diethylaminoethylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol, Dihydrochloride.—The sodium mercaptide was prepared by adding 8.1 g. (0.06 mole) of β-diethylaminoethyl mercaptan to sodium ethoxide prepared from 1.15 g. (0.05 g. atom) of sodium in 200 cc. of absolute ethanol. To this solution was added 12 g. (0.34 mole) of α-bromomethyl-6-methoxy-2-phenyl-4-quinolinemethanol, prepared by the reduction of the corresponding bromoacetyl compound with aluminum isopropoxide.[3] The mixture was refluxed gently for ten minutes with stirring. Subsequent to filtration to remove a small quantity of solid, the solution was made acidic with ethanolic hydrogen chloride. Most of the ethanol was removed by distillation at reduced pressure, and the residue was dissolved in water. The aqueous extract was

(1) A portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Iowa State College.

(2) Gilman, Plunkett, Tolman, Fullhart and Broadbent, THIS JOURNAL, **67**, 1845 (1945). See, also, Gilman and Woods, *ibid.*, **67**, 1843 (1945); and Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(3) Lutz, *et al.*, *ibid.*, **68**, 1813 (1946).

(4) (a) Gilman and Fullhart, *ibid.*, **67**, 1585 (1945); Gilman and Woods, *ibid.*, **67**, 1843 (1945); Gilman and Tolman, *ibid.*, **67**, 1847 (1945); Clinton and co-workers, *ibid.*, **67**, 594 (1945). (b) The Survey Number assigned to this drug by the Survey of Antimalarial Drugs is SN-13,719-4. The activities of these compounds will be tabulated in a forthcoming monograph. (c) The Survey Number assigned to this drug is SN-14,057-4.

neutralized with ammonium hydroxide and extracted with ether. After drying the ethereal extract, ethanolic hydrogen chloride was added until no further precipitation occurred. The mixture was cooled and filtered to give 14 g. of product melting at 206–211°. A recrystallization from about 100 cc. of 95% ethanol gave 10 g. (72%) of compound melting at 218–224°. Another crystallization from the same solvent gave 7.5 g. (54%) of light yellow needles melting at 220–224°.

Anal. Calcd. for $C_{24}H_{32}O_2N_2Cl_2S$: Cl, 14.69; S, 6.63; N, 5.80. Found: Cl, 14.92; S, 6.38; N, 5.79.

α-(3-Diethylaminopropylmercaptomethyl)-6-methoxy-2-phenyl-4-quinolinemethanol, Dihydrochloride.—The sodium mercaptide was prepared by adding 5.9 g. (0.04 mole) of γ-diethylaminopropylmercaptan to sodium ethoxide prepared from 0.69 g. (0.03 g. atom) of sodium in 150 cc. of absolute ethanol. After addition of 7.8 g. (0.022 mole) of the bromohydrin, the reddish solution was refluxed with stirring for one-half hour. The subsequent operations were those described above for the next lower homolog. It was found desirable to crystallize the yellow dihydrochloride, obtained subsequent to addition of ethanolic hydrogen chloride, from absolute ethanol. The first crystallization yielded a hygroscopic solid, but the product obtained after another crystallization was essentially non-hygroscopic. This yellow amorphous solid, after drying in a vacuum desiccator over phosphorus pentoxide, melted at 182–185° with preliminary softening. The yield was 8 g. (73%).

Anal. Calcd. for $C_{25}H_{34}O_2N_2Cl_2S$: Cl, 14.28; S, 6.45. Found: C, 13.95; S, 6.69.

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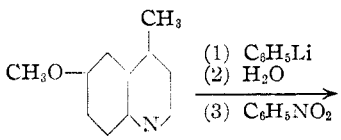
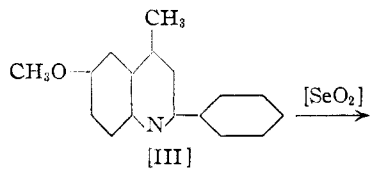
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

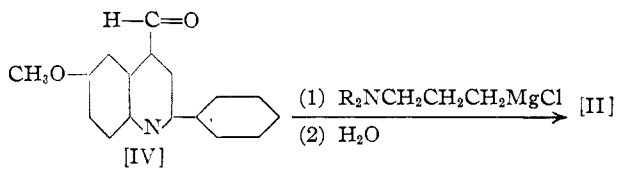
α-(3-Dialkylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanols[1]

BY HENRY GILMAN, FREDERICK J. MARSHALL AND ROBERT A. BENKESER

Incidental to studies on experimental avian malaria, it was desirable to compare the effectiveness of α-(dialkylaminomethyl)-2-phenyl-6-methoxy-4-quinoline methanols [I][2] with homologs like α-(3-dialkylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanols [II]. Several unsuccessful attempts[3a] were made to prepare compounds of type [II]. Finally, the compounds (where R = $-N(C_2H_5)_2$[3b] and $-N(C_4H_9\text{-}n)_2$) were synthesized by the sequence of reactions





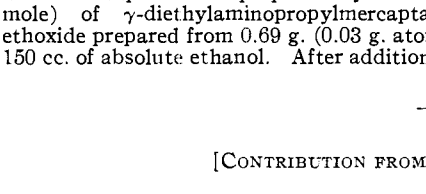


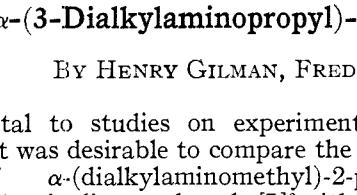
In the conversion of the aldehyde [IV] to the 4-quinolinemethanol [II] it was necessary to use the activated copper–magnesium alloy[4,11] to form the Grignard reagent from γ-diethylaminopropyl chloride and γ-di-*n*-butylaminopropyl chloride.

The arylation of 6-methoxy-4-methylquinoline to give a 2-aryl type may be a procedure of choice in some cases. This general procedure was used recently[5a] for the preparation of some quinolines patterned as "open models" of atebrin. In the present study [III] was formed in satisfactory yields (73–87%) by the action of phenyllithium, followed by the use of nitrobenzene as an oxidizing agent to remove the two hydrogens in the precursory dihydro compound. The compound [III] was previously obtained in 9% yield by John and Noziczka[5b] from *p*-anisidine hydrochloride and benzalacetone.

Experimental

2-Phenyl-6-methoxy-4-methylquinoline.—To a stirred solution of 75 g. (0.435 mole) of 6-methoxy-4-methylquinoline, prepared both by the method of Ainley and King[6]





(1) Most of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Iowa State College.

(2) *Cf.* Lutz *et al.*, THIS JOURNAL, **68**, 1813 (1946).

(3) (a) Gilman and Tolman, *ibid.*, **68**, 1848 (1946). (b) The Survey Number, assigned to this drug by the Survey of Antimalarial Drugs is SN-12,858-4. The activities of these compounds will be tabulated in a forthcoming monograph.

(4) Gilman, Peterson, and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

(5) (a) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944); (b) John and Noziczka, *J. prakt. Chem.*, [2] **111**, 65 (1925).

(6) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938). This procedure was found more adaptable to large runs.