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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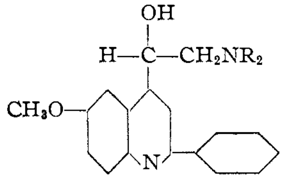
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

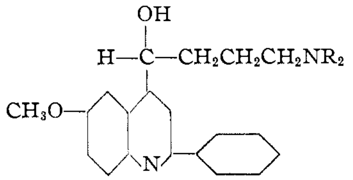
α-(3-Dialkylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanols[1]

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



[I]



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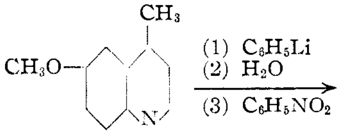

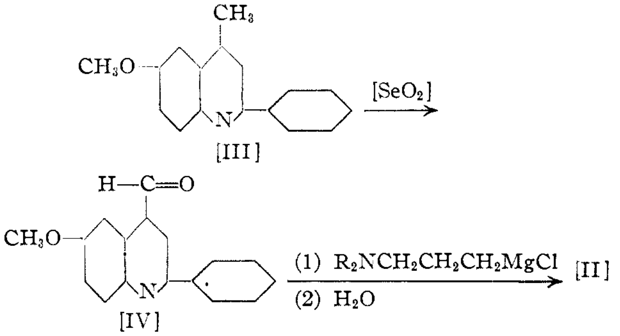

[III]

[IV]

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]

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[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.

and of Campbell and Schaffner,[7] in 250 cc. of dry ether cooled in an ice-bath was added at a rapid dropwise rate a solution of 0.5 mole of phenyllithium[8] in 300 cc. of anhydrous ether. The reaction was carried out in a dry nitrogen atmosphere, with stirring, and the time of addition was forty minutes. Stirring was continued for fifteen minutes with cooling provided by an ice-bath, and then for an additional thirty minutes after removal from the ice-bath; and hydrolysis was effected by pouring the mixture into one liter of ice water. The ether layer was separated, the aqueous layer was extracted four times with ether, and the combined ether solutions were added to 75 cc. of nitrobenzene. During this dehydrogenation by nitrobenzene, the solution turned deep red in color, and after standing overnight the ether was removed by distillation. Then, during the removal of nitrobenzene by steam distillation, the product solidified. After filtration, the solid was recrystallized from a mixture of 180 cc. of benzene and 360 cc. of petroleum ether (b. p., 60–68°) to give 80 g. (73%) of product melting at 128–130°.[9]

2-Phenyl-6-methoxyquinoline-4-aldehyde.—To a stirred solution, heated to gentle reflux, of 49.8 g. (0.2 mole) of 2-phenyl-6-methoxy-4-methylquinoline was added, during two and one-half hours, a warm solution of 26.2 g. (0.184 mole) of freshly sublimed selenium dioxide in 230 cc. of dioxane and 12 cc. of water.[10] After stirring and refluxing for an additional two hours, the hot solution was filtered to remove the selenium, and the dioxane was then removed by distillation under reduced pressure. On cooling, the product solidified; and after dissolving in 325 cc. of absolute ethanol, the solution was decanted from a residuum of selenium. Recrystallization was effected by dissolving in 425 cc. of absolute ethanol, filtering and then concentrating to 300 cc. to yield 19.2 g. (37%) of compound melting at 135–137°. The melting point was raised to 136.5–137.5° after another crystallization from absolute ethanol and then from a mixture of benzene and petroleum ether (b. p., 60–68°).

Anal. Calcd. for $C_{17}H_{13}ON$: N, 5.33. Found: N, 5.08.

The **2-phenyl-6-methoxyquinoline-4-aldoxime** melted at 185.5–187° after recrystallization from methanol.

Anal. Calcd. for $C_{17}H_{14}ON_2$: N, 10.08. Found: N, 10.05.

α-(3-Diethylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanol.—The procedure employed was essentially that of Marxer.[11] To a suspension of 1 g. of pure magnesium and 1 g. of activated copper–magnesium alloy[4] in 15 cc. of dry ether was added ten drops of dry ethyl bromide. Then 8.5 g. (0.057 mole) of freshly distilled γ-diethylaminopropyl chloride[12] was added over a three-minute period. A white precipitate formed and an exothermic reaction set in. Ten more drops of ethyl bromide was added, and the mixture was heated at reflux for five minutes. Then 5 g. (0.019 mole) of 2-phenyl-6-methoxyquinoline-4-aldehyde in 85 cc. of dry thiophene-free benzene was added portionwise over a seventy-five minute period. There was little evidence of reaction, but the precipitate appeared to dissolve. After refluxing for twenty hours, the mixture was hydrolyzed by an iced saturated ammonium chloride solution. Subsequent to filtration to remove the alloy and a trace of magnesium, the organic layer was separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over sodium sulfate; the solvent was removed under reduced pressure on a water-bath, and the heavy, brown oily residue which remained was dissolved in a small volume of ether. The dropwise addition of ethanolic hydrogen chloride precipitated the hydrochloride which was obtained in a yield of 8.3 g. (97%). After two recrystallizations from a warm mixture of 95% ethanol and ether, the compound melted with decomposition in a rapidly heated bath at 238–244°. The yield of purified compound was 63%.

Anal. Calcd. for $C_{24}H_{30}O_2N_2 \cdot 2HCl$: N, 6.22; Cl, 15.74. Found: N, 6.12; Cl, 15.80.

α-(3-Di-*n*-butylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanol.—The procedure used for this synthesis was like that described for the preceding preparation. The reactants were 5 g. (0.019 mole) of the aldehyde, 1 g. of magnesium, 1 g. of the activated copper–magnesium alloy, and 11.7 g. (0.057 mole) of γ-di-*n*-butylaminopropyl chloride, prepared in accordance with the method of Marxer.[11] After refluxing the mixture for twenty-four hours, 8 g. of a gummy hydrochloride was obtained. This was recrystallized three times from a mixture of 95% ethanol and ether to give 5 g. (52%) of a light yellow product melting at 200–203°.

Anal. Calcd. for $C_{28}H_{38}O_2N_2 \cdot 2HCl$: N, 5.54; Cl, 14.0. Found: N, 5.80; Cl, 13.83.

Summary

α-(3-Diethylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanol and α-(3-di-*n*-butylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanol were prepared by reaction of 2-phenyl-6-methoxyquinoline-4-aldehyde with the Grignard reagents prepared from $R_2NCH_2CH_2CH_2Cl$. It was necessary to use the activated copper-magnesium alloy to prepare the RMgCl compounds.

The aldehyde was prepared by the selenium dioxide oxidation of the corresponding 4-methyl compound, and this 2-phenyl-6-methoxy-4-methylquinoline was obtained in satisfactory yield from 6-methoxy-4-methylquinoline and phenyllithium.

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[7] Campbell and Schaffner, THIS JOURNAL, **67**, 86 (1945).

[8] See, Gilman, Zoellner and Selby, *ibid.*, **54**, 1957 (1932) for a general procedure for the preparation of RLi types.

[9] From a comparable experiment, Mr. A. E. Lindblad obtained an 87% yield of product melting at 128–129.5°.

[10] See, Kaplan, THIS JOURNAL, **63**, 2654 (1941), and Johnson and Hamilton, *ibid.*, **63**, 2864 (1941), for some recent applications of the oxidation of methylquinolines to aldehydes by selenium dioxide.

[11] Marxer, *Helv. Chim. Acta.*, **24**, 209E (1941). See, also Gilman and Heck, *Ber.*, **62**, 1379 (1929) for an early application of the activated copper-magnesium alloy for the preparation of Grignard reagents of the type: $R_2NCH_2CH_2MgCl$.

[12] Gilman and Shirley, THIS JOURNAL, **66**, 888 (1944).