NOTES

The Preparation of Aryldialkylaminomethylcarbinols[1]

By David R. V. Golding[2a] and William H. McNeely[2b]

6-Methoxy-4-(α-di-*n*-hexylaminomethyl)-quinolinemethanol (SN-2572)[3] prepared by King and Work[4] by treatment of 6-methoxy-4-bromoacetylquinoline with di-*n*-hexylamine, followed by reduction of the ketone, was shown to possess antimalarial activity and it was desired to resynthesize it for further pharmacological testing. Since King and Work had found that the synthesis did not proceed smoothly, a model experiment was first carried out, using phenacyl bromide and di-*n*-butylamine.

$$\underset{\text{I}}{\text{ArCOCH}_2\text{Br}} + \underset{\text{II}}{\text{HNR}_2} \longrightarrow$$

Series a

Ar	Phenyl
R	*n*-Butyl

$$\underset{\text{III}}{\text{ArCOCH}_2\text{NR}_2} \longrightarrow \underset{\text{IV}}{\text{ArCHOHCH}_2\text{NR}_2}$$

Series b

Ar	6-Methoxy-4-quinolyl
R	*n*-Hexyl

The phenyl di-*n*-butylaminomethyl ketone (IIIa) so obtained could be distilled without appreciable decomposition at 123° (1 mm.) but deteriorated rapidly when kept at 0° in contact with the atmosphere. Other workers[5,6] have also noted the instability of aryl dialkylaminomethyl ketones. In order to clarify the nature of this decomposition, phenyl di-*n*-butylaminomethyl ketone (IIIa) was shaken with oxygen in a closed system; one molecular equivalent of oxygen was absorbed rapidly yielding a product which was easily broken down into benzoic acid and di-*n*-butylamine (IIa). Under similar conditions the hydrochloride of (IIIa) did not react appreciably so that the oxidation effect is markedly dependent[7] upon *p*H conditions.

It thus appears that difficulties in obtaining carbinolamines by reduction of type (III) ketones may be due, at least in part, to autoxidation phenomena. More successful results are to be anticipated employing the technique suggested by Jacobs, Winstein, *et al.*,[6] of carrying out operations involving such ketones in an inert atmosphere. Making use of this principle we were able to reproduce[8] the King–Work synthesis of 6-methoxy-4-(α-di-*n*-hexylaminomethyl)quinolinemethanol (IVb).

Experimental[9]

Phenyl Di-*n*-butylaminomethyl Ketone (IIIa).—Di-*n*-butylamine (IIa) (49 g. = 0.38 mole) (Sharples, redistilled) was dissolved in 70 ml. of anhydrous ether[10]; the system was swept out with nitrogen and a solution of 25.2 g. (0.127 mole) of phenacyl bromide (Ia) (Eastman Kodak Co.) in 80 ml. of ether added dropwise with stirring. A crystalline precipitate of (IIa) hydrobromide[11] formed; the mixture was stirred for two and one-half hours, filtered, the precipitate washed with ether, and the solvent stripped from the combined filtrate and washings. Distillation of the residual oil *in vacuo* (nitrogen pulled through capillary) gave a main fraction consisting of a golden yellow oil, phenyl di-*n*-butylaminomethyl ketone (IIIa), b.p. 122–123° at 1 mm., weight 21.5 g. (68.5%).

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.74; H, 10.20; N, 5.67. Found: C, 77.72; H, 9.92; N, 6.08.

Prepared in the usual way by mixing *i*-propyl ethereal solutions of the components, the picrate of (IIIa) was obtained as an oil (which in a single experiment crystallized on standing, m.p. 87.5–89°[12]); the 3,5-dinitrobenzoate[13] as an oil which crystallized, m.p. 154–155° from isopropyl ether–ethanol.

Autoxidation of Phenyl Di-*n*-butylaminomethyl Ketone (IIIa).—On shaking 0.172 g. of (IIIa) in an oxygen atmosphere with no solvent, the gas was absorbed at a moderate rate until approximately one equivalent had been taken up (twelve hours); the absorption then continued at a slower rate, approximately 1.3 equivalents being taken up in twenty-six hours. The red oil which remained was treated with cold aqueous 3*N* potassium hydroxide; then ether was added and the phases separated. Acidification of the aqueous solution gave benzoic acid (mixed m.p.); addition of ethereal 3,5-dinitrobenzoic acid to the dried ether layer precipitated the di-*n*-butylamine salt (mixed m. p.).

Treatment of an ethereal solution of (IIIa) with oxygen under the same conditions resulted in the absorption of

(1) 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 the California Institute of Technology Dr. E. R. Buchman, Director.

(2) Present address: (a) Experimental Station, E. I. du Pont de Nemours, Wilmington, Delaware, (b) Kelco Company, San Diego 1, California.

(3) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which survey numbers have been assigned will be tabluated in a forthcoming monograph.

(4) (a) King and Work, *J. Chem. Soc.*, 1307 (**1940**); (b) 401 (**1942**).

(5) Rabe and Schneider, *Ber.*, **41**, 875 (1908), report that phenyl piperidinomethyl ketone decomposes on standing and is easily split in the presence of alkali (sodium benzoate was formed after treatment with sodium ethylate).

(6) Jacobs, Winstein, *et al.*, *J. Org. Chem.*, **11**, 22 (1946), noted the instability of aryldialkylaminomethyl ketones; in the 4-methoxy-naphthyl-1 series these authors found it necessary to work in a nitrogen atmosphere; otherwise 4-methoxy-1-naphthoic acid was the only product isolated.

(7) The reaction with oxygen also depends upon structural factors: phenyl α-*N*-methylpiperidyl ketone (Buchman, Reims and Sargent, unpublished) and 6-methoxyquinolyl-4 α-piperidyl ketone (Sargent, This Journal, **68**, in press (1946)) decompose (presumably by the autoxidation mechanism) while 6-methoxyquinolyl-4 α-quinuclidyl ketone has been shown (D. R. Howton, unpublished) to be stable to oxygen (cf. Doering and Chanley, This Journal, **68**, 586 (1946)).

(8) King and Work[4a] converted (IIIb) to (IVb) by catalytic reduction while, in this work, this step was accomplished using aluminum isopropoxide. The studies of Campbell and Kerwin, This Journal, **68**, 1837 (1946), indicate that this latter method possesses no advantages in this series.

(9) All melting points are corrected. For microanalyses, we are indebted to Dr. G. Oppenheimer and her staff of this Institute.

(10) A run employing acetone as solvent (final reaction temperature 50°) gave a comparable yield (73%) of (IIIa).

(11) This salt is extremely soluble in chloroform; (IIb) hydrobromide is somewhat less soluble; the hydrochloride of (IIa) may be extracted readily from an aqueous solution by this solvent.

(12) Di-*n*-butylamine picrate, m.p. 64.5°, Mitchell and Bryant, This Journal, **65**, 136 (1943).

(13) Corresponding derivative of di-*n*-butylamine, m.p. 148.0–149.3°.

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.

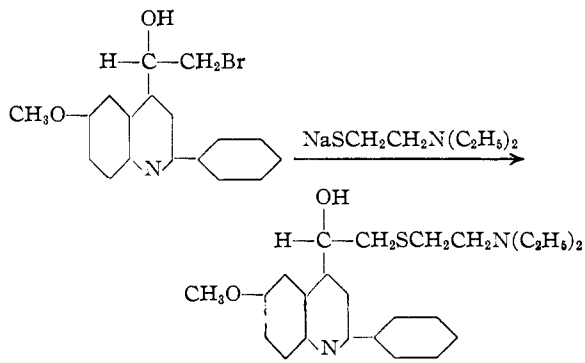
(17) Prepared by the method of Rabe, Pasternack and Kindler, *Ber.*, **50**, 150 (1917); yield 75%, m.p. 195–196° dec.

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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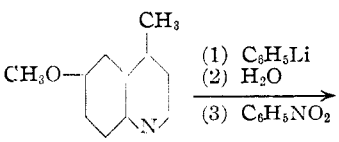
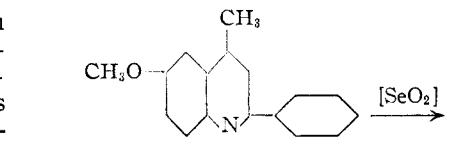
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

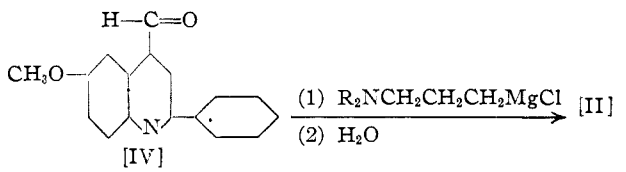
α-(3-Dialkylaminopropyl)-2-phenyl-6-methoxy-4-quinolinemethanols[1]

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.