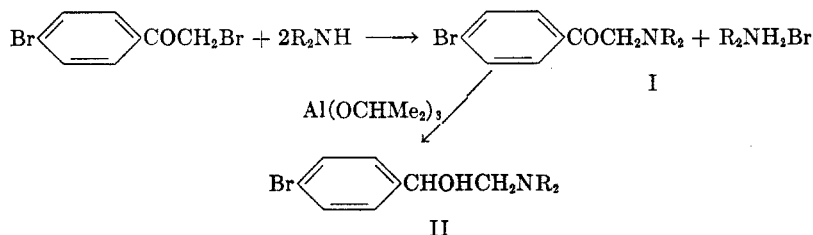


SYNTHETIC ANTIMALARIALS. β -DIALKYLAMINOETHANOLS¹NATHAN L. DRAKE AND LEON GOLDMAN²

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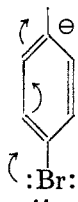
Certain amino alcohols, notably the cinchona alkaloids, *e.g.*, quinine, and some 4-quinoline methanols, *e.g.*, α -(6'-methoxy-1'-quinolyl)- β -di-*n*-butylaminoethanol, have been found to possess antimalarial activity (1, 2, 3, 4, 5). Both these types of compounds possess the grouping ArCHOHCHN— . In order to evaluate the β -dialkylaminoethanol moiety, compounds of structure (II) were synthesized according to the following scheme:



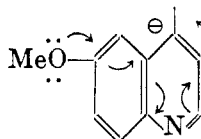
in I where $\text{NR}_2 = \text{N}(\text{C}_2\text{H}_5)_2$, III; hydrobromide, IV; hydrochloride, V
 $= \text{N}(\text{C}_3\text{H}_7\text{-}n)_2$, VI; hydrobromide, VII; hydrochloride, VIII
 $= \text{N}(\text{C}_4\text{H}_9\text{-}n)_2$, IX; hydrobromide, X
 $= \text{NC}_5\text{H}_{10}$,³ XI; hydrochloride, XII

in II where $\text{NR}_2 = \text{NH}(\text{C}_2\text{H}_5)_2^+ \text{Br}^-$, XIII
 $= \text{NH}(\text{C}_3\text{H}_7\text{-}n)_2^+ \text{Br}^-$, XIV
 $= \text{NH}(\text{C}_4\text{H}_9\text{-}n)_2^+ \text{Br}^-$, XV
 $= \text{NHC}_5\text{H}_{10}^+ \text{Cl}^-$, XVI

The *p*-bromophenyl group was chosen because of its nearly identical molecular weight to the methoxyquinolyl group, the former being 156 and the latter 158; and also because of the similar electron displacements of the two groups (XVII) and (XVIII).



XVII



XVIII

¹ Taken in part from a thesis submitted by Leon Goldman to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, 1944.

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³ NC_5H_{10} represents the piperidyl group.

The ω -dialkylamino-*p*-bromoacetophenones (III), (VI), (IX), and (XI), were prepared according to Marvel and du Vigneaud (6) and were isolated as their hydrobromide and hydrochloride salts, (IV), (V), (VII), (VIII), (X), and (XII), in yields of 87–100%.

The amino ketones (III), (VI), and (XI), were reduced as free bases by means of aluminum isopropoxide according to Meerwein and Schmidt (7) and Ponndorf (8) to produce the desired amino alcohols which were isolated as the salts (XIII), (XIV), and (XVI), in yields of 70, 70, and 81%, respectively. The free base of the di-*n*-butylamino ketone (IX) was too sensitive to this reagent, being decomposed by it even at room temperature. Acting on the suggestion of Dr. Lyndon F. Small of the National Institute of Health the hydrobromide salt (X), instead of the free base (IX), was reduced with aluminum isopropoxide. There was no sign of decomposition and the amino alcohol hydrobromide (XV) was obtained in 93% yield.

The amino ketones could not be reduced to amino alcohols by means of Adams' platonic oxide catalyst and hydrogen. The only crystallizable products from catalytic reduction of amino ketone hydrobromides (IV) and (X) were recovered starting material. Catalytic reduction of amino ketone hydrochlorides (V), (VIII), and (XII), gave products which proved to be mixtures of the hydrobromides and hydrochlorides of recovered amino ketones. Reductive fission of some bromine atoms in the *para* position must have occurred, producing hydrogen bromide. The unreacted amino ketone molecules were then obtained as crystalline mixed hydrobromides and hydrochlorides. Thus the product, m.p. 186.4–187.4°, isolated from catalytic reduction of (V) had the following analysis: C, 41.62; H, 4.97, which is not in agreement with the calculated values for the ethanolamine hydrochloride, $C_{12}H_{19}BrClNO$: C, 46.69; H, 6.20; but rather corresponds to a mixture of (IV) and (V). In fact, the product of the reduction, when treated with alkali, yielded a free base which was converted to a hydrochloride identical with (V). The aqueous solution from the liberation of the free base was found to contain bromide ions.

Compounds (XIII), SN 5668, (XIV), SN 5651, (XV), SN 5862, and (XVI), SN 5854, were submitted for antimalarial testing to the Survey of Antimalarial Drugs and were found to be active.

EXPERIMENTAL

Condensation of secondary amines with p-bromophenacyl bromide. To a solution of one mole of *p*-bromophenacyl bromide in the minimum amount of anhydrous benzene necessary for complete solution at 0° was added two moles of secondary amine. The mixture was shaken and cooled in ice to remove the heat of reaction. The secondary amine hydrobromide usually started to precipitate after several minutes. After refrigerating for two to twenty-four hours the suspension was treated with excess anhydrous ether and a nearly quantitative yield of secondary amine hydrobromide was obtained by filtration and washing with anhydrous ether until colorless.

The combined benzene-ether filtrate was chilled with ice and saturated with dry hydrogen bromide or hydrogen chloride and the precipitated amino ketone salt was removed by filtration, washed with anhydrous ether, and crystallized from absolute ethanol-anhydrous ether.

ω-Diethylamino-*p*-bromoacetophenone hydrobromide (IV). Reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide with 7.3 g. (0.1 mole) of diethylamine in 150 cc. of anhydrous benzene for two hours at ice temperature yielded 7.5 g. (98%) of diethylamine hydrobromide. The yield of amino ketone hydrobromide, obtained as pale yellow crystals, was 17.5 g. (100%). Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 193.1–193.8°.

Anal. Calc'd for $C_{12}H_{17}Br_2NO$: C, 41.05; H, 4.88; Br,⁴ 22.76.

Found: C, 41.57;⁵ H, 4.88;⁵ Br, 22.6.

ω-Diethylamino-*p*-bromoacetophenone hydrochloride (V). This compound was prepared in 96% yield from *p*-bromophenacyl bromide and diethylamine as described above, and from the hydrobromide salt (IV): a solution of 21.1 g. (0.06 mole) of *ω*-diethylamino-*p*-bromoacetophenone hydrobromide in 100 cc. of water was made alkaline with aqueous potassium carbonate to liberate the free amino ketone base as a yellow oil. The oil was extracted with ether, and the ether extract was dried over Drierite and saturated with dry hydrogen chloride. The resulting pale yellow gummy precipitate was dried in a vacuum desiccator over phosphorus pentoxide and crystallized from absolute ethanol-anhydrous ether, yielding 17.7 g. (97%) of colorless crystals. When recrystallized from absolute ethanol-anhydrous ether the product melted at 172.6–173.6°.

Anal. Calc'd for $C_{12}H_{17}BrClNO$: C, 47.00; H, 5.59; Cl,⁴ 11.56.

Found: C, 46.51;⁶ H, 5.69;⁶ Cl, 11.5.

ω-Di-*n*-propylamino-*p*-bromoacetophenone hydrobromide (VII). A twenty-hour reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide with 10.1 g. (0.1 mole) of di-*n*-propylamine in 150 cc. of anhydrous benzene, followed by addition of 300 cc. of anhydrous ether, yielded 8.8 g. (97%) of di-*n*-propylamine hydrobromide. The benzene filtrate was concentrated on the steam-bath to 200 cc., cooled in ice, and saturated with dry hydrogen bromide. After adding 300 cc. of anhydrous ether, 17.1 g. (90%) of pale green hydrobromide was obtained. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 184.2–184.8°.

Anal. Calc'd for $C_{14}H_{21}Br_2NO$: C, 44.35; H, 5.53; Br,⁴ 21.09.

Found: C, 44.46, 44.60, 44.70; H, 5.38, 5.86, 5.54; Br, 21.3.

ω-Di-*n*-propylamino-*p*-bromoacetophenone hydrochloride (VIII). This compound was obtained in 95% yield (16.2 g.) by saturating an anhydrous benzene solution of *ω*-di-*n*-propylamino-*p*-bromoacetophenone (VI) (from reaction of 13.9 g. of *p*-bromophenacyl bromide and 10.1 g. of di-*n*-propylamine) with dry hydrogen chloride, with the addition of anhydrous ether. Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 171.7–172.6°.

Anal. Calc'd for $C_{14}H_{21}BrClNO$: C, 50.24; H, 6.32; Cl,⁴ 10.59.

Found: C, 49.11, 49.73, 49.27; H, 6.08, 6.26, 6.03; Cl, 10.4.

ω-Di-*n*-butylamino-*p*-bromoacetophenone hydrobromide (X). Reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide dissolved in 150 cc. of anhydrous benzene with 12.9 g. (0.1 mole) of di-*n*-butylamine for twenty-four hours in the refrigerator, followed by dilution with anhydrous ether, yielded 10.4 g. (99%) of di-*n*-butylamine hydrobromide. Saturation of the filtrate with dry hydrogen bromide yielded 35.3 g. (87%) of nearly colorless amino ketone hydrobromide. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 176.5–177.5° (transition point at 145–146°).

Anal. Calc'd for $C_{16}H_{25}Br_2NO$: C, 47.19; H, 6.19; Br,⁴ 19.62.

Found: C, 47.23, 47.17; H, 6.21, 6.06; Br, 19.7.

ω-Piperidyl-*p*-bromoacetophenone hydrochloride (XII). Reaction of 27.8 g. (0.1 mole) of *p*-bromophenacyl bromide dissolved in 250 cc. of anhydrous benzene with 17 g. (0.2 mole) of freshly distilled piperidine for twenty-four hours in the refrigerator yielded 16.6 g.

⁴ Volhard titration of ionizable halogen.

⁵ Analysis by courtesy of Dr. Robert C. Elderfield, Columbia University.

⁶ Analysis by courtesy of Dr. Lyndon F. Small, National Institute of Health.

(100%) of piperidine hydrobromide. Saturation of the chilled filtrate with dry hydrogen chloride yielded 31.8 g. (100%) of cream-colored amino ketone salt. Crystallization from absolute ethanol yield colorless crystals, m.p. on slow heating 224.7–225.7°, on rapid heating 230.5–231.5°.

Anal. Calc'd for $C_{13}H_{17}BrClNO$: C, 49.00; H, 5.38; Cl, 11.13.

Found: C, 48.96, 48.79; H, 5.05, 5.13; Cl, 10.9.

Reduction of amino ketones with aluminum isopropoxide. Amino ketones (III), (VI), and (XI), were reduced in the following manner: a solution of 0.05 mole of amino ketone and 15.3 g. (0.075 mole) of aluminum isopropoxide in 100 cc. of anhydrous benzene was slowly distilled through a helix-packed fractionating column with controlled take-off until most of the benzene was removed, care being taken not to distil to dryness. To the residue was added 100 cc. of isopropanol and distillation was continued until the distillate no longer gave a test for acetone with 2,4-dinitrophenylhydrazine reagent. The remainder of the solvent was removed at 20 mm. pressure and the red-brown semi-crystalline residue was chilled and acidified with 100 cc. of ice-cold 10% hydrochloric acid to decompose the aluminum complex. The resulting solution was made strongly alkaline with ice-cold potassium hydroxide solution to liberate the free base of the amino alcohol and keep the aluminum in solution as the aluminate ion. The amino alcohol was extracted with benzene, the benzene solution was washed with water and dried over Drierite or by distillation into a moisture-point receiver, and the hydrobromide or hydrochloride salt precipitated by saturation with dry hydrogen bromide or hydrogen chloride.

α -(*p*-Bromophenyl)- β -diethylaminoethanol hydrobromide (XIII). Saturation of the benzene solution of the free base with hydrogen bromide produced a brown oil. All the benzene was removed *in vacuo*, and the residual oily hydrobromide was dissolved in absolute ethanol. When the ethanol solution was cooled in a dry ice-acetone bath, 12.1 g. (70%) of tan crystalline product was obtained. Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 135.0–135.5°.

Anal. Calc'd for $C_{12}H_{15}Br_2NO$: C, 40.81; H, 5.42; Br, 22.63.

Found: C, 40.93, 41.00; H, 5.28, 5.30; Br, 22.5, 22.5.

α -(*p*-Bromophenyl)- β -di-*n*-propylaminoethanol hydrobromide (XIV). The hydrochloric acid solution from decomposition of the aluminum complex contained a small amount of dark red oil in suspension. The oil was removed by extraction with ether. The amino alcohol hydrobromide was obtained as tan crystals which were crystallized from absolute ethanol-anhydrous ether to yield 13.4 g. (70%) of product. Further crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 138.3–139.3°.

Anal. Calc'd for $C_{14}H_{23}Br_2NO$: C, 44.11; H, 6.08; Br, 20.97.

Found: C, 44.15, 44.20; H, 5.85, 5.96; Br, 20.9.

α -(*p*-Bromophenyl)- β -piperidylethanol hydrochloride (XVI). The hydrochloric acid solution from decomposition of the aluminum complex contained a tan precipitate. Addition of 800 cc. of warm water dissolved all except a small amount of dark-colored gummy material which was removed by filtration. Saturation of the benzene solution of the amino alcohol free base produced a cream-colored precipitate. After adding 200 cc. of anhydrous ether, 13.0 g. (81%) of the hydrochloride was obtained. Crystallization from absolute ethanol yielded colorless crystals, m.p. 237.7–238.2°.

Anal. Calc'd for $C_{13}H_{19}BrClNO$: C, 48.69; H, 5.97; Cl, 11.06.

Found: C, 48.48, 48.53; H, 6.03, 6.10; Cl, 11.0.

α -(*p*-Bromophenyl)- β -di-*n*-butylaminoethanol hydrobromide (XV). A solution of 11.6 g. (0.0285 mole) of ω -di-*n*-butylamino-*p*-bromoacetophenone hydrobromide and 14.5 g. (0.071 mole) of aluminum isopropoxide in 100 cc. of anhydrous isopropanol was slowly distilled through a helix-packed fractionating column with controlled take-off until 60 cc. of distillate was collected. At this point the distillate gave a negative test for acetone with 2,4-dinitrophenylhydrazine reagent. The remainder of the isopropanol was removed by distillation at reduced pressure, leaving a colorless semi-solid residue. The residue was cooled in ice, acidified with 100 cc. of ice-cold 10% hydrochloric acid, and the resulting

suspension was completely dissolved by adding 700 cc. of water, yielding a colorless solution. The solution was cooled with ice and made strongly alkaline with ice-cold potassium hydroxide, causing a white solid to separate after the aluminum hydroxide, which first precipitated, redissolved. The suspension was extracted with five 50-cc. portions of benzene, and the colorless benzene extract was washed with water and then dried by distilling into a moisture-point receiver. The dry benzene solution was distilled to a volume of 150 cc. and then saturated with dry hydrogen bromide. The addition of 350 cc. of anhydrous ether caused a colorless oil to separate from solution. After standing overnight in the refrigerator the oil completely changed to colorless crystals weighing 10.8 g. (93%), m.p. 112–114°. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 113.0–114.0°.

Anal. Calc'd for $C_{16}H_{27}Br_2NO$: C, 46.96; H, 6.65; Br, 19.54.

Found: C, 46.90, 46.92; H, 6.76, 6.70; Br, 19.6.

SUMMARY

Reactions of *p*-bromophenacyl bromide with secondary amines were used to synthesize the following compounds: ω -diethylamino-*p*-bromoacetophenone hydrobromide and hydrochloride, ω -di-*n*-propylamino-*p*-bromoacetophenone hydrobromide and hydrochloride, ω -di-*n*-butylamino-*p*-bromoacetophenone hydrobromide, and ω -piperidyl-*p*-bromoacetophenone hydrochloride.

Aluminum isopropoxide reduction of the amino ketones, as the free bases, produced the following compounds: α -(*p*-bromophenyl)- β -diethylaminoethanol hydrobromide, α -(*p*-bromophenyl)- β -di-*n*-propylaminoethanol hydrobromide, and α -(*p*-bromophenyl)- β -piperidylethanol hydrochloride. α -(*p*-Bromophenyl)- β -di-*n*-butylaminoethanol hydrobromide was obtained by aluminum isopropoxide reduction of the amino ketone hydrobromide. The amino alcohol salts were found to possess antimalarial activity.

COLLEGE PARK, MD.

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