

resulting precipitate recrystallized from ethyl acetate-ethanol, giving 0.23 g. of the hydrochloride (60.5%), m.p. 184°.

Reaction with Dry Acetic Acid-Sodium Acetate to Give *dl-cis-2-Aminocyclohexanol*.—The resulting solution by refluxing 5 g. of glacial acetic acid, 1 g. of acetic anhydride and 1 g. of fused sodium acetate was added to 2 g. of "Product A" *p*-toluenesulfonate and the mixture refluxed for four hours with exclusion of moisture. After cooling, the reaction mixture was poured into water, causing the separation of an oily product which could not successfully be crystallized. After extracting with ether, washing with water, 5% sodium carbonate solution and water and evaporating to dryness, the oily residue was added to 20 ml. of 10% hydrochloric acid and refluxed for two hours. After cooling, separated benzoic acid was filtered off and the filtrate was evaporated to dryness on a steam-bath. The solid residue so obtained weighed 0.7 g. (90.9%) and was recrystallized from ethyl acetate-ethanol, giving 0.55 g. (71.4%) of colorless crystals, m.p. 184–185°. A mixed m.p. with *dl-cis-2-aminocyclohexanol* hydrochloride showed no depression.

Reaction with Acetic Anhydride to Give *dl-cis-2-Aminocyclohexanol*.—A mixture of 2 g. of "Product A" *p*-toluenesulfonate and 4 g. of acetic anhydride was refluxed. After cooling, and pouring of the reaction mixture into water the resulting oily product was extracted with ether and treated as previously described with dry AcOH-AcONa, giving 0.5 g. (65%) of *dl-cis-2-aminocyclohexanol* hydrochloride.

N-Ethylation of the 2-Aminocyclohexanols. *dl-trans-2-Ethylaminocyclohexanol*.—A mixture of 7.0 g. (1.3 mols) of ethyl bromide, 2.1 g. (1 mol) of sodium carbonate, 50 ml. of ethanol and 6 g. (1 mol) of *dl-trans-2-aminocyclohexanol* was refluxed on a steam-bath and after cooling the insoluble solid separated. The filtrate was concentrated to dryness, a small amount of water added and made alkaline with concd. sodium hydroxide. The resulting oil layer was extracted with ether, dried over fused sodium sulfate and distilled under reduced pressure; b.p. 104–105° (12 mm.) weight 5.5 g. (73%). Its hydrochloride melted at 155°, which was identified with a sample obtained from ethylamine and cyclohexene oxide.⁵

Anal. Calcd. for C₈H₁₇ON·HCl: N, 7.82. Found: N, 7.62.

***dl-trans-2-Diethylaminocyclohexanol* (a).**—A mixture of 5 g. of ethyl bromide, 4 g. of potassium carbonate, 50 ml. of ethanol and 5 g. of *dl-trans-2-ethylaminocyclohexanol* was refluxed on a steam-bath for five hours and after cooling the precipitate filtered off. The filtrate was made alkaline with

concd. sodium hydroxide and the resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure; the yield was 4 g. (67%), b.p. 111° (15 mm.), hydrochloride m.p. 173°. A mixed melting point with the diethyl compound obtained from cyclohexene oxide and diethylamine did not depress.

(b).—To one gram (1 mol) of *dl-trans-2-aminocyclohexanol* dissolved in warm dried nitrobenzene was added 4.2 g. (2 mols) of ethyl *p*-toluenesulfonate and the mixture heated at boiling point in an oil-bath for ten minutes. After cooling, excess of hydrochloric acid was added and the nitrobenzene removed by steam distillation. After filtering, the mother solution was made alkaline with sodium carbonate. The resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure, giving *dl-trans-2-diethylaminocyclohexanol* in lower yield.

***dl-cis-2-Ethylaminocyclohexanol* (a).**—*dl-cis-2-Aminocyclohexanol* was treated analogously with the *trans* isomer, giving *dl-cis-2-ethylaminocyclohexanol*; yield 42%, b.p. 111–112° (18 mm.), m.p. 63–65°; melting points of the hydrochloride and picrate were 189° and 169°, respectively.

Anal. Calcd. for C₈H₁₇ON·C₆H₃O₇N₃: C, 45.20; H, 5.37; N, 15.05. Found: C, 44.99; H, 5.76; N, 14.98.

dl-cis-2-(Phenylcarbamyl)-ethylaminocyclohexyl phenylcarbamate was prepared from phenyl isocyanate and *dl-cis-2-ethylaminocyclohexanol*. Recrystallization from ethanol gave colorless needles, m.p. 205°.

Anal. Calcd. for C₂₂H₂₇N₃O₃: C, 69.29; H, 7.09; N, 11.02. Found: C, 69.34; H, 6.97; N, 11.32.

(b).—To 1 g. (1 mol) of the *dl-cis-2-aminocyclohexanol* dissolved in 10 ml. of warm dried nitrobenzene, was added 4 g. (2 mols) of ethyl *p*-toluenesulfonate and the mixture was heated at 230° in an oil-bath for three minutes. The crystalline precipitate was collected, washed with ether, water added and the aqueous solution made alkaline with concd. sodium hydroxide on cooling in ice. The resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure, giving 0.9 g. (78.3%) of *dl-cis-2-ethylaminocyclohexanol*.

(16) This product could not be converted to the diethyl compound by ethyl bromide and potassium carbonate.

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Adrenergic Blocking Agents. IV. β -Haloethylammonium Compounds¹

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The reported adrenergic blocking action of several β -haloethylammonium compounds is difficult to account for on the basis of a probable accepted mode of production of adrenergic blockade. This apparent discrepancy is explained by the presence of tertiary β -haloethylamines in the "quaternary" compounds tested by other investigators. A series of nine β -haloethylammonium salts were prepared; all failed to reverse the pressor effect of epinephrine. The inactivity of these compounds as compared with tertiary β -haloethylamines can be correlated with the chemical reactivities of the two types.

In considering structure activity relationships of drugs which block a normal function of the autonomic nervous system, attention is usually focused on the geometry of the molecule. The presence of certain appropriately situated atoms or groups provides a means for a loose attachment to cellular surfaces through operation of electrostatic or van der Waals forces. It is assumed that the continued adherence of the blocking drug prevents the approach of stimulant molecules.²

(1) Presented before the Division of Medicinal Chemistry at the 118th Meeting of the American Chemical Society in Chicago, Illinois, September, 1950. A preliminary communication describing this work appeared in *Science*, **113**, 315 (1951).

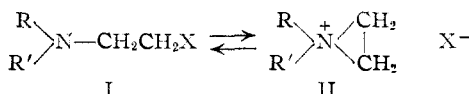
(2) (a) A. J. Clark, "Mode of Action of Drugs on Cells," Arnold, London, 1933; (b) C. C. Pfeiffer, *Science*, **107**, 94 (1948).

In contrast to this passive mode of action, the β -haloethylamines may block the excitatory effects of epinephrine by entering into a definite chemical reaction.³ In adrenergic blockade there is an initial phase during which the drug competitively inhibits epinephrine.^{3,4} This competitive antagonism may well be dependent solely upon the stereochemistry and physical properties of the molecule. However, the prolonged, non-competitive blockage which follows the initial effect is thought to be caused by alkylation of some tissue constituent of sympathetic receptors. Furthermore, there is considerable

(3) M. Nickerson, *J. Pharmacol. Exptl. Therap.*, Part II, **95**, 27 (1949).

(4) G. Chen and D. Russell, *ibid.*, **99**, 401 (1950).

evidence³ to indicate that the alkylating agent is not the β -haloethylamine (I) *per se* but is the ethyl-imonium ion (II) formed from it.



If the transformation from I to II is a necessary prelude to irreversible adrenergic blocking action, quaternization of the β -haloethylamine (I) would be expected to render the compound inactive. Nevertheless, several such quaternary compounds have been reported⁵⁻⁷ to be effective in reversing the pressor action of epinephrine. In view of the significance of these results which controvert an otherwise reasonable hypothesis, we decided to re-investigate this type of compound. In this report we present evidence that quaternary derivatives of β -haloethylamines are not adrenergic blocking agents.

In order to prepare the compound designated as dibenzyl-(β -chloroethyl)-ethylammonium bromide, Nyman and Plantin⁸ heated N,N-dibenzyl- β -chloroethylamine with ethyl bromide in *n*-butanol. On repeating this experiment with 10 moles of bromide⁹ per mole of amine we obtained a solid (m.p. 178–179.5° dec.). This proved to be a mixture of about 8% N,N-dibenzyl- β -chloroethylamine hydrobromide and 92% N,N-dibenzyl- β -bromoethylamine hydrobromide from which the latter was obtained pure¹⁰ by recrystallization from alcohol, although the melting point did not change appreciably.

Nyman and Ostlund⁶ described the pharmacological properties of the "quaternary" compound prepared by Nyman and Plantin.⁸ It was more potent than "Dibenamine"¹¹ as an adrenergic blocking agent, elicited its full effect in a shorter period of time and was more toxic. N,N-Dibenzyl- β -bromoethylamine hydrobromide also has these characteristics.^{7,10,12}

Similarly, there was no evidence of quaternization when dibenzylaminoethanol was heated with ethyl bromide in *n*-butanol¹³; the only product isolated was the hydrobromide salt of the starting amine. With methyl iodide alkylation did occur with both dibenzylaminoethanol and the corresponding chloro compound. The product from the latter, however, was found by analysis to contain more iodine and less chlorine than calculated for dibenzyl-(β -chloroethyl)-methylammonium iodide. It is probable that halogen interchange preceded quaternization so that a mixture of β -iodo and β -chloro compounds resulted.

(5) E. Nyman, *Nature*, **164**, 269 (1949).

(6) E. Nyman and E. Ostlund, *Act. Physiol. Scand.*, **19**, 4 (1949).

(7) M. Nickerson and W. S. Gump, *J. Pharmacol. Exptl. Therap.*, **97**, 25 (1949).

(8) E. Nyman and L. Plantin, *Acta Physiol. Scand.*, **19**, 1 (1949).

(9) Nyman and Plantin (ref. 8) employed "a great excess" of bromide.

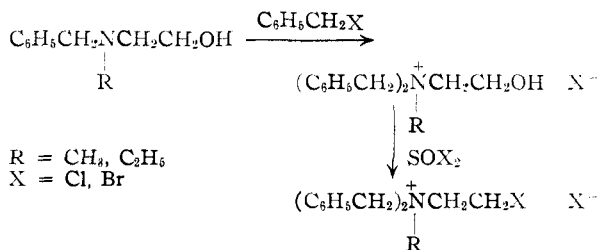
(10) W. S. Gump and E. J. Nikawitz, *THIS JOURNAL*, **72**, 1309 (1950).

(11) Smith, Kline and French trade mark name for N,N-dibenzyl- β -chloroethylamine.

(12) E. J. Fellows, E. Macko, R. A. McLean, J. F. Kerwin, G. Hall, F. J. Milnes and G. E. Ulliyot, *J. Pharmacol. Exptl. Therap.*, **101**, 11 (1951).

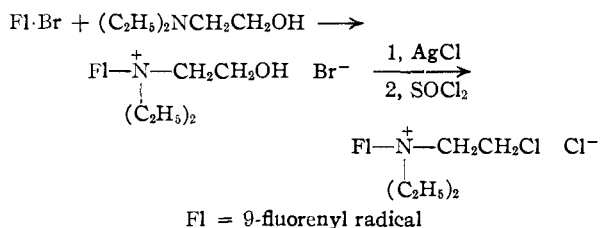
(13) The product obtained by Nyman and Plantin (ref. 8) from this reaction was assumed to be the quaternary derivative.

In order to prepare quaternary derivatives of N,N-dibenzyl- β -chloroethylamine without complicating side reactions, N-benzyl-N-alkylaminoethanols were quaternized with benzyl halides and the hydroxy group was replaced with thionyl chloride or bromide.



Dibenzyl-(β -chloroethyl)-methylammonium chloride, prepared by the above method, was isolated as a sirup which did not crystallize; it was converted into the solid, sparingly soluble iodide by treating an aqueous solution with potassium iodide. All of these quaternary derivatives were inactive.

To ascertain whether this property was peculiar to dibenzyl compounds, quaternary derivatives of other active β -haloethylamines were prepared. The ethobromide salt of N-(9-fluorenyl)-N-ethyl- β -chloroethylamine¹⁴ was formed



To prepare methosulfate salts it was necessary to rely on direct interaction of a tertiary β -haloethylamine with dimethyl sulfate. In our hands this method always gave a mixture, and a salt of the starting amine was often a constituent of the crude reaction product.

N,N-Dibenzyl- β -chloroethylamine and dimethyl sulfate in refluxing alcohol formed an ether-insoluble sirup.¹⁵ An aqueous solution of the sirup was acid and on neutralization with sodium bicarbonate an oil layer formed. The oil was extracted into ether and identified as N,N-dibenzyl- β -chloroethylamine by conversion to the hydrochloride salt.^{10,16} The amount of tertiary amine recovered accounted for 66% of the starting material. Potassium iodide was added to the aqueous solution left after removal of the base to precipitate 9% of dibenzyl (β -chloroethyl)-methylammonium iodide.

When the reaction was conducted in benzene the principal products were the methosulfate (III) and a dimerization product (IV).

It is interesting to note that no appreciable dimerization occurred when the β -chloroethylamine alone was heated in benzene solution.

The methosulfate (III) was not obtained in crystalline form. However, the presence of the ammo-

(14) J. F. Kerwin, T. F. Herdegen, R. Y. Heisler and G. E. Ulliyot, *THIS JOURNAL*, **72**, 940 (1950).

(15) W. S. Gump and E. J. Nikawitz, U. S. Patent 2,504,977 (1950).

(16) O. Bisleb, U. S. Patent 1,949,247 (1934).

chloric acid). The aqueous solution was evaporated after filtration and the chloride was washed with ether and recrystallized twice from alcohol and ether, wt. 9.5 g. (65%), m.p. 154–155°. Identity with the product prepared by Method A was established by analysis and a mixed melting point determination.

Dibenzyl-(β -chloroethyl)-methylammonium Iodide.—A solution of 20 g. (0.17 mole) of thionyl chloride in 20 ml. of chloroform was added slowly to 24 g. (0.08 mole) of dibenzyl-(β -hydroxyethyl)-methylammonium chloride dissolved in 50 ml. of chloroform. The solution was refluxed four hours on a water-bath and the solvent and excess thionyl chloride removed under reduced pressure. The oily residue was washed repeatedly with ether but could not be induced to crystallize. The crude chloride was dissolved in water and an aqueous solution of potassium iodide was added until precipitation was complete. The iodide separated as an oil at first but solidified after a few minutes and was recrystallized twice from alcohol, m.p. 151–152° dec. (78% yield).

Anal. Calcd. for $C_{17}H_{21}NClI$: C, 50.82; H, 5.27; I, 31.59. Found: C, 50.87; H, 5.49; I, 31.66.

Dibenzyl-(β -hydroxyethyl)-methylammonium Bromide.—When 16.5 g. (0.1 mole) of benzyl bromide was added to 17.1 g. (0.1 mole) of *N*-benzyl-*N*-methylethanolamine in 50 ml. of benzene, the solvent was brought to boiling by the exothermic reaction and the quaternary salt began to separate almost immediately. When the reaction had moderated, the mixture was cooled and the salt was recrystallized twice from alcohol, m.p. 158.5–159.5° (77% yield).

Anal. Calcd. for $C_{17}H_{22}NOBr$: Br, 23.77. Found: Br, 23.94.

Dibenzyl-(β -bromoethyl)-methylammonium Bromide.—Redistilled thionyl bromide²⁴ (6.2 g.) (0.03 mole) was added to 6.7 g. (0.02 mole) of dibenzyl-(β -hydroxyethyl)-methylammonium bromide, 1.58 g. (0.02 mole) of dry pyridine and 25 ml. of chloroform. The mixture was warmed until the salt dissolved and then the red solution was refluxed for an hour. After removal of the solvent the residue was washed with ether, acetone was added and the acetone solution filtered from pyridine hydrobromide. Cautious addition of ether to the acetone solution filtrate and cooling caused the product to crystallize. It was collected and recrystallized twice from alcohol and ether to give 1.5 g. (19%) of colorless crystals, m.p. 164° dec.

Anal. Calcd. for $C_{17}H_{21}NBr_2$: C, 51.15; H, 5.30; Br⁻, 20.02. Found: C, 51.18; H, 5.04; Br⁻, 20.23.

Dibenzyl-(β -hydroxyethyl)-ethylammonium Chloride.—A mixture of 0.1 mole of *N*-benzyl-*N*-ethylethanolamine²⁵ and 0.1 mole of benzyl chloride, was heated at 150° for 10 minutes. The partially solid reaction mixture was allowed to cool, about 20 ml. of acetone was added and the acetone insoluble solid was collected. After two recrystallizations from alcohol and ether the salt weighed 11 g. (36%) and melted at 140.5–142.5°.

Anal. Calcd. for $C_{18}H_{24}NOCl$: C, 70.68; H, 7.91. Found: C, 70.59; H, 7.67.

Dibenzyl-(β -chloroethyl)-ethylammonium Chloride.—Five grams (0.016 mole) of dibenzyl-(β -hydroxyethyl)-ethylammonium chloride, 6 g. (0.05 mole) of thionyl chloride and 20 ml. of chloroform were refluxed 1.5 hours. The solvent was evaporated under reduced pressure, the product was washed with ether and recrystallized from acetone and chloroform (58% yield), m.p. 177–178° dec.

Anal. Calcd. for $C_{18}H_{23}NCl_2$: C, 66.66; H, 7.15; Cl⁻, 10.94. Found: C, 66.71; H, 7.36; Cl, 11.06.

Dibenzyl-(β -hydroxyethyl)-ethylammonium Bromide.—Benzyl bromide (17.1 g., 0.1 mole), 17.9 g. (0.1 mole) of *N*-benzyl-*N*-ethylethanolamine and 50 ml. of benzene were refluxed five hours. Ether was added to the cooled mixture and a layer of oil solidified on stirring. Recrystallization from alcohol and ether yielded 17 g. (50%) of salt, m.p. 129.5–131.5° dec.

Anal. Calcd. for $C_{18}H_{24}NOBr$: Br, 22.81. Found: Br, 22.84.

Dibenzyl-(β -bromoethyl)-ethylammonium Bromide.—A solution of 6.2 g. (0.03 mole) of redistilled thionyl bromide,

7 g. (0.02 mole) of dibenzyl-(β -hydroxyethyl)-ethylammonium bromide, 1.5 g. (0.02 mole) of pyridine and 40 ml. of chloroform was refluxed two hours. Acetone was added to the residue after the solvent has been removed under reduced pressure. The acetone solution was filtered and an oil was precipitated from the filtrate on addition of ether. The oil was redissolved in acetone and on standing a solid crystallized slowly. It was collected and recrystallized twice from alcohol and ether to give 0.7 g. of product, m.p. 154.5–156.5° dec.

Anal. Calcd. for $C_{18}H_{22}NBr_2$: C, 52.32; H, 5.61; Br⁻, 19.34. Found: C, 52.31; H, 5.78; Br⁻, 19.36.

(9-Fluorenyl)-(β -hydroxyethyl)-diethylammonium Bromide and Chloride.—Six grams of 9-bromofluorene,²⁶ 5 ml. of diethylaminoethanol and 15 ml. of alcohol were refluxed three hours. Ether was added to the cooled solution and the precipitated bromide was recrystallized twice from alcohol, wt. 6 g. (70%), m.p. 154–155° dec.

Anal. Calcd. for $C_{19}H_{24}NOBr$: Br, 22.06. Found: Br, 22.33.

A solution of 20 g. (0.055 mole) of the bromide in 300 ml. of water was shaken mechanically for one hour with silver chloride prepared from 11.8 g. (0.07 mole) of silver nitrate and dilute hydrochloric acid. The silver bromide was filtered, the aqueous solution was evaporated to dryness at reduced pressure and the chloride was recrystallized twice from alcohol and ether. It weighed 15 g. (88%), m.p. 152.5–153.5° dec.

Anal. Calcd. for $C_{19}H_{24}NOCl$: Cl, 11.16. Found: Cl, 11.02.

(9-Fluorenyl)-(β -chloroethyl)-diethylammonium Chloride.—A solution of 6.3 g. (0.02 mole) of the above β -hydroxyethyl compound, 1.6 g. (0.02 mole) of pyridine, 40 ml. of chloroform and 4.7 g. (0.04 mole) of thionyl chloride was refluxed 1.5 hours. After removal of the solvent the crude product was washed with ether and recrystallized twice from alcohol and ether to yield 2 g. (30%) of crystals, m.p. 150.5–152.5° dec.

Anal. Calcd. for $C_{19}H_{23}NCl_2$: Cl, 21.09. Found: Cl, 21.03.

Reaction of *N,N*-Dibenzyl- β -chloroethylamine with Ethyl Bromide.—The directions of Nyman and Plantin⁸ were followed. Thirteen grams (0.05 mole) of freshly distilled amine, 54.5 g. (0.5 mole) of ethyl bromide (Nyman and Plantin used "a great excess" of bromide) and 100 ml. of *n*-butanol were refluxed 40 hours. As the last of the solvent and excess ethyl bromide were being removed at reduced pressure the product solidified. It was washed with ether and recrystallized from alcohol and ether, wt. 10 g., m.p. 178–179.5° dec. Nyman and Plantin⁸ report m.p. 178–180° dec. for their product and a yield of about 50%.

Anal. Calcd. for $C_{18}H_{23}NClBr$ (dibenzyl-(β -chloroethyl)-ethylammonium bromide): C, 58.63; H, 6.29; Cl, 9.62; Br, 21.67. Calcd. for $C_{18}H_{19}NBr_2$ (*N,N*-dibenzyl- β -bromoethylamine hydrobromide): C, 49.89; H, 4.76; Br (ionic), 20.75; Br (total), 41.50. Found: C, 50.04; H, 5.23; Br (ionic), 21.11; Br (total), 39.23; Cl, 0.87.

The analyses²⁷ indicate that the major product of the reaction is *N,N*-dibenzyl- β -bromoethylamine hydrobromide contaminated with some (about 8%) *N,N*-dibenzyl- β -chloroethylamine hydrobromide. Treatment of an aqueous solution (acid) with sodium bicarbonate liberated an ether-soluble base. Recrystallization from alcohol with a recovery of 85% did not affect the melting point materially (177.5–179° dec.), but the recrystallized material no longer contained chlorine and the bromine analysis corresponded with that calculated for pure *N,N*-dibenzyl- β -bromoethylamine hydrobromide. There was no depression melting point of a mixture with *N,N*-dibenzyl- β -bromoethylamine hydrobromide,¹⁰ m.p. 177–179° dec.

Anal. Calcd. for $C_{18}H_{19}NBr_2$: Br, 41.50. Found: Br, 41.35.

Reaction of Dibenzylaminoethanol with Ethyl Bromide.—The amine (2.5 g., 0.01 mole), 10.9 g. (0.1 mole) of ethyl

(26) C. Wittig and G. Felletschiu, *ibid.*, **555**, 133 (1944).

(27) Nyman and Plantin (ref. 8) found 3.85% nitrogen. The calculated nitrogen content of dibenzyl-(β -chloroethyl)-ethylammonium bromide is 3.80%, of *N,N*-dibenzyl- β -bromoethylamine hydrobromide 3.63%.

(24) Dow Chemical Company.

(25) E. Wedekind and E. Bruch, *Ann.*, **471**, 73 (1929).

bromide and 40 ml. of *n*-butanol were refluxed 40 hours. The solid remaining after evaporation of the solution was recrystallized from alcohol to yield 2.5 g. of material, m.p. 163–165° dec., which did not depress the melting point of dibenzylaminoethanol hydrobromide. Treatment of an aqueous solution of the salt with sodium bicarbonate produced a base, m.p. 46–48°, identical with dibenzylaminoethanol.¹⁶ Nyman and Plantin's product is reported⁶ to melt at 155–160° dec. and is formulated as dibenzyl-(β -hydroxyethyl)-ethylammonium bromide. Dibenzylaminoethanol hydrobromide was prepared from the base and hydrogen bromide in ether and recrystallized from alcohol, m.p. 164–166° dec.

Anal. Calcd. for $C_{16}H_{20}NOBr$: Br, 24.80. Found: Br, 24.46.

Reaction of *N,N*-Dibenzyl- β -chloroethylamine with Methyl Iodide.—A dark oil formed when 6.5 g. (0.025 mole) of amine and 7 g. (0.05 mole) of methyl iodide in 20 ml. of dioxane were kept at room temperature for two weeks. When the mixture was stirred with 50 ml. of ether, the oil solidified. Recrystallization from alcohol gave 5.5 g. of neutral material, m.p. 155.5–157.5° dec. The analytical results showed a lower chlorine and higher iodine value than those calculated for the expected product. This suggests that halogen interchange occurred and analysis indicates that the product is a 50–50 mixture of the β -chloroethyl and β -iodoethylammonium iodides.

Anal. Calcd. for $C_{17}H_{21}NCI$ (dibenzyl-(β -chloroethyl)-methylammonium iodide): C, 50.82; H, 5.27; Cl, 8.83; I, 31.59. Calcd. for $C_{17}H_{21}NI_2$ (dibenzyl-(β -iodoethyl)-methylammonium iodide): C, 41.40; H, 4.29; I, 51.40. Found: C, 45.91; H, 4.42; Cl, 4.58; I, 41.60.

When dibenzyl-(β -chloroethyl)-methylammonium iodide was heated with methyl iodide in alcohol solution, the chloro compound was recovered unchanged. Therefore, it appears probable that halogen interchange took place before quaternization of the tertiary amine.

Reaction of *N,N*-Dibenzyl- β -chloroethylamine with Dimethyl Sulfate in Alcohol.—Thirteen grams (0.05 mole) of freshly distilled *N,N*-dibenzyl- β -chloroethylamine,¹⁰ 14 g. (0.11 mole) of dimethyl sulfate and 40 ml. of alcohol were refluxed four hours. Evaporation of the alcohol at reduced pressure left a brown oil which was washed several times with ether. The ether washings remained clear when treated with dry hydrogen chloride. The oil which could not be caused to crystallize was dissolved in 225 ml. of water. The aqueous solution was strongly acid (*pH* less than 2), contained sulfate ion as evidenced by a precipitate with barium chloride solution, but no chloride ion (silver nitrate test). Sodium hydroxide solution was added until the solution was slightly alkaline and the base which separated was extracted into ether. The ether solution was dried over anhydrous potassium carbonate, filtered and saturated with hydrogen chloride gas. The hydrochloride was recrystallized from alcohol and ether, m.p. 189–191° (9 g., 61%) and was identified as *N,N*-dibenzyl- β -chloroethylamine hydrochloride by mixed melting point determination with a sample of authentic material.¹⁰

The aqueous solution was then extracted with five 25-ml. portions of chloroform. Evaporation of the dried solution left 1.5 g. of oil which did not solidify. It was dissolved in water and potassium iodide solution added. The iodide weighed 1.3 g., m.p. 150.5–152° dec. Recrystallization from alcohol and ether gave faintly yellow crystals, m.p. 155.5–156.5° dec., which did not depress the melting point of dibenzyl-(β -chloroethyl)-methylammonium iodide.

Reaction of *N,N*-Dibenzyl- β -chloroethylamine with Dimethyl Sulfate in Benzene.—Forty grams (0.135 mole) of freshly distilled amine, 17 g. (0.135 mole) of dimethyl sulfate and 200 ml. of dry benzene were refluxed for 15 hours. Soon after the boiling point had been reached an oil layer began to form; some hours later a solid began to collect at the interface. The benzene was decanted from the cooled reaction mixture and the brown residue was washed with ether. The mixture of oil and solid was stirred with 200 ml. of acetone and the insoluble solid was collected. It weighed 13 g. and was recrystallized from water with a recovery of 10.5 g., m.p. 205–207° dec. This solid was identified as a dimerization product *N,N,N',N'*-tetrabenzylpiperazinium dimethosulfate (IV). The 10.5 g. corresponds to a 23% yield; in a similar preparation a yield of 18% was obtained.

Anal. Calcd. for $C_{32}H_{42}N_2O_8S_2$: C, 60.87; H, 6.31; S, 9.56. Found: C, 60.49; H, 6.08; S, 9.43.

Evaporation of the acetone solution *in vacuo* left 32 g. of crude dibenzyl-(β -chloroethyl)-methylammonium methosulfate as a thick dark sirup. All attempts to obtain a crystalline product from this material failed. The sirup was dissolved in 250 ml. of water to form a slightly acid (*pH* about 4) solution. A qualitative test for chloride ion was negative while a slight turbidity resulted with barium chloride. The aqueous solution was made slightly alkaline with 5% sodium carbonate solution and the cloudiness was removed by an ether extraction. The volume of the water solution was adjusted to 300 ml. and to a 50-ml. aliquot was added 5 g. of potassium iodide in 15 ml. of water. The yellow oil which separated solidified on stirring with a glass rod. The iodide was collected, dried and recrystallized from alcohol and ether to give 4.0 g. of faintly yellow needles, m.p. 151.5–152.5° dec., which did not depress the melting point of dibenzyl-(β -chloroethyl)-methylammonium iodide. This corresponds to a 44% yield of dibenzyl-(β -chloroethyl)-methylammonium cation. Another 50-ml. portion of the original aqueous solution was used for the pharmacological experiments. The concentration of quaternary methosulfate was assumed to be equivalent to the amount of iodide precipitated by potassium iodide, a value which is thus a minimum concentration. The acetone-insoluble solid (IV), m.p. 205–207° dec., was identified as *N,N,N',N'*-tetrabenzylpiperazinium dimethosulfate in the following manner. Eight and one-half grams of the solid was dissolved in 125 ml. of boiling water and 25 ml. of 10% sodium hydroxide solution was added whereupon an orange-yellow oil began to form. The mixture was refluxed one-half hour, cooled and extracted into ether. The sirup which was left after evaporation of the ether was dissolved in hot alcohol; on cooling 1.8 g. of yellow needles, m.p. 87–89.5°, was deposited. The dihydrochloride was prepared in ether solution and recrystallized twice from alcohol and ether, m.p. 197–198.5°. It analyzed correctly for *N,N,N',N'*-tetrabenzylethylenediamine dihydrochloride.

Anal. Calcd. for $C_{30}H_{34}N_2Cl_2$: Cl, 14.37. Found: Cl, 14.11.

The dihydrochloride was converted to the free base which crystallized from alcohol in long slender needles. It melted at 94–95° and did not depress the melting point of an authentic sample of *N,N,N',N'*-tetrabenzylethylenediamine.

Anal. Calcd. for $C_{30}H_{32}N_2$: C, 85.67; H, 7.67. Found: C, 85.56; H, 7.68.

The dipicrate was prepared from the free base and alcoholic picric acid and recrystallized from acetone, m.p. 199–200°.

Anal. Calcd. for $C_{42}H_{38}N_8O_{14}$: C, 57.40; H, 4.35. Found: C, 57.43; H, 4.61.

The presence of the piperazine ring was further established by catalytic debenzylation. Two grams of IV was dissolved in 50 ml. of water and shaken with palladium-carbon catalyst at 60 p.s.i. and 70–80° for two hours. The warm solution (strongly acid) was filtered and benzoyl chloride and sodium hydroxide solution added. After a few minutes of stirring, a solid dibenzoyl derivative formed. It was collected and recrystallized from alcohol, m.p. 192–194°. It did not depress the melting point of an authentic sample of *N,N'*-dibenzoyl-piperazine,²⁸ m.p. 194–195°.

***N,N,N',N'*-Tetrabenzylethylenediamine.**—A solution of 6.5 g. (0.025 mole) of *N,N*-dibenzyl- β -chloroethylamine, 9.8 g. (0.05 mole) of dibenzylamine and 50 ml. of xylene was refluxed five hours. Ether was added to the cooled mixture, dibenzylamine hydrochloride was filtered and the product was isolated as the dihydrochloride (52% yield) by passing dry hydrogen chloride into the filtrate. The dihydrochloride, m.p. 198–199 dec., was converted into the free base which melted at 93.5–94.5° after recrystallization from alcohol.²⁹

Reaction of *N,N*-Dibenzyl- β -chloroethylamine with Dimethyl Sulfate in Ether.—Fifty-two grams (0.2 mole) of amine, 0.2 mole of dimethyl sulfate in 200 ml. of ether were allowed to stand at room temperature for five weeks. The

(28) M. M. A. P. N. Franchimont and E. Kramer, *Rec. trav. chim.*, **81**, 40 (1912).

(29) G. Lob, *ibid.*, **55**, 859 (1936), reports m.p. 95° for the free base and 140–150° dec. for the dihydrochloride.

36 g. of clear yellow sirup which separated was treated in the same manner as the reaction product from benzene. Only 1.5 g. (2.2%) of dimer (IV), m.p. 207–208° dec., was formed. From the aqueous solution of quaternary salt there was obtained a 31% yield of dibenzyl-(β -chloroethyl)-methylammonium iodide, m.p. 154.5–155° dec., which analyzed correctly for iodine and was identical with an authentic sample.

Anal. Calcd. for $C_{17}H_{21}NClI$: I, 31.59. Found: I, 31.31.

N-(α -Naphthylmethyl)-N-ethyl- β -chloroethylamine.³⁰—One-half mole of α -chloromethylnaphthalene was added with cooling to one mole of ethylaminoethanol. After the initial reaction had subsided the mixture was maintained at 90–100° for five hours and poured into water. Sodium hydroxide solution was added, the amine was taken up in ether and dried. Distillation gave a 55% yield of colorless oil, b.p. 170–176° (2 mm.). The hydrochloride was prepared by introducing hydrogen chloride gas into an alcohol solution of the amine. After recrystallization from alcohol and acetone, the salt melted at 144–146°.

Anal. Calcd. for $C_{15}H_{19}NOCl$: C, 67.80; H, 7.59. Found: C, 67.98; H, 7.26.

Forty grams (0.15 mole) of the hydrochloride in 70 ml. of chloroform was cooled while 35.7 g. (0.3 mole) of thionyl chloride in 50 ml. of chloroform was added. The solution was warmed slowly and finally refluxed four hours. The solvent was removed *in vacuo*, the residue was washed with ether and then recrystallized from alcohol and ether to give 30 g. of colorless needles, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{19}Cl_2N$: C, 63.39; H, 6.73. Found: C, 63.51; H, 6.27.

The free base distilled as a faintly yellow oil, b.p. 155–157° (1 mm.).

(α -Naphthylmethyl)-ethyl-(β -chloroethyl)-methylammonium Methosulfate and Iodide.—Freshly distilled amine (12.3 g., 0.05 mole), 6.3 g. (0.05 mole) of dimethyl sulfate and 75 ml. of ether were kept at room temperature for 19 days. The ether was decanted from the light yellow sirup (wt. 6.3 g.) which was dissolved in 50 ml. of acetone. Ether was added dropwise to cloudiness. On cooling and scratching the walls of the flask, an unidentified solid crystallized, wt. 0.25 g., m.p. 230–235° dec. Addition of more ether precipitated an oil. The ether and acetone were evaporated and the residue was dissolved in 50 ml. of water to give a strongly acid solution. Twelve ml. of 5% sodium carbonate solution was added to render the solution slightly alkaline. The turbid solution was extracted with ether, the extracts were dried and acidified with dry hydrogen chloride. Five-tenths gram of N-(α -naphthylmethyl)-N-ethyl- β -chloroethylamine hydrochloride, m.p. 172.5–173.5° was obtained. The aqueous solution was adjusted to a volume of 70 ml. and to a 25-ml. portion was added 2 g. of

potassium iodide in 5 ml. of water. The iodide separated as a yellow oil which slowly solidified, wt. 1.05 g. Recrystallization from alcohol and ether gave 0.85 g. (12%) of nearly colorless needles, m.p. 120.5–122° dec. The remaining 35 ml. of aqueous solution of the methosulfate was used for pharmacological testing. Substantially the same results were obtained when 0.05 mole each of amine and dimethyl sulfate were refluxed in 75 ml. of benzene for three hours. The solid obtained from the acetone solution by addition of a small amount of ether weighed 0.6 g., m.p. 213–223° dec. The crude quaternary salt was dissolved in water (200 ml.), potassium iodide was added to one-half this solution to give 2.7 (28%) of iodide, m.p. 119.5–120.5° dec. after recrystallization from alcohol and ether.

Anal. Calcd. for $C_{15}H_{21}NClI$: Cl, 9.10; I, 32.57. Found: Cl, 8.95; I, 32.16.

(*o*-Tolyloxyethyl)-benzyl-(β -chloroethyl)-methylammonium Methosulfate.—A solution of 10 g. (0.033 mole) of N-(*o*-tolylloxyethyl)-N-benzyl- β -chloroethylamine,¹⁹ b.p. 140–142° (0.1 mm.), 4.2 g. (0.033 mole) of dimethyl sulfate and 25 ml. of benzene was refluxed 3.5 hours. During the heating period an insoluble oil and a solid were formed. The cooled mixture was diluted with ether, allowed to settle and the solvents decanted. Acetone was added to dissolve the oil and the insoluble solid, wt. 2.0 g. was collected in a filter. After recrystallization from water, it weighed 1.3 g., m.p. 213–214°. It contained sulfur but no chlorine and was not further identified. The acetone solution was evaporated, the oily residue was dissolved in alcohol and ether was added. After standing for several days, 0.7 g. of solid, m.p. 178.5–180.5°, crystallized from the solution; it did not contain halogen. Concentration of the alcohol-ether filtrate left 7.5 of oily material. Water was added and the partially water soluble material was extracted with three 25-ml. portions of chloroform. Upon evaporation of the chloroform and addition of ether the residual oil solidified slowly to give 6.3 g. of nearly colorless solid. After three recrystallizations from alcohol and ether the methosulfate weighed 2.5 g. and melted at 94.5–96.5°.

Anal. Calcd. for $C_{20}H_{28}NO_5SCl$: S, 7.46; Cl, 8.25. Found: S, 7.17; Cl, 8.03.

Hydrolysis Experiments.—A weighed amount of quaternary salts or tertiary amine hydrochloride was dissolved in alcohol and added to aqueous alcohol containing sodium bicarbonate so that the concentration was 0.004 mole of amine or quaternary compound and 0.016 mole of sodium bicarbonate per liter of solution (70% alcohol and 30% water by volume). At intervals, 50-ml. aliquots were withdrawn and the chloride ion concentration determined electrometrically. In the case of the tertiary amines, the aliquot was immediately acidified with sulfuric acid to prevent further hydrolysis during titration. The times for 50% hydrolysis were read from a plot of per cent. hydrolysis *versus* time.

(30) The pharmacology of this compound is described by E. R. Loew and A. Micetich, *J. Pharmacol. Exptl. Therap.*, **94**, 339 (1948).