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N,N'-SUBSTITUTED ETHYLENEDIAMINE DERIVATIVES

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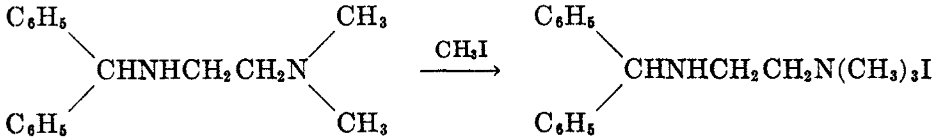
Some years ago, the fundamental work of Fourneau, Bovet, and Viaud on the antihistaminic activity associated with certain ethylenediamine derivatives became known in this country. At that time, an investigation was undertaken in these laboratories with a view towards further evaluating the relationship between structure and activity. The present report concerns some of the representative types of N-substituted ethylenediamine derivatives prepared during the course of this investigation. They are summarized in Table I.

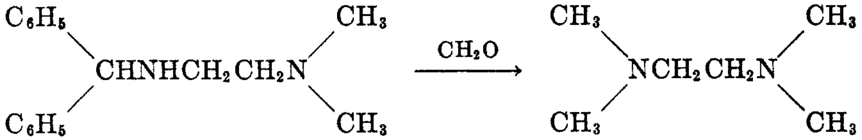
N-Benzyl-N',N'-dimethylethylenediamine (I) was the simplest trisubstituted derivative of type A made. In order to determine the effect of an increase in size of the substituent grouping on the activity, N-benzhydryl-N',N'-dimethylethylenediamine (II), N-(2-fluorenyl)-N',N'-dimethylethylenediamine (III), and N-(α,β-diphenylethyl)-N',N'-dimethylethylenediamine (V) were prepared. None of these could be condensed to the tetrasubstituted derivatives of type C. When II was treated with methyl iodide, the desired ditertiary base, which has since been prepared in a different way by Cromwell and Fitzgibbon (1), was not obtained. Only the tertiary nitrogen was attacked with the resulting formation of the quaternary salt, VI.



$$(C_6H_5)_2CHNHCH_2CH_2N(CH_3)_2 \xrightarrow{CH_3I} (C_6H_5)_2CHNHCH_2CH_2N(CH_3)_3I$$

II VI

In a further effort to methylate the secondary amino grouping, the dihydrochloride of II was heated under pressure at 130–140° with aqueous formaldehyde. Instead of the desired product, N,N,N',N'-tetramethylethylenediamine (VII) (2) was obtained.



$$(C_6H_5)_2CHNHCH_2CH_2N(CH_3)_2 \xrightarrow{CH_2O} (CH_3)_2NCH_2CH_2N(CH_3)_2$$

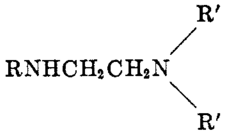
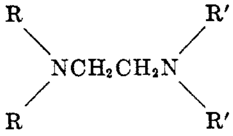
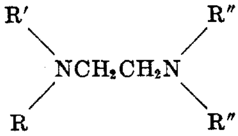
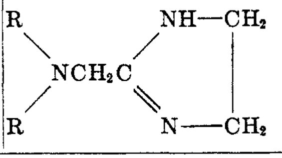
II VII

N-(2-thiazolyl)-N',N'-diethylethylenediamine (VIII) was prepared in order to determine the influence of a heterocyclic substituent on the pharmacological activity. Since it could not be satisfactorily benzylated with benzyl chloride, the desired N-benzyl-N-(2-thiazolyl)-N',N'-diethylethylenediamine (IX) was finally prepared by the catalytic hydrogenation of a mixture of VIII and benzaldehyde.

The tetrasubstituted N,N-diphenyl-N′,N′-dimethylethylenediamine (XI) and N,N-dibenzyl-N′,N′-dimethylethylenediamine (XII) were readily obtained by reacting diphenylamine and dibenzylamine respectively with dimethylaminoethyl chloride. Both of these compounds have since been described in part by others (3, 4, 5). In an effort to synthesize N-benzyl-N-(α,β-diphenylethyl)-N′,N′-dimethylethylenediamine, α,β-diphenylethylamine was reacted with benzyl chloride. Two products were obtained, namely, N-benzyl-α,β-diphenylethylamine (XIII) (6) and N,N-dibenzyl-α,β-diphenylethylamine (XIV). On treatment of XIII with dimethylaminoethyl chloride hydrochloride, instead of the desired ethylenediamine derivative, only stilbene (XV) was obtained, indicating extensive breakdown of the heavily-substituted molecule.

TABLE I

ETHYLENEDIAMINE DERIVATIVES

TYPE	FORMULA	SUBSTITUENTS		
		R	R′	R″
A	 $RNHCH_2CH_2N(R')_2$	Benzyl Benzhydryl Fluorenyl *sym*-Diphenylethyl Thiazolyl	Methyl Ethyl	
B	 $R_2NCH_2CH_2NR'_2$	Benzyl Phenyl	Methyl	
C	 $R'(R)NCH_2CH_2NR''_2$	Benzyl	Thiazolyl	Ethyl
D		Benzyl Cyclohexyl		

The imidazoline derivatives of type D were prepared according to the procedure outlined by Hill and Aspinall (7).

It was previously noted above that when II was treated with formaldehyde under relatively mild conditions the benzhydryl grouping split off. This was not very surprising. The lability of the benzyl group is well known, and on purely theoretical grounds, the benzhydryl group should be even more labile since it offers more possibilities for resonance and steric effects. This concept was borne out by the results of an attempt to prepare 2-(benzhydrylaminomethyl)imidazoline by reacting N-benzhydrylglycine ethyl ester (XXII) with ethylenediamine according to the established procedure. Instead of the desired imidazoline, 1,1,2,2-tetraphenylethane (XXIII) and 2-methylimidazoline were obtained, indicating cleavage of the heavy benzhydryl group from the imidazoline ring.

In the pharmacological tests carried out by the late Dr. Lehmann and Dr. Randall of our Pharmacological Department, the described compounds showed only weak antihistaminic properties. One interesting exception, however, deserves mention. It is generally observed that ethylenediamine derivatives show antihistaminic activity only when both nitrogen atoms are tertiary. Compounds containing the group —NH— are practically inactive. Compound II, however, is an exception to this rule since it exhibits a fairly strong antihistaminic activity even though it contains an imino group. In the usual histamine spray test (8) 30 mg./kg. of II protected five out of six guinea pigs against an otherwise lethal dose of histamine. This is in keeping with the fact that the benzhydryl group exerts powerful pharmacogenetic effects in a wide variety of therapeutically useful compounds, such as 6-dimethylamino-4,4-diphenyl-3-heptanone, 2-benzhydryloxy-N,N-dimethylethylamine, and 1-(3,3-diphenylpropyl)piperidine.

Acknowledge. The authors wish to acknowledge their indebtedness to Dr. A. Steyermark for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

I. *N-Benzyl-N',N'-dimethylethylenediamine.* A mixture of 41 g. (1 equiv.) of dimethylaminoethyl chloride hydrochloride and 90 g. (3 equiv.) of benzylamine in 200 cc. of dry toluene was heated on a steam-bath with stirring for about 2 hours. The mixture was shaken with an excess of 6 *N* sodium hydroxide, and the toluene layer separated and distilled at atmospheric pressure. The oily residue was fractionated *in vacuo*, yielding 17 g. of N-benzyl-N',N'-dimethylethylenediamine, b.p. 91–93°/1 mm.; n_D^{25} 1.5074. The *dihydrochloride* was obtained as a white crystalline material, m.p. 209.5–210°, soluble in water and hot ethanol.

Anal. Calc'd for $C_{11}H_{18}N_2 \cdot 2HCl$: C, 52.6; H, 8.0.
Found: C, 52.7; H, 8.1.

II. *N-Benzhydryl-N',N'-dimethylethylenediamine.* Benzhydrylamine was prepared in 85% yield from benzophenone oxime by the procedure outlined for *sym*-diphenylethylamine in experiment IV. It was also prepared by catalytic (Raney nickel) hydrogenation of the oxime at 70° and 500 p.s.i. in practically quantitative yield.

To a refluxing solution of 40 g. of benzhydrylamine in 30 cc. of ethanol was added dropwise 20 g. of dimethylaminoethyl chloride hydrochloride in 40 cc. of water. The mixture was heated for about 7 hours on a steam-bath. After standing for some time, 21 g. of benzhydrylamine hydrochloride crystallized out and was removed. The filtrate was made strongly alkaline with 6 *N* sodium hydroxide and extracted with benzene. The benzene extract was fractionated, and the fraction, b.p. 118–131°/0.3 mm., was redistilled to yield 10.5 g. of N-benzhydryl-N',N'-dimethylethylenediamine as a colorless oil; b.p. 131–133°/0.35 mm.; n_D^{22} 1.5555. The *dihydrochloride* is a white powder which decomposes at 222–223°.

Anal. Calc'd for $C_{17}H_{22}N_2 \cdot 2HCl$: C, 62.4; H, 7.3.
Found: C, 62.1; H, 7.3.

III. *N,N-Dimethyl-N'-(2-fluorenyl)ethylenediamine oxalate.* A mixture of 42 g. of 2-aminofluorene, 33.2 g. of dimethylaminoethyl chloride hydrochloride, 15 cc. of pyridine, and 50 cc. of ethanol was heated in an autoclave under nitrogen at 200 p.s.i. and 170° for 20 hours. The reaction product was dissolved in water, saturated with sodium acetate, and extracted with ether. The ether solution was fractionated to yield the free base as a red fluorescent oil, b.p. 188–193°/0.7–0.8 mm.; n_D^{25} 1.6311.

The *oxalate* was obtained as flesh-colored crystals, m.p. 147–149°.

Anal. Calc'd for $C_{17}H_{20}N_2 \cdot H_2C_2O_4 \cdot 2\ 1/2\ H_2O$: C, 58.9; H, 7.0; N, 7.2.

Found: C, 58.9; H, 7.0; N, 7.2.

In another experiment the oxalate crystallized as a pink *monohydrate*, m.p. 139.5–141.5°.

Anal. Calc'd for $C_{17}H_{20}N_2 \cdot H_2C_2O_4 . H_2O$: C, 63.3; H, 6.7.

Found: C, 63.4; H, 6.6.

In both instances the samples used for analysis were dried under a high vacuum at 80° over phosphorus pentoxide indicating firm retention of water of crystallization.

IV. *α,β-Diphenylethylamine.* This compound was readily prepared in excellent yield by a modification of the procedure for the preparation of *n*-heptylamine (10).

Desoxybenzoin oxime (143 g.) dissolved in 1850 cc. of absolute ethanol was heated to boiling under reflux, and 166 g. of metallic sodium cut into small pieces was added to it as rapidly as possible. When all of the sodium was in solution, the reaction mixture was cooled, and 1990 cc. of water was added. The mixture was then distilled under a vacuum until about 2 liters of solvent had been removed. The residue, consisting of an oily and an aqueous phase, was extracted three times with benzene, and the benzene extracts were dried over potassium carbonate, and the benzene removed under a vacuum. The residual oil distilled at 117–120°/0.6 mm. to yield 115 g. (86%) of colorless α,β-diphenylethylamine.

V. *N,N-Dimethyl-N'-(α,β-diphenylethyl)ethylenediamine dihydrochloride.* To a mixture of 30 cc. of ethanol, 20 g. of α,β-diphenylethylamine, and 11.7 g. of sodium bicarbonate heated under reflux was added dropwise 20 g. of β-dimethylaminoethyl chloride hydrochloride in 60 cc. of water over a period of 2 hours. Heating was continued for a total of 4 hours. The ethanol was removed under a vacuum, and the residue was diluted with water, made strongly alkaline, and then extracted with benzene. The dried benzene extract was fractionated to give the base, b.p. 118–124°/0.3 mm. The *dihydrochloride* melted at 190–191°.

Anal. Calc'd for $C_{18}H_{24}N_2 \cdot 2HCl$: C, 63.3; H, 7.6.

Found: C, 63.4; H, 7.6.

VI. *β-Benzyhydrylaminoethyltrimethylammonium iodide.* N-benzhydryl-N',N'-dimethylethylenediamine (7.7 g.), 6 g. of methyl iodide, 4.5 g. of sodium carbonate, and 25 cc. of water were mixed and heated on a steam-bath under reflux overnight. The reaction mixture consisted of an aqueous phase and a heavy oily layer. The latter solidified on cooling to a white solid which was soluble in hot water and hot dilute alcohol and insoluble in benzene and ether. Recrystallization from isopropanol containing a little water gave white needles, m.p. 185–186°.

Anal. Calc'd for $C_{18}H_{25}IN_2$: C, 54.6; H, 6.3.

Found: C, 54.5; H, 6.2.

The product was obviously the quaternary salt rather than the hydroiodide, because it was recovered unchanged on boiling with dilute sodium hydroxide.

VII. *N,N,N',N'-Tetramethylethylenediamine dihydrochloride.* A mixture of 10 g. of N-benzhydryl-N',N'-dimethylaminoethylenediamine dihydrochloride and 120 g. of 36–38% aqueous formaldehyde was heated in an autoclave for 3 hours at 130–140° under 500 p.s.i. of nitrogen. The clear reaction mixture was evaporated to dryness under a vacuum, and the solid residue was dissolved in a little hot 3 *N* hydrochloric acid and again evaporated to dryness on the steam-bath under a vacuum. The residue was recrystallized from methanol to give small white crystals which decomposed at 288°. The analysis showed that the product was N,N,N',N'-tetramethylethylenediamine dihydrochloride. [Lit., sinters at 280°, dec. 300° (2)].

Anal. Calc'd for $C_6H_{16}N_2 \cdot 2HCl$: C, 38.1; H, 9.5; N, 14.8.

Found: C, 38.5; H, 9.6; N, 14.3.

VIII. *N-(2-Thiazolyl)-N',N'-diethylethylenediamine.* To a mixture of 42 g. of 2-aminothiazole, 35 g. of sodium acetate, and 100 cc. of water heated under reflux was added dropwise an aqueous solution of 72 g. of diethylaminoethyl chloride hydrochloride. The mixture was refluxed for about 3 hours after addition was complete and was then cooled and extracted several times with benzene. The aqueous layer was made strongly alkaline with sodium hydroxide to give an oil which was removed. The alkaline aqueous layer was extracted with benzene, and the benzene extracts and oil were combined and dried over potassium carbonate. The benzene was removed, and the oily residue on vacuum-distillation yielded 33.5 g. of a colorless fraction; b.p. 94–108°/0.7–0.9 mm. Upon redistillation the product boiled at 107–110°/0.9 mm.; n_D^{25} 1.537.

Anal. Calc'd for $C_9H_{17}N_3S$: C, 54.2; H, 8.5.

Found: C, 53.9; H, 8.6.

IX. *N-Benzyl-N-(2-thiazolyl)-N′,N′-diethylethylenediamine.* An ethanolic solution of 8 g. of benzaldehyde and 15 g. of N-(2-thiazolyl)-N′,N′-diethylethylenediamine was catalytically reduced with Raney nickel and hydrogen at 200 p.s.i. and 70°. When the hydrogen uptake ceased, the reaction mixture was filtered, the ethanol was removed, and the partially crystalline residue was washed with a little petroleum ether. The product was purified by recrystallization from dilute ethanol and was obtained as long, flat, white needles; m.p. 121–122°. It was soluble in benzene, alcohol, and dilute hydrochloric acid; slightly soluble in petroleum ether; and insoluble in water and alkali.

Anal. Calc'd for $C_{16}H_{23}N_3S$: C, 66.5; H, 8.0; N, 14.5.

Found: C, 66.8; H, 7.7; N, 14.1.

X. *2-Benzylaminoquinoline.* A mixture of 37 g. of 2-chloroquinoline and 48.5 g. of benzylamine was heated at about 125° overnight. The reaction mixture was diluted with ether, and the precipitated benzylamine hydrochloride was filtered off. The filtrate on evaporation of the ether gave a yellow oil which solidified on scratching. Recrystallization from dilute methanol gave 47 g. of faintly yellow 2-benzylaminoquinoline, m.p. 99–100°. The product was soluble in the common organic solvents and insoluble in water.

Anal. Calc'd for $C_{16}H_{14}N_2$: C, 82.1; H, 6.0.

Found: C, 81.5; H, 5.9.

XI. *N,N-Diphenyl-N′,N′-dimethylethylenediamine monohydrochloride.* A mixture of 59 g. of diphenylamine and 20 g. of dimethylaminoethyl chloride hydrochloride was heated at 175–180° for about 22 hours. It was then cooled slightly, boiled with an excess of dilute hydrochloric acid for a few minutes, and finally cooled and extracted with benzene. The aqueous phase contained an insoluble material which yielded 14 g. of N,N-diphenyl-N′,N′-dimethylethylenediamine monohydrochloride as pink-colored plates decomposing at 244–247° on recrystallization from ethyl alcohol. [Carrara *et al.*, (4); m.p. 252–254°].

Anal. Calc'd for $C_{16}H_{20}N_2 \cdot HCl$: C, 69.4; H, 7.6; N, 10.1.

Found: C, 69.7; H, 7.7; N, 9.9.

XII. *N,N-Dibenzyl-N′,N′-dimethylethylenediamine oxalate.* To a refluxing aqueous solution of 40 g. of dibenzylamine was added dropwise an aqueous solution of 30 g. of dimethylaminoethyl chloride hydrochloride. After an additional hour of refluxing, the reaction mixture was made strongly alkaline and was extracted with benzene. The benzene extracts were dried and fractionally distilled to give N,N-dibenzyl-N′,N′-dimethylethylenediamine as a colorless oil, b.p. 130–132°/0.45 mm.; n_D^{25} 1.548.

The *oxalate*, prepared in ether solution, is soluble in methanol, ethanol, butanol, and water. On crystallization from ethyl acetate or dioxane it melts at 134–136°.

Anal. Calc'd for $C_{18}H_{24}N_2 \cdot 1\ 1/2\ H_2C_2O_4$: C, 62.5; H, 6.7; N, 6.9.

Found: C, 62.6, 62.5; H, 6.8, 6.7; N, 6.9, 6.9.

XIII. *N-Benzyl-α,β-diphenylethylamine*, and XIV. *N,N-Dibenzyl-α,β-diphenylethylamine.* A mixture of 30 g. of α,β-diphenylethylamine and 21.2 g. of benzyl chloride was heated at about 130°. After a short time, the mixture turned solid. It was treated with sodium hydroxide solution and extracted with benzene. The benzene extracts were dried and fractionated to yield 26 g. of yellow oil boiling between 141–164°/0.2–0.25 mm. and a viscous residue. The distillate solidified on standing and was recrystallized from methanol to yield colorless N-benzyl-α,β-diphenylethylamine; m.p. 52.5–53.5°.

Anal. Calc'd for $C_{21}H_{21}N$: C, 87.8; H, 7.3.
Found: C, 87.6; H, 7.2.

The viscous residue also solidified on standing. It was recrystallized from ethanol to give long, white needles of N,N-dibenzyl-α,β-diphenylethylamine, m.p. 92–93°. The base is insoluble in dilute hydrochloric acid.

Anal. Calc'd for $C_{28}H_{27}N$: C, 89.2; H, 7.2.
Found: C, 89.2; H, 7.2.

XV. In an attempt to prepare *N-benzyl-N-(α,β-diphenylethyl)-N′,N′-dimethylethylenediamine*, 22 g. of N-benzyl-α,β-diphenylethylamine and 11 g. of dimethylaminoethyl chloride hydrochloride were mixed and heated for several hours at 240–260°. The reaction mixture was made alkaline with sodium hydroxide solution and then extracted with ether. The ether extract on standing yielded about 9 g. of a neutral precipitate which was recrystallized from ethanol to give large, colorless, diamond-shaped plates melting at 123–124° and analyzing for stilbene.

Anal. Calc'd for $C_{14}H_{12}$: C, 93.3; H, 6.7.
Found: C, 92.7; H, 6.6.

A mixture melting point with an authentic sample of stilbene showed no depression.

XVI. *N,N-Dibenzylglycine ethyl ester.* A mixture of 117.6 g. of dibenzylamine and 49.2 g. of ethyl chloroacetate in 200 cc. of dry toluene was refluxed for 2 hours. The reaction mixture was filtered, and the filtrate was fractionated to yield a fraction of b.p. 130–145°/0.2 mm. which solidified on standing. It was recrystallized from dilute ethanol to yield 52 g. of long, white needles of N,N-dibenzylglycine ethyl ester; m.p. 53–54°. The ester is soluble in alcohol and benzene and insoluble in water.

Anal. Calc'd for $C_{18}H_{21}NO_2$: C, 76.4; H, 7.4.
Found: C, 76.3; H, 7.1.

XVII. *Bis(dibenzylaminoacetamido)ethane* and XVIII. *2-(Dibenzylaminomethyl)imidazoline.* A mixture of 53 g. of the ethyl ester of dibenzylaminoglycine and 33 g. of ethylenediamine was reacted according to the method of Hill and Aspinall (7). The ethanol extract was fractionated to yield 21 g. of a yellow oil, b.p. 174–180°/0.3 mm., and a dark brown residue. The latter was bis(dibenzylaminoacetamido)ethane, m.p. 139.5–140.5° on recrystallization from dilute isopropanol.

Anal. Calc'd for $C_{34}H_{38}N_4O_2$: C, 76.4; H, 7.1; N, 10.5.
Found: C, 76.1; H, 6.9; N, 10.6.

The yellow distillate was dissolved in petroleum ether (b.p. 30–60°), treated with Norit, filtered, concentrated, and finally cooled to yield pure 2-(dibenzylaminomethyl)imidazoline, m.p. 79–80°; insoluble in water; soluble in the common organic solvents and in dilute mineral acids.

Anal. Calc'd for $C_{18}H_{21}N_3$: C, 77.5; H, 7.5; N, 15.0.
Found: C, 77.8; H, 7.6; N, 14.4.

The *dihydrochloride* melted at 180–181°.

XIX. *N,N-Dicyclohexylglycine ethyl ester.* A mixture of 118 g. of dicyclohexylamine and 80.5 g. of ethyl chloroacetate was heated at 150–160° with stirring for 5 hours. The precipitate was then filtered off and washed with benzene. The filtrate and washings were combined and fractionated to yield N,N-dicyclohexylglycine ethyl ester as a colorless oil, b.p. 113–116°/0.3 mm.; n_D^{27} 1.4779, n_D^{24} 1.479.

Anal. Calc'd for $C_{16}H_{29}NO_2$: C, 71.8; H, 10.9.
Found: C, 71.6; H, 11.0.

XX. *Bis(dicyclohexylaminoacetamido)ethane* and XXI. *2-(Dicyclohexylaminomethyl)-imidazoline.* A mixture of 53.4 g. of N,N-dicyclohexylglycine ester and 36 g. of ethylenediamine was treated as described in experiment XVIII. The hot ethanol extract on standing deposited a crystalline product which was repeatedly recrystallized from ethanol to yield white needles of bis(dicyclohexylaminoacetamido)ethane, m.p. 168–170°.

Anal. Calc'd for $C_{30}H_{54}N_4O_2$: C, 71.6; H, 10.8.
Found: C, 71.8; H, 10.1.

The ethanolic filtrate after removal of the diamide was fractionated to give a viscous yellow oil, b.p. 150–160°/0.25 mm. which crystallized to a soft, yellow solid on standing. On repeated recrystallization from petroleum ether (30–60°) the 2-(dicyclohexylaminomethyl)imidazoline was obtained in the form of white needles, m.p. 105–106°. The product was soluble in most common organic solvents and insoluble in water.

Anal. Calc'd for $C_{16}H_{29}N_3$: C, 73.0; H, 11.0; N, 16.0.
Found: C, 72.9; H, 10.7; N, 15.8.

XXII. *N-Benzhydrylglycine ethyl ester.* Benzhydrylamine (173 g.), 38 g. of magnesium oxide, and 100 cc. of water were mixed and heated under reflux. To the refluxing mixture was added dropwise with stirring over one hour, 116 g. of ethyl chloroacetate. Stirring and heating were continued for a total of about 5 hours. The mixture was extracted with ether, the ether was removed, and the residual oil was fractionated twice, yielding 115 g. of N-benzhydrylglycine ethyl ester as a colorless oil, b.p. 150–152°/0.4 mm.; n_D^{25} 1.5508.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1.
Found: C, 75.5; H, 6.8.

XXIII. *1,1,2,2-Tetraphenylethane.* In an attempt to prepare 2-(benzhydrylaminomethyl)-imidazoline, 54 g. of N-benzhydrylglycine ethyl ester and 36 g. of ethylenediamine were treated as described in experiment XVIII. On fractionation of the reaction mixture at 0.25–0.3 mm. two solids sublimed over, one at about 90° and the other at about 150°. The latter was 1,1,2,2-tetraphenylethane. It was recrystallized from ethanol to give white flakes melting at 211–212° (Lit. m.p. 211°) and was insoluble in water and dilute mineral acids.

Anal. Calc'd for $C_{26}H_{22}$: C, 93.3; H, 6.7.
Found: C, 93.1; H, 6.6.

The solid which sublimed at about 90° was soluble in most of the common organic solvents and, in addition, readily dissolved in water to yield a strongly basic solution. White needles which melted at 104–105° were obtained on recrystallization from Skellysolve B. These properties correspond with those of 2-methylimidazoline (m.p. 105°). The identity of the two was finally established by treating an aqueous solution of the material with benzoyl chloride in the presence of calcium carbonate. A derivative was obtained which melted at 113°. According to Ladenburg (9), 2-methylimidazoline when so treated yielded N-acetyl-N′,N′-dibenzoylethylenediamine, m.p. 113–114°.

SUMMARY

The synthesis of a number of ethylenediamine derivatives, having three or four substituent groups attached to the nitrogen atoms, is reported. Those compounds in which the benzhydryl structure was one of the substituents were found to undergo scission readily.

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