lected boiling between 143 and 144°. This liquid had the boiling point and the characteristic odor of ethyl orthoformate.

Discussion

Experiments involving reactions of aniline with ethyl orthoformate in heptane solutions which are very dilute with respect to aniline show conclusively that ethyl N-phenylformimidate (II) and not N,N'-diphenylformamidine (I) is the product of the reaction. Thus, reaction 3f has been demonstrated. With higher concentrations of aniline, I is formed by reaction of II with aniline. The possibility of II being formed by means of a two-step reaction involving I as an intermediate is ruled out by the fact that I does not react with ethyl orthoformate at an appreciable rate under the conditions of the experiment.

In fact, the experiments indicate that I does not react directly with ethyl orthoformate at all. In the dilute heptane solutions, I is not converted into II unless ethanol is added, confirming the theory that alcoholysis (reaction 4r) is the first step in the conversion. It does not seem likely that the reaction in the presence of ethanol could be due to a change in the physical properties of the reaction medium, since it contained only 1.6% ethanol.

It has been shown previously[3] that the practical preparation of II from the reaction of I with ethyl orthoformate is completely dependent on acid catalysis. It has now been demonstrated that this process involves the two steps 4r and 3f. Reaction 3f seems to be somewhat less dependent on acid catalysis, since it was found to occur even when precautions were taken to remove all acids. So there is indication that reaction 4r is a step which is extremely dependent on and sensitive to acid catalysis. If we assume that this step is more dependent on acid catalysis than any of the other three steps of equations 3 and 4, we can give very satisfactory explanations to some problems which have puzzled the authors for several years.

There is a spectacular difference in the practical course taken by the reaction of aniline with ethyl orthoformate in the absence of or presence of acids, as far as products are concerned: in the absence of acids, only I can be isolated, no matter how large an excess of ethyl orthoformate is used; in the presence of acids, II can be isolated in good yields. Formerly we stated[4] that different mechanisms must operate in the absence of and presence of acids. Although still possible, this does not seem so likely now since the observed facts can be explained quite well in terms of the two reversible equations 3 and 4. In the presence of acid catalysts, II is obtained by the operation of the steps 3f, 4f (fast), followed by 4r, 3f (slow). The isolation of only I in the absence of acid catalysts is attributable to the fact that 4f is much faster than 3f, and to the inappreciable rate of 4r in the absence of acid.

There is also a spectacular difference in the course taken by the reaction of a formimidic ester such as I with an aromatic amine in the absence of or presence of acids, as far as products are concerned, *if the aromatic groups of the ester and amine are not identical:* in the absence of acids the unsymmetrical N,N'-diarylformamidine is obtained; in the presence of acids, a mixture of the unsymmetrical and the two corresponding symmetrical N,N'-diarylformamidines is obtained.[4] Formerly, we ascribed these results, too, to the operation of different mechanisms. Now they can be explained readily in terms of equations 3 and 4. A glance at the mechanisms proposed for acid-catalyzed disproportionation (Fig. 1 of ref. 4) will show that reversibility of the reaction is responsible for formation of the mixture of formamidines. The reverse reactions involved are of the type 4r, and these do not occur at an appreciable rate in the absence of acid catalysts. Hence, the formation of the unsymmetrical N,N'-diarylformamidine is essentially irreversible when acids are excluded, and disproportionation does not occur.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Polyamine Salts with Autonomic Blocking Properties[1]

BY R. H. MIZZONI, M. A. HENNESSEY AND C. R. SCHOLZ

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A series of tris-dialkylaminoalkylamine salts has been prepared and found to possess autonomic ganglionic blocking properties. Direct alkylation of appropriate dialkylaminoalkyl amines with dialkylaminoalkyl halides proved a convenient route to many of these substances.

The ability of certain polymethylene-bis-ammonium salts to effect ganglionic blockade is well known. The familiar "C_6" (hexamethylene-bis-trimethylammonium ion), for example, displays the highest order of potency among the members of that homologous series. The alkylene chain may be interrupted by a tertiary amine function, however, without detriment to its activity,[2] as demonstrated in a series of compounds prepared by Marxer and Miescher.[3]

In the course of our investigations into the properties of polyamines we had occasion to prepare substance I.

$N[CH_2CH_2N(C_2H_5)_2]_3$ (a) trihydrochloride
I (b) trimethiodide

(1) Presented in part at the 121st meeting of the American Chemical Society, Milwaukee, Wisc., March 31, 1952. Publication was delayed in order to complete work which was in progress. Pharmacological work was presented by A. J. Plummer, J. A. Schneider and W. A. Barrett at the Pharmacology Section of the 19th International Congress, Montreal, September 5, 1953, and is in press, *Arch. intern. pharmacodynamie.*

(2) H. J. Bein and R. Meier, *Experientia*, **6**, 351 (1950); *Schweiz. med. Wochr.*, **81**, 446 (1951).

(3) A. Marxer and K. Miescher, *Helv. Chim. Acta*, **34**, 924 (1951).

TABLE I

$A—N<^{B}_{C}$

A	B	C	Empirical formula	Analyses, % Calcd. N	Calcd. X	Found N	Found X	M.p., °C.	Method
$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{18}H_{42}N_4 \cdot 3CH_3I$	7.57	51.42[j]	7.64	51.18	275	A
$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{18}H_{42}N_4 \cdot 3HCl$	13.22	[k]	13.07		224.2–224.8	A
$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{18}H_{42}N_4 \cdot 4HCl$	12.16	30.60	11.87	30.53	193.5–195	
$C_5H_{10}NCH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_{21}H_{42}N_4 \cdot 3HCl(2H_2O)$	11.32	21.49	11.56	21.83	249.5–251	
$Me_2NCH_2CH_2$	$Me_2NCH_2CH_2$	$Me_2NCH_2CH_2$	$C_{12}H_{30}N_4 \cdot 3HCl(1H_2O)$	15.66	29.73	15.52	30.28	276–276.5	C
$i\text{-}Pr_2NCH_2CH_2$	$i\text{-}Pr_2NCH_2CH_2$	$i\text{-}Pr_2NCH_2CH_2$	$C_{24}H_{54}N_4 \cdot 4HCl$	10.29	26.04	10.29	26.14	246–247	D
$Et_2NCH_2CH_2$	$Bu_2NCH_2CH_2$	$Bu_2NCH_2CH_2$	$C_{26}H_{58}N_4 \cdot 3HCl$		19.84		19.71	127.5–129.5	A[a]
$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_4H_8ONCH_2CH_2$	$C_{18}H_{40}N_4O \cdot 3HCl$		24.29[l]		23.77	155–157	A[b]
$Me_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{17}N_{40}N_4 \cdot 3HCl$		25.95		26.23	201	B[c]
$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{19}H_{44}N_4 \cdot 3HCl$	12.88	24.46	12.61	24.13	230–231	B[d]
$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{19}H_{44}N_4 \cdot 4HCl$	11.81	29.89	11.92	29.80	218–220.2	B
$Pr_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{21}H_{48}N_4 \cdot 3HCl(2H_2O)$	11.16	21.19	11.27	20.78	184–184.5	
$Bu_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{23}H_{52}N_4 \cdot 4HCl$	10.56	26.73	10.36	26.74	197–199	B[e]
$H_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{16}H_{36}N_4 \cdot 4HCl(2H_2O)$	12.33	31.22	12.48	31.25	183–185	
$Et_2NCH_2CH_2CH_2$	$i\text{-}Pr_2NCH_2CH_2$	$i\text{-}Pr_2NCH_2CH_2$	$C_{23}H_{52}N_4 \cdot 3HCl$	11.34	21.53	11.22	21.38	193–195	B[f]
$Et_2NCH_2CH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_{21}H_{44}N_4 \cdot 3HCl(2H_2O)$	11.05	21.36	11.03	20.99	226–228	B[g]
$Bu_2NCH_2CH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_5H_{10}NCH_2CH_2$	$C_{29}H_{52}N_4 \cdot 4HCl$	10.10	25.58	10.45	25.69	270 dec.	B
$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2$	$C_{20}H_{48}N_4 \cdot 3HCl$	12.40	23.53	12.85	23.37	244–247	B[h]
$(HOCH_2CH_2)_2N(CH_2)_3$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{19}H_{44}N_4O_2 \cdot 3HCl$	11.95	22.68	11.89	22.20	143–144.5	B
$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2CH_2$	$Et_2NCH_2CH_2CH_2$	$C_{21}H_{48}N_4 \cdot 3HCl$	12.02	22.81	12.01	22.67	275 dec.	B
$(PhCH_2)_2N(CH_2)_3$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{29}H_{48}N_4 \cdot 4HCl$	9.36	23.69[m]	9.40	23.14	222 dec.	B[i]
$Et_2N(CH_2)_3$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{21}H_{48}N_4 \cdot 2H_2PtCl_6(1H_2O)$	4.69	[n]	4.87		216–217 dec.	B
$H_2N(CH_2)_4$	$H_2N(CH_2)_4$	$H_2N(CH_2)_4$	$C_{12}H_{30}N_4 \cdot 4HCl(1H_2O)$	14.21	35.97	14.38	35.34	289–290	
$Me_2N(CH_2)_4$	$Me_2N(CH_2)_4$	$Me_2N(CH_2)_4$	$C_{18}H_{42}N_4 \cdot 4HCl$	12.17	30.80	11.92	30.79	291–292	C
$Me_2N(CH_2)_4$	$MeN(CH_2)_4$	$Me_2N(CH_2)_4$	$C_{16}H_{42}N_4 \cdot 4CH_3I$	6.44		6.64		269–271	
$Me_2N(CH_2)_3$	$Me_2N(CH_2)_3$	$Me_2N(CH_2)_3$	$C_{18}H_{36}N_4 \cdot 3CH_3I$	8.46		8.36		288–290	C
$H_2N(CH_2)_4$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{16}H_{38}N_4 \cdot 4HCl$	12.96	32.80	12.78	32.29	207–210	
$Et_2NCH_2CHOHCH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{19}H_{44}N_4O \cdot 3HCl(1H_2O)$	12.13	23.02	12.04	23.17	207–209	B
$Et_2NCH_2CHOHCH_2$	$Et_2NCH_2CH_2$	$Et_2NCH_2CH_2$	$C_{19}H_{44}N_4O \cdot 3CH_3I$	7.27	49.42	7.49	49.76	230–231 dec.	
$EtNHCH_2CH_2$	$EtNHCH_2CH_2$	$EtNHCH_2CH_2$	$C_{12}H_{30}N_4 \cdot 3HCl$	16.49	31.31	16.16	31.12	250–251	

[a] From $Et_2N(CH_2)_2NH_2$ and $Bu_2N(CH_2)_2Cl$. [b] From $C_4H_8ON(CH_2)_2NH_2$ and $Et_2N(CH_2)_2Cl$. [c] From $Me_2N(CH_2)_3NH_2$ and $Et_2N(CH_2)_2Cl$. [d] From $Et_2N(CH_2)_3NH_2$ and $Et_2N(CH_2)_2Cl$. [e] From $Bu_2N(CH_2)_3NH_2$ and $Et_2N(CH_2)_2Cl$. [f] From $Et_2N(CH_2)_3NH_2$ and $i\text{-}Pr_2N(CH_2)_2Cl$. [g] From $Et_2N(CH_2)_3NH_2$ and $C_5H_{10}N(CH_2)_2Cl$. [h] From $Et_2N(CH_2)_3NH_2$ and $Et_2N(CH_2)_2Cl$. [i] From $(C_6H_5CH_2)_2N(CH_2)_3Cl$ and $(Et_2NCH_2CH_2)_2NH$. [j] Calcd.: C, 34.06; H, 6.94. Found: C, 33.76; H, 7.17. [k] Calcd.: C, 50.99; H, 10.70. Found: C, 50.90; H, 10.64. [l] Calcd.: C, 49.36; H, 9.90. Found: C, 48.78; H, 9.72. [m] Calcd.: C, 58.19; H, 8.76. Found: C, 58.29; H, 8.37. [n] Calcd.: C, 21.11; H, 4.56. Found: C, 20.87; H, 4.44.

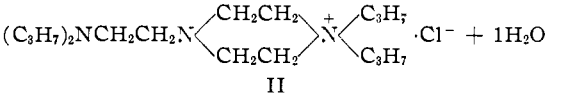
The trimethiodide Ib proved devoid of ganglionic blocking properties. Curiously enough, the trihydrochloride, Ia, displayed a high order of activity. To our knowledge this represents the first instance of a tertiary amine salt with this pharmacological property. A number of related substances were prepared and tested in this connection; data pertaining to these compounds may be found in Table I.

The only previously recorded preparation of this type is that of van Alphen[4] in which 2,2′,2″-tri-(1-piperidyl)-triethylamine was isolated as the picrate salt from the reaction of tris-(2-chloroethyl)-amine hydrochloride and piperidine. Since the substantial completion of this work the preparation of I has appeared in the German literature; this was effected by treatment of tris-(2-chloroethyl)-amine base with diethylamine under mild conditions.[5]

The only successful application of the method of van Alphen[4] in our hands resulted in the reaction of di-isopropylamine with 2,2′,2″-tris-(chloroethyl)-amine hydrochloride. A small amount of 2,2′,2″-tris-(diisopropylamino)-triethylamine was isolated, along with a larger quantity of a white solid. In the case of di-*n*-propylamine, a white solid alone was isolated. This corresponded closely by elementary analysis to $C_{18}H_{40}N_3Cl(H_2O)$. A possible structure which is suggested is shown in II.

(4) J. van Alphen, *Rec. trav. chim.*, **56**, 1007 (1947).

(5) H. Lettre and W. Riemenschneider, *Ann.*, **575**, 18 (1952).



II

This would be compatible with the solubility of the substance in chloroform and water and insolubility in ether, and might be formed from the reaction components shown in Fig. 1 in the following manner

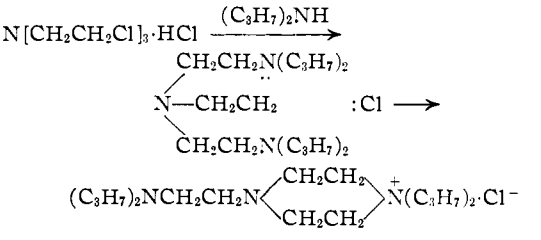


Fig. 1.

The method of Lettre and Riemenschneider[5] employed 2,2′,2″-trichlorotriethylamine base under milder reaction conditions, and may account for the alternate course taken by the reaction.

In spite of the disadvantages inherent in such a process, the direct alkylation of an appropriate dialkylaminoalkylamine with an excess of a dialkylaminoalkyl chloride proved a convenient route to many of the polyamines of interest. From the expected mixtures of amines the desired bases were obtainable in moderate yields. In many cases the

trihydrochloride salts were obtained directly and in a high state of purity.

$$(x)\,(R_1)_2N(CH_2)_mNH_2 + (2x)\,(R_2)_2N(CH_2)_nCl \longrightarrow (R_1)_2N(CH_2)_mN[(CH_2)_nN(R_2)_2]_2\cdot 3HCl + (R_1)_2N(CH_2)_mN[(CH_2)_nN(R_2)_2]_2\ (\text{base}) + (R_1)_2N(CH_2)_mNH(CH_2)_nN(R_2)_2$$

Fig. 2.

Higher ω-dialkylaminoalkylamines were prepared by reduction of the corresponding nitriles with lithium aluminum hydride in ether. These were in turn treated with the appropriate dialkylaminoalkyl chloride in the manner described to yield unsymmetrical polyamines of the type shown in Fig. 3.

The ready dimerization of 2-chloroethyldimethylamine precluded its use as an alkylating agent in the synthesis of 2,2′,2″-tris-(dimethylamino)-triethylamine. Instead, this substance was obtained by reductive methylation of 2,2′,2″-triaminotriethylamine trihydrochloride with formaldehyde and formic acid. 3,3′,3″-Tris-(dimethylamino)-tripropylamine and 4,4′,4″-tris-(dimethylamino)-tributylamine were prepared in an analogous fashion (Fig. 3).

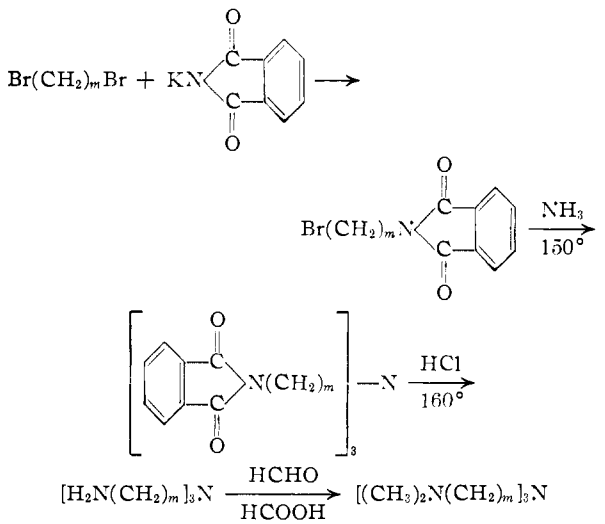


Fig. 3.

Acknowledgment.—We wish to express our thanks to Mr. Louis Dorfman and his staff for the microanalytical results, and to Miss Evelyn Peterson for her technical assistance.

Experimental

Method A. 2,2′,2″-Tris-(diethylamino)-triethylamine Trihydrochloride.—A mixture of 290 g. (2.5 moles) of N,N-diethylethylenediamine and 711 g. (5.25 moles) of 2-chlorotriethylamine was heated carefully with efficient stirring (Hershberg stirrer) until a vigorous reaction set in. Heating was discontinued and the mixture allowed to cool. One liter of water was added with stirring and the dark oil which formed was separated. The remaining aqueous portion was made strongly alkaline with sodium hydroxide solution (1:1) and the layers were separated. The combined oily base was taken up in ethylene dichloride and dried thoroughly with anhydrous potassium carbonate. After filtration of the solution and removal of the solvent, the residue was distilled *in vacuo;* the portion boiling in the range 87–137° (0.05 mm.) (437 g.) was dissolved in 100 cc. of anhydrous ethanol, chilled in an ice–salt-bath, and treated with alcoholic hydrogen chloride (512 cc., 9.0 *N*) at such a rate that the temperature did not exceed 15°. Upon dilution with 1250 cc. of 2-butanone and chilling, a white crystalline material separated out; this material was filtered, washed freely with 2-butanone and dried at 60° *in vacuo* (474 g., 45%, m.p. 224–226°). A second crop was obtained by dilution of the filtrate with 2-butanone (99 g., m.p. 192–210°). Melting points were not altered by recrystallization from isopropyl alcohol.

Method B. N″-(3-Diethylaminopropyl)-N,N,N′,N′-tetraethyldiethylenetriamine Trihydrochloride.—A solution of 130 g. (1.0 mole) of N,N-diethyl-1,3-propanediamine in 500 cc. of butanol contained in a 2-liter flask equipped with a dropping funnel, Hershberg stirrer and an efficient condenser was heated to reflux. 2-Chlorotriethylamine (340 g., 2.5 moles) was added at such a rate that moderate refluxing was maintained. Heating was continued for an additional quarter hour. The cooled mixture was diluted with one volume of 2-butanone and refrigerated; the crystals which deposited were filtered off, washed freely with 2-butanone, then dried at 60° *in vacuo* (127.4 g., m.p. 225.2–227.2°). A second crop resulted upon dilution of the filtrate with methyl ethyl ketone (52.3 g., m.p. 218.8–220.8°). The combined material was not improved by recrystallization from isopropyl alcohol.

Method C. 2,2′,2″-Tris-(dimethylamino)-triethylamine Trihydrochloride.—A mixture composed of 8.2 g. of 2,2′,2″-triaminotriethylamine tetrahydrochloride,[6] 9.6 g. of sodium bicarbonate, 15.6 g. of formalin (37%) and 27.8 g. of formic acid (90%) was heated under reflux for 18 hours. The solution was then acidified with concentrated hydrochloric acid and evaporated to dryness on a steam-bath. The residue was taken up in a little water and made strongly alkaline with potassium hydroxide pellets. The ethylene dichloride extract of this material was dried over anhydrous potassium carbonate and filtered. After removal of the solvent *in vacuo* the residue was distilled, b.p. 62–67° at 0.2 mm. This material was dissolved in ether and treated with anhydrous hydrogen chloride. The white solid was filtered and washed freely with ether, then dried at 50° *in vacuo* (4.3 g., 43%, m.p. 276–276.5°). No change in melting point resulted upon recrystallization from ethanol.

2,2′,2″-Tri-(1-piperidyl)-triethylamine Trihydrochloride Dihydrate.—A solution of 8.8 g. of 1-(2-chloroethyl)-piperidine, 19.5 cc. of alcoholic ammonia (72 mg. per ml.) and 10 cc. of alcohol was maintained at −20° for 3 days, at room temperature for 1 day and then refluxed for ¾ hour. A flocculent white precipitate separated out and was filtered hot. The insoluble residue was recrystallized twice from isopropyl alcohol (2.1 g., m.p. 249.5–251°).

N-(4-Bromobutyl)-phthalimide.—For the preparation of this compound a modification of the method of Salzberg and Supniewski[7] was used.

A mixture of 65 g. (0.35 mole) of potassium phthalimide and 200 g. (0.93 mole) of tetramethylene dibromide was heated with occasional shaking for 12 hours. The residue remaining after removal of excess tetramethylene dibromide was digested with ethanol and then filtered. The material which crystallized on standing was filtered, washed with ethanol and dried *in vacuo* (28.7 g., m.p. 79.5–80°). A second crop was obtained by concentration of combined filtrate and washings (31.8 g., m.p. 79.5–80°). The melting point was not altered by recrystallization from cyclohexane.

Anal. Calcd. for $C_{12}H_{12}BrNO_2$: Br, 28.33; N, 4.96. Found: Br, 28.36; N, 5.05.

4,4′,4″-Triphthalimidotributylamine.[8]—48.2 grams of N-(4-bromobutyl)-phthalimide was melted and heated to 150°. A stream of anhydrous ammonia was passed through the melt for 6 hours with occasional stirring. The cooled residue was digested with alcohol, then filtered hot and dried (17.5 g., m.p. 227–229°).

4,4′,4″-Triaminotributylamine Tetrahydrochloride Monohydrate.—4,4′,4″-Triphthalimidotributylamine (17.5 g.) was heated with 70 cc. of concentrated hydrochloric acid at 150° for six hours. The cooled solution was filtered and the insoluble phthalic acid was washed with a little water. The filtrate was diluted with two volumes of ethanol and chilled. A white solid separated upon the addition of acetone (7.3 g.,

(6) E. Ristenpart, *Ber.*, **29**, 2531 (1896).

(7) P. L. Salzberg and J. V. Supniewski, *Organic Syntheses*, Coll. Vol. I, 2nd edition, John Wiley and Sons, Inc., 1941, New York, N. Y., pp. 119–121.

(8) Adapted from the method of Ristenpart, ref. 6.

m.p. 289–290°). The melting point was lowered to 189–191° dec., upon recrystallization from an acetone–water mixture.

Reaction of 2,2′,2″-Trichlorotriethylamine Hydrochloride with Dipropylamine.—A solution of 10 g. (0.05 mole) of 2,2′,2″-trichlorotriethylamine hydrochloride and 34 g. (0.34 mole) of dipropylamine in 50 cc. of anhydrous ethanol was refluxed for 19 hours. Solvent was removed and the residue was dissolved in a small amount of water. Sufficient sodium hydroxide solution (1:1) was added to effect separation of an oily layer, which was decanted and dried over solid sodium hydroxide. The oil solidified readily and was taken up in ethylene dichloride. The extract was dried further over anhydrous magnesium sulfate, filtered, and the filtrate diluted with ether. A white solid separated out; this was redissolved and reprecipitated in the same manner; yield 6.1 g., m.p. 194–195.5°.

Anal. Calcd. for $C_{18}H_{40}ClN_3 \cdot H_2O$: C, 61.41; H, 12.03; N, 11.94. Found: C, 61.41, 62.03; H, 11.75, 12.11; N, 11.72, 12.15.

N,N-Diethylputrescine.—To a suspension of 15 g. of commercial lithium aluminum hydride in 600 cc. of anhydrous ether (stirred overnight in an atmosphere of dry nitrogen), there was added a solution of 33.7 g. (0.24 mole) of γ-diethylaminobutyronitrile[9] in 100 cc. of anhydrous ether, with stirring during one-half hour. During the addition the reaction mixture refluxed at a vigorous rate. Stirring was continued for an additional hour and was followed by the cautious addition of 20 cc. of ethyl acetate. One hundred cc. of 20% sodium potassium tartrate solution was then added carefully, followed by additional stirring for two hours. The suspension was filtered and the residue washed with ether. After drying the extract with anhydrous sodium sulfate, the solvent was removed and the product distilled *in vacuo*, b.p. 81–86° at 14 mm.[10] (61.4%).

β-[Bis-(2-diethylaminoethyl)-amino]-propionitrile.—To a refluxing solution of 64.5 g. (0.3 mole) of bis-(2-diethylaminoethyl)-amine[11] in 100 cc. of glacial acetic acid there was added 31.8 g. (0.6 mole) of acrylonitrile during one-half hour. After refluxing for seven hours the reaction mixture was cooled and treated with an excess of saturated aqueous potassium carbonate solution. The chloroform extract of this material was dried over anhydrous magnesium sulfate and then distilled to remove solvent. The oily residue was distilled *in vacuo*, b.p. 104–109° at 0.2 mm. (40.4 g., 49.8%); picrate, m.p. 202–203°.

Anal. Calcd. for $C_{24}H_{35}N_9O_{14}$: N, 18.72. Found: N, 18.94.

N″-(3-Aminopropyl)-N,N,N′,N′-tetraethyldiethylenetriamine.—A 40.4-g. quantity of β-[bis-(2-diethylaminoethyl)-amino]-propionitrile was reduced with 6 g. of lithium aluminum hydride according to the procedure previously described; b.p. 77–88° (0.1 mm.) (14 g., 34.4%).

Tetrahydrochloride salt (from ethanol), m.p. 152–156° (see Table I).

N″-(3-Dipropylaminopropyl)-N,N,N′,N′-tetraethyldiethylenetriamine trihydrochloride Dihydrate.—To a boiling solution of 48.5 g. N′,N′,N‴,N‴-tetraethyldiethylenetriamine (b.p. 72–80° (0.01 mm.); $n^{23}D$ 1.4468) in 100 cc. of butanol, there was added during 1 hour with stirring 42.7 g. of 3-chlorotripropylamine. Refluxing was continued for one hour, the solvent then being removed as completely as possible under vacuum. Water (200 cc.) was added and the basic material taken up in ethylene dichloride and dried over anhydrous potassium carbonate. After filtration of the drying agent, the solvent was removed *in vacuo* and the oily residue fractionated under high vacuum after removal of material boiling below 120° with a water pump (b.p. 135–158° at 0.07 mm., $n^{24}D$ 1.4573, 45 g.). This material was dissolved in alcohol and treated with three equivalents of alcoholic hydrogen chloride per mole of base. A fine white crystalline solid separated out upon dilution with about one volume of 2-butanone. The solution was filtered and the salt washed freely with 2-butanone, then dried *in vacuo* at 60° (60 g., m.p. 126.5°, resolidified, remelted at 183–184.5°). Upon recrystallization from an isopropyl alcohol–2-butanone mixture, the melting point was 184–184.5° (50 g.).

γ-[Bis-(2-diethylaminoethyl)-amino]-butyronitrile.—A solution of 86 g. of N,N,N′,N′-tetraethyldiethylenetriamine and 41 g. of γ-chlorobutyronitile in 200 cc. of butanol was refluxed for 24 hours. The solvent was removed by distillation *in vacuo*. The solidified product was triturated with ether and filtered, then recrystallized from an ethanol–2-butanone mixture (48 g., m.p. 123–132°). Recrystallization from ethanol resulted in an improvement in the melting point to 132–134°.

Anal. Calcd. for $C_{16}H_{36}Cl_2N_4$: Cl, 19.95. Found: Cl, 20.47.

This material was converted to the base by dissolving in water and adding concentrated sodium hydroxide solution (1:1), then extracting with ether, drying the extract and distilling after removal of solvent, b.p. 138–148° (0.2 mm.).

N″-(4-Aminobutyl)-N,N,N′,N′-tetraethyldiethylenetriamine Tetrahydrochloride.—To a solution of five grams of lithium aluminum hydride in 50 cc. of ether there was added during one-half hour with stirring a solution of 16.2 g. (0.057 mole) of γ-[bis-(2-diethylaminoethyl)-amino]-butyronitrile in 50 cc. of ether. After standing overnight, 25 cc. of ethyl acetate was added to destroy excess reagent. This was followed by the addition of aqueous caustic soda in excess. The solution was filtered through a sintered glass funnel and the layers separated. The ether solution was dried over anhydrous magnesium sulfate and the filtrate distilled. The product (6.3 g., b.p. 120–145° at 0.15 mm.) was dissolved in ether and treated with anhydrous hydrogen chloride. The white solid was filtered and recrystallized from an ethanol–2-butanone mixture, m.p. 207–210°.

2,2′,2″-Tris-(*p*-toluenesulfonamido)-triethylamine.—A 2.5-g. quantity of 2,2′,2″-triaminotriethylamine was treated with *p*-toluenesulfonyl chloride according to the usual procedure. Upon recrystallization from alcohol, a white solid was obtained, m.p. 105–108°.

Anal. Calcd. for $C_{27}H_{36}N_4O_6S_3$: N, 9.22; S, 15.80. Found: N, 9.23; S, 15.54.

2,2′,2″-Tri-(ethylamino)-triethylamine.—Fourteen grams of material prepared by the method described above was alkylated with ethyl iodide by the method of Kurzer.[12] Fourteen and eight tenths grams of material, m.p. 80.5–83.5°, was obtained. This was treated with 80% sulfuric acid at 150–160° for five minutes, then diluted with water. The cooled solution was made strongly alkaline with concentrated sodium hydroxide solution (1:1) and then extracted with three 100-ml. portions of ether. The ether extract was dried over magnesium sulfate, filtered and treated with anhydrous hydrogen chloride. The white solid thus obtained was recrystallized from an isopropyl alcohol–2-butanone mixture (1.9 g., m.p. 242–244°).

2,2′,2″-Tris-(diisopropylamino)-triethylamine Tetrahydrochloride.—A solution of 10 g. of tris-(2-chloroethyl)-amine hydrochloride and 33.5 g. of diisopropylamine in 75 cc. of alcohol was allowed to reflux for 23 hours. After removal of most of the alcohol on a steam-bath, water was added and the solution made strongly alkaline with sodium hydroxide solution (1:1). The oily material was extracted with ethylene dichloride and the extract dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the solvent was removed *in vacuo* and the remaining oil was distilled, b.p. 105–122° (0.1 mm.) (5.4 g.). This material was converted to its hydrochloride salt by dissolving in ether and treating with anhydrous hydrogen chloride. The white salt was recrystallized from aqueous isopropyl alcohol (3.5 g., m.p. 246.5–247°).

SUMMIT, NEW JERSEY

(9) W. P. Utermohlen and C. S. Hamilton, THIS JOURNAL, **63**, 156 (1941).

(10) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, THIS JOURNAL, **66**, 725 (1944). The boiling point reported in this paper is 85–88° at 18 mm.

(11) This material was isolated from the forerun during the preparation of 2,2′,2″-tris-(2-diethylaminoethylamine), and had a boiling point of 85–95° (0.3 mm.). Picrate, m.p. 121.5–122.5°. *Anal.* Calcd. for $C_{30}H_{38}N_{12}O_{21}$ (tripicrate): N, 18.62. Found: N, 19.11.

(12) F. Kurzer, *J. Chem. Soc.*, 3434 (1949).