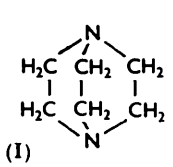
355. *Triethylenediamine* (1 : 4-*Diaza*bicyclo[2 : 2 : 2]*octane*) *and Hexaethylenetetramine. Part III.* The Interaction of* 2 : 2′ : 2″-*Trichlorotriethylamine Hydrochloride and Dimethylamine.*

By Frederick G. Mann and F. C. Baker.

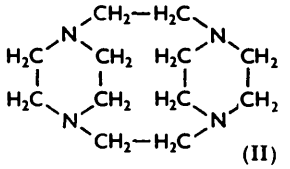
Interaction of 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride and methanolic dimethylamine, and thermal decomposition of certain of the products, have been re-investigated in detail. No evidence for the formation of hexaethylenetetramine during these decompositions has been obtained, the main high-boiling product being 1 : 2-di-(4-methyl-1-piperazinyl)ethane.

Four disubstituted piperazines which occur in this work are of almost identical composition. To aid the necessary accurate identification, a series of highly purified derivatives of each base has been prepared, and the m. p. of each derivative determined under specified conditions.

Mann and Mukherjee investigated the interaction of 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride, $(Cl{\cdot}CH_2{\cdot}CH_2)_3N,HCl$, with methanolic dimethylamine and stated that thermal dissociation of one of the products of this reaction gave rise to triethylenediamine (I) and hexaethylenetetramine (II). In view of the criticisms of certain aspects of this work by Hromatka and Kraupp,[2] we have carried out



(I)



(II)

a thorough investigation of the above subject, and, by working on a considerably larger scale, have been able in particular to separate the products of the thermal decomposition by fractional distillation, in place of the unsatisfactory fractional crystallisation of their picrates previously employed. We have thus been able to extend considerably the range of this investigation, and to correct certain of the earlier statements.[1]

We find that a mixture of trichlorotriethylamine hydrochloride and a 40% (w/v) solution of methanolic dimethylamine (3·4 mols.), when set aside at room temperature for 24 hours or heated at 45—50° for 1·5 hours, and then worked up with hydrogen chloride, gives the monohydrated 1-2′-chloroethyl-4 : 4-dimethylpiperazinium chloride hydrochloride (III) : this product is also obtained when the proportion of dimethylamine is varied from 2·0 to 6·6 mols. with the above heating. The salt (III), hydrated or anhydrous, has m. p. 264° with two well-defined stages of effervescence (p. 1886). A methanolic solution of the salt (III), when shaken with silver oxide, filtered, and treated with methyl iodide (*a*) in the cold, or (*b*) boiling under reflux, gives the piperazinium iodide (IV) or the iodide methiodide (V) respectively.

When trichlorotriethylamine hydrochloride is heated with the methanolic dimethylamine (12·8 mols.) at 40—45° for 8 hours, the product after similar working up is 1-2′-dimethylaminoethyl-4 : 4-dimethylpiperazinium chloride dihydrochloride (VI), m. p. 227—228°. The hydrochloride, when heated however with the methanolic dimethylamine (10·7 mols.) at 125° for 7 hours, yields 1-2′-dimethylaminoethyl-4-methylpiperazine trihydrochloride (VII), m. p. 262° after crystallisation, 270° after sublimation. The identity of the salt (VII) is shown by the fact that concentrated aqueous alkalis liberate

* Part II, Mann and Senior, *J.*, 1954, 4476.

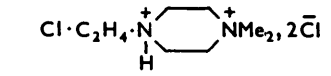
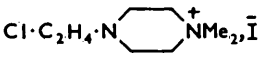
[1] Mann and Mukherjee, *J.*, 1949, 2298.

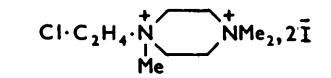
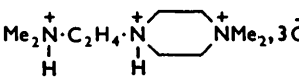
[2] Hromatka and Kraupp, *Monatsh.*, 1951, **82**, 880.

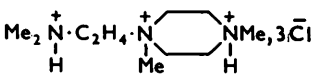
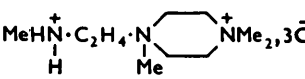
the base (VIII), b. p. 94°/12 mm.: hence the salt cannot contain a quaternary ammonium chloride group which any other formulation would entail.

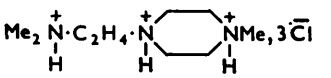
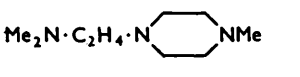
Hromatka and Kraupp [2] state however that the hydrochloride, when heated with 55·7% (w/w) methanolic dimethylamine (3·57 mols.) at 45° for 100 min., gives a mixture of the salt (III), m. p. 260—262°, and the salt (VI), m. p. 305—307°, and when heated with 40% methanolic dimethylamine (13·1 mols.*) at 125° for an unspecified time gives the salt (VII), m. p. 265—266°.

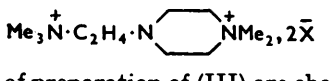
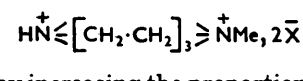
Our results above were obtained independently of (and before the publication of) the results of Hromatka and Kraupp. They agree well, except for the marked difference in the m. p. of the salt (VI), which would indicate that the salts described are structurally different. The following points are therefore noteworthy. (*a*) We have carried out the preparation of our salt, m. p. 228°, on numerous occasions, and have repeatedly checked its m. p. and composition. (*b*) Our salt crystallises from 97% ethanol as a monohydrate, which when confined over phosphoric anhydride at 20 mm. gives the anhydrous salt, having an identical m. p. Hromatka and Kraupp's salt, when crystallised from ethanol formed a dihydrate, which was unaffected by confinement over phosphoric anhydride in a high vacuum: when heated at 140° in this vacuum it decomposed. (*c*) The structure of the chloroethyl salt (III) is not in reasonable doubt. Since the salt (VI) arises when the

(III)  (IV) 

(V)  (VI) 

(VIA)  (VIB) 

(VII)  (VIII) 

(IX)  (X) 

conditions of preparation of (III) are changed only by increasing the proportion of dimethylamine and the time (but not the degree) of heating, a comparatively simple reaction, such as the conversion of the initial chloroethyl group of (III) into the dimethylaminoethyl group, would be expected. It is very difficult to visualise the formation in these circumstances of any isomeric salt such as (VIA) or (VIB). The formation of the salt (VIA) would involve degradation of the terminal (N^4) quaternary chloride to the tertiary hydrochloride, and quaternisation of the tertiary (N^1) group: that of the salt (VIB) would involve conversion of the initial 2′-Me_2N-group into a MeNH-group, with quaternisation of the N^1 group as before. Although Hromatka and Kraupp [2] have shown that appropriate amines can be demethylated by an excess of dimethylamine, which is converted into trimethylamine, this process, like the degradation of a quaternary salt, requires a much higher temperature than that employed in the preparation of the salt (VI). (*d*) Our salt (VI), when heated just above its m. p., undergoes effervescence with the formation of the salt (VII). (*e*) The base (VIII), when treated with an excess of methanolic methyl bromide (with or without heating), gives a dimethobromide (IX; X = Br), and similarly with methyl iodide yields a dimethiodide (IX; X = I). A methanolic solution of the salt (VI), when shaken with silver oxide, filtered, and treated with these methyl halides under these conditions gives the same products. There is very little doubt that these dimethohalides have the structure (IX), for the inductive effect of the positive poles on

* Calculated on w/v basis: the basis is not specified by these authors.

the two outer quaternary nitrogen atoms would considerably deactivate the central tertiary nitrogen atom : this cumulative effect would not occur if the poles were on any other two of the nitrogen atoms. This is strong evidence for the structure of the salt (VI), and would be decisive if the quaternary ammonium group in the salt (III) undergoes no change during the conversion (III) ⟶ (VI).

We consider therefore that our salt, m. p. 228°, has almost certainly the structure (VI), but we cannot explain the different result obtained by Hromatka and Kraupp.[2]

The thermal decomposition of the salts (III), (VI), and (VII) has been studied in detail.

The salt (III), when heated at 250—254°, *i.e.*, until the first effervescence was complete, gave triethylenediamine hydrochloride methochloride (X; X = Cl), which was identified by treatment in methanolic solution with silver oxide and methyl iodide in turn, whereby triethylenediamine dimethiodide was obtained. Hromatka and Kraupp [2] decomposed the salt (III) at 270°, and isolated only piperazine and 1 : 4-dimethylpiperazine, both as derivatives.

Thermal decomposition of the salts (VI) and (VII) gave a mixture of amines. We have consequently submitted each salt, on a 250—300 g. scale, to decomposition at 280° at atmospheric pressure (*i.e.*, under the conditions employed by Mann and Mukherjee [1]), the crude product being then strongly basified and the liberated amines extracted with ether and then fractionally distilled. The properties of picrates of the amines thus isolated showed clearly that separation of the main components of the crude product by fractional crystallisation of their picrates, as described by Mann and Mukherjee,[1] without any preliminary fractional distillation, was unsatisfactory. On the other hand, the curiously volatile properties of triethylenediamine (I), had it occurred in these mixed amines, would have made its isolation from the mixture by distillation extremely difficult.

The properties of triethylenediamine must therefore be first discussed. We have prepared this base by a modification of Hromatka and Kraupp's method,[2] whereby triethylenediamine dimethobromide (prepared by the combination of 1 : 4-dimethylpiperazine and ethylene dibromide [1]) was heated at 230—240°/0·001 mm. in a glass vessel connected to a receiver cooled in carbon dioxide–acetone (p. 1890). The crystalline base slowly sublimed into the receiver, and when resublimed was obtained in large, exceedingly beautiful pure crystals, which were identified by analysis and by molecular-weight determinations in boiling ethanol and benzene. The base has m. p. 156—157° in a sealed tube : Hromatka [3] gives m. p. 158—160° in an evacuated tube, but we find that its ready sublimation in an evacuated tube (which occurs slowly even at room temperature) makes this determination unsatisfactory. The base readily sublimes when heated at 45°/15 mm., crystals forming on the cooler upper portions of the tube : this ready volatilisation is similar to that of the analogous quinuclidine recorded by Meisenheimer.[4] Furthermore, at room temperature the powdered amine steadily volatilises in a desiccator at 1 atm. containing paraffin wax shavings, and in a desiccator containing sodium hydroxide pellets at 15 mm. The amine is volatile in the vapour of boiling ethanol and benzene, but not appreciably so in that of ether. The difficulties attending the separation of the base from other amines by distillation are obvious.

The identity of the triethylenediamine (I) is further confirmed by its ready union with methyl bromide to re-form the original dimethobromide. Mann and Mukherjee,[1] who had available only salts of this base, sought evidence that the base was in fact the diamine and not hexaethylenetetramine, by determining the " apparent " molecular weight of this methobromide cryoscopically in dilute aqueous solution, where almost complete ionisation would have occurred. Hromatka and Kraupp [2] were subsequently unable to obtain similar results, but an independent series of determinations (p. 1891), kindly undertaken by Dr. A. Senior, confirms our earlier results. A number of derivatives of this diamine are recorded (see Table, p. 1885).

[3] Hromatka, *Ber.*, 1942, **75**, 1302.
[4] Meisenheimer, *Annalen*, 1920, **420**, 194.

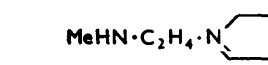
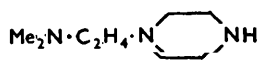
The thermal decomposition of the salts (VI) and (VII) at atmospheric pressure gave closely similar products: this was expected in view of the ready thermal conversion (VI) ⟶ (VII). In a typical experiment using the salt (VII), distillation of the ethereal extracts of the liberated amines gave the following fractions.

(A) The ether distillate. This contained much 1 : 4-dimethylpiperazine, which is readily volatile in boiling ether [5] and was isolated as its dihydrochloride.

(B) A fraction, b. p. 130—133°, of 1 : 4-dimethylpiperazine, from which a very small quantity of piperazine was also isolated.

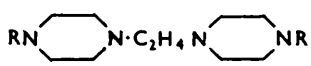
(C) A considerable fraction, b. p. 86—87°/12 mm., consisting of the base (VIII), contaminated with a base, $C_8H_{19}N_3$, which may have been the amine (XI) or the isomer (XII).

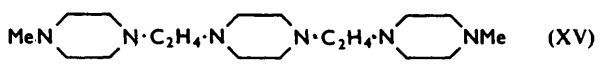
(D) A small fraction, b. p. 74—76°/0·01 mm., which initially appeared to consist mainly of hexaethylenetetramine (II), $C_{12}H_{24}N_4$. This base was purified by recrystallisation of its tetrahydrobromide, and when regenerated had b. p. 91°/0·03 mm., m. p. 40—43°. A number of derivatives of this base were prepared, particularly for comparison with those of triethylenediamine. Its behaviour on quaternisation, whereby a trimethobromide and -iodide were obtained, cast doubt on this identification, for the various conformations of hexaethylenetetramine, in which the two piperazine rings have the chair and/or the boat form, would usually allow only diquaternisation. The synthesis of 1 : 2-di-

(XI)   (XII)

(4-methyl-1-piperazinyl)ethane (XIII), $C_{12}H_{26}N_4$, was therefore kindly undertaken by Mr. H. R. Watson, who has obtained this amine by the hydrolysis of the diethoxycarbonyl derivative (XIV; R = CO_2Et), followed by formaldehyde–formic acid methylation of the hydrolysis product (XIV; R = H). Comparison of the two bases and certain of their crystalline derivatives showed undoubtedly that our amine obtained by thermal decomposition is the amine (XIII).

(E) On one occasion, a higher fraction, b. p. 105—108°/0·065 mm., was isolated: it was almost insoluble in water, whereas the amine (XIII) is freely soluble. Its molecular weight and the analyses of the base and its available derivatives indicated a molecular formula $C_{18}H_{36\text{-}38}N_6$. By analogy, it is highly probable that this amine is 1 : 4-di-[2-(4-methyl-1-piperazinyl)ethyl]piperazine (XV), $C_{18}H_{38}N_6$. It is unfortunate that the very small quantity of the amine available allowed only one molecular-weight determination, for the analysis of its salts would not differentiate between the amine (XV) and hexaethylenetetramine (II).

(XIII)   (XIV)

 (XV)

The products of the thermal decomposition of the salt (VI) differed from those of the salt (VII) only in that (*a*) fraction (B) now contained only a trace of piperazine, (*b*) fraction (C) was the almost pure amine (VIII), the partially demethylated amine $C_8H_{19}N_3$ being present in very small proportion, and (*c*) the fraction (E) was not detected.

Our investigation has therefore given no evidence for the formation of hexaethylenetetramine during the thermal decomposition of the salt (III), (VI), or (VII).

It is noteworthy that the triamine (VIII) gives a stable tri-hydrochloride, -hydrobromide, -picrate, and (hydrogen oxalate), but only the dihydriodide is sufficiently stable to allow crystallisation from hot solvents: the amine also forms only diquaternary salts

[5] Mann and Senior, *J.*, 1954, 4476.

(p. 1888). Similarly the tetramine (XIII) gives a stable tetra-hydrochloride, -hydrobromide, -picrate, and -(hydrogen oxalate), but only a trihydriodide and di- and triquaternary salts. It is clear in each case that progressive salt formation tends to deactivate the final tertiary nitrogen atom: this is insufficient to prevent formation of stable full salts by strong acids or by weak non-volatile acids but does prevent such formation by hydriodic acid. Salt formation by quaternisation apparently exerts this deactivating effect more powerfully than that by proton addition.

There has clearly in the past been considerable confusion in this section of piperazine chemistry, which we have been at pains to clarify in the derivatives discussed above. Particular difficulty can arise here, because: (*a*) both 1 : 4-dimethylpiperazine and the base (VIII) have the empirical formula $(C_3H_7N)_n$ ($n = 2$ or 3), and the diamine (I) and the tetramine (XIII) have the formulæ $C_6H_{12}N_2$ and $C_{12}H_{26}N_4$ respectively, so that analysis of these amines or their normal derivatives is virtually useless for differentiation; (*b*) the m. p.s of many of their derivatives are markedly affected by the extent and rate of heating, and a statement of m. p. without that of temperature of immersion may be misleading; (c) several pairs of corresponding salts have almost identical m. p.s, which are not always depressed on admixture. For rapid reference, the Table gives the m. p.s, under the conditions specified in the Experimental section, of an extensive comparable series of derivatives of each of the above four amines.

M. p.s of derivatives of triethylenediamine (I), 1 : 2-*di*-(4-*methyl*-1-*piperazinyl*)*ethane* (XIII), 1 : 4-*dimethylpiperazine, and* 1-2′-*dimethylaminoethyl*-4-*methylpiperazine* (VIII).

	(I)	(XIII)	Dimethylpiperazine	(VIII)
Base : b. p.	(Sublimes)	91°/0·03 mm.	131—132°	94°/12 mm.
m. p.	156—157°	40—43°	—	—
Hydrochloride	320	286—288	265°	262°
Hydrobromide	360	267	244	239
Hydriodide	>360 [a]	231 [b]	237	266 [c]
Methobromide	296	296 [d]	364 [e]	315 [f]
Methiodide	284	288,[f] 270 [d]	334 [g]	320 [f]
Methopicrate	324	212 [d]	320	220 [f]
p-Nitrophenoxide	182—183	184	125—126	139
2 : 4-Dinitrophenoxide	158	221	216	165
Picrate	290	292	300	254
Nitrate	176	245	210	164
Oxalate	290	239—240	276	228
Chloroplatinate	324	287	282	242

[a] Chars without melting. [b] Trihydriodide. [c] Dihydriodide. [d] Triquaternary salt. [e] In evacuated tube. [f] Diquaternary salt. [g] In sealed tube.

It will be seen that the following pairs of salts have almost identical m. p.s: (i) the hydrochlorides of dimethylpiperazine and of the triamine (VIII); (ii) the *p*-nitrophenoxides of the amines (I) and (XIII); (iii) the picrates of (I) and (XIII); (iv) the chloroplatinates of (XIII) and dimethylpiperazine: mixtures of the components of each of these pairs show depression of m. p. On the other hand, mixtures of the dimethopicrates of (I) and of dimethylpiperazine do not show a depression, nor do those of the dihydrobromides of (I) and of piperazine.

As examples of possible misdirection due to identification by m. p.s, McElvain and Bannister [6] state that the thermal decomposition of 1-2′-bromoethylpiperazine gives triethylenediamine, identified as its (unanalysed) di-*p*-nitrophenoxide, m. p. 182·5—183·5°, and hexaethylenetetramine, identified as its tetrapicrate, m. p. 275° (decomp.). The former m. p. clearly does not differentiate between the amines (I) and (XIII). The m. p. of the picrate is very close to that given for hexaethylenetetramine tetrapicrate (277°) by Mann and Mukherjee,[1] but we have found that some salts in this series, more particularly the picrates, when prepared from thermal decomposition products, give satisfactory analytical values after repeated recrystallisation, although the m. p. has meanwhile

[6] McElvain and Bannister, *J. Amer. Chem. Soc.*, 1954, **76**, 1126.

risen to a constant but low value (for other examples, see p. 1890), and the true m. p. can be obtained only from the salt prepared from the pure base. Consequently the identity of McElvain and Bannister's picrate also remains uncertain. The method of preparation virtually precludes its being the picrate of the methylated amine (XIII): it might possibly be the dipicrate of the apparently unknown vinylpiperazine.

Schwarzenbach *et al.*[7] decomposed a salt, stated to be the chloride monohydrochloride corresponding to the salt (VI), and fractionally extracted the picrates of the crude product, as Mann and Mukherjee [1] describe. The hydrochloride obtained from the more soluble picrate was extensively purified and then had m. p. 290°; it was not analysed, but converted into a diperchlorate, which analysis showed was hydrated. The hydrochloride was considered to be that of the amine (I), but we find this salt to be a highly deliquescent compound, m. p. 320° (lit.,[2] 310—311°) whereas the non-hygroscopic tetrahydrochloride of the amine (XIII) has m. p. 286—288°. Hromatka [3] describes the perchlorate of the amine (I) without analysis or m. p.

The therapeutic properties of triethylenediamine (I) have been kindly investigated by Imperial Chemical (Pharmaceuticals) Ltd., who report: "Because of the chemical relationship of triethylenediamine to piperazine, it was studied against an infection of of *Heterakis spumosa* in mice. It showed no activity at doses of 1·25 g./kg. given three times. Piperazine would have been fully active at this dose level. The diamine (I) produced no marked pharmacological effects in the cat, apart from a transient decrease in blood pressure.

"The diamine (I) is also without action in cotton rats infected with *Litomosoides carinii* at a dose of 4 × 250 mg./kg. There are 1 : 4-disubstituted piperazines which show activity against this infection, although piperazine is without effect."

Mr. O. D. Standen, of the Wellcome Laboratories of Tropical Medicine, has kindly investigated the value of the chloride dihydrochloride (VI) and the trihydrochloride (VII) as possible schistosomicides, and finds that they are inactive.

Experimental

All compounds were colourless unless otherwise described. The m. p.s of most compounds were dependent on the temperature of immersion, which is indicated as (T.I. −°) immediately after the recorded m. p. Many compounds were almost insoluble in boiling methanol or ethanol, but readily dissolved when water was cautiously added dropwise to the boiling suspension, and would then crystallise on cooling: the approximate dilution by water is indicated as, for example, 95% ethanol when 5% (by wt.) of water has thus been added.

1-2′-*Chloroethyl*-4 : 4-*dimethylpiperazinium Chloride Monohydrochloride* (III).—(i) The clear solution obtained by the addition of trichlorotriethylamine hydrochloride (7·5 g.) to a 40% (w/v) solution of methanolic dimethylamine (12 c.c.; 3·4 mols. of amine) was heated in a sealed tube at 45—50° for 1·5 hr. The cold solution, containing a very small amount of crystalline material, was cooled to 0° whilst being saturated with hydrogen chloride, and the resulting clear solution was evaporated to dryness in a vacuum desiccator. The pale brown residue, when recrystallised first from ethanol to remove a trace of insoluble material, then from ethanol containing 2—3 drops of concentrated hydrochloric acid, and again from ethanol, furnished the *monohydrate* (1·7 g.) of the monohydrochloride (III) (Found: C, 36·1; H, 8·1; N, 10·5; Cl, 39·4. $C_8H_{18}N_2Cl_2,HCl,H_2O$ requires C, 35·9; H, 7·9; N, 10·5; 3Cl, 39·7%), which when heated at 110°/0·1 mm. for 4 hr. gave the anhydrous salt (Found: C, 38·5; H, 7·8; N, 11·1. Calc. for $C_8H_{18}N_2Cl_2,HCl$: C, 38·5; H, 7·7; N, 11·3%). The behaviour of the monohydrate on heating is characteristic: (*a*) immersed at 150°, the hydrate effervesced at 245—250° to form a gum which appeared to solidify and then melted with gentle effervescence at 263—264°; (*b*) immersed at 160°, gentle effervescence with shrinking immediately occurred, and the behaviour then followed (*a*); (*c*) immersed at 250°, it underwent a slight brief effervescence at 254—255° and melted with vigorous effervescence at 264°. The anhydrous salt behaved as in (*c*).

Aqueous solutions of the monohydrochloride (III) and picric acid when mixed deposited

[7] Schwarzenbach, Maissen, and Ackermann, *Helv. Chim. Acta*, 1952, **35**, 2333.

a picrate, m. p. 196—198° (decomp.) (T.I. 180°), which when twice recrystallised from water underwent complete hydrolysis to the chlorine-free 1-2′-*hydroxyethyl*-4 : 4-*dimethylpiperazinium dipicrate*, yellow crystals, m. p. 220° (decomp.) (T.I. 200°) (Found : C, 38·85; H, 3·9; N, 17·6. $C_{20}H_{24}O_{15}N_8$ requires C, 38·95, H, 3·9; N, 18·2%). This compound, being unaffected in m. p. and composition by being heated at 70°/0·1 mm. for 6 hr. (Found : C, 38·55; H, 3·8%), is unlikely to be the monohydrated vinyl derivative.

A methanolic solution of the monohydrochloride (III) was shaken with silver oxide and filtered. One portion of the filtrate was diluted with methyl iodide and set aside for 24 hr., crystals slowly separating. These were soluble in cold methanol, but when thrice recrystallised from 98% ethanol furnished 1-2′-*chloroethyl*-4 : 4-*dimethylpiperazinium iodide* (IV), m. p. 236° (decomp.) (T.I. 230°) (Found : C, 31·6; H, 5·9; N, 9·0. $C_8H_{18}N_2ClI$ requires C, 31·5; H, 6·0; N, 9·2%). This salt, heated (*a*) rapidly from room temperature, (*b*) more slowly, had m. p. 246° (decomp.) and 265—270° (decomp.) respectively. A second portion of the filtrate, similarly diluted, boiled under reflux for 2 hr., then concentrated and taken to dryness in a vacuum, gave a residue which, recrystallised as before, afforded the 1-2′-*chloroethyl*-1 : 4 : 4-*trimethylpiperazinium di-iodide* (V), m. p. 182° (decomp.) (T.I. 170°) (Found : C, 24·2; H, 4·35. $C_9H_{21}N_2ClI_2$ requires C, 24·2; H, 4·7%).

(ii) Experiments similar to (i) were carried out with the 40% methanolic dimethylamine solution (2·0, 2·7, and 6·6 mols.) with heating as before, and with the dimethylamine (3·4 mols.), the solution in this experiment being set aside at room temperature for 24 hr. : all these conditions furnished the above monohydrate (Found, using 2·7 mols. of amine at 45° : C, 36·0; H, 8·0% : using 3·4 mols. of amine at room temperature : C, 36·2; H, 7·8; N, 10·5%).

(iii) The solution, prepared as in (i), was heated at 45—50° for 4 hr. The dry product was extracted with boiling ethanol, leaving a very small residue, which, recrystallised from 95% ethanol, gave crystals, m. p. 316° (decomp.) (T.I. 300°) which appeared to be 1-2′-chloroethyl-4 : 4-dimethylpiperazinium chloride monohydrate (Found : C, 41·8; H, 8·3; N, 12·2. $C_8H_{18}N_2Cl_2,H_2O$ requires C, 41·6; H, 8·7; N, 12·1%). An aqueous solution, treated with aqueous picric acid and sodium picrate, gave a picrate, yellow crystals, m. p. 290° (vigorous decomp.) (T.I. 280°), after recrystallisation from water, whereas the above salt should have given the picrate, m. p. 220°, described above. Insufficient material precluded decisive identification.

The residue from the evaporation of the ethanolic extract, recrystallised as in (i), gave the hydrated hydrochloride (III).

(iv) The solution, prepared as in (i), was heated at 45—50° for 2 hr. When an ethanolic solution of the crude dry product was treated with a small quantity of ethanolic hydrogen chloride, a cream-coloured powder separated during 36 hr. This product, m. p. 216° (decomp.) (T.I. 200°), although approximating in composition to the monohydrated monohydrochloride (III), was a mixture, and two recrystallisations from ethanol containing hydrochloric acid gave a white powder, m. p. 226° (effervescence) (T.I. 210°), which was still impure (Found : C, 35·8; H, 8·2; N, 11·6; Cl, 38·2%). Repeated and wasteful crystallisation from ethanol ultimately gave the hydrated monochloride (III). If however the cream-coloured powder was collected after only 16—18 hr., a second constituent could be isolated by repeated dissolution in ethanol followed by addition of sufficient ethanolic hydrogen chloride to cause crystallisation, giving a highly deliquescent *compound* of m. p. 290° (effervescence) (T.I. 280°) in very small yield (Found : C, 42·1; H, 8·4; N, 13·8; Cl, 35·2. $C_7H_{16}N_2Cl_2$ requires C, 42·2; H, 8·1; N, 14·1; Cl, 35·6%). A cold methanolic solution of this salt, when shaken with silver oxide, filtered, and treated with methyl iodide, rapidly deposited crystals, m. p. 304—305° (T.I. 280°) which when twice recrystallised from 80% methanol had m. p. 310° (decomp.) (T.I. 300°) (Found : C, 29·75; H, 5·9; N, 9·9%) and when then thrice recrystallised from 80% ethanol had the same m. p. (Found, after drying at 60°/0·1 mm. for 7 hr. : C, 30·25; H, 5·8; N, 9·7. $C_7H_{16}N_2ClI$ requires C, 29·0; H, 5·5; N, 9·65%). A solution of this *methiodide* in hot 90% methanol, when diluted with methyl iodide, boiled under reflux for 2 hr. and evaporated, gave apparently the unchanged methiodide, m. p. 308—310° (decomp.) (T.I. 295°) after two recrystallisations from 80% methanol (Found : C, 30·2; H, 6·0; N, 9·4%). The identity of the chloride of m. p. 290° remains uncertain : it cannot be 1-2′-chloroethyl-4-methylpiperazine hydrochloride or triethylenediamine hydrochloride methochloride, for the first compound, treated as above in the cold, would give the methiodide (IV), m. p. 236°, and the second would give triethylenediamine dimethiodide, m. p. 284° (cf. p. 1891).

Mann and Mukherjee [1] record m. p. 218° for the monohydrochloride (III) and m. p. 302—305° for its methiodide: it is probable that their recrystallised monohydrochloride was analogous to the above impure product, m. p. 226°, and that it also furnished the above methiodide.

1-2′-*Dimethylaminoethyl*-4-*methylpiperazine* (VIII). *Preparation of the Trihydrochloride* (VII).—A freshly prepared mixture of 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride (50 g.) and a 40% (w/v) methanolic solution of dimethylamine (250 c.c.; 10·7 mols. of amine) was electrically stirred in an autoclave at 125° for 7 hr. The cold partly crystalline liquid was transferred to a beaker and thoroughly chilled, whilst saturated with hydrogen chloride: during this process, it initially became a clear liquid, which then deposited crystals. The crystals, when collected, washed with methanol, and recrystallised twice from methanol, gave the trihydrochloride (VII) (47 g.), m. p. 262° (Found: C, 38·6; H, 8·7; N, 15·2; Cl^-, 37·5. Calc. for $C_9H_{21}N_3$,3HCl: C, 38·5; H, 8·6; N, 15·0; Cl, 37·9%). A mixture of this salt with dimethylpiperazine dihydrochloride had m. p. 240—242° (decomp.) (T.I. 230°).

Very many successful runs were carried out using the above conditions: however, on one occasion a leak in the top of the autoclave released much dimethylamine vapour, and this run furnished solely the dihydrochloride (VI). Mann and Mukherjee's experiments [1] were carried out in a rotating autoclave, in which the sealing, temperature, and rotation were difficult to adjust satisfactorily, and this may have accounted for isolation of the salt (VI) apparently under the above conditions.

The hydrochloride (VII) (20 g.) was decomposed with concentrated aqueous potassium hydroxide, and the liberated *base* (VIII), after extraction with ether and further drying (KOH), was obtained as a colourless, almost odourless liquid, b. p. 94°/12 mm., freely soluble in water (Found: C, 63·3; H, 12·4%; *M*, cryoscopic in benzene, 167. $C_9H_{21}N_3$ requires C, 63·1; H, 12·4%; *M*, 171).

The following derivatives were prepared from the base or its hydrochloride for decisive characterisation.

A solution of the hydrochloride in aqueous methanol was shaken with silver oxide, filtered, treated with concentrated hydrobromic acid, again filtered, and evaporated in a desiccator. The syrupy residue when rubbed with ethanol gave the crystalline *trihydrobromide*, m. p. 238—239° (decomp. with effervescence) (T.I. 225°) after crystallisation from ethanol (Found: C, 26·0; H, 6·2; N, 10·2. $C_9H_{21}N_3$,3HBr requires C, 26·1; H, 5·85; N, 10·15%). An ethanolic solution of the base was added to an excess of chilled, stirred hydriodic acid (of constant b. p.); the precipitated crystals, when twice recrystallised from 95% ethanol, gave the *dihydriodide*, m. p. 266° (decomp.) (T.I. 250°) (Found: C, 25·5; H, 5·5; N, 9·9. $C_9H_{21}N_3$,2HI requires C, 25·3; H, 5·4; N, 9·8%).

A methanolic solution of the base, diluted with methyl bromide and set aside for 3 hr., gave heavy crystals of the *dimethobromide* (IX; X = Br), m. p. 315° (effervescence) (T.I. 300°) after crystallisation from methanol (Found: C, 36·65; H, 7·3; N, 11·85. $C_{11}H_{27}N_3Br_2$ requires C, 36·6; H, 7·5; N, 11·7%). A methanolic solution of the base, diluted with methyl iodide and set aside for 16 hr., deposited the dimethiodide (IX; X = I), which when recrystallised from 98% methanol, formed a *dimethanolate*, m. p. 320° (effervescence) (T.I. 310°) (Found: C, 29·6; H, 6·5; N, 8·9. $C_{11}H_{27}N_3I_2$,2CH_4O requires C, 29·6; H, 6·4; N, 8·6%); heating at 75°/0·1 mm., for 6 hr. gave the solvent-free *salt* of unchanged m. p. (Found: C, 29·2; H, 6·05; N, 9·1. $C_{11}H_{27}N_3I_2$ requires C, 29·0; H, 6·0; N, 9·2%). The m. p. of this salt is markedly affected by the rate of heating. When the above solution containing methyl iodide was refluxed for 1 hr., the same product was obtained. The addition of an aqueous solution of this salt to aqueous sodium picrate deposited the *dimethopicrate*, deep orange crystals, m. p. 220° (decomp.) (T.I. 210°) from methanol (Found: C, 42·5; H, 4·5; N, 19·2. $C_{23}H_{31}O_{14}N_9$ requires C, 42·0; H, 4·75; N, 19·4%).

When ethereal solutions of the base and an excess of *p*-nitrophenol were mixed, the tri-*p*-nitrophenoxide was immediately deposited, and formed bright yellow crystals, m. p. 139° (T.I. 130° or from room temperature), from ethanol (Found: C, 55·4; H, 6·5. Calc. for $C_9H_{21}N_3$,3$C_6H_5O_3N$: C, 55·1; H, 6·2%). Hromatka and Kraupp [2] give m. p. 142—142·5°. The *tri*-2 : 4-*dinitrophenoxide*, similarly prepared, formed orange plates, m. p. 164—165° (T.I. 160°), after crystallisation from ethanol (Found: C, 44·65; H, 4·4; N, 17·3. $C_9H_{21}N_3$,3$C_6H_4O_5N_2$ requires C, 44·8; H, 4·6; N, 17·4%). Hromatka and Kraupp [2] mention this compound without analytical identification.

The base in aqueous solution gave a yellow *tripicrate*, m. p. 254° (decomp.) (T.I. 240° and 250°) after crystallisation from water (Found : C, 37·85; H, 3·4; N, 19·75. $C_9H_{21}N_3,3C_6H_3O_7N_3$ requires C, 37·75; H, 3·5; N, 19·6%).

An aqueous solution of the base when added (i) to dilute nitric acid deposited the *trinitrate*, m. p. 164° (vigorous decomp.) (T.I. 150°) (Found : C, 30·1; H, 6·8; N, 22·85. $C_9H_{21}N_3,3HNO_3$ requires C, 30·0; H, 6·7; N, 23·3%), and (ii) to saturated aqueous oxalic acid slowly deposited the *tri(hydrogen oxalate)*, m. p. 228° (decomp.) (T.I. 220°) (Found : C, 41·0; H, 6·4; N, 9·25. $C_9H_{21}N_3,3C_2H_2O_4$ requires C, 40·8; H, 6·2; N, 9·5%). The hydrochloride gave a *chloroplatinate*, orange crystals, m. p. 242° (decomp. with effervescence) (T.I. 230°) (Found : C, 13·6; H, 3·45; N, 5·6. $2C_9H_{21}N_3,3H_2PtCl_6$ requires C, 13·7; H, 3·0; N, 5·3%). The nitrate and oxalate recrystallised from aqueous ethanol and the chloroplatinate rapidly from water.

1-2′-*Dimethylaminoethyl*-4 : 4-*dimethylpiperazinium Chloride Dihydrochloride* (VI).—This preparation was most conveniently carried out in pressure-bottles, having rubber stoppers wired in place. A mixture of trichlorotriethylamine hydrochloride (10 g.) and 40% (w/v) methanolic dimethylamine (60 c.c.; 12·8 mols. of amine) was thus heated in a water-bath at 45—50° for 8 hr. The united liquid products from five such experiments were then chilled and saturated with hydrogen chloride. The precipitated salt, when twice recrystallised from 97% ethanol, gave the dihydrochloride (VI) as the monohydrate (58 g.), m. p. 228° (effervescence) (Found : C, 38·6; H, 8·75; N, 13·4. Calc. for $C_{10}H_{24}N_3Cl,2HCl,H_2O$: C, 38·4; H, 9·0; N, 13·4%), which when confined in a vacuum over phosphoric anhydride for several days gave the anhydrous salt of unchanged m. p. (lit.,[7] m. p. 225°) (Found : C, 40·9; H, 9·2; N, 13·7; Cl, 35·8. Calc. for $C_{10}H_{24}N_3Cl,2HCl$: C, 40·7; H, 8·9; N, 14·2; Cl, 36·1%). The salt is only sparingly soluble in boiling absolute ethanol.

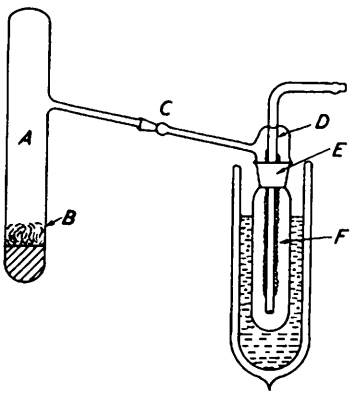
The chloride dihydrochloride (VI) gave the following derivatives. An aqueous solution of the salt, when shaken with silver oxide, filtered, acidified with hydrobromic acid, and evaporated to dryness in a desiccator, gave the very hygroscopic *bromide dihydrobromide*, m. p. 270° (effervescence) (T.I. 260°) after crystallisation from ethanol (Found : C, 34·0; H, 7·5; N, 11·8. $C_{10}H_{24}N_3Br,2HBr$ requires C, 34·6; H, 7·3; N, 12·1%). A methanolic solution of the salt (VI), when treated in turn with silver oxide and methyl bromide, gave a salt (IX ; X = Br) identical with the dimethobromide of the base (VIII), m. p. 315° (effervescence) (T.I. 300°) after crystallisation from methanol (Found : C, 36·15; H, 8·2; N, 11·4%), and with methyl iodide gave the dimethiodide (IX ; X = I), m. p. 317° (effervescence) (T.I. 310°) (Found, after heating at 75°/0·1 mm. for 7 hr. : C, 29·1; H, 6·0; N, 9·4%).

The salt (VI) also gave a *tripicrate*, yellow crystals, m. p. 218—220° (decomp.) (T.I. 215°) after crystallisation from aqueous ethanol (Found : C, 38·7; H, 3·9; N, 19·4. $C_{16}H_{28}O_7N_6,2C_6H_3O_7N_3$ requires C, 38·5; H, 3·7; N, 19·25%), and a *chloroplatinate*, orange crystals, m. p. 248° (decomp.) (T.I. 240°), after crystallisation from water [Found : C, 15·3; H, 3·4; N, 5·4. $(C_{10}H_{26}N_3)_2(PtCl_6)_3$ requires C, 15·0; H, 3·3; N, 5·15%].

Triethylenediamine (I).—*Preparation.* Because only comparatively small quantities of this base can be prepared in one operation, it was most convenient to insert pure powdered triethylenediamine dimethobromide (2 g.) into the glass tube *A* (through a paper cylinder temporarily inserted to ensure complete absence of the salt from the upper part of *A*), then to cover the salt with a plug of glass wool *B* to prevent the fine solid particles being subsequently thrown upwards, and finally to seal the top of *A*. The side-arm was then fitted by a ground-glass joint *C* into the receiver *D*–*E*, joints being covered with a " high temperature vacuum " lubricant. The receiver *E* was immersed in carbon dioxide–acetone, the apparatus evacuated to 0·003 mm., and the vessel *A* then heated in a Silicone bath to 230—240°. In 4—5 hr., crystals of the base (0·6 g., 81%) slowly formed, almost exclusively in zone *F* of the central tube, a fine sandy residue (0·6 g.) remaining in *A*. Repetition of this experiment, using (*a*) the dimethobromide (3 g.) and the above conditions, (*b*) the bromide (4 g.) with heating extended to 7 hr., gave yields of the crystalline base of 0·66 g. (59%) and 0·85 g. (57%) respectively : a series of short runs with the dimethobromide (2 g.) was thus found to be most effective. The base (I) so obtained contained a trace of bromide, but when resublimed from a similar apparatus gave the pure base, m. p. 156—157° (in a sealed tube, from room temperature) when thoroughly dried in a vacuum (KOH) (Found : C, 64·1; H, 11·1; N, 24·75; *M*, ebullioscopic in ethanol, 112; in benzene, 120. Calc. for $C_6H_{12}N_2$: C, 64·2; H, 10·8; N, 25·0% ; *M*, 112).

Although the period of heating in the above experiment was continued until no further increase in the sublimed crystals was detected, the residue in *A* apparently still contained

unchanged dimethobromide. A sample of this residue was dissolved in cold 48% w/w hydrobromic acid, filtered to remove a trace of insoluble material, and diluted with ethanol. The fine crystalline deposit, when thrice recrystallised from methanol–ethanol and dried at 50°/0·01 mm., gave the dimethobromide, m. p. 285—286° (decomp.) (T.I. 280°) (Found: C, 32·1; H, 6·3; N, 9·3. Calc. for $C_8H_{18}N_2Br_2$: C, 31·8; H, 6·0; N, 9·3%). A methanolic solution of this product, when added to an acetone solution of sodium iodide, deposited the dimethiodide,



m. p. 270° (decomp.) (T.I. 260°) (Found: C, 24·4; H, 4·6; N, 7·3. Calc. for $C_8H_{18}N_2I_2$: C, 24·3; H, 4·6; N, 7·1%). The m. p.s of these two compounds, compared with those of the authentic salts described below, indicate that, in spite of the analytical values, they still were not quite pure.

In the hope of reducing the time required for the preparation of the diamine, a number of experiments were performed in which the thermal decomposition was carried out at a much higher temperature: the receiver *D–E* was now duplicated in series to enable different condensation temperatures to be employed. In no case was the free diamine (I) thus obtained. As examples, the dimethobromide (2 g.) was heated in *A* at 300°/0·002 mm., the temperature rising to 350° during 30 min. The first receiver, cooled in water at 15°, remained empty. The second receiver, cooled in liquid oxygen, collected a white semi-solid product, which was allowed to attain room temperature whilst still in the vacuum, a volatile liquid, presumably methyl bromide, boiling off as slight " crackling " of the product indicated possible reconversion. This product was dissolved in hydrobromic acid and evaporated to dryness: the residue, thrice recrystallised from methanol and dried at 50°/0·1 mm., afforded apparently *triethylenediamine hydrobromide methobromide* (X; X = Br), m. p. 286° (effervescence) (T.I. 275°) (Found: C, 29·0; H, 5·1; N, 9·3. $C_7H_{15}N_2Br,HBr$ requires C, 29·2; H, 5·6; N, 9·7%). The residue in *A* was extracted with boiling methanol, which on cooling gave a pale brown deposit, furnishing piperazine dihydrobromide, m. p. 360° (decomp.) (T.I. 354°) after repeated crystallisation from 95% methanol (Found: C, 19·1; H, 4·95%).

An authentic sample of this salt was prepared by dissolving pure piperazine in 48% hydrobromic acid, which rapidly deposited dense crystals: these were almost insoluble in boiling absolute methanol and ethanol, but when recrystallised from aqueous ethanol furnished the dihydrobromide, heavy needles, m. p. 360° (decomp.) (T.I. 300°) (Found: C, 19·5; H, 4·9. Calc. for $C_4H_{10}N_2,2HBr$: C, 19·4; H, 4·9%).

In another experiment, the dimethobromide (8 g.) was heated gently at first and then strongly with a " brush " flame, a dark brown liquid ultimately collecting in the first receiver. This liquid, when evaporated with hydrobromic acid, gave a very impure product, which after seven recrystallisations from ethanol–methanol furnished 1 : 4-dimethylpiperazine dihydrobromide, m. p. 240—241° (T.I. 230°) (Found: C, 26·2; H, 5·5. Calc. for $C_6H_{14}N_2,2HBr$: C, 26·1 ; H, 5·8%). The product in the second receiver was insufficient for purification and identification.

The diamine (I) is soluble in cold water, methanol, ethanol, ether, and benzene: it can be recrystallised from *cyclo*hexane and from light petroleum (b. p. 60—80°), but the crystals when contaminated with these solvents become exceedingly volatile in a vacuum, and direct sublimation affords a more rapid amd effective purification.

Derivatives. An ethanolic solution of the base, when added to chilled concentrated hydrochloric acid, deposited crystals; the clear solution, obtained by warming this mixture, on cooling deposited the dihydrochloride as long very deliquescent needles, m. p. 320° (decomp.) (T.I. 310°) (Found : N, 15·5. Calc. for $C_6H_{12}N_2$,2HCl : N, 15·4%). Hromatka and Kraupp [2] give m. p. 310—311°. A concentrated solution of the base in 48% hydrobromic acid, when diluted with ethanol, gave the *dihydrobromide*, m. p. 360° (decomp.) (T.I. 350°), after crystallisation from aqueous ethanol (Found : C, 26·45; H, 5·4; N, 10·3. $C_6H_{12}N_2$,2HBr requires C, 26·3; H, 5·15; N, 10·2%). A mixture of this salt and piperazine dihydrobromide, carefully dried, also had m. p. 360° (decomp.) (T.I. 330°) with some preliminary softening.

The *dihydriodide*, prepared as the dihydrochloride, and recrystallised from ethanol, charred with melting from *ca.* 360° upwards (Found : C, 19·6; H, 4·0; N, 7·6. $C_6H_{12}N_2$,2HI requires C, 19·6; H, 3·8; N, 7·6%); when exposed to daylight at room temperature it remained colourless for several days.

The *dimethochloride* was prepared by heating a methanolic solution of the base and an excess of methyl chloride in a sealed tube at 55—60° for 2 hr.; after cautious removal of the unused methyl chloride, evaporation gave a white residue of the dimethochloride, which, after two recrystallisations from ethanol, still formed exceedingly deliquescent crystals, m. p. 284° (decomp.) (T.I. 140°, 260°, the samples being thoroughly dried in the capillary tubes, which were then sealed) (Found : C, 44·5; H, 8·8; N, 12·6. $C_8H_{18}N_2Cl_2$ requires C, 45·1; H, 8·5; N, 13·1%). Alternatively, a methanolic solution of the dimethiodide (see below), mixed with an excess of silver chloride, was boiled for 1 hr. and filtered : the filtrate evaporated without residue. The silver halide was extracted with boiling 85% methanol, which on filtration and evaporation gave the dimethochloride, having identical m. p. after crystallisation.

The dimethobromide, prepared in cold methanol, recrystallised from 98% ethanol and dried (P_2O_5), had m. p. 296° (T.I. 290°), unchanged by admixture with the salt obtained by combining 1 : 4-dimethylpiperazine and ethylene dibromide (Found : C, 31·7; H, 5·9; N, 9·1%; *M*, cryoscopic in 0·5981% aqueous solution, 101; in 0·7729%, 100; in 1·037%, 105. Calc. for $C_8H_{18}N_2Br_2$: C, 31·8; H, 6·0; N, 9·3%; *M*, 302). These molecular weight values, determined by Dr. A. Senior, confirm those of Mann and Mukherjee,[1] and indicate complete ionisation at these concentrations.

The dimethiodide, similarly prepared and recrystallised from methanol, had m. p. 284° (decomp.) (T.I. 276°) (Found : C, 24·5; H, 4·8; N, 6·85. Calc. for $C_8H_{18}N_2I_2$: C, 24·3; H, 4·6; N, 7·1%). Hromatka and Engel [8] do not record a m. p. The *dimethopicrate*, prepared from the bromide and recrystallised from much water, formed deep yellow needles, m. p. 324—325° (effervescence) (T.I. 310°) (Found : C, 40·2; H, 3·9. $C_{20}H_{22}O_{14}N_8$ requires C, 40·15; H, 3·7%).

The di-*p*-nitrophenoxide, prepared in ether and recrystallised from ethanol, formed deep yellow crystals, m. p. 182—183° (T.I. 20° or 170°) (Found : C, 55·5; H, 6·3; N, 14·3. Calc. for $C_6H_{12}N_2$,2$C_6H_5O_3N$: C, 55·4; H, 5·7; N, 14·35%). Solutions of this salt in ethanol and in boiling ether are pale yellow and colourless respectively, the salt apparently undergoing complete dissociation in ether. The di-2 : 4-dinitrophenoxide, prepared in benzene and recrystallised from ethanol, formed yellow crystals, m. p. 158° (T.I. 145°) (Found : C, 45·3; H, 4·5; N, 17·3. Calc. for $C_6H_{12}N_2$,2$C_6H_4O_5N_2$: C, 45·0; H, 4·2; N, 17·5%). The dipicrate, prepared in ethanol and recrystallised from water, formed pale yellow crystals, m. p. 290° (moderately vigorous decomp.) (T.I. 285°) (Found : C, 38·05; H, 3·4; N, 20·1. Calc. for $C_6H_{12}N_2$,2$C_6H_3O_7N_3$: C, 37·9; H, 3·2; N, 19·6%). Hromatka [2,3] states that these compounds melt at 183°, 159°, and " not below 280° " respectively.

The *dinitrate* separated as fine needles, m. p. 176° (decomp.) (T.I. 165°), when the base in ethanol was added to moderately dilute nitric acid (Found : C, 30·2; H, 5·7; N, 23·2. $C_6H_{12}N_2$,2HNO_3 requires C, 30·25; H, 5·9; N, 23·5%). The di(hydrogen oxalate) readily crystallised when ethanolic solutions of the base and oxalic acid were mixed. After crystallisation from 95% ethanol and drying (P_2O_5), it had m. p. 290° (decomp.) (open tube, T.I. 220°), 270° (decomp.) (evacuated tube, T.I. 240°), and when heated rapidly from room temperature decrepitated at *ca.* 200°, softened at *ca.* 280°, and melted at 287° (decomp.), the value given by Hromatka [3] (Found : C, 40·7; H, 5·6; N, 9·3. Calc. for $C_6H_{12}N_2$,2$C_2O_4H_2$: C, 41·1; H, 5·5; N, 9·6%). The *chloroplatinate*, prepared from the base and an excess of chloroplatinic acid, each in 20% hydrochloric acid, formed orange crystals, m. p. 324° (decomp., preliminary

[6] Hromatka and Engel, *Ber.*, 1943, **76**, 713.

darkening) (T.I. 310°) (Found: C, 14·1; H, 2·7; N, 5·5; Pt, 37·5. $C_6H_{12}N_2,H_2PtCl_6$ requires C, 13·8; H, 2·7; N, 5·4; Pt, 37·4%).

The volatility of triethylenediamine can be further assessed from the following experiments. (i) The weight of the powdered amine (0·0968 g.), confined at room temperature in an atmospheric desiccator (1·6 l.) containing paraffin wax shavings and sodium hydroxide pellets, fell to 0·0778, 0·0718, and 0·0708 g. after 2, 5, and 7 days respectively. (ii) The weight of the amine (0·1098 g.), similarly confined in this desiccator at 15 mm., over sodium hydroxide alone, was 0·0218 and 0·0058 after 3 and 5 days respectively: sublimation was complete after 6 days. (iii) The base (0·100 g.) slowly volatilised in the air at room temperature; after 2 days the powdered material had formed a glass, which completely volatilised in 8 days. (iv) A solution of the base (0·2 g.) in dry ether (30 c.c.) in an all-glass apparatus was very slowly distilled (from a Silicone bath) into a receiver closed by a calcium chloride tube. The distillate gave only a faint turbidity with ethanolic picric acid, and crystalline base remained in the distillation flask. (v) Solutions of (*a*) the base (0·1200 g.) in ethanol (20 c.c.), and (*b*) the base (0·116 g.) in benzene (20 c.c.), were similarly distilled during 1·5 hr. The distillate, when treated in (*a*) with aqueous picric acid, and in (*b*) with ethanolic picric acid, gave a suspension of the picrate too fine for adequate filtration and weighing. The residue in the distillation flasks, when dissolved in water and treated with aqueous picric acid, deposited the amine dipicrate (0·240 and 0·3610 g.) indicating a recovery of 39 and 61% respectively of the base. The dipicrate has a low solubility in cold water, and these figures give a reasonably accurate assessment of the volatility of the base.

The base has considerable stability to acids. A solution of the base (0·3 g.) in 48% w/v hydrobromic acid (5 c.c.), when boiled under reflux for 2 hr., concentrated, and cooled, deposited long needles of the dihydrobromide, m. p. 355—357° (decomp.) (T.I. 350°) after recrystallisation from aqueous ethanol, of the base (Found: C, 25·8; H, 4·9; N, 9·6%). The filtrate from the needles was basified and extracted with ether: the extract, when boiled with methanolic methyl iodide, gave the dimethiodide, m. p. and mixed m. p. 281—283° (decomp.) (T.I. 275°). The stability of the base to sulphuric and nitric acids has been noted by Hromatka.[3]

1:4-Dimethylpiperazine, b. p. 131—132°, prepared by Mann and Senior's method,[5] gave the following derivatives, recorded here for comparison with those obtained from thermal decomposition products described later. Certain of these compounds have been recorded by Mann and Senior, who usually gave the m. p. when the compound was heated from room temperature.

The dihydrochloride, recrystallised from ethanol, has m. p. 265° (decomp., effervescence) (T.I. 235°, 250°) (Found: C, 38·4; H, 8·85; N, 14·75. Calc. for $C_6H_{14}N_2,2HCl$: C, 38·5; H, 8·6; N, 14·9%); in an evacuated tube, it had m. p. 241° (decomp. as before) (T.I. 220°) with decrepitation on immersion. The dihydrobromide, recrystallised from ethanol, had m. p. 244° (decomp.) (T.I. 230°) and, in an evacuated tube, m. p. 233° (decomp.) (T.I. 220°) (Found: C, 25·9; H, 5·6; N, 10·2. Calc. for $C_6H_{14}N_2,2HBr$: C, 26·1; H, 5·8; N, 10·15%).

The *dihydriodide* was precipitated when hydriodic acid (of constant b. p.) was cautiously added to a chilled ethanolic solution of the base; after crystallisation from 90% ethanol, it had m. p. 237° (decomp.) (T.I. 228°) (Found: C, 19·7; H, 4·2; N, 7·3. $C_6H_{14}N_2,2HI$ requires C, 19·45; H, 4·3; N, 7·6%).

A methanolic solution of the base was chilled, diluted with an excess of methyl chloride, sealed in a tube, and set aside for 20 hr. at room temperature. The clear solution was then exposed to the air to remove unused chloride, and evaporated to dryness in a desiccator. The residue, when recrystallised from ethanol–ether, gave the *monomethochloride*, very deliquescent crystals, which when immersed in a sealed tube at 330° effervesced, resolidified, and then sublimed with decomp. at 355° (Found: C, 51·3; H, 10·6; N, 17·0. $C_7H_{17}N_2Cl$ requires C, 51·05; H, 10·4; N, 17·0%). It is very soluble in methanol and ethanol. This experiment was repeated, but the sealed tube was heated at 55° for 5 hr. The considerable crystalline deposit, which separated on cooling, was collected and recrystallised from much methanol, giving the very slightly hygroscopic *dimethochloride*, which when immersed in a sealed tube at 350° sublimed at 360—365° with decomp. (Found: C, 44·9; H, 9·0; N, 12·8. $C_8H_{20}N_2Cl_2$ requires C, 44·7; H, 9·4; N, 13·0%).

The dimethobromide, prepared by the action of methyl bromide on the methanolic base at 60°, recrystallised from 95% ethanol and dried at 50°/0·1 mm., had m. p. 364° (decomp.) (evacuated tube, T.I. 350°); when it was immersed in an open tube at 360°, sublimation and

decomposition were complete by 375° (Found: C, 31·8; H, 6·4; N, 9·0. Calc. for $C_8H_{20}N_2Br_2$: C, 31·6; H, 6·6; N, 9·2%).

The dimethiodide, prepared by the interaction of methyl iodide and the base in cold methanol, and recrystallised from 30% v/v methanol, had m. p. 330°, 334° (decomp.) (T.I. 310°, 330°, both in sealed tubes); when it was heated in an open tube considerable sublimation occurred (Found: C, 24·0; H, 4·8; N, 7·2. Calc. for $C_8H_{20}N_2I_2$: C, 24·1; H, 5·0; N, 7·0%).

The pale yellow dimethopicrate, prepared from the aqueous methobromide and sodium picrate, and recrystallised from much water, had m. p. 320° (vigorous decomp.) (T.I. 290°) and in an evacuated tube, m. p. 310° (decomp.) (T.I. 280°, 300°) (Found: C, 40·0; H, 4·2; N, 18·6. Calc. for $C_{20}H_{24}O_{14}N_8$: C, 40·0; H, 4·0; N, 18·7%). It is insoluble in the usual organic solvents. A mixture of this salt and triethylenediamine dimethopicrate, m. p. 324—325°, had m. p. 320° (decomp.) (T.I. 290°): the two salts may be distinguished by the more vigorous (almost explosive) thermal decomposition of the former, and the darker and richer yellow colour of the latter.

The *di*-p-*nitrophenoxide*, prepared and recrystallised in ether, formed pale yellow crystals, m. p. 125—126° (Found: C, 55·0; H, 6·0; N, 14·1. $C_6H_{14}N_2,2C_6H_5O_3N$ requires C, 55·1; H, 6·2; N, 14·3%). It is readily soluble in water, methanol, ethanol, and acetone, but less so in ether and benzene.

The *di*-2 : 4-*dinitrophenoxide* separated, when ethereal solutions of the base and the phenol were mixed, as deep yellow crystals, m. p. 216° (decomp.) (T.I. 210°) after crystallisation from methanol (Found: C, 45·1; H, 4·6; N, 17·6. $C_6H_{14}N_2,2C_6H_4O_5N_2$ requires C, 44·8; H, 4·6; N, 17·4%).

The dipicrate, recrystallised from much water, formed yellow crystals, m. p. 300° (vigorous decomp.) (T.I. 295°); in an evacuated tube it explodes violently at 300° (T.I. 290°) (Found: C, 37·85; H, 3·55; N, 19·45. Calc. for $C_6H_{14}N_2,2C_6H_3O_7N_3$: C, 37·9; H, 3·2; N, 19·65%). It is almost insoluble in the common organic solvents.

The *dinitrate*, which readily separated when the base was added to concentrated nitric acid diluted with an equal volume of water, had m. p. 210° (moderately vigorous decomp.) (T.I. 200°) after crystallisation from 95% ethanol (Found: C, 30·3; H, 6·5; N, 23·2. $C_6H_{14}N_2,2HNO_3$ requires C, 30·0; H, 6·7; N, 23·3%).

The *di*(*hydrogen oxalate*) separated as a heavy crystalline deposit when concentrated ethanolic solutions of the base and acid were mixed; it had m. p. 276° (decomp.) (T.I. 270°) after crystallisation from 90% ethanol (Found: C, 40·7; H, 5·75; N, 9·0. $C_6H_{14}N_2,2C_2H_2O_4$ requires C, 40·8; H, 6·15; N, 9·5%).

The chloroplatinate, prepared in hydrochloric acid solutions of the base and acid, formed pale orange needles, m. p. 282° (effervescence) (T.I. 270°), unaffected by rapid recrystallisation from water (Found: C, 13·7; H, 2·9; N, 5·5; Pt, 37·3. Calc. for $C_6H_{14}N_2,H_2PtCl_6$: C, 13·75; H, 3·05; N, 5·35; Pt, 37·25%).

Thermal Decomposition of 1-2′-*Chloroethyl*-4 : 4-*dimethylpiperazinium Chloride Hydrochloride* (III).—The dry powdered monohydrate (0·9 g.), in a 25 c.c. conical flask to obtain a shallow layer and hence even heating, was immersed in a Silicone bath at 245—250° with stirring until effervescence ceased (5 min.). The cold pale amber glass was boiled with ethanol to which water was very cautiously added to give complete dissolution: the cold solution slowly deposited a microcrystalline powder, m. p. 280° (effervescence) (T.I. 270°). The united products from two such experiments, when twice so recrystallised, gave *triethylenediamine hydrochloride methochloride* (X; X = Cl), m. p. 288—289° (effervescence) (T.I. 280°) (Found: C, 42·3; H, 8·5; N, 14·1. $C_7H_{15}N_2Cl,HCl$ requires C, 42·2; H, 8·1; N, 14·1%): the salt is hygroscopic but undergoes deliquescence only very slowly.

A methanolic solution of the salt was shaken with silver oxide, filtered, diluted with methyl iodide, boiled under reflux for 1 hr., and cooled. The deposited crystals, m. p. 281—282° (T.I. 270°), when recrystallised from methanol gave triethylenediamine dimethiodide (Found: C, 24·5; H, 4·65%), m. p. 283—284° (decomp.) (T.I. 270°), unchanged by admixture with the authentic salt.

Synthesis of 1 : 2-*Di*-(4-*methyl*-1-*piperazinyl*)*ethane* (XIII).—The corresponding 4-ethoxycarbonyl derivative (XIV; R = CO_2Et) was prepared by the method of Stewart *et al.*[9] These

[9] Stewart, Turner, and Denton: Kushner, Brancone, McEwen, Hewitt, and Subbarow, *J. Org. Chem.*, 1948, **13**, 134.

workers extracted the ester (obtained as an oil in water) with ether. During this process the ester crystallises readily, probably as a hydrate, from the extract, even when copious quantities of ether are used. It was found advantageous therefore to stir the aqueous mixture until the oil solidified. It was then collected, washed with water, and dried. The combined filtrate and washing was twice extracted with ether, and the dried extract and the solid on distillation gave the pure ester, b. p. 165—168°/16 mm., in 81% yield.

The ester is only very slowly hydrolysed by boiling 20% hydrochloric acid. A mixture of the ester (30 g.) and 48% hydrobromic acid (150 c.c.) was boiled under reflux for 5 hr.: carbon dioxide evolution from the clear solution had then ceased. The cold solution readily deposited the tetrahydrobromide, which was collected, washed with ethanol, dried, and decomposed with a large excess of saturated aqueous potassium hydroxide. The vigorously stirred sludge was continuously extracted with ether. Distillation of the dried extract gave the highly hygroscopic 1:2-*di*-(1-*piperazinyl*)*ethane* (XIV; R = H), b. p. 166—168·5°/15 mm., m. p. 102° (Found: C, 60·2; H, 11·6; N, 28·0. $C_{10}H_{22}N_4$ requires C, 60·6; H, 11·1; N, 28·3%), readily soluble in cold methanol and ethanol and in hot water, and sparingly so in hot ether, benzene, and light petroleum. For characterisation, 48% hydrobromic acid was cautiously added to a chilled ethanolic solution of the base, the *tetrahydrobromide* rapidly separating; it crystallised as needles, m. p. 270—272° (decomp.) (T.I. 260°), from 95% ethanol (Found: C, 22·75; H, 5·45; N, 10·4. $C_{10}H_{22}N_4$,4HBr requires C, 23·0; H, 5·0; N, 10·7%). The base gave a *dibenzoyl derivative*, needles, m. p. 136·5—137°, from ethyl acetate (Found: C, 70·5; H, 7·6; N, 13·7%; *M*, in boiling chloroform, 400. $C_{24}H_{30}O_2N_4$ requires C, 70·9; H, 7·4; N, 13·8%; *M*, 406).

This base (11·4 g.) when gently warmed in formic acid (50 c.c.) and 40% aqueous formaldehyde (17 c.c.), underwent vigorous reaction (cooling), after which it was boiled under reflux for 6 hr. The cold solution was diluted with concentrated hydrochloric acid (20 c.c.) and evaporated at 15 mm. The solid residue was basified as before and extracted with ether. Distillation gave 1:2-*di*-(4-*methyl*-1-*piperazinyl*)*ethane* (XIII) (9·9 g., 85%), b. p. 100—103°/0·1 mm., m. p. 38—38·5° (in an open or sealed tube) (Found: C, 63·6; H, 11·3; N, 24·2. $C_{12}H_{26}N_4$ requires C, 63·7; H, 11·5; N, 24·8%). The base is only very slightly volatile in boiling ether, for the ether distillate gave only faint traces of the almost insoluble tetrapicrate described below.

This base was characterised by the following derivatives.

A cold stirred ethanolic solution of the base was cautiously diluted with a slight excess of 48% hydrobromic acid. The precipitated crystalline *tetrahydrobromide*, when recrystallised from 98% ethanol and then dried at 100°/0·5 mm., had m. p. 267° (decomp.) (T.I. 260°) (Found C, 26·45; H, 5·5; N, 10·0; Br, 58·5. $C_{12}H_{26}N_4$,4HBr requires C, 26·2; H, 5·45; N, 10·2, Br, 58·15%).

The *tetra*-p-*nitrophenoxide* was precipitated from ethereal solutions as pale lemon crystals, m. p. 182·5—183·5° (decomp.) (T.I. 175°), after crystallisation from ether (Found: C, 55·0; H, 6·3; N, 14·0. $C_{12}H_{26}N_4$,4$C_6H_5O_3N$ requires C, 55·4; H, 5·9; N, 14·3%). A mixture of this salt and the di-*p*-nitrophenoxide (m. p. 182—183°) of the base (I) had m. p. 166—170°. The two salts differ in that the tetramine salt is more soluble in cold ethanol and ether and is distinct in colour from the deep yellow crystals of the diamine salt.

The *tetra*-2:4-*dinitrophenoxide*, similarly prepared, formed bright yellow crystals, m. p. 221—222° (decomp.) (T.I. 210°) after crystallisation from 95% ethanol (Found: C, 45·2; H, 4·4; N, 17·3. $C_{12}H_{26}N_4$,4$C_6H_4O_5N_2$ requires C, 44·9; H, 4·4; N, 17·5%).

The addition of the base to picric acid, both in ethanol, precipitated the *tetrapicrate*, golden-yellow needles, m. p. 292° (vigorous decomp.) (T.I. 280°) (from much hot water) (Found: C, 38·2; H, 3·5; N, 19·7. $C_{12}H_{26}N_4$,4$C_6H_3O_7N_3$ requires C, 37·8; H, 3·35; N, 19·6%). A mixture of this tetrapicrate and the dipicrate (m. p. 290°) of the diamine (I) had m. p. 280° (decomp.) (T.I. 270°); the tetrapicrate is much the less soluble in boiling water, and on melting decomposes much more vigorously.

A methanolic solution of the base was heated with a large excess of methyl bromide at 75° for 12 hr. The products, after evaporation of the unchanged bromide, were taken to dryness in a desiccator at reduced pressure. The powdered residue, when thrice extracted with boiling anhydrous methanol and then recrystallised from 98% methanol, gave the *trimethobromide*, m. p. 285—287° (decomp.) (T.I. 270°) (Found: C, 35·4; H, 6·95; N, 11·0. $C_{15}H_{35}N_4Br_3$ requires C, 35·3; H, 6·85; N, 11·0%).

In an attempt to form the tetramethobromide, an intimate mixture of the base and methyl toluene-*p*-sulphonate (8 mols.) was heated at 130° for 30 min. Unchanged sulphonate was

removed from the gummy product by repeated extraction with ether, but the crystalline residue of quaternary sulphonate proved too deliquescent for useful recrystallisation. Its methanolic solution, when added to a similar solution of lithium bromide, slowly deposited the above trimethobromide, m. p. 290—291° (decomp.) (T.I. 280°) when recrystallised as before (Found : C, 34·85; H, 7·3%).

The m. p. of this trimethobromide is markedly affected by the temperature of immersion and (particularly) by traces of impurity : this applies also to the trimethiodide (p. 1899). The sample of the trimethobromide described below (p. 1896), of m. p. 296° (T.I. 290°), when mixed with triethylenediamine dimethobromide, also of m. p. 296°, had m. p. 287° (decomp.) (T.I. 280°).

The trimethobromide, treated with sodium picrate, both in aqueous solution, deposited the *trimethopicrate*, yellow needles, m. p. 212—212·5° (decomp.) (T.I. 210°) (Found : C, 41·7; H, 4·4; N, 19·2. $C_{33}H_{41}O_{21}N_{13}$ requires C, 41·5; H, 4·3; N, 19·0%).

Thermal Decomposition of 1-2′-*Dimethylaminoethyl*-4-*methylpiperazine Trihydrochloride* (VII).—The pure dry powdered salt was used throughout.

(a) *Under reduced pressure.* These experiments were carried out on a small scale using the apparatus employed for the decomposition of triethylenediamine dimethobromide (see Figure, p. 1890). The pure powdered salt (VII) (1 g.) was heated at 0·004 mm. pressure in a Silicone bath, the temperature of which was slowly raised to 220° and there maintained for 2 hr. A sublimate formed in the tube *A* just above the Silicone surface, but no distillate collected in the receiver. The powdered sublimate, m. p. 259—260° (decomp.) (T.I. 250°), was twice extracted with cold ethanol (2 × 5 c.c.).

The dried residue, consisting of the unchanged (VII), had m. p. 269—270° (decomp.) (T.I. 260°), unaffected by crystallisation from 99% ethanol (Found : C, 38·6; H, 8·8; N, 14·4%) or from ethanol containing 2% of concentrated hydrochloric acid; a mixture with the sample, m. p. 262° (p. 1888), had m. p. 264° (decomp.) (T.I. 260°). It is noteworthy that the ethanolic mother-liquor from the crystallisation of this salt, m. p. 269—270°, when saturated with hydrogen chloride, deposited the salt, m. p. 260° (decomp.) (T.I. 250°). The identity of the salt, m. p. 269—270°, was confirmed by conversion into the trihydrobromide, m. p. 238° (effervescence) (T.I. 230°) (Found : C, 26·3; H, 5·7%), and into the dihydriodide, m. p. 265—266°(T.I. 260°) : the m. p.s of these two salts were unchanged on admixture with authentic samples.

The ethanolic extracts of the sublimate, evaporated in a desiccator, gave residues having m. p. 272—274° and 270—273° (decomp.) (T.I. 260°) respectively. They were united and again extracted with cold ethanol (4 c.c.) leaving a small undissolved portion. The extract, when filtered and evaporated, gave the pure hygroscopic dihydrochloride, m. p. 278° (decomp.) (T.I. 260°), of the amine (VIII) (Found : C, 44·2; H, 9·9; N, 17·5. Calc. for $C_9H_{21}N_3,2HCl$: C, 44·3; H, 9·4; N, 17·2%). This salt, which is markedly more soluble in cold ethanol than the trihydrochloride, was first prepared by Stewart *et al.*[9] by the interaction of 2-chloroethyldimethylamine, 1-methylpiperazine, and sodium carbonate in ethanol; they give m. p. 262—264°.

(b) *At atmospheric pressure.* To ensure uniform heating, a shallow layer of the salt (VII) in only 8 g. lots, contained in a conical flask fitted with a reflux air-condenser, was heated in a Silicone bath for 1 hr. at 280°, and for 30 min. at 250°, *i.e.*, the conditions used by Mann and Mukherjee.[1] The greater part of the small sublimate which formed around the neck of the flask fell back into the main product, which ultimately formed a pale brown liquid. When cold, the solid product was thoroughly chilled, treated with 100% (w/v) aqueous potassium hydroxide and then extracted 8 times with ether. In a typical experiment, the salt (VII) (304 g.) was thus decomposed in batteries of four flasks heated together in a large bath. The united ethereal extracts were dried (KOH), filtered, and distilled, and gave the following main fractions. (i) the ether distillate; (ii) b. p. 128—142°, 43 g.; (iii) b. p. 76—94°/15 mm., 17 g.; (*iv*) b. p. 75—130°/0·06 mm., 10·3 g. A dark viscous liquid remained.

(i) The ether distillate was extracted with dilute hydrochloric acid, which when evaporated gave a crude hygroscopic hydrochloride (63 g., after thorough drying); repeated recrystallisation of a portion from ethanol eliminated mixed methylamine hydrochlorides and gave 1 : 4-dimethylpiperazine dihydrochloride, m. p. 262° (decomp.) (T.I. 255°) (Found : C, 38·1; H, 8·9%).

Fraction (ii). Refractionation gave 1 : 4-dimethylpiperazine, b. p. 130—133°, identified as its dipicrate, m. p. 295° (vigorous decomp.) (T.I. 285°) (Found : C, 37·9; H, 3·8; N, 19·4%), and its dimethiodide, m. p. 333° (decomp.) (T.I. 325°, sealed tube) (Found : C, 24·2; H, 5·1;

N, 6·7%). When about two-thirds of this fraction had thus passed over the rate of distillation slackened. The residue liquid was cooled and the fractionation restarted under reduced pressure. The remainder of the dimethylpiperazine now distilled at 37—42°/15 mm., but was accompanied by piperazine which sublimed in small quantity in the condenser. These crystals were subsequently collected, drained and identified (*a*) by conversion into the dihydrobromide, m. p. 360° (decomp.) (T.I. 350°), after recrystallisation from 90% ethanol (Found: C, 19·6; H, 5·2%), and (*b*) by sublimation at 0·1 mm., giving the pure base, m. p. and mixed m. p. 106°.

Fraction (iii). Repeated refractionation gave a liquid, b. p. 86—87°/12 mm., apparently a mixture of the base (VIII) and the *base* $C_8H_{19}N_3$ (Found: C, 61·7; H, 12·4%; *M*, cryoscopic in benzene, 169. $C_9H_{21}N_3$ requires C, 63·1; H, 12·4%; *M*, 171. $C_8H_{19}N_3$ requires C, 61·15; H, 12·1%; *M*, 157). The evidence for the former is that the fraction (*a*) in chilled ethanol, when treated with hydrogen chloride, deposited rather sticky crystals, which after three recrystallisations from 98% ethanol afforded the trihydrochloride of the base (VIII), m. p. 262° (effervescence) (T.I. 240°), depressed to 240—243° (decomp.) (T.I. 230°) by admixture with dimethylpiperazine dihydrochloride (Found: C, 38·7; H, 9·05%), and (*b*) gave the chloroplatinate, orange plates, m. p. 242° (decomp.) (T.I. 230°) (Found: C, 13·7; H, 3·0; N, 5·3%), of (VIII). The evidence for the base $C_8H_{19}N_3$ is that the fraction (*a*) with saturated ethanolic oxalic acid gave a *tri(hydrogen oxalate)*, m. p. 215° (effervescence) (T.I. 210°) after crystallisation from aqueous ethanol (Found: C, 39·0; H, 5·85; N, 9·6. $C_8H_{19}N_3,3C_2H_2O_4$ requires C, 39·3; H, 5·9; N, 9·8%) [a mixture of this salt with the similar oxalate, m. p. 228°, of the base (VIII) shrank considerably at 210° and melted at 215—217° (effervescence)], and (*b*) when added in ethanol to dilute nitric acid gave a *trinitrate*, leaflets, m. p. 143° (vigorous decomp.) (T.I. 120°) when crystallised from ethanol–dilute nitric acid (Found: C, 27·8; H, 6·45; N, 24·1. $C_8H_{19}N_3,3HNO_3$ requires C, 27·7; H, 6·4; N, 24·3%) [a mixture with the nitrate, m. p. 164°, of the base (VIII) had m. p. 142—143° (vigorous decomp.) (T.I. 120°)].

The fraction, when treated in methanol with methyl bromide gave the dimethobromide of the base (VIII), m. p. 315° (decomp.) (T.I. 300°) (Found: C, 36·2; H, 7·4%), and with methyl iodide gave the corresponding dimethiodide, m. p. 324° (effervescence) (T.I. 310°) (Found: C, 29·0; H, 5·6; N, 9·4%). The formation of these salts, however, does not differentiate between (VIII) and the base $C_8H_{19}N_3$, for the latter might undergo ready methylation and then quaternisation to give the same products.

The final fraction, b. p. 86—87°/12 mm., always retained an odour resembling that of stale tobacco smoke, whereas the pure synthetic base (VIII) was almost odourless.

Fraction (iv). Repeated fractionation gave two main fractions (*a*), b. p. 77—79°/0·015 g. (4 g.); (*b*) b. p. 105—108°/0·065 mm. (*ca.* 1 g.).

Fraction (*a*), a very faintly green liquid, soluble in water, was almost pure 1 : 2-di-(4-methyl-1-piperazinyl)ethane (XIII) (Found: C, 64·0; H, 11·4%; *M*, cryoscopic in benzene, 244. Calc. for $C_{12}H_{26}N_4$: C, 63·7; H, 11·5%; *M*, 226). The remainder of the fraction was further purified by conversion into the tetrahydrobromide, hygroscopic plates, m. p. 266° (decomp., gentle effervescence) (T.I. 250°) after four recrystallisations from 98% ethanol and thorough drying (P_2O_5) in a vacuum (Found: C, 26·1; H, 5·4; N, 10·1; Br, 57·8%). This pure salt gave a tetra-*p*-nitrophenoxide, m. p. 183—184° (decomp.) (T.I. 180°) (Found: C, 55·3; H, 5·9; N, 14·4%), a tetra-2 : 4-dinitrophenoxide, m. p. 220—221° (decomp.) (T.I. 210°) (Found: C, 45·2; H, 4·3; N, 17·75%), and a tetrapicrate, m. p. 292° (vigorous decomp.) (T.I. 280°) (Found: C, 37·8; H, 3·5; N, 19·7%). The base was heated with methanolic methyl bromide at 60° for 6 hr.; the product, worked up as previously described, gave the trimethobromide, m. p. 296° (decomp.) (T.I. 290°) (Found: C, 35·4; H, 6·7%), which in turn gave the trimethopicrate, m. p. 208—210° (decomp.) (T.I. 200°) (Found: C, 41·2; H, 3·8; N, 18·7%). The m. p. of each of these five salts was unaffected by admixture with the corresponding salt prepared from the synthetic tetramine (XIII).

A cold methanolic solution of the amine was diluted with methyl bromide and set aside in a closed flask overnight, crystals rapidly separating. Unchanged bromide was then allowed to evaporate, and the mixture taken to dryness in a desiccator. Recrystallisation of the residue proved unsatisfactory. It was recrystallised from aqueous methanol, giving a crop, m. p. 235—238° (T.I. 200°), too small for reliable investigation: the chilled filtrate was then cautiously treated with 48% hydrobromic acid, giving an immediate crystalline precipitate, m. p. 226—228° (T.I. 200°). It was purified by dissolution in 98% methanol and reprecipitation by the acid;

the *dimethobromide dihydrobromide dihydrate* separated in firm non-hygroscopic crystals, m. p. 240—242° (T.I. 235°) (Found: C, 27·7; H, 6·1; N, 9·1; Br, 52·5. $C_{14}H_{32}N_6Br_2,2HBr,2H_2O$ requires C, 27·4; H, 6·2; N, 9·1; Br, 52·1%). The same compound was obtained when the first methanolic extract of (*a*) the above crude trimethobromide and (*b*) that prepared from the synthetic tetramine (XIII) was similarly treated with hydrobromic acid [Found: (*a*) C, 27·5; H, 6·15; N, 9·15; (*b*) C, 28·0; H, 5·9; N, 9·25%].

An aqueous solution of this salt, when added to one containing sodium picrate and picric acid, deposited the yellow *dimethopicrate dipicrate*, m. p. 232—233° (decomp.) (T.I. 220°) after crystallisation from water and drying at 60°/0·1 mm. for 5 hr. (Found: C, 38·9; H, 3·5; N, 19·0. $C_{26}H_{36}O_{14}N_{10},2C_6H_3O_7N_3$ requires C, 39·0; H, 3·45; N, 19·2%).

The pure tetrahydrobromide, when added to chilled concentrated aqueous potassium hydroxide, liberated the oily base, which rapidly solidified. The mixture was rapidly extracted with ether, and the dried ethereal extract distilled. The tetramine (XIII), b. p. 91°/0·03 mm., readily solidified and the highest m. p. determined was 40—43°; satisfactory analyses were not obtained, possibly owing to the small amounts distilled and consequent slight absorption of water or carbon dioxide (Found: C, 62·8; H, 12·2%; *M*, ebullioscopic in benzene, 218, in ethanol, 230. Calc. for $C_{12}H_{26}N_4$: C, 63·7; H, 11·5%; *M*, 226).

Fraction (*b*), a bright yellow liquid which rapidly became pale olive in colour, and which was almost insoluble in cold water, was apparently 1 : 4-*di*-[2-(4-*methyl*-1-*piperazinyl*)*ethyl*]-*piperazine* (XV) (Found: C, 64·8; H, 11·2%; *M*, cryoscopic in benzene, 325. $C_{18}H_{38}N_6$ requires C, 63·9; H, 11·3%; *M*, 338). A stirred, thoroughly chilled solution of the base in 97% ethanol was cautiously treated dropwise with 48% hydrobromic acid: the crystals which rapidly separated, when then collected, washed with ethanol (in which they were insoluble) and dried, effervesced at *ca.* 100° to a semi-molten mass which again effervesced with darkening and decomposition at 220°. For purification, a solution of the crystals in warm 97% ethanol was allowed to cool to *ca.* 40°, and the hydrobromic acid again cautiously added: the *hexahydrobromide dihydrate* rapidly separated as needles, which effervesced at 96° and again at 240° (darkening and decomp.); these values were unaffected by repetition of this process (Found: C, 25·2; H, 5·3; N, 10·5. $C_{18}H_{38}N_6,6HBr,2H_2O$ requires C, 25·1; H, 5·6; N, 9·8%). This sample was confined over phosphoric anhydride at 0·1 mm. for 14 days, and the presumably anhydrous salt had m. p. 240° (gentle effervescence) (T.I. 130°, 160°) without the preliminary effervescence; on exposure to the air it rapidly became damp, and then in a desiccator reformed the original non-hygroscopic crystalline dihydrate (Found: C, 25·25; H, 5·35%). The salt appeared to be decomposed by hot hydrobromic acid.

This salt gave a *hexapicrate*, which recrystallised from much hot water in flat yellow plates, m. p. 272° (decomp., mild effervescence) (T.I. 240°) (Found: C, 37·8; H, 3·5; N, 20·0. $C_{18}H_{38}N_6,6C_6H_3O_7N_3$ requires C, 37·8; H, 3·3; N, 19·6%). A mixture of this picrate and that of base (VIII) had m. p. 265° (moderate effervescence) (T.I. 240°).

The remainder of the hydrobromide was decomposed with concentrated aqueous potassium hydroxide and extracted in turn with benzene and ether. The united, dried, filtered extracts were evaporated, and the residual oil heated in methanolic methyl bromide at 35—40° for 5 hr. in a sealed tube, heavy sugar-like crystals being deposited. Recrystallisation from 97% methanol gave the non-hygroscopic *trimethobromide dihydrate*, m. p. 305° (decomp., effervescence) (T.I. 300°) (Found: C, 38·6; H, 7·1; N, 12·8. $C_{21}H_{47}N_6Br_3,2H_2O$ requires C, 38·2; H, 7·8; N, 12·75%).

The dark viscous residue obtained in the initial fractionation, when dissolved in benzene, dried, and distilled, gave small indefinite dark fractions which could not be profitably investigated.

Thermal Decomposition of 1-2′-*Dimethylaminoethyl*-4 : 4-*dimethylpiperazinium Chloride Dihydrochloride* (VI).—(A) *Under reduced pressure.* The apparatus used was that shown in the Figure. The powdered salt (VI) (1 g.), when heated at 220°/0·003 mm. for 4 hr., gave a small quantity of a hygroscopic sublimate on the upper, colder portion of the tube *A*, and left a residual friable cream-coloured powder. The receiver *E* contained a very small amount of liquid, which when treated with hydrobromic acid and evaporated gave a negligible residue. The sublimate consisted chiefly of the trihydrochloride (VII), for its aqueous solution when added to aqueous sodium picrate deposited the tripicrate of the base (VIII), m. p. 258—260° (decomp.) (T.I. 250°), after recrystallisation from water (Found: C, 38·3; H, 3·9%); this m. p. was unaffected when this salt was mixed with the authentic tripicrate.

The residue, m. p. 280° (decomp.) (T.I. 270°), was very soluble in ethanol. Its suspension in boiling acetone, when cautiously diluted with ethanol until clear, and then filtered and cooled, deposited colourless 1-*2'-dimethylaminoethyl*-4 : *4-dimethylpiperazinium chloride hydrochloride monohydrate*, of unchanged m. p. (Found : C, 43·5; H, 9·8; N, 15·5. $C_{10}H_{24}N_3Cl,HCl,H_2O$ requires C, 43·5; H, 9·85; N, 15·2%). This salt, and also the unrecrystallised residue, when recrystallised from ethanol containing 5% (v/v) of concentrated hydrochloric acid, gave the original dihydrochloride monohydrate (VI) (Found : C, 38·5; H, 9·4; N, 13·5%), m. p. 228° (decomp.) (T.I. 220°), unchanged on admixture with an authentic sample.

(B) *At atmospheric pressure.* (1) The salt (VI) (1 g.) was heated in a thin-walled tube in an oil-bath to 235°, and the melt gently stirred until effervescence ceased (*ca.* 5 min.). The cold solid product, when powdered, washed with ethanol, and recrystallised from ethanol containing concentrated hydrochloric acid, gave the trihydrochloride (VII), m. p. 260—261° (decomp.) (T.I. 250°) (Found : C, 58·55; H, 8·4%).

(2) The anhydrous salt (VI) (320 g.) was decomposed in 8 g. lots precisely as the salt (VII), and the product similarly basified and extracted with ether. The united ether extracts on distillation gave the following main fractions : (i) ether distillate; (ii) b. p. 135—144° (25 g.); (iii) b. p. 90—94°/12 mm. (41 g.), with a preliminary very small deposit of crystalline piperazine in the condenser; (iv) b. p. 48—85° (mainly 82—85°)/0·003 mm. (7 g.). The residue (1—2 g.) began to decompose with blackening and without distillation when the temperature of the oil-bath reached 260° (0·0004 mm., internal pressure) and was not further investigated.

The ether distillate (i), treated as previously described, furnished crude 1 : 4-dimethylpiperazine dihydrochloride (31 g.), identified as the pure salt, m. p. 262—263° (decomp.) (T.I. 250°) (Found : C, 38·2; H, 8·9%). Fraction (ii) on refractionation gave 1 : 4-dimethylpiperazine, b. p. 132—134°, identified as its dipicrate, m. p. 293° (vigorous decomp.) (T.I. 280°) (Found : C, 37·8; H, 3·0; N, 19·5%), and its dimethiodide, m. p. 330° (decomp.) (T.I. 320°, sealed tube) (Found : C, 24·2; H, 5·1; N, 6·9%). Fraction (iii) on refractionation gave a liquid, b. p. 91—92·5°/12 mm., consisting of the almost pure base (VIII) (Found : C, 62·5; H, 11·85%; *M*, cryoscopic in benzene, 169). In chilled ethanolic solution, when treated with hydrogen chloride, it gave a copious deposit of the trihydrochloride (VII), m. p. 262° (decomp.) (T.I. 250°) after crystallisation from 98% ethanol (Found : C, 38·6; H, 8·2%). It also gave the trinitrate, m. p. 154° (vigorous decomp.) (T.I. 140°) unchanged by repeated recrystallisation (Found : C, 30·4; H, 6·9; N, 23·6%), the chloroplatinate, orange crystals, m. p. 242° (decomp.) (T.I. 235°) (Found : C, 13·5; H, 3·0; Pt, 37·0%), the picrate, yellow crystals, m. p. 252° (decomp.) (T.I. 240°), and the dimethiodide dimethanolate, 318° (decomp.) (T.I. 300°) (Found : C, 29·6; H, 5·8; N, 9·1%). The identity of these salts was confirmed by mixed m. p. determinations. A sample of the crude fraction (iii) when set aside for several months deposited a trace of crystalline piperazine.

Fraction (iv) on refractionation gave almost pure tetramine (XIII), b. p. 88—90°/0·002 mm. (Found : C, 62·9; H, 10·6%; *M*, cryoscopic in benzene, 240). This sample gave the hygroscopic tetrahydrobromide, m. p. 266° (effervescence) (T.I. 260°) after crystallisation from ethanol (Found : C, 25·9; H, 5·9; N, 9·9%), and the *tetra(hydrogen oxalate)*, prepared in ethanol and recrystallised from aqueous ethanol, m. p. 239° (effervescence) (T.I. 230°) (Found : C. 40·7; H, 5·8; N, 9·3. $C_{12}H_{26}N_4,4C_2H_2O_4$ requires C, 40·9; H, 5·85; N, 9·55%).

Derivatives of the tetramine (XIII). These additional derivatives were prepared from the pure base for comparison with those of other amines (see Table). Ethanolic solutions of the base and of hydrogen chloride were mixed and evaporated to dryness in a desiccator, giving fine, non-hygroscopic crystals, m. p. 286—288° (decomp.) (T.I. 280°), of the *tetrahydrochloride dihydrate* (Found : C, 35·8; H, 7·6. $C_{12}H_{26}N_4,4HCl,2H_2O$ requires C, 35·3; H, 8·4%). A cold ethanolic solution of this salt, treated with hydrogen chloride, deposited fine crystals of unchanged m. p., which when heated at 60°/0·1 mm. for 7 hr., furnished the anhydrous *salt* (Found : Cl^-, 38·4. $C_{12}H_{26}N_4,4HCl$ requires Cl, 38·1%). This salt is thus markedly different from the deliquescent dihydrochloride of the base (I).

An ethanolic solution of the base, when treated dropwise with concentrated hydriodic acid, deposited crystals, which after crystallisation from 98% ethanol, afforded the *trihydriodide monohydrate*, m. p. 231° (decomp.) (T.I. 220°) (Found : C, 23·3; H, 4·6; N, 8·5. $C_{12}H_{26}N_4,3HI,H_2O$ requires C, 23·0; H, 4·9; N, 8·9%). The crystals on exposure to light slowly develop a buff colour.

A cold methanolic solution of the base, with an excess of methyl iodide, readily deposited

crystals which were collected after 2 hr. and recrystallised from 95% methanol, furnishing the *dimethiodide hemihydrate*, m. p. 288° (T.I. 275°) (Found : C, 32·4; H, 6·4. $C_{14}H_{32}N_4I_2,0{\cdot}5H_2O$ requires C, 32·4; H, 6·4%), which heated at 50°/0·1 mm. for 5 hr., gave the anhydrous *salt* (Found : C, 32·9; H, 6·4; N, 10·8. $C_{14}H_{32}N_4I_2$ requires C, 32·9; H, 6·3; N, 11·0%). When the initial solution was set aside overnight, the crystals became contaminated with the trimethiodide.

The above solution, when boiled under reflux for 4 hr., deposited crystals which, recrystallised from 95% methanol, gave the *trimethiodide*, m. p. 270° (T.I. 260°) (Found : C, 27·7; H, 5·2; N, 8·3. $C_{15}H_{35}N_4I_3$ requires C, 27·6; H, 5·4; N, 8·6%). Repetition of this experiment, but with the solution heated in a sealed tube at 75° for 5 hr., gave the same salt, m. p. 266° (T.I. 260°) (Found : N, 8·6%). In case a tetramethiodide was formed in these experiments and decomposed to the trimethiodide when heated during recrystallisation, the above solution was heated in a sealed tube at 80° for 5 hr., and the excess of methyl iodide then allowed to evaporate at room temperature from the mixture. The crystals were collected, washed with methanolic methyl iodide, and dried in a vacuum (P_2O_5) for 3 days to ensure absence of a hydrate. The residue was crude trimethiodide (Found : C, 27·2; H, 5·3; N, 8·2%) but having m. p. 248—249° (decomp.) (T.I. 240°), increased to 274—276° (decomp.) (T.I. 260°) on crystallisation from methanol.

It is noteworthy that the trimethobromide and the above di- and tri-methiodide are insoluble in boiling anhydrous methanol, but readily dissolve on the addition of a very small amount of water.

An aqueous solution of the trimethiodide, when added to an aqueous solution of sodium picrate and picric acid, gave yellow crystals which, after recrystallisation from water, furnished the trimethopicrate, m. p. 209—210° (decomp.) (T.I. 200°) (Found : C, 41·7; H, 4·2%) : in these circumstances a trimethopicrate picrate is either not formed or dissociates during crystallisation to the trimethopicrate.

The addition of 50% nitric acid to a cold ethanolic solution of the base deposited the *tetranitrate* as a gel which did not crystallise for 2 days and was collected with difficulty. Recrystallisation from aqueous ethanol readily gave large glistening plates, m. p. 245° (effervescence) (T.I. 228°) (Found : C, 30·0; H, 6·1. $C_{12}H_{26}N_4,4HNO_3$ requires C, 30·1; H, 6·3%). If immersed at 230° or above, it immediately explodes.

Dilute solutions of the base and of chloroplatinic acid, both in dilute hydrochloric acid, when mixed deposited the *di(chloroplatinate)*, orange plates, m. p. 287° (decomp.) (T.I. 270°), unchanged by crystallisation from water (Found : C, 14·0; H, 3·2; N, 5·55; Pt, 37·2. $C_{12}H_{26}N_4,2H_2PtCl_6$ requires C, 13·8; H, 2·9; N, 5·4; Pt, 37·3%). A mixture of this salt and the chloroplatinate of dimethylpiperazine (m. p. 282°) had m. p. 273° (decomp.) (T.I. 260°).

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