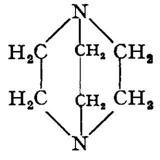
486. *Triethylenediamine* (1 : 4-*Diaza*bicyclo[2 : 2 : 2]*octane*) *and Hexaethylenetetramine. Part I. Synthesis and Properties.*

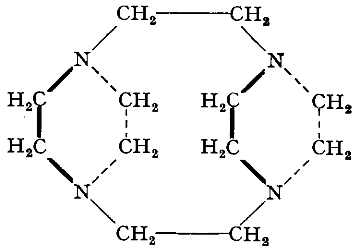
By Frederick G. Mann and Deb. P. Mukherjee.

Dimethylamine in methanol solution reacts with 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride at 125° to form 4 : 4-dimethyl-1-2′-dimethylaminoethylpiperazinium chloride, the hydrochloride of which decomposes at 280—290° to give the hydrochlorides of triethylenediamine and hexaethylenetetramine. These amines can be separated by fractional crystallisation of their picrates. Their identity has been determined by molecular-weight determination on their quaternary methobromides. The dimethobromide of triethylenediamine can also be readily prepared by the union of ethylene dibromide and 1 : 4-dimethylpiperazine.

Triethylenediamine (1 : 4-diaza*bicyclo*[2 : 2 : 2]octane) (I) is a compound of considerable interest for various reasons, in particular for its stereochemical features, its relationship to quinuclidine, and its possible therapeutic properties. Hofmann (*Proc. Roy. Soc.*, 1859, **9**, 153) first claimed to have isolated this diamine, as one of the by-products of the interaction of ethylene dibromide and ammonia (cf. Mann, *J.*, 1934, 461). Harries later asserted (*Annalen*, 1897, **294**, 350) that Hofmann's compound was actually hexaethylenetetramine (1 : 4 : 7 : 10-tetraaza*tricyclo*[8 : 2 : 2 : $2^{4,7}$]hexadecane) (II), although he adduced no evidence in support of his assertion. It should be noted, however, that this tetramine should possess a strainless ring system and hence presumably considerable stability. The configuration of this ring system is shown in (II), where the two piperazine rings are represented as being at right angles to the plane of the paper, so that the bonds shown as heavy and as broken lines are respectively above and below this plane, whereas those shown by normal lines are in the plane of the paper; if the piperazine ring is effectively planar, the normal intervalency angle of 3-covalent nitrogen (*ca.* 110°) could thus be retained.



(I.)

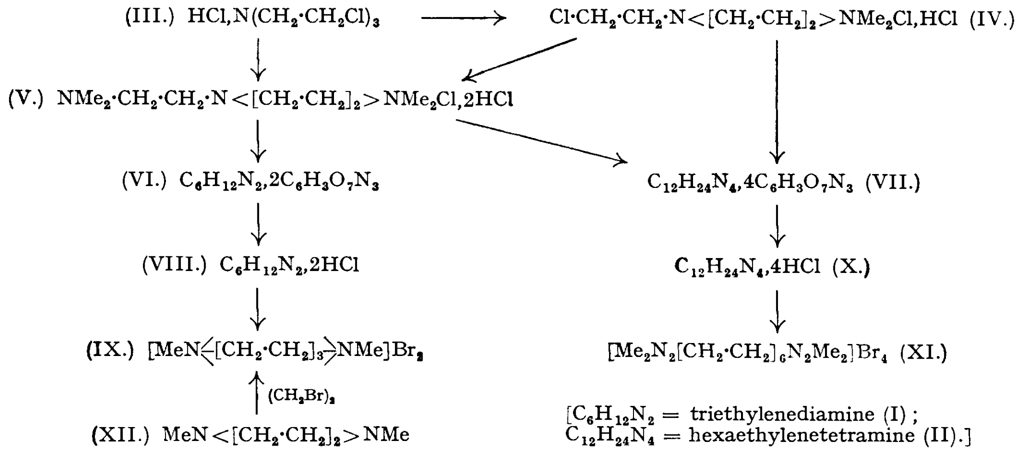


(II.)

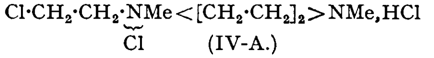
Mann and Pope (*Proc. Roy. Soc.*, 1925, *A*, **109**, 450) failed to detect the diamine (I) in the products of the thermal decomposition of 2 : 2′ : 2″-triaminotriethylamine trihydrochloride, $N(CH_2{\cdot}CH_2{\cdot}NH_2,HCl)_3$, whilst Prelog, Cerkovnikov, and Ustricev (*Annalen*, 1938, **535**, 37) were unable to synthesise it by the action of sodium hydroxide on 1-2′-bromoethylpiperazine.

Hromatka (*Ber.*, 1942, **75**, 1302) has claimed to have prepared the diamine (I) in 2% yield by the thermal decomposition of 2 : 2′-dihydroxydiethylamine hydrochloride. His identification of the base as the diamine (I) rests on a molecular-weight determination of its *p*-nitrophenoxide in molten camphor, and of the highly deliquescent free base in xylene by the vapour-pressure method. The nitrophenoxide, as would be expected, underwent considerable dissociation in molten camphor and gave an apparent molecular weight of 144, whereas the undissociated salt of the diamine (I) has the value 390·4; the free base in xylene gave values of 124, 112, 99, and 101, whereas the diamine (I) requires 112·2. Hromatka and Engel (*Ber.*, 1943, **76**, 712) obtained the same base in 25·5% yield by the thermal decomposition of 1-2′-bromoethylpiperazine dihydrobromide, in 22·5% yield by the similar decomposition of 1-2′-chloroethylpiperazine dihydrochloride, and in 2·8% yield by the decomposition of 1-2′-hydroxyethylpiperazine dihydrochloride. Since the weight of the salts used in these experiments ranged only from 0·1 to 0·56 g., the accuracy of the yields claimed is doubtful, particularly as the required diamine (I) had usually to be separated from piperazine which was formed simultaneously.

We have developed a synthesis by means of which salts of both the diamine (I) and the tetramine (II) can be readily isolated in good yield. When 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride (III) was heated with an excess of 40% methanolic dimethylamine at 40—45° for 1·5 hours in a pressure bottle, and the product subsequently treated with hydrogen chloride, the *hydrochloride* of 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium chloride* (IV), m. p. 218°, was obtained. The fact that this product has the constitution (IV) and is not the isomeric hydrochloride of 1 : 4-dimethyl-1-2′-chloroethylpiperazinium chloride (IV-A) is shown both by the method of preparation and by the fact that a methanolic solution of the compound when shaken with an excess of silver oxide, filtered, and then treated with an excess of cold methyl iodide yielded 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium iodide* (IV-B); in this compound, the 1-nitrogen atom is deactivated by the combined electronic attraction of the positively charged $N_{(4)}$ and of the 2′-chlorine atom (cf. Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502). If, however, the hydrochloride had had the structure (IV-A) instead of (IV), the cold methyl iodide would almost certainly have yielded a dimethiodide instead of the monomethiodide (IV-B).



[$C_6H_{12}N_2$ = triethylenediamine (I); $C_{12}H_{24}N_4$ = hexaethylenetetramine (II).]


$\mathrm{Cl{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{Cl}{\underbrace{N}}Me{<}[CH_2{\cdot}CH_2]_2{>}NMe,HCl}$

(IV-A.)

$\mathrm{Cl{\cdot}CH_2{\cdot}CH_2{\cdot}N{<}[CH_2{\cdot}CH_2]_2{>}NMe_2I}$ (IV-B.)

When, however, the monohydrochloride (III) was heated with an excess of methanolic dimethylamine in an autoclave at 125° for 7 hours, the product on treatment with hydrogen chloride gave the *dihydrochloride* of 4 : 4-*dimethyl*-1-2′-*dimethylaminoethylpiperazinium chloride* (V), m. p. 225°. It is therefore highly probable (although not certain) that the chloroethyl compound (IV) is an intermediate in the formation of the dimethylaminoethyl compound (V); since however only the latter was of major importance in our synthesis it was always prepared directly from the monohydrochloride (III).

The dihydrochloride (V), when heated at 280—290°, underwent smooth decomposition with the evolution of basic vapours, and when decomposition was complete the molten residue gave on cooling a brown glass. The latter, consisting of crude amine hydrochlorides, when dissolved in ethanol and treated with ethanolic picric acid gave a copious precipitate whence fractional recrystallisation ultimately furnished *triethylenediamine dipicrate* (VI), m. p. 298°, and *hexaethylenetetramine tetrapicrate* (VII), m. p. 277° (the identification of these isomeric products is described later). The chloroethyl compound (IV), when subjected similarly to thermal decomposition, ultimately gave the tetrapicrate (VII); however, this experiment was conducted on only a small scale, and the existence of the isomeric diamine salt may have escaped detection.

The diamine dipicrate (VI) was converted into the corresponding *dihydrochloride* (VIII), m. p. 290°, and a methanolic solution of this salt was treated with silver oxide, filtered, and then heated with an excess of methyl bromide at 100° in a sealed tube; *triethylenediamine dimethobromide* (IX), m. p. 335°, was obtained.

The tetrapicrate (VII) was similarly converted into the *tetrahydrochloride* (X), m. p. 291°, but the isolation of this very hygroscopic salt in the pure state was difficult and wasteful. Its methanolic solution when treated as above readily gave crystalline *hexaethylenetetramine tetramethobromide* (XI), m. p. 320°.

An alternative synthesis of quaternary salts of the diamine series has also been developed. When 1 : 4-dimethylpiperazine (XII) was heated under suitable conditions with ethylene dibromide, the product readily yielded the dimethobromide (IX) in high yield, and this compound can thus be prepared in quantity. We have some evidence that in this condensation a small proportion of the isomeric tetramethobromide (XI) may also be formed, but the isolation of pure derivatives of the tetra-amine series involves repeated recrystallisation and is not a practicable synthesis by this route.

It is clear that a decisive identification of the diamine and the isomeric tetramine series must be based on molecular-weight determinations. Such determinations should ideally be made upon the free bases, but Hromatka (*loc. cit.*) found the isolation of his free base in the pure state to be very difficult; moreover the base itself, being deliquescent and also absorbing carbon dioxide, does not lend itself to accurate determinations. Salts of the amines with acids are also unsuitable, since both dissociation and ionisation will occur in aqueous solution. We have therefore investigated the methobromides, which are freely soluble in water, cannot dissociate, and moreover in dilute solution, being salts of a strong acid and a strong base, should be fully ionised. The dimethobromide (IX), has a molecular weight of 301·9, and in aqueous solution should give three ions and thus show an apparent molecular weight which could not be less than 100·6. The tetramethobromide (XI) has twice this molecular weight but, since in aqueous solution it gives five ions, its apparent molecular weight cannot be less than 120·8. The following results were obtained cryscopically.

	*c.**	*M.*
Methobromide (IX) obtained from picrate (VI)	1·076	110
	1·333	108
	1·980	105
Methobromide (IX), obtained from 1 : 4-dimethylpiperazine (XII)	0·414	102
	0·622	105
Methobromide (XI), obtained from picrate (VII), first sample (cf. p. 2302)	1·500	121
	1·726	123
	2·250	127
second sample	1·138	125
	1·474	126
	2·241	128

* G. of solute per 100 g. of water.

These results leave little doubt that (IX) is the dimethobromide, and that (XI) is the tetrabromide, and it is on the basis of these results that the formulæ on p. 2299 have been allocated. Comparison with Hromatka's base is difficult, because Hromatka does not record m. p.s above 280°, and most of our derivatives melt above this temperature. He obtained, however, from his base a *p*-nitrophenoxide of m. p. 183°; our diamine gives a crystalline di-*p*-nitrophenoxide of m. p. 182°, and it is highly probable therefore that Hromatka's base was correctly regarded as triethylenediamine.

This work is now being extended, in particular to the study of the substitution derivatives of the diamine and tetramine.

EXPERIMENTAL.

Many of the salts obtained in this investigation were highly hygroscopic, and considerable care was necessary therefore in their analysis and in the determination of their m. p.s.

2 : 2′ : 2″-*Trichlorotriethylamine Hydrochloride* (III).—This salt was prepared from triethanolamine by the method of McCombie and Purdie (*J.*, 1935, 1217).

4 : 4-*Dimethyl*-1-2′-*chloroethylpiperazinium Chloride Hydrochloride* (IV).—A mixture of the above hydrochloride (III) (7·5 g.) and methanol (12 c.c.) containing 40% of dimethylamine was heated in a pressure bottle at 40—45° for 1·5 hours. Hydrogen chloride was passed into the cold solution to precipitate the *hydrochloride* (IV), which after recrystallisation from ethanol containing a few drops of concentrated hydrochloric acid formed colourless crystals, m. p. 218° (decomp.) (Found : C, 38·6; H, 7·9; N, 11·0. $C_8H_{18}N_2Cl_2,HCl$ requires C, 38·5; H, 7·7; N, 11·3%). The hygroscopic nature of the crude salt diminished markedly on recrystallisation.

A solution of this salt (1 g.) in methanol (15 c.c.) was shaken with silver oxide (2 g.), filtered, mixed with methyl iodide (3 g.), and set aside. The residue after crystallisation from ethanol containing 20% of water gave colourless crystals of 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium iodide monohydrate* (IV-B), m. p. 302—305° (decomp.) (Found : C, 29·4; H, 5·7; N, 8·1. $C_8H_{18}N_2ClI,H_2O$ requires C, 29·7; H, 6·2; N, 8·6%); dehydration at 150°/2 mm. gave the anhydrous *iodide* (Found : C, 31·3; H, 6·2; N, 8·9. $C_8H_{18}N_2ClI$ requires C, 31·5; H, 6·0; N, 9·2%).

4 : 4-*Dimethyl*-1-2′-*dimethylaminoethylpiperazinium Chloride Dihydrochloride* (V).—A mixture of the monohydrochloride (III) (75 g.) and 40% methanolic dimethylamine (460 c.c.) was heated in a rotating autoclave for 7 hours at 125°. The cold product was saturated with hydrogen chloride. The precipitated material, when recrystallised from anhydrous ethanol and then thoroughly dried, gave the *dihydrochloride* (V) as colourless hygroscopic crystals, m. p. 225° (decomp.) (73 g., 84%) (Found : C, 39·5; H, 8·95; N, 14·2; Cl, 36·25. $C_{10}H_{24}N_3Cl,2HCl$ requires C, 40·7; H, 8·9; N, 14·2; Cl, 36·1%). Recrystallisation from aqueous ethanol gave the *monohydrate* (Found : C, 38·6; H, 9·2; N, 13·0. $C_{10}H_{24}N_3Cl,2HCl,H_2O$, requires C, 38·4; H, 9·0; N, 13·4%).

A portion of this salt (2·5 g.) was shaken with saturated aqueous potassium hydroxide (2 c.c.) and ether (10 c.c.). The ethereal extract was mixed with methyl iodide, heated under reflux for 30 minutes, and then evaporated. Recrystallisation of the residue from aqueous ethanol gave 4 : 4-*dimethyl*-1-2′-*dimethylaminoethylpiperazinium iodide methiodide*, m. p. 312° (decomp.) (Found : C, 28·7; H, 5·8; N, 9·4; I, 55·4. $C_{11}H_{27}N_3I_2$ requires C, 28·8; H, 5·9; N, 9·2; I, 55·6%). The same compound was obtained when a methanolic solution of the salt was treated in turn with silver oxide and with cold methyl iodide. It is probable that the second methyl iodide residue in this salt is combined with the 2′-dimethylamino-group, and the salt has the formula $[Me_3N{\cdot}CH_2{\cdot}CH_2{\cdot}N<[CH_2{\cdot}CH_2]_2>NMe_2]I_2$; the strong inductive effect of the positive poles on the two outer quaternary nitrogen atoms would then deactivate the central tertiary nitrogen atom (cf. Mann and Watson, *loc. cit.*).

Thermal Decomposition of the Dihydrochloride (V).—The dihydrochloride (15 g.), contained in a flask carrying an air-condenser closed by a calcium chloride tube, was heated in a metal-bath to 280° and maintained at this temperature for 45 minutes, whereafter the evaporation of volatile material had ceased. The temperature was then dropped to 250° for 30 minutes (to lessen the risk that the required products might themselves slowly decompose), and the product then allowed to cool. The brown glass was dissolved in boiling ethanol (30 c.c.), and the solution when cold filtered to remove a small dark deposit. The filtrate was treated with saturated ethanol picric acid (*ca.* 250 c.c.). The crude yellowish-green picrate (17 g.) was extracted with boiling water containing 5% of ethanol. The filtrate deposited the *tetrapicrate* (VII) which after repeated crystallisation from water containing 30% of ethanol formed yellow crystals, m. p. 277° (decomp.) (Found : C, 38·1; H, 3·2; N, 19·7. $C_{12}H_{24}N_4,4C_6H_3O_7N_3$ requires C, 37·9; H, 3·2; N, 19·6%).

The undissolved residue from the above aqueous extraction was recrystallised repeatedly from glacial acetic acid, and the *dipicrate* (VI), m. p. 298° (decomp.), obtained (Found : C, 37·95; H, 3·2; N, 19·6. $C_6H_{12}N_2,2C_6H_3O_7N_3$ requires C, 37·9; H, 3·2; N, 19·6%). These crystals, even when analytically pure, had a yellowish-green colour, the tint varying with the individual preparation; recrystallisation of a small sample from much boiling water (charcoal) gave a yellow sample of unchanged m. p., but this process was not adopted on the larger scale. A mixture of the picrates (VII) and (VI) had m. p. 257° (decomp.) with preliminary softening.

Thermal Decomposition of the Monohydrochloride (IV).—The hydrochloride (2·5 g.) was heated as above at 270° for 20 minutes. The cold residue was extracted with boiling ethanol (50 c.c.), and the extract treated with saturated ethanolic picric acid. The crude precipitated picrate (2·0 g.) was recrystallised from water containing 30% of ethanol and ultimately furnished the pure tetrapicrate (VII), m. p. 277° (decomp.), unchanged by admixture with that obtained above (Found : C, 38·3; H, 3·7; N, 19·7%).

Derivatives of Triethylenediamine.—Dihydrochloride (VIII). The dipicrate (VI) was thoroughly shaken with an excess of 15% hydrochloric acid, and the product then repeatedly extracted with ether until the aqueous solution was almost colourless. The latter was then evaporated in a desiccator, and the residue, when twice recrystallised from absolute ethanol, gave colourless hygroscopic crystals of the *dihydrochloride* (VIII), m. p. 290° (decomp.) (Found : C, 39·4; H, 8·1; N, 15·3. $C_6H_{12}N_2,2HCl$ requires C, 38·9; H, 7·6; N, 15·1%).

Dimethobromide (IX).—(a) *From the dihydrochloride* (VIII). A solution of the dihydrochloride (VIII) (1 g.) in methanol (20 c.c.) to which water (0·5 c.c.) had been added was shaken with silver oxide (1·5 g.), filtered, transferred to a Carius tube, and chilled to −5°. Methyl bromide (5 g.), also cooled to −5°, was then added, and the sealed tube heated at 80° for 6 hours (although the reaction appeared to be rapid). The contents of several tubes were then united and evaporated in a desiccator. The residue, after recrystallisation from ethanol to which a few drops of water had been added to increase the solvent action, gave the pure *dimethobromide* (IX) as colourless crystals, m. p. 334° (decomp.) (Found : C, 31·4; H, 6·0; N, 9·5; Br, 52·3. $C_8H_{18}N_2Br_2$ requires C, 31·8; H, 6·0; N, 9·3; Br, 52·9%).

Ethanolic solutions of this dimethobromide and of sodium picrate were mixed, and the precipitated *dimethopicrate* was collected, washed with water, and recrystallised from boiling ethanol, in which it was only sparingly soluble : it formed yellow crystals, m. p. 330° (decomp.) (Found : C, 40·5; H, 3·45; N, 19·3. $C_{20}H_{22}O_{14}N_8$ requires C, 40·1; H, 3·7; N, 18·8%).

(b) *From* 1 : 4-*dimethylpiperazine* (XII). A mixture of 1 : 4-dimethylpiperazine (8·3 g.) and ethylene dibromide (13·65 g., 1 mol.), each freshly distilled, was heated in a flask fitted with a reflux air-condenser, slowly to 140°. The faint turbidity which appeared at room temperature gradually became more prominent, and the crystalline salt started to separate at 90—95°, causing considerable " bumping." After the temperature had been maintained at 140° for 1·5 hours, it was reduced to 125° for a further 2 hours, and the solid product then allowed to cool. The pulverised product was thoroughly extracted with cold ethanol (50 c.c.), and the extract filtered and set aside (see below). The undissolved residue was thrice recrystallised from ethanol containing traces of water, and the dimethobromide (16·8 g., 77%) thus obtained as colourless crystals, m. p. 335° (decomp.), unchanged by admixture with that prepared by method (a) [Found : C, 31·4; H, 6·3; N, 9·0; Br (ionic) 52·5%]. This salt also gave the dimethopicrate, m. p. 331° (decomp.), unchanged by admixture with the previous preparation (Found : N, 19·1%).

The cold ethanolic extract of the above crude product was treated with ethanolic sodium picrate, and the precipitated methopicrate, when once recrystallised from ethanol containing a trace of water, had m. p. 238° (decomp.) and when twice recrystallised had m. p. 252° (decomp.); its composition was then that of a pure methopicrate (Found : C, 40·1; H, 3·5; N, 19·2%). Further recrystallisation from ethanol containing 20% of water (to increase the solubility of the picrate) caused however the following changes : (3) m. p. not recorded, (4) 262—268°, (5) 279—280°, (6) 286—287°, (7) 293—294°, (8) 296—297°, (9) 296—297° (all with decomp.). The product after 9 recrystallisations had the same m. p. (mixed and unmixed), and the same composition, as the monoethanolate of the tetramethopicrate (see p. 2302) (Found : H, 4·1; N, 17·6%. Consistent values for carbon could not be obtained). It differed however in that even after the ninth recrystallisation it softened and became slightly brown at *ca.* 10—15° below its m. p., whereas this behaviour was not shown by the product prepared directly from the authentic tetramethobromide.

It is noteworthy that the above combination of 1 : 4-dimethylpiperazine and ethylene dibromide is considerably inhibited by traces of solvents (*e.g.*, ether), or by even a small excess of the dibromide. Hence the necessity to use correct quantities of the pure reagents.

The molecular weights of the dimethobromide prepared by methods (a) and (b) are recorded on p. 2300.

*Di-*p*-nitrophenoxide.* Solutions of the dihydrochloride (VIII) (0·2684 g.) and of sodium *p*-nitrophenoxide (0·5915 g., 2 mols.), each in aqueous ethanol, were mixed and evaporated to dryness in a desiccator. The residue, when recrystallised from ether, gave yellow crystals of the di-*p*-nitrophenoxide, m. p. 182° (Found : N, 14·6. Calc. for $C_6H_{12}N_2,2C_6H_5O_3N$: N, 14·4%). Hromatka (*loc. cit.*) gives m. p. 183°.

Derivatives of Hexaethylenetetramine.—Tetrahydrochloride (X). The tetrapicrate (VII) was decomposed with hydrochloric acid, precisely as was (VI), and the aqueous solution evaporated in a desiccator to a white pasty mass. Recrystallisation of this salt proved difficult and very wasteful as it separated as an oil from all but very dilute solutions. A small quantity of the white crystalline hygroscopic *tetrahydrochloride* (X), m. p. 291° (decomp.), was however obtained from absolute ethanol (Found : C, 38·7; H, 7·5; N, 15·0. $C_{12}H_{24}N_4,4HCl$ requires C, 38·9; H, 7·6; N, 15·1%). A mixture of (X) with the dihydrochloride (VI) had m. p. 241—242°.

Tetramethobromide (XI). The pasty mass of unrecrystallised tetrahydrochloride was dissolved in methanol and treated with silver oxide and methyl bromide precisely as for the dimethobromide (IX). The dried residue, when recrystallised from methanol containing a few drops of water, gave the *tetramethobromide monohydrate* (XI), white crystals, m. p. 309—310° (decomp.) (Found : C, 31·1; H, 6·2; N, 8·4. $C_{16}H_{36}N_4Br_4,H_2O$ requires C, 30·9; H, 6·2; N, 8·9%). This material, when dried at 120°/0·1 mm., gave the anhydrous *salt* (XI), m. p. 320° (decomp.) (Found : C, 31·7; H, 6·3; N, 9·0. $C_{16}H_{36}N_4Br_4$ requires C, 31·8; H, 6·0; N, 9·3%). In the table of molecular-weight determinations (p. 2300), the values for the first sample were obtained using the monohydrate (the concentrations having been calculated for the anhydrous salt), whereas those for the second sample were determined using the anhydrous salt itself.

A solution of this tetramethobromide in ethanol containing a small quantity of water was treated with alcoholic sodium picrate solution. The precipitated yellow *tetramethopicrate*, when collected, washed with water, and recrystallised from ethanol, separated as the crystalline *monoethanolate*, m. p. 298° (Found : C, 40·8; H, 4·5; N, 17·8. $C_{40}H_{44}O_{28}N_{16},C_2H_6O$ requires C, 40·6; H, 4·1; N, 18·0%); the latter, when dried at 150°/2 mm., gave the ethanol-free tetramethopicrate of unchanged m. p. (Found : N, 18·6. $C_{40}H_{44}O_{28}N_{16}$ requires N, 18·8%). A mixture of this compound and the dipicrate (VI), which have the same m. p., had m. p. 258—259°.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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