300. *The Amino-derivatives of Pentaerythritol. Part I. Preparation.*

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The tetramine $C(CH_2\cdot NH_2)_4$ has been prepared expeditiously by the interaction of $C(CH_2Br)_4$ and sodio-*p*-toluenesulphonamide, followed by acid hydrolysis of the condensation product. Various organic derivatives of this tetramine have been prepared, but only the methylation derivatives are now described. The tertiary amine $C(CH_2\cdot NMe_2)_4$ combines directly with only two molecules of methyl iodide, but the $C(CH_2\cdot NMe_2)_2(CH_2\cdot NMe_3I)_2$ so obtained gives $C(CH_2\cdot NMe_3I)_4$ on being heated.

The remainder of the paper deals with other products obtained in the above condensation, and in that of $C(CH_2Br)_3(CH_2\cdot OAc)$ with the sodio-amide. By these reactions the following amines have been isolated as salts: $C(CH_2\cdot NH_2)_3(CH_2\cdot OH)$; $C(CH_2\cdot NH_2)_3(CH_2Cl)$; $(NH_2\cdot CH_2)_2C{:}[CH_2]_2{:}NH$; $NH{:}[CH_2]_2{:}C{:}[CH_2]_2{:}NH$. The interrelationships of these compounds have been investigated in detail.

Govaert (*Proc. Roy. Acad. Sci. Amsterdam*, 1934, **37**, 156) has shown that tetrakisbromomethylmethane (I), when heated with alcoholic ammonia in sealed tubes, gives tetrakisaminomethylmethane (III), of which he isolated various salts. Van Alphen (*Rec. Trav. chim.*, 1938, **57**, 265) repeated this preparation and isolated the tetramine as a liquid monohydrate. It is clear, however, that this method of preparation is unsatisfactory: the yield is low, and van Alphen states that the tetrabromide "reacts with ammonia only with difficulty: the reaction mixture consists of highly condensed amines and only a small quantity of the tetramine can be isolated"; furthermore, the use of sealed tubes places a severe practical limit on the quantities of tetrabromide employed.

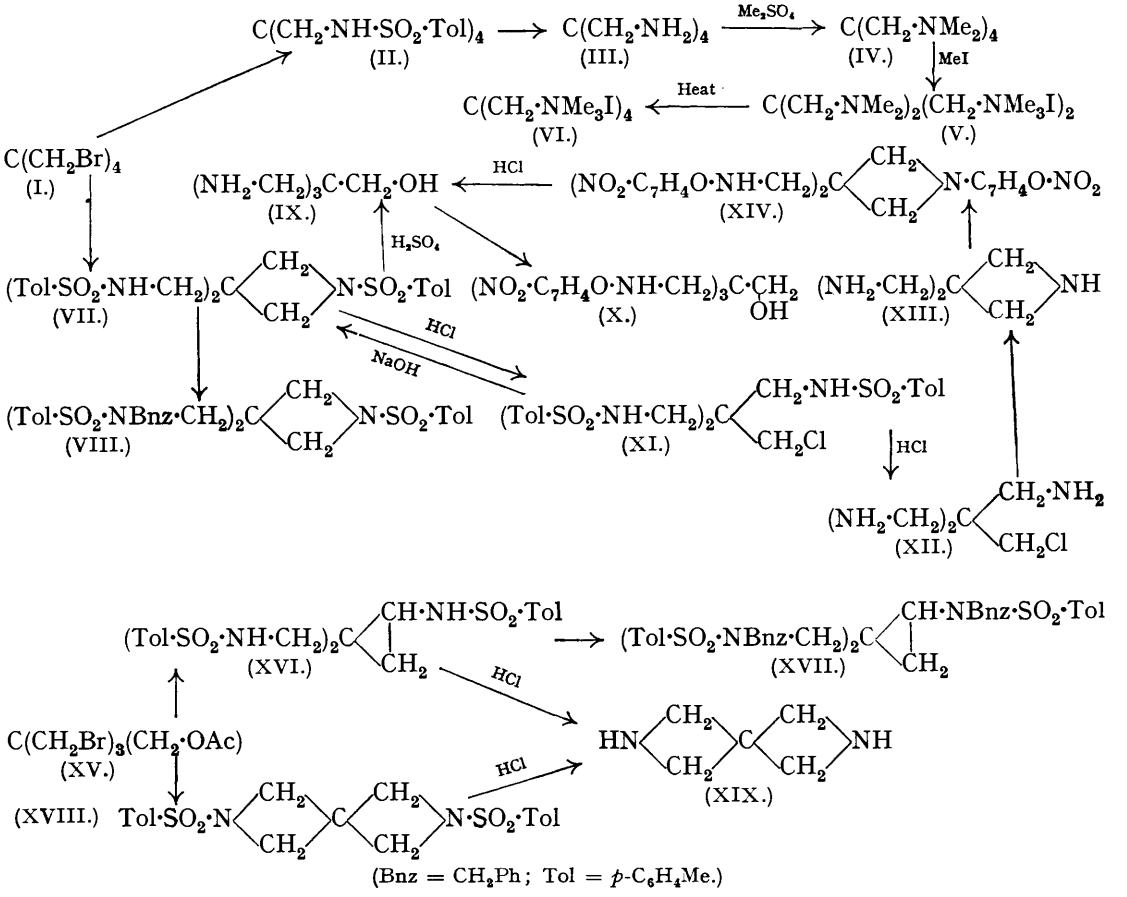
Requiring moderately large quantities of this tetramine, we sought a simple method of preparation. When the tetrabromide (I) was heated at 210° for 10 hours with sodio-*p*-toluenesulphonamide, $C_6H_4Me\cdot SO_2\cdot NHNa$, the chief product was *tetrakis*-p-*toluenesulphonamidomethylmethane* (II), which on hydrolysis with 80% sulphuric acid gave the *disulphate* of the tetramine (III); this salt is soluble in concentrated sulphuric acid but almost insoluble in dilute acid and in water, and can thus be readily isolated. Alternatively, the tetramine can be isolated from the crude hydrolysis product as the tetrapicrate, or the amine may be distilled in superheated steam and then isolated as the tetrahydrochloride.

Govaert (*loc. cit.*) was unable to obtain the pure tetrahydrochloride, and states that this salt in hot aqueous solution loses ammonium chloride and ultimately gives the dihydrochloride of the spiran (XIX). We find, however, that the tetrahydrochloride possesses great stability, and it was recovered unchanged after being submitted to the following processes: (*a*) evaporation of its aqueous solution for 36 hours, (*b*) boiling with hydrochloric acid under reflux for 20 hours, (*c*) heating with concentrated hydrochloric acid in sealed tubes at 160° for 5 hours. We cannot therefore explain Govaert's isolation of the *spiro*-diamine (XIX).

A detailed crystallographic examination of various salts of the tetramine (III) is now being conducted by Mr. E. G. Cox. In view of the earlier controversy regarding the disposition of the central carbon valencies in pentaerythritol derivatives, it is of interest that even a preliminary examination of the tetrahydrochloride of the amine (III) establishes clearly the tetrahedral disposition of these valencies in this salt.

The tetramine (III) on treatment with methyl sulphate under the usual conditions gave *tetrakisdimethylaminomethylmethane* (IV), which was isolated as the *tetrapicrate* and *tetrahydrochloride*. All attempts to combine this amine directly with 4 mols. of methyl iodide failed, however, and the product in every case was the *bi-quaternary iodide* (V). When this was heated to just above its m. p., however, vigorous effervescence occurred, and from the residue was isolated the *quadri-quaternary iodide* (VI). It is clear, therefore, that only under extreme conditions can the second pair of methyl iodide molecules be added to the dimethiodide (V). The reason for this is probably two-fold. If an attempt is made to construct a model of the quadrivalent organic cation of (VI) by using Stuart's "sphere of

action" atomic models (*Z. physikal. Chem.*, 1934, *B*, **27**, 350), difficulty is experienced owing to lack of space-accommodation around the central carbon atom, and so there is probably a small but definite steric obstruction. Furthermore, it is possible that the octamethyl molecule (IV) shows a progressive reluctance to the increase in its ionic charges by methyl iodide addition, *i.e.*, the energy changes accompanying progressive addition of methyl iodide molecules may fall steadily from those of an exothermic reaction to those of a markedly endothermic reaction: hence, only when considerable energy is applied externally does the second pair of methyl iodide molecules combine to form the tetraiodide (VI).



(Bnz = CH_2Ph; Tol = p-C_6H_4Me.)

The preparation of the tetrasulphonamido-compound (II) always gave as a by-product a small quantity of N-p-*toluenesulphonyl*-3 : 3-*bis*-p-*toluenesulphonamidomethyltrimethyleneimine* (VII). The constitution of this compound is placed beyond doubt by its reactions, and in particular, by the fact that its sodium derivative when treated with excess of benzyl bromide gave only the *dibenzyl* derivative (VIII), in marked contrast to the behaviour of the isomeric trisulphonamido-compound (XVI) described below. The formation of the 4-membered ring in the compound (VII) was not unexpected, as Marckwald and co-workers (*Ber.*, 1898, **31**, 3264; 1899, **32**, 2031) have shown that, when trimethylene dibromide is heated with *p*-toluenesulphonamide in the presence of sodium hydroxide, one product is N-*p*-toluenesulphonyltrimethyleneimine, $CH_2{:}[CH_2]_2{:}N{\cdot}SO_2{\cdot}C_7H_7$.

When the trisulphonamido-compound (VII) was heated with 70% sulphuric acid, opening of the ring accompanied hydrolysis of the toluenesulphonyl groups, and *hydroxymethyltrisaminomethylmethane* (IX) was obtained; this was characterised by

benzoylation: excess of benzoyl chloride gave the *tetrabenzoyl* derivative, but *o*-nitrobenzoyl chloride under similar conditions gave only the *hydroxymethyltris*-o-*nitrobenzamidomethylmethane* (X), m. p. 229°. This derivative at once distinguishes this triamine from the cyclic triamine (XIII) discussed later.

When the trisulphonamido-compound (VII) was heated, however, with concentrated hydrochloric acid, opening of the ring occurred to give *chloromethyltris*-p-*toluenesulphonamidomethylmethane* (XI), a reaction that was readily reversed by sodium hydroxide; further hydrolysis removed the toluenesulphonyl residues to give *chloromethyltrisaminomethylmethane* (XII). There is some evidence, however, that this triamine was also formed directly from (VII) without the intermediate formation of (XI).

The chloro-triamine (XII), when subjected to steam distillation in alkaline solution, lost hydrogen chloride and thus by ring closure gave 3 : 3-*bisaminomethyltrimethyleneimine* (XIII), which has been identified as its *trihydrochloride*, *tripicrate*, and its *tri*-o-*nitrobenzoyl* derivative (XIV), m. p. 285°; furthermore, the triamine (XIII) in alkaline solution on treatment with excess of *p*-toluenesulphonyl chloride, gave the original trisulphonamido-compound (VII). When the compound (XIV) was hydrolysed with hydrochloric acid, however, the nitrobenzoyl groups were removed and ring fission occurred to give the monohydroxytriamine (IX).

The opening and closing of the four-membered ring shown by the compounds (VII)—(XIV) are typical properties of trimethyleneimine derivatives. In general, it may be said that strong inorganic acids open the ring by direct addition, giving *n*-propylamine derivatives having the acid radical attached to the γ-carbon atom (*e.g.*, $-CH_2 \cdot SO_4H$, $-CH_2Cl$): in acidic solution, the acid radical may be hydrolysed, giving the $-CH_2 \cdot OH$ group, which then does not readily undergo ring closure; in alkaline solution, particularly when steam distillation is also applied, the inorganic acid is readily split off, with production of the original four-membered ring.

The tetrakisbromomethylmethane (I) used in the above experiments was prepared by the action of phosphorus tribromide on pentaerythritol (Backer and Schurink, *Rec. Trav. chim.*, 1931, **50**, 924). When it is prepared by the action of hydrobromic acid on pentaerythritol tetra-acetate (Perkin and Simonsen, J., 1905, **87**, 860), some trisbromomethylacetoxymethylmethane (XV) is always formed as a by-product. When this was heated with sodio-*p*-toluenesulphonamide at 180°, it gave two compounds: (i) 1-p-*toluenesulphonamido*-2 : 2-*bis*-p-*toluenesulphonamidomethyl*cyclo*propane* (XVI), isomeric with (VII), and the constitution of which was placed beyond doubt by its conversion into the *tribenzyl* derivative (XVII); (ii) NN′-*di*-p-*toluenesulphonylbistrimethyleneimine*-3 : 3′-*spiran* (XVIII). The fact that the latter compound does not also possess *cyclo*propane rings is clearly shown by its insolubility in hot aqueous sodium hydroxide solution: the presence of *cyclo*propane rings would entail acidic *p*-toluenesulphonamido-groups, which would confer upon (XVIII) the ready solubility in hot alkali characteristic of (II), (VII), and (XVI).

When the trisulphonamido-compound (XVI) was hydrolysed with hydrochloric acid, and the product made alkaline and steam-distilled, ammonia and the spiran (XIX) were obtained. Fission of the *cyclo*propane ring by the acid had evidently been followed by closure to the four-membered ring during steam distillation, but the formation of the second ring to give the spirocyclic diamine was unexpected: it was clear, however, that the latter compound, which was obtained in low yield, was not the only amine produced in the above process. When the disulphonamido-compound (XVIII) was similarly hydrolysed, however, the spirocyclic diamine (XIX) was produced in higher yield and as the main product.

Prof. E. C. Dodds has kindly tested the hydrochlorides of the tetramine (III) and the hydroxytriamine (IX) for physiological activity, but they had no effect on the blood pressure of cats, or on the isolated uterus.

The general chemistry of the tetramine (III) is now being investigated, particularly with regard to its organic spirocyclic derivatives and its complex metallic salts.

Experimental.

Sodio-*p*-toluenesulphonamide was prepared by pouring a hot solution of the sulphonamide (100 g.) in alcohol (300 c.c.) into cold alcoholic sodium ethoxide (from sodium, 16 g., and alcohol, 350 c.c.). The mixture was rapidly cooled with stirring, and the sodio-amide collected, washed with alcohol, and dried; yield, 100 g., 88%.

Tetrakisbromomethylmethane (I) was prepared by Backer and Schurink's method (*loc. cit.*), but the crude product was more conveniently purified by washing it with water and alcohol, and then extracting the residue with boiling toluene (800 c.c. per 100 g. of pentaerythritol). The filtered extract deposited most of the tetrabromo-compound (I) on cooling, and the remainder was obtained by evaporation of the mother-liquor: the whole of the product was then recrystallised from alcohol.

Tetrakis-p-*toluenesulphonamidomethylmethane* (II).—A mixture of the tetrabromo-compound (I) (25 g.) and the sodio-amide (50 g.) was thoroughly powdered, and then heated at 210—212° for 10 hours in a conical flask closed by a soda-lime tube. The yield of the final product was apparently unaffected if the heating was interrupted at night: it was, however, markedly decreased if the temperature moved beyond these limits. The crude product was ground with cold water, collected, washed again with water, drained, and finally extracted by boiling with acetic acid (100 c.c.) diluted with water (50 c.c.). The insoluble residue was separated, washed with acetic acid, and then crystallised from acetic acid (500 c.c.) (charcoal). The *tetrasulphonamido*-compound (II) separated as colourless crystals, m. p. 248°; yield, 15 g., 31% (Found: C, 53·1; H, 5·2; N, 7·8. $C_{33}H_{40}O_8N_4S_4$ requires C, 52·9; H, 5·4; N, 7·5%). It was found inadvisable to heat more than the above quantities in one conical flask, otherwise uniform heating of the reaction mixture became difficult.

The dilute acetic acid used for the extraction deposited on cooling the crude N-p-*toluenesulphonyl*-3 : 3-*bis*-p-*toluenesulphonamidomethyltrimethyleneimine* (VII). This was recrystallised first from dilute acetic acid (2 vols. acid : 1 vol. water) and then from amyl acetate (charcoal). The hot amyl acetate solution was allowed to cool to 60° with stirring, and the compound (VII) which had separated was then collected; if the solution was cooled to room temperature, traces of the tetrasulphonamido-compound (II) also separated. The compound (VII) was finally obtained from alcohol as colourless crystals, m. p. 214°; yield, 3·5 g. (Found: C, 53·9; H, 5·0; N, 7·3; *M*, in boiling acetone, 630; *M*, in camphor, 528. $C_{26}H_{31}O_6N_3S_3$ requires C, 54·1; H, 5·4; N, 7·3%; *M*, 579). *p*-Toluenesulphonamide was isolated from the acetic acid mother-liquors.

Hot aqueous sodium hydroxide solution dissolves both the compounds (II) and (VII), and deposits white crystals again on cooling.

Hydrolysis of the Tetrasulphonamido-compound (II).—(A) *With sulphuric acid.* The powdered sulphonamide (30 g.) was heated with 80% sulphuric acid (90 c.c.) at 200° for 2½ hours. The tetramine (III) was isolated from this crude hydrolysis product by three methods.

(i) As the disulphate. The solution was cooled and diluted with water (*ca.* 500 c.c.) and alcohol (250 c.c.), thus completing the precipitation of the *disulphate*, which was collected, and purified by dissolution in dilute sodium hydroxide solution, filtration, and reprecipitation with dilute sulphuric acid. It separated in colourless crystals, m. p. 303° (decomp.) (Found: C, 18·4; H, 6·0; N, 16·9. $C_5H_{16}N_4,2H_2SO_4$ requires C, 18·3; H, 6·1; N, 17·1%).

(ii) As the tetrapicrate. The hydrolysis product was diluted with water and almost neutralised with sodium hydroxide. Sodium picrate solution was added until separation of the tetrapicrate was complete. This, when collected and washed with cold water, was sufficiently pure for the preparation of other salts. It was also purified by recrystallisation from hot water, separating as orange-yellow needles of the *trihydrate*,* m. p. 196—197° (decomp.) (Found: C, 31·8; H, 3·55; N, 20·45; loss on dehydration in a vacuum, 4·9. $C_5H_{16}N_4,4C_6H_3O_7N_3,3H_2O$ requires C, 31·6; H, 3·1; N, 20·3; $3H_2O$, 4·9%. Found for the anhydrous *picrate*: C, 33·5; H, 3·1; N, 21·8. $C_5H_{16}N_4,4C_6H_3O_7N_3$ requires C, 33·2; H, 2·7; N, 21·4%).

(iii) As the tetrahydrochloride. The hydrolysis product was made strongly alkaline and then distilled in steam heated to 140°. The distillate was acidified with hydrochloric acid and evaporated to dryness, the residue recrystallised from dilute hydrochloric acid (1 : 1 by vol.), and the *tetrahydrochloride* obtained as colourless crystals, which on rapid heating were apparently

* Govaert (*loc. cit.*) by an error in calculation has described this trihydrate as the anhydrous substance. He gives the values: Found: N, 19·38, 19·47; calculated for the anhydrous tetrapicrate of *M*, 1148; N, 19·51%. Actually *M* = 1048, and the calculated value for N is that given above.

unaffected up to 300°, but on slow heating decomposed above *ca.* 260° (Found: C, 21·9; H, 7·2; N, 19·9. $C_5H_{16}N_4,4HCl$ requires C, 21·6; H, 7·25; N, 20·1%).

(B) *With hydrochloric acid.* The tetrasulphonamide (2 g.) was heated with concentrated hydrochloric acid (5 c.c.) in a sealed tube at 190° for 6 hours. The product, which had undergone slight decomposition, was diluted with water, the solution filtered and evaporated to small bulk, and the crude tetrahydrochloride purified as before. This method of hydrolysis is clearly inferior to the sulphuric acid method.

The tetrahydrochloride was also readily obtained by boiling an aqueous suspension of the disulphate with an equivalent quantity of barium chloride, and by decomposing the tetrapicrate with hydrochloric acid and extracting the free picric acid with amyl alcohol. The stability of the tetrahydrochloride is clearly shown by the following experiments, in all of which it was ultimately recovered unchanged: (a) An aqueous solution of the hydrochloride was evaporated on the water-bath for 36 hours, water being occasionally added to replace evaporation losses; the solution was finally taken to dryness, and the hydrochloride recrystallised as above (Found: C, 21·8; H, 7·0; N, 20·0%). (b) The hydrochloride was boiled with dilute hydrochloric acid (1 : 1 by vol.) for 8 hours and then isolated as in (a) (Found: C, 22·6; H, 7·3%). (c) This experiment was repeated with more dilute acid (1 : 5) and 20 hours' heating (Found: C, 22·1; H, 7·3%). (d) The hydrochloride was heated with concentrated hydrochloric acid in a sealed tube at 160° for 5 hours and then isolated as before (Found: C, 22·0; H, 7·2%).

Mr. E. G. Cox has kindly furnished the following preliminary report: "The tetrahydrochloride forms tetragonal bipyramidal combinations of $m\{110\}$ with $d\{011\}$, usually of acicular habit. The unit cell, which contains two molecules of $C(CH_2{\cdot}NH_3Cl)_4$, has dimensions $a = 9{\cdot}44$, $c = 6{\cdot}53$ A. (*d*, obs., 1·54 approx.; calc., 1·576 g./c.c.). The space group is $P4_2/n$ (C_{4h}^4), and the central carbon atom in each molecule lies on a position of S_4 (tetragonal alternating) symmetry, in agreement with a tetrahedral disposition of its valencies."

The thermal decomposition of the pure tetrahydrochloride was investigated, the powdered salt being heated at 265—270° for 2—3 hours. Ammonium chloride was liberated. The residue was converted in turn into a picrate and then into a hydrochloride; the latter appeared to be a mixture of the hydrochlorides of the triamine (XIII) and the diamine (XIX), but the amount available was too small to allow either compound to be isolated in a pure state.

Tetrakisbenzamidomethylmethane, obtained in the usual manner and recrystallised from alcohol, formed colourless crystals, m. p. 276° (Found: C, 72·4; H, 5·7; N, 10·4. $C_{33}H_{32}O_4N_4$ requires C, 72·3; H, 5·9; N, 10·2%).

Methylation of the Tetramine (III): *Tetrakisdimethylaminomethylmethane* (IV).—To ensure complete methylation, excess of both methyl sulphate (12 mols.) and sodium hydroxide (20 mols.) was used. The solution obtained by adding the tetramine disulphate (20 g.) to 10% aqueous sodium hydroxide solution (250 c.c.) was chilled in ice, and methyl sulphate (30 c.c.) added in small quantities with shaking. The solution was again chilled, and 10% alkali (250 c.c.) and methyl sulphate (40 c.c.) added as before. The solution was shaken mechanically for 2 hours, and the octamethyl base isolated by either of the following methods. (1) The solution was made strongly alkaline and distilled in steam, in which the base was readily volatile; the distillate was acidified with hydrochloric acid, evaporated to dryness, and the powdered residue recrystallised by boiling with methyl alcohol and adding concentrated hydrochloric acid drop by drop until a clear solution was obtained; on cooling, the *tetrahydrochloride* separated as colourless crystals of the *trihydrate* (yield, 14 g., 52%), which lost water slowly over calcium chloride and rapidly over phosphoric oxide (Found: C, 35·45; H, 9·5; N, 12·9. $C_{13}H_{32}N_4,4HCl,3H_2O$ requires C, 35·1; H, 9·5; N, 12·6%. Found for the anhydrous material: C, 39·8; H, 9·1; N, 14·5. $C_{13}H_{32}N_4,4HCl$ requires C, 40·0; H, 9·3; N, 14·35%). Both the hydrated and the anhydrous material melted at 231°. (2) The solution was made weakly acidic and then run slowly with stirring into a saturated solution of excess of picric acid in aqueous alcohol (4 vols. of water : 1 vol. of alcohol). The *tetrapicrate* which separated was collected, washed with water, and dried (Found: C, 37·9; H, 3·85; N, 19·4. $C_{13}H_{32}N_4,4C_6H_3O_7N_3$ requires C, 38·3; H, 3·8; N, 19·3%). The picrate was also converted into the tetrahydrochloride by the usual methods.

Dimethiodide of (IV).—The finely powdered octamethyl tetrahydrochloride (8 g.) was shaken with 15% methyl-alcoholic potassium hydroxide solution (45 c.c.) until no unchanged hydrochloride remained. Methyl iodide (40 c.c.) was added, and the mixture shaken for 6 hours. It was then filtered and the filtrate allowed to evaporate spontaneously. The residue was finally dried in a desiccator, powdered, and recrystallised twice from alcohol. The *dimethiodide* (V) separated as colourless leaflets, which when dried in a desiccator crumbled to a powder and may

therefore have originally contained loosely combined alcohol molecules; m. p. 149° (efferv.) (Found: C, 34·3; H, 7·5; N, 10·35; ionised I, 48·1. $C_{15}H_{38}N_4I_2$ requires C, 34·1; H, 7·3; N, 10·6; I, 48·1%). A mixture of the pure dimethiodide (1·5 g.) and methyl iodide (25 c.c.) was boiled under reflux for 4 hours, and all the former was then recovered unchanged.

Tetramethiodide of (IV).—The powdered dimethiodide was heated in an oil-bath to 150—155°, *i.e.*, just above its m. p. On melting, vigorous effervescence occurred, and a vapour having a pronounced amine-like odour was evolved. After about 30 minutes the effervescence had entirely subsided, and on cooling a sticky pale brown product remained. This was washed with cold methyl alcohol, which removed the sticky component and left a fine white powder. The latter was apparently insoluble in boiling methyl alcohol (unlike the dimethiodide). It was therefore boiled with much methyl alcohol, and water then added drop by drop until a clear solution was obtained; on cooling, fine white crystals of the *dihydrate* of the *tetramethiodide* (VI) separated. These slowly lost water on exposure to phosphoric oxide in a vacuum (Found: C, 23·9; H, 5·7; N, 6·7; ionised I, 59·5. $C_{17}H_{44}N_4I_4,2H_2O$ requires C, 24·0; H, 5·7; N, 6·6; I, 59·8%. Found for the anhydrous salt: C, 24·6; H, 5·4; N, 6·7; I, 62·4. $C_{17}H_{44}N_4I_4$ requires C, 25·1; H, 5·45; N, 6·9; I, 62·5%). The tetramethiodide is apparently unaffected by heating to 300°; it is freely soluble in water.

Reactions of the Trisulphonamide (VII).—(1) *Benzylation.* A suspension of the powdered trisulphonamide (2 g.) in alcohol (100 c.c.) was added with stirring to a solution prepared from sodium (1 g.) in alcohol (50 c.c.). The clear solution so obtained rapidly gave a white deposit of the sodio-derivative; this (which was very readily hydrolysed by water) was collected, washed with alcohol and ether, and at once heated with benzyl bromide (1·4 c.c.) at 170° for 1½ hours. The cold product was washed with water and then alcohol, and finally recrystallised from alcohol (*ca.* 500 c.c.). The N-p-*toluenesulphonyl*-3 : 3-*bis*-p-*toluenesulphonbenzylamidomethyltrimethyleneimine* (VIII) separated as colourless crystals, m. p. 181° (Found: C, 63·3; H, 5·5; N, 5·8. $C_{40}H_{43}O_6N_3S_3$ requires C, 63·5; H, 5·55; N, 5·6%). When this compound was hydrolysed with 70% sulphuric acid, the benzyl groups were split off and the ring opened, giving the hydroxy-triamine (IX) (see below).

(2) *Hydrolysis.* (A) With sulphuric acid. The powdered trisulphonamide (VII) (15 g.) was heated with 70% sulphuric acid (45 c.c.) at 170° for 2½ hours. The product was diluted, neutralised with sodium hydroxide, some sodium sulphate removed, and the filtrate added to excess of aqueous sodium picrate solution. The precipitated picrate was collected, and recrystallised from water, and the *dihydrated tripicrate* of *hydroxymethyltrisaminomethylmethane* (IX) obtained as deep yellow crystals, which lost water when placed in a vacuum over phosphoric oxide; m. p. 145° (decomp.) when placed in an oil-bath at 135° and rapidly heated (Found: N, 19·6; loss on dehydration, 4·4. $C_5H_{15}ON_3,3C_6H_3O_7N_3,2H_2O$ requires N, 19·6; $2H_2O$, 4·2%. Found for *anhydrous* picrate: C, 33·8; H, 3·4; N, 20·8. $C_5H_{15}ON_3,3C_6H_3O_7N_3$ requires C, 33·7; H, 2·9; N, 20·5%). The same tripicrate was obtained when the crude hydrolysis product was made alkaline and distilled in steam at 140°, the distillate acidified with hydrochloric acid and evaporated to dryness, and the aqueous solution of the residue poured into sodium picrate solution.

The *trihydrochloride* of the hydroxy-triamine (IX) was obtained from the picrate in the usual way, and also by steam distillation of the alkaline hydrolysis product; recrystallised from concentrated hydrochloric acid, it separated as colourless crystals, m. p. 298° (decomp.) (Found: C, 24·8; H, 7·6; N, 17·5; ionised Cl, 43·7. $C_5H_{15}ON_3,3HCl$ requires C, 24·75; H, 7·4; N, 17·7; Cl, 43·9%). This compound is clearly differentiated from any possible hydrated form of the trihydrochloride of the cyclic amine (XIII) by the fact that it loses no water on exposure to phosphoric oxide in a vacuum, and by the formation of its *o*-nitrobenzoyl derivative (see below).

The *chloroplatinate* separated in large crystals when concentrated solutions of the trihydrochloride and of chloroplatinic acid were mixed and kept; it decomposed when boiled with water, and was partly dehydrated in a vacuum, affording the *dihydrate* (Found: C, 8·0; H, 2·9; N, 5·6; Pt, 38·4. $2C_5H_{15}ON_3,3H_2PtCl_6,2H_2O$ requires C, 7·8; H, 2·6; N, 5·5; Pt, 38·2%). The *tetrabenzoyl* derivative of (IX), prepared in the usual manner, was recrystallised from benzene and then from alcohol; m. p. 231—232° (Found: C, 71·9; H, 6·0; N, 7·7. $C_{33}H_{31}O_5N_3$ requires C, 72·1; H, 5·7; N, 7·65%). The *tri*-o-*nitrobenzoyl* derivative was obtained even when excess of *o*-nitrobenzoyl chloride was employed; it was recrystallised from acetone, and had m. p. 229° (Found: C, 53·6; H, 4·6; N, 14·6. $C_{26}H_{24}O_{10}N_6$ requires C, 53·8; H, 4·1; N, 14·5%).

(B) With hydrochloric acid. The powdered trisulphonamide (2 g.) and concentrated hydrochloric acid (5 c.c.) were heated in a sealed tube at 160—170° for 6 hours. The solid product was collected and washed with water; yield from 4 tubes, 8 g. *Chloromethyltris*-p-*toluene*-

sulphonamidomethylmethane (XI), thus obtained, was insoluble in most organic liquids, but was recrystallised from glycol monoethyl ether; it separated as colourless crystals, m. p. 271—272° (slight decomp.) (Found: C, 50·8; H, 5·5; N, 6·9; Cl, 6·0. $C_{26}H_{32}O_6N_3ClS_3$ requires C, 50·85; H, 5·2; N, 6·8; Cl, 5·8%). Since the trisulphonamide (VII) is unaffected by boiling dilute hydrochloric acid, and the monochloro-compound (XI) is unaffected by cold dilute sodium hydroxide, it is clear that (XI) cannot be a hydrochloride of (VII), and must have the constitution assigned. When the compound (XI) was boiled with dilute sodium hydroxide, hydrogen chloride was removed, and the trisulphonamide (VII) regenerated. The aqueous mother-liquor, from which the crude hydrolysis product separated, gave on distillation in steam at 140° a small quantity of the cyclic triamine (XIII).

The trisulphonamide, similarly heated with 47% hydrobromic acid at 140° for 3½ hours, gave the *monobromo*-compound corresponding to (XI); it was similarly recrystallised, and had m. p. 268° (Found: C, 47·4; H, 4·6; N, 6·3; Br, 12·4. $C_{26}H_{32}O_6N_3BrS_3$ requires C, 47·4; H, 4·9; N, 6·4; Br, 12·2%). No other compound was obtained even when the heating was prolonged to 6 hours.

When the powdered trisulphonamide (VII; 2 g.), concentrated hydrochloric acid (6 c.c.), and water (2 c.c.) were *rapidly* heated in a sealed tube to 200°, and kept at this temperature for 7 hours, subsequent cooling gave a clear solution containing colourless needles. These, when collected, washed with alcohol, and twice recrystallised from concentrated hydrochloric acid, gave the *trihydrochloride* of *chloromethyltrisaminomethylmethane* (XII), m. p. 276° (decomp.) (Found: C, 23·5; H, 6·5; N, 15·9; ionised Cl, 41·0; total Cl, 54·1. $C_5H_{14}N_3Cl,3HCl$ requires C, 23·0; H, 6·5; N, 16·1; ionised Cl, 40·8; total Cl, 54·4%). This compound gave the corresponding *tripicrate*, which, when dried over phosphoric oxide, had m. p. 122° (Found: N, 19·8; Cl, 4·0. $C_5H_{14}N_3Cl,3C_6H_3O_7N_3$ requires N, 20·0; Cl, 4·2%).

The chloro-trisulphonamide (XI) is also similarly hydrolysed at 200°, but far less readily than the trisulphonamide (VII) itself; it is probable, therefore, that although hydrochloric acid at 165° gives chiefly the chloro-sulphonamide (XI), yet at 200° it first hydrolyses the *p*-toluenesulphonyl groups, giving the cyclic triamine (XIII), which then undergoes ring fission to the chloro-triamine (XII).

An aqueous solution of the trihydrochloride of the chloro-triamine (XII) was made alkaline and distilled in steam at 140°; the distillate was acidified with hydrochloric acid and evaporated to dryness, and the residue once recrystallised from concentrated hydrochloric acid. The crude trihydrochloride of 3 : 3-*bisaminomethyltrimethyleneimine* (XIII) so obtained was purified by conversion into the *tripicrate*, which on recrystallisation from water separated as a *dihydrate*, m. p. 212—213° (decomp., after losing water at *ca.* 140°) (Found: C, 33·0; H, 2·95; N, 20·2. $C_5H_{13}N_3,3C_6H_3O_7N_3,2H_2O$ requires C, 32·9; H, 3·1; N, 20·05%). The corresponding *trihydrochloride*, regenerated from the pure tripicrate, recrystallised from concentrated hydrochloric acid, and dried over phosphoric oxide, had m. p. 272° (decomp.), depressed by admixture with the hydrochloride of the triamine (XII) (Found: C, 26·5; H, 7·4. $C_5H_{13}N_3,3HCl$ requires C, 26·7; H, 7·1%). When this trihydrochloride was added to aqueous sodium hydroxide solution and then shaken with *p*-toluenesulphonyl chloride, the trisulphonamide (VII) readily separated.

The *tri*-o-*nitrobenzoyl* derivative (XIV) of the amine (XIII), prepared in the usual way, was insoluble in most solvents; recrystallised from acetic acid, it had m. p. 285° (Found: C, 55·5; H, 4·1; N, 14·9. $C_{26}H_{22}O_9N_6$ requires C, 55·5; H, 3·9; N, 14·95%). This derivative (1 g.) and concentrated hydrochloric acid (6 c.c.) were heated in a sealed tube at 140° for 3½ hours; the product was diluted with water, nitrobenzoic acid removed with ether, the aqueous solution evaporated to dryness, and the residue recrystallised from concentrated hydrochloric acid; it had m. p. 298° (decomp.), unchanged by admixture with the hydrochloride of the hydroxy-triamine (IX). Also, it now gave the tri-*o*-nitrobenzoyl derivative (X), m. p. 230°, unchanged by admixture with that described on p. 1593: the fission of the ring on hydrolysis of the derivative (XIV) was thus confirmed.

Trisbromomethylacetoxymethylmethane (XV).—Tetra-acetylpentaerythritol (6 g.) (Perkin and Simonsen, *loc. cit.*) and a 50% solution of hydrogen bromide in acetic acid (50 g., 35 c.c.) were heated in a sealed tube at 140° for 6 hours; the cold product was poured into much water, cooled, collected, dried, and recrystallised from petrol (b. p. 40—50°): yield, 7 g. (95%). This acetoxy-compound had m. p. 42—43°, and was sufficiently pure for the following work.

*Interaction with sodio-*p-*toluenesulphonamide.* The powdered acetoxy-compound (XV) (20 g.) and the sodio-amide (41 g.) were thoroughly mixed and heated in a conical flask at 180° for 7 hours. The crude product was ground with water, collected, dried, and dissolved in hot methyl alcohol (50 c.c.), and the solution set aside for 1 week. The crystals which had

separated were then collected, and washed with methyl alcohol and water; they had m. p. 155—160°, being a mixture of the compounds (XVI) and (XVIII). This was powdered and extracted with boiling benzene (20 c.c.); the insoluble residue was recrystallised from alcohol (charcoal), 1-p-*toluenesulphonamido*-2 : 2-*bis*-p-*toluenesulphonamidomethyl*cyclo*propane* (XVI) being obtained as colourless crystals (1·7 g.), m. p. 171° (Found : C, 53·8; H, 5·3; N, 7·2; *M*, in camphor, 503. $C_{26}H_{31}O_6N_3S_3$ requires C, 54·0; H, 5·4; N, 7·3%; *M*, 579). The benzene extract was evaporated to dryness, and the residue recrystallised from alcohol (300 c.c.) (charcoal); NN′-*di*-p-*toluenesulphonylbistrimethyleneimine*-3 : 3′-*spiran* (XVIII) separated as colourless crystals (1·6 g.), m. p. 186°, insoluble in boiling dilute sodium hydroxide solution (Found : C, 56·2; H, 5·6; N, 7·0; *M*, in camphor, 384. $C_{19}H_{22}O_4N_2S_2$ requires C, 56·1; H, 5·5; N, 6·9; *M*, 406). The low yield of these substances is due primarily to the considerable decomposition accompanying the initial reaction.

1-p-*Toluenesulphonbenzylamido*-2 : 2-*bis*-p-*toluenesulphonbenzylamidomethyl*cyclo*propane* (XVII).—The powdered trisulphonamide (0·5 g.) was dissolved in a warm solution obtained by dissolving sodium (0·5 g.) in alcohol (10 c.c.), ether (200 c.c.) was added, and the mixture cooled. The sodio-derivative, which separated on scratching, was rapidly collected, and heated with benzyl bromide (0·5 g.) at 150° for 1 hour. The semi-solid cold product was washed thoroughly with water and alcohol and finally recrystallised from alcohol (50 c.c.). The *tribenzyl* derivative separated as colourless crystals, m. p. 146° (Found : C, 66·6; H, 5·8; N, 4·9. $C_{47}H_{49}O_6N_3S_3$ requires C, 66·6; H, 5·8; N, 5·0%).

Hydrolysis of the Disulphonamide (XVIII).—This compound appeared to be completely decomposed when heated with 70% sulphuric acid, and only slightly hydrolysed when boiled with hydrochloric acid under reflux. A mixture of the disulphonamide (2 g.) and concentrated hydrochloric acid (5 c.c.) was therefore heated in a sealed tube at 140° for 6 hours. The product was made alkaline, and distilled in steam at 140°. The distillate was evaporated with hydrochloric acid to dryness, and the residue recrystallised from ethyl alcohol containing a little methyl alcohol; the dihydrochloride was further purified by conversion into the picrate, which after recrystallisation from water and drying in a vacuum proved to be the *dipicrate* of the spiran (XIX), m. p. 243° (decomp. with preliminary blackening) (Found : N, 20·5. $C_5H_{10}N_2,2C_6H_3O_7N_3$ requires N, 20·2%). The dipicrate was converted into the *dihydrochloride*, m. p. 275° (decomp.) (Found : N, 16·2. $C_5H_{10}N_2,2HCl$ requires N, 16·3%). Consistent analyses for carbon could not be obtained with either of these two salts.

The identity of these salts was confirmed by conversion into the *di*-o-*nitrobenzoyl* derivative of the diamine, which after recrystallisation from methyl alcohol had m. p. 218° (Found : C, 56·7; H, 4·1; N, 14·2. $C_{19}H_{16}O_6N_4$ requires C, 57·6; H, 4·0; N, 14·1%. Low carbon values were always obtained with this compound). When this product was hydrolysed with hydrochloric acid in a sealed tube, the amine produced gave an *o*-nitrobenzoyl derivative of m. p. 128—132°. The amount available was insufficient for identification, but by analogy with the behaviour of the compound (XIV), this new amine may have been the dihydroxy-diamine, $C(CH_2{\cdot}OH)_2(CH_2{\cdot}NH_2)_2$.

Hydrolysis of the Trisulphonamide (XVI).—This was hydrolysed precisely as for the above disulphonamide. When the alkaline hydrolysis product was distilled in steam at 140°, much ammonia was at first evolved. The distillate which followed was evaporated to dryness with hydrochloric acid : the presence of the spirocyclic diamine (XIX) in this crude product was confirmed by isolation of its dihydrochloride and preparation of the di-*o*-nitrobenzoyl derivative (as above), but the yield was low. It is clear, however, that some 1-amino-2 : 2-bisaminomethyl*cyclo*propane is formed in the hydrolysis and is not entirely destroyed in the subsequent distillation and evaporation, since the crude hydrochloride, when shaken in alkaline solution with *p*-toluenesulphonyl chloride, gave a very small quantity of the original trisulphonamide.

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