

HEXAMETHONIUM BITARTRATE AND OTHER HEXA-ALKONIUM SALTS

BY H. J. BARBER and K. GAIMSTER

From the Research Laboratories, May and Baker, Ltd., Dagenham

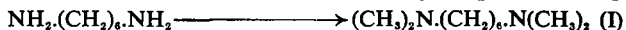
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HEXAMETHONIUM salts are being used widely in the clinical treatment of hypertension. Of these salts the bromide has been more commonly used, though the use of iodide and chloride has also been described in medical literature. It was evident at an early stage that the administration of either iodide or bromide at the customary dose levels would, in all probability, produce undesirable side effects in a number of cases owing to the effect of the bromide or iodide anion. There have now been several notes^{1,2,3} in the medical literature on bromide retention. The use of the chloride was recently advocated by Paton and Walker⁴ to avoid this difficulty, but as the chloride is deliquescent there would have been considerable difficulties in presenting it in a form suitable for oral administration. The clinical use of hexamethonium bitartrate has now been mentioned by Campbell and Robertson⁵ and it is therefore desirable to give some description of this new salt and the experiments which led up to it. Hexamethonium bromide has been described by Balaban, Levy and Wilde⁶, the iodide some forty years ago by von Braun⁷ and more recently by Zaimis⁸. The chloride has not been described in chemical literature, so far as we can ascertain.

In seeking an alternative salt to the bromide, we had the following desiderata to consider :

1. The salt should give an anion known to be essentially free from undesirable pharmacological activity at the prescribed dose level.
2. It should be easily crystallised in a form suitable for manipulation in subsequent pharmaceutical processes.
3. It should not be unduly hygroscopic (we used a 66 per cent. relative humidity atmosphere at about laboratory temperature as a rough practical test of this property).
4. The anion should not have a molecular weight so high as to reduce unduly the proportion of hexamethonium in the salt (though requirement (1) would exclude many complex acids).
5. It should be stable.
6. It should involve an acid which is industrially available.

1:6-Bis-dimethylaminohexane (I), a useful intermediate in this field of synthesis, was originally obtained by von Braun⁷ from 1:6-diiodohexane but is now more conveniently prepared from the industrially available 1:6-diaminohexane using the well-known formic acid-formaldehyde method which has been described⁹ as the Eschweiler-Clarke modification of the classical reaction originally due to Leuckart and to Wallach. This reaction has been discussed by Staple and Wagner¹⁰ :



The bis-tertiary base readily yielded bis-quaternary salts with the standard alkylating agents, and the bis-quaternary methosulphate was

used as a source of other quaternary salts. A solution of "hexamethonium hydroxide" was prepared in an essentially conventional manner by hydrolysing the methosulphate to sulphate and removing the sulphate anion by means of baryta. Portions of the solution were neutralised with various acids and concentrated to a point at which crystallisation might take place. In some cases crystallisation occurred readily, in other cases addition of a suitable solvent such as ethanol or acetone induced crystallisation; in yet other cases the salts remained as intractable syrups. Where di- or tribasic acids were used the ratio of acid to base was varied appropriately to produce the several possible salts. These results are summarised in Table I.

TABLE I
HEXAMETHONIUM SALTS—PRELIMINARY EXAMINATION

Salt	Properties
Adipate, neutral	Deliquescent white solid
Adipate, acid	Very hygroscopic white needles
Benzoate	" "
Carbonate	Deliquescent white solid
Chloride*†	" "
Citrate	Only obtained as a syrup
Maleate, acid	Very hygroscopic white needles
Methosulphate*... ..	Hygroscopic white needles
Phosphate, dihydrogen*	" "
Succinate, neutral	Very hygroscopic white solid
Succinate, acid	" "
Sulphate, neutral*	Hygroscopic irregular plates
Sulphate, acid*	White needles, stable at 66 per cent. humidity
Tartrate, neutral	Hygroscopic white solid
Tartrate, acid*	Fine white needles, stable at 66 per cent. humidity

* Described in more detail in the experimental section. † This compound was first prepared in these laboratories by Dr. J. N. Ashley.

As a result of these preliminary experiments the following salts remained as candidates for further examination: methosulphate, bisulphate, bitartrate and dihydrogen phosphate. The methosulphate was rejected because the methosulphate anion, CH_3SO_4^- , while exhibiting little acute toxicity, might show some cumulative effect on continued administration over a prolonged period. Moreover, it was hygroscopic at 66 per cent. humidity. The bisulphate was a highly crystalline salt, but as would be expected was strongly acid and it was thought preferable to avoid this for various practical reasons. The neutral sulphate, incidentally, was very hygroscopic. The phosphate was somewhat hygroscopic, but would otherwise have been acceptable. The bitartrate however, seemed to fulfil all the desiderata and its properties are described more fully in the experimental section.

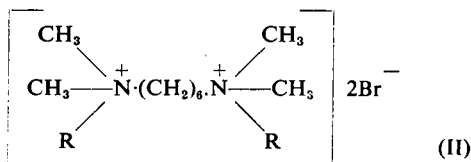
HEXA-ALKONIUM SALTS

The development of a more suitable industrial route to the bitartrate is in progress and will be reported in due course.

In view of current interest in alkane bis-quaternary ammonium salts we prepared certain readily accessible homologues of hexamethonium in which one or more of the methyl substituents in the bis-trimethylammonium groups were replaced by other small alkyl groups. Pharmacological studies by our colleagues on these compounds will be reported elsewhere, but it is convenient to record their preparation and properties here.

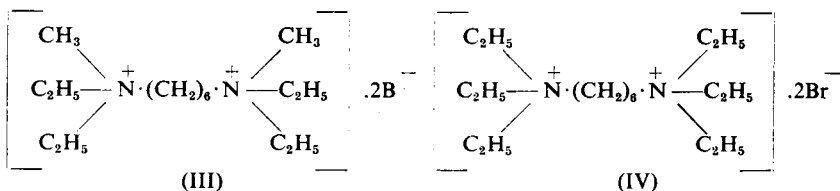
Barlow and Ing¹¹, in their pharmacological paper, described a considerable number of alkane diammonium salts with varying types of quaternary ammonium group but the hexane series was not included. Paton and Zaimis¹², on the other hand, in their pharmacological studies were concerned exclusively with trimethylammonium salts, the preparation of which as iodides has been described later by Zaimis⁸.

1:6-Bis-dimethylamino-hexane (I) served also as a convenient source of the homologues II which were obtained by quaternation with the appropriate alkyl bromide.



Where R = $-\text{C}_2\text{H}_5$, $-\text{C}_3\text{H}_7(n)$, $-\text{C}_3\text{H}_7(i)$, $-\text{C}_4\text{H}_9(n)$, $-\text{C}_4\text{H}_9(i)$, $-\text{CH}_2\text{-CH}=\text{CH}_2$.

The homologues III and IV.



were, however, obtained by reacting 1:6-dibromo-hexane with methyl-diethylamine and triethylamine respectively.

Since hexane 1:6-bis-ethyl-dimethylammonium salts are of some clinical interest, the bitartrate of this homologue was made and found to have very similar properties to hexamethonium bitartrate. This salt would thus meet the desiderata already discussed in relation to hexamethonium itself.

EXPERIMENTAL

All melting points are uncorrected.

1:6-Bisdimethylamino-hexane. Formic acid, 90 per cent. (225 g.) was added slowly to 1:6-diamino-hexane (58 g.) with strong cooling. This solution was heated to 60°C. and 40 per cent. formaldehyde solution (165 ml.) added over 30 minutes. When the evolution of carbon dioxide began to abate, the solution was heated on a steam bath for 18 hours.

The solution was cooled, hydrochloric acid (200 ml.) was added and the bulk of the water removed by distillation. The residue was cooled in ice, made strongly alkaline with 50 per cent. sodium hydroxide solution (200 ml.) and extracted with ether. The ethereal extract was dried over potassium hydroxide, the ether removed and the residue distilled under reduced pressure, to give 1:6-bis-dimethylamino-hexane (57 g.) distilling at 96° to 98°C./15 mm. or 209° to 211°C./760 mm. Found: C, 69.5; H, 13.8; N, 15.8. $C_{10}H_{24}N_2$ requires: C, 69.8; H, 13.8; N, 16.3 per cent. Titre against standard acid was equivalent to 99.2 per cent. w/w of $(CH_3)_2N(CH_2)_6N(CH_3)_2$.

This base, although pure on the basis of other analytical figures, gave persistently low figures for nitrogen whether by the Kjeldahl or Dumas methods. Nevertheless, all the compounds derived from it gave satisfactory nitrogen analyses. No explanation is offered for this anomaly.

1:6-Bis-dimethylamino-hexane dihydrochloride. This was prepared by neutralising the base with hydrochloric acid, evaporating to dryness and crystallising the residue from 80 per cent. ethanol. The hydrochloride was obtained as colourless plates, m.pt. 248°C. Found: N, 11.6; $C_{10}H_{26}N_2Cl_2$ requires N, 11.4 per cent.

Hexane 1:6-bis(trimethylammonium methosulphate). (Hexamethonium methosulphate). 1:6-Bis-dimethylamino-hexane (17.2 g.) was dissolved in methanol (100 ml.) and dimethyl sulphate (20 ml.) added over 30 minutes with stirring at the boil. The product, which crystallised on cooling, was recrystallised from methanol. Hexamethonium methosulphate (25 g.) was obtained as fine white needles, m.pt. 184° to 186°C. (with decomposition). Found: C, 39.7; H, 8.4; N, 6.55; $C_{14}H_{36}N_2O_8S_2$ requires: C, 39.7; H, 8.5; N, 6.6 per cent.

"Hexamethonium hydroxide" solution. A solution of hexamethonium methosulphate (21.2 g.) in 25 per cent. sulphuric acid (100 ml.) was slowly distilled for 8 hours, the solution being periodically made up to its original volume with water. The solution was diluted to 500 ml. with water, and treated at the boil with sufficient baryta solution to precipitate all the sulphate as barium sulphate, which was then filtered and washed with hot water. The filtrate and washings were evaporated to 100 ml. to give a clear colourless solution containing about 0.1 g. of hexamethonium hydroxide per ml.

Hexane 1:6-Bis(trimethylammonium hydrogen tartrate)monohydrate. (Hexamethonium bitartrate.) "Hexamethonium hydroxide" solution (100 ml.) was titrated against a solution of tartaric acid (15 g.) in water (100 ml.), using phenolphthalein as an external indicator. A further quantity of the tartaric acid solution equal to that used in the titration was added, the solution evaporated to a syrup on a steam bath, and granulated by the addition of acetone. The white granular material was filtered and recrystallised from methanol. Hexamethonium bitartrate (15 g.) was obtained as the monohydrate, occurring as fine white needles, m.pt. about 180° to 185°C. with decomposition (the melting point varies with the rate of heating).

HEXA-ALKONIUM SALTS

Hexamethonium bitartrate is soluble to the extent of 1 part in about 0·8 parts of water (a 10 per cent. aqueous solution having pH about 3·8); it is readily soluble in hot methanol, crystallising on cooling, sparingly soluble in ethanol and insoluble in acetone, ether, chloroform and benzene, hot or cold. Found: C, 46·3; H, 8·4; N, 5·45. $C_{20}H_{40}N_2O_{12} \cdot H_2O$ requires: C, 46·4; H, 8·1; N, 5·4 per cent. Found tartaric acid 59·5 per cent. (on material dried at 100°C.). $C_{20}H_{40}N_2O_{12}$ requires 59·8 per cent.

Hexamethonium chloride, sulphate, bisulphate and dihydrogen phosphate were prepared in a manner analogous to that of the bitartrate.

Hexane 1 : 6-bis(trimethylammonium chloride) dihydrate (Hexamethonium chloride) was obtained as colourless, deliquescent irregular plates (from ethanol), m.pt. 284°C.

Found: N, 9·2; Cl, 23·2; $C_{12}H_{30}N_2Cl_2 \cdot 2H_2O$ requires: N, 9·06; Cl, 23·0 per cent.

Hexane 1 : 6-bis(trimethylammonium) sulphate dihydrate (Hexamethonium sulphate) crystallises in hygroscopic irregular plates (from 90 per cent. ethanol), m.pt. 247°C. (with decomposition). Found: N, 8·35; $C_{12}H_{30}N_2SO_4 \cdot 2H_2O$ requires N, 8·37 per cent.

Hexane 1 : 6-bis(trimethylammonium bisulphate) (Hexamethonium bisulphate) crystallises in fine white needles (from methanol) m.pt. 282° to 283°C. (with decomposition). Found: N, 6·9; $C_{12}H_{30}N_2S_2O_8$ requires N, 7·06 per cent.

Hexane 1 : 6-bis(trimethylammonium dihydrogen phosphate) dihydrate (Hexamethonium dihydrogen phosphate) crystallises in fine white needles (from methanol/acetone) m.pt. 275° to 276°C. (with decomposition). Found: N, 6·55; $C_{12}H_{34}N_2P_2O_8 \cdot 2H_2O$ requires N, 6·50 per cent.

Hexane 1 : 6-bis(ethyltrimethylammonium bromide). A solution of ethyl bromide (43·6 g.) in ethanol (80 ml.) was added slowly to a solution of 1 : 6-bis-dimethylamino-hexane (34·4 g.) in ethanol (120 ml.) which was heated under a reflux condenser. The resulting solution was refluxed for a further 2 hours, then cooled in ice; the white solid which separated was filtered, washed with acetone and recrystallised from ethanol (80 ml.). Hexamethylene 1 : 6-bis(ethyltrimethylammonium bromide) (43 g.) was obtained as slightly hygroscopic, micro-prisms, m.pt. 258°C. (with decomposition). Found: N, 7·15; Br, 40·9; $C_{14}H_{34}N_2Br_2$ requires: N, 7·2; Br, 41·0 per cent. One part dissolves in about 0·45 parts of water; apart from being somewhat more soluble in ethanol and methanol, its solubilities in organic solvents resemble those of hexamethonium bromide.

The other homologues were prepared and crystallised in a similar manner.

Hexane 1 : 6-bis(n-propyldimethylammonium bromide) monohydrate was obtained as colourless micro-prisms, m.pt. 234°C. (with decomposition). Found: N, 6·48; Br, 37·0; $C_{16}H_{38}N_2Br_2 \cdot H_2O$ requires: N, 6·42; Br. 36·6 per cent.

Hexane 1 : 6-bis(isopropyldimethylammonium bromide) monohydrate was obtained as colourless, hygroscopic micro-prisms, m.pt. 255° to

257°C. (with decomposition). Found: N, 6.32; Br, 36.45; $C_{16}H_{38}N_2Br_2 \cdot H_2O$ requires: N, 6.42; Br, 36.6 per cent.

Hexane 1 : 6-bis(n-butyltrimethylammonium bromide) monohydrate was obtained as colourless hygroscopic micro-needles, m.pt. 253°C. (with decomposition). Found: N, 6.2; Br, 34.5; $C_{18}H_{42}N_2Br_2 \cdot H_2O$ requires: N, 6.0; Br, 34.5 per cent.

Hexane 1 : 6-bis(isobutyltrimethylammonium bromide) was obtained as colourless, hygroscopic micro-prisms, m.pt. 248° to 250°C. (with decomposition). Found: N, 6.23; Br, 35.3; $C_{18}H_{42}N_2Br_2$ requires: N, 6.3; Br, 35.8 per cent.

Hexane 1 : 6-bis(allyltrimethylammonium bromide) dihydrate was obtained as colourless, hygroscopic micro-prisms, m.pt. 185°C. (with decomposition). Found: N, 6.12; Br, 35.6; $C_{18}H_{34}N_2Br_2 \cdot 2H_2O$ requires: N, 6.2; Br, 35.6 per cent.

Hexane 1 : 6-bis(ethyltrimethylammonium hydrogen tartrate) monohydrate was obtained (from methanol/acetone) as colourless, irregular micro-plates, m.pt. 169° to 170°C. (with decomposition). Found: N, 5.2; $C_{22}H_{44}N_2O_{12} \cdot H_2O$ requires: N, 5.13 per cent. The solubilities of the compound resemble those of hexamethonium bitartrate.

Hexane 1 : 6-bis(methyldiethylammonium bromide). 1 : 6-Dibromohexane (24.4 g.), methyldiethylamine (17.4 g.) and ethanol (100 ml.) were refluxed together for 3 hours. Acetone (100 ml.) was added, the solution cooled, the crude product filtered, and then recrystallised from ethanol/acetone. *Hexane 1 : 6-bis(methyldiethylammonium bromide)* was obtained as colourless, hygroscopic micro-prisms, m.pt. 269° to 270°C. (with decomposition). Found: N, 6.4; Br, 38.6; $C_{17}H_{38}N_2Br_2$ requires: N, 6.7; Br, 38.3 per cent.

Hexane 1 : 6-bis(triethylammonium bromide) (Hexa-ethonium bromide) was prepared by a similar method, using triethylamine. The compound was obtained as colourless, hygroscopic, irregular micro-plates, m.pt. 267° to 269°C. (with decomposition). Found: N, 6.24; $C_{18}H_{42}N_2Br_2$ requires: N, 6.28 per cent.

SUMMARY

1. A number of hexamethonium salts with therapeutically inactive anions have been prepared.

2. Of those prepared, hexamethonium bitartrate has been found to be the most suitable from a pharmaceutical point of view.

3. A number of homologues of hexamethonium have been prepared in which one or more methyl groups on each nitrogen atom are replaced by ethyl or other groups.

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NOTE. Since this paper was written, hexamethonium chloride has been described by Balaban and Beton (*J. Pharm. Pharmacol.*, 1951, 3, 360). These authors do not, however, describe it as a hydrate, nor do they give the method of preparation or crystallisation.

HEXA-ALKONIUM SALTS

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