THE PROPERTIES AND REACTIONS OF SOME METHONIUM COMPOUNDS

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In 1949 Balaban, Levy and Wilde[1] described the properties of decamethonium iodide and hexamethonium bromide, and mention was made of the suggested use of the latter in hypertension and vascular diseases. A growing medical literature on methonium compounds is gradually unfolding their possible applications, and the treatment of peptic ulcers (Kay and Smith[2], Scott, Kay, O'Hare and Simpson[3] and Douthwaite and Thorne[4]) and of hypertension (Campbell and Robertson[5], Smirk[6], Turner[7] and Frankel[8]) and bloodless field surgery (Enderby[9], Enderby and Pelmore[10] and Hughes[11]) are three spheres where much clinical information has already been collected. With regard to hypertension the use of methonium bromides, together with a low-salt diet, has resulted in cases of bromism being reported (Rosenheim[12], Holt and Litchfield[13]), and it has been shown that such a salt-poor diet enhances the effects of these halides. The use of the iodides would no doubt give rise to cases of iodism. A recent investigation by Paton and Walker[14] has now clearly demonstrated that hexamethonium chloride, bromide and iodide are of equal potency, and they suggest that the chloride would be free from other actions and should be fully tested therapeutically. We are, therefore, describing the physical and chemical properties of this substance together with others which are being used in medicine.

Tetramethonium Iodide

Tetramethonium iodide is a colourless, odourless, crystalline powder, which when dried for 4 hours at 70°C./20 mm. pressure and then placed in a melting-point apparatus at room temperature, heated rapidly to 277°C. and then at 2°/minute, had m.pt. 287·5° C. (corr.). For analysis it was dried at 70°C. *in vacuo*. Found: C, 26·97; H, 6·07; N, 6·46; I, 55·62 per cent.; $C_{10}H_{26}N_2I_2$ requires C, 28·04; H, 6·07; N, 6·54; I, 59·4 per cent. Loss at 100°C. *in vacuo*, 4·73 per cent.; on material dried at 100°C. *in vacuo*, I, 59·7 per cent.

It is soluble in water at 22°C., 1·6 g. in 1 ml., and at 100°C., 7 g. in 1 ml. A 1 per cent. solution is clear and colourless and has *p*H 6·68; a 10 per cent. solution has *p*H 6·44. The sterilised ampouled 0·1 per cent. solution in physiological saline solution has *p*H 5·92. In ethanol at 20° C. its solubility is 1 g. in 650 ml., and at 78·5°C. 1 g. in 18 ml., whereas in methanol at 22°C. it is 1 g. in 19 ml. and at 64·1°C. 1 g. in 1 ml. In boiling acetone, benzene, chloroform and ether the solubility is

less than 1 g. in 500 ml. At 100°C. the material lost 1·1 per cent. On ignition 0·15 per cent. of ash remained.

Reactions.

Effect of heat.	The solid melts, vapour is evolved and some material sublimes. The residue turns dark brown.
Concentrated sulphuric acid. Cold.	Effervescence. Iodine liberated. Insoluble black particles. On shaking with carbon tetrachloride, violet solution obtained.
Hot.	Effervescence. Purple colour. Insoluble black particles. On heating iodine liberated, and the solution becomes clear.
Concentrated nitric acid. Cold.	Brown colour. Black particles precipitated. On shaking with carbon tetrachloride, clear violet solution obtained.
Hot.	As cold, solution becomes colourless and iodine sublimes.
Sodium hydroxide solution, 20 per cent.	Immediate white precipitate which redissolves on heating and reappears on cooling again.
Aqueous sodium nitrite solution. Cold.	Immediate dark brown precipitate. Violet extract in carbon tetrachloride.
0·1N silver nitrate.	Pale yellow precipitate not soluble in strong solution of ammonia.
Folin-Ciocalteu phenol reagent.	Immediate yellow precipitate which turns green on standing. Heated becomes lighter green, but darkens again on cooling.
Acid potassium iodate solution. Cold.	Immediate dark brown precipitate. Completely soluble in carbon tetrachloride to violet solution.
Reinecke salt solution, 4 per cent.	Pink precipitate produced at once.
Saturated aqueous picric acid solution.	Bright yellow precipitate, m.pt. 290°C. (decomp.). Recrystallised from methanol m.pt. 292°C. (decomp.).
Saturated aqueous picrolonic acid solution.	No immediate precipitate. Slow crystallisation on standing. Yellow needles, m.pt. 277°C. (decomp.).
Aqueous gold chloride solution, 10 per cent.	Immediate yellowish-brown precipitate, becoming reddish-brown on standing, m.pt. 230° to 242°C. (decomp.). Recrystallised from aqueous alcohol, m.pt. 234° to 237°C. (decomp.).
Aqueous platinic chloride solution, 10 per cent.	Immediate black precipitate, m.pt. 259° to 260°C. (decomp.).

Mayer's reagent.	White precipitate.
Halogen determination (Volhard method).	99·4 per cent. purity.

Stability of solution. Solutions at concentrations of 1 in 250, 1 in 500, and 1 in 1000 in physiological saline solution were heated at 95°C. to 100°C. for 30 minutes and kept in sealed tubes for 8 weeks, some in a cool dark place and others exposed to daylight at room temperature. All the solutions remained clear and colourless.

Assay for non-quaternary material. 0·2 g., accurately weighed was added to a separating funnel containing water (200 ml.), followed by saturated sodium bicarbonate solution (5 ml.) and extracted with chloroform (3 × 20 ml.). The combined chloroform extracts were washed with water (10 ml.), filtered through a plug of cotton wool into a tared beaker, and evaporated and dried at 100°C. for 1 hour. Residue on original material, 0·46 per cent.

Pentamethonium Iodide

Pentamethonium iodide is a colourless, odourless crystalline powder, which, when dried for 4 hours at 70°C./20 mm. pressure and placed in a melting-point apparatus at 150°C., heated rapidly to 270°C. and then at 2°/minute had m.pt. 295°C. (corr.). For analysis it was dried at 70°C. *in vacuo*. Found: C, 29·3; H, 6·05; N, 5·61; I, 57·3 per cent. $C_{11}H_{28}N_2I_2$ requires C, 29·86; H, 6·33; N, 6·33; I, 57·5 per cent.

It is soluble in water at 22°C., 2 g. in 1 ml., and at 100°C., 5 g. in 1 ml. A 1 per cent. solution is clear and colourless and has *p*H 6·67; a 10 per cent. solution has *p*H 6·48. The sterilised ampouled 0·1 per cent. solution in physiological saline solution has *p*H 5·97. In ethanol at 22°C. its solubility is 1 g. in 900 ml., and at 78·5°C. 1 g. in 40 ml., whereas in methanol (22°C.) it is 1 g. in 21 ml. and at 64·1°C., 0·69 in 1 ml. In boiling acetone, benzene, chloroform and ether the solubility is less than 1 g. in 500 ml. At 100°C. the material lost 0·39 per cent. On ignition the ash content was 0·05 per cent.

Reactions.

Effect of heat.		The solid melts, vapour is evolved and some material sublimes. The residue turns dark brown.
Concentrated sulphuric acid.	Cold.	Effervescence. Iodine liberated. Insoluble black particles. On shaking with carbon tetrachloride, violet solution obtained.
	Hot.	Effervescence. Purple colour. Insoluble black particles. On heating iodine liberated and the solution becomes clear.

Concentrated nitric acid. Cold.	Brown colour. Insoluble black particles. On shaking with carbon tetrachloride, a clear violet solution obtained.
Hot.	As cold, but on heating iodine sublimed. Solution becomes colourless.
Sodium hydroxide solution 20 per cent.	Immediate white precipitate which redissolves on heating and reappears on cooling.
Aqueous sodium nitrate solution. Cold.	Immediate dark brown precipitate. Violet extract in carbon tetrachloride.
0·1N silver nitrate.	Pale yellow precipitate not soluble in strong solution of ammonia.
Folin-Ciocalteu phenol reagent.	Immediate yellow precipitate which turns green on standing. Heated becomes lighter green but darkens again on cooling.
Acid potassium iodate solution. Cold.	Immediate dark brown precipitate. Completely soluble in carbon tetrachloride to violet solution.
Reinecke salt solution, 4 per cent.	Pink precipitate produced at once.
Saturated aqueous picric acid solution.	Bright yellow precipitate, m.pt. 268°C. Recrystallised from methanol, m.pt. 269°C.
Saturated aqueous picrolonic acid solution.	Long yellow needles, m.pt. 150°C. (decomp.) after thirteen days. Recrystallised from ethanol, orange rhomboids, m.pt 250° to 252°C. decomp.).
Aqueous gold chloride solution, 10 per cent.	Immediate dark brown precipitate. Recrystallised from aqueous ethanol, m.pt. 260° to 262°C.
Aqueous platinic chloride solution 10 per cent.	Immediate dark brown precipitate, m.pt. 262°C.
Mayer's reagent.	Very pale yellow precipitate.
Halogen determination (Volhard method).	99·7 per cent. purity.

Stability of solution. Solutions at concentrations of 1 in 250, 1 in 500 and 1 in 1000 in physiological saline solution were heated at 95° to 100°C. for 30 minutes, and kept in sealed tubes for 8 weeks, some in a cool dark place and others exposed to sunlight at room temperature. All the solutions remained clear and colourless.

Assay for non-quaternary material. 0·2 g., accurately weighed was added to a separating funnel containing water (200 ml.), followed by

saturated sodium bicarbonate solution (5 ml.) and extracted with chloroform (3 × 20 ml.). The combined chloroform extracts were washed with water (10 ml.), filtered through a plug of cotton wool into a tared beaker and evaporated and dried at 100°C. for 1 hour. Residue on original material, 0·15 per cent.

Hexamethonium Chloride

Hexamethonium chloride is a colourless, odourless, crystalline powder, which when dried for 1 hour at 100°C./20 mm. pressure and then placed in a melting-point apparatus at 200°C., heated rapidly to 275°C. and then at 2°/minutes had m.pt. 289°C. (decomp.), (corr.). For analysis it was dried at 100°C. *in vacuo*. Found: C, 52·72; H, 11·02; N, 9·44; Cl, 25·5; 25·9 per cent.; $C_{12}H_{30}N_2Cl_2$ requires C, 52·74; H, 10·99; N, 10·24; Cl, 26·0 per cent.

It is soluble in water (20°C.) 1 g. in 0·65 ml. and at 100°C., 1 g. in 0·3 ml. A 1 per cent. solution is clear and colourless and has *p*H 6·0; a 10 per cent. solution has *p*H 3·56. The sterilised ampouled 0·1 per cent. solution in physiological saline solution has *p*H 5·56. In ethanol at 20°C. its solubility is 1 g. in 3·2 ml., and at 78·5°C. 1 g. in 1·7 ml., whereas in methanol at 20°C. it is 1 g. in 1·4 ml. and at 64·1°C. 1 g. in 0·8 ml. In boiling acetone, benzene, chloroform and ether the solubility is less than 1 g. in 500 ml. At 100°C. the material lost 2·0 per cent. On ignition no ash remained.

Reactions.

Effect of heat.	White fumes evolved, and then as liquid boiled small amount of charred residue left. Strong odour of hexamethylenediamine-like substances.
Concentrated sulphuric acid. Cold.	Effervescence. Clear solution remained.
Hot.	Brown colouration.
Concentrated nitric acid. Cold.	Clear solution.
Hot.	Slightly yellow solution.
Sodium hydroxide solution 20 per cent.	Clear solution.
Aqueous sodium nitrite solution.	No reaction.
0·1N silver nitrate.	White precipitate. Soluble in ammonia.
Folin-Ciocalteu phenol reagent.	Greenish-yellow precipitate, becomes yellow on heating, and remains so when cooled.
Acid potassium iodate solution.	No reaction.
Reinecke salt solution 4 per cent.	Pink precipitate formed immediately.

Saturated aqueous picric acid solution.	Yellow precipitate, m.pt. 238° to 240°C. Recrystallisation from methanol orange needles but no change in m.pt. (The picrate prepared from hexamethonium bromide had m.pt. 238° to 240°C. when determined in the same bath.)
Saturated aqueous picrolonic acid solution.	Yellow crystals on shaking, m.pt. 241° to 242°C. Recrystallisation from ethanol m.pt. unchanged.
Aqueous gold chloride solution, 10 per cent.	Immediate yellow precipitate, m.pt. 269° to 270°C. Recrystallisation from 50 per cent. aqueous ethanol, m.pt. 270° to 271°C. (decomp.).
Aqueous platinic chloride solution, 10 per cent.	Immediate pinkish-yellow precipitate, m.pt. 300°C. (decomp.).
Mayer's reagent.	Yellow precipitate.
Halogen determination (Volhard method).	99·6 per cent. purity.

Stability of solution. Solutions at concentrations of 1 in 250, 1 in 500, and 1 in 1000 in physiological saline solution were heated at 95° to 100°C. for 30 minutes and kept in sealed tubes for 8 weeks, some in a cool dark place and others exposed to daylight at room temperature. All the solutions remained clear and colourless.

Assay for non-quaternary material. 0·2 g. accurately weighed was added to a separating funnel containing water (200 ml.) followed by saturated sodium bicarbonate solution (5 ml.) and extracted with chloroform (3 × 20 ml.). The combined chloroform extracts were washed with water (10 ml.) filtered through a plug of cotton wool into a tared beaker, and evaporated and dried at 100°C. for 1 hour. Residue on original material, 0·18 per cent.

Hexamethonium Iodide

Hexamethonium iodide is a colourless, odourless crystalline powder which when dried for 1 hour at 100°C./2 mm. pressure and then placed in a melting-point apparatus at 200°C., heated rapidly to 260°C. and then at 2°/minute had m.pt. 277° to 278°C. (corr.). For analysis it was dried at 70°C. *in vacuo*. Found: C, 31·65; H, 6·17; N, 6·15; I, 55·57 per cent.; $C_{12}H_{30}N_2I_2$ requires C, 31·58; H, 6·58; N, 6·14; I, 55·7 per cent.

It is soluble in water (22°C.) 1 g. in 1·8 ml. and at 100°C., 1 g. in 0·3 ml. A 1 per cent. solution is clear and colourless and has *p*H 6·37; a 10 per cent. solution has *p*H 6·24. The sterilised ampouled 0·1 per cent. solution in physiological saline solution has *p*H 534. In ethanol at 20°C. its solubility is 0·3 g. in 1000 ml. and at 78·5°C. 1 g. in 390 ml., whereas in methanol at 22°C. it is 1 g. in 260 ml. and at 64·1°C. 1 g. in 12 ml.

In boiling acetone, benzene, chloroform and ether the solubility is less than 1 g. in 500 ml. At 100°C. the material lost 0·12 per cent. On ignition 0·04 per cent. of ash remained.

Reactions.

Effect of heat.	Solid melts, appears to boil and finally chars. No iodine evolved.
Concentrated sulphuric acid. Cold or hot.	Effervescence. Reddish brown colour changing to dull violet. Violet colour extracted by carbon-tetrachloride to give violet extract.
Concentrated nitric acid. Cold.	Brown colour. Insoluble brown particles. On shaking with carbon tetrachloride violet solution obtained.
Hot.	As cold but solution becomes colourless and iodine sublimed.
Sodium hydroxide solution, 20 per cent.	Immediate white precipitate, which redissolved on heating and reappeared on cooling again.
Aqueous sodium nitrite solution. Cold.	Immediate brown colour. Violet extract in carbon tetrachloride.
0·1N silver nitrate.	Pale yellow precipitate, not soluble in concentrated ammonium hydroxide.
Folin-Ciocalteu phenol reagent.	Green precipitate which remained so on heating.
Acid potassium iodate solution.	Brown precipitate. Completely soluble in carbon tetrachloride to violet solution.
Reinecke salt solution, 4 per cent.	Pink precipitate formed immediately.
Saturated aqueous picric acid solution.	Bright yellow precipitate, m.pt. 239° to 240°C. Recrystallisation from methanol did not change m.pt.
Saturated aqueous picrolonic acid solution.	Yellow crystals on shaking, m.pt. 246° to 247°C. (decomp.).
Aqueous gold chloride solution, 10 per cent.	Dark brown precipitate, m.pt. 242° to 244°C. (decomp.). Recrystallised from 50 per cent. ethanol, m.pt. 248° to 249°C. (decomp.).
Aqueous platinic chloride solution, 10 per cent.	Dark-reddish-brown precipitate, m.p.t. 275°C. (decomp.).
Mayer's reagent.	Pale yellow precipitate.
Halogen determination (Volhard method).	99·7 per cent. purity.

Stability of solution. Solutions at concentrations at 1 in 250, 1 in 500, and 1 in 1000 in physiological saline solution were heated at 95° to 100°C.

for 30 minutes and kept in sealed tubes for 8 weeks, some in a cool dark place and others exposed to daylight at room temperature. All the solutions remained clear and colourless.

Assay for non-quaternary material. 0·2 g. accurately weighed was added to a separating funnel containing water (200 ml.) followed by saturated sodium bicarbonate solution (5 ml.) and extracted with chloroform (3 × 20 ml.). The combined chloroform extracts were washed with water (10 ml.) filtered through a plug of cotton wool into a tared beaker, and evaporated and dried at 100°C. for 1 hour. Residue on original material, 0·03 per cent.

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