

THE PROPERTIES AND REACTIONS OF DECAMETHONIUM IODIDE AND HEXAMETHONIUM BROMIDE

BY I. E. BALABAN, M. B. LEVY AND B. E. WILDE

From the Pharmaceutical Laboratory, The Geigy Company, Ltd., Trafford Park, Manchester, 17

Received May 23, 1949

THE work of Paton and Zaimis¹ on decamethonium iodide ($\alpha:\omega$ -hexamethyldiaminodecane diiodide, known as C.10) showed that it was a very potent substance, and that it was capable of replacing *d*-tubocurarine chloride in medicine. An antidote exists for decamethonium iodide in hexamethonium bromide ($\alpha:\omega$ -hexamethyldiaminohexane dibromide, known as C.6), and owing to its pharmacological properties this substance has been suggested for use in hypertension and vascular diseases, thereby replacing tetraethylammonium iodide. Hexamethonium bromide is 10 to 20 times as active as the tetraethyl compound. In view, therefore, of the possible importance of the new drugs, it was considered desirable that an examination should be made of their physical and chemical properties.

DECAMETHONIUM IODIDE

Decamethonium 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 235°C. and then at 2°/minute, had m.pt. 245° to 246°C. (corr.). If, however, it was put in the bath at 230°C., it melted at once with decomposition. For analysis it was dried at 70°C. *in vacuo*. Found: C, 38.25; H, 7.45; N, 5.14; I, 47.8 per cent.; C₁₆H₃₈N₂I₂ requires C, 37.5; H, 7.4; N, 5.47; I, 49.6 per cent.

It is soluble in water (21°C.) 1 g. in 10 ml. and at 100°C., 5 g. in 1 ml. A 1 per cent. solution is clear and colourless and has pH 6.6; a 10 per cent. solution has pH 6.4. The sterilised ampouled 0.1 per cent. solution in physiological saline solution has pH 6.06. In ethyl alcohol at 20°C., its solubility is less than 1 g. in 100 ml., and at 78.5°C. 1 g. in 3 ml., whereas in methyl alcohol (20°C.) it is 1 g. in 40 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 0.26 per cent. and turned a yellow colour. On ignition no ash remained.

Reactions.

Effect of heat.

The solid melts, appears to boil and finally chars. No iodine evolved.

Concentrated sulphuric acid. Cold or hot.

Effervescence. Red brown colour changing to dull violet. Violet colour extracted by carbon tetrachloride to give violet extract.

Concentrated nitric acid.	
	Cold. Effervescence. Brown colour. Insoluble brown particles. On shaking with carbon tetrachloride violet solution obtained.
	Hot. As cold, but solution became 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.
0.1 N silver nitrate.	Pale yellow precipitate not soluble in strong solution of ammonia.
Folin-Ciocalteu phenol reagent.	Little or no visible change.
Acid potassium iodate solution.	Brown precipitate. Completely soluble in carbon tetrachloride to violet solution. Probably iodine.
Reinecke salt solution, 4 per cent.	Pink precipitate produced at once.
Saturated aqueous picric acid solution.	Bright yellow precipitate, m.pt. 146° to 148°C. Not changed by recrystallisation from methyl alcohol.
Saturated aqueous picronic acid solution.	No immediate precipitate. Slow crystallisation on standing. Dull yellow crystals m.pt. 238 to 239°C.
Aqueous gold chloride solution, 10 per cent.	Immediate brown, precipitate, m.pt. 170°C. Recrystallised from aqueous alcohol, m.pt. 174°C.
Aqueous platinum chloride solution, 10 per cent.	Chocolate-brown precipitate m.pt. 300°C.
Mayer's reagent.	Pale yellow precipitate.
Halogen determination (Volhard method).	98.74 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

DECAMETHONIUM IODIDE AND HEXAMETHONIUM BROMIDE

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 BROMIDE

Hexamethonium bromide is a colourless, odourless, crystalline powder which, when dried for 2 hours at 95°C./20 mm, pressure and placed in a melting-point apparatus at 150°C. or below, heated rapidly to 260°C. and then at 2°/minute, had m.p.t. 272°C. (decomp., corr.). If it was put in the bath above 230°C. it sintered slightly and then had m.pt. 273°C. (decomp.) This salt has a tendency to take up moisture, as shown by the sintering which is observed when its m.pt. is taken some weeks later. For analysis it was dried at 100°C. *in vacuo*. Found: C, 39.9; H, 8.18; N, 7.95; Br, 43.8 per cent.; $C_{12}H_{30}N_2Br_2$ requires C, 39.77; H, 8.28; N, 7.73; Br, 44.21 per cent.

It is soluble in water (21°C.) 1 g. in 1 ml. and at 100°C. 5 g. in 1 ml. A 1 per cent. solution is clear and colourless and has pH 6.56; a 10 per cent. solution has pH 6.0. The sterilised ampouled 1 per cent. solution in physiological saline solution has pH 6.0. In ethyl alcohol at 20°C. its solubility is 1 g. in 30 ml. and at 78.5°C. 1 g. in 3 ml., whereas in methyl alcohol (20°C.) it is 1 g. in 5 ml. and at 64.1°C. 1 g. in 1 ml. It is insoluble in acetone, benzene, chloroform and ether, both hot and cold. At 100°C. the material lost 0.64 per cent. On ignition the ash content was 0.02 per cent.

Reactions.

Effect of heat.	Solid melts and blackens.
Concentrated sulphuric acid.	
Cold.	Light yellow colouration.
Hot.	Very slight colour.
Concentrated nitric acid.	
Cold or Hot.	Deep yellow. Bromine liberated.
Sodium hydroxide solution.	White precipitate which dissolved on heating.
Aqueous sodium nitrite solution, 20 per cent.	Cold. No apparent reaction, very slight yellow colour.
0.1 N. silver nitrate.	Yellow precipitate soluble in concentrated ammonium hydroxide.
Folin-Ciocalteu phenol reagent.	Colour changes to pale yellow after boiling, but on standing in the cold becomes turquoise.
Acid potassium iodate solution.	No reaction—cold or hot.
Reinecke salt solution, 4 per cent.	Pink precipitate formed immediately. The solution on standing did not change.

Saturated aqueous picric acid solution.	Bright yellow precipitate, m.pt. 232° to 234°C. Recrystallisation from methyl alcohol did not change m.pt.
Saturated aqueous picronic acid solution.	No immediate precipitate. Crystallised slowly on standing to give greenish-yellow crystals m.pt. 243°C. (decomp.).
Aqueous gold chloride solution, 10 per cent.	Immediate orange - brown precipitate m.pt. 259°C. (decomp). Recrystallised from 50 per cent. aqueous ethyl alcohol, m.pt. 260°C. (decomp).
Aqueous platinum chloride solution, 10 per cent.	Immediate buff-coloured precipitate m.pt. 300°C.
Mayer's reagent.	Yellow precipitate.
Halogen determination (Volhard method).	99.15 per cent. purity.

Stability of solution. Solutions at concentrations of 1 in 250, 1 in 500 and 1 in 1000 in physiological saline 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, 0.15 per cent.

We are indebted to Mr. F. Ridgway for carrying out some of the determinations.

REFERENCES

1. Paton and Zaimis, *Nature*, 1948, **161**, 718; 1948, **162**, 810.