MICROCHEMICAL IDENTIFICATION OF LOCAL ANÆSTHETIC DRUGS

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During the last fifty years the search for a substitute for cocaine has resulted in the introduction of a number of basic nitrogenous compounds that may conveniently be regarded as synthetic alkaloids. Although these substances are seldom the cause of poisoning except in circumstances where the toxic agent is beyond doubt, their identification is a matter of some importance. Like the plant alkaloids, they may be extracted from viscera by the Stas-Otto process, and yield crystalline precipitates with many of the alkaloidal reagents. Unless they can be identified with complete certainty, considerable confusion may be caused through traces of one of these substances, possibly of therapeutic origin, being mistaken for one of the more toxic vegetable bases.

The reactions of procaine, one of the first of these drugs to come into general use, have been studied in detail by Fulton[1], while tests for a number of the others have been described by Fischer[2], Offerhaus and Baert[3,4,5], Wagenaar[6], Whitmore and Wood[7], Sabon and Grignon[8], Hucknall and Turfitt[9] and Bamford[10]. Some of these tests require milligram quantities of material, while others entail special procedures. The work to be described was undertaken not only to investigate the reactions of some of the newer local anæsthetics, but also to provide a technique, based on normal alkaloidal tests, for identifying these drugs when present in μg. quantities.

Experimental Procedure

Microcrystalline tests

The hanging-microdrop technique described by Clarke and Williams[11] was used. In addition to the reagents there described, a saturated aqueous solution of trinitrobenzoic acid was employed.

The results obtained for 21 drugs are given in Table I. Owing to the importance of distinguishing between these drugs and the plant alkaloids all crystalline precipitates, not merely the most distinctive, have been recorded. Thus it is usually considered that the formation of plates with zinc chloride solution is a specific test for papaverine, whereas the Table shows that crystals very similar in shape are also formed with butacaine.

The descriptions given in the Table are intended to serve as a rough guide only. Final identification depends upon comparing the crystals formed from the test material with those formed from a known sample of the drug.

Colour tests

These are of less value than the crystal tests. Neither sulphuric acid alone nor sulphuric acid in combination with formaldehyde, ammonium

TABLE I

MICROCRYSTALLINE TESTS

Reagent	Crystals	Sensitivity in μg.
Amethocaine		
Gold bromide	Fine irregular crystals	0·025
Gold bromide hydrochloric acid	Plates and feathery needles	0·025
Lead iodide	Clusters of small plates	0·05
Mercuric chloride	Small oily crystals	1·0
Picric acid	Rosettes of fine needles	1·0
Potassium chromate	Sheaves of long needles	0·05
Potassium iodide	Needles and blades in rosettes	0·05
Trinitrobenzoic acid	Yellow rods and plates	0·25
Amydricaine		
Gold bromide	Irregular blades	0·25
Gold bromide hydrochloric acid	Bunches of irregular crystals	0·05
Gold chloride	Tufts of curved needles	0·1
Lead iodide	Serrated needles	0·05
Picric acid	Branching needles	0·05
Potassium bismuth iodide	Irregular blades and needles	0·025
Potassium chromate	Yellow plates	0·5
Potassium iodide	Small needles	0·25
Potassium permanganate	Needles and serrated plates	1·0
Potassium tri-iodide (1)	Blades and plates	0·025
Potassium tri-iodide (3)	Serrated yellow blades	1·0
Amylocaine		
Gold bromide	Long thin needles	0·05
Gold bromide hydrochloric acid	Long thin needles	0·05
Gold chloride	Serrated plates	0·05
Lead iodide	Rosettes of rods	0·1
Picric acid	Bunches of thin rods	0·05
Benzamine		
Picric acid	Clusters of plates and rods	0·05
Potassium iodide	Rosettes of rods	0·5
Trinitrobenzoic acid	Hedgehogs	0·25
Benzocaine		
Gold bromide	Dendrites and rosettes (ON)	0·05
Gold bromide hydrochloric acid	Dendrites and rosettes (ON)	0·05
Lead iodide	Short rods	0·1
Mercuric chloride	Long rods	0·1
Picric acid	Dendrites	0·05
Platinum chloride	Needles from edge	0·5
Platinum iodide	Branching rods	0·25
Potassium bismuth iodide	Rosettes of branching rods	0·25
Potassium chromate	Small rods	0·25
Potassium tri-iodide (1)	Yellow rhomboids	0·5
Sodium carbonate	Short rods	0·25
Sodium phosphate	Rosettes of rods	0·25
Butacaine		
Gold bromide hydrochloric acid	Very small needles and plates	0·025
Picric acid	Branching rods	1·0
Potassium chromate	Serrated rods and needles	0·1
Potassium iodide	Small rods in bunches	0·05
Zinc chloride	Plates	1·0
Butyl Aminobenzoate		
Gold bromide	Small blades in stars	0·1
Lead iodide	Long plates	0·1
Picric acid	Tufts of needles	0·25
Platinum chloride	Needles	0·1
Platinum iodide	Dark needles	0·1
Potassium tri-iodide (1)	Dark rods	0·5
Potassium tri-iodide (3)	Long red plates	0·5
Sodium carbonate	Long plates	0·05
Sodium phosphate	Long plates	0·5
Trinitrobenzoic acid	Long needles	1·0
Cinchocaine		
Gold bromide	Bunches of small rods (2 days)	0·25
Gold bromide hydrochloric acid	Irregular plates and needles	0·025
Gold chloride	Dense rosettes	1·0
Lead iodide	Dense rosettes	0·1
Mercuric chloride	Dense rosettes	0·1
Platinum chloride	Stout needles	1·0
Potassium bismuth iodide	Needles	0·25

TABLE I—*continued.*

Reagent	Crystals	Sensitivity in μg.
Cinchocaine (contd.)		
Potassium tri-iodide (1)	Branching needles	0·5
Potassium tri-iodide (3)	Branching needles	1·0
Sodium carbonate	Bunches of rods	0·25
Trinitrobenzoic acid	Small rosettes of needles	0·1
iso*Butyl Aminobenzoate*		
Gold bromide	Yellow blades	1·0
Platinum chloride	Tufts of fine needles	0·5
Platinum iodide	Rosettes	0·1
Potassium chromate	Plates	0·5
Sodium carbonate	Segmented rods	0·25
Sodium phosphate	Segmented rods	0·25
Trinitrobenzoic acid	Long needles	1·0
Larocaine		
Gold bromide	Bunches of serrated plates	0·025
Gold bromide hydrochloric acid	Bunches of plates	0·025
Lead iodide	Rosettes	0·25
Platinum chloride	Shell-like rosettes (2 days)	1·0
Platinum iodide	Rosettes of branching needles	0·1
Potassium mercuric iodide	Serrated rods	0·25
Lignocaine		
Gold bromide	Serrated needles	0·05
Gold bromide hydrochloric acid	Serrated needles	0·25
Gold chloride	Yellow plates	0·5
Lead iodide	Long branching needles	0·25
Picric acid	Yellow plates and rods	0·1
Platinum iodide	Small plates	0·1
Potassium cadmium iodide	Serrated blades	0·1
Potassium mercuric iodide	Bunches of irregular rods	0·1
Potassium permanganate	Mass of needles	0·05
Potassium tri-iodide (1)	Yellow hexagonal crystals	0·05
Monocaine		
Gold bromide	Needles and serrated plates	0·025
Gold bromide hydrochloric acid	Long needles	0·1
Picric acid	Rosettes of plates	0·1
Potassium iodide	Prisms	0·5
Potassium tri-iodide (3)	Prisms	0·5
Orthocaine		
Gold bromide	Small plates	
Gold bromide hydrochloric acid	Small plates	0·5
Mercuric chloride	Rosettes of rods	0·1
Picric acid	Curved needles	0·05
Trinitrobenzoic acid	Long prisms	0·25
		1·0
Panthesine		
Gold bromide	Serrated plates (2 days)	0·5
Gold bromide hydrochloric acid	Dense rosettes (2 days)	0·1
Sodium carbonate	Branching needles	0·25
Trinitrobenzoic acid	Hedgehogs	0·5
Piperocaine		
Gold chloride	Irregular plates	0·1
Lead iodide	Small irregular needles	0·05
Picric acid	Rosettes of blades	0·025
Trinitrobenzoic acid	Rosettes of needles	0·25
Procainamide		
Gold bromide hydrochloric acid	Rosettes of plates	0·5
Platinum chloride	Rosettes of pointed plates	0·5
Potassium bismuth iodide	Rhomboidal plates	0·025
Trinitrobenzoic acid	Fans of plates	1·0
Procaine		
Gold bromide	Plates and needles	0·05
Gold bromide hydrochloric acid	Needles and plates	0·25
Mercuric chloride	Overlapping prisms	0·5
Platinum chloride	Plates or rosettes	0·25
Platinum iodide	Bunches of prisms	0·05
Potassium tri-iodide (1)	Rosettes of rods	0·25
Ravocaine		
Gold bromide hydrochloric acid	Bunches of small serrated plates	0·1
Platinum chloride	Bunches of blades, some dense rosettes	0·25

TABLE I—*continued*

Reagent	Crystals	Sensitivity in μg.
Tropacocaine		
Gold bromide	Bunches of serrated needles	0·025
Gold bromide hydrochloric acid	Bunches of serrated needles	0·025
Gold chloride	Bunches of serrated needles	0·025
Lead iodide	Plates and rods	0·025
Mercuric chloride	Segmented rods and plates	0·05
Picric acid	Feathery rosettes	0·025
Platinum chloride	Serrated needles	0·025
Platinum iodide	Curved needles	0·5
Potassium bismuth iodide	Branching needles	0·025
Potassium cadmium iodide	Rosettes of feathery needles	0·025
Potassium chromate	Serrated plates	0·5
Potassium iodide	Long plates	0·05
Potassium permanganate	Irregular plates	0·025
Potassium mercury iodide	Plates and rods	0·025
Potassium tri-iodide (1)	Plates	0·025
Potassium tri-iodide (3)	Plates	0·5
Trinitrobenzoic acid	Rosette of needles	0·25
Tutocaine		
Gold bromide	Rosettes	1·0
Gold bromide hydrochloric acid	Dendrites and irregular rods	0·25
Unacaine		
Gold bromide	Dense rosettes	0·5
Platinum iodide	Rosettes of branching needles	0·1

ON (overnight) indicates that the crystals do not usually form until the following day.

vanadate, ammonium molybdate or selenium dioxide gives any colours that are of use for the identification of μg. quantities of these drugs. Three tests, however, while not specific, are of some value. These are: (*a*) The diazo reaction. Many of these drugs contain a primary arylamino group, and may be diazotised and coupled with β-naphthol to give red dyes[12]. On the microscale, this test is carried out as follows: A microdrop (0·1 μl.) of the test solution is placed on a piece of opal glass.

TABLE II

VITALI'S TEST

Substance	Colour with nitric acid	Colour of residue after heating	Colour with potassium hydroxide
Amethocaine	Yellow	Yellow	Pink–purple
Benzocaine	—	"	Orange
Butacaine	—	"	"
Butyl aminobenzoate	—	Yellow brown	Yellow
*iso*Butyl aminobenzoate	—	"	"
Larocaine	—	Yellow	"
Monocaine	—	"	"
Orthocaine	Black	Red brown	Dark brown
Panthesine	—	Yellow	Orange
Procainamide	—	Light brown	Yellow brown
Procaine	—	Yellow	Orange
Ravocaine	Red orange	Brown	Brown
Tutocaine	—	Light brown	Yellow
Unacaine	—	Yellow	"

Microdrops of N hydrochloric acid, of 1 per cent. sodium nitrite solution and of a 4 per cent. solution of β-naphthol in 2 N sodium hydroxide solution are added in that order. Bright red colours are given by benzocaine, butacaine, butyl aminobenzoate, *iso*butyl aminobenzoate, larocaine, monocaine, orthocaine, panthesine, procaine, procainamide, ravocaine, tutocaine and unacaine. With orthocaine the drop slowly becomes plum coloured. The limit of the reaction is about 0·1 μg. (*b*) Paradimethylaminobenzaldehyde. The reagent is made by adding

20 drops of concentrated sulphuric acid to a solution of 1 g. of the substance in 100 ml. of ethanol[10]. A microdrop of the test solution is evaporated to dryness on opal glass, and a microdrop of reagent added. A bright yellow colour is given by benzocaine, butacaine, butyl aminobenzoate, *iso*butyl aminobenzoate, larocaine, monocaine, orthocaine, panthesine, procaine, procainamide, ravocaine, tutocaine and unacaine, the limit of the reaction being about 0·025 μg. Amethocaine and amylocaine give a pale yellow colour, but with these substances the sensitivity of the test is considerably less, being near 0·5 μg. (*c*) Vitali's test. This is carried out by the micromethod described by Clarke and Williams[11]. The results obtained are given in Table II. The sensitivity is about 0·1 μg.

Discussion

Whereas each of the substances tested yields a number of microcrystalline derivatives, several of them give no colour reactions at all. It follows that identification must be established by means of the former test, the latter being of value for confirmatory purposes. As most of the microcrystalline tests are very delicate no difficulty should be experienced in identifying a few μg. of one of these substances. This high sensitivity is desirable owing to the fact that many of these drugs are rapidly hydrolysed and excreted by the body, so that the quantity of unchanged substance likely to be isolated from cadaveric material is extremely small.

The results described in this paper were obtained using pure substances. A technique for extracting and purifying μg. quantities of these and other basic nitrogenous drugs will be described in a subsequent paper.

Summary

Crystal and colour tests are described for the identification of μg. quantities of 21 local anæsthetic drugs.

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