MICROCHEMICAL IDENTIFICATION OF SOME ATROPINE-LIKE DRUGS

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Crystal and colour tests are described for 48 atropine-like drugs.

Few plant alkaloids are used for such a wide variety of purposes as atropine, serving as it does as a mydriatic, a spasmolytic, or an anti-secretogogue. In some ways this is a disadvantage, as it is the cause of unpleasant side effects, and for this reason a search has been made for drugs that are more restricted in their action. None of the available substitutes for atropine is entirely specific although in many of them one effect is predominant. Different substances have therefore been developed for use either as mydriatics, or as spasmolytics, while similar substances have found more specialised uses as antitussives, tranquillisers, or hypotensive agents, or for the treatment of Parkinson's disease.

These substances all contain basic nitrogen, many of them being quarternary ammonium compounds. The first to come into use were synthetic tropeines such as homatropine. Subsequently it was found that many simpler substances had similar anti-acetylcholine properties. The majority of these compounds are esters formed by the combination of an amino alcohol with a substituted acetic acid, but the ester linkage is not essential, and both amines and amides with atropine-like properties are known.

It is the purpose of this paper to describe tests for microgram quantities of 48 of these compounds. As it is difficult to discern any clear connection between chemical structure and pharmacological activity, no attempt has been made to classify them under either of these headings. For the sake of convenience, atropine, hyoscyamine, hyoscine and homatropine have been included here, although tests for these alkaloids have been published previously[1].

Experimental Procedure

Crystal Tests

The hanging microdrop technique developed by Clarke and Williams[1] was employed. All substances were dissolved in 1 per cent acetic acid with the exception of butylhyoscine bromide which was dissolved in a mixture of 1 volume of 5N HCl with 2 volumes of ethanol.

The results obtained are given in Table I. Usually two tests are given for each substance, but where there is difficulty in distinguishing between two closely related drugs three tests have been recorded. For some, only a single test could be found, and for three compounds no crystal tests at all. These substances must therefore be identified by their colour reactions.

TABLE I

Substance	Reagent	Crystals	Sensitivity μg.
Adiphenine HCl (Trasentin, 2-diethylaminoethyl diphenylacetate)	— —	— —	— —
Aminopentamide sulphate (Centrine, γ-dimethylamino-αα-diphenylvaleramide)	Potassium tri-iodide 3 Sodium carbonate Platinum bromide	Small plates or needles Oily needles or fans of rods Rosettes of rods	0·05 0·1 0·25
Amolanone HCl (Amethone, γ-diethylamino-*a*-*o*-hydroxyphenyl-*a*-phenylbutyrolactone)	Gold bromide/HCl Gold chloride	Plates and blades O/N Serrated plates	0·1 0·1
Amprotropine dihydrogen phosphate (Syntropan, 3-diethylamino-2,2-dimethylpropyl (±)-tropate)	Lead iodide	*Hexagonal plates	1·0
*apo*Atropine HCl (Atropyltropine)	Platinum chloride Potassium chromate Potassium tri-iodide 2	Small blades and plates often cruciform and serrated Plates, some serrated Shell-like crystals	0·1 0·5 0·25
Atropine acetate	Picric acid Potassium tri-iodide 3	Bunches of plates Rhomboids and wedge-shaped crystals	0·25 0·025
Atropine methonitrate Q (Eumydrin, methylatropine)	Gold chloride Mercuric chloride	Leaflike plates (P) Plates and prisms	0·025 0·1
Atropine-N-oxide HCl Q (Genatropine)	Platinum iodide Potassium bismuth iodide	Rectangular plates, often transparent Rectangular plates	0·025 0·025
Benactyzine HCl (Cafron, Suavital, α-ethylamino-ethyl-benzilate)	—	—	—
Benzhexol HCl (Artane, Pipanol, 1-cyclohexyl-1-phenyl-3-piperidino-1-propanol)	Potassium permanganate Sodium carbonate Gold cyanide	Curved irregular plates Needles, often curving Bunches of plates	0·1 0·1 0·05
Benztropine methanesulphonate (Cogentin, 3-(diphenylmethoxy) tropane)	Potassium chromate Potassium iodide Ammonium thiocyanate	Long plates or blades Fine dendrites Small plates	0·1 0·25 0·25
Caramiphen HCl (Parpanit, 2-diethylaminoethyl-1-phenylcyclopentane-1-carboxylate)	Lead iodide Platinum chloride	Rosettes of branching needles Rhomboidal plates	0·1 0·25
Convenil citrate (Phenesin, phenyl ethylacetic acid β-diethylaminoethyl ester)	Lead iodide	Branching needles, often in rosettes	0·1
Cyclopentolate HCl (Cyclogyl, 2-dimethylaminoethyl-(1-hydroxycyclopentyl)-phenylacetate)	Gold bromide/HCl Platinum chloride	Starlike rosettes Plates or prisms	0·05 0·5
Cycrimine HCl (Pagitane, 1-cyclopentyl-1-phenyl-3-piperidinopropan-1-ol)	Potassium iodide Sodium carbonate Picrolonic acid	Rosettes of rods Masses of rods Branching needles O/N	1·0 0·05 0·25
Dibutoline sulphate Q (Dibuline, (2-dibutylcarbamoyloxyethyl) ethyldimethylammonium)	Gold bromide Mercuric chloride Lead iodide	Masses of small plates (P) Small plates O/N Bunches of blades or needles	0·25 0·05 0·1

Q Quaternary bases.
O/N Overnight.
(P) Best seen under polarised light.
* Crystals form very slowly, and may fail to appear.
† Dilute solutions only.
‡ Concentrated solutions only.

TABLE I—*continued*

Dicyclomine HCl (Merbentyl, 2-diethylaminoethyl-dicyclohexyl-1-carboxylate)	Potassium iodide Trinitrobenzoic acid	Branching needles Rosettes of plates	0·5 0·5
Diphemanil methylsulphate^{Q} (Diphenatil, Prantal, 4-diphenyl-methylene-1 : 1-dimethylpiperidinium)	Mercuric chloride Potassium chromate Zinc chloride	Rhomboids Needles or long plates Rosettes of rods	0·1 0·1 0·1
Dipropyline citrate (Profenil, ethyldi-(3-phenylpropyl) amine)	Gold bromide/HCl Lead iodide	Thin transparent plates$^{O/N}$ †Oily rosettes or irregular crystals	0·25 0·025
Eucatropine HCl (4-mandeloyloxy-1,2,2,6-tetramethyl piperidine	Gold bromide Potassium tri-iodide 3	Bunches of curved plates Elongated plates	0·025 0·25
Hexahydroadiphenine HCl (Trasentin 6H, 2-diethylaminoethyl cyclohexylphenylacetate)	Picrolonic acid	Fine branching needles	0·1
Hexocyclium methylsulphate^{Q} (Tral, 1-(2-cyclohexyl-2-hydroxy-phenethyl-4 : 4-dimethyl-piperazinium)	Platinum chloride Ammonium thiocyanate	Snowflake rosettes Bunches of rods	0·1 1·0
Homatropine HCl	Gold chloride Potassium bismuth iodide Potassium tri-iodide 3	Plates and prisms Bunches of plates$^{O/N}$ Plates, some serrated	0·0 5 0·05 0·05
Homatropine methobromide^{Q} (Novatropine, methyl homatropinium)	Gold chloride Potassium permanganate Potassium tri-iodide 1	Small needles, often in crosses or snowflakes Long plates Long plates	0·025 0·1 0·05
Hyoscine HBr (Scopolamine, (−)-hyoscine)	Gold bromide/HCl Potassium bismuth iodide	Curving plates Rosettes of plates	0·25 0·05
Hyoscine butobromide^{Q} (Buscopan, Scopolamine-N-butyl bromide)	Potassium tri-iodide 2 Di-sodium phosphate	Bundles of rods Masses of rods	0·25 0·25
Hyoscine methonitrate^{Q} (Skopyl, methoscopolamine)	Gold bromide/HCl Mercuric chloride Picric acid	Plates often in bunches Plates sometimes in rosettes Dense rosettes$^{O/N}$	0·05 0·05 0·25
Hyoscine-N-oxide HBr^{Q} (Genoscopolamine, scopolamine-*N*-oxide)	Potassium permanganate Potassium iodide	Rods or irregular rosettes Rods	0·25 0·25
Hyoscyamine HCl ((−)-hyoscyamine)	Gold bromide/HCl Picric acid Potassium tri-iodide 3	Long plates or needles$^{O, N}$ Rosettes of plates or needles Small plates	0·25 0·25 0·025
Lachesine HCl^{Q} ((2-benziloyl oxyethyl) ethyldimethyl ammonium)	Gold bromide/HCl Gold chloride Lead iodide	Irregular rods and needles Rods and needles Small needles in dense bundles	0·025 0·025 0·025
Mepiperphenidol HBr^{Q} (Darstine, 1-(3-hydroxy-5-methyl-4-phenyl-hexyl-1-methylpiperidinium)	Platinum chloride	‡Bunches of long plates	5·0
Methanthelinium metho bromide^{Q} (Banthine, 2-diethylaminoethyl xanthen-9-carboxylate)	Lead iodide Zinc chloride	Bunches of plates$^{O/N}$ Coarse needles	0·25 1·0

TABLE I—*continued*

Substance	Reagent	Crystals	Sensitivity μg.
Octaverine HCl (Spascol, 1-(3,4,5-triethoxyphenyl)-6,7-dimethoxy isoquinoline)	Potassium chromate Sodium carbonate Platinum bromide	Small needles in bundles Plates, mostly rhomboids Bunches of small needles	0·1 0·1 0·1
Oxeladin citrate (Pectamol, 2-(2-diethylaminoethoxy)ethyl diethylphenylacetate)	Lead iodide	Sheaves of fine needles	0·1
Oxyphenonium bromideQ (Antrenyl, 2-diethylaminoethyl α-cyclohexyl-α-phenylglycollate methobromide)	Gold bromide/HCl Gold chloride	Bunches of plates, often serrated Masses of needles and serrated plates	0·025 0·025
Pavatrine HCl (2-diethylaminoethyl-9-fluorene carboxylate)	—	—	—
Penthienate bromideQ (Monodral, 2-diethylaminoethyl-α-cyclopentyl 2-thiopheneglycollate methobromide)	Lead iodide	‡Oily plates (P)	5·0
Pentoxyverine citrate (Carbetapentane, Toclase, 2-(2-diethylaminoethoxy) ethyl-1-phenylcyclopentyl-1-carboxylate)	Lead iodide	Network of hairlike crystals	0·05
Phenactropinium HClQ (Trophenium, N-phenacyl homatropinium)	Potassium iodide Ammonium thiocyanate	Rosettes of elongated plates Dense rosettes	1·0 0·5
Phenglutarimide HCl (Aturbane, 3-phenyl-3-(β-diethylaminoethyl)-2-6-dioxy piperidine)	Platinum iodide	Dense rosettes or hair-like crystals	1·0
Piperidolate HCl (Dactil, 1-ethyl-3-piperidyl diphenylacetate)	Lead iodide	Rosettes of plates	0·25
Pipenzolate methobromideQ (Piptal, N-ethyl-3-piperidyl benzilate)	Lead iodide Platinum chloride	Oily rosettes Oily rosettes	1·0 1·0
Poldine methosulphateQ (Nacton, 2-benziloyloxymethyl-1-methylpyrrolidine)	Gold bromide/HCl Gold chloride Lead iodide	Masses of small blades and plates Masses of blades Small feathery rosettes or sheaves of plates	0·05 0·1 0·1
Procyclidine HCl (Kemadrin, 1-cyclohexyl-1-phenyl-3-pyrolidinopropan-1-ol)	Sodium carbonate Picrolonic acid	Curving needles Clusters of branching needles and oily plates(P)	0·1 0·1
Propantheline bromideQ (Probanthine, 2-di-isopropylaminoethyl xanthen-9-carboxylate methobromide)	Lead iodide Potassium iodide Potassium tri-iodide 1	Small dense rosettesO/N Prisms Small oily plates O/N (P)	0·25 1·0 0·25
Spasmadryl HCl (Diethylaminoethyl-α-β-diphenylpropionate)	Lead iodide Picrolonic acid	Small rosettes and masses of rods Oily rods or plates O/N	0·1 0·1
Tricyclamol HClQ (Lergine, Elorine, (±)-1-(3-cyclohexyl-3-hydroxy-3-phenylpropyl)-1-methylpyrrolidinium)	Potassium chromate Platinum bromide	Small oily rods, sometimes in rosettes Rosettes or sheaves of needles	0·05 0·25
Tridihexethyl iodideQ (Pathilon, Triethyl (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-ammonium)	Potassium chromate	Hedgehogs or rosettes of fine needles	1·0

TABLE II

Substance	Result	Sensitivity μg.
Formaldehyde-sulphuric acid test (Marquis)		
Benactyzine	Orange–green–blue	0·1
Benzhexol	Faint purple	1·0
Benztropine	Yellow	0·025
Caramiphen	Yellow	1·0
Convenil	Faint orange, fading	1·0
Cycrimine	Dull red	1·0
Dibutoline	Red	1·0
Diphemanil	Orange-red	0·1
Dipropyline	Red	0·25
Hexahydroadiphenine	Orange, fading	1·0
Hexocycline	Dull purple	1·0
Lachesine	Orange–green–blue	0·025
Mepiperphenidol bromide	Dull purple–brown	0·25
Methantheline bromide	Blue	0·25
Octaverine	Green-brown	0·1
Oxeladin	Orange	0·5
Pavatrine	Green, fading	0·25
Penthienate bromide	Blue-green–brown	0·25
Pentoxyverine	Slowly orange	1·0
Piperidolate	Faint orange	1·0
Pipenzolate bromide	Orange–green	0·1
Poldine	Orange–green–blue	0·25
Procyclidine	Faint purple	1·0
Propantheline bromide	Green–yellow	0·5
Spasmadryl	Faint orange, fading	1·0
Tricyclamol	Dull purple	1·0
Tridihexethyl iodide	Brown–black-violet–brown	0·5
Ammonium vanadate test		
Adiphenine	Green–blue	0·1
Benactyzine	Orange–olive-brown	0·05
Benzhexol	Dull green	0·25
Benztropine	Yellow	0·1
Cyclopentolate	Brown	0·5
Cycrimine	Red-brown	0·25
Diphemanil	Brown–blue	0·25
Dipropyline	Grey-green	0·25
Hexahydroadiphenine	Faint green	1·0
Hexocycline	Blue-grey	0·25
Lachesine	Orange–olive	0·05
Methantheline bromide	Orange	0·1
Octaverine	Red-brown	0·1
Pavatrine	Brown*	0·1
Penthienate bromide	Purple	0·1
Pentoxyverine	Brown slowly	1·0
Piperidolate	Olive	1·0
Pipenzolate bromide	Orange–green	0·05
Poldine	Orange–green–dull purple	0·05
Procyclidine	Grey-black	0·25
Propantheline bromide	Orange	0·05
Tricyclamol	Grey-purple	0·25
Tridihexethyl iodide	Brown–black-violet	0·5
Ammonium molybdate test		
Amprotropine	Blue	1·0
Benactyzine	Orange–olive-brown	0·25
Benzhexol	Blue-grey	1·0
Benztropine	Yellow	0·025
Cyclopentolate	Blue	1·0
Cycrimine	Brown	0·5
Dibutoline	Faint blue-grey	1·0
Diphemanil	Yellow–green–blue	0·25
Hexocycline	Dull purple	1·0
Homatropine methyl bromide	Orange–blue	0·5
Hyoscine-N-oxide bromide	Blue-green	0·5
Lachesine	Orange–green–blue	0·05

* Green may be seen first.
† Green does not always appear.
‡ Orange forms before the addition of sulphuric acid.

TABLE II—*continued*

Substance	Result	Sensitivity μg.
Ammonium molybdate test—contd.		
Mepiperphenidol bromide	Blue-grey	0·25
Methantheline bromide	Green	0·05
Octaverine	Green	0·1
Oxeladin	Faint blue	1·0
Oxyphenonium bromide	Green	1·0
Pavatrine	Green†	0·1
Penthienate bromide	Purple	0·1
Pipenzolate bromide	Orange–green	0·05
Poldine	Orange–blue	0·05
Procyclidine	Blue-grey	0·5
Propantheline bromide	Green–yellow	0·05
Tricyclamol	Grey	1·0
Tridihexethyl iodide	Green†–blue-grey	0·5
Selenium dioxide test		
Benactyzine	Orange–olive-brown	0·25
Benzhexol	Brown	0·25
Benztropine	Yellow	0·1
Caramiphen	Pale yellow	1·0
Cyclopentolate	Brown	0·5
Cycrimine	Brown	0·5
Dicyclomine	Faint orange	1·0
Diphemanil	Green–grey	0·5
Hexocycline	Brown	0·5
Homatropine methyl bromide	Yellow	0·5
Lachesine	Orange–yellow	0·05
Mepiperphenidol bromide	Faint brown	1·0
Methantheline bromide	Orange	0·5
Octaverine	Green	1·0
Oxyphenonium bromide	Light brown–orange	0·25
Pavatrine	Brown	1·0
Penthienate bromide	Purple-brown	0·05
Pipenzolate bromide	Orange–green	0·25
Poldine	Orange, fading	0·05
Procyclidine	Brown	0·5
Propantheline bromide	Orange	0·25
Tricyclamol	Brown	0·5
Tridihexethyl iodide	(Orange)‡ brown	0·5
Vitali's test		
Adiphenine	—/—/Intense blue-violet	0·025
Amolanone	—/Pale brown/bright yellow	0·25
*apo*Atropine	—/—/Violet	0·1
Atropine	—/—/Violet	0·025
Atropine methonitrate	—/—/Violet	0·025
Atropine-N-oxide	—/—/Violet	0·025
Convenil	—/—/Purple	0·5
Cyclopentolate	—/—/Violet	0·05
Cycrimine	—/Brown/brown	1·0
Dibutoline	—/—/Faint yellow	1·0
Diphemanil	—/—/Black-purple	0·1
Hexahydroadiphenine	—/—/Brown	0·25
Hyoscine	—/—/Violet	0·025
Hyoscine methonitrate	—/—/Violet	0·025
Hyoscine-N-oxide bromide	—/—/Violet	0·025
Hyoscyamine	—/—/Violet	0·025
Methantheline bromide	Faint yellow/—/green	0·5
Octaverine	Red-brown/brown/red-orange	0·1
Pavatrine	Yellow/brown/dull green	0·25
Penthienate bromide	Brown/brown/red-brown	1·0
Piperidolate	—/—/Blue	0·05
Propantheline bromide	Yellow/—/green	0·5
Spasmadryl	—/—/Purple	0·05
Tridihexethyl iodide	Violet, fading/—/—	1·0

Colour Tests

These are made with microdrops on opal glass as described previously[1]. The results obtained are given in Table II and discussed below.

Two further colour reactions may be employed. With the microdiazo test[2], amolanone gives a bright purple colour when coupled with diazotised *p*-nitroaniline, while phenactropinium gives a brown purple, quickly changing to reddish brown. With the paraformaldehyde/phosphoric acid reagent[3] introduced for the identification of solanine, penthienate gives a bright mauve colour, while methantheline and propantheline give a pale orange. It should be noted that the yellow colour originally described[3] as being given by octaverine with the paraformaldehyde/phosphoric acid reagent has been found to be caused by dihydro-octaverine present as an impurity.

Discussion

Microchemical tests for alkaloids and synthetic bases must serve to identify not only the pure substance, but also the same substance extracted from organic material. In the former the base will be combined with some particular acid, while in the latter it will be present as the free base or combined with some acid of the analyst's choice. It is not always realised that colour tests, and occasionally crystal tests, may be modified by the nature of the acid radical present. The outstanding example of this among the compounds dealt with in this paper is tridihexethyl iodide. Here the intense colour of the iodine liberated by the addition of concentrated sulphuric acid masks any colour due to the base. In some of the bromides the liberated hydrobromic acid, which on its own gives a green colour changing to blue with the ammonium molybdate/sulphuric acid reagent, may modify any colour caused by the alkaloid itself.

The tests given in Table II are for the actual drugs containing the acid radicals given in Table I. Investigation of the colours caused by the alkaloid alone was made by treating a solution of the drugs with silver nitrate solution, and removing excess silver with sodium chloride. The precipitated silver halides were filtered off, and tests made on the filtrate. The following differences were noted. Tridihexethyl gave a faint dull purple with all the sulphuric acid reagents, and no colour with Vitali's test. Methyl homatropine and oxyphenonium gave no colours. Mepiperphenidol gave a yellow colour with the Marquis reagent, and no colour with the other reagents. With pipenzolate there was no change in the colours observed, and with methantheline, propantheline and penthienate the only difference was with the Marquis reagent, where the first two substances gave an orange colour, and the last-named a purple. Hyoscine-*N*-oxide gave the same colour (violet) with Vitali's test, but no colour with the ammonium molybdate-sulphuric acid reagent.

The crystal tests described in Table I are not affected by the nature of the acid radical present.

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