

# MICROCHEMICAL IDENTIFICATION OF SOME ANTIHISTAMINE DRUGS

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Crystal and colour tests are described for 50 antihistamine drugs.

SINCE the discovery<sup>1</sup> some 20 years ago that certain substituted alkylene diamines and alkamine ethers were able to antagonise the effects of histamine *in vivo*, many hundreds of substances have been tested for antihistamine activity. Of these about 50 have come into clinical use.

Chemically these antihistamine drugs are all basic nitrogenous substances. In general the free bases are soluble in chloroform, and the salts soluble in water or alcohol. They can thus be extracted from viscera by the Stas-Otto process, and since they give crystal and colour tests similar to those given by natural alkaloids, their absolute identification is a matter of some importance.

Tests for a number of these substances have been described by Auerhoff<sup>2-4</sup>, Haley and Keenan<sup>5,6</sup>, Osol and Sideri<sup>7</sup>, and Eijkel, Hofstra and Nauta<sup>8</sup>. It is the purpose of this paper to describe crystal and colour tests for  $\mu\text{g}$ . quantities of 50 of these compounds. Because of their similarity in chemical structure, certain substances such as chlorpromazine and ethopropazine, which are not normally used as histamine antagonists, have been included.

## EXPERIMENTAL PROCEDURE

### *Microcrystalline Tests*

The hanging microdrop technique described by Clarke and Williams<sup>9</sup> was used. Increased experience with this method has shown that, unless speed is a primary consideration, the pedestal slide originally described is not necessary. The cover slip may be mounted directly on an ordinary cavity slide; evaporation takes place slowly by diffusion through the gum, crystals forming usually within 24 hours. When non-aqueous solvents are used, it is advisable to add the microdrop of the test material to the microdrop of the reagent in order to avoid spreading.

Solutions were made in 1 per cent HCl with the following exceptions: Histaphene and Alfadryl were dissolved in water; phenindamine, Pacatal and Hystryl in 1 per cent acetic acid; Kolton, diethazine and pyrrobutamine in ethanol; and meclozine, buclizine and prochlorperazine in glacial acetic acid. Incidal proved too insoluble in the ordinary reagents to give satisfactory tests. It was therefore treated as follows: 50 mg. of the substance was triturated with 2 ml. of 2N sodium hydroxide solution for several minutes. Anhydrous sodium sulphate 5 g. was then added, and the whole extracted with 25 ml. of chloroform. After filtration the chloroform was evaporated, and the residue dissolved in 2N acetic acid.

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TABLE I

Substance	Reagent†	Crystals	Sensitivity µg.
Alfadryl ( $\alpha$ -methylbenzhydryl $\beta$ -dimethylaminoethyl ether HCl)	Lead iodide Potassium tri-iodide (3)	Branching rods Rods and irregular plates	0-1 0-1
Allercur (1- <i>p</i> -chlorobenzyl-2-pyrrolidinomethyl-benzimidazole HCl)	Zinc chloride Potassium cyanide	Rosettes or fans of needles Plates	0-1 0-5
Ambodryl (Bromazine, 2-dimethylaminoethyl <i>p</i> -bromo benzhydryl ether HCl)	Gold chloride Lead iodide	Plates and rods Plates, sometimes in small rosettes	0-1 0-1
Antadryl (2-imidazolylmethyl benzhydryl ether HCl)	Lead iodide Picric acid	Branching rods Curved or serrated needles	0-1 0-1
Antazoline (Antistin, 2-( <i>N</i> -benzyl- <i>N</i> -phenylaminoethyl) imidazole line HCl)	Sodium carbonate Potassium cyanide	Needles Needles and rods	1-0 0-5
Antergan ( <i>N</i> '-phenyl- <i>N</i> '-benzyl <i>NN</i> -dimethyl ethylenediamine HCl)	Gold bromide/HCl Picric acid	Dumb-bells Feathery rosettes	0-1 0-1
Anthallan (3-dibutylaminoethyl-4:5:6-trihydroxybenzo (1:2-c) furan-1-one)	Potassium tri-iodide (1) Picric acid	Rods Bunches of plates	0-5 0-5
Bucizine (Longifene, 1- <i>p</i> -chlorobenzhydryl-4- <i>tert</i> -butylbenzylpiperazine HCl)	Gold bromide Mercurous nitrate/HNO <sub>3</sub>	Smudge rosettes Small splinters	0-5 0-5
Carbinoxamine (Clistin, <i>p</i> -chlorophenyl-2-pyridylmethyl 2-dimethylaminoethyl ether maleate)	Gold chloride Lead iodide	Bunches of rods Dense rosettes	0-25 1-0
Chlorcyclizine (Histantin, Diparalene, 1-( <i>p</i> -chlorobenzhydryl)-4-methylpiperazine HCl)	Platinum chloride Potassium bismuth iodide	Small oily needles Small needles	0-1 0-1
*Chlorpromazine (Largactil, 3-chloro-10-(3'-dimethylamino- <i>n</i> -propyl) phenothiazine HCl)	Gold bromide/HCl Gold chloride	Bundles of curved needles Bunches of plates	0-25 0-1
Chlorpropenpyridamine (Chlortrimeton, Piriton, 1-( <i>p</i> -chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane maleate)	Gold chloride Lead iodide	Irregular rods Dense rosettes	0-1 0-1
Chlorthenylpyramine (Tagathen, Chlorothen, <i>N</i> '-2-pyridyl- <i>N</i> '-5-chloro-2-thenyl- <i>NN</i> -dimethylethylene diamine citrate)	Gold bromide Gold chloride	Oily plates or rods Snowflake rosettes	0-1 0-1
Chlortripellenamine (Synopen, <i>N</i> '- <i>p</i> -chlorobenzyl- <i>N</i> '-2-pyridyl- <i>NN</i> -dimethylethylene diamine HCl)	Gold bromide/HCl Lead iodide	Irregular rosettes or rods Rosettes of needles	0-1 0-1
*Cyclizine (Marzine, 1-benzhydryl-4-methyl-piperazine HCl)	Potassium bismuth iodide Sodium carbonate	Bunches of small irregular needles Long plates	0-25 0-5
Diethazine (Diparcol, Casantin, 10-(2'-diethylaminoethyl)phenothiazine HCl)	Platinum chloride Platinum bromide	Small serrated needles Small wedges	0-1 0-25
Diphenhydramine (Benadryl, 2-dimethylaminoethyl benzhydryl ether HCl)	Gold bromide/HCl Potassium tri-iodide (1)	Needles, some curved Plates	0-1 0-1
Diphenylpyrilene (Hystryl, 1-methyl-4-piperidyl benzhydryl ether HCl)	Platinum chloride Styphnic acid	Rosettes of oily blades Feathery rosettes	0-5 0-25
*Disipal (2-dimethylaminoethyl-2-methyl benzhydryl ether HCl)	Gold bromide/HCl Lead iodide	Small blades or plates Sheaves of oily needles	0-1 0-1
Doxylamine (Decapryn, 2-dimethylamino-1-2'-pyridyl-1-phenyl ethyl ether succinate)	Lead iodide Potassium cadmium iodide	Irregular dense rosettes Serrated needles	0-1 0-1
*Ethopropazine (Lysivane, 10-(2'-diethylamino- <i>n</i> -propyl)phenothiazine HCl)	Mercuric chloride Ammonium thiocyanate	Curved needles Bunches of plates	0-1 0-1
Hibernon ( <i>N</i> '- <i>p</i> -bromobenzyl- <i>N</i> '-2-pyridyl- <i>NN</i> -dimethylethylene diamine HCl)	Gold bromide/HCl Potassium chromate	Rosettes of blades Long plates	0-1 1-0
Histaphene (2-dimethylaminoethyl- <i>p</i> -methoxybenzhydryl ether HCl)	Gold bromide Gold chloride	Needles and plates Rods and plates	0-1 0-25
Incidal (3- <i>N</i> -methyl-9-benzyl-tetrahydro- $\gamma$ -carbolone naphthalene-1:5-disulphonate)	Mercuric chloride Ammonium thiocyanate	Rosettes of needles some-times dense Rosettes	0-25 0-5
Linadryl (2-morpholinoethyl-benzhydryl ether HCl)	Picolonic acid Gold cyanide	Rosettes of rods Segmented blades	0-1 0-1
Luvistin (1-(2- <i>N</i> -benzyl- <i>N</i> -phenylaminoethyl)pyrrolidine HCl)	Platinum iodide Gold bromide/HCl	Needles and plates Needles	0-5 0-25
Meclozine (Meclisine, Postafene, 1- <i>p</i> -chlorobenzhydryl-4-methyl benzylpiperazine HCl)	Gold bromide Picolonic acid	Smudge rosettes and oily blades Rosettes of needles	1-0 1-0
Mepyramine (Pyrilamine, Anthisan, <i>N</i> '- <i>p</i> -methoxybenzyl- <i>N</i> '-2-pyridyl- <i>NN</i> -dimethylethylene diamine maleate)	Gold bromide/HCl Platinum chloride	Small serrated needles or rods Rosettes or fans of needles	0-1 0-25

TABLE I—(continued)

Substance	Reagent	Crystals	Sensitivity μg.
Methaphenilene (Diatrin, <i>N'</i> -phenyl- <i>N'</i> -2-thenyl- <i>NN'</i> -dimethylethylenediamine HCl)	Platinum chloride Picrolonic acid	Serrated plates Rosettes of needles	0·1 0·1
Methapyrilene (Thenylene, Thenylpyramine, <i>N'</i> -2-pyridyl- <i>N'</i> -2-thenyl- <i>NN'</i> -dimethylethylenediamine HCl)	Platinum chloride Styphnic acid	Branching needles Stout blades	0·1 0·1
Neo-benoindine (2-dimethylaminoethyl- <i>p</i> -methylbenzhydryl ether HCl)	Gold chloride Potassium tri-iodide (3)	Curved needles or rods Segmented rods	0·1 0·1
*Notensil (3-acetyl-10(3'-dimethylamino propyl phenothiazine maleate)	Gold chloride Potassium tri-iodide (1)	Masses of very small rods Small plates	0·1 0·1
*Pacatal (Paxital, 10( <i>N</i> -methyl-3-piperidyl-methyl-phenothiazine HCl)	Potassium iodide Ammonium thiocyanate	Small irregular crystals Small blades in bundles	0·1 0·1
Phenindamine (Thephorin, 2-methyl-9-phenyl-1:2:3:4-tetrahydro-2-pyridindene hydrogen tartrate)	Mercuric chloride Potassium tri-iodide (1)	Rosettes, often dense Branching needles	1·0 0·1
Phenyltoxamine (Bristamine, 2-dimethylaminoethyl <i>o</i> -benzylphenyl ether citrate)	Potassium tri-iodide (1) Styphnic acid	Plates and needles Rods, often curved	0·25 0·1
*Prochlorperazine (Stematil, 3-chloro-10[3-(4-methyl-piperazine-1-yl)propyl] phenothiazine maleate)	Gold bromide/HCl Picric acid	Needles Smudge rosettes	0·1 0·1
*Promazine (Sparine, 10(3'-dimethylamino- <i>n</i> -propyl)phenothiazine HCl)	Gold chloride Potassium permanganate	Rods Branching needles	0·25 0·25
Promethazine (Phenergan, 10-(2'-dimethylamino- <i>n</i> -propyl-phenothiazine HCl)	Platinum bromide Gold cyanide	Very small dense rosettes Plates and rods	0·1 0·1
Propenpyridamine (Trimeton, 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate)	Gold bromide/HCl Serrated blades	Small stout needles Serrated blades	0·1 0·1
Pyrazhazine (Pyrrolazote, 10-(2'-pyrrolidinoethyl) phenothiazine HCl)	Platinum chloride Platinum bromide	Small irregular needles Very small irregular needles	0·1 0·1
Pyrobutamine (Pyronil, 1-( <i>p</i> -chlorophenyl)-2-phenyl-4-pyrrolidino butene diphosphate)	Potassium iodide Potassium tri-iodide (2)	Transparent blades Branching needles	0·1 0·1
Soventol (4-( <i>N</i> -benzyl- <i>N'</i> -phenylamino)-1-methylpiperidine HCl)	Potassium chromate Sodium carbonate	Long plates Segmented rods	0·1 0·1
Thenalidine (Sandosten, 1-methyl-4- <i>N'</i> -(2-thenyl)anilinopiperidine tartrate)	Picric acid Styphnic acid	Branching needles Small rosettes	0·1 0·1 0·1
Thenyldiamine (Thenfadil, <i>N'</i> -2-pyridyl <i>N'</i> -3-thenyl- <i>NN'</i> -dimethylethylenediamine HCl)	Gold bromide Platinum chloride	Plates and needles Feathery rosettes	0·1 0·1
Thonzylamine (Neohetramine, 2-[(2-dimethylaminoethyl) ( <i>p</i> -methoxybenzyl)amino] pyrimidine HCl)	Lead iodide Gold chloride	Feathery rosettes Serrated needles	0·25 0·1
Tripelennamine (Pyribenzamine, <i>N'</i> -benzyl- <i>N'</i> -2-pyridyl- <i>NN'</i> -dimethylethylenediamine HCl)	Lead iodide Platinum chloride	Snowflake rosettes Rosettes of plates	0·1 0·1
Triprolidine (Actadil, <i>trans</i> -1(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidino prop-1-ene HCl)	Picric acid Platinum bromide	Rosettes Bunches of blades	0·1 0·1

\* These substances are not normally employed as histamine antagonists.

† See refs. 9-11 for reagents.

The results are recorded in Table I. The reagents used are those described previously<sup>9-11</sup>. The lead iodide reagent is made by saturating potassium acetate solution (*not* lead acetate solution) with lead iodide. Two further reagents<sup>9-11</sup>, namely saturated solutions of mercurous nitrate in water and in N nitric acid, have been introduced. Most of these substances give crystalline precipitates with gold and platinum halides, and with lead iodide, but with few other reagents. As many of the bromaurates and chloraurates are very similar in appearance, it is essential to compare the test crystals with those obtained from an

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TABLE II

Substance	Colour	Sensitivity µg.
<i>Formaldehyde-sulphuric acid test 'Marquis'</i>		
Alfadryl .. .. .	Yellow—green	0.25
Ambodryl .. .. .	Yellow	0.1
Antadryl .. .. .	Yellow	0.1
Avomine .. .. .	Purple	0.1
Chlorpromazine .. .. .	Purple	0.1
Chlorthienylpyramine .. .. .	Purple	0.1
Diethazine .. .. .	Purple	1.0
Dimenhydrinate .. .. .	Yellow	0.1
Diphenhydramine .. .. .	Yellow	0.1
Diphenylpyrilene .. .. .	Yellow	0.1
Disipal .. .. .	Yellow—orange	0.25
Doxylamine .. .. .	Purple	0.25
Ethopropazine .. .. .	Purple	0.25
Histaphene .. .. .	Yellow	0.1
Incidal .. .. .	Grey—blue	1.0
Kolton .. .. .	Yellow	0.1
Linadryl .. .. .	Yellow	0.1
Mepyramine .. .. .	Mauve	1.0
Methaphenilene .. .. .	Dull—purple	0.25
Methapyrilene .. .. .	Black—violet	0.1
Neo—benoidine .. .. .	Yellow	0.1
Notensil .. .. .	Yellow—purple	0.1
Pacatal .. .. .	Purple	0.1
Phenindamine .. .. .	Grey—green	0.1
Phenyltoloxamine .. .. .	Purple	0.1
Prochlorperazine .. .. .	Purple	0.1
Promazine .. .. .	Purple	0.5
Promethazine .. .. .	Purple	0.1
Pyrathiazine .. .. .	Purple	0.25
Pyrrbutamine .. .. .	Grey—purple	0.5
Thenalidine .. .. .	Grey—purple	0.5
Thenylidiamine .. .. .	Black—violet	0.1
Tripelennamine .. .. .	Red—brown	0.1
<i>Ammonium vanadate test</i>		
Alfadryl .. .. .	Yellow—green	0.25
Ambodryl .. .. .	Yellow	0.1
Antadryl .. .. .	Yellow	0.1
Antazolone .. .. .	Reddish purple	0.1
Antergan .. .. .	Reddish purple	0.1
Anthallan .. .. .	Grey	0.5
Avomine .. .. .	Green—purple	0.1
Carbinoxamine .. .. .	Orange	1.0
Chlorpromazine .. .. .	Green—purple	0.25
Chlorthienylpyramine .. .. .	Purple—violet—orange	0.1
Chlortripelennamine .. .. .	Orange	0.5
Cyclizine .. .. .	Orange	1.0
Diethazine .. .. .	Green—purple	0.1
Dimenhydrinate .. .. .	Yellow	0.1
Diphenhydramine .. .. .	Yellow	0.1
Diphenylpyramine .. .. .	Yellow	0.1
Disipal .. .. .	Yellow—orange	0.25
Ethopropazine .. .. .	Green—purple	0.1
Hibernon .. .. .	Red—orange	0.25
Histaphene .. .. .	Yellow	0.1
Incidal .. .. .	Bright blue	0.5
Kolton .. .. .	Yellow	0.1
Linadryl .. .. .	Yellow	0.1
Luvistin .. .. .	Red—purple	0.1
Mepyramine .. .. .	Purple	0.25
Methaphenilene .. .. .	Orange—grey—purple	0.1
Methapyrilene .. .. .	Black—purple	0.1
Neo—benoidine .. .. .	Yellow	0.1
Notensil .. .. .	Brown—purple	0.1
Pacatal .. .. .	Green—purple	0.1
Phenindamine .. .. .	Green	0.1
Phenyltoloxamine .. .. .	Green	1.0
Prochlorperazine .. .. .	Brown—purple	0.1
Promazine .. .. .	Green—purple	0.1
Promethazine .. .. .	Green—purple	0.25
Pyrathiazine .. .. .	Green—purple	0.1
Pyrrbutamine .. .. .	Purple	0.5
Soventol .. .. .	Purple rim	0.5
Thenalidine .. .. .	Orange—brown	0.5
Thenylidiamine .. .. .	Olive	0.1
Thonzylamine .. .. .	Red—violet	0.5
Tripelennamine .. .. .	Yellow—brown	0.5

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TABLE II—(continued)

Substance	Colour	Sensitivity μg.
<i>Ammonium molybdate test</i>		
Alfadryl .. .. .	Yellow—green—blue	0.25
Ambodryl .. .. .	Yellow	0.1
Antadryl .. .. .	Yellow	0.1
Anthallan .. .. .	Blue	0.5
Avomine .. .. .	Black-violet—purple	0.1
Chlorpromazine .. .. .	Blue-violet—purple	0.25
Chlorthénylpyramine .. .. .	Purple	0.1
Diethazine .. .. .	Blue-violet—purple	0.1
Dimenhydrinate .. .. .	Yellow	0.1
Diphenhydramine .. .. .	Yellow	0.1
Diphenylpyraline .. .. .	Yellow	0.1
Disipal .. .. .	Yellow-orange	0.25
Ethopropazine .. .. .	Blue-violet—purple	0.1
Histaphene .. .. .	Yellow	0.1
Incidal .. .. .	Bright blue	0.5
Kolton .. .. .	Yellow	0.1
Linadryl .. .. .	Yellow	0.1
Mepyramine .. .. .	Violet—brown	0.1
Methaphenilene .. .. .	Faint brown	1.0
Methapyrilene .. .. .	Black—green—purple	0.1
Neo-benoidine .. .. .	Yellow	0.1
Notensil .. .. .	Brown—purple	0.1
Pacatal .. .. .	*Purple	0.1
Phenindamine .. .. .	Green	0.1
Phenyltoloxamine .. .. .	Green—blue—yellow	0.5
Prochlorperazine .. .. .	Blue-violet—purple	0.1
Promazine .. .. .	Dull green—purple	0.1
Promethazine .. .. .	Black-violet—purple	0.1
Pyrazithiazine .. .. .	*Violet—purple	0.1
Pyrbutamine .. .. .	Blue—yellow	0.1
Thenalidine .. .. .	Grey	1.0
Thenylidamine .. .. .	Olive	0.25
Thonzylamine .. .. .	Red-violet	0.25
Tripeleannamine .. .. .	Yellow-brown	0.1
<i>Selenium dioxide test</i>		
Alfadryl .. .. .	Yellow—green—grey	0.25
Antadryl .. .. .	Yellow	0.1
Antazolone .. .. .	Purple	0.1
Anthallan .. .. .	Grey	0.5
Avomine .. .. .	*Purple	0.1
Chlorcyclizine .. .. .	Yellow	1.0
Chlorpromazine .. .. .	Purple	0.1
Chlorthénylpyramine .. .. .	Purple	0.25
Diethazine .. .. .	Purple	0.1
Dimenhydrinate .. .. .	Yellow	0.1
Diphenhydramine .. .. .	Yellow	0.1
Diphenylpyrilene .. .. .	Yellow	0.1
Disipal .. .. .	Orange—yellow	0.25
Ethopropazine .. .. .	Purple	0.1
Histaphene .. .. .	Yellow	0.1
Incidal .. .. .	Blue-black	0.5
Kolton .. .. .	Yellow	0.1
Linadryl .. .. .	Yellow	0.1
Mepyramine .. .. .	Purple	0.1
Methaphenilene .. .. .	Purple	0.1
Methapyrilene .. .. .	Purple	0.1
Neo-benoidine .. .. .	Yellow	0.1
Notensil .. .. .	Brown—purple	0.1
Pacatal .. .. .	*Purple	0.1
Phenindamine .. .. .	Brown-orange	0.5
Phenyltoloxamine .. .. .	Orange	1.0
Prochlorperazine .. .. .	Purple	0.1
Promazine .. .. .	*Purple	0.1
Promethazine .. .. .	*Purple	0.1
Pyrazithiazine .. .. .	*Purple	0.1
Pyrbutamine .. .. .	Brown—grey	0.25
Thenalidine .. .. .	Purple	0.5
Thenylidamine .. .. .	Olive	0.5
Thonzylamine .. .. .	Red-purple	1.0
Tripeleannamine .. .. .	Yellow-brown	0.1
<i>Vitali's test</i>		
Allercur .. .. .	—/yellow rim/brown rim	1.0
Antazolone .. .. .	Red/yellow-brown/orange-brown	0.25
Antergan .. .. .	Orange/yellow/brown	0.5
Anthallan .. .. .	Purple/brown/brown	0.5

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TABLE II—(continued)

Substance	Colour	Sensitivity µg.
Avomine .. .. .	Purple—yellow/yellow/yellow	0.5
Chlorpromazine .. .. .	Purple—yellow/yellow/yellow	0.25
Diethazine .. .. .	Purple—yellow/yellow/yellow	1.0
Ethopropazine .. .. .	Purple—yellow/yellow/yellow	1.0
Incidal .. .. .	Green—yellow/yellow/yellow	1.0
Luvistin .. .. .	—/yellow/yellow	0.25
Methaphenilene .. .. .	Brown/brown/brown	0.5
Methapyrilene .. .. .	Purple/purple/purple	0.1
Notensil .. .. .	Purple—yellow/yellow/yellow	0.1
Pacatal .. .. .	Purple—yellow/yellow/yellow	0.1
Prochlorperazine .. .. .	Purple—yellow/yellow/yellow	0.1
Promazine .. .. .	Purple—yellow/yellow/yellow	0.25
Promethazine .. .. .	Purple—yellow/yellow/yellow	1.0
Pyrrathiazine .. .. .	Purple—yellow/yellow/yellow	0.5
Soventol .. .. .	—/yellow/yellow	0.5

\* A transient green colour may sometimes be noticed.

authentic sample of the drug, and to confirm any tentative diagnosis by means of the colour tests given below.

A number of these crystals will not form if the solution is too concentrated; this is particularly true of the picrates.

*Colour Tests*

These are made with microdrops on opal glass as previously described<sup>9</sup>. The results obtained are shown in Table II. Most of these substances give colours with all the reagents used, but many of the tests serve only to allocate a compound to a certain class. For example the derivatives of benzhydral ether give bright yellows with the sulphuric acid reagents, while phenothiazine compounds give pinks or purples. Slight differences of shade which may be of value when identifying milligram quantities are of little use when fractions of a microgram only are available.

DISCUSSION

Special mention must be made of diphenhydramine (Benadryl) and dimenhydrate (Dramamine). The former is the hydrochloride and the latter the 8-chlorotheophyllinate of the same base, 2-dimethylaminoethyl benzhydral ether. They give the same colour reactions and similar microcrystals with the usual reagents. They differ in solubility, the hydrochloride being readily soluble in water, the 8-chlorotheophyllinate insoluble. They may also be distinguished by the following test. A microdrop of a saturated aqueous solution of mercurous nitrate is added to a microdrop of an ethanolic solution of the drug. Dimenhydrate gives bundles of rods, while diphenhydramine gives an amorphous precipitate. The same test may be used to distinguish between the analogous pairs of substances Phenergan (promethazine HCl) and Avomine (promethazine 8-chlorotheophyllinate), and Hystryl (diphenylpyrilene HCl) and Kolton (diphenylpyrilene 8-chlorotheophyllinate).

The identification of meclozine and buclizine also presents certain problems. They give no characteristic colour reactions, and amorphous precipitates only are formed from solutions in water, dilute acids, methanol

or ethanol. The crystals described in Table I were obtained with glacial acetic acid as the solvent, alkaloidal precipitates in general being more soluble in this substance than in water, thus tending to crystallize more readily (Fulton<sup>12</sup>). Another way in which these two substances may be distinguished is by a paper chromatographic separation. If run on a citrate buffered paper with a butanol-water-citric acid solvent<sup>13</sup> they travel much faster than any other drugs included in this study, meclozine having an  $R_f$  value of 0.92 and buclizine of 0.94.

The results recorded above were obtained with pure material. All tests were made on the microscale. No quantity greater than 1  $\mu$ g. was used for any test, nor was any solution employed more concentrated than 1 per cent.

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## REFERENCES

1. Staub, *Ann. Inst. Pasteur*, 1939, **63**, 485.
2. Auterhoff, *Arch. Pharm.*, 1950, **283**, 244.
3. Auterhoff, *ibid.*, 1951, **284**, 123.
4. Auterhoff, *ibid.*, 1952, **285**, 14.
5. Haley and Keenan, *J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38**, 85, 381, 384.
6. Haley and Keenan, *ibid.*, 1950, **39**, 212, 333, 526.
7. Osol and Sideri, *ibid.*, 1955, **44**, 761.
8. Eijkel, Hofstr and Nauta, *Pharm. Weekbl.*, 1956, **91**, 461.
9. Clarke and Williams, *J. Pharm. Pharmacol.*, 1955, **7**, 255.
10. Clarke, *ibid.*, 1956, **8**, 202.
11. Clarke, *ibid.*, 1957, **9**, 187.
12. Fulton, *Amer. J. Pharm.*, 1940, **112**, 51.
13. Curry and Powell, *Nature, Lond.*, 1954, **173**, 1143.