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# SCREENING PROCEDURE FOR THE DETECTION OF ALKANOLAMINE ANTIHISTAMINES AND THEIR METABOLITES IN URINE USING COMPUTERIZED GAS CHROMATOGRAPHY–MASS SPECTROMETRY*

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## SUMMARY

A gas chromatographic–mass spectrometric screening procedure for the detection of the following alkanolamine antihistamines and their metabolites in urine after acid hydrolysis and acetylation is described: bencyclane, carbinoxamine, chlorbenzoxamine, chlorphenoxamine, clemastine, diphenhydramine, diphenylpyraline, doxylamine, mecloxamine, medrylamine, orphenadrine and phenyltoloxamine. The acetylated extract was analysed by computerized gas chromatography–mass spectrometry. An on-line computer allows rapid detection using ion chromatography with the ions *m/z* 58, 139, 165, 167, 179, 182, 218 and 260. The identity of positive signals in the reconstructed ion chromatograms was confirmed by a comparison of the stored full mass spectra with the reference spectra. Possible interferences with related compounds that yield the same hydrolysis products or metabolites are discussed. The ion chromatograms, reference mass spectra and gas chromatographic retention indices (OV-101) are documented. The procedure presented is integrated in a general screening procedure (general unknown analysis) for several groups of drugs.

## INTRODUCTION

Antagonists of the histamine $H_1$-receptor (antihistamines) are widely used for extended periods as allergy remedies, non-prescription hypnotics or in combination with other drugs in cold medicines. Because of their anticholinergic properties, some of the antihistamines are used clinically for the treatment of motion sickness and vertigo. The group of antihistamines is one of the largest groups of drugs. They are usually classified in alkanolamine, alkylamine, ethylenediamine,

*These results were reported in part at the "Symposium Klinisch-Toxikologische Analytik" of the Austrian and German Societies of Clinical Chemistry, Salzburg, September 14–16, 1987 [1].

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piperazine and phenothiazine antihistamines. They are often, alone or in combination with other drugs and/or ethanol, the cause of intoxication [2, 3] or the cause of a decreased fitness to drive a car [4, 5]. Because antihistamines used in ointments can be absorbed transdermally [6], intoxications have been observed, when large areas of skin, especially of children, were embrocated [7–9]. For all these reasons, antihistamines are encountered frequently in clinical or forensic toxicological analysis. Before quantification in plasma, the usually unknown drugs must be first identified. The detection of some of the alkanolamine antihistamines using spectrophotometry [10–12], paper chromatography [13], thin-layer chromatography [14, 15], gas chromatography [11, 16–18], high-performance liquid chromatography [19, 20] and gas chromatography–mass spectrometry (GC–MS) [18, 21–23] has been described. However, none of these procedures allows the rapid and specific identification and differentiation of all alkanolamine antihistamines.

This paper describes a computerized GC–MS screening procedure for the detection of alkanolamine antihistamines and their metabolites in urine. It is preferable to use urine for the screening because the concentrations of alkanolamine antihistamines and their metabolites are higher in urine than those in plasma. However, some of the alkanolamine antihistamines and their metabolites are excreted in urine in a completely conjugated form. Therefore, the conjugates were cleaved by acid hydrolysis, which can be completed more quickly than enzymatic hydrolysis. This method has the advantage that it can be integrated into an existing general screening procedure for the detection of several categories of drugs.

## EXPERIMENTAL

### *Apparatus*

A Hewlett-Packard (HP) Series 5890 gas chromatograph combined with an HP MSD Series 5970 mass spectrometer and an HP Series 59970 C workstation were used. The GC conditions were as follows: injection mode, splitless; column, HP capillary (12 m×0.2 mm I.D.), cross-linked methylsilicone, 0.33 μm film thickness; column temperature, programmed from 100 to 310°C at 30°C/min, initial time 3 min, final time 5 min; injection port temperature, 270°C; carrier gas, helium; flow-rate, 1 ml/min.

The MS conditions were as follows: scan mode; ionization energy, 70 eV; ion-source temperature, 220°C; capillary direct interface heated at 260°C.

Exact measurement of retention indices was performed on a Varian Series 3700 gas chromatograph. The column effluent went to a flame ionization detector and a nitrogen-sensitive flame ionization detector after a 1:1 split by a splitter made from nickel tubing. The column was a steel tube (60 cm×2 mm I.D.) packed with Chromosorb G HP (100–120 mesh) coated with 5% OV-101. The column and injector temperatures were identical with those used for GC–MS, and the temperature for the detectors was 270°C. Nitrogen was used as carrier gas at a flow-rate of 30 ml/min.

TABLE I

MONITORING PROGRAMME FOR THE DETECTION OF ALKANOLAMINE ANTIHISTAMINES AND THEIR METABOLITES IN URINE AFTER ACID HYDROLYSIS AND ACETYLATION

| Spectrum No | Mol. mass | Drug/metabolite (M) | Derivative* | Species | *m/z* (relative intensities)** | | | | | | | | Retention index*** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 58 | 139 | 165 | 167 | 179 | 182 | 218 | 260 | |
| | | Bencyclane | | | | | | | | | | | |
| 25 | 260 | M (oxo-), isomer 1 | HY AC | Man | | | | | | | | + | 1750 FID |
| 26 | 260 | M (oxo-), isomer 2 | HY AC | Man | | | | | | | +++ | + | 1780 FID |
| 22 | 258 | M (hydroxyoxo-) $-H_2O$ | HY AC | Man | | | | + | | | | | 1920 FID |
| 56 | 318 | M (hydroxyoxo-) | HY AC | Man | | | | | | | | | 2240 FID |
| 09 | 290 | Carbinoxamine | | Man | +++ | | | + | | | + | | 2120 |
| 08 | 217 | M (chlorobenzoylpyridine) | | Man | | +++ | | | | + | + | | 1645 |
| 28 | 261 | M (carbinol) | AC | Man | | + | | + | | | +++ | + | 1700 |
| 50 | 305 | M (desaminohydroxy-) | AC | Man | | + | | ++ | | | ++ | | 2240 |
| 57 | 318 | M (nor-) | AC | Man | | + | + | ++ | | | + | | 2400 |
| 49 | 304 | M (bis-nor-) | AC | Man | | + | + | +++ | | | +++ | | 2430 |
| 27 | 260 | Chlorbenzoxamine | HY AC | Man | | + | +++ | + | | | + | + | 1890 FID |
| 13 | 232 | M (N-desalkyl-) | AC | Man | + | | | | + | | | | 2110 |
| 55 | 318 | M (hydroxyphenyl-) | HY AC | Man | | | | | | + | + | + | 2170 |
| 45 | 290 | M (N-desalkylhydroxymethyl-) | AC | Man | | | | | | | ++ | | 2390 |
| 36 | 274 | Chlorphenoxamine | HY AC | Rat | | + | | | | | | | 2180 FID |
| 06 | 214 | $-H_2O$ | HY | Rat | | + | | | +++ | | | | 1700 FID |
| 33 | 272 | M (hydroxy-), isomer 1 $-H_2O$ | HY AC | Rat | | + | + | + | | | | | 2030 FID |
| 34 | 272 | M (hydroxy-), isomer 2 $-H_2O$ | HY AC | Rat | | + | + | + | | | | | 2090 FID |
| 47 | 302 | M (hydroxymethoxy-) $-H_2O$ | HY AC | Rat | | + | + | | | + | | +++ | 2210 FID |
| 36 | 274 | Clemastine | HY AC | Rat | | + | | | | | | | 2180 FID |
| 06 | 214 | $-H_2O$ | HY | Rat | | + | | | +++ | | | | 1700 FID |
| 33 | 272 | M (hydroxy-), isomer 1 $-H_2O$ | HY AC | Rat | | + | + | + | | | | | 2030 FID |
| 34 | 272 | M (hydroxy-), isomer 2 $-H_2O$ | HY AC | Rat | | + | + | + | | | | | 2090 FID |
| 47 | 302 | M (hydroxymethoxy-) $-H_2O$ | HY AC | Rat | | + | + | | | + | | +++ | 2210 FID |

(Continued on p. 46)

TABLE I (continued)

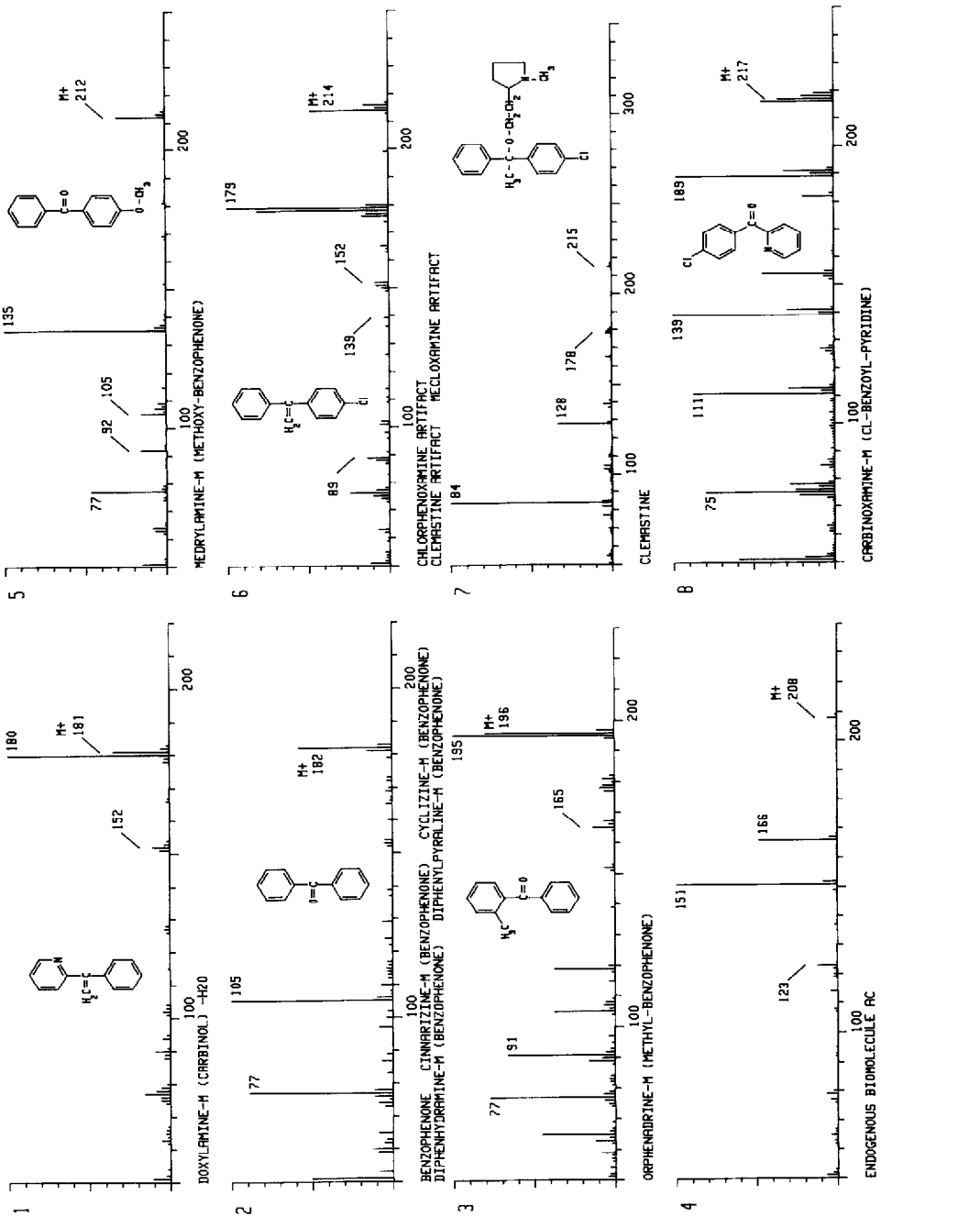
| Spectrum No. | Mol. mass | Drug/metabolite (M) | Derivative* | Species | *m/z* (relative intensities)** | | | | | | | | Retention index*** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 58 | 139 | 165 | 167 | 179 | 182 | 218 | 260 | |
| 10 | 226 | Diphenhydramine | HY AC | Man | | | +++ | + | | | | | 1700 FID |
| 02 | 182 | M (benzophenone) | | Man | | | | | | + | | | 1610 FID |
| 17 | 240 | M (hydroxybenzophenone), isomer 1 | AC | Man | | | | | | + | | | 2010 FID |
| 18 | 240 | M (hydroxybenzophenone), isomer 2 | AC | Man | | | | | | + | | | 2050 FID |
| 31 | 270 | M (hydroxymethoxybenzophenone), isomer 1 | AC | Man | | | | | | | | | 2090 FID |
| 32 | 270 | M (hydroxymethoxybenzophenone), isomer 2 | AC | Man | | | | | | | | | 2110 FID |
| 10 | 226 | Diphenylpyraline | HY AC | Man | | | +++ | + | | | | | 1700 FID |
| 02 | 182 | M (benzophenone) | | Man | | | | | | + | | | 1610 FID |
| 17 | 240 | M (hydroxybenzophenone), isomer 1 | AC | Man | | | | | | + | | | 2010 FID |
| 18 | 240 | M (hydroxybenzophenone), isomer 2 | AC | Man | | | | | | + | | | 2050 FID |
| 31 | 270 | M (hydroxymethoxybenzophenone), isomer 1 | AC | Man | | | | | | | | | 2090 FID |
| 32 | 270 | M (hydroxymethoxybenzophenone), isomer 2 | AC | Man | | | | | | | | | 2110 FID |
| 29 | 270 | Doxylamine | | Man | +++ | | | + | | + | | | 1920 |
| 01 | 181 | M (carbinol) $-H_2O$ | | Man | | | | | + | + | | | 1560 |
| 15 | 239 | M (hydroxycarbinol) $-H_2O$ | AC | Man | | | + | + | | | | | 1940 |
| 44 | 285 | M (desaminohydroxy-) | AC | Man | | | | + | | ++ | | | 1960 |
| 42 | 284 | M (bis-nor-) | AC | Man | | | | ++ | | +++ | | | 2280 |
| 23 | 328 | M (hydroxy-) | AC | Man | +++ | | | | | + | | | 2300 |
| 24 | 358 | M (hydroxymethoxy-) | AC | Man | +++ | | | | | | | | 2320 |
| 46 | 298 | M (nor-) | AC | Man | + | | | ++ | | +++ | | | 2340 |
| 43 | 342 | M (bis-norhydroxy-) | AC | Man | + | | | | | + | | | 2720 |
| 21 | 356 | M (norhydroxy-) | AC | Man | ++ | | | | | | | | 2760 |
| 36 | 274 | Mecloxamine | HY AC | Rat | | | + | | | | | | 2180 FID |
| 06 | 214 | $-H_2O$ | HY | Rat | | | + | | +++ | | | | 1700 FID |
| 33 | 272 | M (hydroxy-), isomer 1 $-H_2O$ | HY AC | Rat | | | + | + | + | | | | 2030 FID |
| 34 | 272 | M (hydroxy-), isomer 2 $-H_2O$ | HY AC | Rat | | | + | + | + | | | | 2090 FID |
| 47 | 302 | M (hydroxymethoxy-) $-H_2O$ | HY AC | Rat | | | + | + | | + | | +++ | 2210 FID |
| 20 | 256 | Medrylamine | HY AC | Rat | | | + | + | + | + | | | 1980 FID |
| 05 | 212 | M (methoxybenzophenone) | | Rat | | | + | | | | | | 1930 FID |
| 18 | 240 | M (hydroxybenzophenone) | AC | Rat | | | | | | + | | | 2050 FID |
| 39 | 284 | M (O-desmethyl-) | HY AC | Rat | | | | + | | +++ | | | 2090 FID |

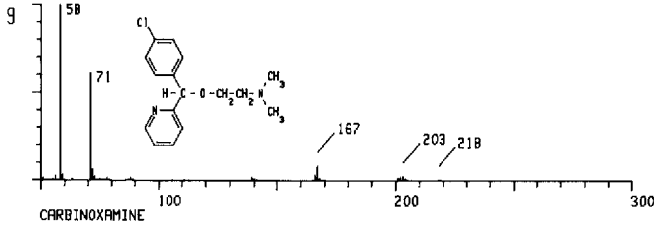
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | 240 | Orphenadrine | HY AC | Man | | | + | | ++ | + | | 1750 FID |
| 03 | 196 | M (methylbenzophenone) | | Man | | | + | + | | + | + | 1700 FID |
| 19 | 255 | Phenyltoloxamine | | Man | +++ | | | | | | | 1950 |
| 11 | 226 | M (O-desalkyl-) | AC | Man | | | + | + | + | + | | 1740 FID |
| 30 | 270 | M (desaminohydroxy-) | AC | Man | | | + | + | + | | | 2080 FID |
| 40 | 284 | M (O-desalkylhydroxy-), isomer 1 | AC | Man | | | | | | | | 2105 FID |
| 41 | 284 | M (O-desalkylhydroxy-), isomer 2 | AC | Man | | + | | | | + | | 2130 FID |
| 52 | 313 | M (hydroxy-), isomer 1 | AC | Man | +++ | | | | | | | 2260 |
| 53 | 313 | M (hydroxy-), isomer 2 | AC | Man | +++ | | | | | | | 2280 |
| 38 | 283 | M (nor-) | AC | Man | + | | + | | | | | 2350 |
| 61 | 343 | M (hydroxymethoxy-) | AC | Man | +++ | | | | | | | 2380 |
| 59 | 341 | M (norhydroxy-), isomer 1 | AC | Man | + | | | | | | | 2580 |
| 60 | 341 | M (norhydroxy-), isomer 2 | AC | Man | + | | | | | | | 2610 |
| 63 | 371 | M (norhydroxymethoxy-) | AC | Man | + | | | | | | | 2770 |
| 58 | 332 | Androsterone | AC | Man | | | | | + | | + | 2580 FID |
| 35 | 272 | Androsterone $-H_2O$ | | Man | | | | | | | ++ | 2240 FID |
| 62 | 368 | Cholesterol $-H_2O$ | | Man | | | | | | | | + 3030 FID |
| 64 | 390 | Diisooctyl phthalate | | Man | | | | + | | | | 2540 FID |
| 04 | 208 | Endogenous biomolecule | AC | Man | | | | + | | | | 1640 FID |
| 14 | 234 | Lidocaine | | Man | + | | | | | | | 1875 |

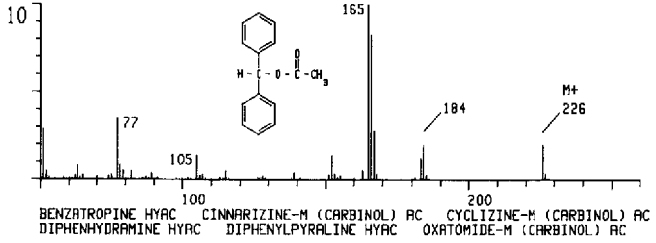
*HY = hydrolysed; AC = acetylated

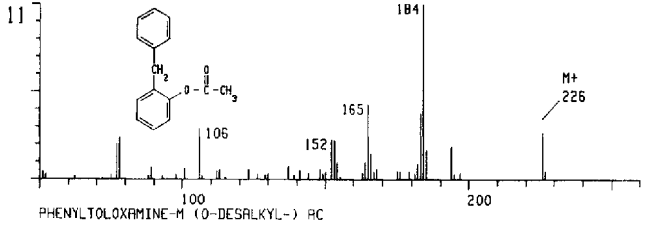
**+++ = >95% relative intensity, ++ = 50–95%; + = <50%

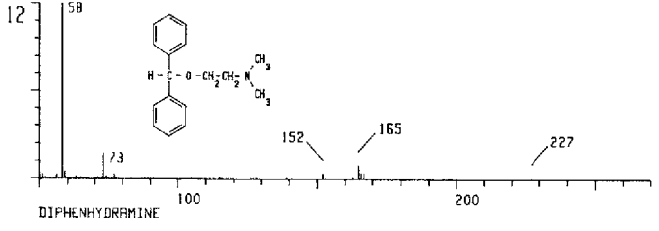
***FID = flame ionization detection.


1
DOXYLAMINE-M (CARBINOL) -H2O
2
BENZOPHENONE CINNARIZINE-M (BENZOPHENONE) CYCLIZINE-M (BENZOPHENONE)
DIPHENHYDRAMINE-M (BENZOPHENONE) DIPHENYLPYRALINE-M (BENZOPHENONE)
3
ORPHENADRINE-M (METHYL-BENZOPHENONE)
4
ENDOGENOUS BIOMOLECULE AC
5
MEDRYLAMINE-M (METHOXY-BENZOPHENONE)
6
CHLORPHENOXAMINE ARTIFACT
CLEMASTINE ARTIFACT MECLOXAMINE ARTIFACT
7
CLEMASTINE
8
CARBINOXAMINE-M (CL-BENZOYL-PYRIDINE)

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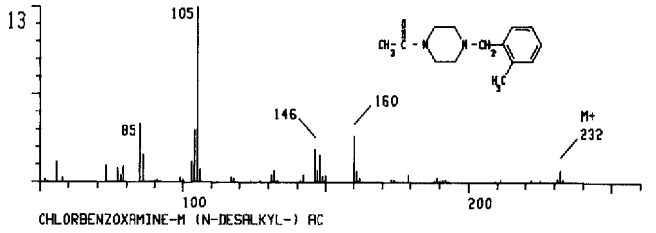
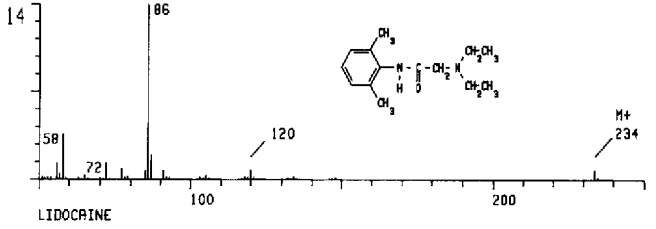
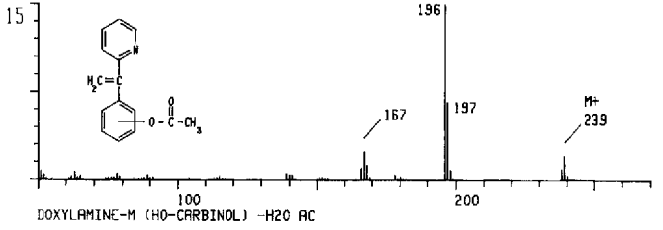
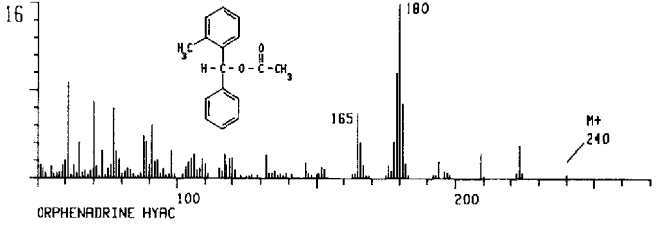
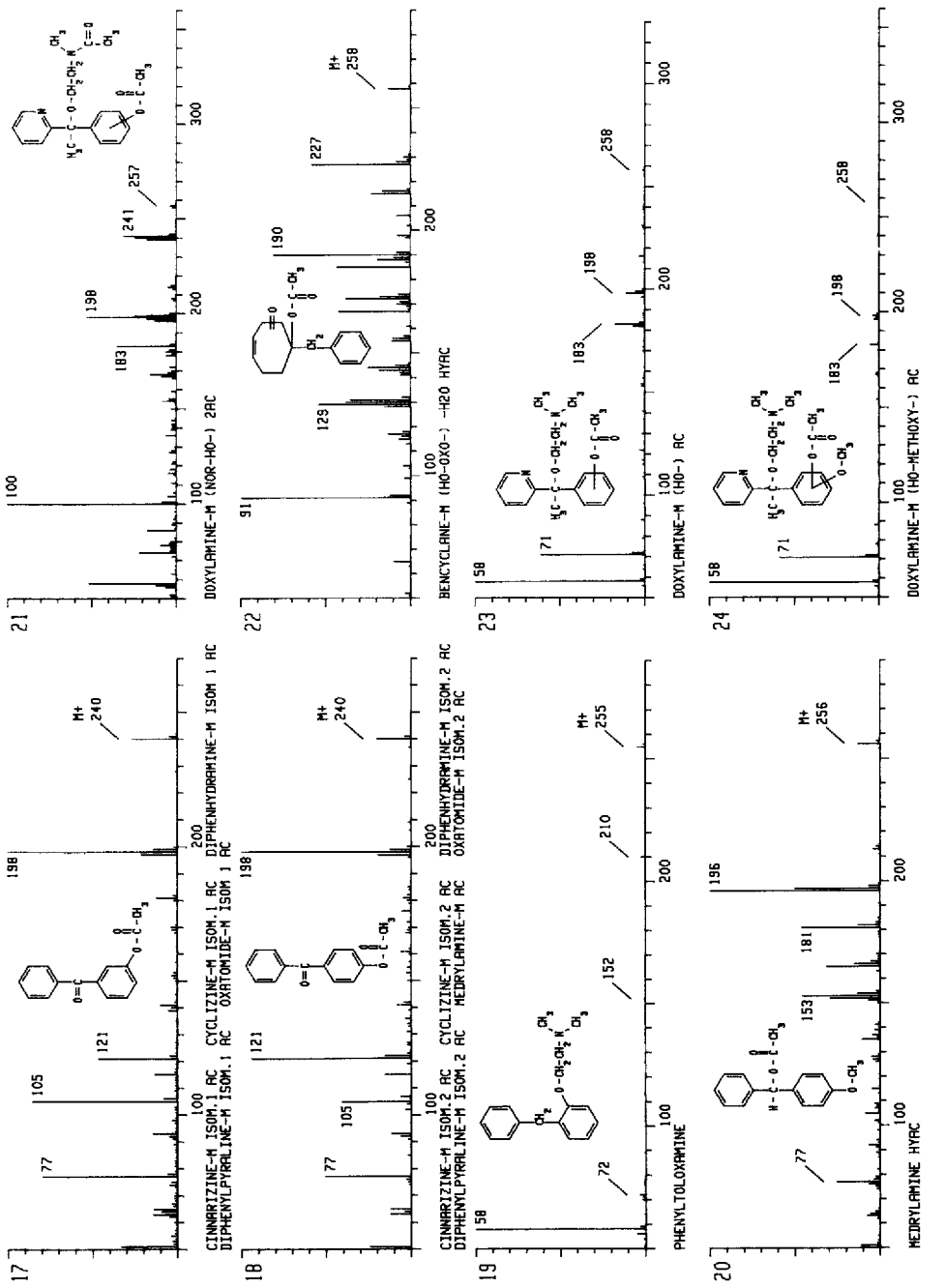
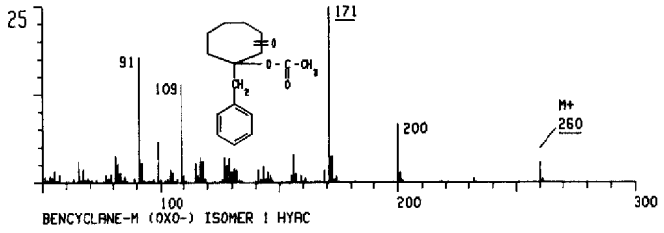


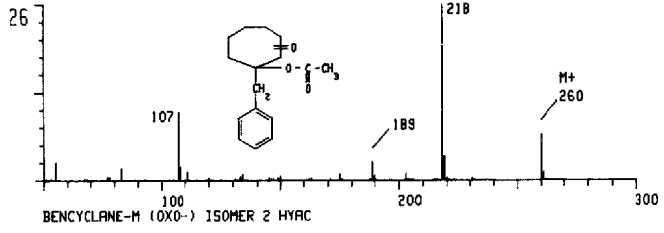




17
CINNARIZINE-M ISOM.1 AC CYCLIZINE-M ISOM.1 AC DIPHENHYDRAMINE-M ISOM 1 AC
DIPHENYLPYRALINE-M ISOM.1 AC OXATOMIDE-M ISOM 1 AC
18
CINNARIZINE-M ISOM.2 AC CYCLIZINE-M ISOM.2 AC DIPHENHYDRAMINE-M ISOM.2 AC
DIPHENYLPYRALINE-M ISOM.2 AC MEDRYLAMINE-M AC OXATOMIDE-M ISOM.2 AC
19
PHENYLTOLOXAMINE
20
MEDRYLAMINE HYAC
21
DOXYLAMINE-M (NOR-HO-) 2AC
22
BENCYCLANE-M (HO-OXO-) -H2O HYAC
23
DOXYLAMINE-M (HO-) AC
24
DOXYLAMINE-M (HO-METHOXY-) AC




BENCYCLANE-M (OXO-) ISOMER 1 HYAC

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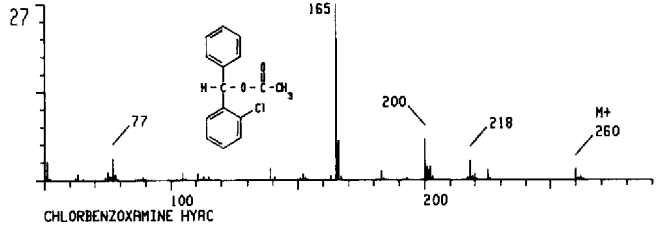
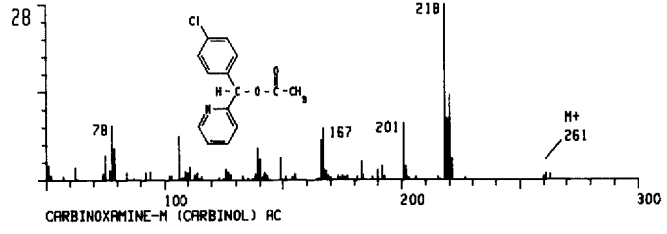
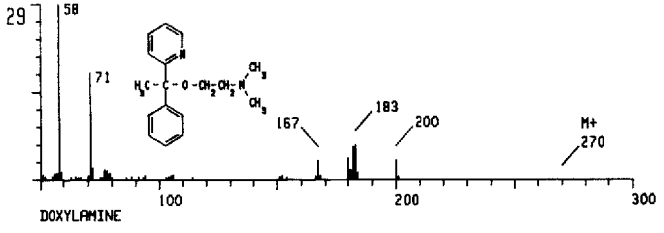


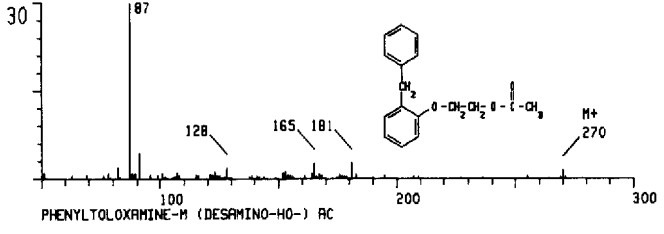

CHLORBENZOXAMINE HYAC



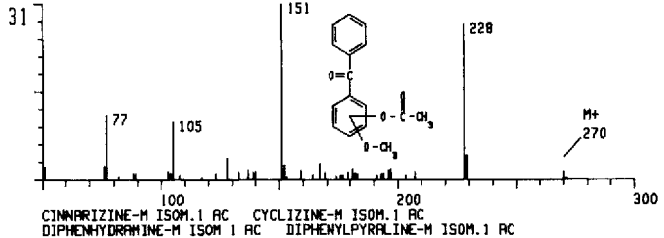

CARBINOXAMINE-M (CARBINOL) AC



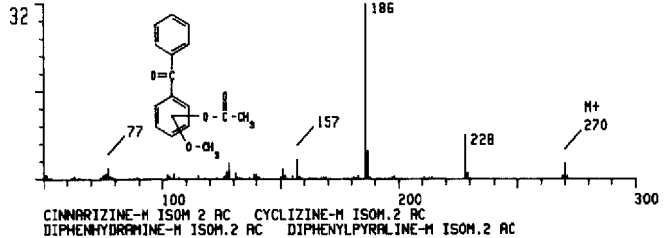

DOXYLAMINE




PHENYLTOLOXAMINE-M (DESAMINO-HO-) AC



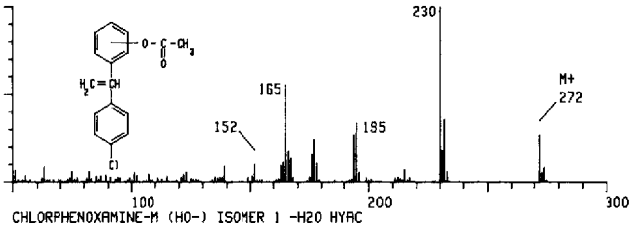

CINNARIZINE-M ISOM.1 AC CYCLIZINE-M ISOM.1 AC
DIPHENHYDRAMINE-M ISOM 1 AC DIPHENYLPYRALINE-M ISOM.1 AC




CINNARIZINE-M ISOM 2 AC CYCLIZINE-M ISOM.2 AC
DIPHENHYDRAMINE-M ISOM.2 AC DIPHENYLPYRALINE-M ISOM.2 AC

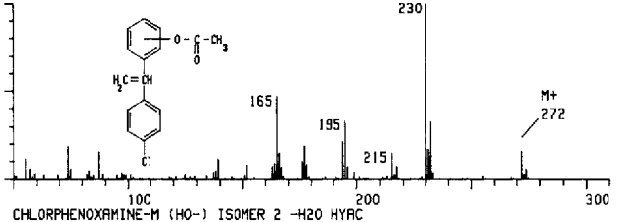
(Continued on p. 52)

33




CHLORPHENOXAMINE-M (HO-) ISOMER 1 -H2O HYAC
CLEMASTINE-M (HO-) ISOMER 1 -H2O HYAC  MECLOXAMINE-M (HO-) ISOMER 1 -H2O HYAC

34

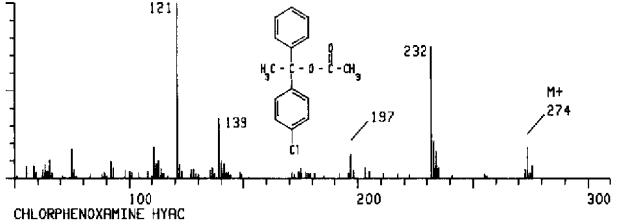



CHLORPHENOXAMINE-M (HO-) ISOMER 2 -H2O HYAC
CLEMASTINE-M (HO-) ISOMER 2 -H2O HYAC  MECLOXAMINE-M (HO-) ISOMER 2 -H2O HYAC

35

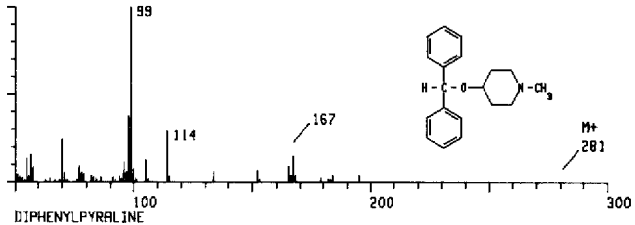

ANDROSTERONE -H2C

36



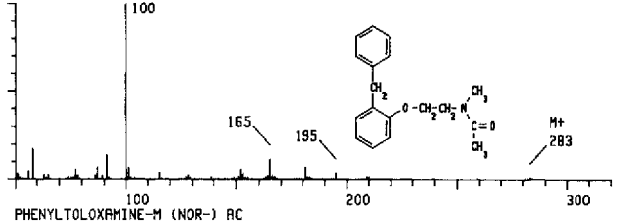

CHLORPHENOXAMINE HYAC
CLEMASTINE HYAC  MECLOXAMINE HYAC

37



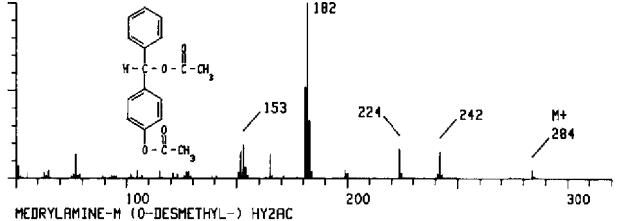

DIPHENYLPYRALINE

38



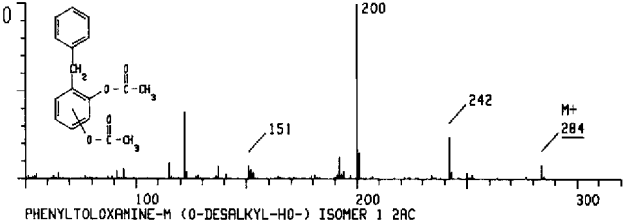

PHENYLTOLOXAMINE-M (NOR-) AC

39

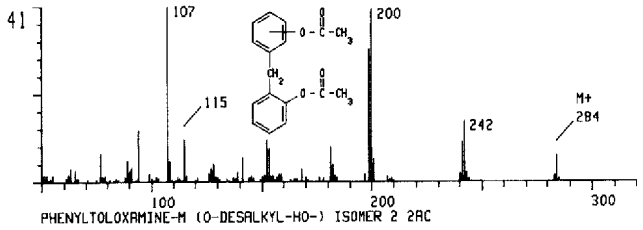



MEDRYLAMINE-M (O-DESMETHYL-) HY2AC

40




PHENYLTOLOXAMINE-M (O-DESALKYL-HO-) ISOMER 1 2AC

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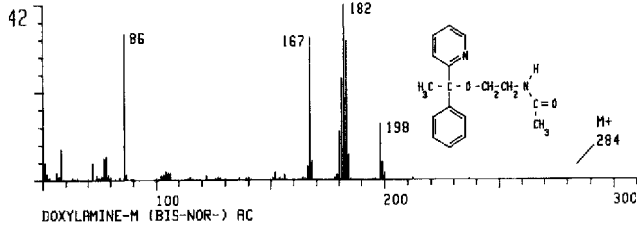
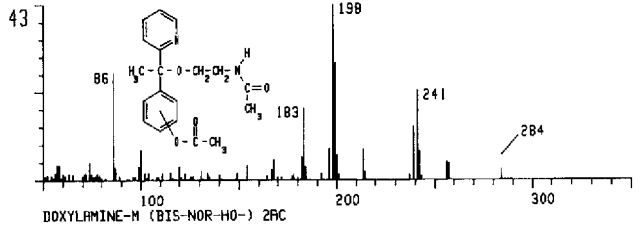
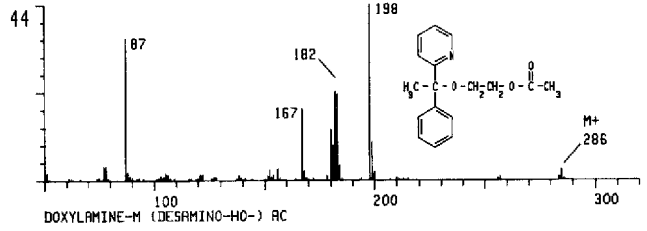



DOXYLAMINE-M (BIS-NOR-) AC

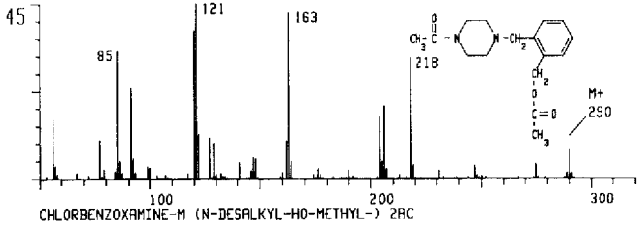



DOXYLAMINE-M (BIS-NOR-HO-) 2AC

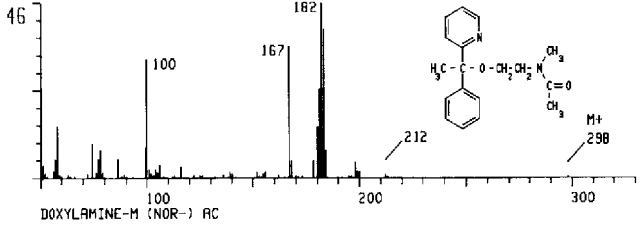



DOXYLAMINE-M (DESAMINO-HO-) AC

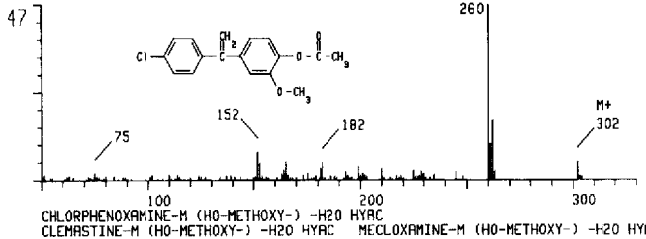
(Continued on p. 54)



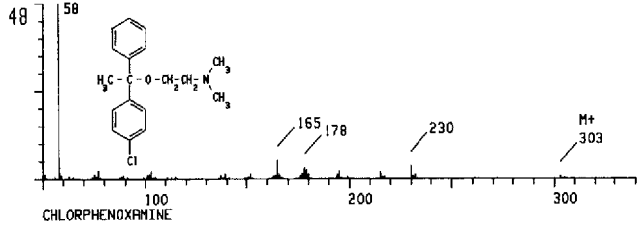

CHLORBENZOXAMINE-M (N-DESALKYL-HO-METHYL-) 2AC



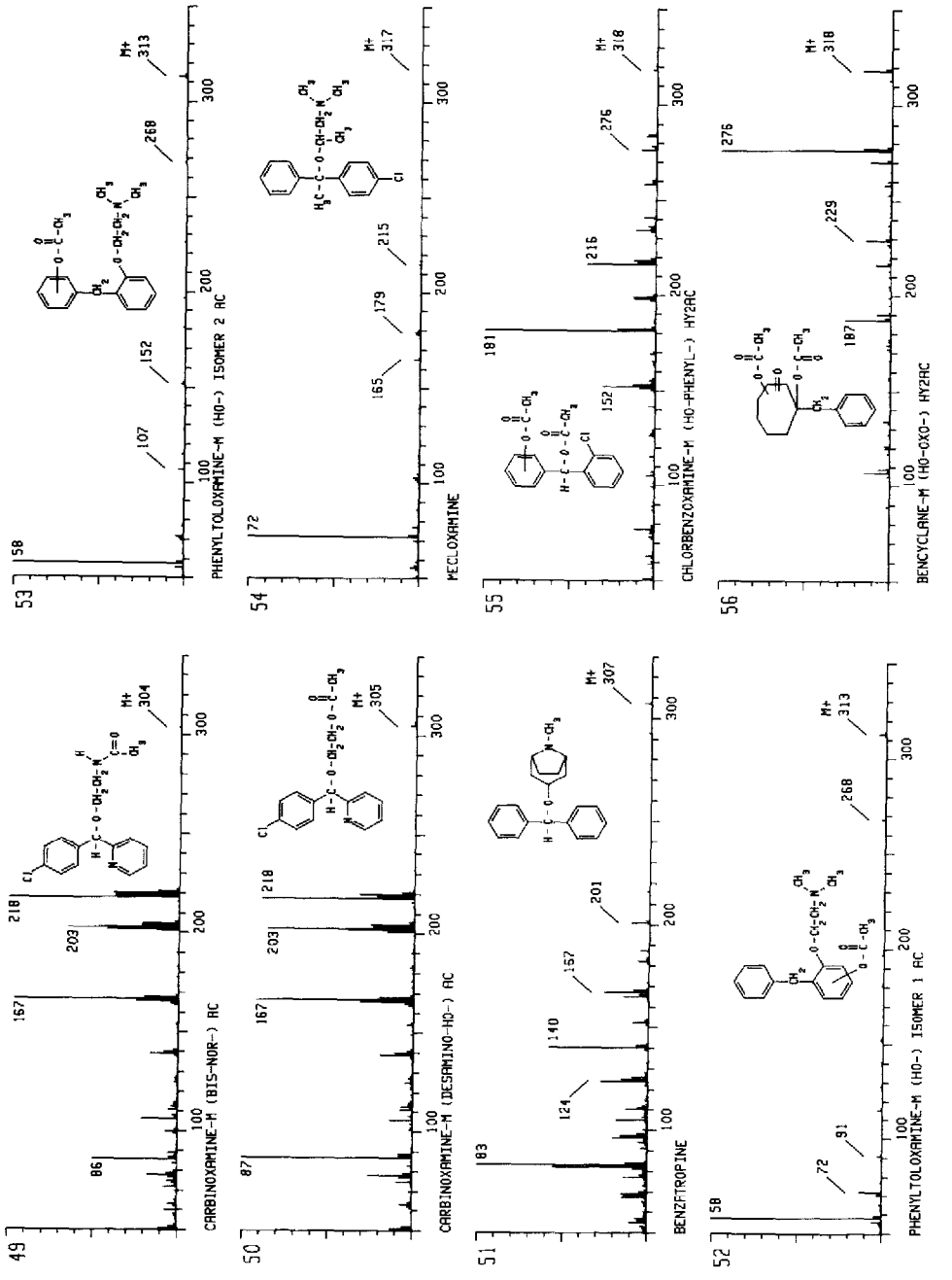

DOXYLAMINE-M (NOR-) AC




CHLORPHENOXAMINE-M (HO-METHOXY-) -H2O HYAC
CLEMASTINE-M (HO-METHOXY-) -H2O HYAC MECLOXAMINE-M (HO-METHOXY-) -H2O HYAC




CHLORPHENOXAMINE


49
CARBINOXAMINE-M (BIS-NOR-) AC
50
CARBINOXAMINE-M (DESAMINO-HO-) AC
51
BENZTROPINE
52
PHENYLTOLOXAMINE-M (HO-) ISOMER 1 AC
53
PHENYLTOLOXAMINE-M (HO-) ISOMER 2 AC
54
MECLOXAMINE
55
CHLORBENZOXAMINE-M (HO-PHENYL-) HY2AC
56
BENCYCLANE-M (HO-OXO-) HY2AC

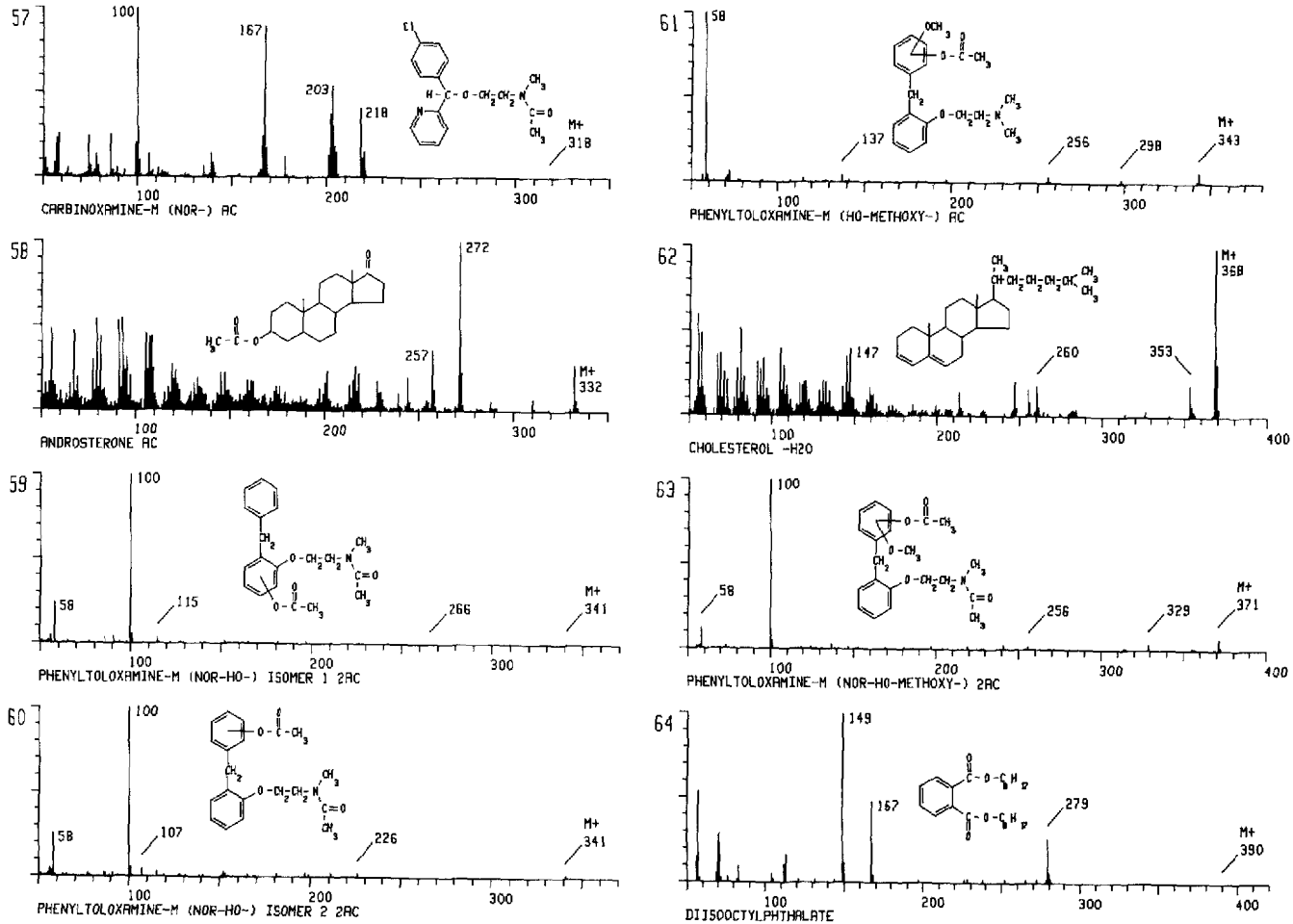



Fig. 1. Mass spectra of alkanolamine antihistamines and their metabolites identified in urine after acid hydrolysis, extraction and acetylation.

*Urine samples*

The investigations were performed on urine from in-patients treated with therapeutic doses of alkanolamine antihistamines. When suitable samples from humans were not available, urine from rats was used (see Species column in Table I). Rats were administered 50 mg/kg body weight of drugs in aqueous suspension by gastric intubation. Urine was collected separated from the faeces [24].

*Hydrolysis and extraction procedure*

A 10-ml volume of urine was refluxed with 3 ml of 37% hydrochloric acid for 15 min. Following hydrolysis, ca. 3 g of potassium hydroxide pellets were added and the resulting solution was mixed with 10 ml of 30% aqueous ammonium sulphate to obtain a pH between 8 and 9. This solution was extracted with a 10-ml portion of dichloromethane–2-propanol–ethyl acetate (1:1:3). Phase separation was accomplished by centrifugation. The organic extract was transferred into a pear-shaped flask and evaporated to dryness under vacuum.

*Acetylation*

The extracted residue was acetylated for 30 min at 60 °C with 100 μl of a mixture of three parts of acetic acid anhydride and two parts of pyridine. The acetylation mixture was then evaporated to dryness, and the resultant residue was dissolved in 100 μl of methanol. A 0.5–2 μl volume of this sample was injected into the gas chromatograph.

*Gas chromatographic–mass spectrometric analysis*

Full mass spectra were recorded at a speed of 1 scan/s and stored on a hard disk during the temperature-programmed GC analysis. The identity of positive signals in the reconstructed ion chromatograms was confirmed by a visual comparison of the full mass spectra with reference spectra (Fig. 1) or by a computer library search [25].

## RESULTS AND DISCUSSION

Table I summarizes the data collected during these investigations. Utilization of the eight proposed ions for construction of the ion chromatograms allows the detection of alkanolamine antihistamines and their metabolites in urine. The data of the vasodilator bencyclane are included because of its structural similarity to these antihistamines. Most of the compounds are derivatized by acetylation following hydrolysis (see Derivative column). The numbers of the mass spectra in Fig. 1, the molecular masses, the species from which the urine was assayed and the GC retention indices are given. These indices were determined using temperature-programmed GC combined with flame ionization detection and nitrogen-sensitive flame ionization detection. In our experience, retention indices provide preliminary indications for the possible presence of the compounds and may be useful to workers without a GC–MS facility. Additionally, they allow one to distinguish between isomeric compounds, which give very similar mass spectra.

Data are listed for only those metabolites that were frequently found. Not all

the listed metabolites were detected in each sample owing to inter-species or inter-individual differences in metabolism, or the variable times that had elapsed after administration. The mass spectra and retention indices of the less abundant metabolites will be included in a forthcoming computer library and handbook [25, 26].

The data for androsterone, its dehydrated artifact, dehydrated cholesterol and an unidentified endogenous biomolecule were included because these physiological compounds were indicated by the ion chromatograms. For the same reason, the data for diisooctyl phthalate, a widespread softener, and for lidocaine, a local anaesthetic often used as a lubricant for urinary catheters, were added.

Two kinds of artifact were produced by this analytical procedure. Complete or partial dehydration was observed for alcoholic hydroxy groups. Furthermore, during acid hydrolysis the diarylmethyl (or diarylethyl) alkyl ethers were cleaved, with the exception of those in the pyridyl analogues carbinoxamine and doxylamine. The metabolites of bencyclane were also cleaved [27]. The mono- and bis-N-desalkyl and desaminohydroxy metabolites of all these drugs were altered to the same hydrolysis products as formed by the corresponding parent compounds. For clarity the latter metabolites are not specified, either in Table I or in Fig. 1. The data for the unaltered metabolites detected in urine after enzymatic hydrolysis will be included in refs. 25 and 26.

The full mass spectra for the precise identification of the compounds are shown in Fig. 1. They are listed primarily in order of ascending mass of the molecular or pseudomolecular ions. For the same nominal mass value, the spectra are arranged in order of ascending retention indices. Formulae are proposed for probable metabolite structures.

The identity of the peaks observed in the ion chromatograms can be positively confirmed by a visual comparison of the underlying mass spectrum with reference spectra (Fig. 1 and ref. 26) or by a computer library search [25]. Therefore, interferences by other drugs are improbable. However, some different alkanolamine antihistamines lead to the same metabolites and/or the same hydrolysis products. In some cases the drug taken can be identified by the metabolite profile in urine. However, on the one hand chlorphenoxamine, clemastine and meclozamine and on the other hand diphenhydramine, diphenylpyraline and the antiparkinsonian drug benzatropine [28] yield the same compounds and cannot be differentiated by this procedure. If differentiation is necessary, the intact drug can be identified in a direct extract of urine [29]. The mass spectra of these drugs are included in Fig. 1 (mass spectra Nos. 48, 7 and 54; 12, 37 and 51). The piperazine antihistamines cinnerizine, cyclizine and oxatomide also lead to compounds produced by diphenhydramine and diphenylpyraline (mass spectra Nos. 2, 10, 17, 18, 31 and 32). However, in addition, further unique metabolites are formed [30].

The sensitivity of the method is sufficient for the detection of therapeutic concentrations of at least those drugs that were studied in human urine.

To illustrate the method, ion chromatograms from the urine of a patient suspected of an intoxication with alkanolamine antihistamines is shown in Fig. 2. Peak 2 indicates the acetylated hydrolysis product of diphenhydramine, peak 1

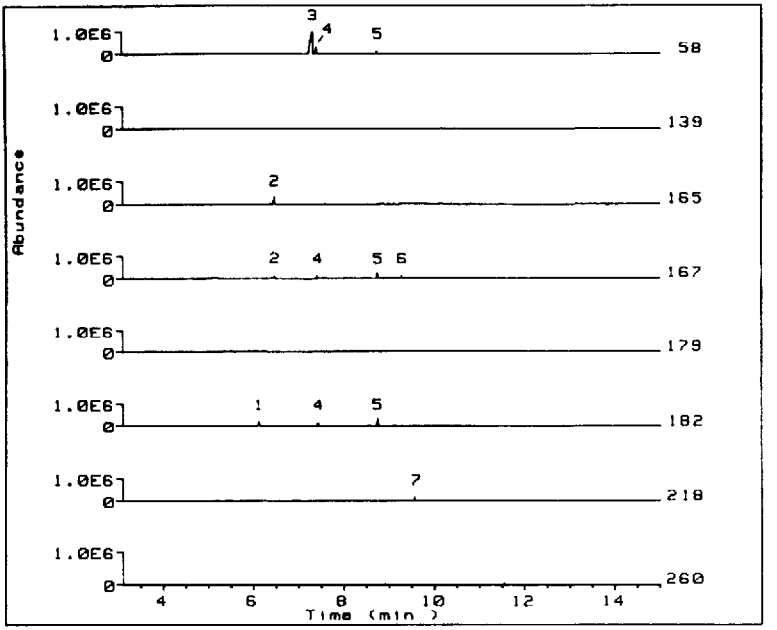



Fig. 2. Ion chromatograms indicating diphenhydramine (2) and one of its metabolites (1), lidocaine (3), doxylamine (4) and one of its metabolites (5), diisooctyl phthalate (6) and androsterone (7) (mass spectra Nos. 10, 2, 14, 29, 46, 64 and 58 in Fig. 1).

its metabolite benzophenone, peak 3 lidocaine, peak 4 doxylamine, peak 5 its nor metabolite, peak 6 diisooctyl phthalate and peak 7 androsterone (mass spectra Nos. 10, 2, 14, 29, 46, 64 and 58 in Fig. 1). It was confirmed that the peaks 1 and 2 result from diphenhydramine by the detection of the intact parent compound in a direct extract of urine.

## CONCLUSIONS

The procedure presented allows the rapid and selective detection of alkanolamine antihistamines and their metabolites in urine. The identified drugs can then be quantified in plasma using methods reviewed by Paton and Webster [31]. The screening procedure in urine has the additional advantage that other classes of drugs can be detected simultaneously by searching for typical fragment ions in the stored spectra and by comparing the underlying mass spectra with reference spectra. Typical ion chromatograms and reference spectra of butyrophenones and bisfluorophenyl neuroleptics [32], anti-inflammatory analgesics [33], opioids and other potent analgesics [34], antidepressants [35], phenothiazine and analogous neuroleptics [36], antiparkinsonian drugs [28], $\beta$-blockers [37], benzodiazepines [38, 39], phenothiazine antihistamines [40], ethylenediamine and piperazine antihistamines [30] and alkylamine antihistamines [41] have been published. Detection and identification of antiarrhythmics by GC–MS is in preparation [42]. Similar data for other compounds of toxicological interest will be

collected. Through the utilization of this technique nearly all relevant drugs will be detectable in urine or other biological materials within 1–2 h.

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