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POSITIVE- AND NEGATIVE-ION MASS SPECTROMETRY OF BUTYROPHENONES

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SUMMARY

Positive-ion electron-impact (EI), positive-ion chemical ionization (CI) and medium-pressure negative-ion CI mass spectra of ten butyrophenones are presented. Low-pressure (0.01 Torr) negative CI spectra are also presented for some compounds. In the positive EI mode, a peak at *m/z* 42, which corresponded to the propyl group, appeared for all compounds; a peak at *m/z* 123 was also common to all compounds except for the two with a bis(fluorophenyl) group. Molecular ions were generally very small or missing in the positive EI mode. In the positive CI mode, strong $[M+H]^+$ quasi-molecular peaks generally appeared together with $[M+C_2H_5]^+$ peaks; $[M-F]^+$ peaks appeared in many compounds and $[M-OH]^+$ peaks also appeared for compounds having a hydroxypiperidinyl group. In the negative CI mode with a 1 Torr chamber pressure, their spectra were generally simple with $[M-H]^-$ quasi-molecular ions; anions of liberated halogens were not observed except for bromine at this pressure. In the negative CI mode at low pressure (0.01 Torr), some fragment peaks in the lower mass range appeared in addition to the quasi-molecular ions; halogen peaks (*m/z* 19 or 35) and anions at *m/z* 95, which corresponded to the fluorophenyl group, appeared in most spectra recorded at this pressure. An procedure for the extraction of butyrophenones from human urine and plasma and their separation by gas chromatography was also developed to serve for their identification in forensic science practice.

INTRODUCTION

Butyrophenones are common tranquillizers, second in importance to phenothiazines, and are frequently encountered in forensic science practice. Their

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analysis in the blood of psychiatric patients is also required in order to provide optimal effective doses [1—5]. However, to our knowledge, no systematic studies of the mass spectra of butyrophenones have been reported, even in the positive-ion electron impact (PIEI) mode. In this paper, we present PIEI, positive-ion chemical ionization (PICI) and negative-ion chemical ionization (NICI) mass spectra of ten butyrophenones, and also methods for their extraction from human samples and their separation by gas chromatography (GC) to serve for the identification of the drugs in real samples.

EXPERIMENTAL

Materials

The butyrophenones tested were haloperidol · HCl (I), moperone · HCl (II), bromperidol (III), trifluperidol · HCl (IV), spiroperidol (V), floropipamide · 2HCl (VI), droperidol (VII), fluanisone (VIII), pimozide (IX) and fluspirilene (X). I was obtained from Dainippon Pharmaceutical (Osaka, Japan), II from Yamanouchi Pharmaceutical (Tokyo, Japan), III and IV from Yoshitomi Pharmaceutical Industries (Osaka, Japan), V and VI from Eisai (Tokyo, Japan), IX from Fujisawa Pharmaceutical (Osaka, Japan) and VII, VIII and X from

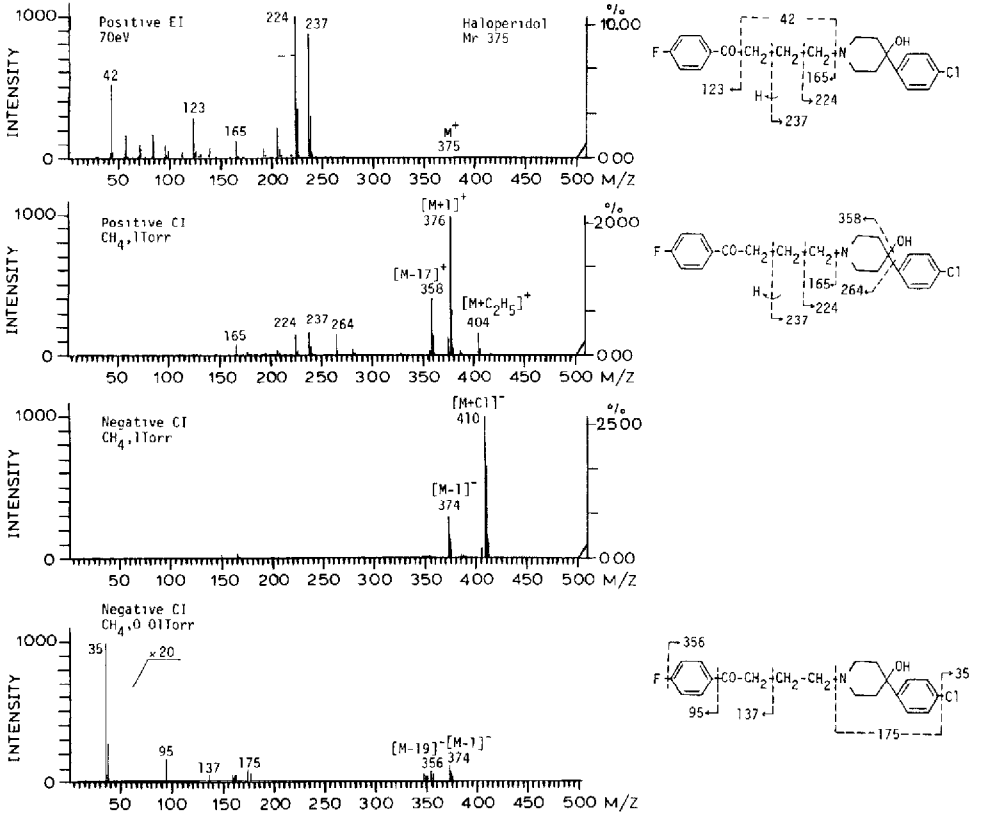

Fig. 1. Positive-ion EI, positive-ion CI, medium-pressure negative-ion CI and low-pressure negative-ion CI mass spectra of haloperidol (I) and its probable fragmentation modes.

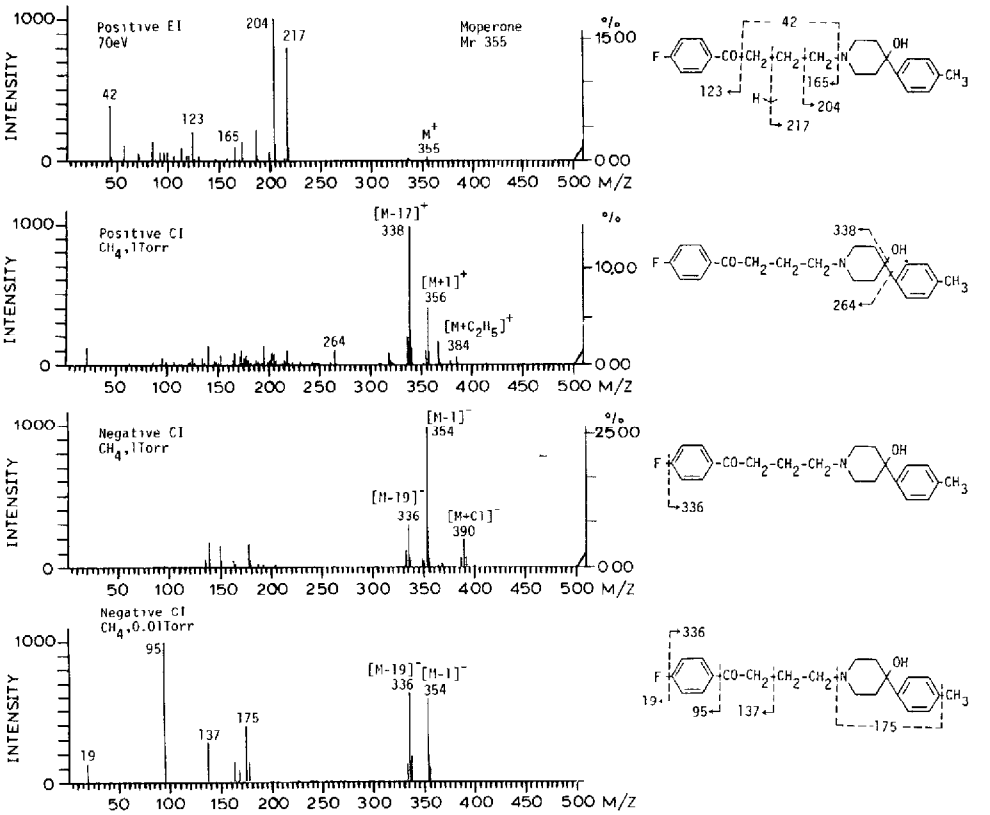

Fig 2. Positive and negative mass spectra of moperone (II) and its probable fragmentation modes.

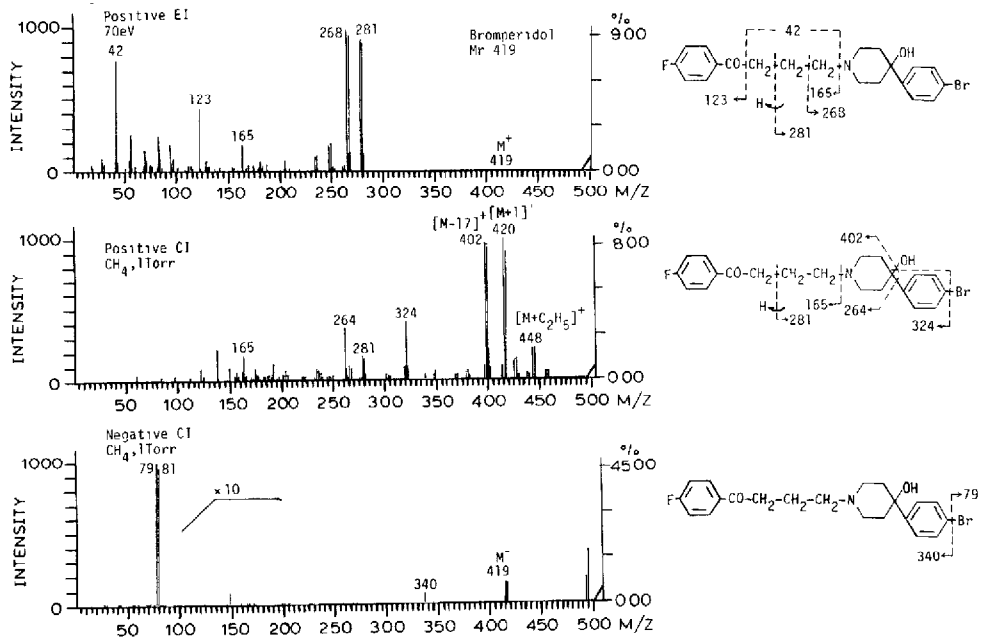

Fig. 3. Positive and negative mass spectra of bromperidol (III) and its probable fragmentation modes.

Janssen Pharmaceutica (Beerse, Belgium). Extrelut was purchased from E. Merck (Darmstadt, F.R.G.) and 5% SP-2100 on Chromosorb W AW DMCS (60—80 mesh) from Gasukuro Kogyo (Tokyo, Japan). Other common chemicals used were of the highest purity commercially available.

Urine and serum obtained from healthy subjects were also used for addition tests with butyrophenones.

Mass spectrometric (MS) conditions

Mass spectra in the PIEI, PICI and medium-pressure NICI modes were recorded in Hamamatsu on a JMS-D300 GC—MS instrument with JMA-2000E computer-controlled data analysis system by the direct inlet method. Less than 1 μg of each butyrophenone dissolved in methanol was applied to the instrument. The MS conditions were as follows: accelerating voltage, 3.0 kV; ionization current, 300 μA; separator temperature, 280°C; ion source temperature, 220°C; in the PIEI mode, electron energy 70 eV; in the PICI and NICI modes, electron energy 200 eV; reagent gas, methane; chamber pressure, 1 Torr.

Mass spectra in the low-pressure NICI mode were recorded in Zürich on an LKB 2091 MS instrument, modified for CI-MS as described by Ryhage [6].

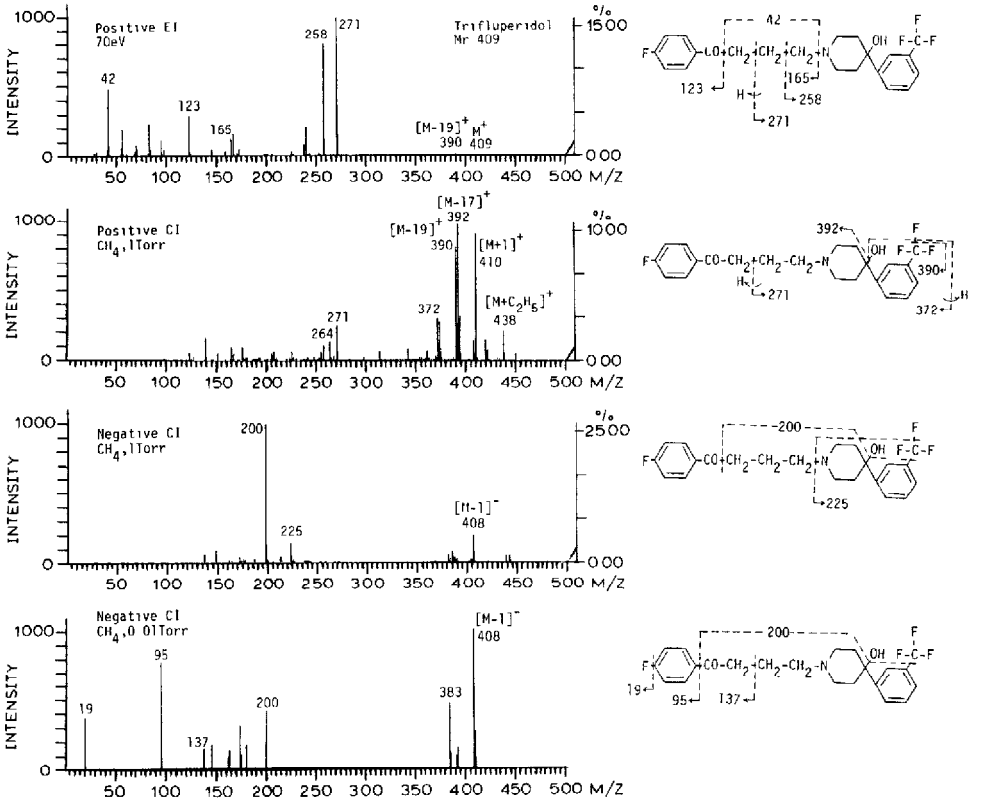

Fig. 4. Positive and negative mass spectra of trifluperidol (IV) and its probable fragmentation modes.

The MS conditions were as follows: accelerating voltage, 3.5 kV; ionization current, 250 μA; electron energy, 100 eV; separator temperature, 270°C; ion source temperature, 300°C; chamber pressure, 0.01 Torr.

Extraction and GC separation of butyrophenones

To 1 ml of urine or serum containing butyrophenones were added 1 ml of water and 0.25 ml of 10 *M* sodium hydroxide solution. The mixture was applied to 3 g of Extrelut packed in a 10-ml glass syringe. After standing for 30 min, the compounds were eluted with 10 ml of chloroform and the eluate was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 50—100 μl of methanol and subjected to GC analysis.

GC was carried out on a Shimadzu GC-4CM instrument with a 1.0 m × 3 mm I.D. glass column packed with 5% SP-2100 on Chromosorb W AW DMCS (60—80 mesh). The injection temperature was 300°C, column temperature 280°C and carrier gas (nitrogen) flow-rate 35 ml/min. The peaks appearing in the gas chromatogram were identified with the JMS-D300 GC—MS instrument.

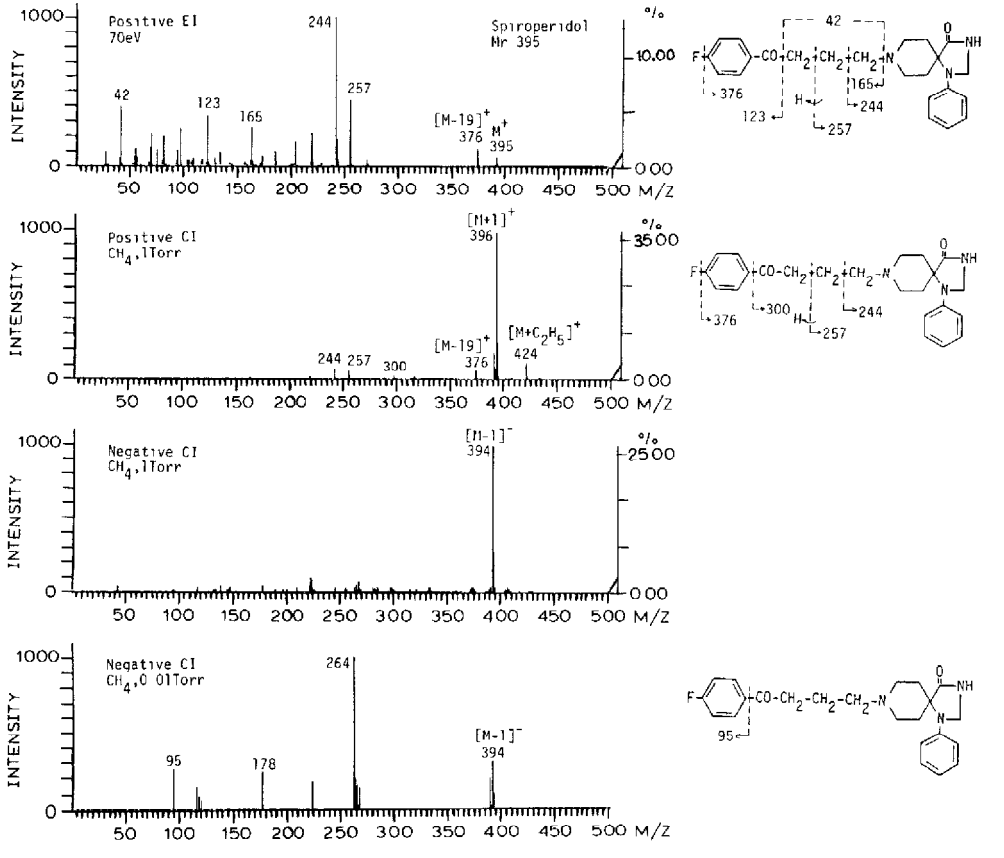

Fig. 5. Positive and negative mass spectra of spiroperidol (V) and its probable fragmentation modes.

RESULTS

PIEI mass spectra

PIEI, PICI, medium-pressure NICI and low-pressure NICI mass spectra of ten butyrophenones, and each probable fragmentation mode, are shown in Figs. 1—10.

In the PIEI mode, the peak at *m/z* 42 was commonly observed for all compounds, showing that it is due to the propyl chain liberated from the compounds. The peak at *m/z* 123, probably due to the fluorobenzoyl group, was also common to I—VIII; it did not appear, of course, with IX and X, which have a bis(fluorophenyl) group. Molecular cations were generally very small or missing in I—VII, but fairly large in the last three compounds. Cleavage of the propyl chain gave the strong peaks with most compounds.

PICI mass spectra

All compounds gave $[M+H]^+$ peaks, which constituted the base peaks in many instances. $[M+C_2H_5]^+$ peaks were also observed for most compounds.

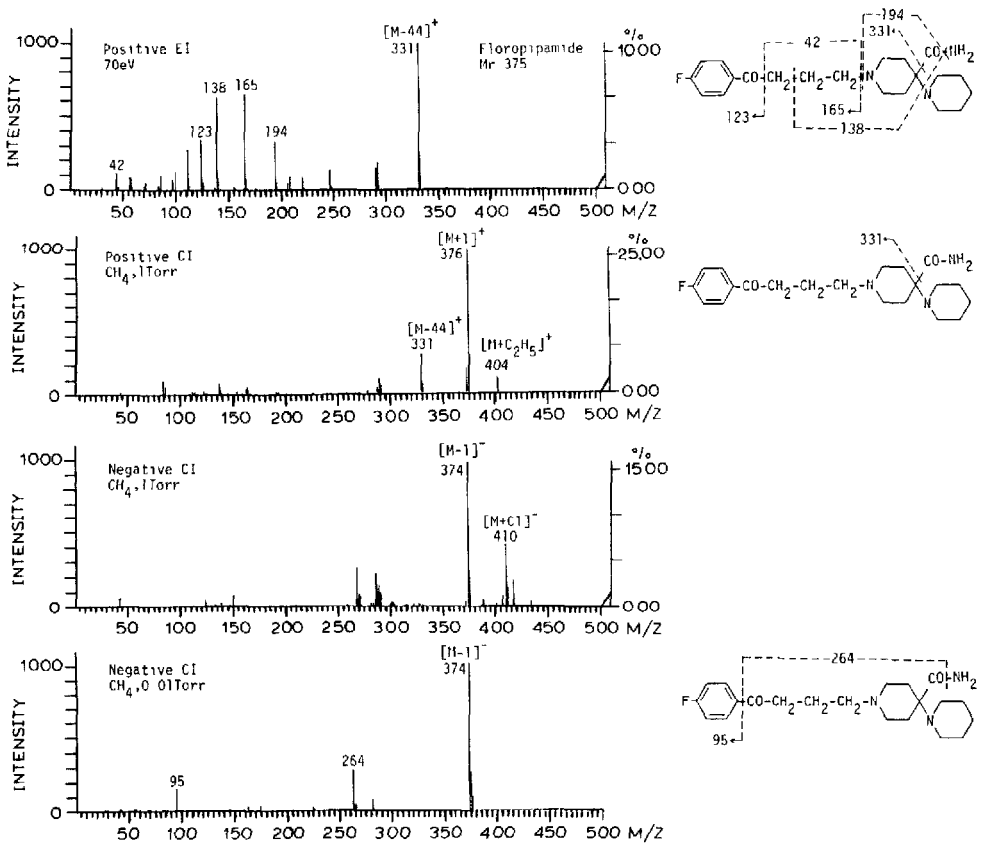

Fig. 6. Positive and negative mass spectra of floropipamide (VI) and its probable fragmentation modes.

For IV, V and VII—X, peaks due to $[M-F]^-$ appeared; for I—IV, which contain hydroxypiperidinyl groups, peaks due to $[M-OH]^+$ also appeared. There were minor cations due to cleavage of the propyl chain in many compounds.

NICI mass spectra at 1 Torr

NICI mass spectra at 1 Torr were much simpler than those in the above two modes. The $[M-H]^-$ quasi-molecular peaks were common to all compounds except III. For I, II, VI and IX, anions due to $[M+Cl]^-$ appeared.

NICI mass spectra at 0.01 Torr

In the NICI mode at 0.01 Torr in the chamber pressure, $[M-H]^-$ anions appeared similar to those at 1 Torr. However, more anions in the lower mass range appeared at this pressure. Halogen anions appeared with many compounds. A chloride ion was easily liberated under these conditions (Fig. 1); however, fluoride anion peaks were generally small (Figs. 2, 4 and 7). The anion at *m/z* 95, probably due to the fluorophenyl group, appeared in all the spectra.

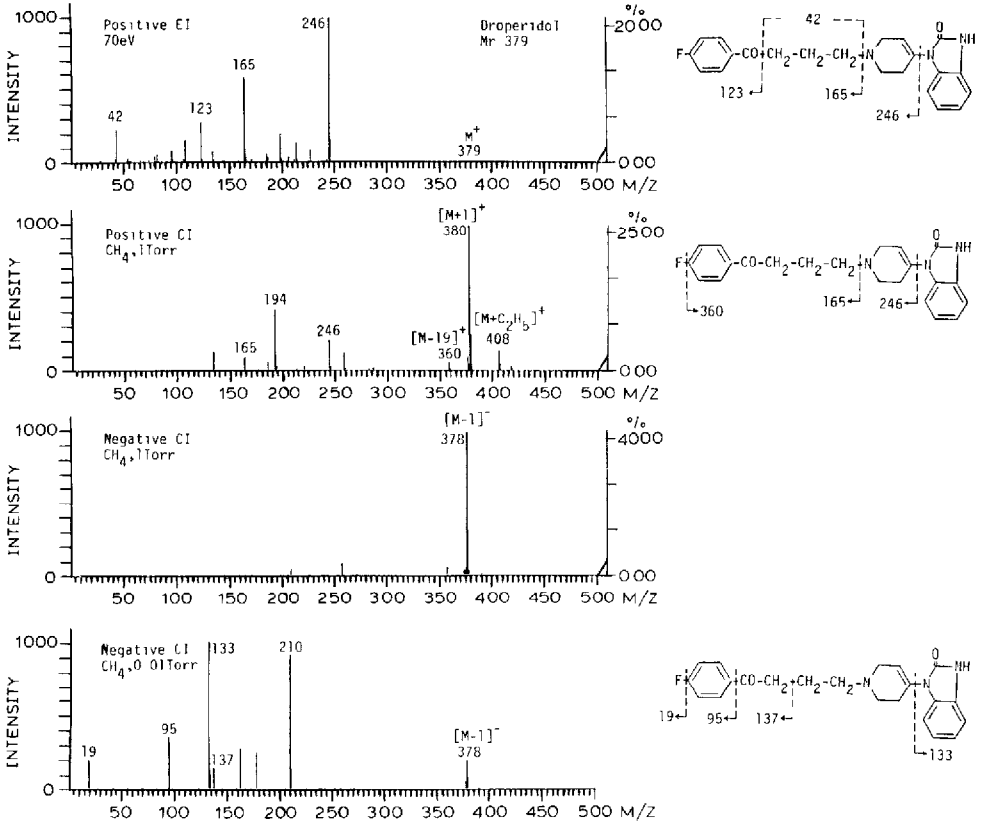

Fig 7. Positive and negative mass spectra of droperidol (VII) and its probable fragmentation modes.

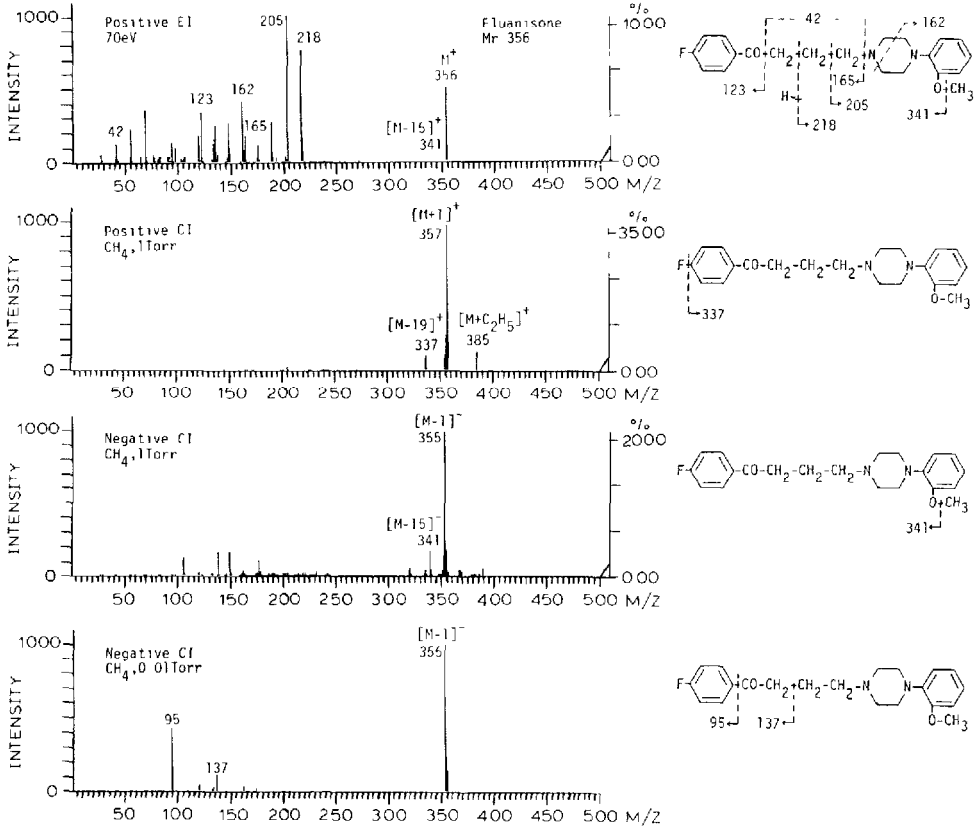

Fig. 8. Positive and negative mass spectra of fluanisone (VIII) and its probable fragmentation modes.

Separation of butyrophenones by GC

To identify butyrophenones in human samples by GC—MS, butyrophenones that had been added to urine or plasma were extracted with Extrelut columns and applied to a GC column (1 m × 3 mm I.D.) of SP-2100 on Chromosorb W at 280°C. The results are shown in Fig. 11. The separation of the compounds from biological impurities and from each other was satisfactory.

DISCUSSION

We have obtained PIEI, PICI and NICI mass spectra of ten butyrophenones that probably cover most of the butyrophenones now commercially available. Such studies, to our knowledge, have never been reported previously, although a few reports dealing with GC—MS assays of haloperidol [3—5] and PIEI mass spectra of some butyrophenones [7] have appeared.

We have presented NICI mass spectra at both low (0.01 Torr) and medium (1 Torr) pressures for some compounds (Figs. 1, 2 and 4—8). The low-pressure mode was first introduced by Ryhage and Brandenberger in 1978 [8] and is being used successfully in Brandenberger's laboratory [9] in forensic investiga-

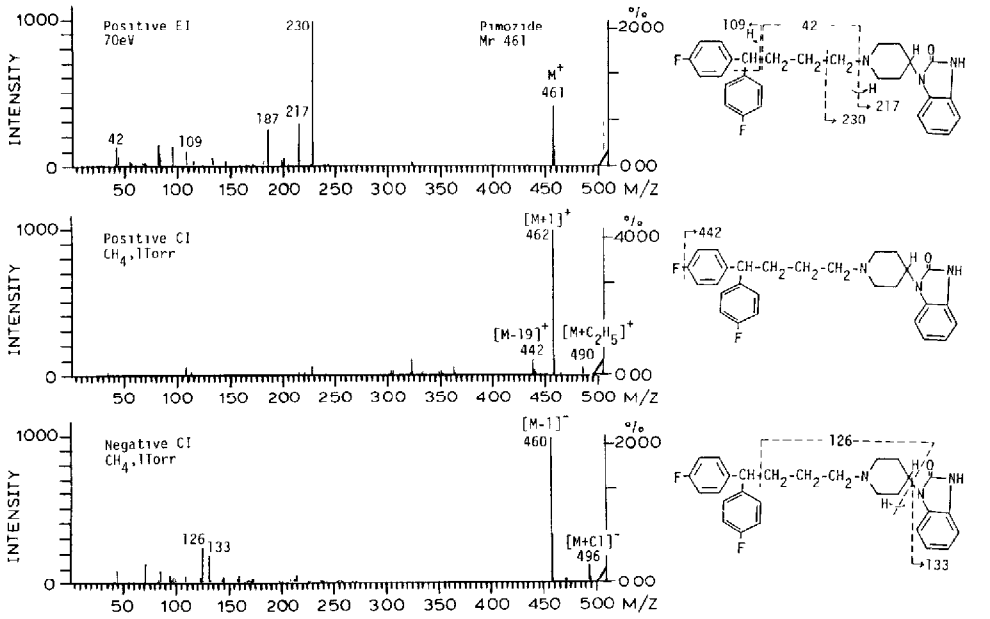

Fig. 9 Positive and negative mass spectra of pimozide (IX) and its probable fragmentation modes.

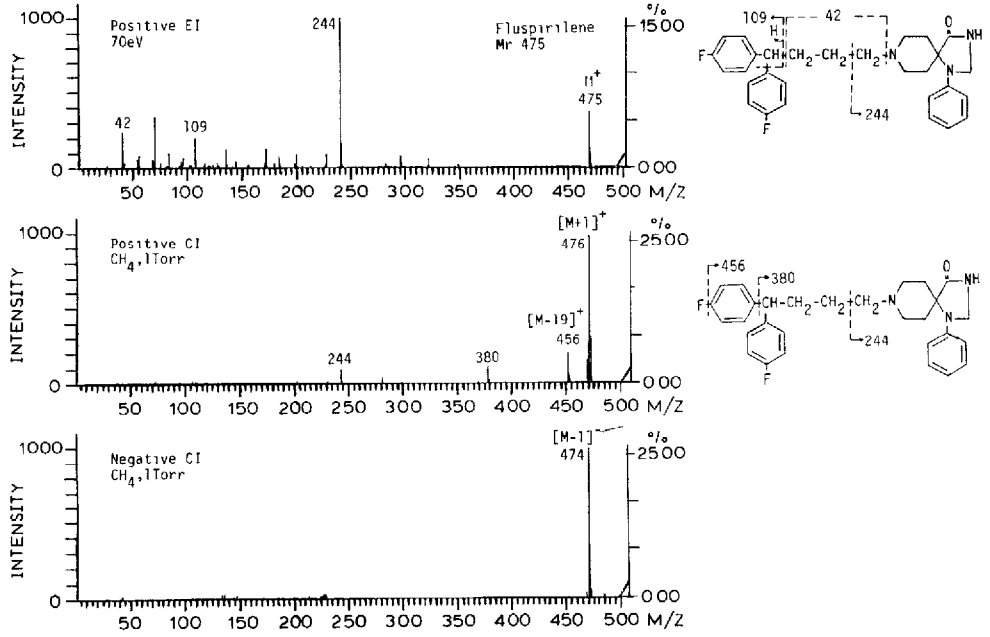

Fig. 10. Positive and negative mass spectra of fluspirilene (X) and its probable fragmentation modes.

tions. The main difference in the spectra at the different pressures is the appearance of more anions in the lower mass range in the low-pressure mode. At medium pressure the only halogen liberated was bromine (Fig. 3), whereas

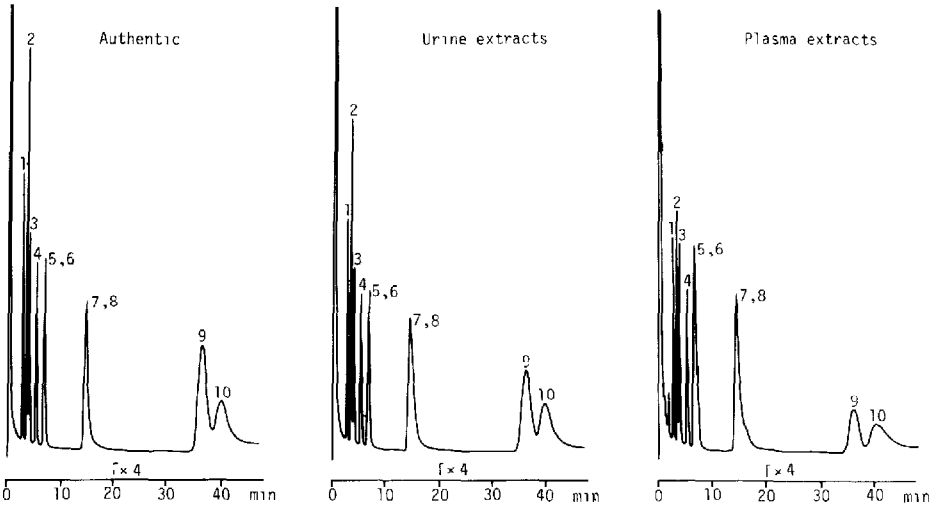

Fig. 11. GC separation of ten butyrophenones extracted from human urine or plasma. GC was carried out with a 1.0 m × 3 mm I.D. glass column packed with 5% SP-2100 on Chromosorb W AW DMCS (60—80 mesh). Column temperature, 280°C; nitrogen flow-rate, 35 ml/min. The mixture of ten butyrophenones (500 ng of each) was injected into the GC port. Equivalent amounts of butyrophenones were also added to human urine and plasma prior to Extrelut extraction. Peaks 1 = trifluperidol; 2 = fluanisone; 3 = moperone; 4 = haloperidol; 5 = floropipamide; 6 = bromperidol; 7 = spiroperidol; 8 = droperidol; 9 = fluspirilene; 10 = pimozide.

at low pressure chlorine and fluorine peaks appeared (Figs. 1, 2, 4 and 7). The halogen that can most easily be liberated is iodine, followed by bromine, chlorine and fluorine, i.e. in order of the activation energies required for their liberation [10].

Our interest is focused on the identification of butyrophenones by GC—MS in forensic samples. In the PIEI mode, the appearance of the peak(s) at m/z 42 and/or 123 is a good indication of the presence of a butyrophenone. The anions due to liberated halogens and/or at m/z 95 in the low-pressure NICI mode can also be used for screening.

The quasi-molecular peaks that appear in the PICI and medium-pressure NICI modes seem useful for the determination of their molecular weights. These peaks may be usable for the sensitive quantitation of butyrophenones by selected-ion monitoring, because they constitute the base peaks and show high percentages of total abundance in many compounds.

A strong cluster anion due to addition of a chloride ion appeared for haloperidol in the medium-pressure NICI mode (Fig. 1). This peak could not be deleted either after its extraction with the Extrelut column or after passage through a GC column, suggesting that Cl^- is firmly bound to haloperidol (unpublished observations). Such cluster anions also appeared with some other compounds (Figs. 2, 6 and 9), but never appeared in the spectra at low pressure. This effect seems to be due to the hydrochloride salts of butyrophenones used in this study. In this connection, such chloride attachment has been reported for organophosphate pesticides in the presence of methylene chloride as a chloride source [11].

In conclusion, we have established a simple method for the extraction of butyrophenones from human urine or plasma, and also their GC conditions (Fig. 11). These studies, together with the mass spectra (Figs. 1—10), should be very useful especially in forensic chemistry.

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