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Note

Gas chromatographic method for the analysis of butyrophenones based on the Hofmann degradation reaction

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The butyrophenones are a class of drugs used both in psychiatry and anesthesiology. Gas chromatographic (GC) methods by electron capture have been reported for haloperidol and trifluperidol[1–3]. We are not aware of a GC method for the analysis of droperidol, a butyrophenone widely used in conjunction with fentanyl in general anesthesia and in the specific technique of neuroleptanesthesia.

Many drugs with poor GC characteristics are usually analyzed after a suitable derivatization procedure which modifies and improves GC characteristics by increasing sensitivity and reducing retention times. However, many basic drugs are tertiary amines and do not readily undergo derivatization. Recently, drugs in the phenothiazine group and other tertiary amine drugs have been derivatized using the Hofmann degradation reaction to produce products with shorter retention times[4]. The present paper reports the successful application of the Hofmann degradation reaction to droperidol, haloperidol and penfluridol.

EXPERIMENTAL

Procedure

The drugs were derivatized using the following procedure.

To the drug solution in benzene is added 1 ml of methyl iodide. The mixture is left at ambient temperature for about 15 min, after which benzene is evaporated under a stream of nitrogen. The residue is dissolved in suitable amount of methanol. A knife-pinch of silver oxide is added to the methanol solution. The vial is gently shaken and left undisturbed for silver oxide to settle down. The supernatant is carefully transferred to another vial by a pasteur pipette. A suitable aliquot is then injected into a gas chromatograph for analysis.

Gas chromatographic details

A Varian 2100 gas chromatograph, fitted with a flame ionization detector was used with oxygen-free nitrogen as the carrier gas at a flow-rate of 50 ml/min. The glass column was 6 ft. (4 mm I.D., 6 mm O.D.) packed with 3% OV-17 on Chromosorb W HP (80–100 mesh). The column temperatures were 150° for droperidol and haloperidol and 175° for penfluridol. The injector port and detector temperatures

were kept at 300°. Identification of the GC peaks was established by a Varian CH-7 gas chromatograph–mass spectrometer, coupled to a Varian MAT SS-100-MS data system. The energy of the ionization beam was kept at 70 eV while the accelerating voltage was 3 kV and the emission current was 300 μA. The temperatures of the Watson–Biemann separator and of the ion source were maintained at 280°.

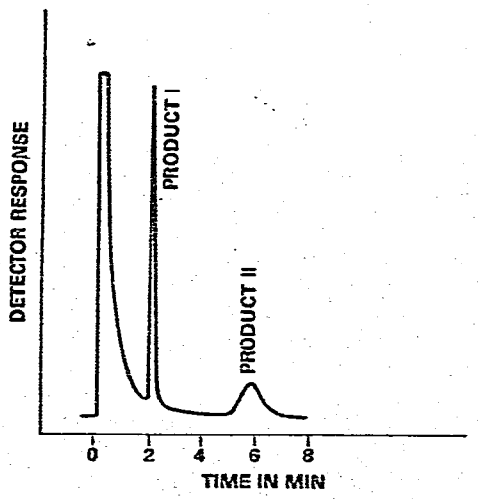
RESULTS AND DISCUSSION

There is considerable literature concerning the pharmacology and the clinical properties of butyrophenone drugs[5–9]. However, only a few methods of analysis are known. Demoen[10], Thomas and Dryon[11] and Haemers and Van den Bossche[12] have described colorimetric methods for the analysis of haloperidol, while Soep[13] employed paper chromatography to determine the fluorine content of haloperidol spot from the urine extract of rats. GC techniques for the butyrophenone drugs have also been reported[1–3]. Marcucci *et al.*[2] have described GC conditions for several butyrophenones except droperidol.

We have attempted a new approach to the analysis of butyrophenones based on the Hofmann degradation reaction. Haloperidol, droperidol and penfluridol readily underwent Hofmann degradation reaction to form the "butyrophenone" fragments characterized by short retention times and symmetrical peak shapes.

Haloperidol showed two peaks (Fig. 1) and the two products were assigned tentative structures based on their low resolution mass spectra (Fig. 2). The proposed reaction mechanism for haloperidol is summarized in Fig. 3.

Droperidol showed a single distinct peak at lower temperature whose retention



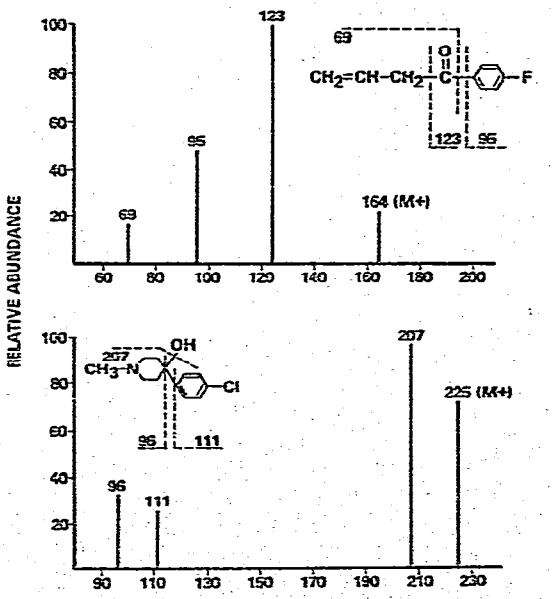


Fig. 1. GLC trace of haloperidol Hofmann reaction products.

Fig. 2. Top: mass spectrum of product I from haloperidol; bottom: mass spectrum of Product II from haloperidol.

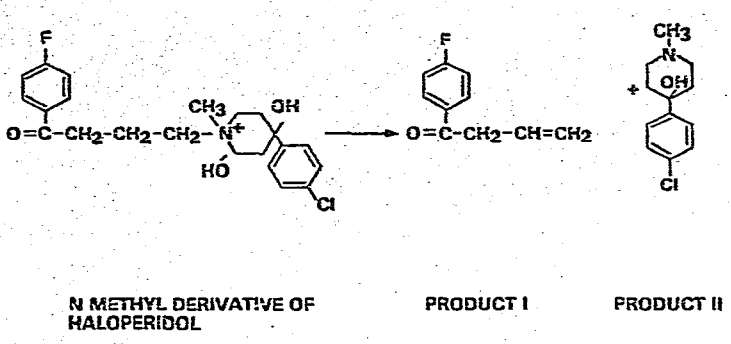


Fig. 3. Hofmann degradation of haloperidol.

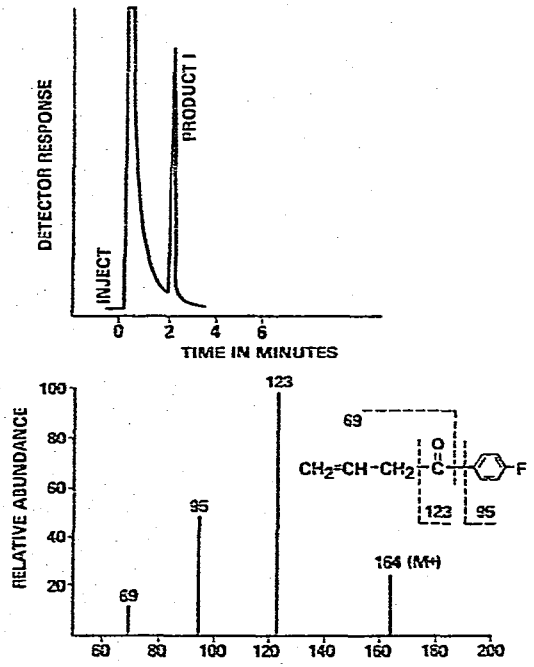


Fig. 4. Top: GLC trace of droperidol Hofmann reaction product; bottom: mass spectrum of product I from droperidol.

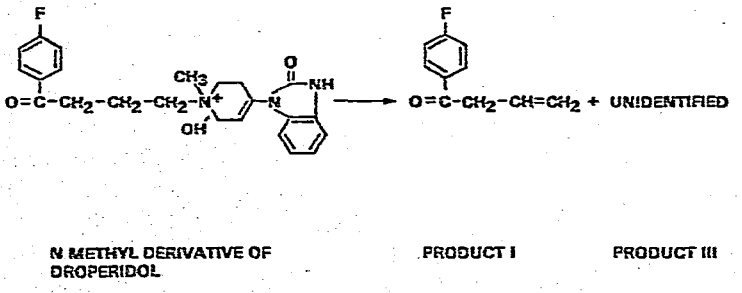


Fig. 5. Hofmann degradation of droperidol.

time and structure was identical to the first product from haloperidol (Fig. 4). A second peak of a more polar product with long retention time was detected by GC at 225°, but no attempt was made to identify this product by gas chromatography–mass spectrometry. The proposed reaction mechanism for droperidol is summarized in Fig. 5.

Penfluridol showed two well defined peaks (Fig. 6) and the two products were tentatively assigned the structures, based on their mass spectra, shown in Fig. 7. The proposed reaction mechanism for penfluridol is summarized in Fig. 8.

The yield of the droperidol Hofmann reaction was determined by derivatization of five droperidol samples of same concentrations. The derivatized samples were analyzed by GC under similar experimental conditions. No underivatized droperidol was seen in any of the samples, indicating total derivatization of the drug and completeness of the reaction. The peak heights of the two fragments from the injections

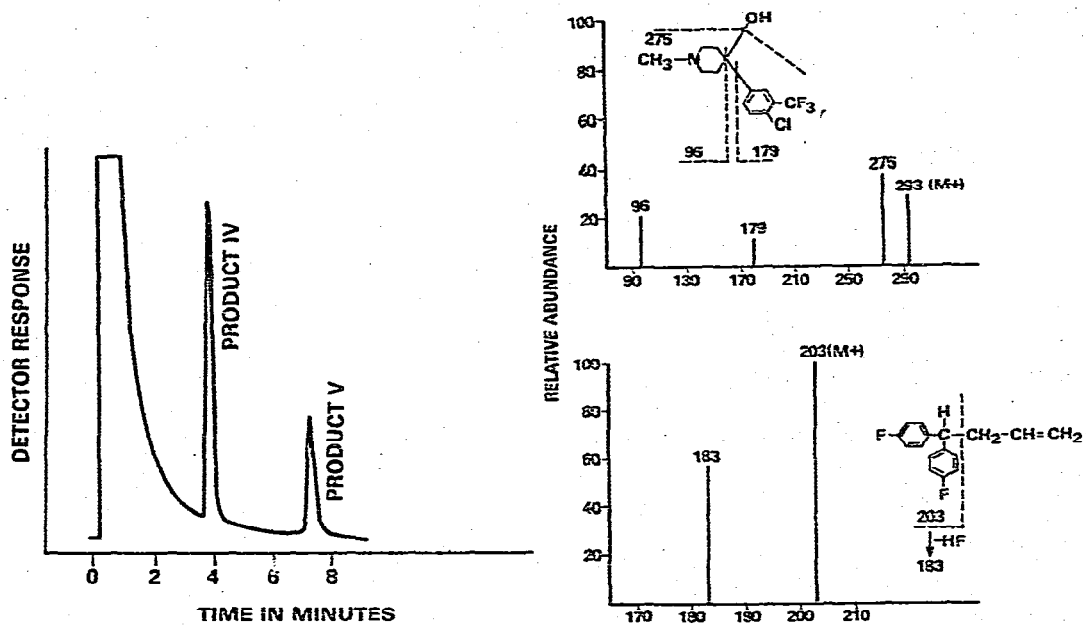


Fig. 6. GLC trace of penfluridol Hofmann reaction products.

Fig. 7. Mass spectra of product V (top) and product IV (bottom) from penfluridol.

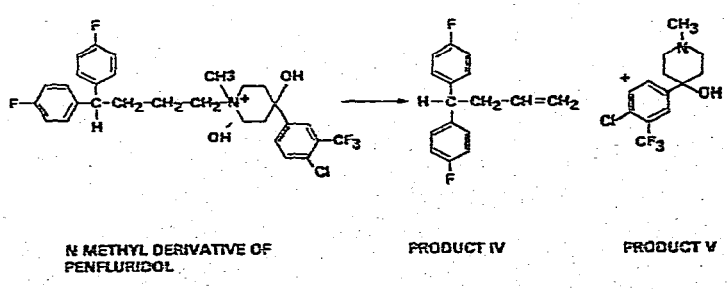


Fig. 8. Hofmann degradation of penfluridol.

of the same volume of five derivatized samples have been summarized in Table I. The reproducibility of the method was examined by repeated injections of the same volume of the same derivatized sample as summarized in Table II.

TABLE I

SUMMARY OF THE PEAK HEIGHTS OF THE TWO FRAGMENTS FROM THE DROPERIDOL-HOFMANN DERIVATIZED SAMPLES

Sample No.	*Amount injected (mg)*	*Peak heights (cm)*	
		Butyrophenone fragment	*Second fragment*
1	10.0	14.25	13.1
2	10.0	14.00	12.5
3	10.0	13.45	11.4
4	10.0	15.2	12.3
5	10.0	14.5	11.7
Mean		14.28 ± 0.64	12.20 ± 0.67

TABLE II

REPRODUCIBILITY OF THE BUTYROPHENONE FRAGMENT FROM A DERIVATIZED SAMPLE IN THE DROPERIDOL HOFMANN REACTION

Injection No.	*Peak height of butyrophenone fragment (cm)*
1	14.6
2	14.8
3	14.8
4	14.2
5	14.2
6	14.9
Mean	14.58 ± 0.31

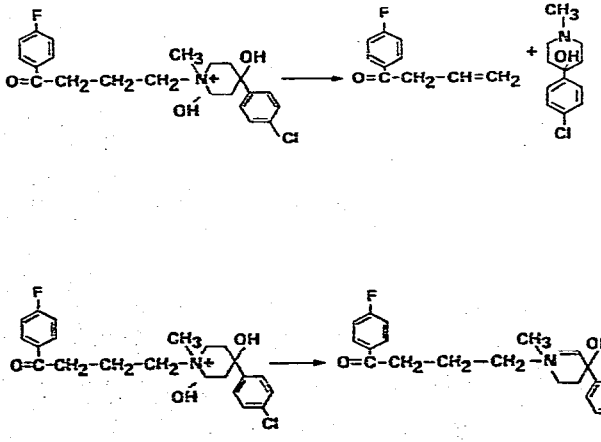


Fig. 9. Possible degradation pathways of haloperido[1] Top: elimination pathway I; bottom: elimination pathway II.

The analogous degradation of the three butyrophenones suggests that the Hofmann degradation reaction can be successfully applied to other butyrophenones as well. Of particular significance is the formation of the two characteristic butyrophenone fragments observed in the case of haloperidol, droperidol (product I) and penfluridol (product IV), respectively. Two possible degradation pathways are shown in Fig. 9, using derivatized haloperidol as an example.

The reproducible and regular elimination of the side-chain in the three butyrophenones suggests that there is a strong driving force towards that particular pathway I. The formation of the butyrophenone, products I and IV, was always observed. With droperidol, the second product was not observed at low column temperature; haloperidol showed both products; penfluridol showed both products IV and V consistently.

The Hofmann degradation products of butyrophenones are characteristic of the drugs. For droperidol, the method represents the first description of a technique that permits its analysis by GC. The chemistry described gives a novel approach to dealing with the GC of the refractory butyrophenones.

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