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Identification of Drugs and Their Derivatives

Identification of abused drugs is a primary endeavor of any comprehensive drug program. While Delaware State College's drug analysis program has long since established workable techniques for the primary screening of drugs in blood, saliva, and urine samples, we investigated rather novel areas, particularly the confirmation of drug identity in confiscated pills by instrumental analyses and the preparation and analysis of derivatives of these drugs. This investigation included these objectives:

(1) preparation of reference spectra of some drugs (infrared, ultraviolet, and gas chromatography were most desirable for this purpose);

(2) perfection of the procedures for producing convenient drug derivatives;

(3) determination of the pill quantities required to proceed through preparation, extraction, purification, and analysis of detectable quantities of a drug or its derivatives; and

(4) development of reasonable proposals for certain other drugs to be analyzed by the derivative procedures used.

Investigated Drugs

Two drugs of interest to the drug analysis program are the narcotic analgesics Darvon® (propoxyphene hydrochloride) and Demerol® (meperidine hydrochloride). The intriguing possibility that propoxyphene hydrochloride might be metabolized into meperidine hydrochloride in the body when taken in conjunction with ethanol was made credible by several recent clinical cases. Analysis by thin-layer chromatography of the urine of several individuals given propoxyphene hydrochloride revealed the presence of meperidine hydrochloride, with the notable absence of propoxyphene hydrochloride. This possibility is currently being investigated by the drug analysis laboratory at Delaware State College.

An examination of structures of these drugs reveals many basic similarities. Functionally, each is an ester (Fig. 1) [*1*] and exists as the hydrochloride salt of a tertiary amine. Conversion of propoxyphene hydrochloride into meperidine hydrochloride would necessitate closure into a ring, with loss of one phenyl and one methyl group. Such changes are possible within the body's metabolic capabilities.

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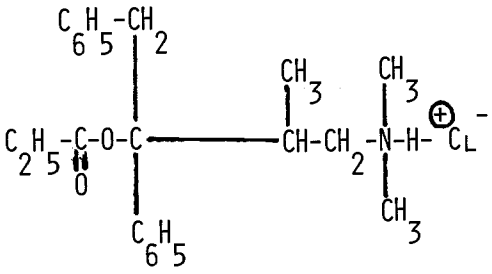
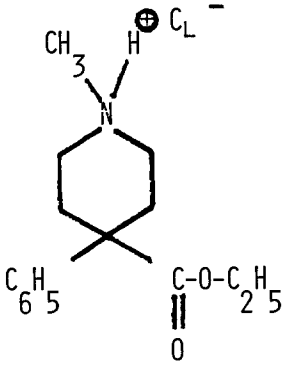


DARVON® (PROPOXYPHENE HCL)

MOL. WT. 375.9



DEMEROL® (MEPERIDINE HCL)

MOL. WT. 283.8

FIG. 1—*Structures of Darvon® (propoxyphene hydrochloride) and Demerol® (meperidine hydrochloride).*

The ensuing discussion is subdivided into two main areas: analysis of the parent drugs and analysis of derivatives.

Analysis of Parent Drugs

Preparation of Infrared Samples

Infrared spectra can be obtained on acidic and basic extracts of propoxyphene hydrochloride and meperidine hydrochloride (Fig. 2) [2]. Preparation of an acidic extract involves adding 5 ml of chloroform ($CHCl_3$) to half of a powdered pill, followed by adding enough concentrated hydrochloric acid (HCl) solution to render the mixture acidic (usually several drops); basic extracts require use of an ammonia solution with the $CHCl_3$.

After the acidic or basic mixture has been thoroughly shaken, water is removed by molecular sieves; these neutral drying agents provide the advantage of leaving the desired pH unaltered while preventing contamination of the solution. Filtering through

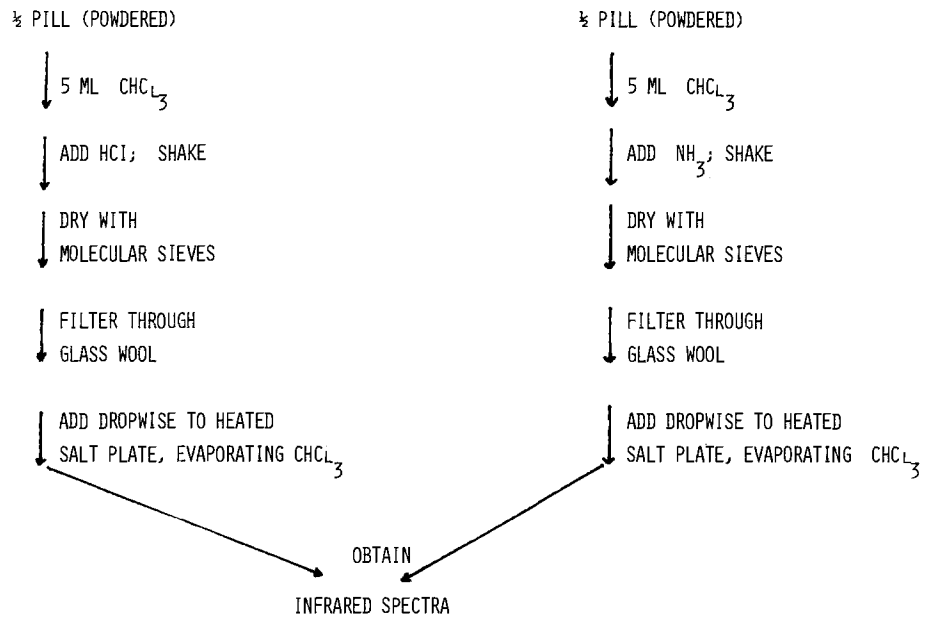


FIG. 2—*Preparation of infrared samples.*

glass wool or centrifugation serves to remove the insoluble filling material. Finally, the $CHCl_3$ solution can be added, a few drops at a time, to a heated (50 to 60°C or 122 to 140°F) salt plate, with evaporation of the solvent leaving a thin film of the drug. Spectra are obtained by mounting the salt plate and scanning through the infrared region with a spectrophotometer; reference cells are unnecessary because no solvent is present.

Analysis of Infrared Spectra

While several reference sources [*1–3*] can aid in the identification of unknown drugs from their prominent infrared peaks, proper confirmation of drugs whose identity has already been tentatively established necessitates demonstration of infrared peaks characteristic of all functional groups in the compounds. Propoxyphene hydrochloride and meperidine hydrochloride should both reveal prominent ester peaks around 1725 and 1200 cm^{-1}, aromatic stretches at 750 and 690 cm^{-1} (monosubstituted benzene), aliphatic and aromatic C-H stretches around 3000 cm^{-1}, a notable absence of N-H peaks in the 3100 to 3500-cm^{-1} region in the basic extracts (since the drug then exists as the free tertiary amine), and the distinct presence of a broad band from 2500 to 2800 cm^{-1} in acidic extracts, indicative of amine hydrochlorides [*2*, pp. AD14K and AD103K]. All of the above features were indeed realized.

It should be mentioned that while scrutiny of the infrared spectra for distinctive functional groups revealed little difference between propoxyphene hydrochloride and meperidine hydrochloride, the sum of all overtone, stretching, and bending vibrations serves as a unique "fingerprint" for each drug. Infrared spectra alone, therefore, could serve as convincing confirmation of identity, should the spectra of a drug under question match those for one contained in Ref *2*. Alternatively, one can always prepare his own reference spectra using standard drug samples.

Preparation of Ultraviolet Samples

Sample preparation for ultraviolet spectra was quite simple (Fig. 3). Acidic and

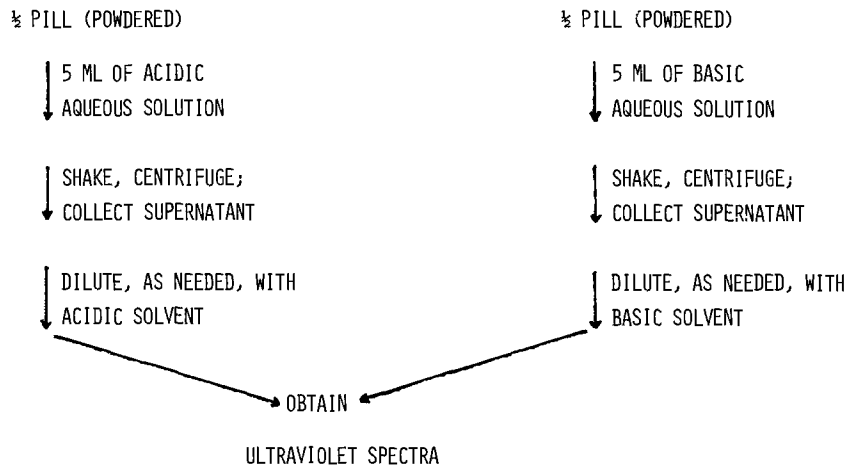


FIG. 3—*Preparation of ultraviolet samples.*

basic salts were prepared by dissolving the powdered pill in 5 ml of an appropriate acidic or basic aqueous solution, centrifuging, collecting the supernatant, and diluting, as needed, with the solvent to obtain spectra. A reference cell was prepared by using the solvent without any drug. Samples were observed over the 350 to 200 nm range.

The type and concentration of acid or base used for these spectra are appropriately dictated by Table 32 of Ref *3*. Such solutions are best suited for making characteristic peaks evident.

Analysis of Ultraviolet Spectra

Characteristic ultraviolet spectra aid in identifying and confirming drugs yet are incapable of confirmation by themselves because it is impossible to accurately deduce the functional groups that are indicated by given peaks.

Inspection of the spectra for propoxyphene hydrochloride and meperidine hydrochloride again reveals their close similarity. The trio of peaks at 251, 257, and 263 nm in these acidic extracts suggest the occurrence of at least one benzene ring in each of the drugs; the fact that propoxyphene hydrochloride contains two such rings, as compared to one in meperidine hydrochloride, is verified by the stronger absorption of the former.

Preparation of Gas Chromatographic Samples

Extraction of the drug into an organic solvent for analysis by gas chromatography is a straightforward process. Following vigorous shaking of a mixture of the powdered pill, 3 ml of cyclohexane, and 2 ml of saturated borax solution, centrifugation separates a clear organic supernatant containing the drug; propoxyphene and meperidine are extracted in the form of the free amine rather than the hydrochloride salt. Samples of the extract, in 1-μl units, are then injected into a gas chromatograph.

Gas Chromatographic Retention Time Study

Propoxyphene and meperidine are separated on a 4-ft (1.2-m) glass column packed with OV-17 at temperatures ranging from 140 to 240°C (284 to 464°F) with retention times varying from 1 to 12 min. The optimum temperature for meperidine was 180°C (356°F) and for propoxyphene, 210°C (410°F). As is the case with ultraviolet analysis, practically no idea can be gained about functional groups occurring in the

drugs. However, for a given set of column conditions (length, packing, flow rate, and temperature), a distinctive retention time results for any drug; this time provides additional confirmation.

Analysis of Drug Derivatives

Preparation of Ester Cleavage Products

A most convenient reaction for esters involves reduction of this functional group by $LiAlH_4$, in an organic solvent, followed by the addition of water (Fig. 4) [*4–6*]. Resulting from the single ester moiety are two cleavage products, both of them alcohols. Shown in Fig. 4 are the respective alcohols expected from propoxyphene and meperidine.

Esterification of Cleavage Products

Reaction of an alcohol with an acid anhydride in the presence of a pyridine catalyst

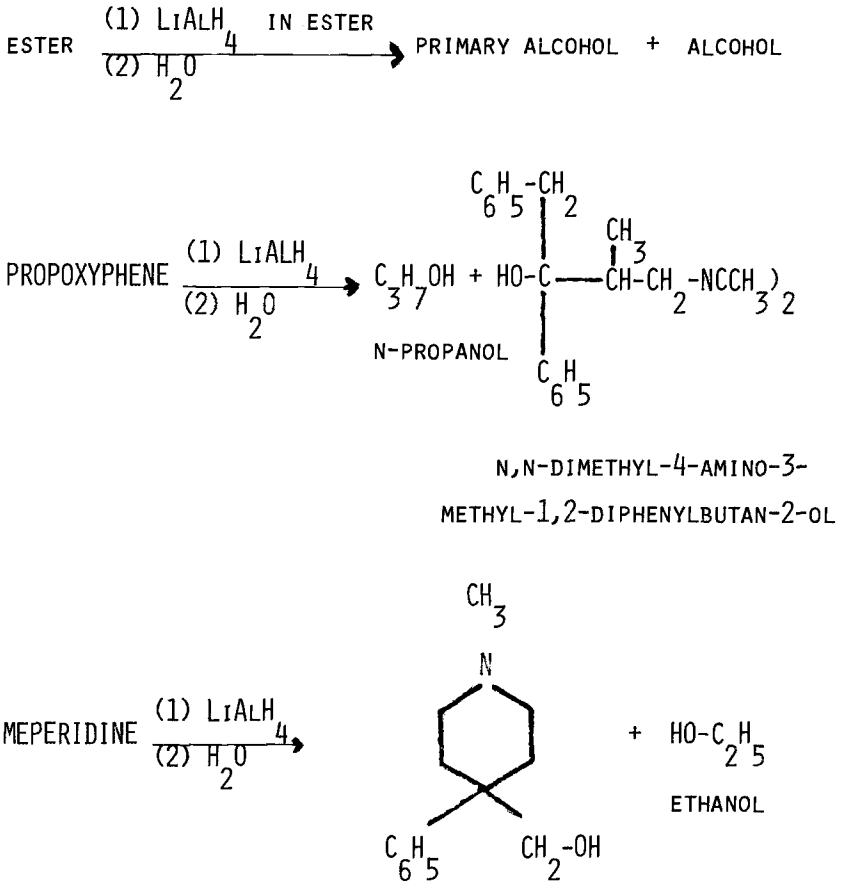


FIG. 4—*Preparation of ester cleavage products.*

results in the formation of a new ester-containing compound (Fig. 5) [7–9]. The two acid anhydrides used in our investigation were trichloroacetic and pentafluoropropionic anhydrides. These halogenated anhydrides provide higher reactivity than most other anhydrides, and their resulting halogenated ester derivatives can be detected, even at very minute concentrations, by gas chromatographic electron-capture detectors.

The ester derivatives resulting from carboxylation of propoxyphene's alcohols are demonstrated in Fig. 5. Figure 6 illustrates the corresponding ester derivatives obtained from meperidine's alcohols. The procedure for the preparation of cleavage products and their subsequent esterification is indicated in Fig. 7. Analysis is primarily by gas chromatography, although preparation of infrared spectra is possible for the heavy molecular weight alcohol derivatives.

Retention Times for Drug Derivatives

Gas chromatographic retention times for the parent drug and its heavy molecular

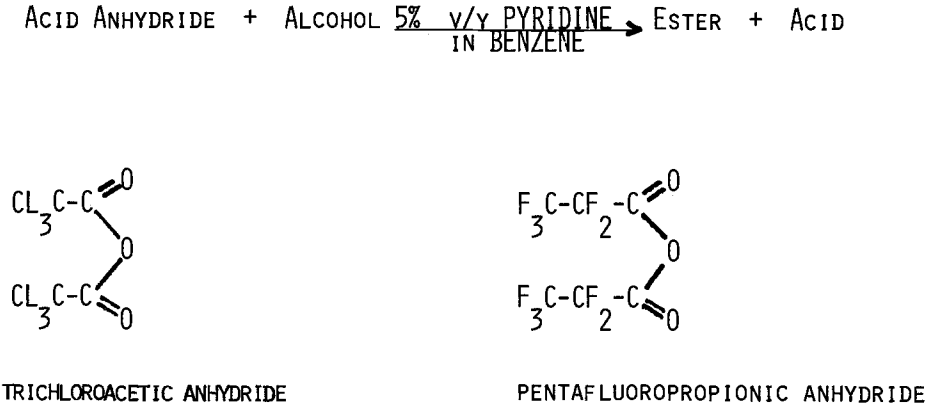


FIG. 5—*Esterification of cleavage products in general and propoxyphene in particular.*

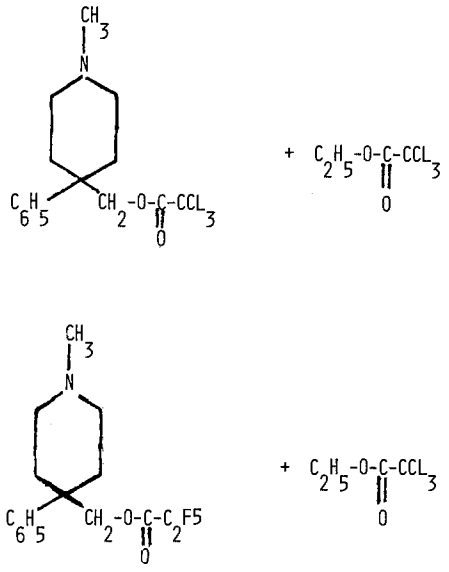


FIG. 6—*The esterification of meperidine's alcohol.*

weight derivatives are shown in Fig. 8. Keeping column conditions identical for a given drug and its derivatives, the retention time for the parent drug was assigned a value of unity; derivatives' times are compared to this figure. Retention times for the

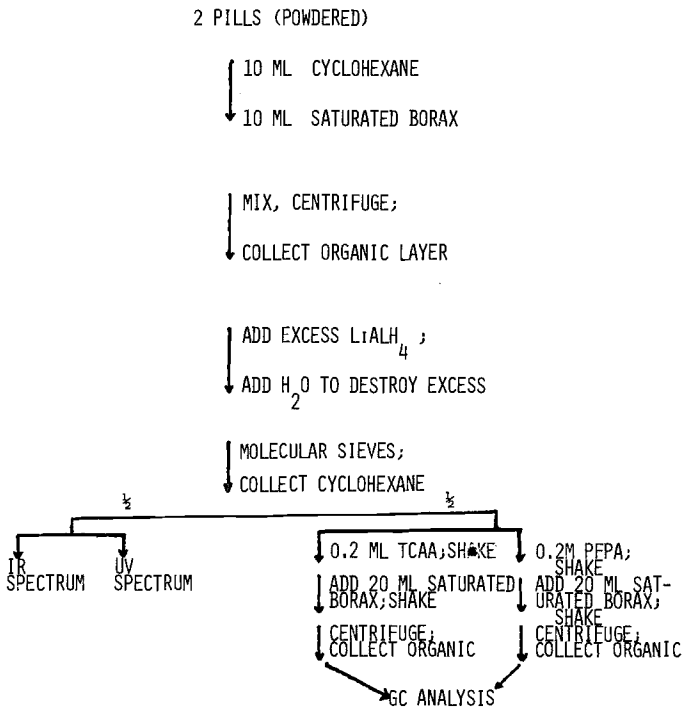


FIG. 7—*Preparation of derivatives for gas chromatographic analysis (TCAA = trichloroacetic anhydride and PFPA = pentafluoropropionic anhydride).*

COMPOUNDS	DEMEROL® (170°C)	DARVON® (210°C)
PARENT DRUG	1.00	1.00
ALCOHOL	0.83	0.64
TRICHLOROACETIC ESTER	---	0.86*
PENTAFLUOROPROPIONIC	0.58	0.37

*REQUIRED ELECTRON CAPTURE DETECTOR

FIG. 8—*Gas chromatographic retention times for drug derivatives based on 1 for the parent drug.*

low molecular weight derivatives are not reported since these relatively volatile compounds were invariably obscured by the large solvent peak (cyclohexane).

Infrared Analysis of Derivatives

Inasmuch as gas chromatographic examination of propoxyphene's and meperidine's alcohols revealed the total disappearance of the parent drug peak, 100% cleavage of these esters apparently occurs if sufficient $LiAlH_4$ is used. Infrared spectra can be obtained from the cyclohexane solution of alcoholic derivatives. By preparing a salt plate film as previously described, the solvent and low molecular weight alcohol are evaporated, leaving only the larger molecular weight alcohol.

Infrared spectra thus acquired reveal that prior ester peaks at 1725 and 1200 cm^{-1} have completely vanished, while a broad $-OH$ peak has appeared above 3000 cm^{-1} (Figs. 9–12).

Discussion

The classical procedures used for confirming the parent drugs by infrared spectroscopy, ultraviolet spectroscopy, and gas chromatography should be readily applicable to any drug. The spectra thus obtained may, in themselves, provide all the proof of identity necessary.

Esters are paricularly suitable for reduction to alcohols, and these can be smoothly converted into new esters. Such confirmation should be readily acquired from most, if not all, ester-containing drugs, including cocaine, benzocaine, orthocaine, amylocaine, butacaine, procaine (Novocain®), aspirin, heroin, and many others.

Although we have not verified the conclusions, we believe that the following derivatives should be capable of being formed:

(1) primary alcohols by $LiAlH_4$ reduction of drugs that are functional carboxylic acids (or their salts),

(2) primary alcohols by $LiAlH_4$ reduction of aldehydes,

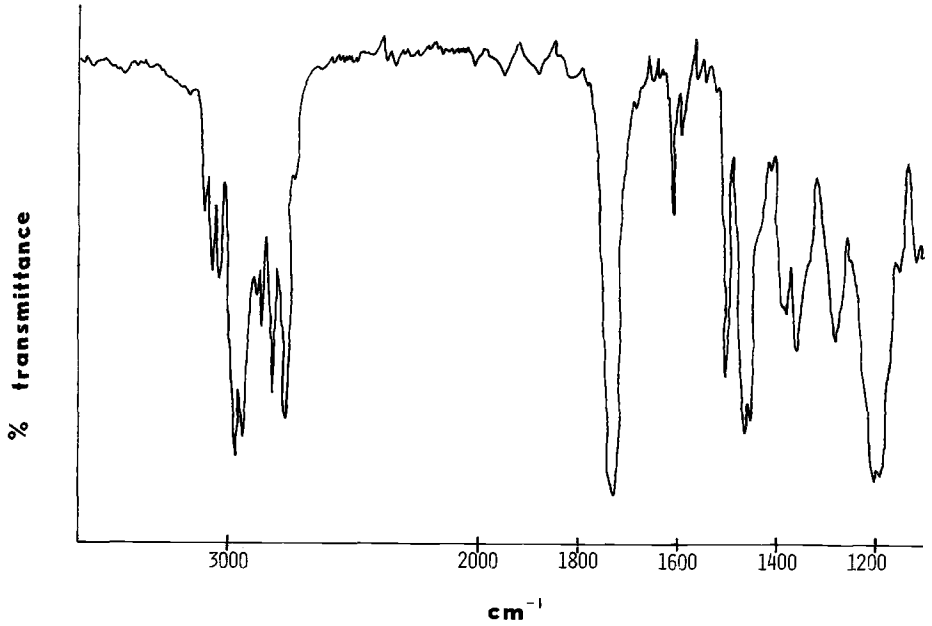


FIG. 9—*Infrared spectrum of propoxyphene hydrochloride.*

(3) secondary alcohols by $LiAlH_4$ reduction of ketones, and

(4) esters by reaction of acid anhydrides with alcohol-containing drugs or with alcoholic derivatives of parent drugs containing a carbonyl group.

Therefore, $LiAlH_4$ should reduce drugs containing a carbonyl group to alcohols; these alcohols, or any alcoholic drug, might then be converted to corresponding esters. When these procedures ensure that the final derivatives contain halogen atoms, then

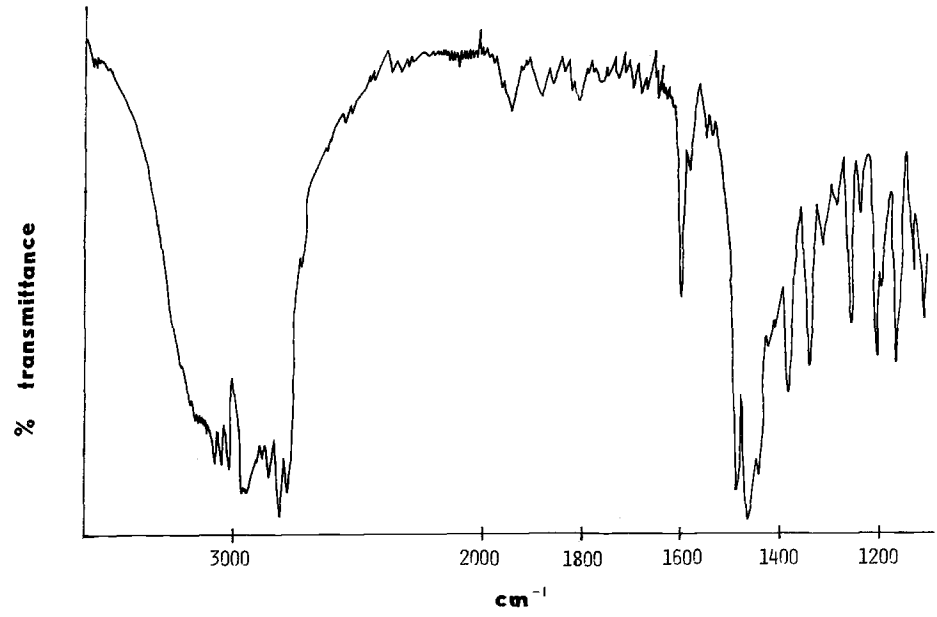


FIG. 10—*Infrared spectrum of propoxyphene hydrochloride's cleaved product (N,N-dimethyl-4-amino-3-methyl-1,2-diphenylbutan-2-ol).*

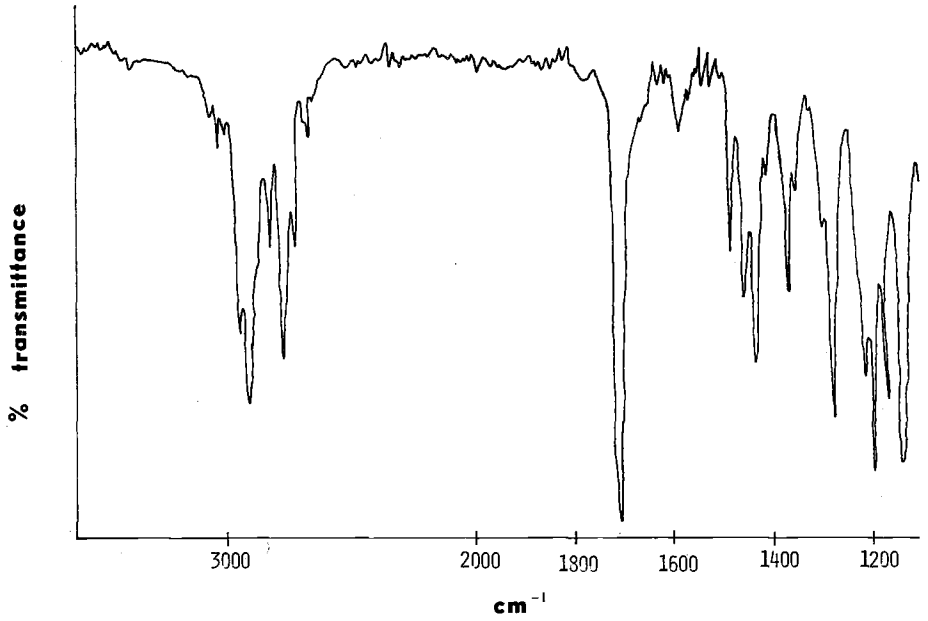


FIG. 11—*Infrared spectrum of meperidine hydrochloride.*

drugs can be confirmed in quantities as meager as those present in urine samples through use of an electron-capture detector [*4*]. Many interesting fields of investigation are thus proposed.

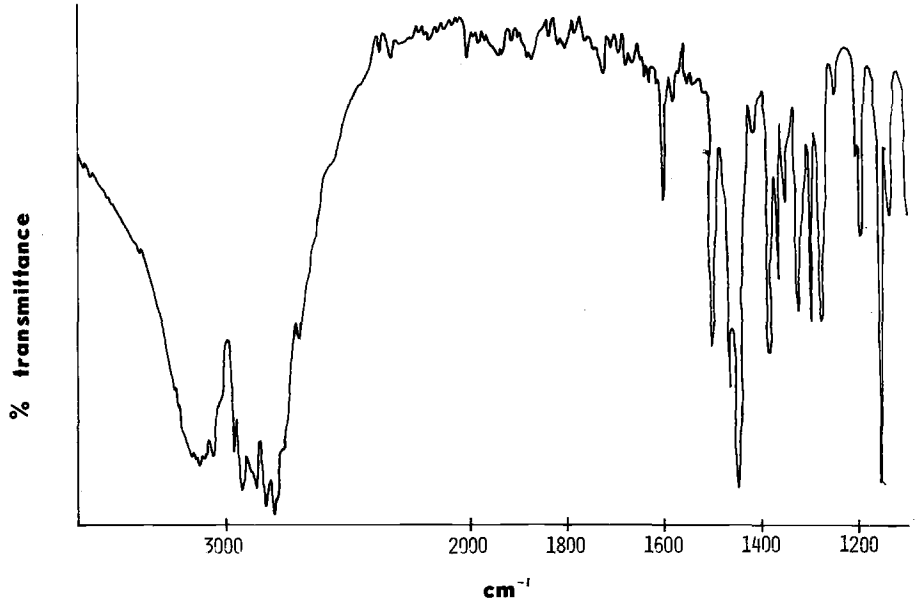


FIG. 12—*Infrared spectrum of meperidine hydrochloride's cleaved product (1-methyl-4-phenyl-4-hydroxy-methylpiperidine).*

Summary

This paper represents a brief review of traditional procedures for the analysis of confiscated drugs and the application of these procedures to the products formed after reductive fragmentation and halogen-acetylated derivatization of the drugs.

Confiscated pills, already tentatively identified by some previous procedure, were analyzed by the use of infrared spectroscopy, ultraviolet spectroscopy, and gas chromatography. The same drugs were confirmed by analyzing the alcohols obtained after reductive fragmentation with $LiAlH_4$ as well as the acetylated derivative fractions.

Infrared spectra were determined from salt plate films after the evaporation of acidic or basic chloroform extracts of the pill; similarly, ultraviolet spectra were obtained by processing each drug in acidic and basic aqueous solutions. Gas chromatographic analyses involved the determination of characteristic retention times as a function of temperature and the preparation of, and determination of retention times for, derivatives of the drugs.

No procedures were specifically included to remove filler material, save its sparing solubility in the extracting solvents; likewise, no special attempts were made to perfect special microtechniques which would allow all analyses to be performed on a single pill. Desired, rather, were the ease, simplicity, and relative speed realized from analysis of approximately five confiscated pills.

References

[1] Clarke, E. G. C., *Isolation and Identification of Drugs,* Pharmaceutical Press, London, 1971, pp. 290 and 476.

[2] *Commonly Abused Drugs, Infrared Grading Spectra,* Sadtler Research Laboratories, Inc., Philadelphia, 1972, p. i.

[3] Sunshine, I., *Handbook of Analytical Toxicology,* Chemical Rubber Co., Cleveland, 1969.

[4] Huffman, R., Blake, J. W., Ray, R., Noonan, J., Murdick, P. W., "Methylphenidate Blood Plasma Levels in the Horse Determined by Derivatives, Gas-Liquid Chromatography—Electron Capture," *Journal of Chromatographic Science,* Vol. 12, June 1974, pp. 382–384.

[5] Gaylord, N., *Reduction with Complex Metal Hydrides,* Interscience, New York, 1956, pp. 96–97.

[6] Roberts, J. D. and Caserio, M. C., *Basic Principles of Organic Chemistry,* W. A. Benjamin, Inc., New York, 1965, p. 535.

[7] March, J., *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* McGraw-Hill, New York, 1968, pp. 376–441.

[8] Buehler, C. A. and Pearson, D. E., *Survey of Organic Synthesis,* Wiley-Interscience, New York, 1970, pp. 651–653.

[9] Litt, M. H., Summers, J. W., and Shimks, T. M., *Journal of Organic Chemistry,* Vol. 57, No. 7, 1972, pp. 1045–1047.

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