TECHNICAL NOTE

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Analytical Characterization of Isoheroin

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ABSTRACT: The synthesis of isoheroin is presented with the analytical data (mass spectroscopy [MS], nuclear magnetic resonance [NMR], infrared spectroscopy [IR], and gas liquid chromatography [GLC]) for this compound. Comparison between analytical results for heroin and isoheroin shows differentiation is possible.

KEYWORDS: toxicology, isoheroin, spectroscopic analysis, chemical analysis

The morphine molecule contains five asymmetric carbons (C-5, C-6, C-9, C-13, and C-14) (Fig. 1). Focusing on position C-6 and the hydroxyl group at this position, it is realized that either an axial or equatorial posture is possible. In morphine, at least, as produced by *Papaver somniferium* L., the hydroxyl group is equatorial. From a nomenclature standpoint, the axial positioning has been designated the "ISO" compound; thus, isomorphine, isoheroin, and isocodeine would signify the functional group at C-6 being axial. It is the purpose of this paper to present the synthesis of isoheroin and the analytical data comparing heroin and isoheroin.

Chemicals and Equipment

All chemicals were analytical grade or better. The *N,N*-dimethylformamide dineopental acetal was obtained from Aldrich Chemical Co. (Milwaukee, WI) and the morphine from Mallinckrodt, Inc. (St. Louis, MO). Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 5880 (Palo Alto, CA). Packed columns were glass, 1.8 m (6 ft), 4-mm inside diameter (ID) containing either OV-1, 3% or OV-101, 10% on (100-120) gas Chrom Q (Applied Science, State College, PA) or OV-17, 3% on (100-120) gas Chrom Q (Alltech Associate, Deerfield, IL). Nitrogen was the carrier gas in the packed columns (30 mL/min) and a flame ionization detector (FID) was used to generate the signal. The capillary column was an Ultra #1 (Hewlett-Packard) cross-linked methyl silicone, 25*M*, 0.31-mm ID, with a 0.52-μm film thickness. Hydrogen was the carrier gas in the capillary column (linear velocity of 40 cm/s) and a FID was used to generate the signal.

Infrared data were obtained using a Perkin-Elmer (Norwalk, CT) Model 283 and pressed KBr pellets. Nuclear magnetic resonance (NMR) data were obtained using a Varian (Palo

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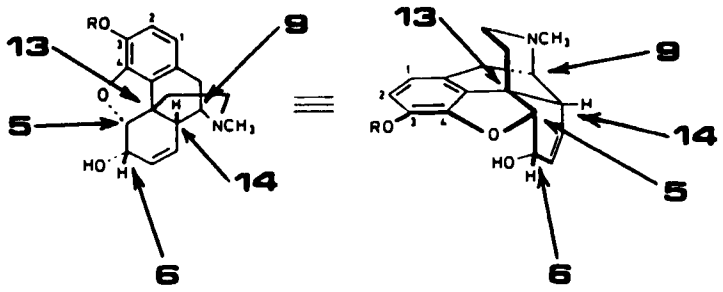

FIG. 1—*Two-and three-dimensional view of morphine type moeity.*
R = H: morphine

$$R = \overset{O}{\overset{\|}{C}}\text{-}CH_3\text{: monoacetylmorphine}$$

Alto, CA) Model EM390 with deuterochloroform ($CDCl_3$) as a solvent and tetramethylsilane (TMS) as a standard.

Mass spectral data were obtained using electron impact (EI) type fragmentation on a Finnigan (Sunnyvale, CA) Model 4530. Sample inlet was through an Ultra #1 capillary GLC column.

High pressure liquid chromatography (HPLC) was performed using a Whatman (Clifton, NJ) Magnum 9 ODS-3, 25-cm column using a Waters Associate (Milford, MA) Model 6000A pump and M440 ultraviolet (UV) detector at 280 nM. The mobile phase was methanol-water (MeOH-H_2O) (30:70), pH 3.5, 1% phosphoric acid (H_3PO_4), 0.02*M* methanesulforic acid (CH_4SO_3) at a flow of 4 mL/min.

Synthesis

The synthesis of isoheroin was based on the method used by Barber and Rapoport [*1*] for the synthesis of isocodeine. Their work utilized a sterically hindered acetal and paralleled a method used by Vorbruggen [*2*] for saturated secondary alcohols. In the present study, 0-3 monoacetylmorphine was reacted with a mixture of *N,N*-dimethylformamide dineopental acetal and acetic acid in toluene to form the isoheroin. After the removal of the toluene and acetal in vacuo, isoheroin was isolated using preparative HPLC.

Results

NMR

Utilization of spectral NMR data will readily distinguish between heroin and isoheroin (Figs. 2 through 4). From a magnetic standpoint, the protons at C-5, C-7, C-8, and C-14 in the "C" ring are greatly affected by the axial/equatorial position at C-6. A study by Batterham et al [*3*] focused on the coupling between H-6 and H-8 in the codeine and isocodeine molecules. Their observations suggested that the near 90° angle between H-6 (axial) and H-8 in codeine was ideal for allylic coupling; additionally, interaction between H-6 (A) and H-14 leads to homoallylic coupling. Further coupling, vicinal in this case, between H-6 (A) and H-5 and H-6 (A) and H-7 leads to a total of 16 peaks centered at 4.16 ppm for the C-6 proton in codeine. Isocodeine, however, with the C-6 proton equatorial produces a quartet (4.24 ppm) since both allylic and homoallylic coupling are not favored. While codeine has a hydroxyl group at C-6 and heroin has an acetyl group at this position, NMR results should at least in some respects mirror the codeine/isocodeine study. Unfortunately, in heroin the position of the H-6 proton

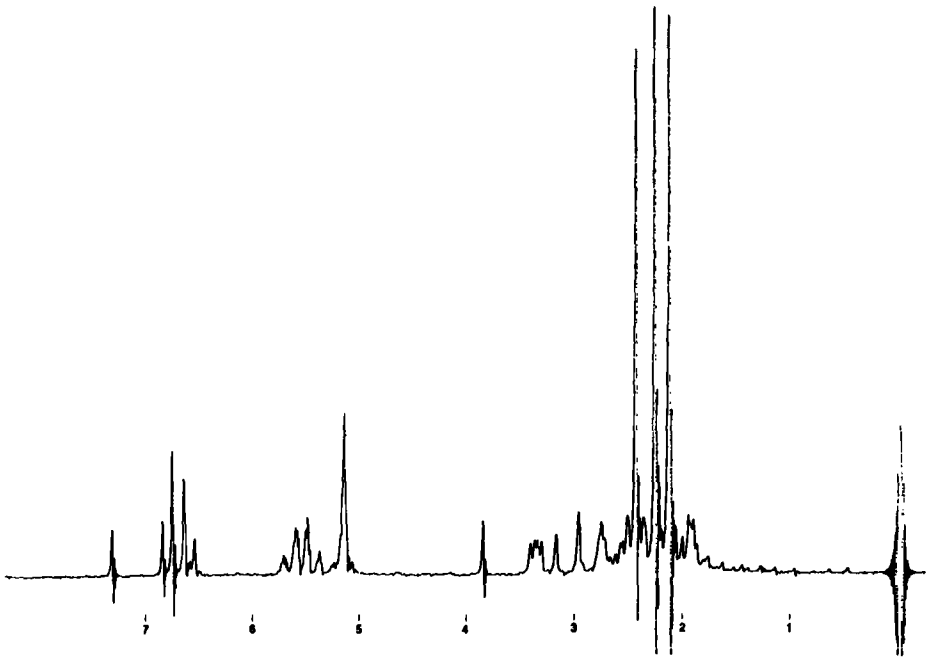

FIG. 2—*NMR of heroin.*

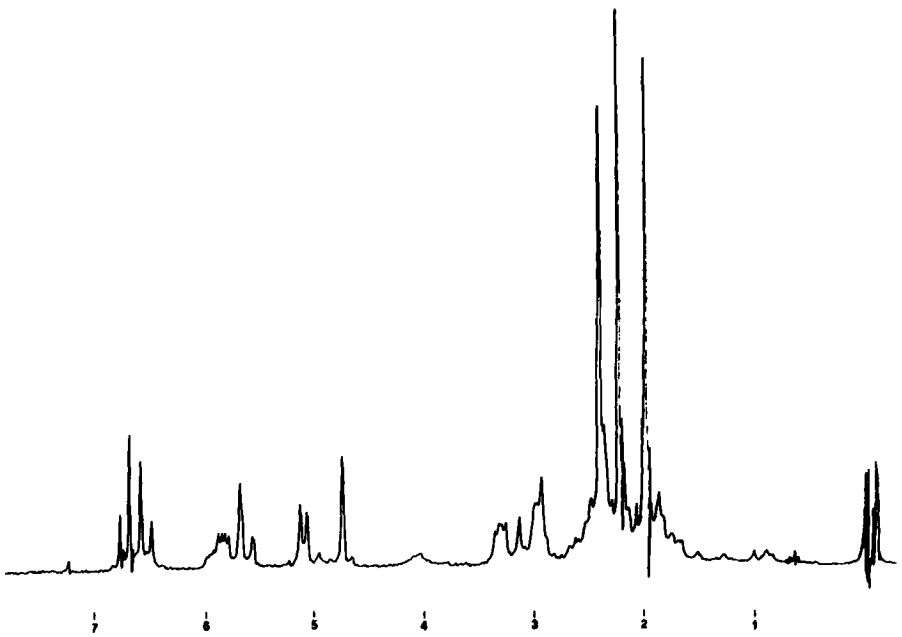

FIG. 3—*NMR of isoheroin.*

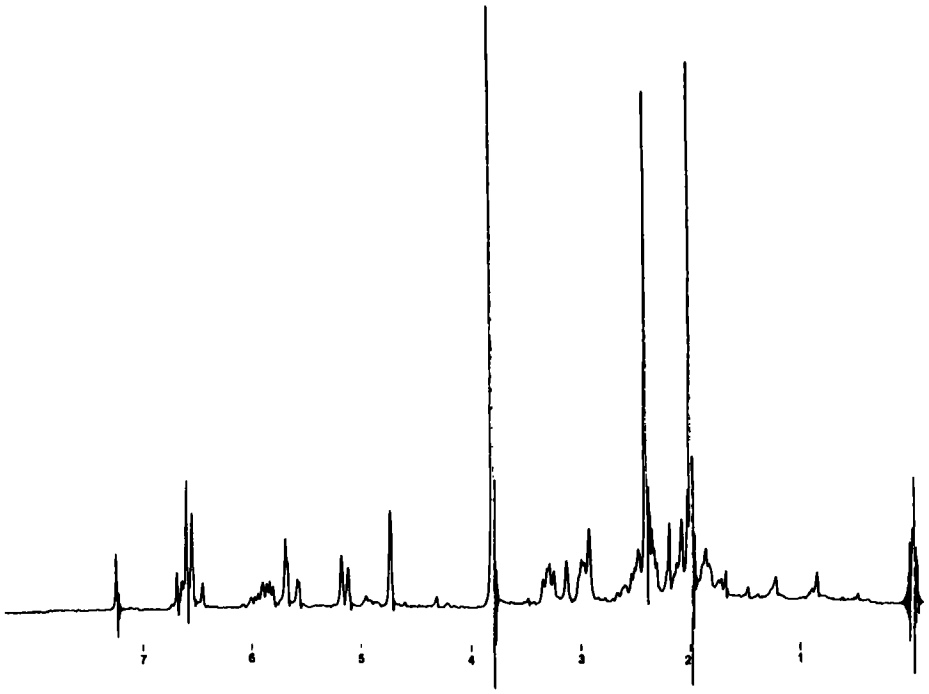

FIG. 4—*NMR of isoacetylcodeine.*

chemical shift is such that it partially coalesces with H-5 (5.1 ppm) at 90 MHz. This same type of shift occurs when codeine is converted to acetylcodeine.

Isoheroin, as expected, produces a simplified H-6 split and overlap between H-5 and H-6 resonances no longer occurs. Further proof of the reliability of this NMR data for isoheroin results from the synthesis of isoacetylcodeine from isocodeine. The exact H-6, H-5 splitting is observed for both isoheroin and isoacetylcodeine.

In a study by Jacabson et al [*4*] using codeine as a model, the authors noted a chemical shift in the signal for H-14 comparing codeine at 2.66 ppm and isocodeine at 3.08 ppm. They suggest H-14 is somewhat deshielded when the hydroxyl group is placed in the axial position (isocodeine). Comparing heroin and isoheroin, H-14 in heroin is positioned at 2.67 ppm while in isoheroin the chemical shift appears around 2.95 ppm.

As might be expected, the vincinal coupling between H-6 and H-7 is readily affected by the spacial arrangement of H-6. Splitting is enhanced as the H-6 goes from axial (heroin) to equatorial (isoheroin). Isoacetylcodeine derived from isocodeine may be used to verify the isolated isoheroin and the resulting NMR data.

Mass Spectroscopy

There are a number of discernible differences between the EI fragmentation of heroin and isoheroin (Figs. 5 and 6). Certainly the appearance of a strong 309 *m/z* in isoheroin and the complete absence of this peak in heroin would readily allow for the differenation between these two compounds. A strong 267 *m/z* is apparent in isoheroin as compared to heroin. Further comparison of the mass spectra shows many other differences, for example, *m/z* 253, 238, and 211 are all pronounced peaks in the mass spectrum of isoheroin yet absent in the mass spectrum of heroin.

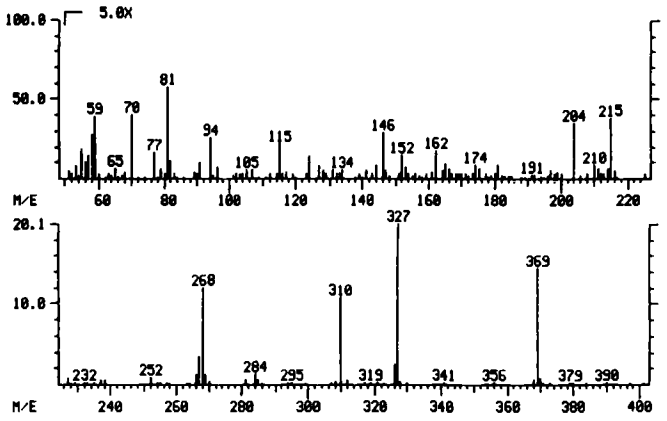

FIG. 5—*MS of heroin.*

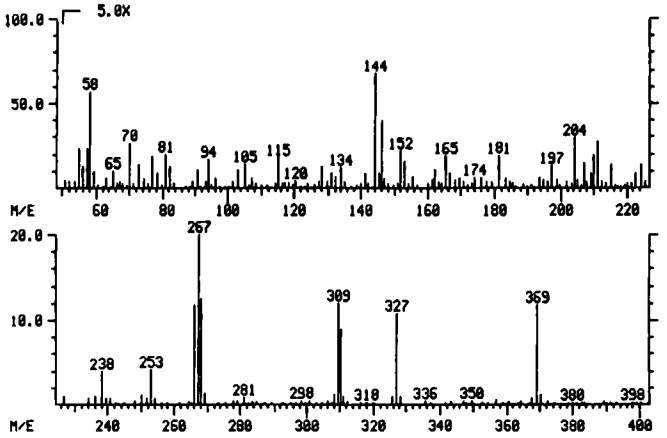

FIG. 6—*MS of isoheroin.*

Infrared (IR)

An objective yet realistic comparison of the infrared spectra for heroin and isoheroin in their free base form shows discrete differences (Figs. 7 and 8). For example, heroin absorbances at 1320, 1270, 1005, 770, 676, 592, 552, and 446 cm^{-1} are absent in the isoheroin IR spectrum. Further, the peak definition in the region 1000 to 800 cm^{-1} is superior in the heroin spectrum. Thus the use of the KBr technique and the resulting IR spectra will differentiate between heroin and isoheroin. Although not presented, the IR spectra for the hydrochloride salts of heroin and isoheroin exhibits few if any differences; thus suggesting IR spectra of the free base should be used to distinguish the two compounds.

GLC

Table 1 depicts the GLC results using three different GLC liquid phases in packed columns and one capillary column. The separation between isoheroin and heroin ranged from 15 s on

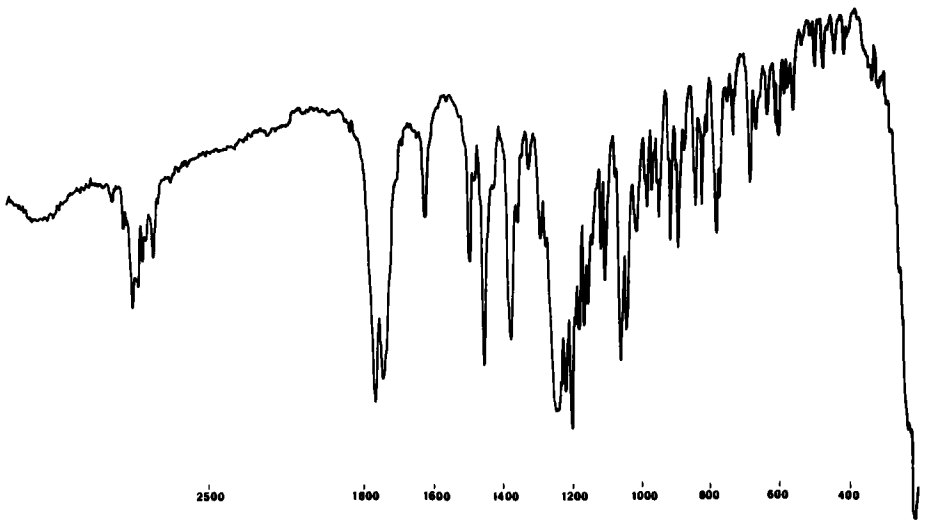

FIG. 7—*IR of heroin.*

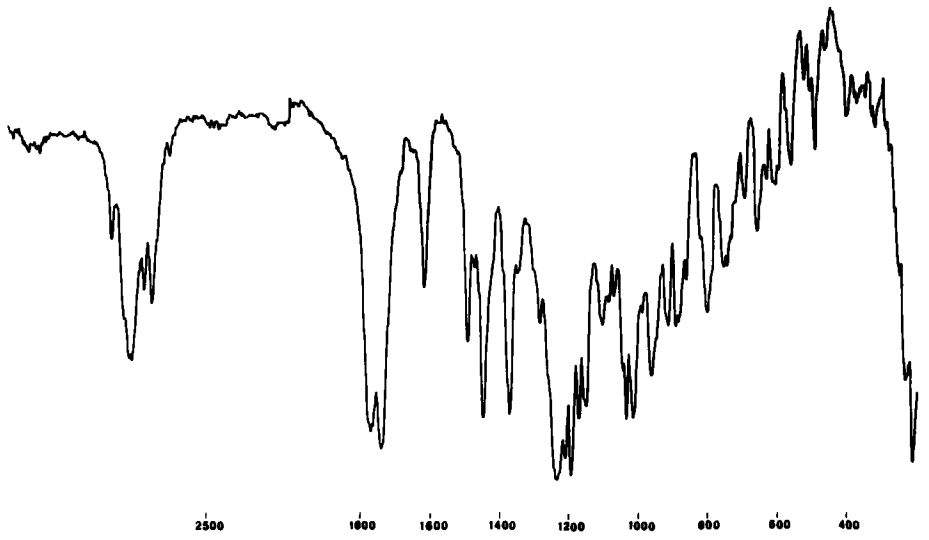

FIG. 8—*IR of isoheroin.*

the OV-1 column to 48 s on the OV-17 and OV-101 columns. A 28-s separation was observed using the capillary column. Thus, GLC is a viable chromatographic technique for the separation of heroin and isoheroin.

Conclusions

Analytical techniques (GLC, IR, NMR, and GC/MS) used by many forensic science laboratories will satisfactorily differentiate heroin from isoheroin. Both gas chromatographic pack-

TABLE 1—*Column temperature for OV-1, OV-17, and capillary column at 250°C and OV-101 at 270°C.*

Column Type	Relative Retention		
	ISO/Heroin	ISO/C-22	ISO/C-24
OV-1	0.95	2.49	1.64
OV-17	0.94	7.94	5.45
OV-101	0.93	2.63	1.68
Capillary	0.94	2.39	1.60

ings and column types used in this study are commonly used by forensic science laboratories; the KBr pellet technique is also routinely used by these laboratories. While NMR and GC/MS may not be as readily available to all laboratories, their use, if available, will certainly discriminate between the title compounds.

References

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