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METHAMPHETAMINE SYNTHESIS VIA HYDRIODIC ACID/RED PHOSPHORUS REDUCTION OF EPHEDRINE

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Summary

The illicit manufacture of methamphetamine from ephedrine via reduction with hydriodic acid and red phosphorus is discussed. The stereochemistry, mechanism, synthetic impurities, and analysis of clandestine methamphetamine samples are addressed.

Key words: Methamphetamine; Ephedrine; Synthesis; Impurities; Hydriodic acid; Red phosphorus

Introduction

The most common method of manufacture of methamphetamine in the United States is the reduction of ephedrine with hydriodic acid and red phosphorus (HI/red P) [1]. Manufacture of methamphetamine from phenyl-2-propanone (P2P) and methylamine yields (+,−)methamphetamine, whereas the reduction of (−)ephedrine or (+)pseudoephedrine yields (+)methamphetamine (Fig. 1).

Even though the HI/red P ephedrine reduction method is relatively new (1982) in clandestine laboratories, the method has been known for many years and has been used to reduce carbonyl groups, nitriles, halides, and alcohols [2,3]. Reduction of ephedrine to methamphetamine is well documented in the literature. The configurations of ephedrine were determined by reduction of the chloro- and bromoephedrines by Emde [4] and Schmidt [5] using various reduction methods not including the HI/red P method. Emde incorrectly cites Ogata [6] as producing (+)methamphetamine in 1919 by heating (−)ephedrine or (+)pseudoephedrine with HI and yellow phosphorus.

The clandestine manufacture of (+)methamphetamine from (−)ephedrine or (+)pseudoephedrine is a very simple process. A mixture of ephedrine, red phorphorus, and hydriodic acid is heated, filtered, made basic, extracted, and crystallized as the hydrochloride salt from ether/acetone with hydrochloric

acid or hydrogen chloride gas or from trichloromonofluoromethane (i.e. "Freon 11") and hydrogen chloride gas. The salt is filtered and dried. The theoretical yield is 92% by weight of the precursor ephedrine, whereas the clandestine yields range from 50 to 75% by weight of the precursor ephedrine. The final product varies from white to orange/brown in color. It is usually greater than 95% in purity and contains no ephedrine.

Experimental

Reactions were carried out in conventional apparatus and were monitored by removal of aliquots with subsequent analysis by capillary gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS). The progress was followed by the decrease in the concentration of the reaction precursors, the increase in concentration of the final product, and the detection of intermediate compounds and side products formed during the reaction.

The gas chromatograph used was a Hewlett-Packard 5880A equipped with a flame ionization detector. It was operated in the split mode (100 : 1) using a 25 m × 0.20 mm fused silica capillary column with a 5% crosslinked phenylmethyl silicone liquid phase (0.11 μm film thickness). The injector temperature was maintained at 250 °C. The oven temperature was programmed as follows: initial temperature, 140 °C; initial hold, 2 min; temperature program rate, 30 °C/min; final temperature, 270 °C; final hold, 5 min. Helium was used as the carrier gas at a column flow rate of 1 ml/min.

Infrared spectra (IR) were obtained on a Pye Unicam PU9514 dispersive infrared spectrophotometer using a 2.5 min scan time in the double beam mode with air as reference.

The GC/MS was performed on a Finnigan 4535 GC/MS system with SUPERINCOS data system interfaced to a Finnigan 9611 gas chromatograph. The gas chromatograph was operated in the split mode (50 : 1) using a 15 m × 0.25 mm i.d. fused silica capillary column with DB-5 liquid phase (0.25 μm film thickness). Injector temperature was maintained at 260 °C. Oven temperature was programmed as follows: initial temperature, 100 °C; initial hold, 2 min; temperature program rate, 20 °C/min; final temperature, 270 °C; final hold, 5 min. The ion source temperature was maintained at 100 °C under electron impact conditions at 70 eV. Helium was used as the carrier gas at a column flow rate of 1 ml/min.

High performance liquid chromatography (HPLC) was carried out using two systems. The first system was a normal phase system utilizing a 15-cm column packed with 5 μm microporasil and a mobile phase of methanol/ammonium hydroxide/ammonium nitrate/water (27 : 2 : 1 : 3 by vol.). The second system was reverse phase with a 15-cm column packed with 5 μm micro C_{18} silica and a mobile phase of TEAP buffer/acetonitrile (90 : 10), the buffer being 0.25 N phosphate adjusted to a pH of 2.2—2.3 with triethanolamine.

Results and Discussion

The HI/red P reduction of ephedrine to methamphetamine involves a cyclic oxidation of the iodide anion to iodine and reduction of iodine back to the anion by the red phosphorus, the latter being converted to phosphorous or phosphoric acids [7,8].

The stereospecificity of the reduction results from mechanistic factors as well as the diastereoisomeric nature of the ephedrines. Ephedrine and pseudoephedrine are 1-phenyl-1-hydroxy-2-methylamino-propane; each contains two chiral centers at the No. 1 and No. 2 carbons of the propane chain. Reduction to methamphetamine eliminates the chiral center at the No. 1 carbon (Fig. 1).

The diastereoisomers, (−)ephedrine and (+)pseudoephedrine, are reduced to (+)methamphetamine, whereas the enantiomers reduce to (−)methamphetamine. The (+ −) mixture of either ephedrine reduces to racemic methamphetamine. The enantiomer and diastereoisomer of ephedrine selected as the precursor dictates what isomer of methamphetamine will be produced

The interesting aspect of the HI/red P ephedrine reduction is that P2P is produced as an impurity in the synthesis. Normally, discovery of P2P in a clandestine laboratory indicates that (+,−)methamphetamine, is the product. However, the P2P is formed as an impurity and has no bearing on the enantiomeric form of the synthesized methamphetamine, since the enantiomer of the methamphetamine product depends solely on the enantiomer of the ephedrine precursor.

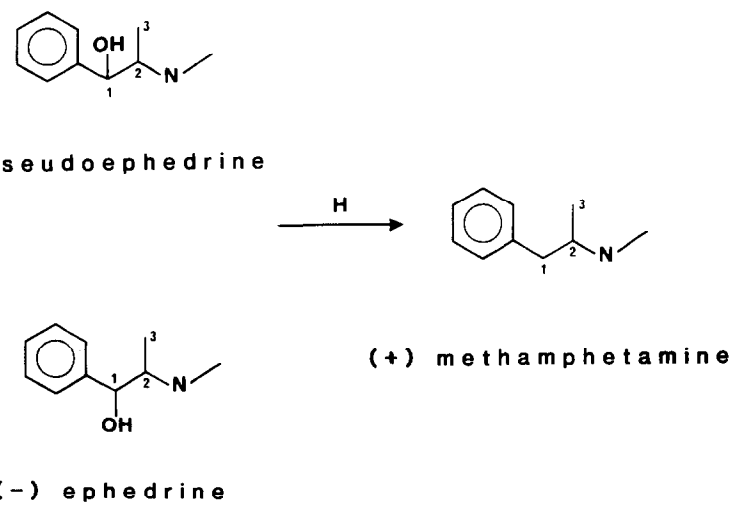

Fig. 1. The diasteroisomers (+)pseudoephedrine and (−)ephedrine reduce to (+)methamphetamine.

The reaction mechanism for the reduction of ephedrine with HI/red P is summarized as follows (Fig. 2). Ephedrine reacts with HI to form iodoephedrine (iodomethamphetamine) which is predominately reduced to methamphetamine. Iodoephedrine can undergo a ring closure to form 'aziridines'. The 'aziridines' (*cis*- and *trans*-1,2-dimethyl-3-phenylaziridine, mol. wt 147), (Fig. 3) could also be formed directly from ephedrine by acid dehydration [9]. However, formation from iodoephedrine is more likely. The 'aziridines' can be reduced to methamphetamine or react to form the impurities found in the reaction. The 'aziridines' can undergo a ring opening acidic hydrolysis to

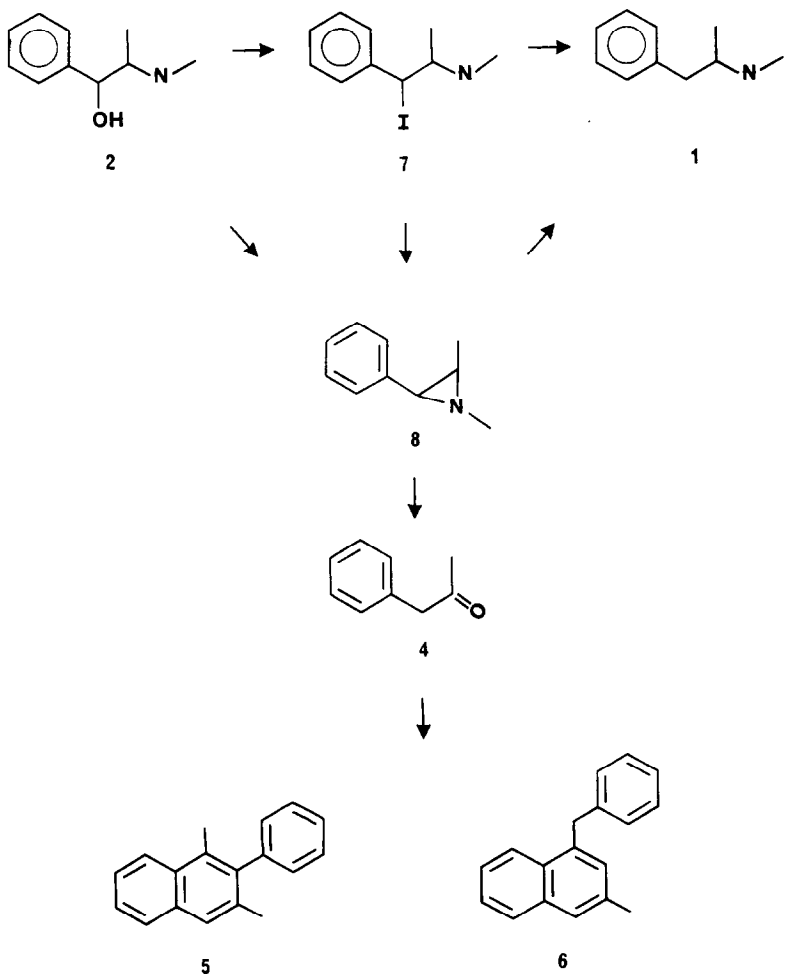

Fig. 2. Route of reaction of HI/red P reduction of ephedrine. 1 = methamphetamine, 2 = ephedrine, 4 = phenyl-2-propanone, 5 = 1,3-dimethyl-2-phenylnaphthalene, 6 = 1-benzyl-3-methylnaphthalene, 7 = iodoephedrine, 8 = *cis*- and *trans*-1,2-dimethyl-3-phenylaziridine.

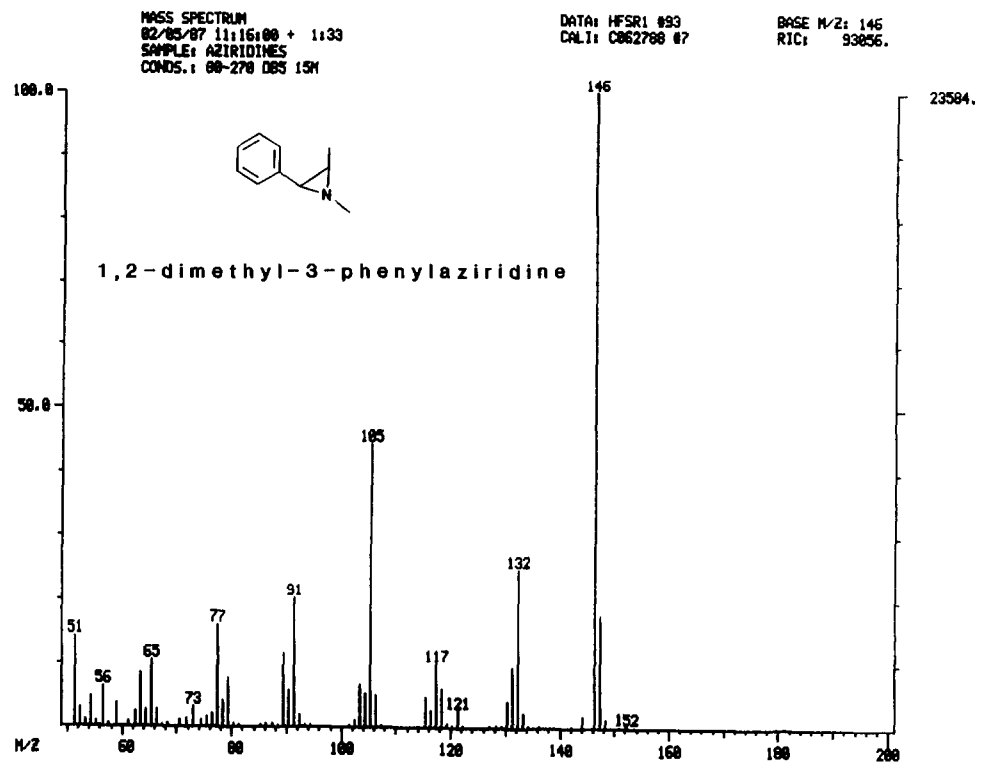

Fig. 3. Mass spectrum of *cis*- and *trans*-1,2-dimethyl-3-phenylaziridine.

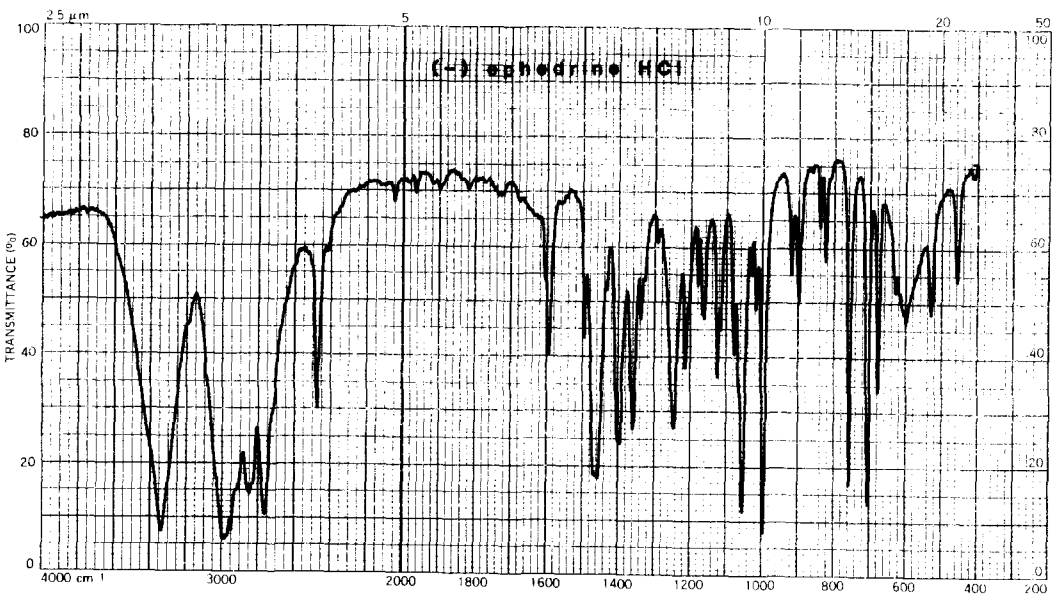

Fig. 4. Infrared spectrum of (−)ephedrine HCl.

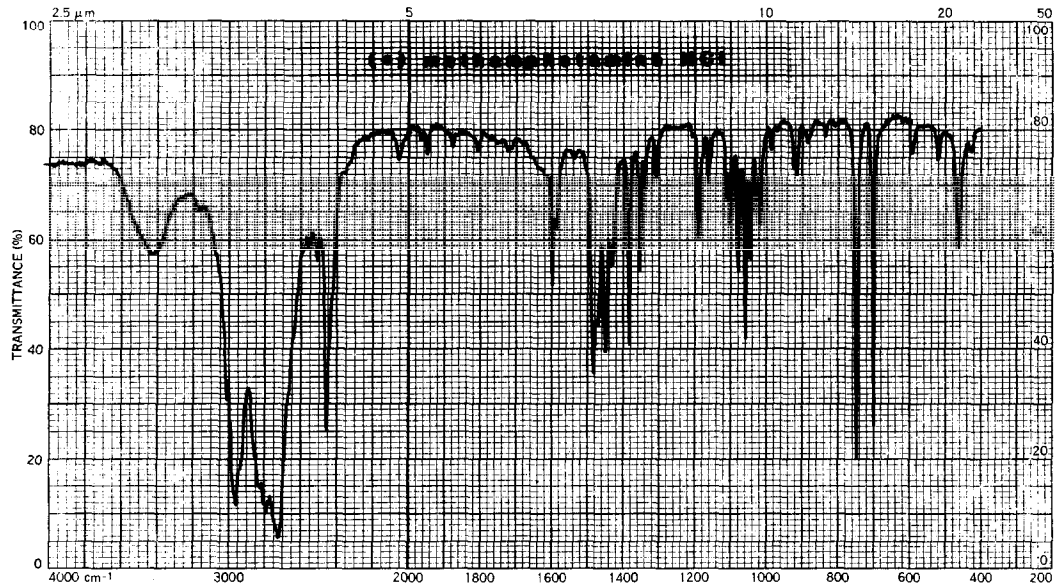

Fig. 5. Infrared spectrum of (+)methamphetamine HCl.

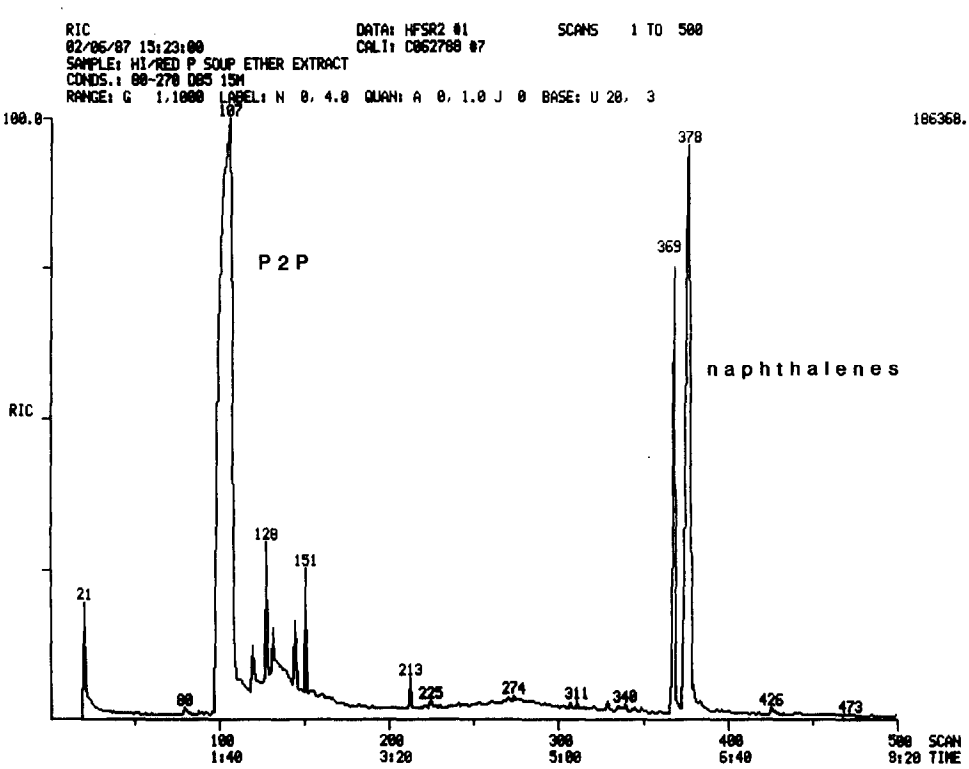

Fig. 6. Ion chromatogram of the ether extract of HI/red P reaction mixture.

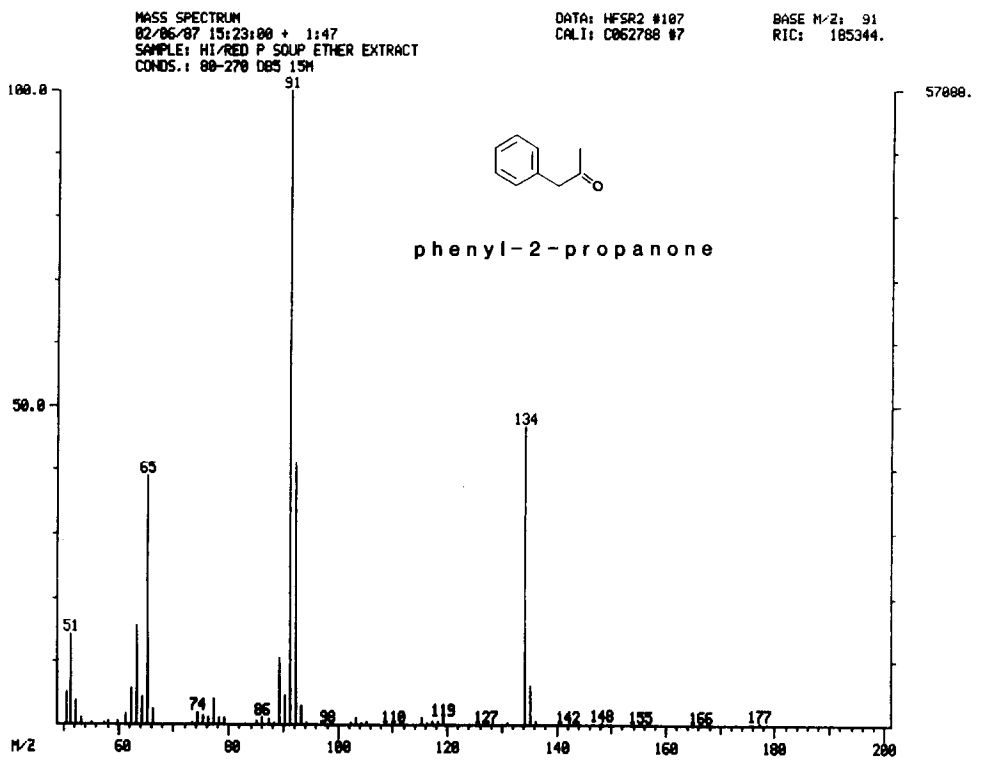

Fig. 7. Mass spectrum of phenyl-2-propanone.

form phenyl-2-propanone. The P2P forms an aldol condensation product with subsequent dehydration to form the 'naphthalene' impurities, 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene [10]. The non-acidic reduction of chloroephedrine produces the 'aziridines' but no P2P [11,12]. The transient existence of iodoephedrine was detected indirectly by the total 'aziridines'. The analogous chloroephedrines undergo thermal decomposition to the 'aziridines' in the injection port of the gas chromatograph (Martin, W., pers. comm.).

Analysis

Samples from HI/red P laboratories vary from bottled precursors, solids, single and multiple phase liquids with a pH range of 1 – 14, to sludges. Identification of methamphetamine is easily made by direct infrared analysis on the finished product or acid/base extraction of most samples with subsequent conversion to the HCl salt. In cases where ephedrine HCl is present, either from addition as an adulterant or from incomplete conversion of the original ephedrine, methamphetamine HCl can be separated by washing the solid with chloroform. The chloroform insoluble portion – ephedrine HCl, and the

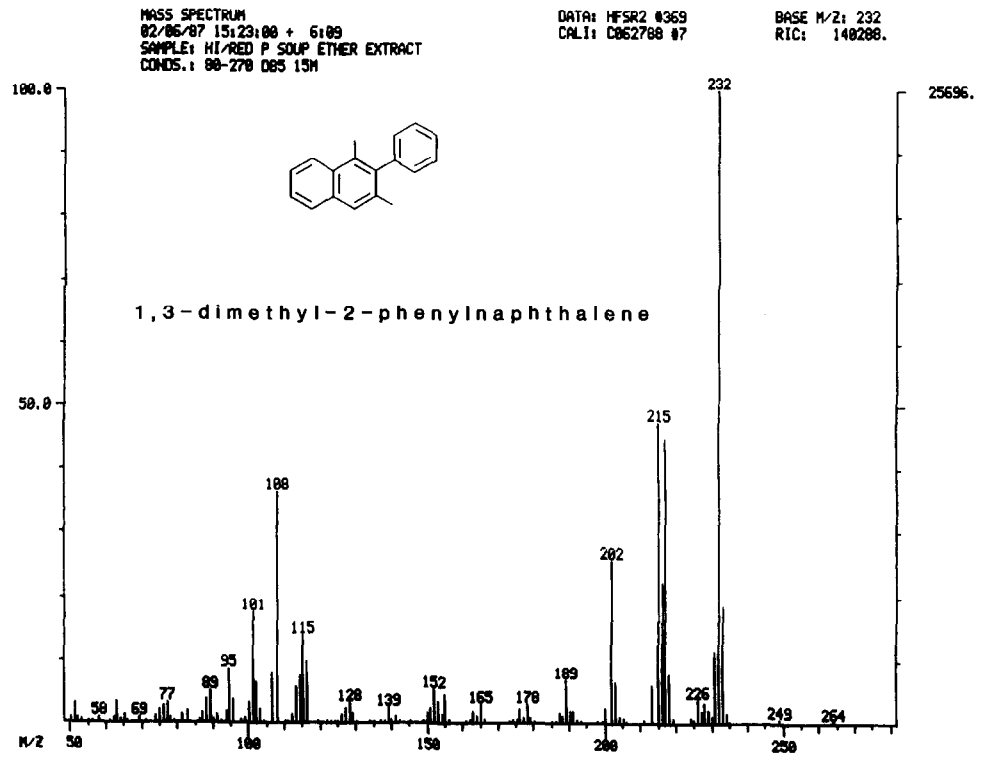

Fig. 8. Mass spectrum of 1,3-dimethyl-3-phenylnaphthalene.

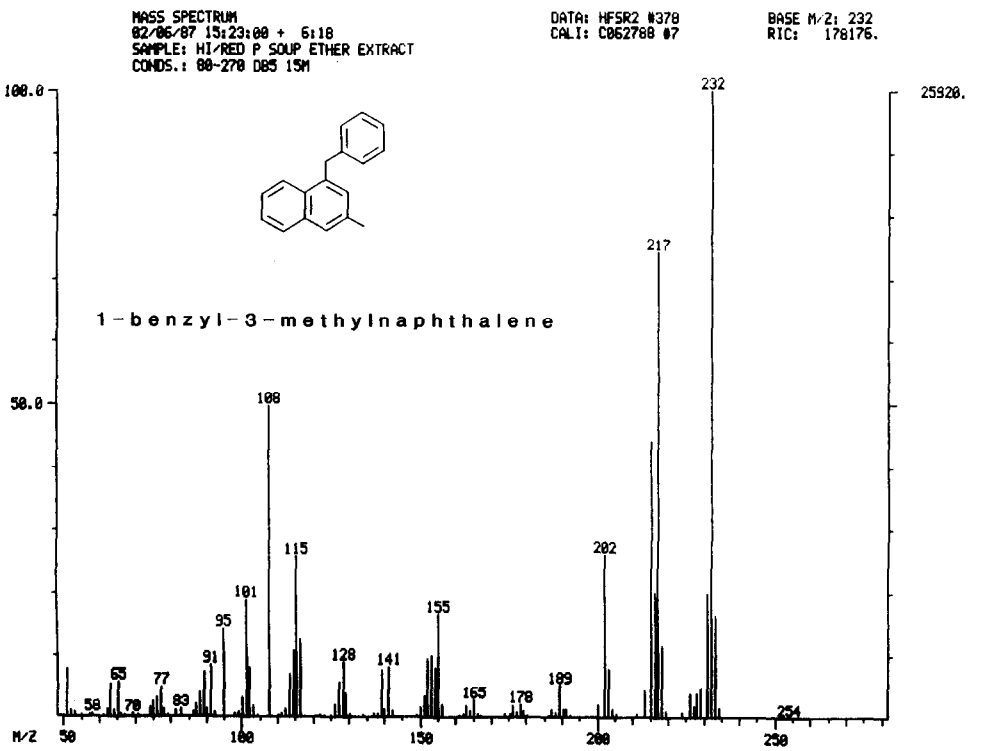

Fig. 9. Mass spectrum of 1-benzyl-3-methylnaphthalene.

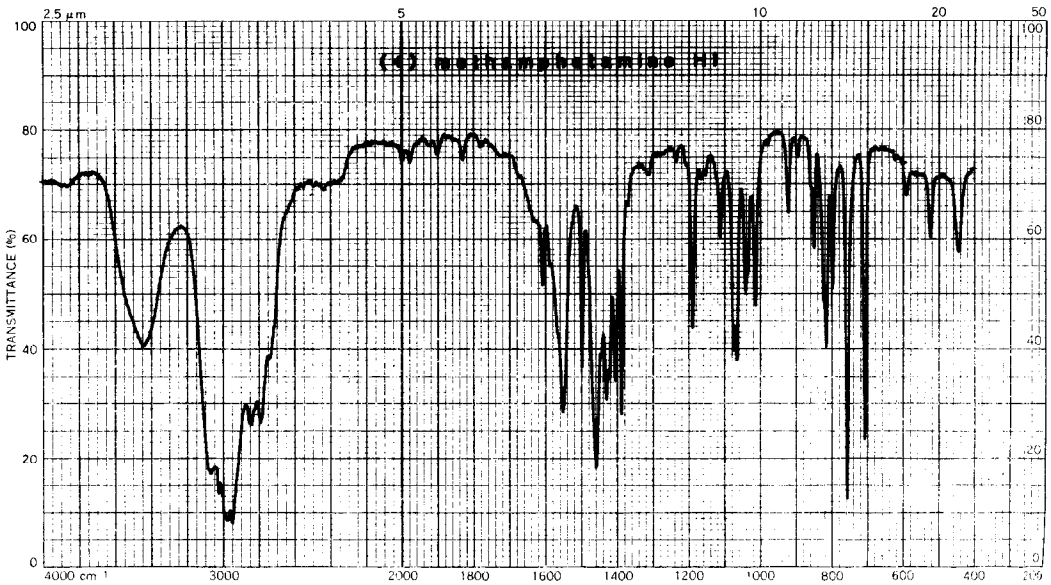

Fig. 10. Infrared spectrum of (+)methamphetamine HI.

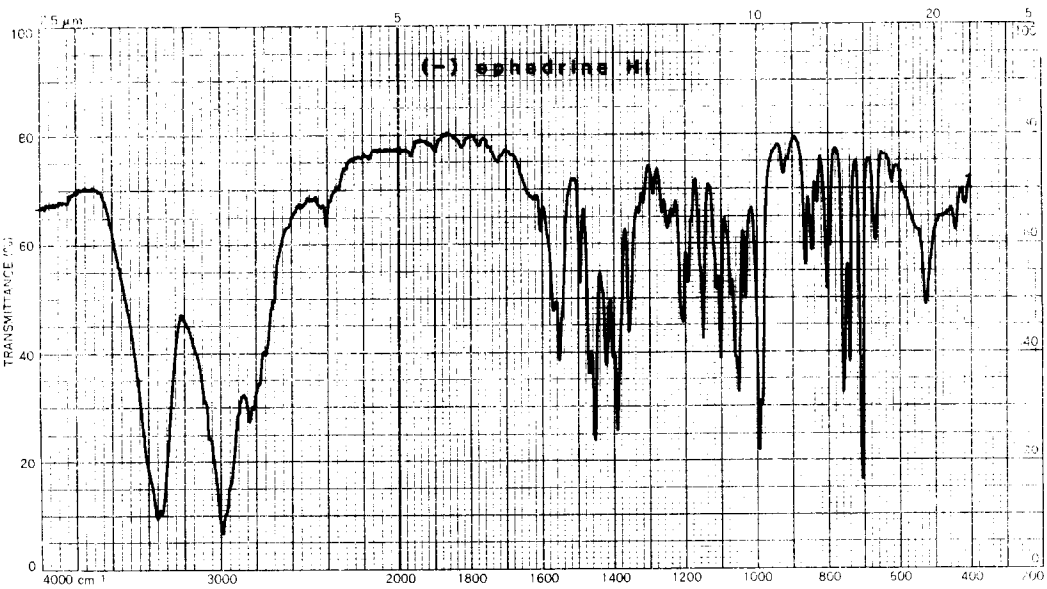

Fig. 11. Infrared spectrum of (−)ephedrine HI.

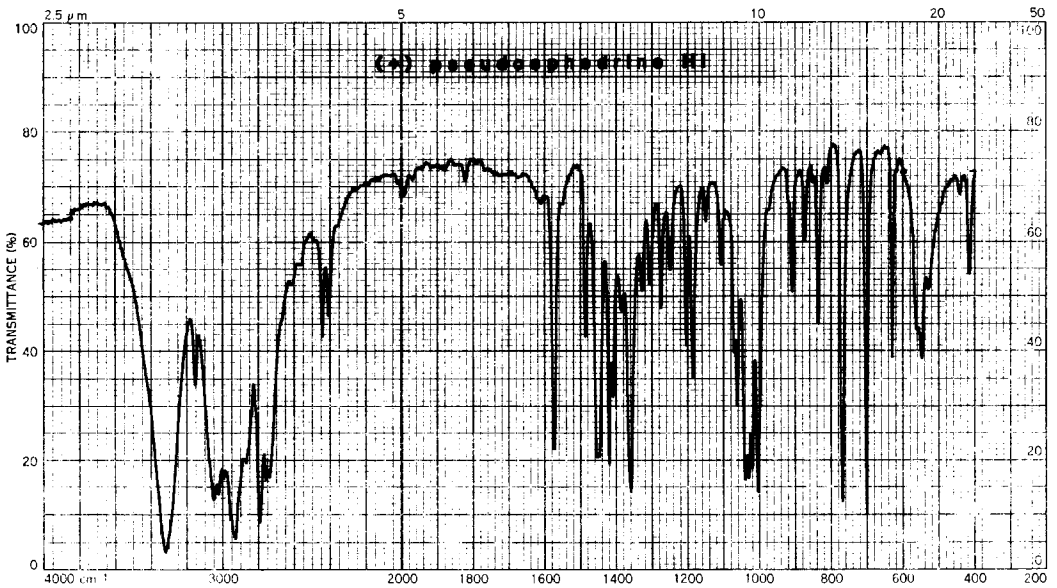

Fig. 12. Infrared spectrum of (+)pseudoephedrine HI.

chloroform soluble portion — methamphetamine HCl, can be easily identified by IR (Figs. 4,5). GC/MS can also be used to identify methamphetamine.

The neutral P2P and 'naphthalene' impurities can be extracted from the methamphetamine in the original reaction mixture (acidic with HI) or any other acidic solution in the clandestine laboratory and can be identified easily by GC/MS techniques (Figs. 6—9).

Ephedrine once exposed to hydriodic acid can form an ion-pair with the hydriodide. The methamphetamine formed in the reaction also can form an ion-pair with the hydriodide. The HCl and HI salts of methamphetamine are both insoluble in ether and soluble in chloroform and very soluble in water. The HI salt is readily soluble in acetone, unlike the HCl salt which is only slightly soluble. The valuable property of the HI ion-pair is that methamphetamine HI can be extracted from an aqueous solution with chloroform. Methamphetamine HCl will not extract into chloroform from an aqueous solution. The HI salts of the ephedrines also have similar properties.

Methamphetamine HI can be identified by IR from the original reaction mixture. This method of identification will also work on the discarded red P sludge. First, an ether wash is required to remove the neutral P2P and 'naphthalene' impurities. This is followed by a chloroform extraction. The chloroform extract is evaporated and the light yellow crystals of methamphetamine HI are identified by IR (Fig. 10).

If the HI/red P reaction is incomplete, ephedrine HI or pseudoephedrine HI can be identified by their IR spectra (Figs. 11,12) using the same extraction procedures given above for methamphetamine HI. Partial conversion will obviously result in a mixture of the HI salts being obtained. Methamphetamine, ephedrine, and pesudoephedrine HI salts are light yellow solids at

TABLE 1

GAS CHROMATOGRAPHY RETENTION TIMES OBTAINED ON A 25 m BY 0.2 mm 5% PHENYL METHYL SILICONE COLUMN WITH A TEMPERATURE PROFILE OF 140°C, 2 min HOLD; RATE 30°C/min; 270°C., 5 min HOLD.

cis/trans-2-methyl-3-phenylaziridine	1.40/1.85 min
cis/trans-1,2-dimethyl-3-phenylaziridine	1.44/1.89
phenyl-2-propanone	1.48
amphetamine	1.50
methamphetamine	1.79
dimethylamphetamine	2.16
phenylpropanolamine	2.80
ephedrine	3.13
methylephedrine	3.35
1,3-dimethyl-2-phenylnaphthalene	6.45
1-benzyl-3-methylnaphthalene	6.54

room temperature. Racemic methamphetamine HI is an oil. The enantiomeric (+) and (−) salts have identical IR spectra. However, the IR spectrum of the (+,−) mixture differs from the enantiomers.

Identification of (+)methamphetamine HI indicates that either (−)ephedrine or (+)pseudoephedrine was reduced via the hydriodic acid/red phosphorus method. Identification of P2P and the 'naphthalenes' as impurities also indicates an ephedrine was reduced under acidic conditions.

The normal screening test for amphetamines is the Marquis reagent which turns orange to orange/brown. However, the Marquis reagent is not a useful test for methamphetamine HI. Methamphetamine HI reacts with the reagent to give an immediate dark brown color with the evolution of iodine. The dark brown color is caused by the iodine formed from the reaction of sulfuric acid with iodide ion. Most organic iodides also produce the same reaction with sulfuric acid. For example, all of the methamphetamine and ephedrine hydriodides, as well as sodium and potassium iodide, also liberate iodine with sulfuric acid. The nitroprusside* screening reagent can be used to differentiate methamphetamine (secondary amine, deep blue color) from amphetamine and dimethylamphetamine (primary and tertiary amines, no color).

Quantitation of both solid and liquid samples found in HI/red P laboratories is routinely done by HPLC and GC. The retention times of compounds are given in Table 1. The enantiomeric form of methamphetamine or ephedrines is determined by one or more of the following: polarimetry, mixed microcrys-

*The nitroprusside (sodium nitroprusside) reagent reacts to give a deep blue color with secondary amines and has no color change with primary and tertiary amines. Ephedrine, a secondary amine, gives a faint blue color. The first part of the reagent is prepared by mixing 25 ml of a one percent sodium nitroprusside solution with 1 ml acetaldehyde. The second part is a two percent sodium carbonate solution. The blue color is formed immediately after the second part of the reagent is added.

tals, mixed melting points, infrared or enantiomeric derivatization GC techniques.

Analysis of an HI/red P clandestine laboratory in the field presents hazards. HI is a toxic and strong irritant and contact must be minimized. Red phosphorus is a flammable/explosive solid and must be handled with care. Phosphine, a highly poisonous gas, can be produced by careless heating of the HI/red P mixture.

Conclusion

The hydriodic acid/red phosphorus reduction of ephedrine to methamphetamine has been discussed. The stereochemistry of the reaction has been shown as well as the route of reaction to the impurities and products. Data obtained from IR spectroscopy and GC/MS spectroscopy have been presented to aid in the analysis of the precursors, intermediates, impurities, and products.

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