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Ephedra's Role As a Precursor in the Clandestine Manufacture of Methamphetamine

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ABSTRACT: In February 1993, an illicit, fully operational methamphetamine laboratory was confiscated in Vacaville, California. In addition to seizing ephedrine and pseudoephedrine tablets, approximately 1.3 kg of ephedra was found at the lab site. Ephedra (also referred to as Ma Huang) is a plant material that contains numerous alkaloids, including l-ephedrine and d-pseudoephedrine. Ephedra products are currently sold over-the-counter in various forms such as tablets and capsules. Quantitative analysis reveals that some ephedra capsules and tablets contain as much methamphetamine precursors as a synthetic 25 mg ephedrine tablet. Because of this, ephedra is becoming a "substitute precursor" for ephedrine compounds for use in the illicit manufacture of methamphetamine.

Ephedra samples were reacted with hydriodic acid and red phosphorus in much the same way as ephedrine would be reacted in order to produce methamphetamine. The progress of the reduction was monitored by obtaining aliquots of the reaction solution at time intervals followed by analyses using GC/IRD and GC/MS. An analysis of the final product of the reaction indicated that *d*-methamphetamine, *d*-amphetamine and *d*-N,N-dimethylamphetamine had been produced as a result of the reduction of ephedra. The latter two compounds result from the reduction of norephedrine and N-methylephedrine, respectively (also present in ephedra), and therefore represent markers for this synthetic methodology.

KEYWORDS: forensic science criminalistics, ephedrine, pseudoephedrine, ephedra, methamphetamine, reduction

In February 1993, local and Federal law enforcement officials raided a suburban home in Vacaville, California, and found an illicit clandestine laboratory involving the manufacturing of *d*-methamphetamine. In addition to confiscating various chemicals and glassware related to the manufacturing operation, approximately 1.3 kg of ephedra plant material was seized at the lab site.

It is known that the oriental crude drug, Ephedra Herba or Ma Huang, has traditionally been used in Chinese medicine for relieving respiratory related ailments such as bronchitis and asthma. These medicinal properties are due to alkaloids that are concentrated in the stems and leaves of the ephedra plant, principally *l*-ephedrine and *d*-pseudoephedrine [*1–4*]. Illicitly, pure ephedrine and/or pseudoephedrine have long been employed as precursors for manufacturing methamphetamine. However, the most common source of these precursors has originated from synthetic pharmaceutical preparations of ephedrine and pseudoephedrine rather than from the ephedra plant [*5*]. Thus, the presence of ephedra at a clandestine laboratory, as in the Vacaville case, is unusual and raises issues concerning the feasibility and practicality of ephedra as a precursor in illicit drug manufacturing operations.

Section I of this report will discuss how factors such as current chemical regulation, accessibility, and profitability will affect ephedra's potential involvement in clandestine drug manufacturing. Section II will present a general summary concerning the chemical analysis of the ephedra alkaloids in addition to the primary by-products that are formed during the reduction of ephedra with hydriodic acid and red phosphorus.

Section I—Ephedra's Potential

Chemical Regulation

Increased chemical regulations of commercially prepared ephedrine and pseudoephedrine may force illicit drug manufacturers to consider ephedra as a new source of these methamphetamine precursors. Prior to 1993, anyone could purchase any desired quantity of ephedrine or pseudoephedrine, with no questions asked. Names of purchasers, dates of transactions, and quantities of sold chemicals were not required to be reported to authorities. In January 1993, the State of California placed ephedrine and pseudoephedrine on its list of regulated chemicals, thus requiring that all transactions involving the sale or transfer of any amount of these chemicals be reported to the Department of Justice [*6*]. In addition, the regulation requires all persons wanting to purchase a regulated chemical to provide proper identification showing current residency as well as a full explanation for the request [*7*]. The intention of the regulation is to help law enforcement officials identify suspected illicit drug laboratories by monitoring the quantities and destinations of precursor chemicals. Ephedra is not subjected to these rules because it is not specifically included on California's list of regulated chemicals. Therefore, in order to avoid exposing their illicit drug operations, clandestine laboratory operators are turning to ephedra.

Accessibility

One of the factors that makes ephedra so appealing is its wide availability within the United States. It is not difficult to find an Asian import/export company that will sell large quantities of either whole or ground ephedra plant material to any interested party. Many companies also import powdered ephedra extracts from Asia and sell the material in the United States through legitimate mail-order businesses. These companies deal strictly with bulk quantities of material and will only sell the extract in multiples of 10 and 25 kilogram packages. Smaller scale companies will

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TABLE 1—*Quantity of ephedrine and pseudoephedrine (E + P) per unit sample of ephedra.*

Sample	Description of Sample	Amount of Ephedrine	Amount of Pseudoephedrine	Total (E + P)
I	Capsules from Manufacturer A	1.5 mg/capsule	1.1 mg/capsule	2.6 mg/capsule
II	Loose Ephedra Material from Manufacturer B	80 grams per kg[a]	not specified	80 grams per kg
III	Tablets from Manufacturer C	16 mg/tablet	8 mg/tablet	24 mg/tablet
IV	Capsules from Manufacturer C	13.7 mg/capsule	6.3 mg/capsule	20 mg/capsule
V	Loose Ephedra Material from Manufacturer D	7.7 grams per kg	1.9 grams per kg	9.6 grams per kg

[a]Value quoted from Certificate of Analysis provided by the manufacturer.

market the ephedra extract as tablets or capsules and sell the product through mail-order businesses or through the numerous chains of herbal and health food stores located throughout the United States. This wide availability enhances ephedra's attractiveness and potential for becoming a significant methamphetamine precursor in clandestine laboratory operations.

Profitability

The primary factor that determines ephedra's potential is its ability to produce a substantial profit in the illicit drug manufacturing business. To examine this issue, five samples of ephedra were obtained from various vendors.[2] Ephedra capsules were obtained from Manufacturers A and C, tablets were obtained from Manufacturer C, and two samples of loose ephedra material was obtained from Manufacturers B and D. Loose ephedra material refers to ephedra that has not been processed into tablet or capsule form. The ephedrine and pseudoephedrine were extracted and quantitated from each sample via a previously described technique that reportedly gives a 96.6% recovery of the alkaloids [*4*]. The combined total amounts of ephedrine and pseudoephedrine, (E + P), for each sample shown in Table 1indicates the total amount of methamphetamine precursor material that is able to be extracted from each sample, assuming this 96.6% recovery. With this information, the amount of methamphetamine able to be synthesized from the ephedra can be calculated. Table 2 depicts the cost and quantity of each ephedra sample needed to produce one kilogram of methamphetamine, assuming that at least 50% of the ephedrine and pseudoephedrine is reduced during the synthesis [*8*].

Results

The data in Tables 1 and 2, illustrate the following points:

1. Profitability is dependent upon the vendor or manufacturer of the ephedra.

2. Some ephedra products are capable of producing a profit from methamphetamine manufacturing that is comparable to profits obtained via current methods.

Profitability is directly related to the amount of methamphetamine precursor or E + P that is contained in each ephedra product. Table 1 illustrates how ephedra's profitability is determined by the manufacturer of the ephedra product. Referring to this table, each capsule obtained from Sample I contains a mere 2.6 mg of E + P while a similar capsule obtained from Sample IV contains 20 mg of E + P. In these cases, both samples are capsules, however, the amounts of E + P differ considerably due to the difference in manufacturers.

Additionally, Samples II and V are described as loose ephedra material; however, Sample II contains eight times more E+P than Sample V, again due to different manufacturers. In the case of Samples III and IV, the differences in E+P are not as significant because the ephedra originated from the same manufacturer.

One of the current methods for obtaining ephedrine or precursor material for synthesizing methamphetamine utilizes synthetically manufactured tablets containing 25 mg of ephedrine [*5*]. In order to produce one kilogram of methamphetamine, approximately 2 kilograms of ephedrine would need to be reduced, assuming at least a 50% conversion [*8*]. If a tablet contains 25 mg of ephedrine, then approximately 80,000 such tablets would be required for each kilogram of methamphetamine produced. In 1993, 25 mg ephedrine tablets were sold at a cost of $24 per 1000 tablets [*9*]. Thus, 80,000 tablets (that is, the cost of ephedrine per kilogram of methamphetamine) would be approximately $1900.

Table 2 provides the amount and cost of each sample of ephedra that would be required to produce one kilogram of methamphetamine. From the data, Sample I is too costly to be profitably used; however, Samples II through V appear to be capable of producing profits that are comparable, if not greater, than those obtained using the synthetic 25 mg ephedrine tablets. In fact, the costs of Samples II and V per kilo of methamphetamine are only half of the cost of the ephedrine tablets; consequently, they would yield twice the profit versus the ephedrine tablets. On the other hand, because Samples III and IV cost five to six times more than synthetic ephedrine, the profits would not be as great. This reduced profit may or may not be significant depending on the selling price of the kilogram of methamphetamine. In 1993, one kilogram of methamphetamine was valued between $9000 and $44,000 depending on the region of the United States in which the drug was sold. For example, in San Francisco, one kilogram of methamphetamine was worth an average of $30,000 in 1993 [*10*].

TABLE 2—*Cost and amount of ephedra sample needed to produce one kilogram of methamphetamine.*

Sample	Price per Unit Sample[a]	Amount of Sample per Methamphetamine Kilo	Sample Cost per Methamphetamine Kilo
I	$0.06 per capsule	769,230 capsules	$48,076
II	$40 per kilo	25 kilos	$1000
III	$0.14 per tablet	83,333 tablets	$11,624
IV	$0.10 per capsule	100,000 capsules	$9,950
V	$4.40 per kilo	208 kilos	$916

[a]1993 price figures.

[2]For security reasons, these vendors are not identified.

Section II—Chemical Analysis of Ephedra

According to literature sources, the ephedra plant contains six alkaloids consisting of three pairs of optically active diastereomers. In addition to the *l*-ephedrine and *d*-pseudoephedrine pair, there also exists the *d*-norpseudoephedrine and *l*-norephedrine and the *l*-methylephedrine and *d*-methylpseudoephedrine pairs [*3,4*]. The alkaloids were extracted from the five ephedra samples utilizing a method reported by Cui [*4*], then analyzed by gas chromatography (GC). Figure 1 depicts a gas chromatogram of standards of the six alkaloids illustrating their retention times. A typical gas chromatogram produced by extracted ephedra is shown in Fig. 2. From the chromatogram, ephedrine, norpseudoephedrine, and methylpseudoephedrine are the three most abundant alkaloids observed. The three remaining alkaloids were present in either trace amounts or below the instrument's limits of detection. The n-pentadecane is present as an internal standard. It should be pointed out that the relative alkaloid concentrations can differ with each species of ephedra.

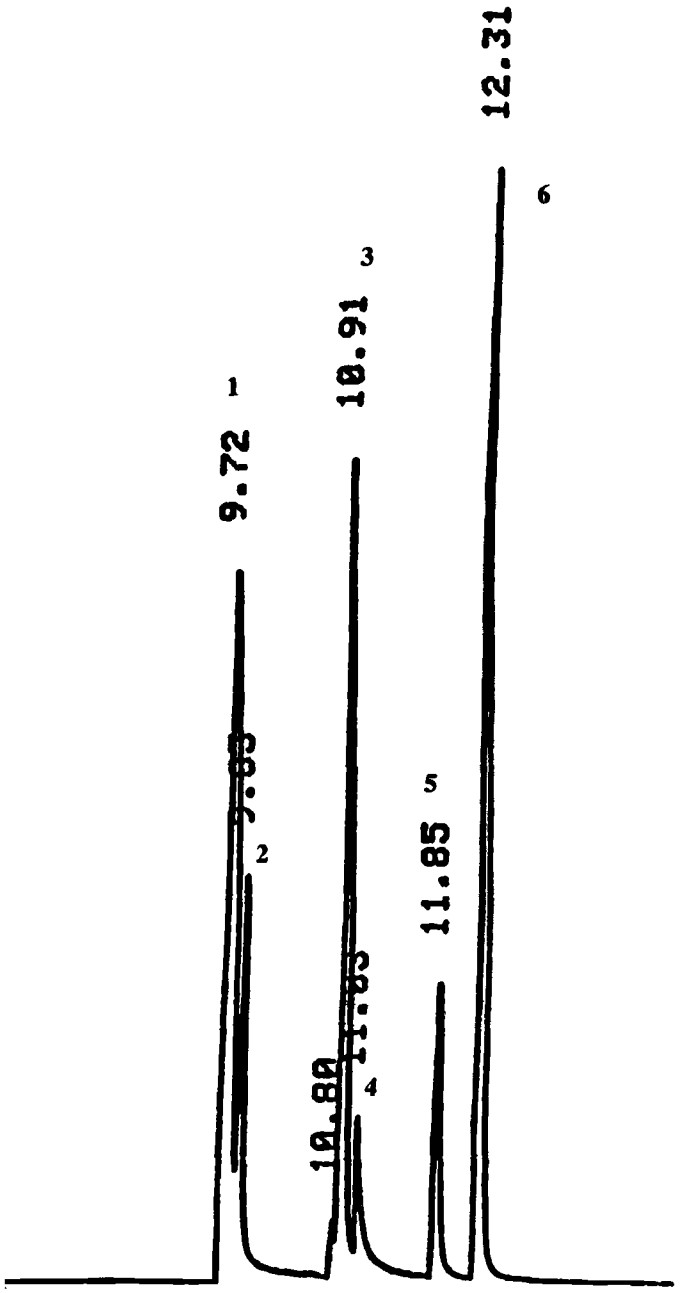

FIG. 1—*Gas chromatogram of the ephedra alkaloids. (1) Norpseudoephedrine, (2) Norephedrine, (3) Ephedrine, (4) Pseudoephedrine, (5) Methylephedrine, (6) Methylpseudoephedrine.*

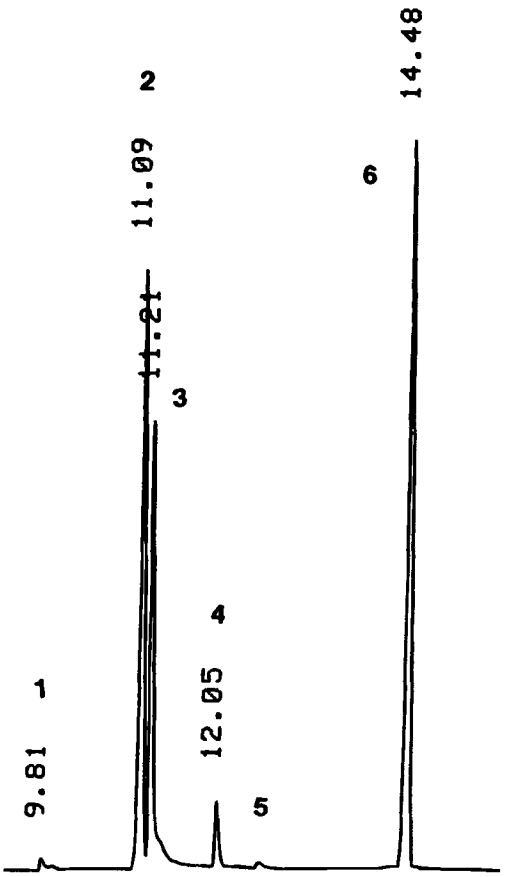

FIG. 2—*Typical gas chromatogram produced by extracted ephedra. (1) Norpseudoephedrine, (2) Ephedrine, (3) Pseudoephedrine, (4) Methylephedrine, (5) Methylpseudoephedrine, (6) n-Pentadecane.*

A study of the reduction of ephedra by hydriodic acid and red phosphorus was initiated. The final product of the reaction was analyzed and the results compared with that synthesized using ephedrine. To prepare the ephedra for the synthesis, a methanol wash was performed on the material to extract out the alkaloids; this technique duplicates the current method used by illicit drug manufacturers for extracting ephedrine from synthetic tablets [*11*]. The progress of the reaction was monitored at various time intervals; aliquots were analyzed using gas chromatography with infrared detection (GC-IRD). The final product was analyzed using gas chromatography with mass selective detection (GC-MSD).

Experimental

Capillary Gas Chromatography-Flame Ionization Detection

A Hewlett-Packard 5880A Gas Chromatograph was used to generate the alkaloid chromatograms. A 5% cross-linked phenylmethylsilicone capillary column (DB-5, 15 m length, 0.304 mm

i.d., 0.25 μm film thickness was used with a flow rate of 1.7 mL/min and a split ratio of 16:1. The oven temperature was programmed as follows: 60°C initial temperature, 2.0 min initial hold; 5.0°C/min program rate; 180°C; final temperature; 4.0 min final hold.

Gas Chromatography-Infrared Detection

A Hewlett-Packard 5890 Series II Gas Chromatograph interfaced with a 5965B Infrared Detector with a Hewlett-Packard HP-5 capillary column (12 m length, 0.32 mm i.d., 0.52 μm film thickness) was used. The oven temperature was programmed as follows: 70°C initial temperature, 1.0 min initial hold; 15°C/min program rate; 270°C final temperature; 5.0 min final hold.

Gas Chromatography-Mass Selective Detection

A Hewlett-Packard 5890 Series II Gas Chromatograph interfaced with a 5971 Series Mass Selective Detector with a Hewlett-Packard HP-5 capillary column (12 m length, 0.2 mm i.d., 0.33 μm film thickness) was used. The oven temperature was programmed as follows: 100°C initial temperature, 1.0 min initial hold; 15°C/min program rate; 280°C final temperature, 5.0 min final hold.

Extraction of Ephedra Alkaloids From the Crude Drug

An aliquot of 200 mg of the ground ephedra plant material was weighed into a 15 mL centrifuge tube. Two mLs of aqueous 0.65 M KOH solution, 1.2 grams of NaCl, and 2.0 mL of diethyl ether were added to the tube, shaken for two minutes and centrifuged. The diethyl ether was collected and dried over sodium sulfate. Reported alkaloid recovery was 96.6–100.1% [*4*]. To 1.0 mL of the diethyl ether was added 1.0 mL of a 0.26 mg/mL solution of *n*-pentadecane in methylene chloride (CH_2Cl_2) as an internal standard.

Standard Solutions

Standards were prepared by dissolving 100 mg of the ephedrine HCl or pseudoephedrine HCl into 50 mL of water. This solution was transferred to a separatory funnel. Concentrated sodium hydroxide was added to make a strong basic solution (pH > 12). Approximately 25 mL of CH_2Cl_2 was added, mixed, and the two layers allowed to separate. The CH_2Cl_2 was collected into a 100 mL volumetric flask. The extractions with CH_2Cl_2 were repeated two more times, and the flask was diluted to volume with CH_2Cl_2. To 5.0 mL of the CH_2Cl_2 solution was added 5.0 mL of a 0.26 mg/mL solution of *n*-pentadecane in CH_2Cl_2 as an internal standard. The quantitations were performed on the GC. The concentrations of the ephedrine and pseudoephedrine for each sample were calculated against the standards.

Synthesizing Methamphetamine with Ephedra

Approximately 425 grams of ground ephedra plant material was washed three times with methanol. The methanol washings were collected and allowed to evaporate to produce a greenish-brown tar-like substance. To this material was added 250 mL of a 57% solution of hydriodic acid and 9.5 grams of red phosphorus in a 1000 mL round-bottom flask. The flask was equipped with a working condensor and a heating mantle. The mixture was heated and allowed to reflux for approximately 5 hours. The aqueous reaction solution was filtered, made basic with NaOH (pH > 12), then extracted into trichlorotrifluoroethane (Freon 113). The organic solution was dried over anhydrous Na_2SO_4. Hydrogen chloride gas was then bubbled into the freon, resulting in the crystallization of the final product as the hydrochloride salt [*8,12*]. Samples of the reaction mixture were taken at various times throughout the synthesis. These samples were basified, extracted into methylene chloride, and analyzed on the GC-IRD and GC-MSD. Samples were taken at 60, 127, and 310 minutes into the reaction synthesis.

Results and Discussion

The reduction of ephedra with hydriodic acid and red phosphorus results in the production of *d*-methamphetamine, *d*-amphetamine, and *d*-N,N-dimethylamphetamine[*8,13–15*]. The presence of these two latter compounds differentiate the final product generated from ephedra material versus the product made with synthetically prepared ephedrine and pseudoephedrine.

Figures 3 and 4, show the chromatograms of samples taken respectively at 60 and 127 minutes into the ephedra reduction reaction. The *cis*- and *trans*-1,2-dimethyl-3-phenylaziridine and the

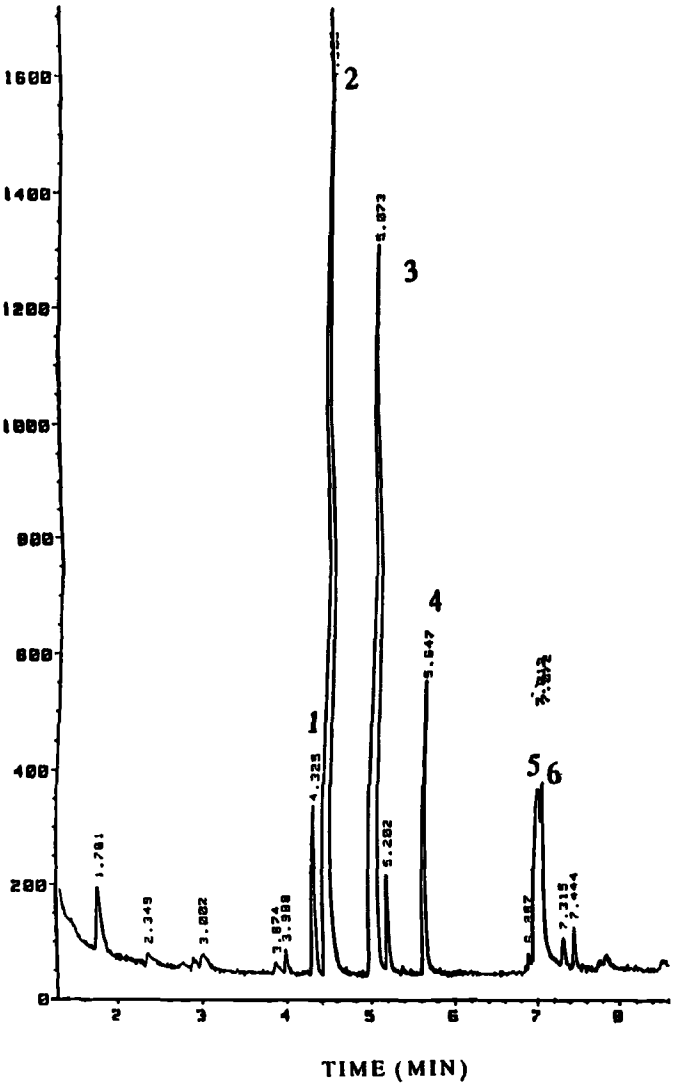

FIG. 3—*Gas chromatogram of sample taken at 60 minutes into the ephedra reduction reaction. (1) trans-1,2-Dimethyl-3-phenylaziridine, (2) Phenyl-2-propanone, (3) Methamphetamine, (4) N,N,-Dimethylamphetamine, (5) Ephedrine, (6) Pseudoephedrine.*

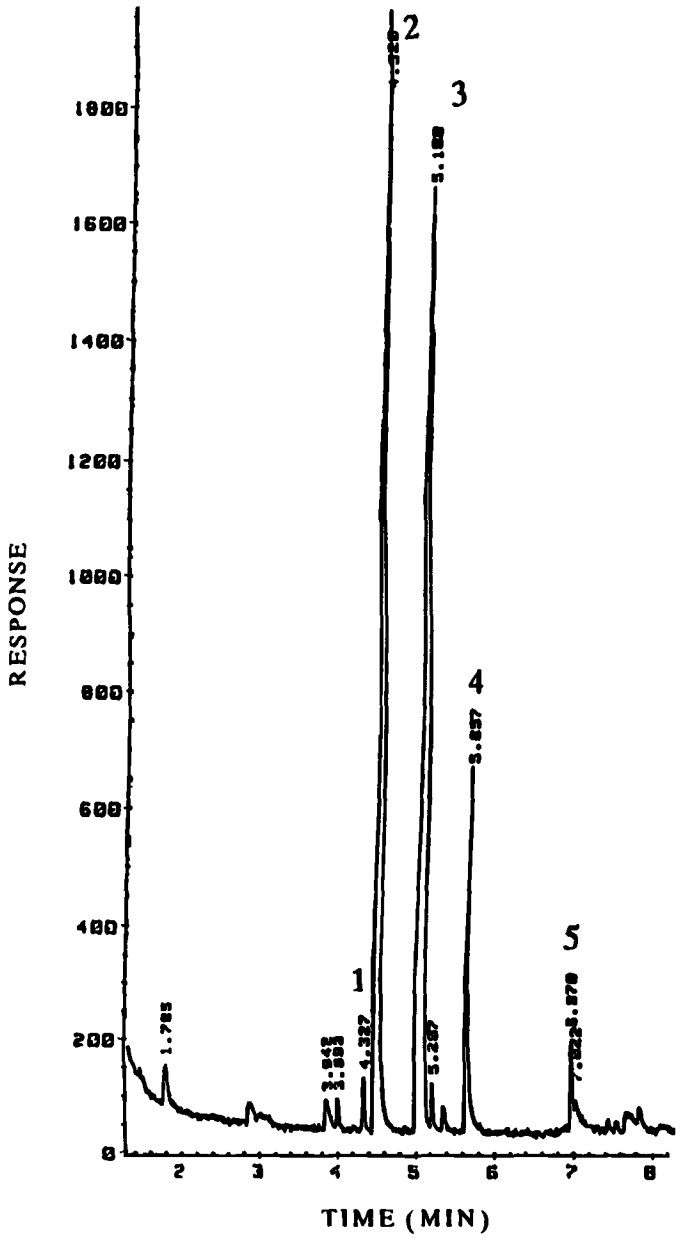

FIG. 4—*Gas chromatogram of sample taken at 127 minutes into the ephedra reduction reaction. (1) trans-1,2-Dimethyl-3-phenylaziridine, (2) Phenyl-2-propanone, (3) Methamphetamine, (4) N,N-Dimethylamphetamine, (5) Ephedrine.*

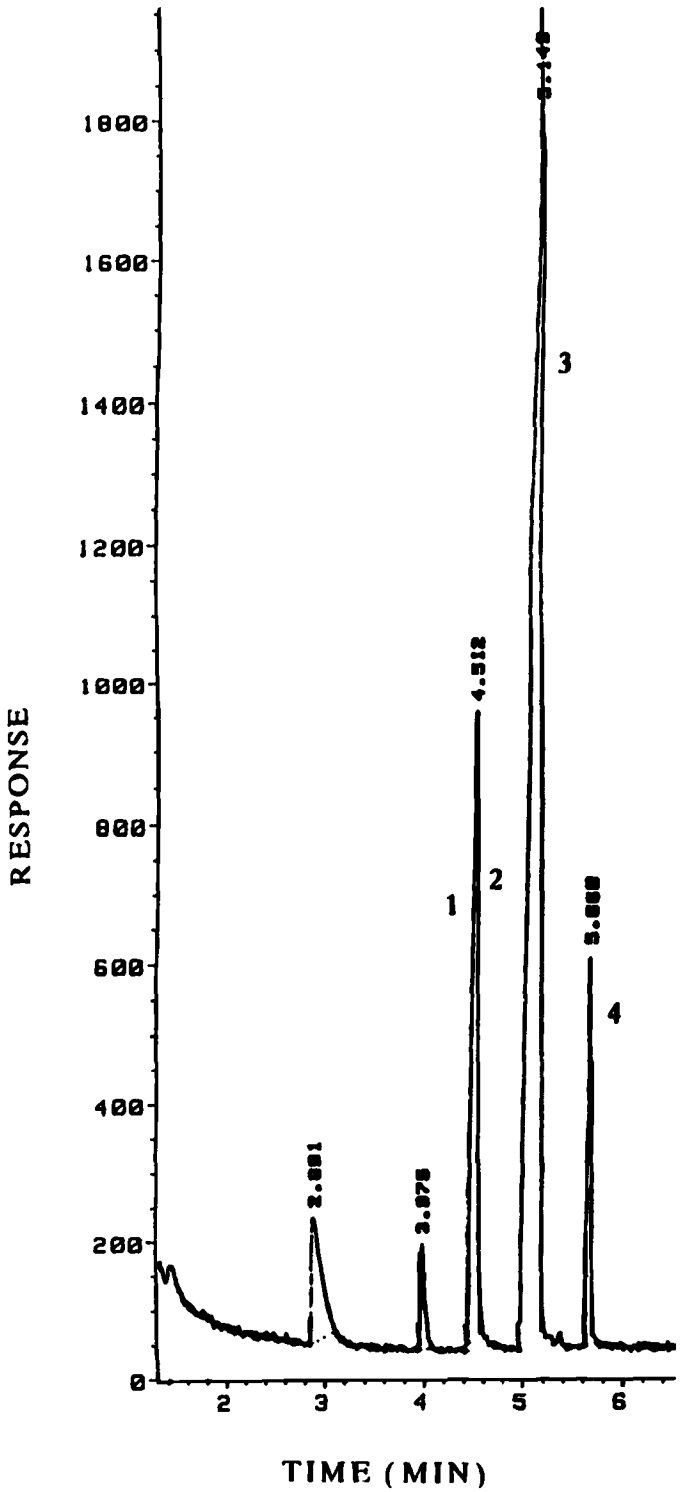

FIG. 5—*Gas chromatogram of sample taken at 310 minutes into the ephedra reduction reaction. (1) Amphetamine co-eluted with, (2) Phenyl-2-propanone, (3) Methamphetamine, (4) N,N-Dimethylamphetamine.*

phenyl-2-propanone (P2P) are typically observed as by-products in reactions involving the reduction of ephedrine with hydriodic acid and red phosphorus [*13*]. Takamatsu [*16*] reported that phenylpropanolamine derivatives will convert to P2P when heated with strong acids. Methamphetamine is the result of the reduction of the ephedrine and pseudoephedrine while the N,N-dimethylamphetamine is formed by reducing the methylephedrine and methylpseudoephedrine pair.

As the reaction continues into the fifth hour, *d*-amphetamine is detected (as is shown in the chromatogram in Fig. 5). It's probable that the amphetamine is synthesized during the first hour of the reaction as are the methamphetamine and N,N-dimethylamphetamine; however, the large amount of P2P present during the initial hours of the reaction probably masked its detection. The generation of the amphetamine results from the reduction of the norephedrine and the norpseudoephedrine, the third ephedra alkaloid pair.

The reaction was stopped after five hours and worked up into its final product, then analyzed using the GC/IRD and the GC/MS. Its chromatogram is depicted in Fig. 6. In this Figure, the

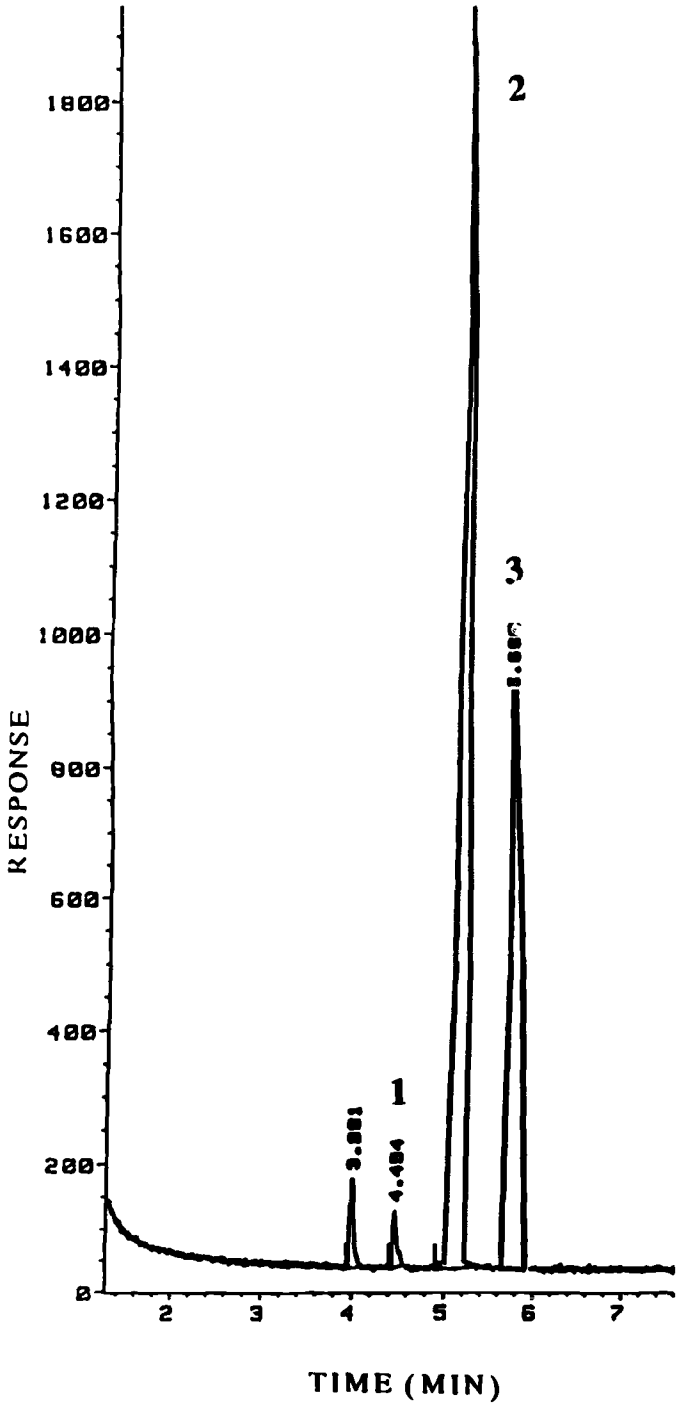

FIG. 6—*Gas chromatogram of the final product of the ephedra reduction reaction. (1) Amphetamine, (2) Methamphetamine, (3) N,N,-Dimethylamphetamine.*

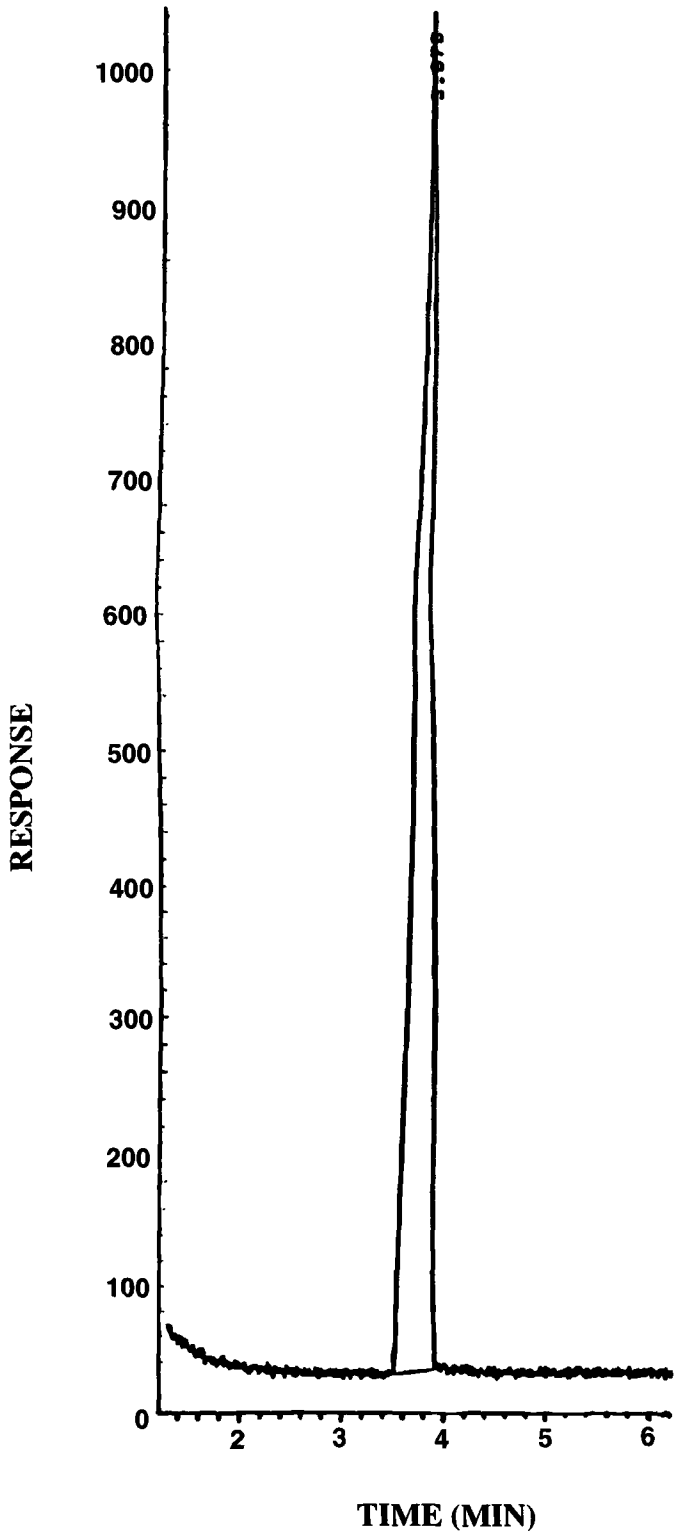

FIG. 7—*Gas chromatogram of methamphetamine, the final product of the ephedrine reduction reaction.*

amphetamine, methamphetamine and N,N-dimethylamphetamine are clearly observed. A chromatogram of the final product of a reduction synthesis with synthetic ephedrine is shown as Fig. 7. Note the absence of the amphetamine and dimethylamphetamine. Because the synthetically prepared ephedrine does not contain the three pairs of ephedra alkaloids, the only compound that can be synthesized reductively is the methamphetamine. Thus, the presence of the amphetamine and N,N-dimethylamphetamine indicate the use of ephedra.

The amounts of amphetamine and dimethylamphetamine will vary depending upon the ephedra product used. In Fig. 6, note the response of the three compounds in relation to one another. In this

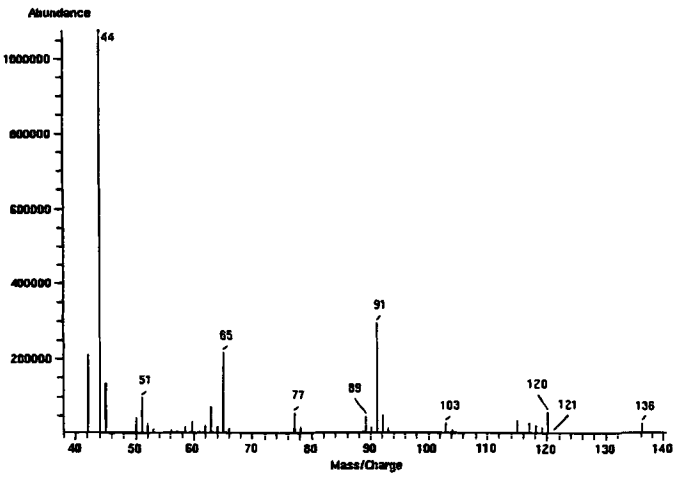

FIG. 8—*Electron ionization mass spectrum of d-amphetamine.*

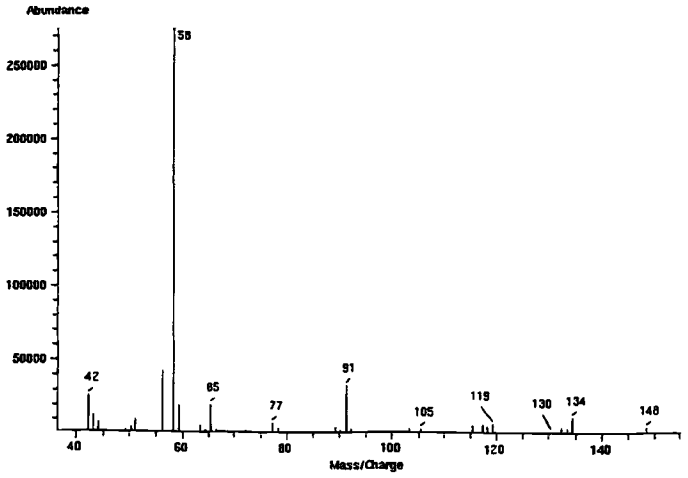

FIG. 9—*Electron ionization mass spectrum of d-methamphetamine.*

particular chromatogram, the height of the N,N-dimethylamphetamine is roughly one-half that of the methamphetamine peak, while the amphetamine is less than one-tenth. In general, the methamphetamine will be the predominant peak in the chromatograms, with the quantity of the amphetamine and the dimethylamphetamine varying depending upon the alkaloid content of the ephedra material.

Figures 8-13 show the electron ionization mass spectra and the gas vapor infrared spectra of amphetamine, methamphetamine, and N,N-dimethylamphetamine, respectively.

Conclusion

Discussed issues concerning accessibility, chemical regulation, and profitability support the theory that ephedra is a feasible and practical material for synthesizing methamphetamine. Therefore, it has the potential for replacing synthetic preparations of ephedrine and pseudoephedrine as a major precursor material for illicit methamphetamine manufacturing. Three "marker compounds" differentiating material synthesized from ephedra versus synthetic ephedrine have been discussed.

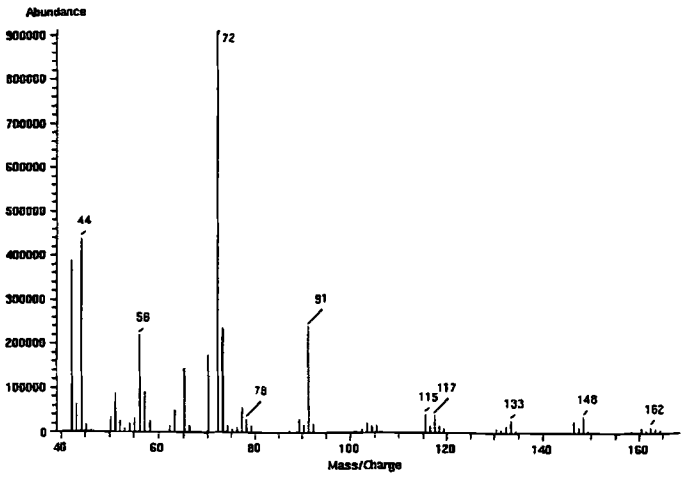

FIG. 10—*Electron ionization mass spectrum of N,N-dimethylamphetamine.*

Acknowledgments

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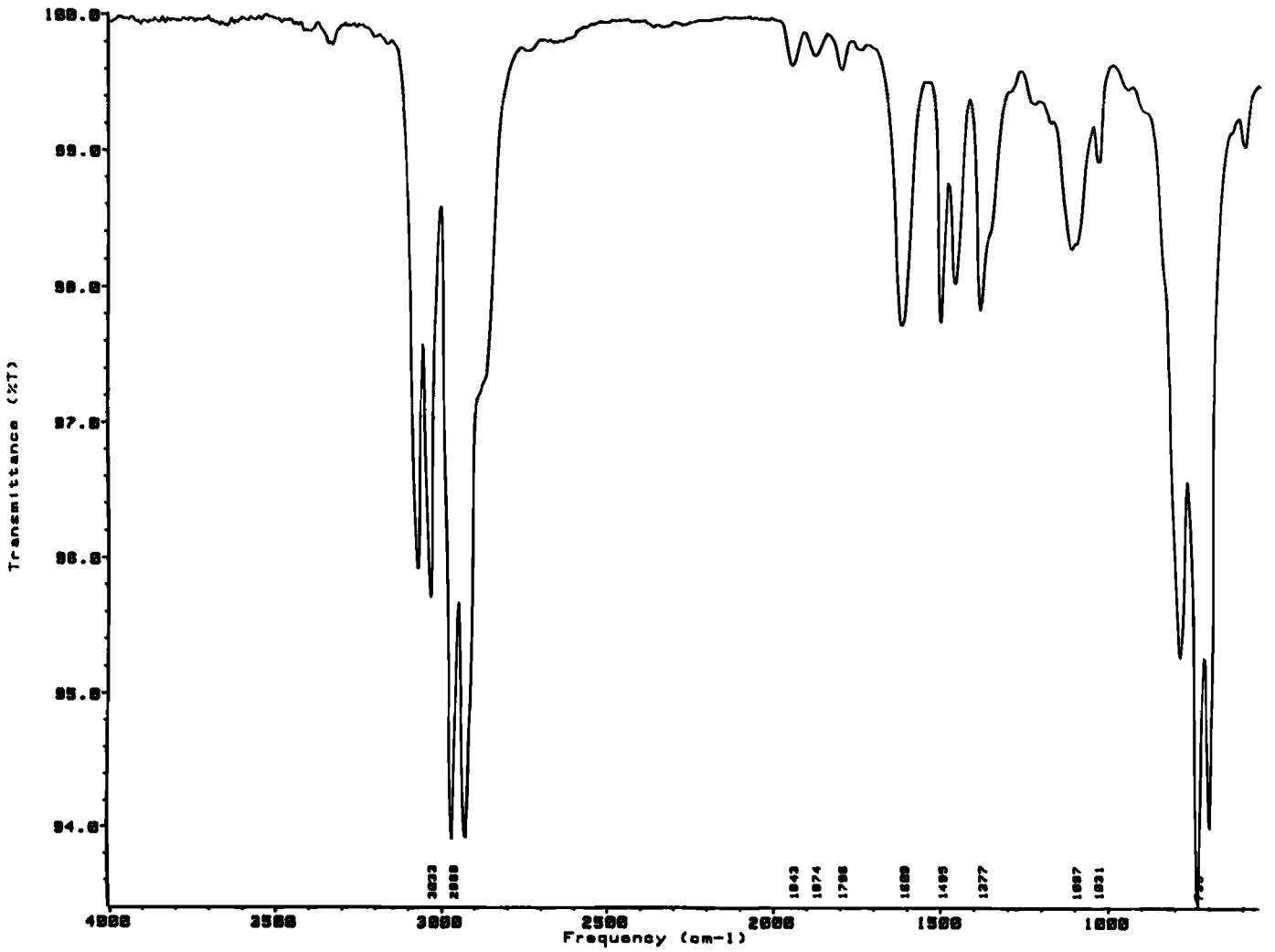

FIG. 11—*Gas vapor infrared spectra of d-amphetamine.*

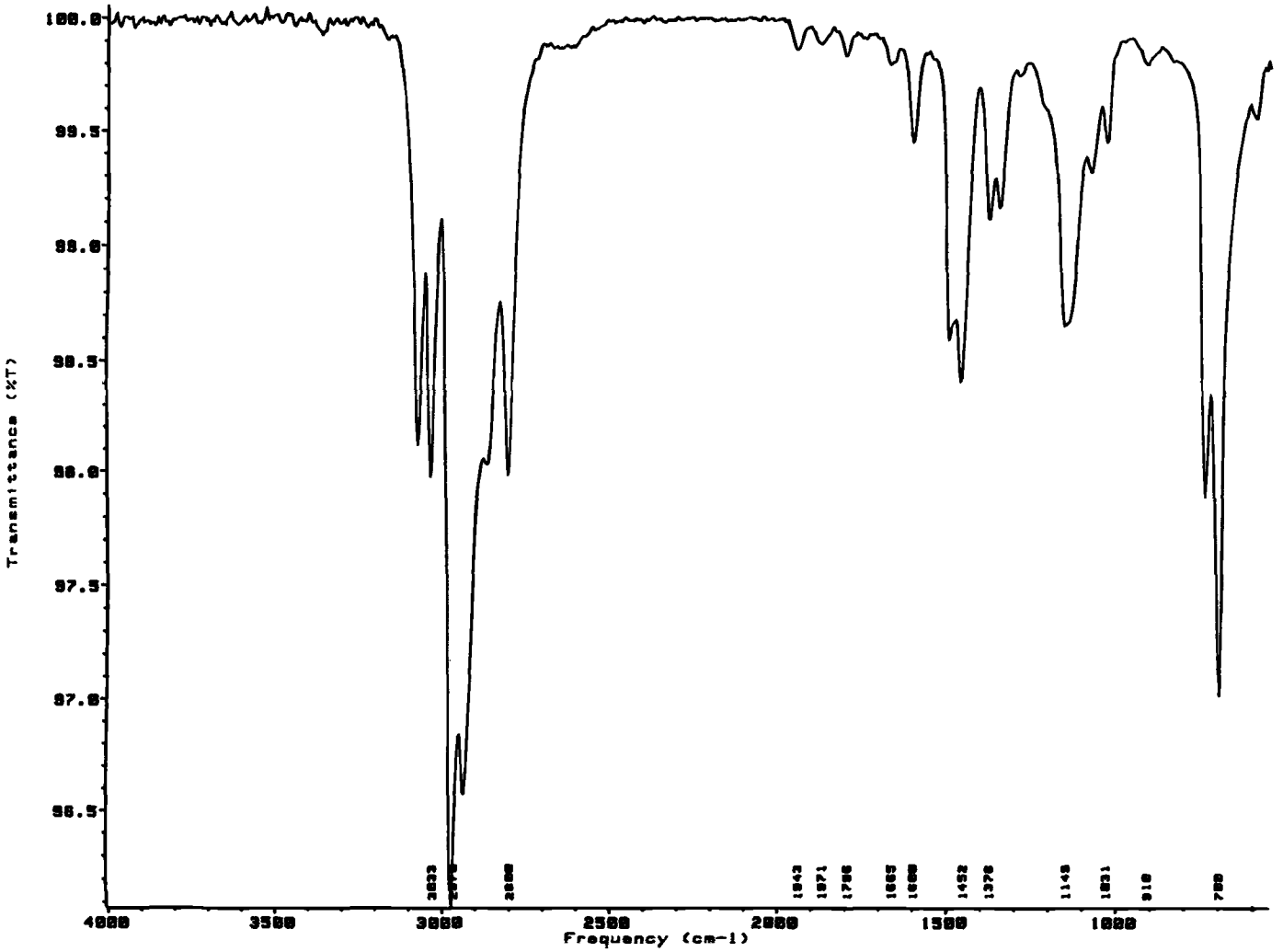

FIG. 12—*Gas vapor infrared spectra of d-methamphetamine.*

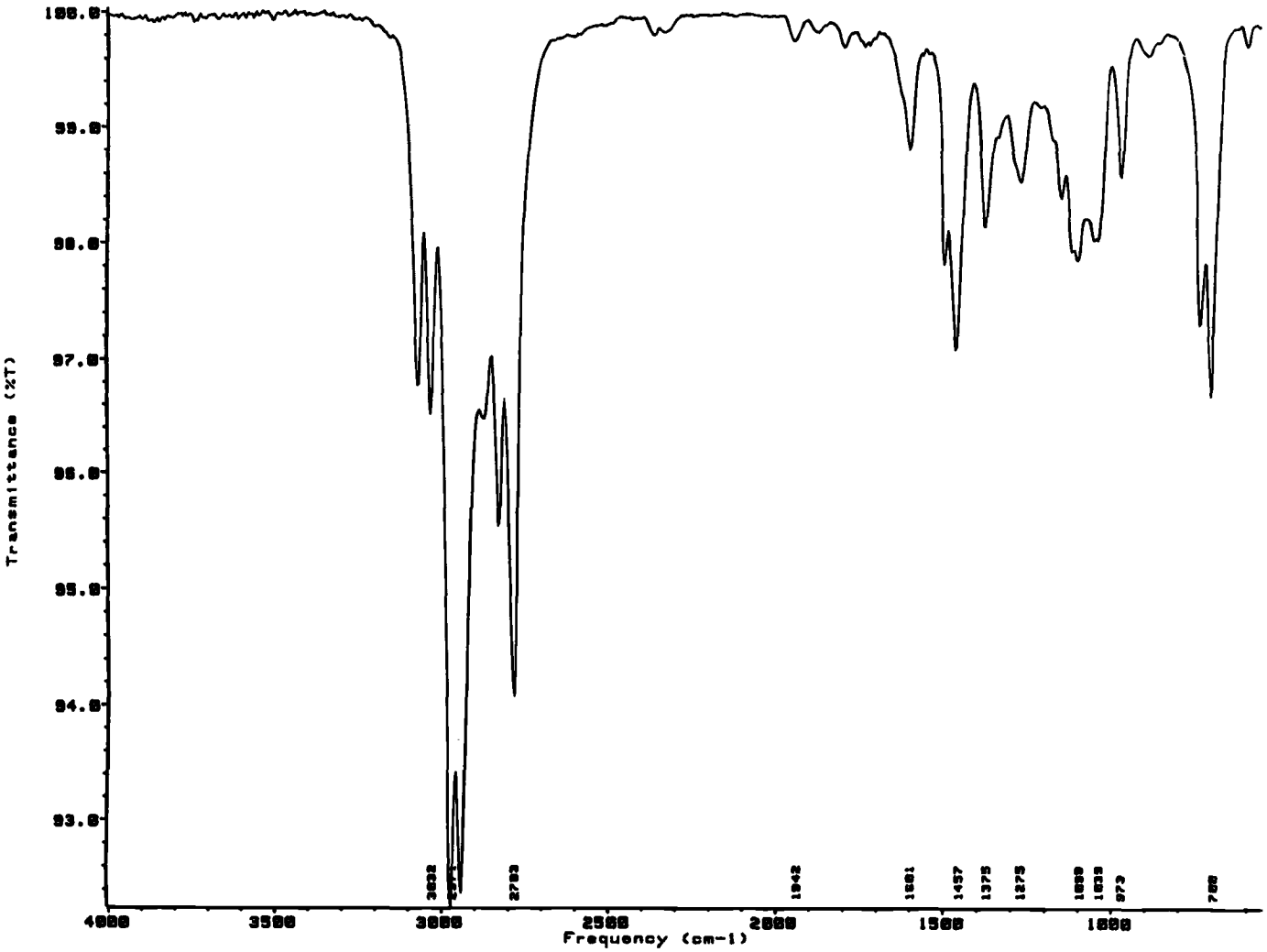

FIG. 13—*Gas vapor infrared spectra of d-N,N-dimethylamphetamine.*

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