Doan-Trang T. Vu,[1] *Ph.D.*

SPME/GC-MS Characterization of Volatiles Associated with Methamphetamine: Toward the Development of a Pseudomethamphetamine Training Material

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ABSTRACT: The headspace profiles of eleven methamphetamine (MA) samples have been analyzed using solid-phase microextraction/gas chromatography-mass spectrometry (SPME/GC-MS). Nine of the eleven are illicit MA seizures from the Southwest U.S. border. One sample is methamphetamine base synthesized in the Drug Enforcement Administration (DEA) Southwest Laboratory, and the remaining sample is pharmaceutical-grade methamphetamine hydrochloride that is used to make training aids for drug detecting canines. In addition, volatiles associated with 1-phenyl-2-propanone (P2P), a methamphetamine precursor, have been identified for comparison with those found in methamphetamine seizure and the two reference samples.

Eighty-seven different compounds were identified from all the samples, not including simple hydrocarbons and aldehydes. Only seven occur consistently in all seizure samples, and these are: acetic acid, benzaldehyde, acetophenone, P2P, 1-phenyl-1,2-propanedione (P12P), 3-phenyl-3-buten-2-one, 1-chloro-1-phenyl-2-propanone. Dimethyl sulfone, a common cutting agent in methamphetamine, was found in six of the nine seizure materials. When the reference methamphetamine and P2P samples are included, only two compounds are common to all twelve samples, and these are benzaldehyde and P2P. As such, these two compounds are likely candidates for use in a pseudomethamphetamine (PM) formulation, and their effectiveness in eliciting a canine response is being evaluated before actual deployment.

KEYWORDS: forensic science, solid-phase microextraction, methamphetamine, pseudomethamphetamine, drug detecting canines, dimethyl sulfone, benzaldehyde, 1-phenyl-2-propanone

The U.S. Customs Service Canine Enforcement Program has had considerable success over its 25 year history, during which time many seizures of marijuana/hashish, cocaine, and heroin have been made with the assistance of drug detecting dogs. More recently, methamphetamine has been added to the training program because of the rise in abuse (1) and consequent illicit trade of this drug. It is well established that canines alert to the odor associated with training materials, drugs in this case, rather than the material itself. Pseudococaine (PC) and pseudoheroin (PH) were developed and have been successfully used based on this premise. No pseudomethamphetamine exists, and the canines are currently being trained with actual methamphetamine. The problem with using authentic drugs is twofold. The material is expensive, and the paperwork trail involved with each training aid can be overwhelming. More important is the safety of the detector dog, whose accidental ingestion of a training aid can be fatal.

The first step toward developing a pseudomethamphetamine training material was determining what components are present in the headspace of typical methamphetamine samples. Volatile components that occur consistently in every sample were then identified as likely candidates for use in a pseudomethamphetamine formulation. The combined SPME/GC-MS technique was used to achieve this goal. The SPME fiber can be thought of as a very short (1 cm) GC column turned inside out. An outer polymer coating absorbs volatiles present in the headspace and releases them only in the heated GC inlet. The fiber is attached to a stainless steel, retractable plunger that is housed inside a thin needle. The needle prevents stripping of the fiber coating by the injector septum and also minimizes environmental contamination during fiber storage. The advantage of SPME over other techniques is that it is quick and simple, unlike purge-and-trap, and is nondestructive, unlike liquid extractions. Supelco publishes an extensive list of SPME applications (2).

Materials and Methods

The following fibers (Supelco, Bellefonte, PA) were tested to determine which would give the most complete headspace profile of methamphetamine: 85 μm polyacrylate (PA), 75 μm Carboxen/PDMS (CAR), 65 μm PDMS/divinylbenzene (DVB), 65 μm Carbowax/DVB (CWDVB), and 50/30-μm divinylbenzene/Carboxen/PDMS (CBXDVB). Before it was used for the first time, each fiber was conditioned according to manufacturer's instructions until a clean chromatogram was obtained under normal run conditions. In addition, to minimize background signals, the fibers were heated in the GC inlet for two to five minutes before each headspace sampling. To eliminate carryover, the fibers were left in the inlet for the full length of a run.

During the method development stage, a 10 g sample of pharmaceutical-grade, 100% pure methamphetamine hydrochloride (Arenol Chemical Corp., Sommerville, NJ) was placed in the bottom pan of the stainless steel pan/sieve (W.S. Tyler, Mentor, OH) arrangement shown in Fig. 1*a*. The two layers of fine mesh (20 and 25 μm) sieves separated the powder sample from the exposed fiber and prevented accidental sampling of the powder itself. The top

[1] U.S. Customs Services, Research Laboratory, 7501 Boston Blvd., Suite 113, Springfield, VA.

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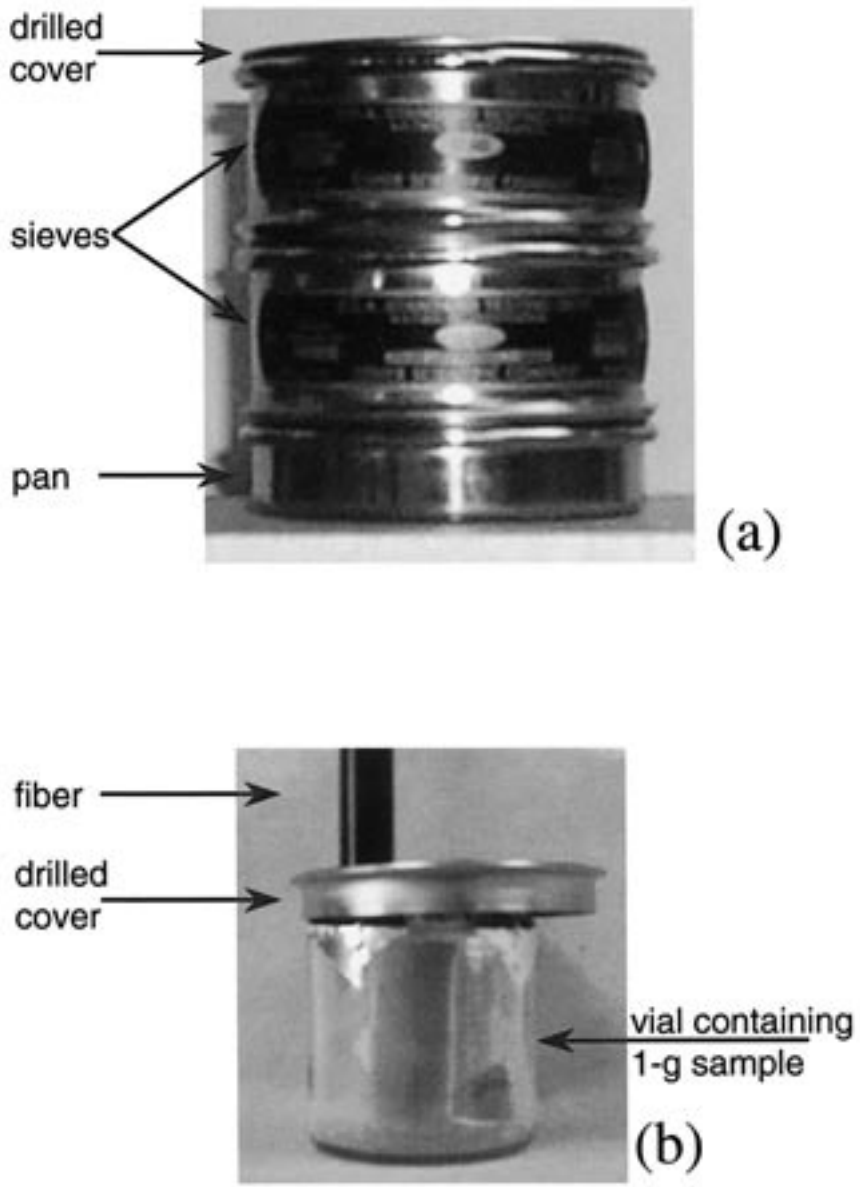

FIG. 1—*Incubation and sampling setup using pan/sieve arrangement for 10 g samples* (a) *and jars for smaller samples* (b).

cover had five predrilled holes to allow simultaneous sampling with several fibers, and the whole assembly was wrapped in aluminum (Al) foil to allow incubation and minimize environmental contamination. Incubation and sampling were done at ambient temperature for various lengths of time up to 24 h.

In subsequent analyses, a 1 g powder sample was placed in a small, uncapped vial, which was then placed inside a 250 mL jar covered with Al foil for incubation. A drilled cover placed over the top of the jar gave the fiber stability while sampling. To minimize accidental sampling of the powder material, sampling was done by puncturing the foil and exposing a CBXDVB fiber inside the jar but not directly over the uncapped vial (Fig. 1*b*). The same arrangement was used to analyze MA base and P2P, but an approximately 6 mL liquid sample was used instead. Solid samples were incubated for 4 h and sampled for 1 h, except for the Arenol MA, which was sampled for 3 h because of the low level of volatiles in its headspace. Liquid samples were incubated for 1 h and sampled for 1 h because of the high volatility of the compounds present.

Data were acquired on an HP 5980/5970 GC/MSD (Hewlett Packard, Palo Alto, CA), fitted with a 30 m by 0.25 mm by 0.25 μm XTI-5 column (Restek, Bellefonte, PA) with He as the carrier gas. The inlet was operated in the constant pressure mode at a pressure of 10 psi. The 0.75 mm ID inlet liner (Supelco) is designed specifically for SPME work. The GC oven temperature was held at 50°C for 3 min, ramped at 5°/min to 150°C then at 25°/min to 275°C, and held for 2 min at the final temperature (a slightly faster temperature program was used during the method development stage). The inlet and MS transfer line temperatures were 260 and 300°C, respectively. Splitless injections were done with a purge activation time of 0.75 min. The MS was operated in electron ionization mode with a scan range of 33 to 150 from 0.75 to 2.5 min and 40 to 440 during the rest of the run. All other MS parameters were set at autotune values.

Headspace components were identified by comparing their mass spectra with those found in reference libraries (Wiley, 6th Edition; Pfleger, 2nd Edition; and NIST, 1998 Edition). A list of possible

compounds was generated using an automated library search routine with probability-based matching (PBM) algorithm, and each mass spectrum was visually inspected to verify the match. Additionally, selected components (marked † in Table 1) were identified by both their retention times and mass spectra as generated from running standards, which were reagent grade chemicals from Aldrich (Milwaukee, WI) and Fisher (Fair Lawn, NJ); P2P was supplied by the DEA Mid-Atlantic Laboratory in Washington, DC.

Results

Previous work in this laboratory (3) established that the dual-layer CBXDVB fiber works best for characterizing volatiles associated with illicit cocaine and heroin samples. Nevertheless, it was important that the same experiment be repeated to determine which fiber would give the most complete headspace profile for methamphetamine. Figure 2 compares the headspace profiles for a 10 g sample of Arenol MA using the setup in Fig. 1*a.* The CAR fiber (Fig. 2*a*) worked best for low molecular weight (early eluting) volatiles, but it did not do a good job of extracting higher molecular weight compounds as indicated by the lack of signal in the latter part of the chromatogram. The DVB fiber (Fig. 2*b*) worked well for high molecular weight volatiles but extracted almost nothing at the lower end. The CBXDVB fiber (Fig. 2*c*) extracted high molecular weight compounds almost as well as the DVB, but it also extracted reasonably well low molecular weight compounds that were indicated when using the CAR fiber. These results agree with the manufacturer's specifications (4) that the CBXDVB fiber covers a broader range of analytes than other fibers and indicates that it is the fiber of choice when analyzing unknowns such as the volatile components of methamphetamine. Of the remaining two fibers, CWDVB gave a moderate performance at the high end with nothing at the lower end, and PA indicated the presence only of benzoic acid within the time frame of the experiment. Thus, the CBXDVB fiber was chosen for all subsequent analyses.

Figure 3 compares the headspace profiles of an illicit MA sample, MA base, P2P, and Arenol MA. The last, being highly pure, had few volatiles as indicated by the relatively flat chromatogram. The major volatile compound associated with this sample is 1-phenyl-2-propanol, a synthetic byproduct from the Leuckart reduction of P2P. Closer inspection revealed the presence of eleven other compounds, including residual P2P. It is important to note that the absence of acetic acid for Arenol MA in Fig. 3*d* was due to the smaller sample used (1 g); Fig. 2*c* clearly indicates its presence in the 10 g sample. Not surprisingly, MA base had a large amount of P2P and methamphetamine itself in the headspace, and yet perceived odor was overwhelmingly that of the solvent diethyl ether. P2P itself had a sweet odor despite the fact that the headspace contained a significant amount of acetic acid. The illicit MA sample had the most complex headspace profile, including the cutting agent dimethyl sulfone and a number of synthetic byproducts such as P2P and P12P. The latter compound, in particular, gave strong evidence that ephedrine or pseudoephedrine was the precursor material (Fig. 4), and it was present in all nine seizure MA samples.

In all, 87 compounds were identified among the twelve samples, and these are listed in Table 1 along with the number of occurrences of each (5). Most occurred only in trace amounts (less than one percent total integrated area), and the list does not include simple hydrocarbons such as hexane and xylene or simple aldehydes such as nonanal. Many compounds listed occurred in only one or two samples, illustrating great variability in the headspace profiles of methamphetamine. Besides MA base, MA itself was detected in

TABLE 1—*Volatile components found in nine MA seizures, pharmaceutical MA, MA base, and P2P. The list is organized roughly by key functional groups and counts the number of times each compound was found in all twelve samples.* †*Marks compounds that were identified by both their retention times and mass spectra.*

ID	# Occurrence Out of 12
Acid	
acetic acid†	10
benzoic acid†	2
benzoylformic acid	1
formic acid†	3
propanoic acid	3
Alcohol	
1-phenyl-1-propanol	2
1-phenyl-2-propanol†	2
2-butoxyethanol	2
2-ethyl-1-hexanol	7
3-t-butylphenol	4
benzyl alcohol	6
butylated hydroxy toluene (BHT)	9
di-t-butyl-phenol	6
lonol	9
phenol	2
propylene glycol	1
Aldehyde	
2-hydroxybenzaldehyde†	2
4-methoxybenzaldehyde	1
acetaldehyde	1
benzaldehyde†	12
Amide/Amine	
1,2-dimethyl-3-phenyl-aziridine	3
amphetamine formyl artifact	1
benzonitrile	4
benzyl cyanide	2
mephentermine	1
methamphetamine†	3
Methoxyphenamine acetate	1
N-(phenylmethylene)-methanamine	6
N,N,alpha-trimethylphenethylamine	2
N-methyl acetamide	3
N-methyl formamide	1
Ester	
2-(2-ethoxyethoxy)-ethanol acetate	1
benzyl acetate	1
diethyl phthalate	5
ethyl acetate	1
methyl acetate	3
methyl benzoate†	6
methyl phenyl acetate	3
octyl acetate	4
Ether	
2-methylbenzofuran	6
ethyl ether†	1

TABLE 1—*Continued.*

ID	# Occurrence Out of 12
Halogenated Compounds	
1-chloro-2-propanone	2
1-iodohexane	1
4-phenylbutyl chloride	8
benzoyl chloride	1
benzyl chloride	8
chloroacetaldehyde	2
chloroiodomethane	3
chloropropylbenzene	6
iodomethane	1
iodomethylbenzene	1
methyl chloroacetate	1
methylene chloride	1
1-chloro-1-phenyl-2-propanone (1-chloro-P2P)	9
tetrachloroethene	1
trichlorofluoromethane	6
dichloromethylbenzene	2
Hydrocarbon	
(-)-.alpha.-terpineol	1
(1-methylbutyl)benzene	3
1,2,3,4-tetrahydro-1,5, 8-trimethyl-naphthalene	1
2-phenyl-1-propene	2
benzene	7
dimethyl naphthalene	2
limonene	1
methyl naphthalenes	4
naphthalene	1
propenylbenzene isomers	5
propyl benzene	1
styrene	2
toluene	4
Inorganic Acid	
hydrochloric acid†	1
Ketone	
1-phenyl-1,2-propanedione†	11
1-phenyl-1-propanone	8
1-phenyl-2-butanone (BEK)	1
1-phenyl-2-propanone†	12
2-methyl-2-cyclopenten-1-one	6
2-methylcyclopentanone	1
3-methyl-2-cyclopenten-1-one	2
3-methylcyclopentanone	1
3-phenyl-3-buten-2-one	11
4-hydroxy-4-methyl-2-pentanone	1
5-phenyl-3-penten-2-one	4
acetone†	4
acetophenone	9
Sulfur Compounds	
benzothiazole	1
dimethyl sulfone†	6
ethyl methyl sulfone	2

only trace amounts in two of the seizure samples, indicating perhaps incomplete salt formation. On the other hand, a trace of hydrochloric acid (HCℓ) in another sample was due to occluded acid after salt formation. Interestingly, one seizure sample contained a trace of 4-methoxybenzaldehyde (Fig. 5), a compound that has been reported in association with illicit 4-methoxyamphetamine (6), but this sample's overall headspace profile was still indicative of MA. Seven of the seventeen halogenated compounds found, including trichlorofluoromethane and methylene chloride, were residual solvents, while the remaining ten compounds were possible byproducts. 1-Chloro-1-phenyl-2-propanone (Fig. 6), in particular, was found in abundance in all nine seizure MA but was completely absent in the two reference MA and P2P samples. Benzothiazole is an odor component of latex and could have come about because the seizure was packaged in a condom or because it was handled with latex gloves.

Figure 7 shows how the headspace profile changed when care was not taken to avoid sampling particulate matter. Instead of either arrangements shown in Fig. 1, 10 g Arenol MA was placed in a foil-covered jar, and the fiber exposed directly over the loose powder for 30 min. The major component in the chromatogram was methamphetamine along with a number of other amphetamine-related compounds. This is significantly different from the profile in Fig. 2*c,* in which a pan/sieve arrangement allowed only volatiles to come into contact with the fiber and consequently no methamphetamine was detected.

Discussion

It has been suggested that methamphetamine particles may be responsible for the canine alerts and that methamphetamine should not be ruled out as the universal key odor component. However, Dr. Ed Morrison at the Institute for Biological Detection Systems (Auburn University, AL) has mapped out how particles travel through the canine respiratory/olfactory system and shown that most of them are trapped in the respiratory chamber and only very few particles make it back into the olfactory chamber after more than 6 h (7). This time scale is inconsistent with the near instantaneous response when a canine alerts to a trained target and indicates that it is the gaseous compounds associated with the training material, and not the solid, that causes a canine alert. Although MA base has significant volatility and can induce a canine response, there is no known report of an MA base seizure being smuggled across the border, and it is no safer or more convenient to use than MA hydrochloride.

Thus, a PM training material must be based on the volatile components found in MA seizures. The importance of identifying even trace odor components in MA cannot be overemphasized since it is not yet known which compounds result in canine detection of MA. On the one hand, it could be hypothesized that a canine will key in on the most abundant component in the headspace. This would be 1-phenyl-2-propanol in the case of Arenol MA training material. Experience has shown, however, that Customs' detector dogs are able to find illicit MA, most of which do not contain this compound (Table 1). These trained canines are also able to detect MA base and P2P, neither of which contains 1-phenyl-2-propanol. Furthermore, when deployed as a target, this compound failed to elicit consistent alerts from certified drug detecting dogs at the U.S. Customs Canine Enforcement Training Center. It would appear that some other minor odor component(s) is responsible for canine detection of MA. These results are perhaps not surprising when one considers that a mi-

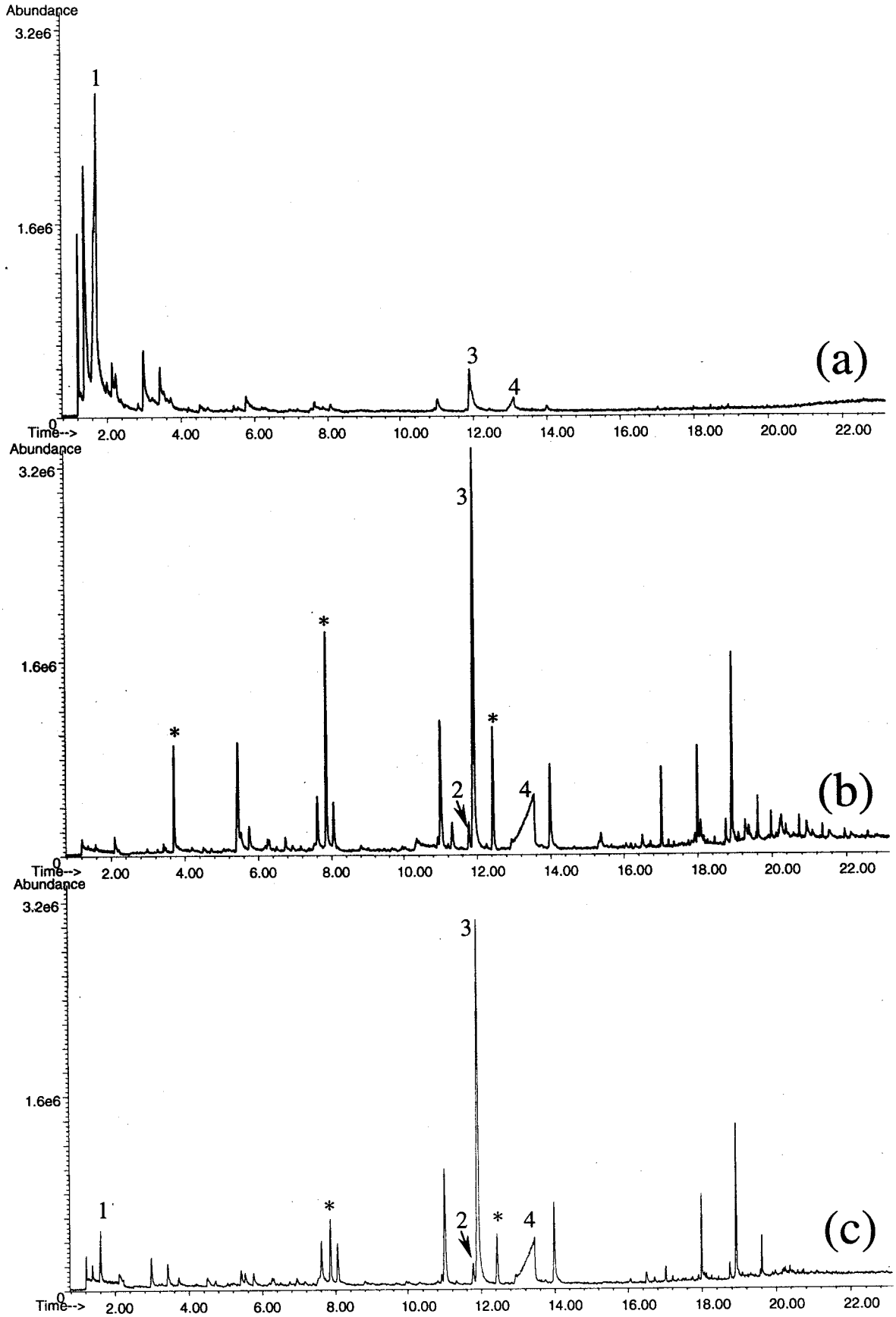

FIG. 2—*Comparison of headspace profiles of a 10 g MA sample when using CAR* (a)*, DVB* (b) *or CBXDVB* (c) *fiber. Incubation and sampling times were 21 and 20 h, respectively. Peaks 1 through 4 are, respectively, acetic acid, P2P, 1-phenyl-2-propanol, and benzoic acid. The retention times are different from those in Fig. 3 because a slightly faster temperature program was used during this method development stage. * = fiber bleed signals.*

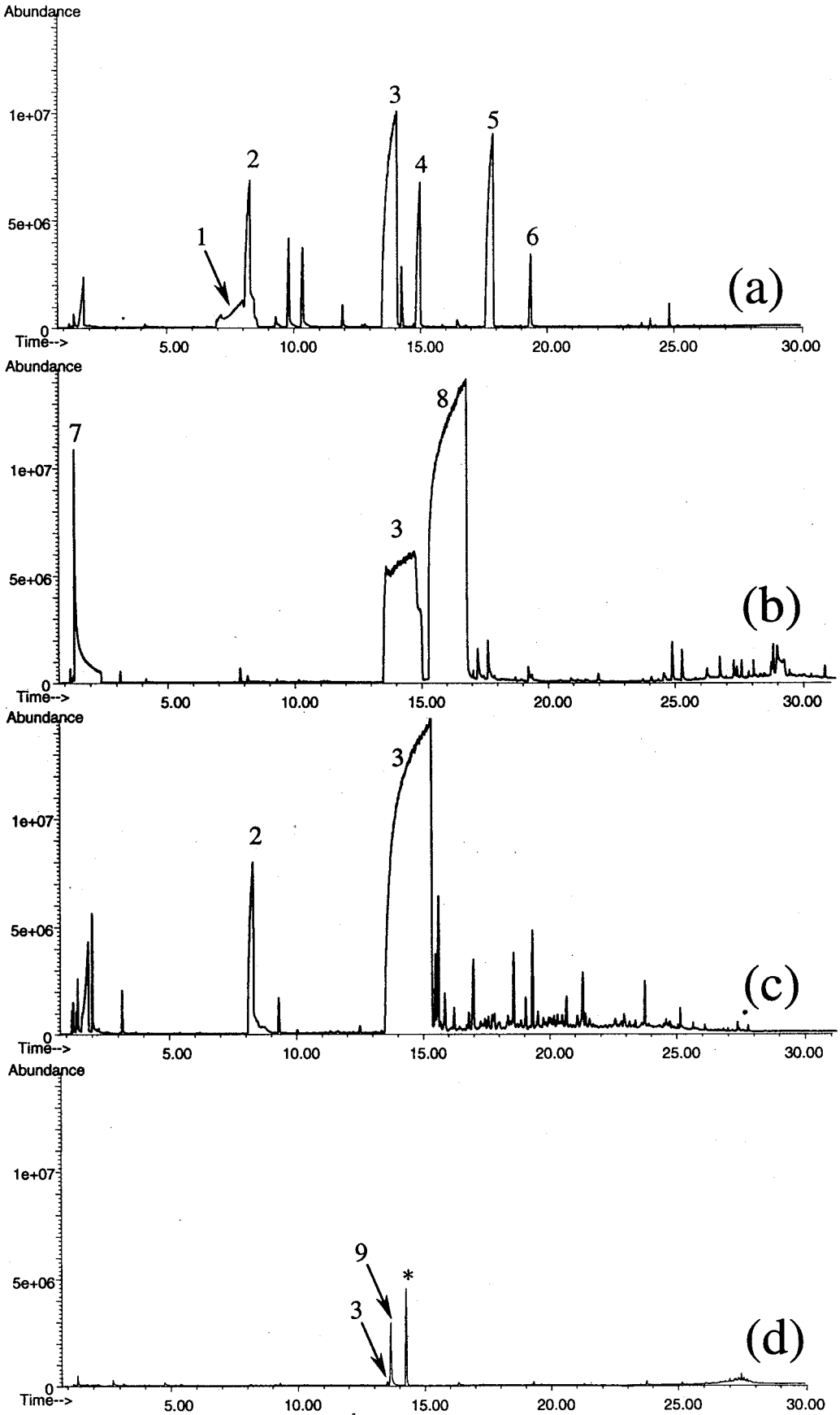

FIG. 3—*Comparison of headspace profiles for 1 g samples of a methamphetamine seizure* (a)*, methamphetamine base* (b)*, P2P* (c)*, and pharmaceutical-grade methamphetamine hydrochloride* (d)*. Compounds corresponding to labeled peaks are (1) dimethyl sulfone, (2) benzaldehyde, (3) P2P, (4) 4-phenylbutyl chloride, (5) 1-phenyl-1,2-propanedione, (6) 1-chloro-1-phenyl-2-propanone, (7) diethyl ether, (8) methamphetamine, and (9) 1-phenyl-2-propanol. * = a fiber bleed signal.*

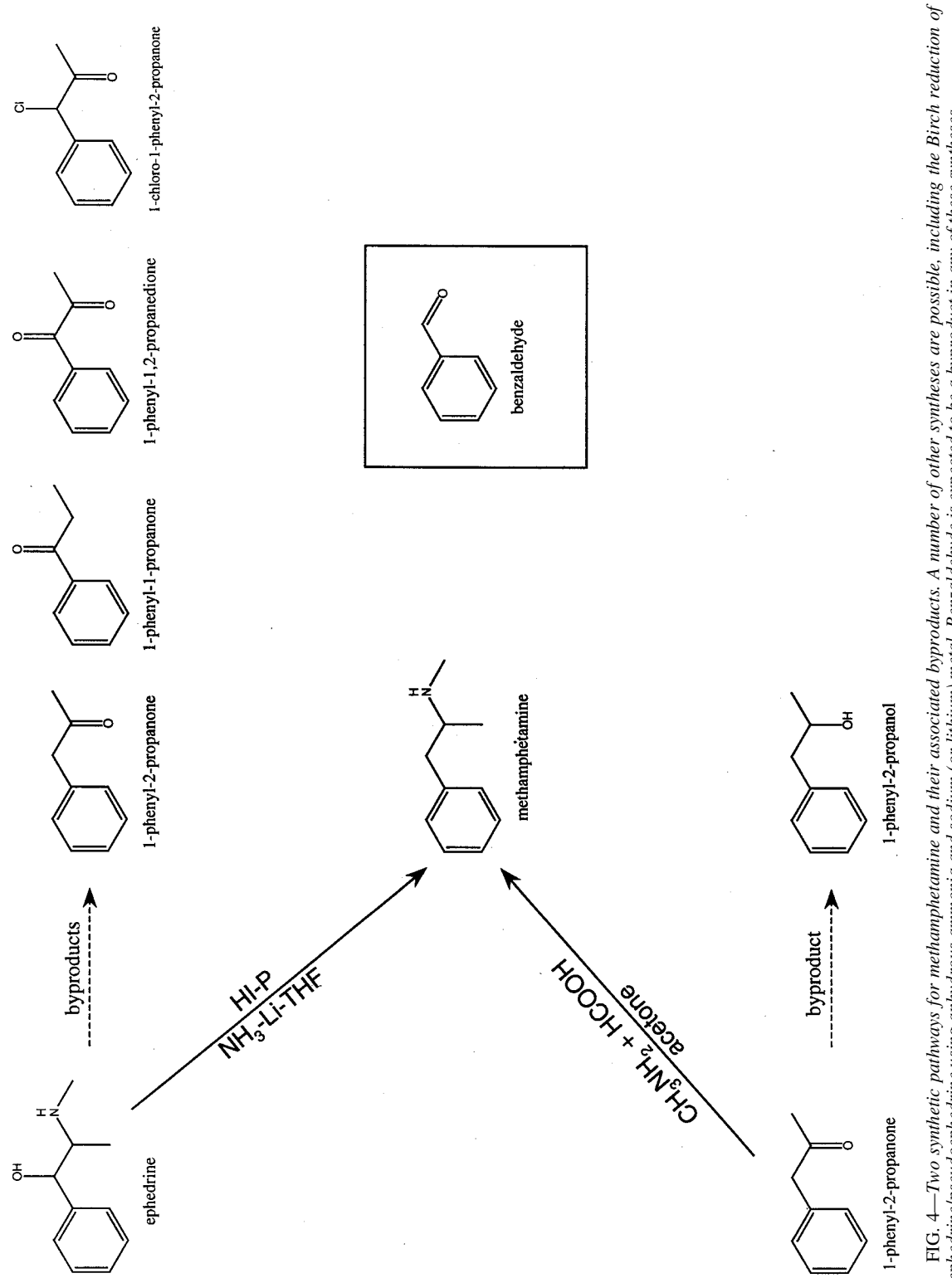

FIG. 4—*Two synthetic pathways for methamphetamine and their associated byproducts. A number of other syntheses are possible, including the Birch reduction of ephedrine/pseudoephedrine using anhydrous ammonia and sodium (or lithium) metal. Benzaldehyde is expected to be a byproduct in any of these syntheses.*

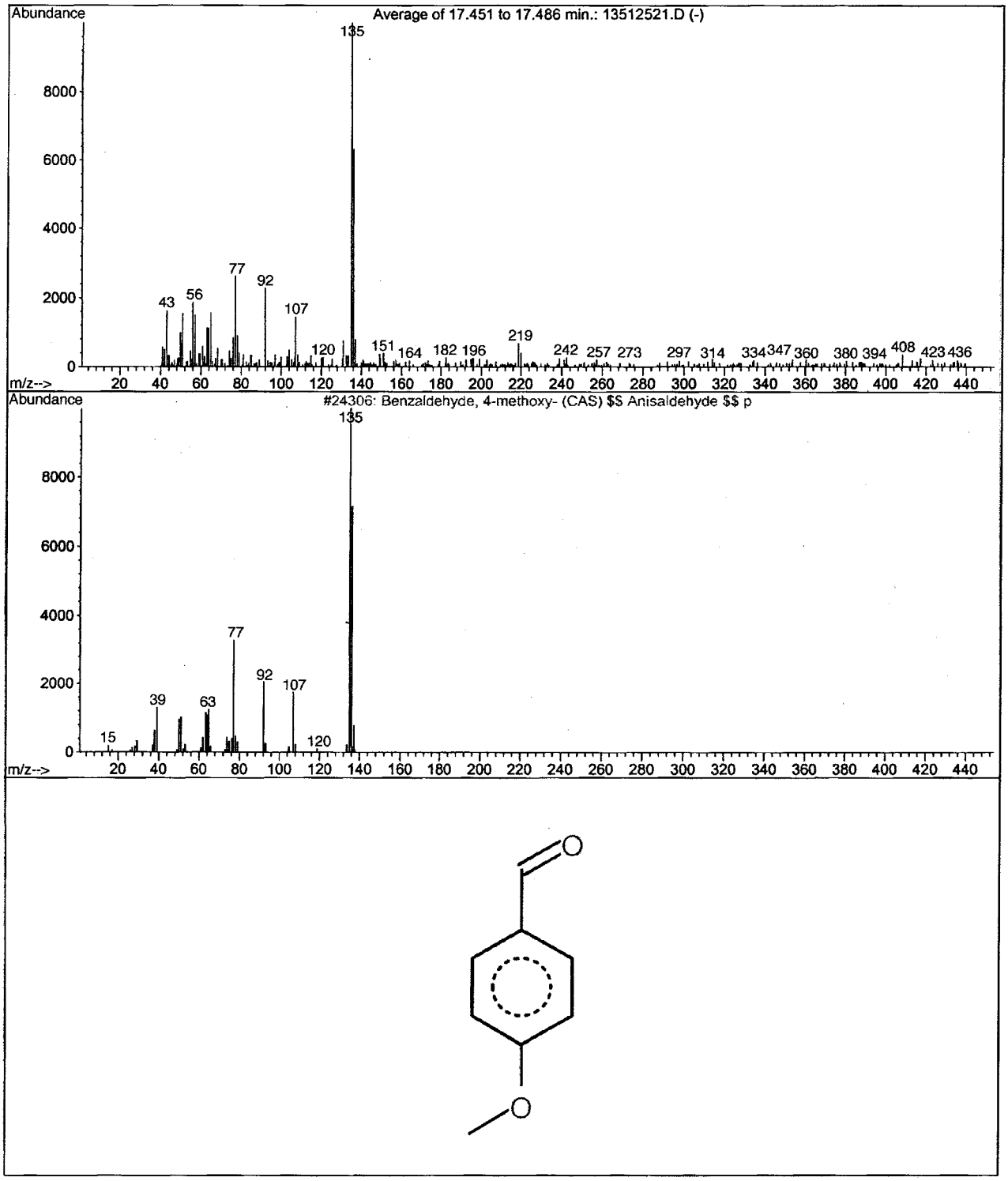

FIG. 5—*Experimental and reference library match spectra for 4-methoxybenzaldehyde.*

nor component in the headspace may contribute significantly to the perceived odor if its threshold concentration is low. This concept of "odor value" has been used extensively in perfumery, and it has also been used to develop a synthetic opium odor (8).

While it was important to identify every component that may contribute to the odor of MA, for the purpose of developing a PM detector dog training aid, it was more relevant to identify compounds that occur consistently in all MA samples, regardless of the synthetic route. Table 2 identifies those compounds that were common to all nine MA seizures and correlates them to those found in MA base, pharmaceutical MA, and P2P. Only P2P and benzaldehyde were common to all twelve samples, making them likely candidates for use in a PM formulation. Even when P2P was excluded from the comparison, no additional compounds were found to be

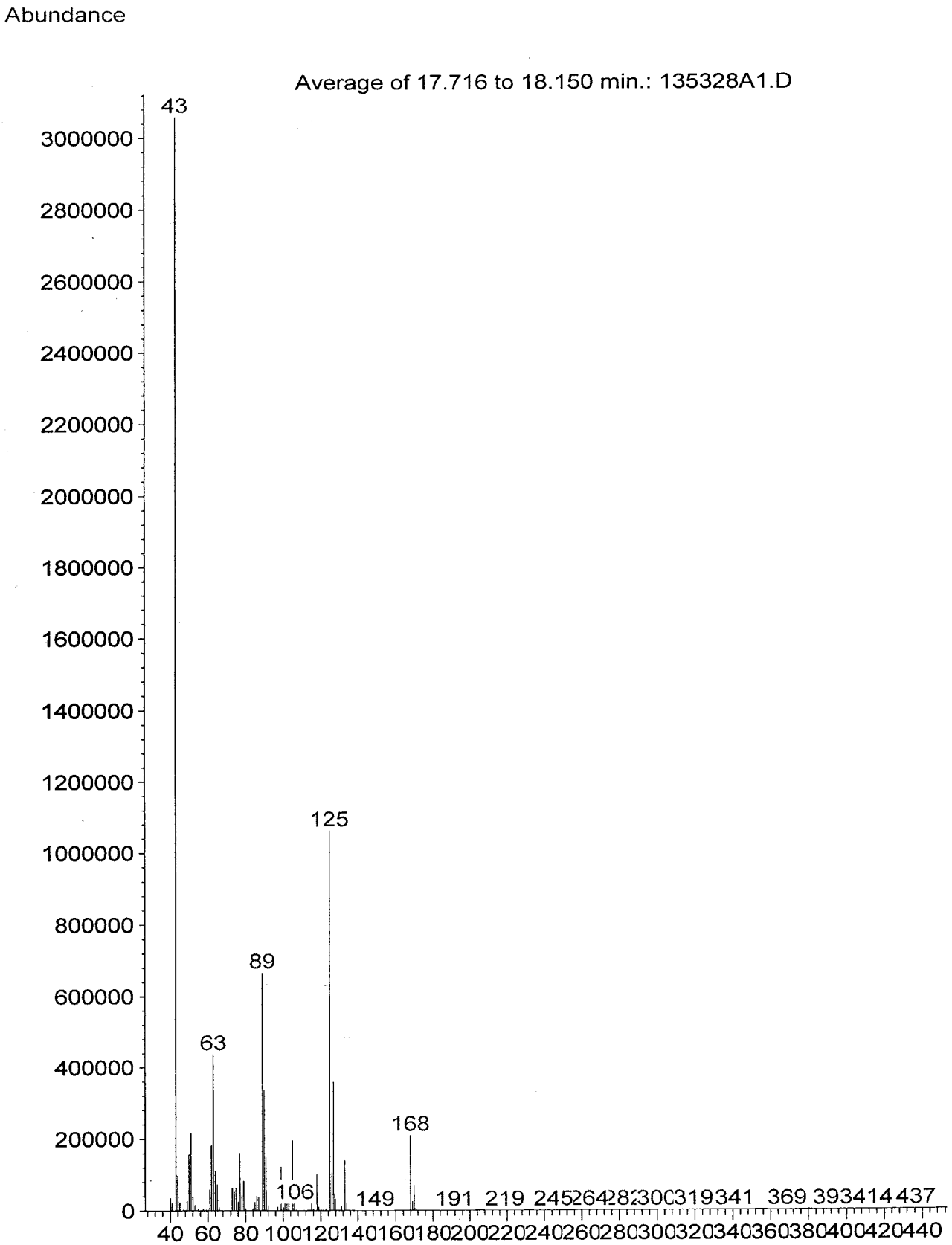

FIG. 6—*Experimental mass spectrum of 1-chloro-1-phenyl-2-propanone.*

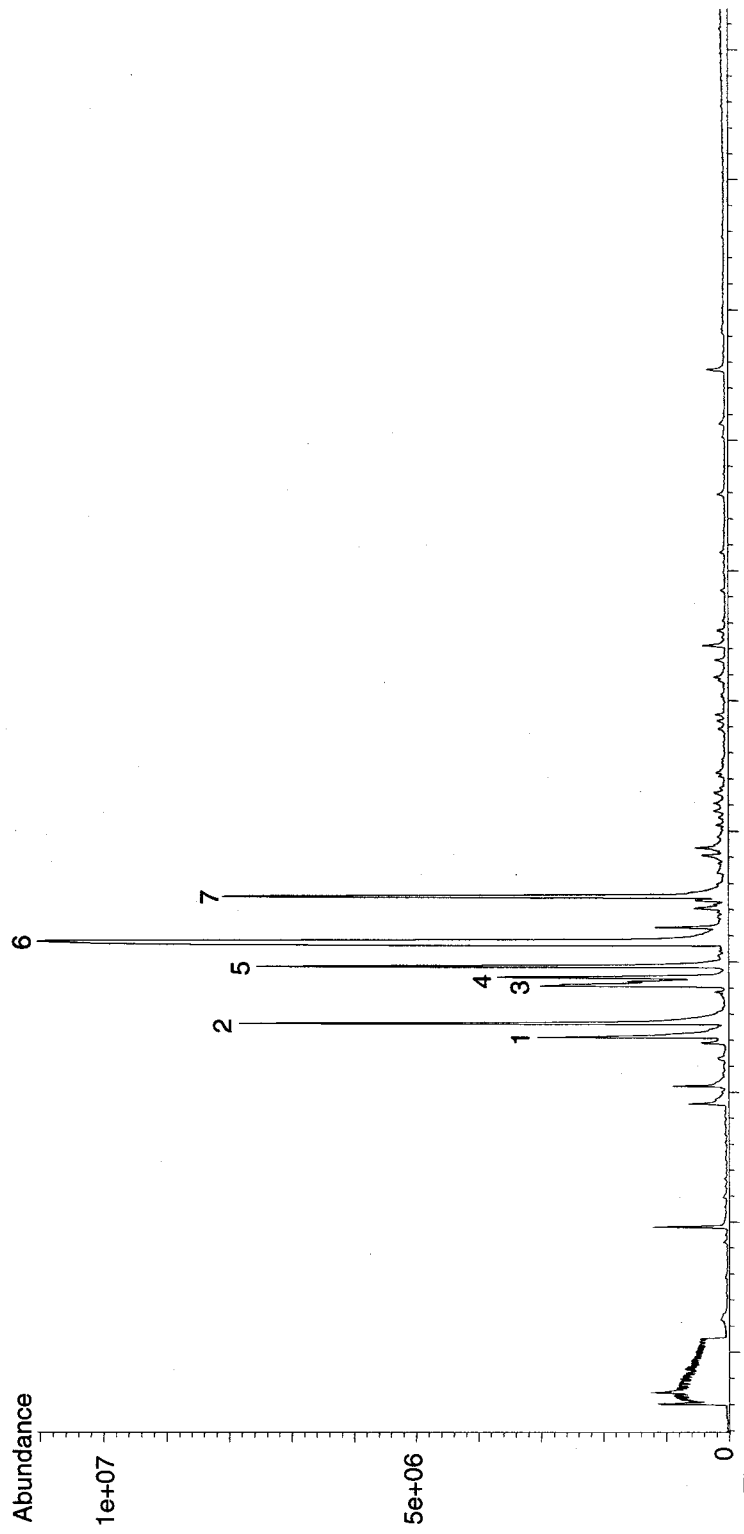

FIG. 7—*Headspace profile of Arenol MA when the SPME fiber was exposed directly over 10 g loose powder, resulting in sampling of particles as well as volatiles. Labeled peaks correspond to (1) N-methyl-benzenemethamine, (2) N,α-dimethyl-benzenemethamine, (3) P2P, (4) 1-phenyl-2-propanol, (5) 1,1-phenylmethylaminopropane, (6) methamphetamine, and (7) mephentermine.* (cf, *Fig.* 2c).

TABLE 2—*The list of seven compounds found in common in MA seizures (the first nine samples) is narrowed to only two compounds when pharmaceutical MA (i4s3_1g), MA base (Base 11), and P2P (P2P11) are included. Excluding P2P from the comparison has no effect on the final result. Approximate relative amounts (based on total integrated area) are indicated as − for trace, + for <1%, ++ for 1 to 5%, +++ for 5 to 10%, and ++++ for >10%.*

	1-chloro-P2P	1-phenyl-1,2-propanedione	1-phenyl-2-propanone	Benzaldehyde	Acetic Acid	3-phenyl-3-buten-2-one	Acetophenone
135328A1	++++	+	++++	+	+	−	−
135328B1	+	+	++++	+	−	−	−
135328C1	+	+	++++	++	+	−	−
135328D1	++++	+++	++	++++	+	−	−
113544_1	++++	+++	+++	+++	+	−	−
134677_1	+	+	++++	−	−	−	−
13512511	−	+	++++	+	−	+	−
13512521	+	+++	++++	++++	++	−	−
135255_1	+++	++	++++	+++	+	−	−
i4s3_1g	…	…	−	−	…	…	…
Base11	…	…	+++	−			
P2P11	…	…	++++	+	…	…	…

common among the remaining eleven MA samples. P2P is ideal because it is both a precursor and a byproduct, and its use as a PM training aid would address the safety issue. One drawback, however, is that P2P is a Schedule II controlled substance in the United States, and its use would require extensive paperwork to track the training aids as though they were actual drugs and the aids must be stored in a secure location to ensure their integrity.

Benzaldehyde, on the other hand, is not controlled, is relatively inexpensive, and is relatively safe to use. In addition, benzaldehyde has also been detected in significant amounts in all ten cocaine seizures and in smaller amounts in all eight heroin seizures analyzed thus far, making it an ideal pseudo-drug training aid for multiple drugs. Like P2P, benzaldehyde is present as either a residual precursor or as a byproduct of MA synthesis; it could also have come from the oxidation of trace amounts of toluene in any of the solvents used. Preliminary evaluations using a canine that had not been exposed to any cocaine, heroin, or methamphetamine odors indicated that it can find both seizure MA and Arenol MA once it has been trained on benzaldehyde. A more extensive test using three uninitiated canines over a period of two weeks supported the initial findings: BZA-trained canines were able to find concealed MA in 20 out of 22 exercises (excluding the performance of one canine which often failed only because it had no search intent). In addition, all four canines (from both evaluations) alerted to a cocaine hydrochloride sample even though none had been trained on PC.

There are no plans to replace methyl benzoate and acetic acid as the respective odorants in PC and PH, however, since these compounds are the breakdown products of cocaine and heroin and will therefore always be present in the corresponding drug regardless of purity and processing methods. One drawback of using benzaldehyde in PM is the possibility of alerts to things other than controlled substances, since this compound is a common flavoring ingredient, with a strong cherry-almond or bitter almond odor. This possibility is slim, however, since acetic acid is perhaps even more frequently used in foods and there have been no reports of canine alerts to pickle jars, for example. The effectiveness of benzaldehyde as a pseudomethamphetamine training odor will have to be assessed once the material has been deployed and data are collected on the rate of alerts to drugs versus nondrugs. Finally, it must be emphasized that the Customs drug detecting canines have always been and will always be certified on actual drugs and that pseudo narcotic materials are used for initial scent association training and proficiency or maintenance training.

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Additional information and reprint requests:
Doan-Trang T. Vu
U.S. Customs Services Research Laboratory
7501 Boston Blvd., Suite 113
Springfield, VA 22135