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The Identification of Impurities in Illicit Methamphetamine Exhibits by Gas Chromatography/Mass Spectrometry and Nuclear Magnetic Resonance Spectroscopy

Methamphetamine, a drug frequently abused in the United States, is often manufactured illicitly. One method commonly employed for this purpose is the Leuckart reaction, which is initiated with methyl benzyl ketone (IV) and either methylamine (I) and formic acid (II) or N-methylformamide (III), producing N-formylmethamphetamine (IX) as an intermediate [*1*]. Hydrolysis of IX with a strong acid such as hydrochloric acid produces methamphetamine (VI). (See Table 1 for a list of abbreviations and Fig. 1 for corresponding

TABLE 1—*Nomenclature used throughout text.*

I	Methylamine
II	Formic acid
III	N-methylformamide
IV	Methyl benzyl ketone
V	Amphetamine
VI	Methamphetamine
VII	N,N-dimethylamphetamine
VIII	N-formylamphetamine
IX	N-formylmethamphetamine
X	Dibenzylketone
XI	α-benzyl-N-methylphenethylamine
XII	N-methyldiphenethylamine
XIII	α,α'-dimethyldiphenethylamine
XIV	N,α,α'-trimethyldiphenethylamine

structures.) As the synthesis proceeds, various impurities are accumulated: reactants, by-products, and intermediates, as well as contaminants arising from within the reagents themselves. The identification of such impurities thus far encountered in this laboratory by gas chromatography/mass spectrometry (GC/MS) and nuclear magnetic resonance (NMR) spectroscopy will be the subject of this discussion.

Some of these compounds were found in clandestine laboratory exhibits that represented various intermediate stages of the Leuckart reaction to produce methamphetamine. Others were found in exhibits containing the finished product, methamphetamine hydrochloride.

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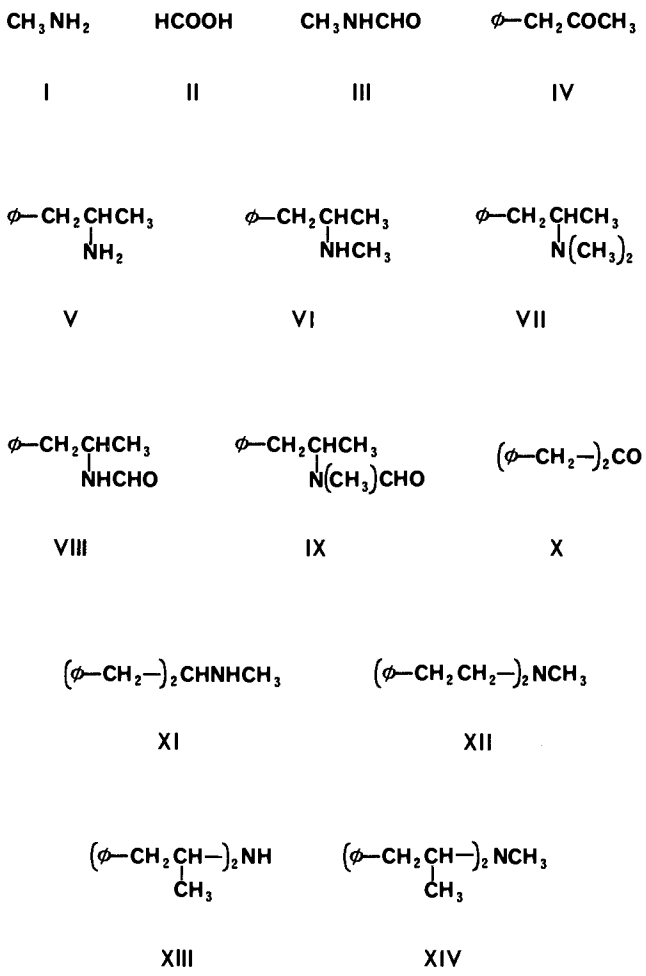

FIG. 1—*Structures of compounds found in methamphetamine samples; Roman numerals correspond to the listing in Table 1.*

The importance of identifying impurities in the former type exhibits cannot be overestimated since their eventual recognition in finished products is thereby facilitated. In addition, they may provide significant clues towards characterization of the manufacturing process in the absence of a finished product.

Beckett et al [*2*] have demonstrated the usefulness of an alkaline Apiezon® column for the separation of amphetamine (V), methamphetamine (VI), and N,N-dimethylamphetamine (VII). It was thought, therefore, that it might provide good separation of amine impurities frequently found in methamphetamine. As it developed, we also obtained separation with eventual identification of impurities not previously observed, including some that were not amines.

The use of NMR spectroscopy has been quite successful for screening mixtures not amenable to GC/MS examination or for providing supplementary information.

Two exhibits containing, between them, nearly all the compounds to be discussed were analyzed in this laboratory and exemplified the applicability of the chosen GC column. The first, received from a clandestine laboratory, consisted of a flask of brown oil. The liquid was found by NMR to consist primarily of IX; GC/MS confirmed this

and also indicated the presence of III, IV, VI, VII, N-formylamphetamine (VIII), α,α'-dimethyldiphenethylamine (XIII), and N,α,α'-trimethyldiphenethylamine (XIV) (Fig. 2).

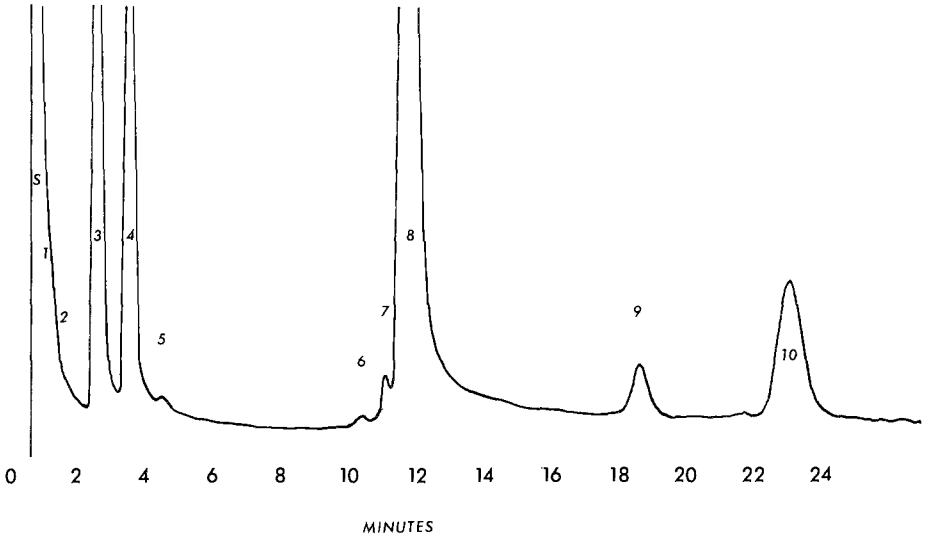

FIG. 2—*Chromatogram of laboratory exhibit as obtained in GC/MS analysis. Column temperature, 140°C; 6 min hold; raised 15°C/min to 230°C.* S = *solvent front (methanol)*; 1 = *chloroform*; 2 = *N-methylformamide (III)*; 3 = *methyl benzyl ketone (IV)*; 4 = *methamphetamine (VI)*; 5 = *N,N-dimethylamphetamine (VII)*; 6 = *unknown*; 7 = *N-formylamphetamine (VIII)*; 8 = *N-formylmethamphetamine (IX)*; 9 = *α,α'-dimethyldiphenethylamine (XIII)*; 10 = *N,α,α'-trimethyldiphenethylamine (XIV)*.

The second, a "finished" product, was extracted with chloroform from acid (HCl) solution. It was found to contain, in addition to methamphetamine, dibenzylketone (X), α-benzyl-N-methylphenethylamine (XI), XIII, and XIV (Fig. 3). The similarity of pattern and ingredient identity served as a basis for comparison with several other exhibits in a recent case.

The presence of all but two of those compounds, VIII and XIII, could be confirmed by comparison with standard materials or with data obtained previously [*3–6*]. Strong support for structure XIII was obtained by consideration of the processes that produce the four most intense peaks for the other, known, diphenylalkylamines. Tentative identification for VIII was based on its mass fragmentation and GC retention relative to IX. Evidence leading to the identification of these and other compounds is discussed in the paper.

Experimental Procedures

Apparatus

The GC/MS System—A Finnigan Model 3000 quadrupole EI-MS interfaced via glass tubing/jet separator to a Finnigan Model 9500 gas chromatograph was used. The electron energy was 70 eV, the ion source pressure was approximately 7×10^{-6} torr (9×10^{-4} Pa), and the carrier gas was helium.

The GLC Column—A 5-ft (1.5-m) by $^3/_{32}$-in. (2-mm) inside diameter glass column packed with 10% Apiezon-L, 2% potassium hydroxide, and Supelcon WAW (80/100)[2] was used.

[2] Supelco, Inc., Supelco Park, Belleponte, Pa. 16823.

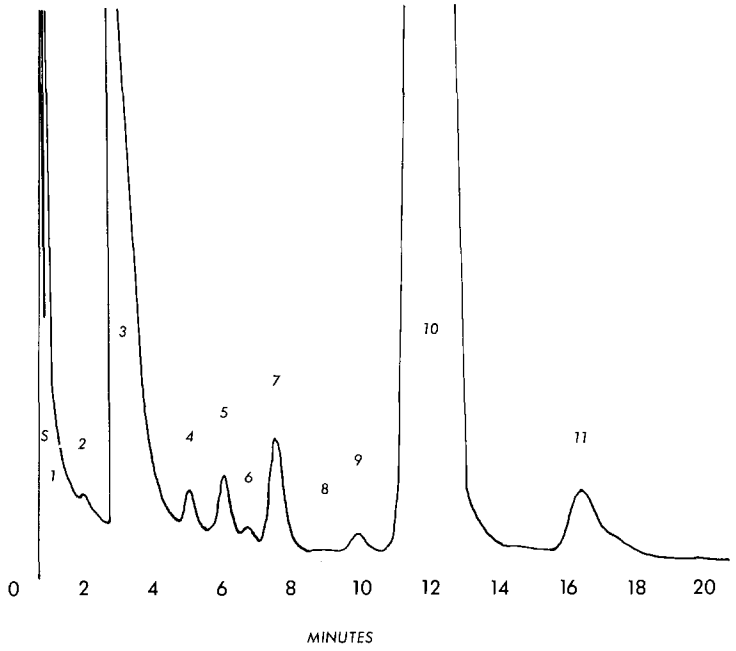

FIG. 3—*Chromatogram of extracted laboratory exhibit as obtained in GC/MS analysis. Column temperature, 230°C.* S = *solvent front (methanol)*; 1 = *methamphetamine (VI)*; 3 = *N-formylmethamphetamine (IX)*; 4 = *dibenzylketone (X)*; 5 = *α-benzyl-N-methylphenethylamine (XI)*; 7 = *α,α'-dimethyldiphenethylamine (XIII)*; 10 = *N,α,α'-trimethyldiphenethylamine (XIV)*; 2, 6, 8, 9, 11 = unknown.

The NMR Spectrometer—A Japan Electron Optics Laboratory C-60HL, 60-MHz unit was used. The probe temperature was 25°C (77°F). Chemical shifts are reported in units of ppm δ.

Screening by GC/MS Spectroscopy

For routine sample screening by GC/MS, 2 to 3 μl of a methanolic extract (approximately 2 mg/ml) are injected with the column temperature set at 135 to 140°C. After elution of the methamphetamine peak, the temperature is programmed at a rate of 8 to 12°C/min to a maximum of 230°C. Insoluble residues are reserved for examination by infrared or microscopic techniques.

For the initial examination of liquid exhibits, NMR spectroscopy is used. Such samples are examined neat, then, if necessary, partitioned between aqueous (D_2O) and organic (CCl_4 or $CDCl_3$) phases or subjected to pH modification, then re-examined.

If, in the course of GC/MS analysis, little or no response is observed for compounds other than methamphetamine, an aqueous (5%/D_2O) solution is then prepared for examination by NMR. The presence of methamphetamine may be confirmed. Also, contaminants such as methylamine (I) may be observed.

Subsequent to this examination, the aqueous solution is acidified with HCl, then extracted with $\frac{1}{10}$ volume carbon tetrachloride. This will isolate and concentrate IV, VII, IX, and X. These will be detectable by NMR if present in the exhibit in concentrations of at least 0.1%. Similar extraction with deuterochloroform will also remove XI, N-methyldiphenethylamine (XII), XIII, XIV, and, in part, III and VII. The NMR detectability will be the same, but there may be some interference from methamphetamine which will be extracted to the extent of 1 to 2%. The organic extracts may then be

evaporated gently to dryness and the residues dissolved in methanol and examined by GC/MS.

Discussion

Table 2 depicts the order of elution, with accompanying mass spectral data, for a number of compounds detected in this laboratory in Leuckart synthesis methamphetamine

TABLE 2—*Elution order of methamphetamine impurities and quadrupole mass fragmentation* (m/e *of most intense fragments in decreasing order of intensity*).

Molecular Weight	Compound	Fragments
59	III	B59-58-60-28-41-42
134	IV	B91-134-92-43-65-77-89-51-63-105
135	V	B44-91-65-51-63-77
149	VI	B58-91-56-65-51-77-134
163	VII	B72-44-42-91-56-65-58-...-162
163	VIII	B72-44-118-91-65
177	IX	B86-58-91-56-65-42-39-118-117-51-115-...-177
210	X	B91-65-39-119-92-63-89-51-...-210
225	XI	B134-91-42-119-65-135-58-86-77-105
239	XII	B148-105-91-44-77-79-65-56-119
253	XIII	B91-44-162-119-65-70
267	XIV	B91-58-176-119-42-41-56-65-39-92-134

exhibits. N-methyldiphenethylamine (XII), recently identified as an impurity of less than 1 ppm concentration in a non-Leuckart methamphetamine exhibit and discussed by Weibel and Hesse [*3*], has been included for comparison purposes. The elution is in approximate order of molecular size. Mass spectral data are presented for the most intense peaks in decreasing order of peak intensity. The *m/e* values that are preceded by dotted lines are of a lower level of intensity but have a significant bearing on the identification process. For example, X produces a spectrum with a base peak at *m/e* 91 and fragmentation characteristic of a benzyl ion [*7*] (intense peaks, in addition to *m/e* 91, at 39, 51, and 65) with little else to distinguish it except a small yet significant peak at *m/e* 210, corresponding to the molecular ion. The *m/e* 119 peak may then be attributed to loss of benzyl from the parent ion.

The NMR chemical shift assignments obtained in this laboratory are shown in Table 3. This table also refers the reader to the literature where spectra obtained under similar conditions have already been presented. Phentermine and mephentermine have been included for comparison with VI and VII, respectively, since the corresponding mass spectra are quite similar.

Identification of Compounds

Methylamine, Formic Acid, N-Methylformamide

Compounds I, II, and III, reactants in the Leuckart synthesis, have appeared in exhibits representing early stages of the process. Only I has thus far been encountered in finished products; however, in these instances, the exhibits were not believed to have been synthesized by the Leuckart procedure.

Detection of III by GC/MS is rendered difficult by its tendency to elute almost with the solvent, even at low temperature. Once detected, however, it will produce a characteristic spectrum. Typical of low molecular weight amides, the parent ion produces the

TABLE 3—*Nuclear magnetic resonance spectroscopic data.*

Compound	Solvent	Chemical Shift (ppm δ)[a]	References[b]
I·HCl	0.1*N* HCl/H_2O	CH_3(q):2.60 NH_2(m):7.35	12, p. 55
I·HCl	D_2O	CH_3(s):2.60	23, #6841
II	D_2O	CH(s):8.22	23, #6653
III	H_2O	*trans*[c]-conformer-CH_3(m):2.73 CH:8.02 *cis*[c]-CH_3(m):2.87 CH:7.84	
III	$CDCl_3$	*trans*-conformer-CH_3(m):2.76 CH:8.25 *cis*-CH_3(m):2.95 CH:7.94	23, #9350
N,N-dimethylformamide	H_2O	*trans*[c]-CH_3(s):2.82 *cis*[c]-CH_3(s):2.98 CH:7.93	
N,N-dimethylformamide	$CDCl_3$	*trans*-CH_3(s):2.82 *cis*-CH_3(s):2.94 CH:7.98	24, #39
IV	CCl_4	CH_3(s):2.00 CH_2(s):3.56 ArH:∼7.2	23, #1855
V·HCl	D_2O	αCH_3(d):1.29 CH_2:∼2.9 CH(m):3.64 ArH:∼7.37	23, #3984 (sulfate)
V·FB[d]	CCl_4	αCH_3(d):1.06 CH_2:∼2.5 CH(m):3.06 ArH:∼7.2	25, #R19M
VI·HCl	D_2O	αCH_3(d):1.26 NCH_3(s):2.69 CH_2:∼3.0 CH(m):3.52 ArH:∼7.35	4, Fig. 2
VI·FB	CCl_4	αCH_3(d):0.95 NCH_3(s): 2.31 CH_2:∼2.7 CH(m):∼3.8 ArH:∼7.2	23, #1876
Phentermine·HCl	D_2O	2×αCH_3(s):1.36 CH_2(s):2.95 ArH:∼7.39	
Phentermine·FB	CCl_4	2×αCH_3(s):1.06 CH_2(s):2.56 ArH:∼7.12	23, #18853
VII·HCl	D_2O	αCH_3(d):1.22 2×NCH_3(s):2.84 CH_2:∼3.0 CH(m):3.53 ArH:∼7.35	
VII·HCl	$CDCl_3$	αCH_3(d):1.28 2×NCH_3(s):2.89 CH_2:3.1–3.7 CH(m):2.7–3.1 ArH:∼7.3	...
Mephentermine·½H_2SO_4	D_2O	2×αCH_3(s):1.30 NCH_3(s):2.67 CH_2(s):2.97 ArH:∼7.4	
Mephentermine·FB	$CDCl_3$	2×αCH_3(s):1.07 NCH_3(s):2.40 CH_2(s):2.70 ArH:∼7.27	25, #R166M
IX	CCl_4	rotamer 1-αCH_3(d):1.28 NCH_3(s):2.70 CH_2:∼2.7 NCH(m):3.71 ArH:∼7.2 OCH(s):7.65	4, Fig. 7
IX	CCl_4	rotamer 2-αCH_3(d):1.15 NCH_3(s):2.70 CH_2:∼2.7 NCH(m):4.61 ArH:∼7.2 OCH(s):7.82	
X	CCl_4	CH_2(s):3.53 ArH:7.0–7.5	24, #638
XI·HCl	D_2O	CH_3(s):2.65 CH_2(d):3.01 CH(m):3.81 ArH:∼7.4	4, Fig. 15
XIV·HCl	D_2O	αCH_3(d):1.27 NCH_3(s):2.87 CH_2:∼3.2 CH:3.90 ArH:∼7.33	4, Fig. 11
XIV·FB	$CDCl_3$	αCH_3(d):0.96 NCH_3(s):2.87 CH_2,CH:2.3–3.3 ArH:∼7.2	6, Fig. 3

[a] s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet (other); only those patterns that are clearly definable have been so designated.

[b] Spectra obtained under similar conditions.

[c] With respect to the formyl hydrogen.

[d] FB = free base.

base peak. The *m/e* 28 ion is attributed to CO^+. Lack of an intense *m/e* 44 fragment ($CONH_2^+$) [*8*] readily distinguishes III from acetamide.

In the NMR spectrum of III, the formyl proton produces a broad absorption band at 8.02 ppm and another of lower intensity at 7.84 ppm (H_2O). These have been attributed, respectively, to the *trans*- and *cis*-conformers (formyl-H to CH_3) [*9*]. Long-range coupling with the methyl and amido protons produces broad peaks because of poorly resolved splitting. The methyl protons of the *trans*-conformer are split into a pair of doublets by coupling with both formyl and amido protons (δ = 2.73 ppm, H_2O). For the *cis*-methyl protons only the splitting because of NH coupling is evident, as splitting from formyl proton coupling remains unresolved (δ = 2.87 ppm).

The method of choice for detection of I and II is NMR spectrometry. Factors such as low molecular weight, high volatility, and poor chromatographic characteristics render these compounds unsuited to GC/MS analysis.

In the NMR spectrum of II (H_2O) a singlet is observed for the formyl proton at 8.22 ppm. The peak is shifted upfield upon acidification and downfield when the solution is made alkaline. The dependence of chemical shift on pH serves as an aid to the identification of II, particularly when considered in conjunction with standard addition techniques.

Effects of pH modification on the spectrum of I are even more pronounced. Although discussed previously [*10*], these effects are perhaps best illustrated within the context of an example such as the following.

An alkaline aqueous exhibit retrieved from an illicit laboratory was examined by NMR and was found, with the aid of standard addition, to consist primarily of III and I in addition to small amounts of II and DMF (N,N-dimethylformamide) (Fig. 4 *top*). The presence of DMF could not be explained, particularly as it had not been observed in related exhibits from that laboratory.[3] Acidification of this solution produced the expected changes in absorption patterns or chemical shifts of the suspected ingredients (Fig. 4 *bottom*). Substance I undergoes the most prominent change as both intermolecular and intramolecular exchange of the amino hydrogens are slowed considerably [*10,12*]. The CH_3 signal, shifted downfield, is split into a quartet by coupling with the NH_3^+ protons. The amino proton signal is split by nitrogen into a triplet (J_{NH} = 55 Hz), centering at 7.35 ppm. Further splitting of the triplet, from coupling with the methyl protons, is obscured somewhat by broadening from electrical quadrupole effects of the nitrogen nucleus [*13*]. The other N-methyl signals, also shifted downfield, are otherwise unaffected. The formyl proton of II is shifted upfield.

Methyl Benzyl Ketone and Dibenzyl Ketone

Methyl benzyl ketone (IV) is a starting material for methamphetamine synthesis not only for the Leuckart reaction but for other methods as well [*14,15*]. Although it is commercially available, it has often been synthesized by clandestine laboratory operators engaged in methamphetamine manufacture. One such synthesis begins with phenylacetic acid and produces dibenzyl ketone (X) as a by-product [*4,14,16*]. If IV is used without purification for methamphetamine synthesis, X may appear in the finished product of methamphetamine hydrochloride.

Although X was not reported in methamphetamine exhibits previously, its presence had been manifested by the frequent appearance of XI in the finished product [*4*]. Lately, small amounts of X have been identified in the finished product as well. Although both IV and X have been found in methamphetamine known to have been made by the Leuckart synthesis, their presence is not precluded in products made by other procedures. Substance

[3]DMF produces singlets for CH_3 *trans* and *cis* to the formyl hydrogen at 2.82 and 2.98 ppm, respectively [*11*], and a broad CH peak at 7.93 ppm. The formyl signal for DMF is superimposed on that of the *cis*-conformer of III.

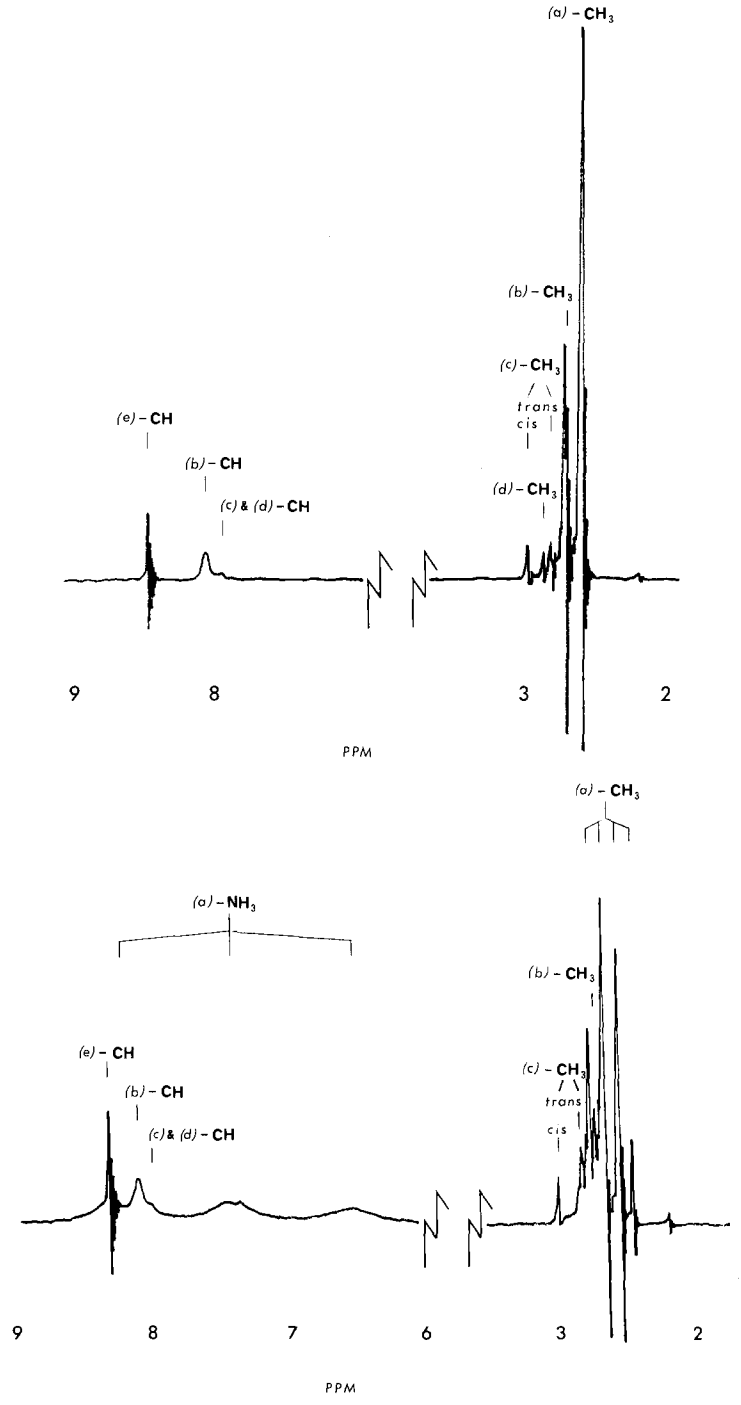

FIG. 4—*Sixty megahertz spectrum of aqueous exhibit from clandestine laboratory*; (a) = *methylamine* (*I*); (b) = *N-methylformamide* (*III*); trans-(*CH*$_3$/*CH*)-*conformer*; (c) = *N,N-dimethylformamide*; (d) = *N-methylformamide* (*III*), cis-*conformer*; *and* (e) = *formic acid* (*II*).

IV has been found in a "street" sample of "liquid" methamphetamine containing, in addition, I, V, VII, and phenyl-2-propanol. It has been also found in seized laboratory exhibits accompanied by acetic anhydride and phenylacetic acid.

In the mass spectroscopy of IV, two of the most intense fragments are produced by competing processes: cleavage β to the phenyl ring with formation of the charge-stabilized tropylium ion, *m/e* 91 [*17*], and α to C=O, where loss of the heavier attachment is favored, to produce $CH_3C \equiv O^+$, *m/e* 43 [*18*].

Other significant peaks in the spectrum of IV are produced by the parent ion, *m/e* 134, and by fragmentation of the benzyl ion. The mass fragmentation of X has been described in the discussion of Table 2.

The NMR spectra of IV and X are supportive of $C_6H_5CH_2C=O$ compounds, five-hydrogen phenyl absorption occurring at 7.0 to 7.5 ppm and, for a slightly broadened singlet representing two hydrogen atoms, at about 3.5 ppm. In addition, IV produces uncoupled methyl absorption at 2.0 ppm, predictable for $CH_3C=O$.

N-Formylmethamphetamine and N-Formylamphetamine

The production of IX as an intermediate in the Leuckart synthesis and its presence as an impurity in methamphetamine exhibits have been discussed [*4,5*]. The compound of proposed structure VIII has been found in a seized laboratory exhibit of which IX was the major component. Tentative identification of VIII was accomplished by a study of its mass spectral fragmentation relative to IX. One possible explanation of its presence is contamination of the methylamine starting material with ammonia.[4]

In accordance with the findings of Gilpin [*8*], IX is believed to produce its base peak *m/e* 86 by a β-cleavage mechanism (Fig. 5). The *m/e* 58 fragment is believed to arise

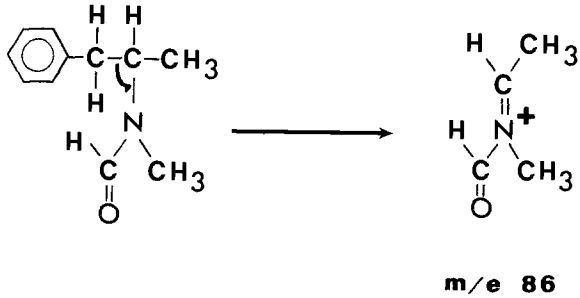

FIG. 5—*Proposed mechanism for formation of* m/e *86 ion from N-formylmethamphetamine* (*IX*).

from simultaneous β-cleavage and loss of CO with transfer of the formyl hydrogen to the nitrogen (Fig. 6). Intense *m/e* 91 (tropylium) and *m/e* 118 (phenylpropyl minus 1 H) fragments are also observed. The *m/e* 72, 44, 91, and 118 fragments produced by the proposed VIII are believed to be formed similarly. This structure proposal is also supported by its GC retention relative to IX.

Diphenylalkylamines

Three diphenylalkylamines have been encountered as impurities in methamphetamine exhibits. Two of these, XI and XIV, have been previously reported [*4,6*].

[4] N-Formylamphetamine is an intermediate in the Leuckart synthesis of amphetamine and could be present as an impurity in amphetamine samples produced by this method.

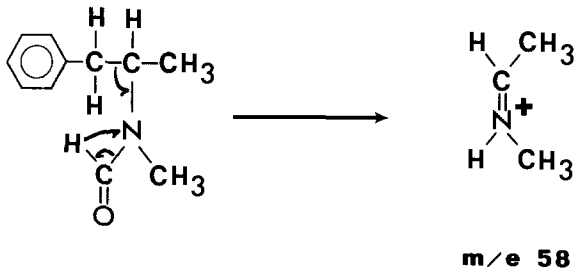

FIG. 6—*Proposed mechanism for formation of* m/e *58 ion from N-formylmethamphetamine (IX).*

As explained elsewhere [*4*], XI can occur as a by-product of methamphetamine synthesis if X is present as a contaminant of IV used as starting material. Substance XIV can be obtained as a by-product of the Leuckart synthesis of methamphetamine as well as from reductive alkylation of I with IV.

The third diphenylalkylamine found as an impurity in methamphetamine exhibits is XIII. This compound may be formed as a by-product of amphetamine synthesis in a manner analogous to the formation of XIV as a by-product in methamphetamine synthesis. Substance XIV has frequently been accompanied by XIII in exhibits representing both intermediate and finished product. The structure proposed for XIII has been deduced from a comparative study of its mass spectral data with those of XI, XIV, and XII. Although XII has not been implicated in the Leuckart synthesis of methamphetamine, the relationship between its structure and mass fragmentation is significant to this study. Mass spectral fragmentation processes for these compounds are as follows.

1. The fragmentation pattern characteristic of benzyl ions is observed [*7*].
2. The β fission process for alkylamines has been postulated by Gohlke and McLafferty [*19*] and later applied to the interpretation of phenylalkylamines [*2,20*] (Fig. 7). Where

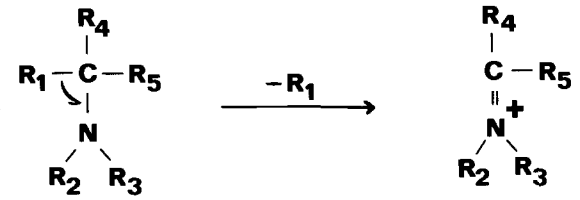

FIG. 7—*Beta-fission of alkylamines.*

two of the nitrogen substituents are sufficiently small (V, VI, VII, for example), this process will produce the most intense peak in the spectrum. However, this may not be the case for large fragments, particularly when obtained with a quadrupole spectrometer, which, in comparison with magnetic instruments, discriminates against fragments of higher *m/e* value. For example, in spectra of XIV obtained magnetically [*4,6*] the *m/e* 176 fragment produced the base peak, whereas on a quadrupole instrument (Table 2) it has been overshadowed by the *m/e* 91 and 58 fragments. For XI, the base peak has been observed at *m/e* 134 for both instruments.

3. Production of an intense *m/e* 119 fragment for XIII and XIV and at *m/e* 105 for XII is unlikely to result from simple C-N cleavage of the parent ion [*19*]. It is rather probable that such ions are produced by C-N cleavage of the intense ion emanating from the β-fission process. This hypothesis is supported by Weibel and Hesse [*3*], who have

reported a metastable ion confirming the transition $148^+ \rightarrow 105^+$ in the magnetically scanned mass spectrum of XII. Similarly, a metastable ion at *m/e* 87.6 has confirmed the transition $162^+ \rightarrow 119^+$ for XIII. It may be further noted from inspection of Table 2 that no *m/e* 119 fragment is evident among the most intense peaks for the monophenylisopropylamines.

In compound XI, however, the *m/e* 119 ion probably results from loss of the methyl group from the *m/e* 134 fragment. As may be seen in Fig. 8, cleavage between nitrogen

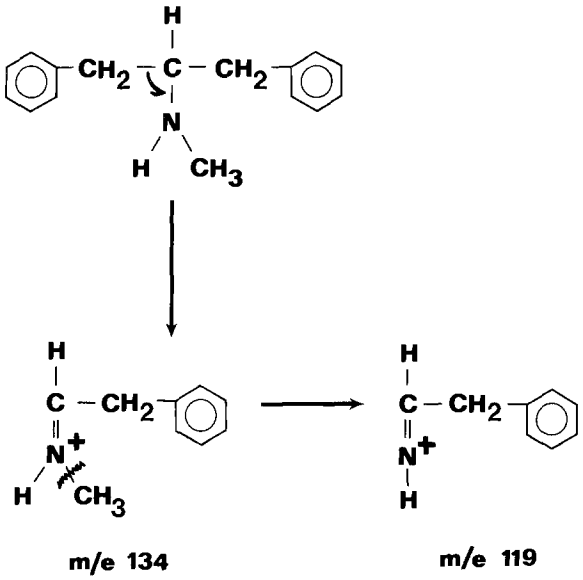

FIG. 8—*Postulated mechanism for formation of* m/e *119 ion from α-benzyl-N-methylphenethylamine (XI).*

and its larger substituent is of minimal significance since, as a result of β-fission, they are doubly bonded. Such is not the case for the other diphenylalkylamines.

4. Another ion of great intensity results from an α,β-cleavage with hydrogen rearrangement (Fig. 9) [*19*]. In the case of XIV, for example, where $R_3 = R_4 = CH_3$, this process

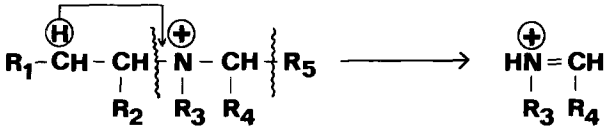

FIG. 9—*Alpha, beta-cleavage with hydrogen rearrangement (after Gohlke and McLafferty* [19]).

produces an intense *m/e* 58 fragment; for XII ($R_3 = CH_3$, $R_4 = H$) and for XIII ($R_3 = H$, $R_4 = CH_3$), an intense *m/e* 44 peak is observed.

Confirmation of structure XIII has been obtained recently with infrared and chemical ionization mass spectroscopy.

Amphetamine and N,N-Dimethylamphetamine

Both V and VII have been found in methamphetamine exhibits believed to be manufactured by the Leuckart reaction as well as by other methods.

Detection of V in methamphetamine samples represents a third example of an N-demethylated impurity. A possible explanation of the presence of such N-demethylated analogs of methamphetamine and its impurities has already been given in the discussion of VIII and XIII.

The occurrence of VII in methamphetamine may arise from contamination of the methylamine or N-methylformamide used for methamphetamine synthesis with DMF [*1*]. Identification of DMF in an exhibit seized in a clandestine methamphetamine laboratory has already been mentioned.

The mass spectroscopy of V and VI has been treated extensively [*2,20*]. Mass spectroscopic data for VII have been reported by Finkle [*21,22*]. As expected, β-fission produces the most intense fragment for these compounds. Formation of tropylium and its fragmentation are also observed.

The common elements in the alkyl region of their NMR spectra are evident in Table 3. The distinctive pattern of chemical shifts and splitting produced by the isopropyl hydrogen atoms readily distinguishes these compounds from positional isomers which may produce similar mass spectra. The mass spectra of phentermine and mephentermine, for example, are similar to those of VI and VII,[5] respectively, but their NMR alkyl absorption, characterized by the exclusive appearance of singlets, indicates the absence of hydrogen spin-spin coupling.

Conclusions

Detection and identification of impurities found in illicit methamphetamine exhibits has been accomplished through the use of GC/MS and NMR spectroscopy. Separation and characterization of most of these compounds has been facilitated, in the former technique, by application of an alkaline Apiezon column.

The usefulness of NMR as an identification tool has been enhanced by employment of in-situ techniques such as pH modification, solvent partitioning, and standard addition. When properly applied, these devices will frequently permit rapid and unequivocal assignments of structure.

Summary

A number of impurities arising from the Leuckart synthesis of methamphetamine have been identified by GC/MS and NMR spectroscopy. In addition to compounds discussed in an earlier paper, products were found to contain methyl benzyl ketone, amphetamine, N,N-dimethylamphetamine, dibenzylketone, and α,α'-dimethyldiphenethylamine. Seized laboratory exhibits were also found to contain, in addition to some of the preceding, N-methylformamide, formic acid, methylamine, and N-formylamphetamine.

The identification of the impurities described in this paper can provide numerous points on which to base comparative analyses of different exhibits. It also can assist in identifying the type of procedure used in the clandestine manufacture of methamphetamine, or, alternatively, show that a controlled substance was in the process of being made despite the absence of the finished product. Although all of these impurities have been found to be associated with the Leuckart synthesis, it must be recognized that other synthetic methods may produce these impurities to a greater or lesser degree. Only N-formylmethamphetamine can be associated specifically with the Leuckart synthesis of methamphetamine.

[5] An *m/e* 44 fragment, very intense in VII, is virtually lacking in the spectrum of mephentermine. However, since many amine impurities produce this ion in great abundance, conclusions based on its presence in exhibit analysis should be drawn with due caution.

References

[1] Novelli, A., *Anales de la Asociacion Quimica Argentina,* Vol. 27, 1939, pp. 169–171, abstracted in *Chemical Abstracts,* Vol. 34, No. 6, 1940, p. 1627.
[2] Beckett, A. H., Tucker, G. T., and Moffat, A. C., *Journal of Pharmacy and Pharmacology,* Vol. 19, 1967, pp. 273–294.
[3] Weibel, P. A. and Hesse, M., *Helvetica Chimica Acta,* Vol. 56, No. 7, 1973, pp. 2460–2479.
[4] Barron, R. P., Kruegel, A. V., Moore, J. M., and Kram, T. C., *Journal of the Association of Official Analytical Chemists,* Vol. 57, No. 5, 1974, pp. 1147–1158.
[5] LeBelle, M., Sileika, M., and Romach, M., *Journal of Pharmaceutical Sciences,* Vol. 62, No. 5, 1973, p. 862.
[6] Bailey, K., Boulanger, J. G., Legault, P., and Taillefer, S. L., *Journal of Pharmaceutical Sciences,* Vol. 63, No. 10, 1974, pp. 1575–1578.
[7] Grubb, H. M. and Meyerson, S., in *Mass Spectrometry of Organic Ions,* F. W. McLafferty, Ed., Academic Press, New York, 1963, p. 505.
[8] Gilpin, J. A., *Analytical Chemistry,* Vol. 31, No. 5, 1959, pp. 935–939.
[9] LaPlanche, L. A. and Rogers, M. T., *Journal of the American Chemical Society,* Vol. 86, No. 3, 1964, pp. 337–341.
[10] Roberts, J. D., *Journal of the American Chemical Society,* Vol. 78, No. 17, 1956, pp. 4495–4496.
[11] Anet, F. A. L. and Bourn, A. J. R., *Journal of the American Chemical Society,* Vol. 87, No. 22, 1965, pp. 5250–5251.
[12] Casy, A. F., *PMR Spectroscopy in Medicinal and Biological Chemistry,* Academic Press, New York, 1971, p. 55.
[13] Roberts, J. D., *Nuclear Magnetic Resonance. Applications to Organic Chemistry,* McGraw-Hill, New York, 1959.
[14] Aonuma, S., Hama, T., and Kametami, T., *Japanese Journal of Pharmacy and Chemistry,* Vol. 27, 1955, pp. 607–611; abstracted in *Chemical Abstracts,* Vol. 50, No. 18, 1956, p. 13292g.
[15] Ogata, A., *Journal of the Pharmaceutical Society of Japan,* Vol. 451, 1919, pp. 751–764; abstracted in *Chemical Abstracts,* Vol. 14, No. 6, 1920, p. 745.
[16] Herbst, R. M. and Manske, R. H., *Organic Syntheses, Collective Volume,* Vol. 2, 1943, pp. 389–391.
[17] Rylander, P. N., Meyerson, S., and Grubb, H. M., *Journal of the American Chemical Society,* Vol. 79, No. 4, 1957, pp. 842–846.
[18] Sharkey, A. G., Schultz, J. L., and Friedel, R. A., *Analytical Chemistry,* Vol. 28, No. 6, 1956, pp. 934–940.
[19] Gohlke, R. S. and McLafferty, F. W., *Analytical Chemistry,* Vol. 34, No. 10, 1962, pp. 1281–1287.
[20] Reisch, J., Pagnucco, R., Alfes, H., Jantos, N., and Mollman, H., *Journal of Pharmacy and Pharmacology,* Vol. 20, 1968, pp. 81–86.
[21] Finkle, B. S. and Taylor, D. M., *Journal of Chromatographic Science,* Vol. 10, No. 5, 1972, pp. 312–333.
[22] Finkle, B. S., Foltz, R. L., and Taylor, D. M., *Journal of Chromatographic Science,* Vol. 12, No. 5, 1974, pp. 304–328.
[23] *Sadtler Nuclear Magnetic Resonance Spectra,* Sadtler Research Laboratories, Philadelphia, 1966–1974.
[24] Bhacca, N. S., Hollis, D. P., Johnson, L. F., and Pier, E. A., *NMR Spectra Catalog,* Vol. 1, Varian Associates, Palo Alto, Calif., 1963.
[25] *Sadtler Nuclear Magnetic Resonance Pharmaceutical Spectra,* Sadtler Research Laboratories, Philadelphia, 1970.

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