Identification of Hallucinogens in Illicit Seizures I: 2,5-Dimethoxyamphetamine

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Abstract □ The identification of the hallucinogen, 2,5-dimethoxyamphetamine, in illicit seizures using spectroscopic techniques is described. The difficulties in the interpretation of the IR spectra as a result of positional isomers and also the anomalies found during GC analysis are covered. The NMR and mass spectroscopic data are explained.

Keyphrases □ 2,5-Dimethoxyamphetamine—identification in illicit drug seizures, NMR spectroscopy and mass spectroscopy □ Hallucinogens—identification by NMR spectroscopy and mass spectroscopy of 2,5-dimethoxyamphetamine in illicit drug seizures □ NMR spectroscopy—identification of 2,5-dimethoxyamphetamine □ Mass spectroscopy—identification of 2,5-dimethoxyamphetamine

Recent studies on the correlation of structure–function activities of drugs with specific biological effects have produced encouraging results concerning the ability to predict whether a certain compound in a series of congeners will elicit a specific biological response (1, 2). These studies have been extended to the hallucinogens and especially the amphetamines and phenylethylamines, thus making it possible to give an educated guess as to which compounds will produce hallucinogenic activity (3).

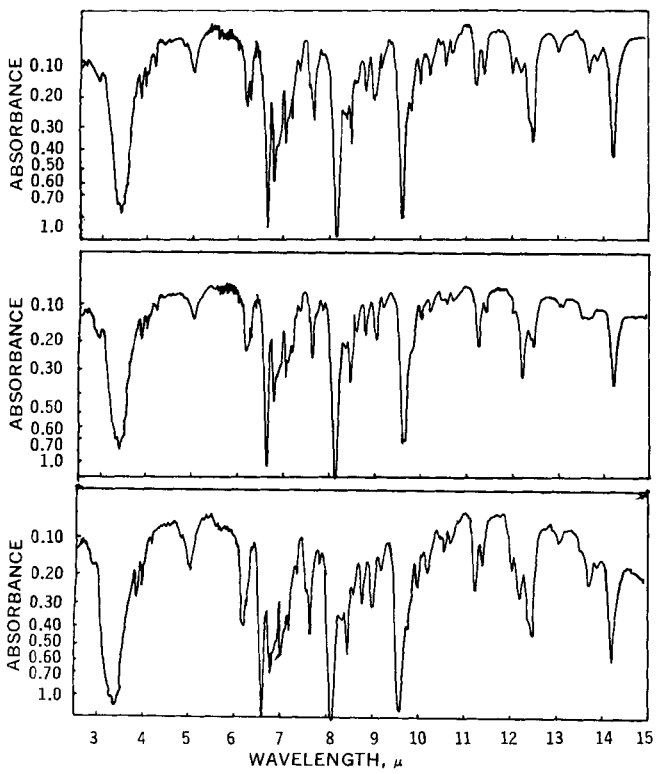


Figure 1—*IR spectrum of 2,5-dimethoxyamphetamine as received in the illicit sample.*

Since the current federal drug abuse laws regulating the sale and possession of drugs are not sufficiently broad to cover all possible derivatives of the amphetamines, it would be extremely profitable and legal to synthesize those derivatives that could be predicted to have hallucinogenic activity.

In recent months, this laboratory has received several seizures from law enforcement agencies containing suspect hallucinogens reportedly being sold as the potent psychomimetic agent mescaline (3,4,5-trimethoxyphenylethylamine). The compound in these seizures was identified as 2,5-dimethoxyamphetamine. This compound has no current medical use, but it is utilized by the photographic industry[1]. This report is concerned with the identification of this hallucinogenic compound in illicit seizures.

EXPERIMENTAL

Preparation of Material for Analysis—Purification of the material was accomplished by GC after extraction from pH 8.5 solution with chloroform. A gas chromatograph[2] equipped with a 3% OV-17, 0.63-cm. × 1.8-m. (0.25-in. × 6-ft.), stainless steel column

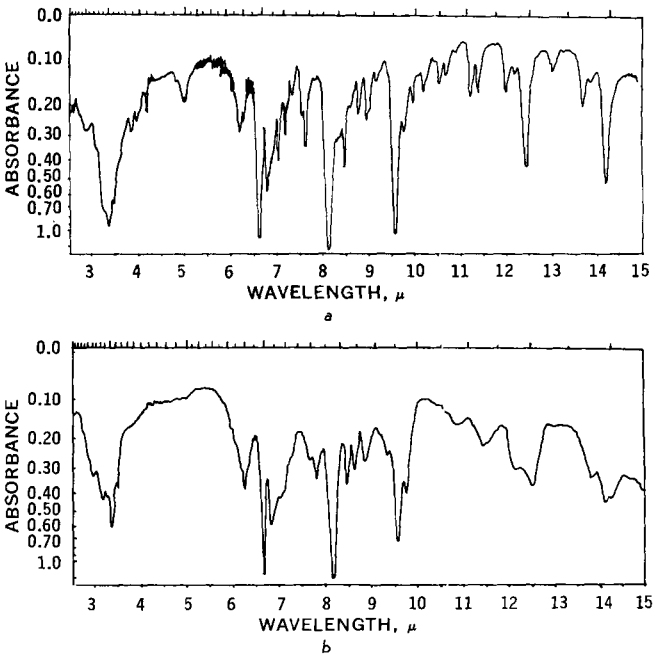
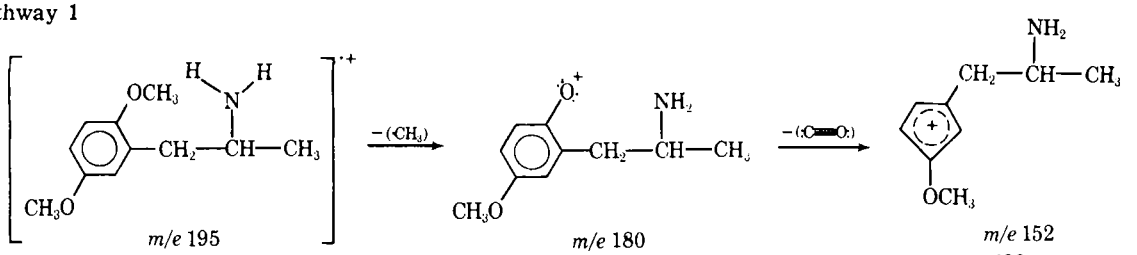


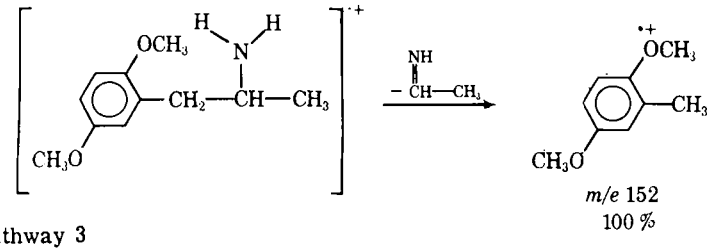
Figure 2—(a) *IR spectrum of 2,5-dimethoxyamphetamine hydrochloride. The hydrochloride salt was prepared from material purified by GC on a 3% OV-17 column maintained at 220°.* (b) *IR spectrum of 2,5-dimethoxyamphetamine base. The material, as received, was purified by GC using the same conditions as for Fig. 2a.*

[1] Personal communication with Upjohn.
[2] Barber-Coleman model 5320 or Varian series 1800.

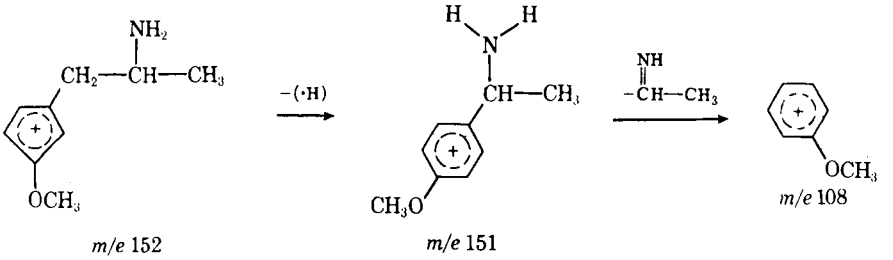
pathway 1



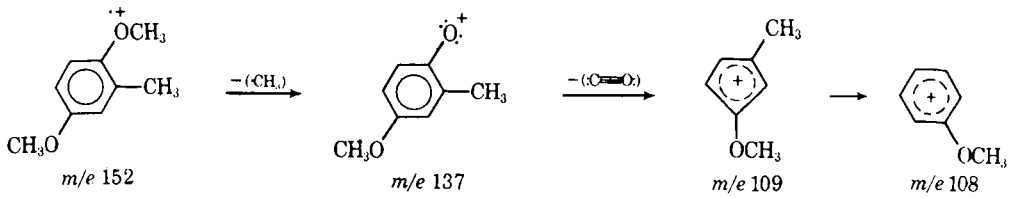
pathway 2



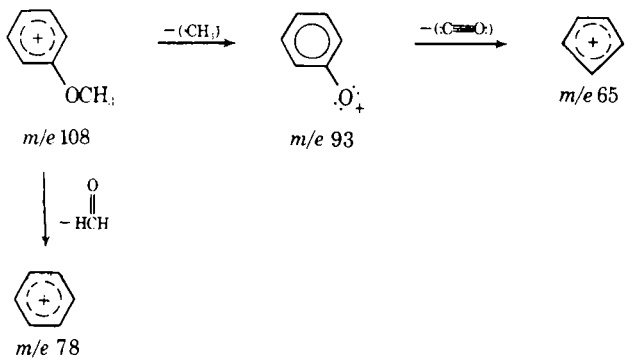
pathway 3



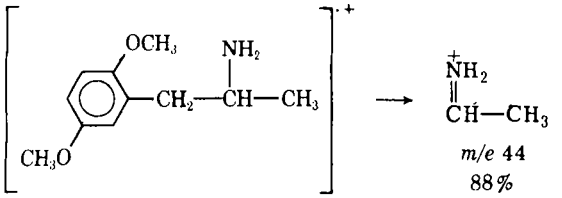
pathway 4



pathway 5



pathway 6



Scheme I

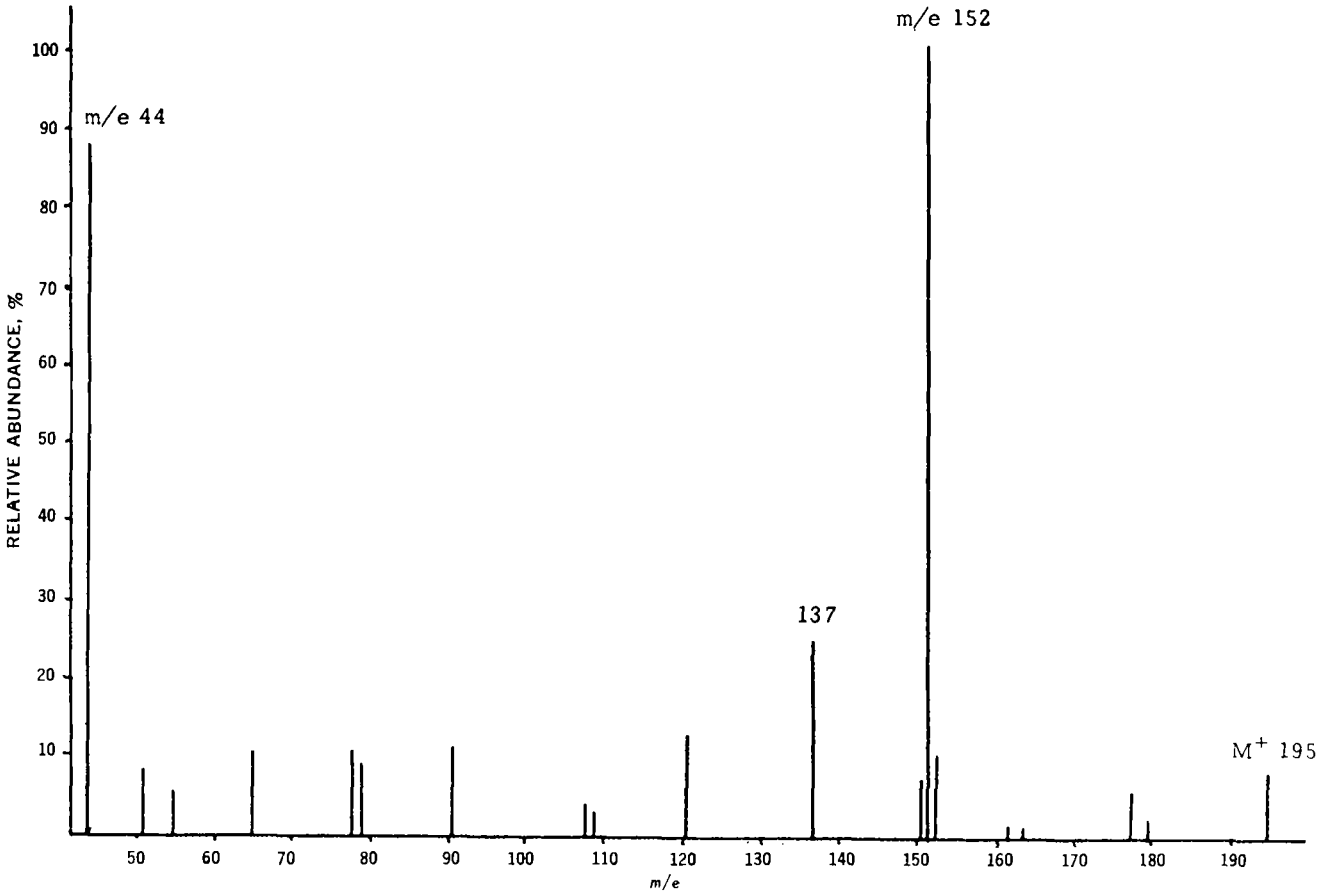


Figure 3—*Mass spectral fragmentation pattern of 2,5-dimethoxyamphetamine.*

was operated isothermally at 220° with injector and detector temperatures of 265 and 295°, respectively, and a flow rate of 44 ml./min. The fractions were collected manually and prepared for either IR or NMR spectroscopy.

IR Spectroscopy—IR analysis was performed on a sodium chloride spectrophotometer[3] using a 1.3-mm. KBr pellet. The material purified by GC was used to obtain IR spectra of the free base and of the hydrochloride.

IR analysis was also performed on the material as it was received in the laboratory.

NMR—NMR spectroscopy was done using an NMR spectrometer[4] on either the base as prepared by GC or the material as received in the laboratory. Tetramethylsilane was used as the internal standard.

Mass Spectroscopy—Mass spectroscopic analysis was performed using a combined gas chromatograph–mass spectrometer[5]. The gas chromatograph was equipped with a 3% OV-1 column and operated isothermally at 150°.

RESULTS

IR Analysis—The substance, as received, melted at 122–125°. Replicate samples showed IR spectra of three types, the most noticeable variations occurring between 835 and 800 cm.$^{-1}$, where absorption reflects out-of-plane deformation of aromatic hydrogens (Fig. 1) and also $-{}^{+}NH_3$ rocking frequency. Identical spectra and melting points were obtained with known 2,5-dimethoxyamphetamine hydrobromide.

The hydrochloride salt of the material (11 mg.), prepared from the gas chromatograph, melted at 115–116°. In this study, it gave IR patterns of the first two types, one of which is shown in Fig. 2*a*. The spectrum of 2,5-dimethoxyamphetamine base, purified by GC, is shown in Fig. 2*b*.

In all of these IR patterns, strong aromatic and aliphatic ether bands are present at 1225 and 1045 cm.$^{-1}$. A strong absorption due to the aromatic nucleus is seen at 1500 cm.$^{-1}$; and a broad weaker aromatic band, including the primary amine deformation frequency, is seen at 1600 cm.$^{-1}$.

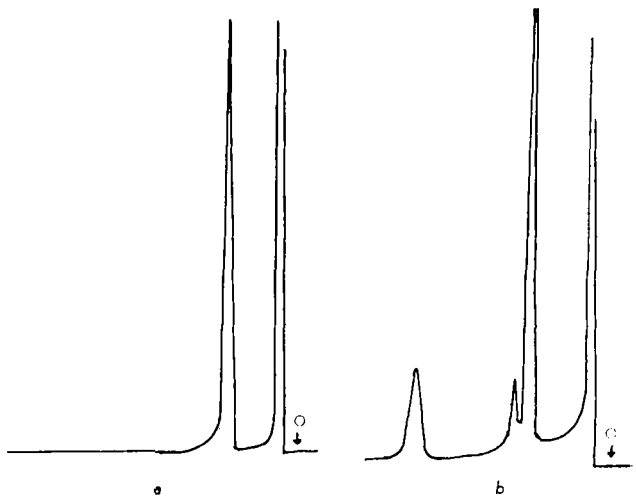


Figure 4—(a) *GC analysis of the material as received, The base was extracted from bicarbonate (pH 8.5) solution with chloroform. The GC conditions are described in the text.* (b) *GC analysis of the material as received. The base was extracted from ammonium hydroxide (pH > 10) solution. The GC conditions are described in the text.*

[3] Perkin-Elmer.
[4] Varian A-60.
[5] LKB model 9000.

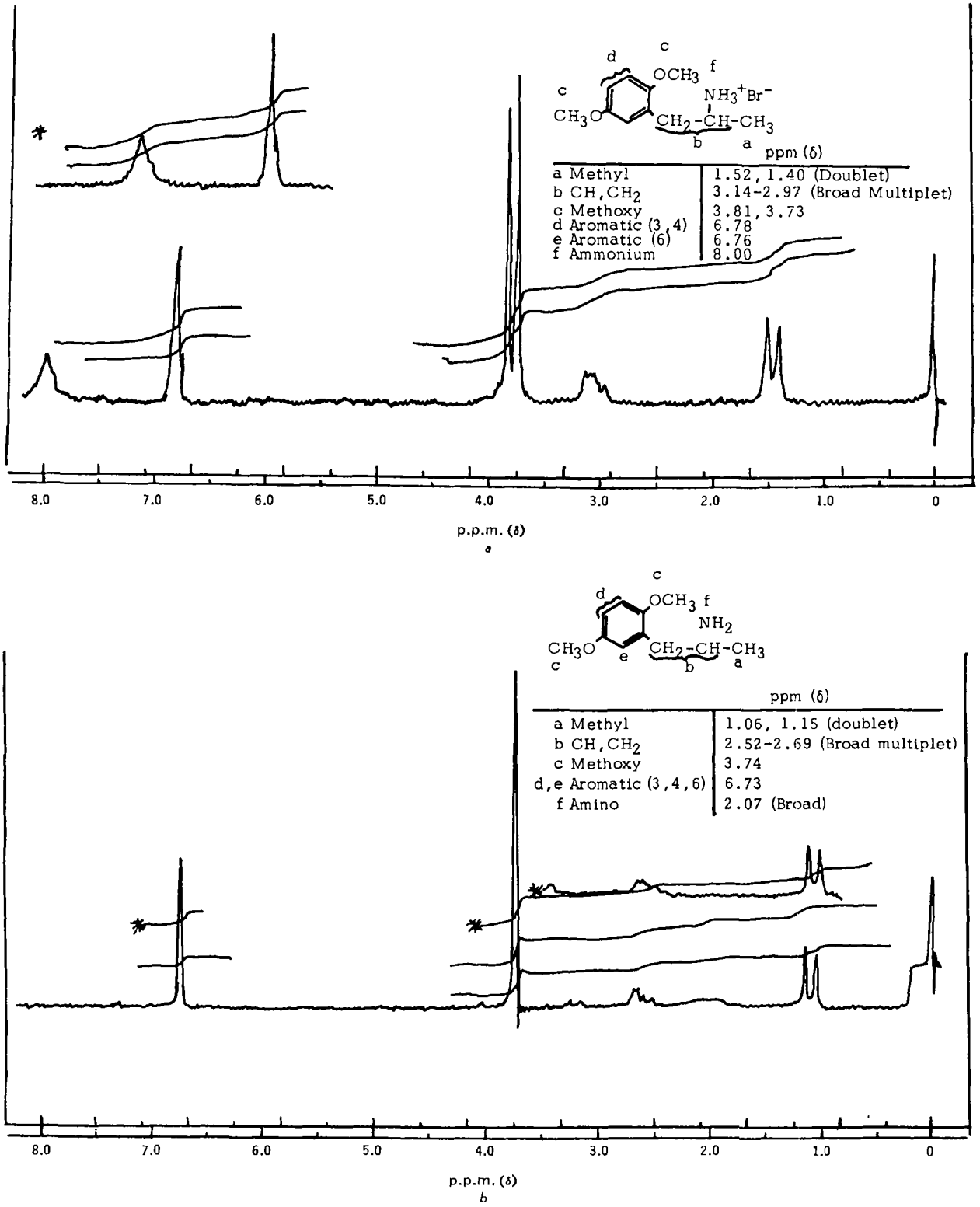


Figure 5—(a) *NMR spectrum of the salt as received. The spectrum was made in $CDCl_3$ with tetramethylsilane as the internal standard.* (b) *NMR spectrum of the base. The base was purified by GC using the same conditions as for Fig. 4b.*

In the base, a prominent absorption occurs at 800 $cm.^{-1}$. This can be assigned to the out-of-plane bending of the two adjacent hydrogen atoms on the benzene ring. The isolated aromatic hydrogen absorbs in a broad band of medium strength centered at 875 $cm.^{-1}$. This pattern of substitution is also reflected in the three aromatic hydrogen in-plane deformation modes at 1180, 1155, and 1125 $cm.^{-1}$.

Interactions at these frequencies by themselves do not permit a decision to be made regarding the three possible positional isomers of dimethoxyamphetamine; but methoxamine [β-hydroxy-β-(2,5-dimethoxyphenyl)isopropylamine], which differs from 2,5-dimethoxyamphetamine only by the existence of a hydroxyl substituent in the β-position, has the same aromatic hydrogen out-of-plane bending modes as 2,5-dimethoxyamphetamine plus an identical absorption at 710 $cm.^{-1}$. A single difference is seen in the pattern of the methoxamine in-plane deformations (none at 1125 $cm.^{-1}$), and another difference is found in the higher frequency aromatic ether band (1215 $cm.^{-1}$) when a comparison is made with the corresponding dimethoxy-

amphetamine absorptions. These discrepancies may be attributed to the occurrence of the hydroxyl group close to the aromatic nucleus and its ether substituent in the 2-position.

Other features of note are the presence in the hydrobromide and hydrochloride spectra of absorptions at 2950 and 1980 $cm.^{-1}$, indicating the presence of a primary amine group and the absence of the 1370-$cm.^{-1}$ band, which is due to C—CH_3 symmetrical bending and which is commonly used in differentiating amphetamines from phenethylamines (4–6).

Mass Spectral Analysis—The fragmentation of 2,5-dimethoxyamphetamine follows the pattern postulated for other methoxylated amphetamine derivatives: 3,4,5-trimethoxyphenylethylamine (mescaline) and 2,5-dimethoxy-4-methylamphetamine (7).

The parent peak, *m/e* 195 (Fig. 3), is readily identifiable but is only 8.5% of the base peak, *m/e* 152. A possible mechanism for the formation of the base peak is seen in pathway 1 (Scheme I). The molecular ion loses a methyl radical, forming the *m/e* 180 peak with a subsequent loss of carbon monoxide giving rise to the *m/e* 152 fragment. Fragmentation such as this is characteristic of methoxyphenyl compounds (8). The *m/e* 152 fragment could also arise by elimination of 43 mass units as the neutral fragment, NH=CH—CH_3, as postulated by Bellman (9) (pathway 2, Scheme I).

The formation of *m/e* 108, pathway 3, from *m/e* 152 in pathway 1 might arise by rearrangement with a loss of a hydrogen radical forming *m/e* 151, followed by a loss of 43 mass units as in pathway 2. The *m/e* 108 fragment could also arise from the *m/e* 152 fragment in pathway 2 by a loss of a methyl forming *m/e* 137 and a rearrangement with the loss of hydrogen.

The formation of *m/e* 78 and 65, pathway 4, occurs by accepted modes of fragmentation (8).

The formation of the *m/e* 44 peak follows a process that is characteristic of primary amines with elimination of the most stable radical (8), pathway 5.

GC—The 2,5-dimethoxyamphetamine free base was purified by GC and subsequently used for IR and NMR analyses. During these purification procedures, certain anomalies were found.

Figure 4*a* shows that extraction of the 2,5-dimethoxyamphetamine salt at pH 8.5 with bicarbonate gives a single peak from the gas chromatograph; analysis of this peak using combined GC–mass spectroscopy shows it to be pure 2,5-dimethoxyamphetamine. Other conditions change the GC patterns in unpredictable ways. Figure 4*b* illustrates this by showing the chromatographic pattern after extraction of the 2,5-dimethoxyamphetamine salt with ammonium hydroxide solution. Peak 1 was identified as 2,5-dimethoxyamphetamine, and preliminary mass spectroscopic analysis of peaks 2 and 3 showed that they probably have molecular weights of 235 and 329, respectively.

NMR Analysis—The NMR spectrum of the salt, as received, is shown in Fig. 5*a*. The extreme solubility of the salt in $CDCl_3$ makes it readily suitable for direct analysis.

The methyl group is seen as a doublet at δ 1.52 and 1.40, while the CH and CH_2 groups are indistinguishable as a broad multiplet between δ 3.14 and 2.97. The aromatic protons are easily distinguishable. One would expect two different types of protons. The 3 and 4 protons on the ring are seen as a singlet at δ 6.78, while the number 6 proton is seen at δ 6.76. The two methoxyl groups on the aromatic ring are seen as singlets at δ 3.81 and 3.73. The ammonium group is seen as a broad peak around δ 8.00. The NMR spectrum of the free base (Fig. 5*b*) was also made in $CDCl_3$, with tetramethylsilane as the internal reference.

The methyl group is seen as a doublet at δ 1.06 and 1.15. The CH and CH_2 groups are seen as a broad multiplet between δ 2.52 and 2.69. The methoxyl groups are seen as a singlet at δ 3.74. The three aromatic protons are also seen as a singlet at δ 6.73. The integration substantiates that the six methoxyl protons and the three aromatic protons occur as singlets. The amino group is seen as a broad peak at about δ 2.07. This is substantiated by the fact that it disappears after shaking the sample with deuterated water.

It is clear that, using NMR, the salt of the amphetamine is required for identification purposes since the free base does not give the resolution required to distinguish all of the protons, especially the methoxyl and aromatic protons.

SUMMARY

The identification of the hallucinogenic compound 2,5-dimethoxyamphetamine in illicit seizures was described utilizing IR, NMR, and mass spectroscopic techniques.

Problems do arise in the interpretation of the IR spectra of the compound. In this regard, evidence was presented which shows that there are at least three different spectral types without the knowledge of which the identification might be missed. Their occurrence, however, cannot be predicted.

Other parameters that aided in the identification of dimethoxyamphetamine were discussed.

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