Journal of Criminal Law and Criminology

Volume 63 | Issue 2 Article 13

1972

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THE JOURNAL OF CRIMINAL LAW, CRIMINOLOGY AND POLICE SCIENCE
Vol. 63, No. 2

Printed in U.S.A.

PROBLEMS IN IDENTIFICATION OF METHYLENEDIONY AND METHOXY AMPHETAMINES*

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A new series of amphetamines, in which the hydrogen atoms in the phenyl ring are substituted by methoxy or methylenedioxy groups seems to confer a hallucinogenic property to these compounds. Initial identification of these compounds are made by means of a combination of IR, NMR, and Mass Spec methods. Spectroscopic properties of some of these compounds are presented.

Amphetamine and methamphetamine are two well-known phenylethylamines. For a number of years, these stimulating agents are being commercially manufactured in large quantities; and are abused, at times, by our ever-increasing drug-seeking population. Clinical and forensic chemists and toxicologists are well aware of this problem and standardised procedures (generally using GC methods) are available to test the presence of these drugs.

Lately, however, perhaps due to increased demand for all types of mind-altering, hallucinogenic, drugs, new series of phenylethylamines are coming into the hands of drug abusers. This complicates the problem of detecting these compounds. About thirteen phenylethylamines are discussed in the book by Clarke (1). Some spectral properties of at least fourteen phenylethylamines are given in Sadtler (2). Recently, Ho and co-workers have described the synthesis and pharmacological activity of many methylenedioxy and methoxy phenylethylamines (3, 4). This paper deals with some of these phenylethylamines and discusses the methods of identification by various spectroscopic methods, with their inherent difficulties.

MATERIALS AND METHODS

STP (DOM, alpha-methyl, 2,5 dimethoxy 4-methyl phenylethylamine), Mescaline (3,4,5 trimethoxy phenylethyl amine), TMA (alpha-methyl, 3,4,5 trimethoxy phenylethylamine) and MDA (alpha-methyl, 3,4 methylenedioxy phenylethylamine) were obtained as standards from government sources. Compounds A and B are two unknown white crystalline powders (selected for the purposes of our discussion) among many similar compounds seized from apparent drug abusers. These compounds were purified by classical extraction and crystallization procedures. Cary-15 UV spectrophotometer, Varian NMR instruments, Perkin-Elmer infrared spectrophotometer, RMU-6D Mass spectrometer and Hitachi fluorescence spectrophotometer are among the instruments used to obtain the respective spectra. All UV and fluorescence spectra are taken in spectrograde methanol solvent. The infrared spectrum is obtained either in the form of a KBr pellet, or in the case of pure liquids, in between NaCl salt plates.

RESULTS AND DISCUSSION

Figure 1 shows the infrared spectra of STP and MDA hydrochloride salts. The infrared spectra of mescaline and TMA are presented in Figure 2.

It is well-known that simple phenylethylamines, with no active groups in the phenyl ring, have a characteristic benzyl UV absorption spectrum with maximum at about 258 nm. However, the substitution by one or more active groups in the phenyl ring shifts the peaks to lower and higher wavelengths. STP has UV absorption peaks at about 225 and 291 μm and MDA at about 235 and 286 μm (Fig. 3). Mescaline and TMA have a single maximum absorption peak (within normal experimental range) at about 269 μm in methanol (1).

Spectrofluorescence spectra of STP and MDA are given in Figure 4, and it seems both of them have excitation and emission peaks near 300 and 320 nms, respectively.

* Received for publication February 5, 1971.

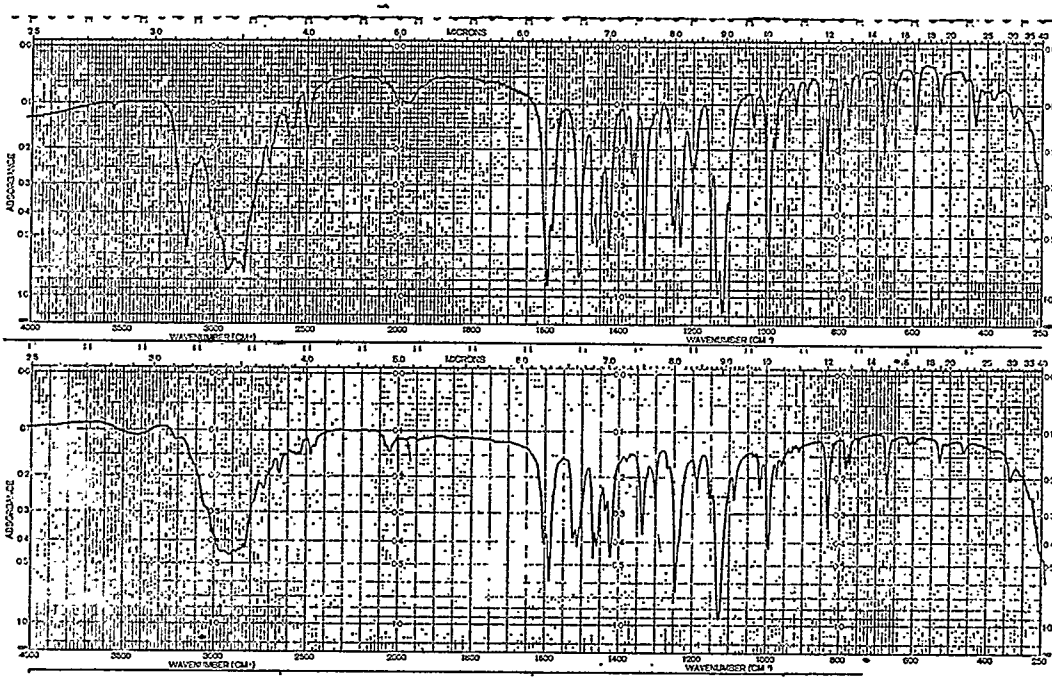


FIGURE 1.

Infrared spectra (top) STP-HCl (bottom) MDA-HCl.

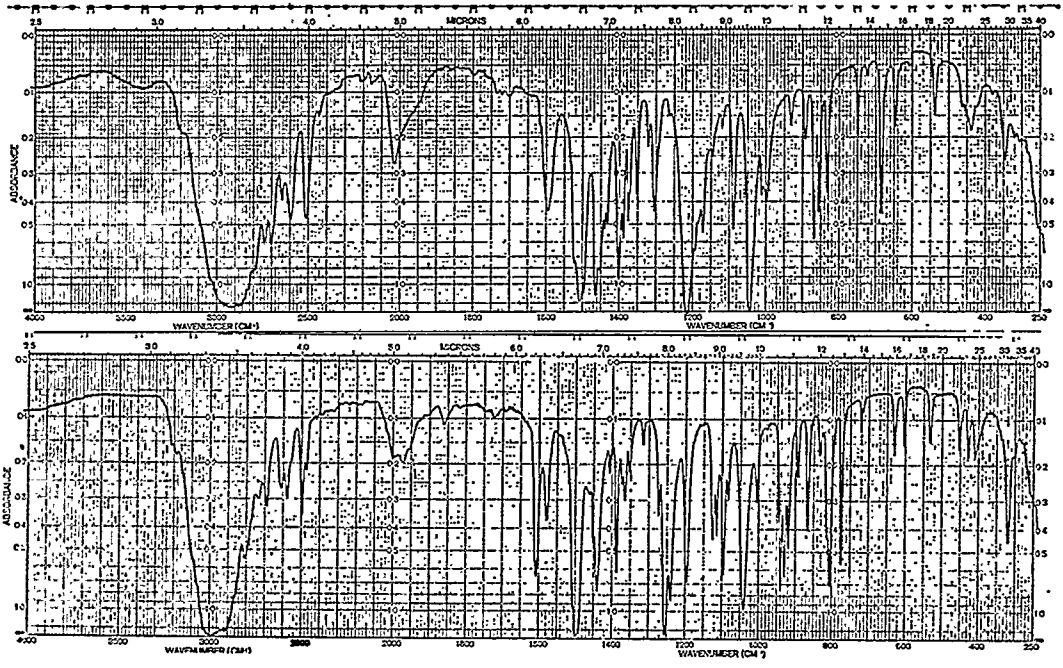


FIGURE 2.

Infrared spectra (top) TMA (bottom) Mescaline.

Compound A has a UV spectrum with peaks at 227 and 291 nm (Fig. 5); and this indicates the compound to be STP. Compound B has got absorption peaks at 287 and 236 nm (Fig. 5) and again, disregarding the minor difference in the actual ratio between the peaks, this compound seems to be MDA. The spectrofluorescence spectra of these compounds have excitation and emission peaks near 305 and 320 nm respectively (Fig. 6); the emission peaks are almost in the same position as that of STP and MDA. (The spectrofluorescence spectra, although highly sensitive, depend largely on the general structure of the molecule and the environment; hence, a positive identification based solely on these spectra is bound to lead to erroneous conclusions.)

Most of these compounds give deep colors with conventional color tests. (For example: with Marquis' Reagent MDA—red-purple; compound A—green; compound B—purple-black. With Mecke's Reagent, MDA—Blue purple; compound A—brown-green-red; compound B—green-black. With Nitric acid, MDA—yellow gold; compound A—orange; compound B—yellow. With Froehde's Reagent, MDA—grey-green-red; compound A—green; compound B—green-black. With Mandelin's Reagent, compound B—blue-green. With Sulfuric Acid, compound A—green tint and compound B—red-purple The reliability of these colors is not yet known.) The melting points of salts of A and B are different from that of STP and MDA (compound A has a m.pt for its HCl salt at about 120°C; for compound B, at about 148°C.). This, along with X-ray diffraction and GC data, confirmed

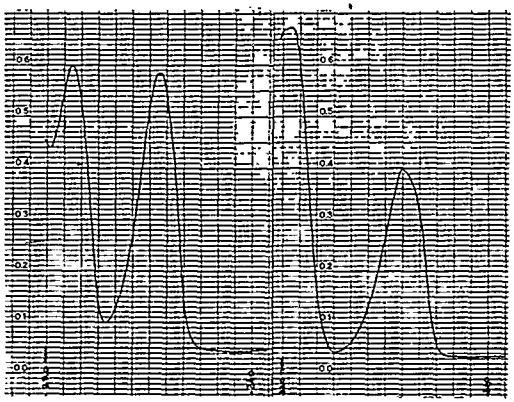


FIGURE 3.

Ultraviolet absorption spectra in methanol (left) MDA, (right) STP.

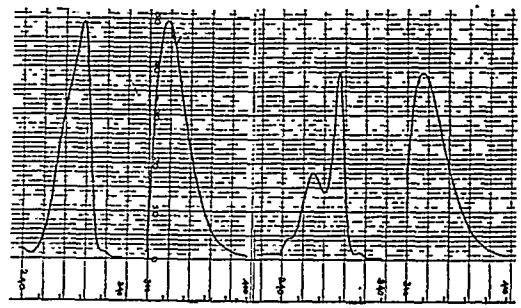


FIGURE 4.

Spectrofluorescence spectra in methanol (left) STP-HCl, (right) MDA-HCl.

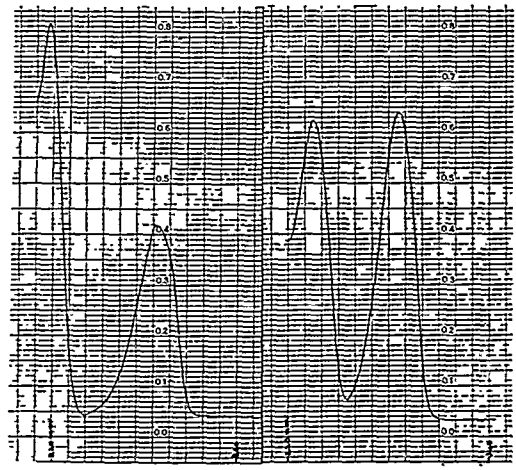


FIGURE 5.

Ultraviolet absorption spectra in methanol (left) Compound A, (right) Compound B.

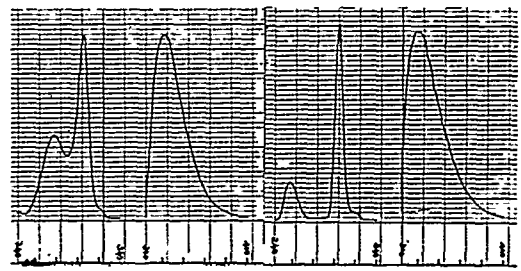


FIGURE 6.

Spectrofluorescence spectra in methanol (left) Compound A, (right) Compound B.

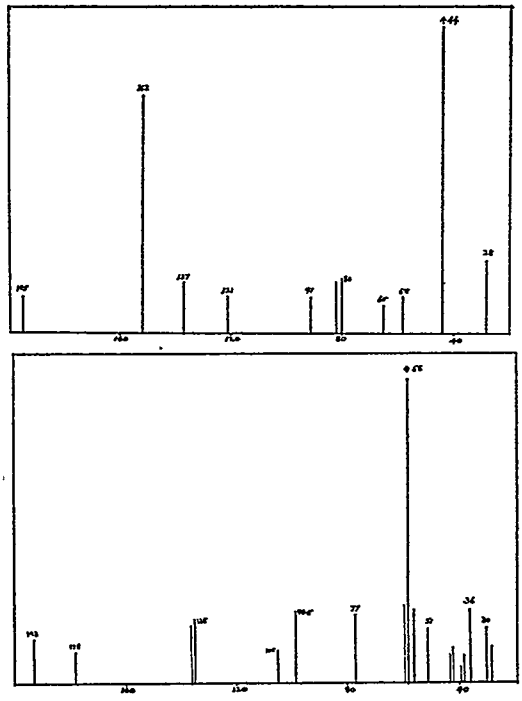


FIGURE 7.

Mass spectra (top) Compound A, (bottom) Compound B.

that compounds A and B are not really STP or MDA. Having thus been unable to identify these compounds, we undertook to identify them by means of a combination of mass spec, nmr, and infrared methods.

The mass spectra of these two unknown compounds are illustrated in Figure 7. The NMR spectrum of compound B (10–15% in $CDCl_3$) is shown in Figure 8. Figure 9 presents the NMR spectra of this solution when shaken with D_2O. In Figure 10, the NMR spectra of both A and B in $CDCl_3$ are given. The infrared spectra of these compounds are given in Figures 11 and 12.

The NMR and Mass spectra of MDA, STP, and Mescaline are available from literature (5, 6, 7). The NMR spectra of MDA, 3,4 dimethoxyphenylethylamine and p-methoxy phenylethylamine are also given in Sadtler (2).

Without getting into a detailed discussion of these spectra, the following conclusions can be reached.

Compound A has a molecular weight of 195. A strong m/e peak at 44 indicates the presence of a $(CH_3CHNH_2)^+$ ion. Strong peaks at 44, 152, and 137 suggest that compound A is actually a compound similar to STP minus the phenyl substituted methyl group. The NMR spectrum contains a singlet at 3.7 ppm assigned to six protons of $-OCH_3$ group, at 6.7 ppm due to three pheny-

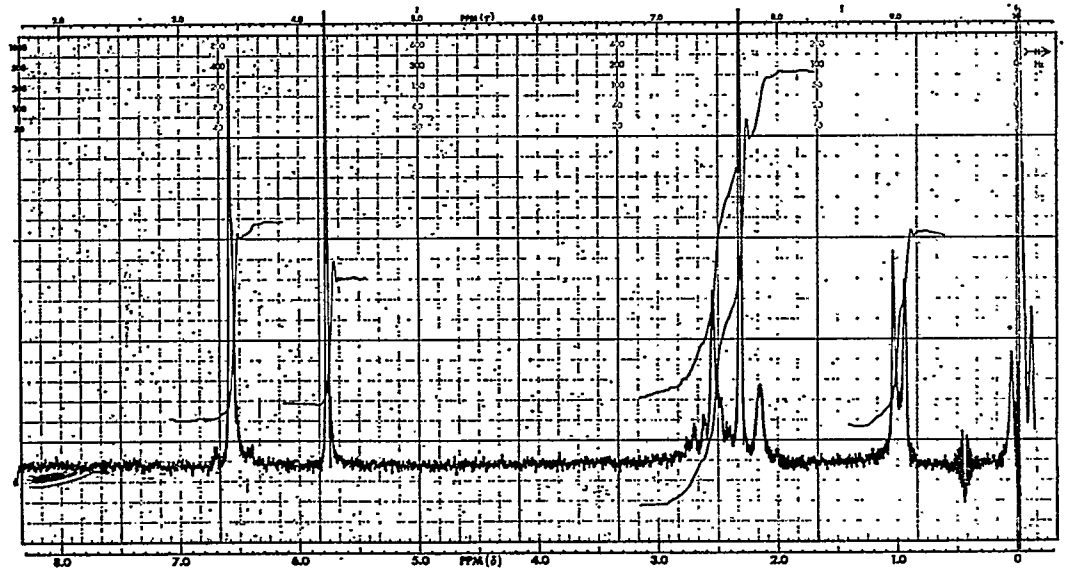


FIGURE 8.

NMR spectrum of compound B (10–15% in $CDCl_3$) sweep width 500 Hz.

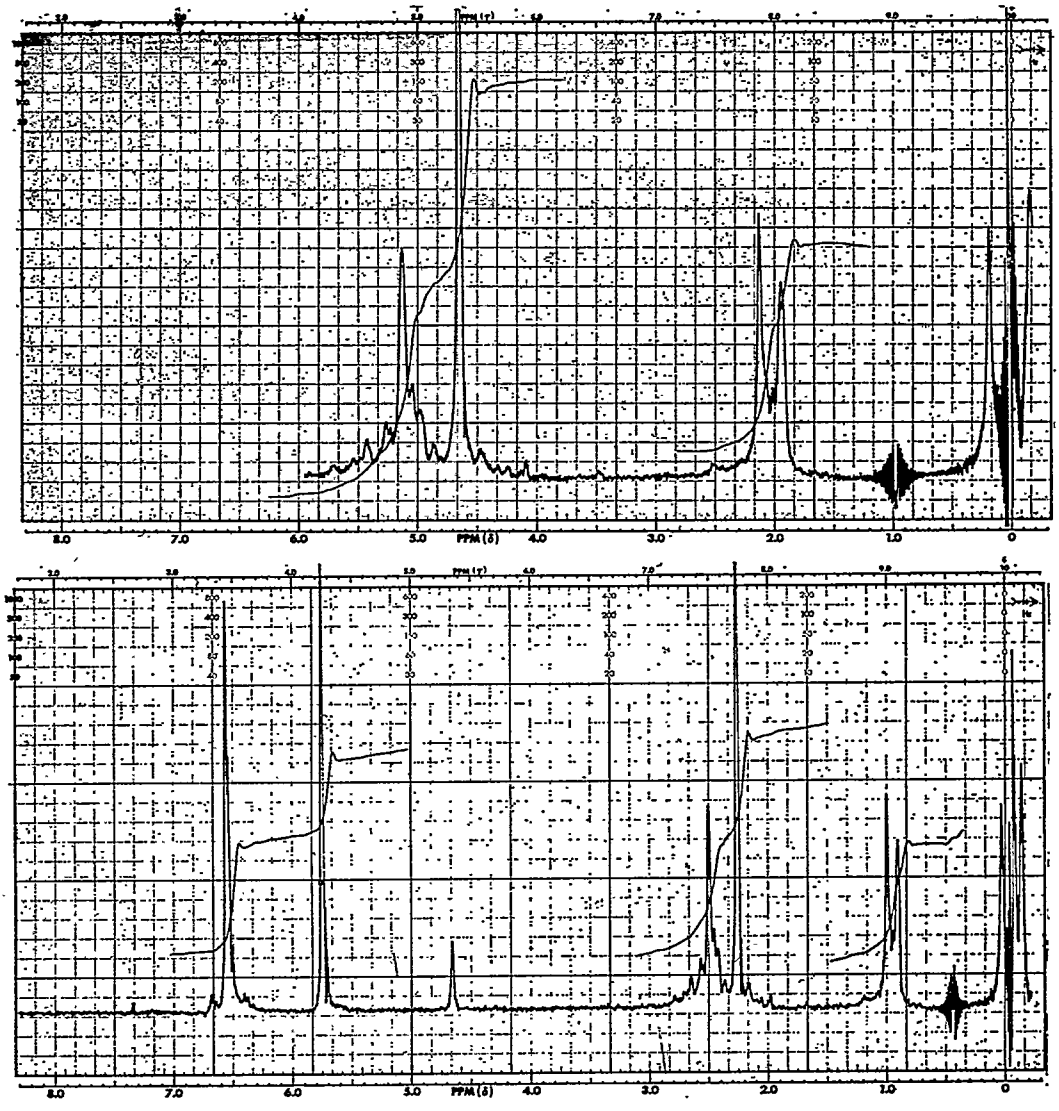


FIGURE 9.

NMR spectra of compound B (10–15% in $CDCl_3$ shaken with D_2O (top) sweep width 250 Hz (bottom) sweep width 500 Hz.

protons, a doublet at 1.05 ppm due to three protons of a CH_3 group adjacent to a —CH group, at 2.0 ppm probably due to two protons of a primary amino group and multiplets near 2.8 ppm due to three protons from a CH and a CH_2 group. The infrared spectrum again confirms the presence of a primary amino group (near 3200 cm^{-1}) and a aryl-alkyl ether group (1230 cm^{-1}).

The molecular weight of compound B is 193, which is 14 units greater than that of MDA. A strong peak at 58, compared to a peak at 44 for MDA, indicates the substitution of a methyl group for a hydrogen atom in the side chain. This, along with other peaks at 135, 105, and 77, suggests that compound B is a side-chain methyl substituted methylenedioxy amphetamine. From the NMR spectra, the following conclusions can be reached; a singlet at 5.8 ppm due to two protons from a methylenedioxy group, at 6.6 ppm due to three phenyl protons, the concentration dependent one

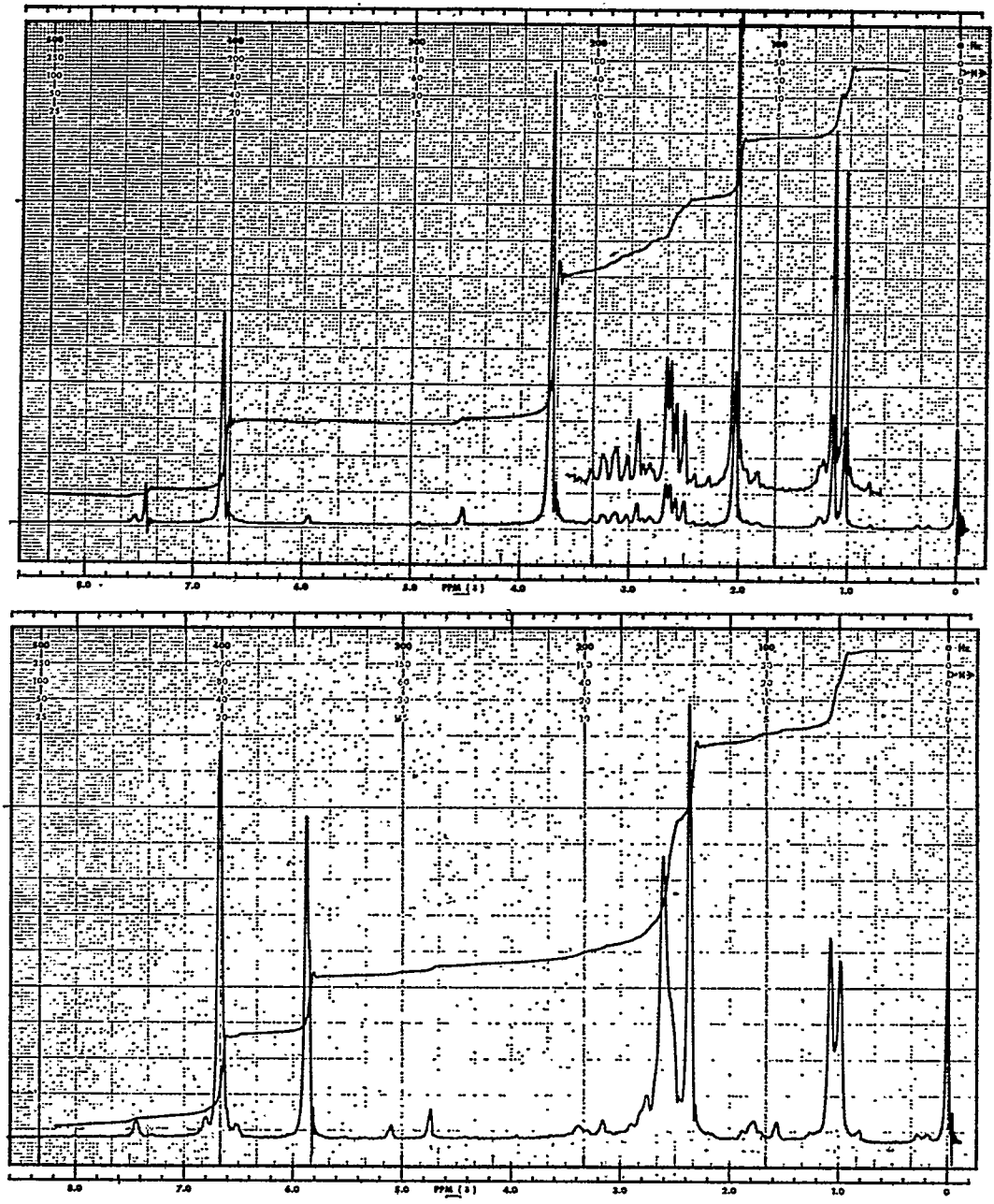


FIGURE 10.

NMR spectra of (top) compound A and (bottom) compound B in $CDCl_3$.

proton N-H peak which disappears in D_2O, singlet peak at 2.3 ppm due to three N-methyl protons, doublet at 1.0 ppm due to a methyl group attached to CH group and multiplets in the region of 2,6 ppm due to CH_2 and CH groups. The infrared spectrum agrees with these suggestions.

It is therefore possible to conclude that compound A is alpha-methyl, dimethoxy phenyethylamine (dimethoxyamphetamine, I may call it DMA) and compound B is methylenedioxy N-methyl alpha-methyl phenylethylamine (N-methyl methylene dioxy amphetamine). These results are

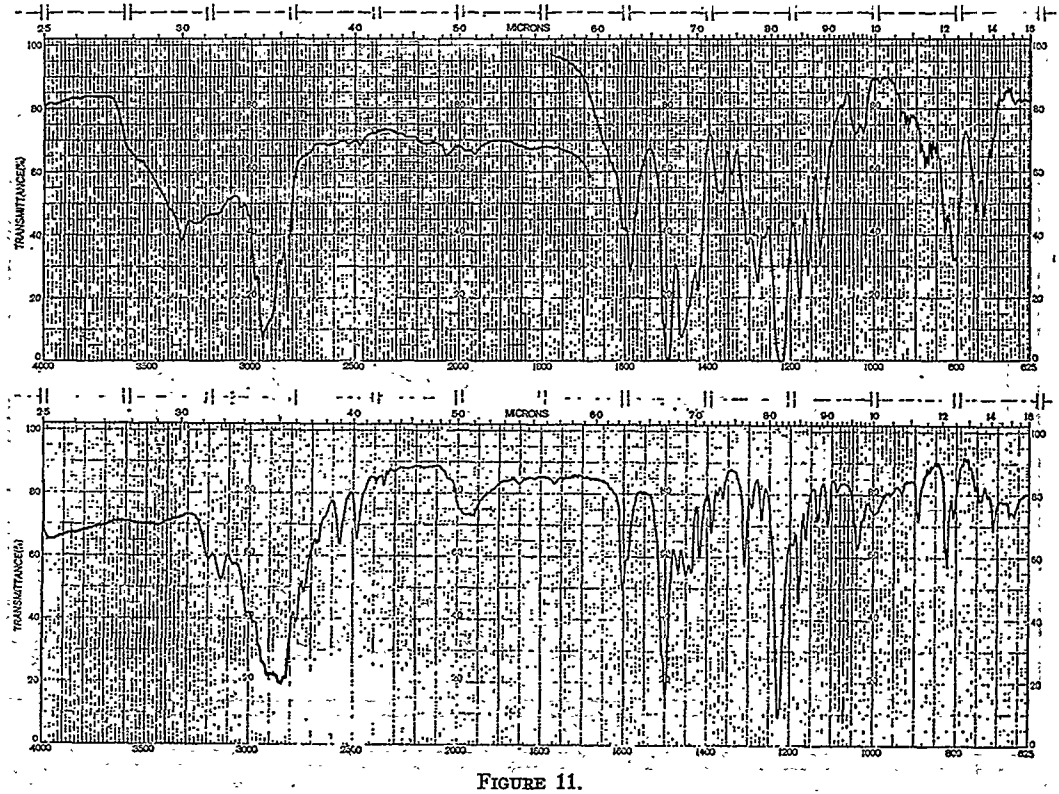


FIGURE 11.

Infrared spectra of compound A (top) base (bottom) HCl salt.

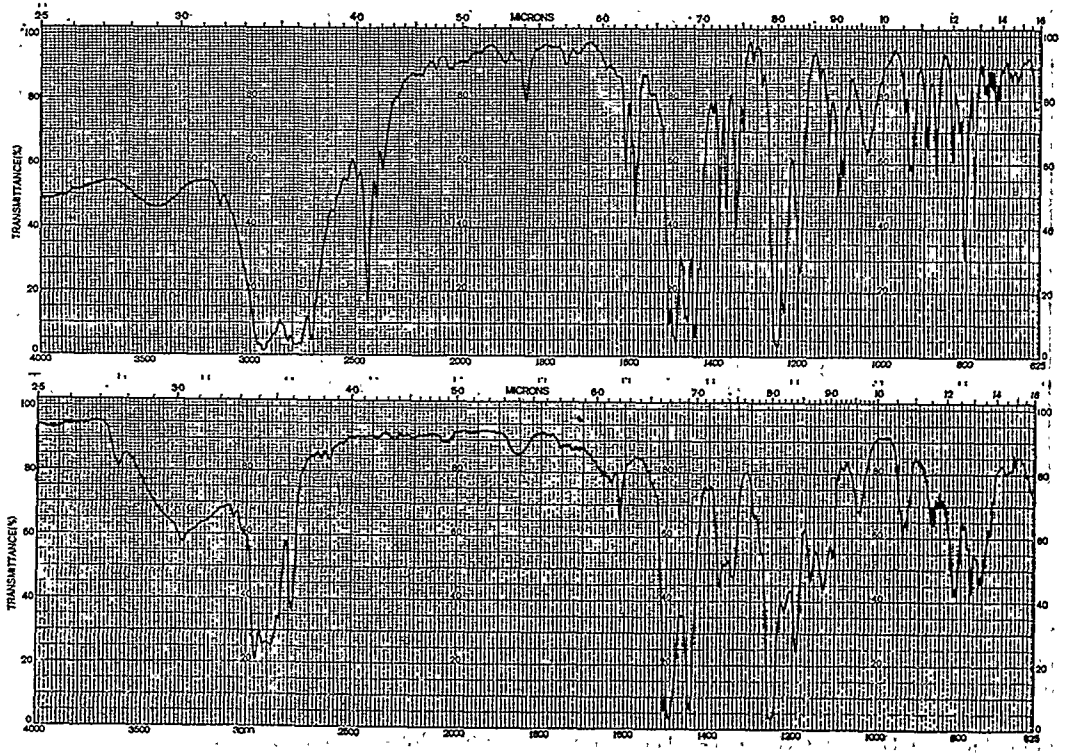


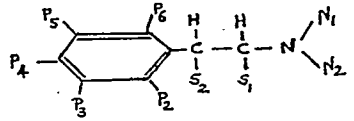
FIGURE 12.

Infrared spectra of compound B (top) HCl salt (bottom) base.

TABLE 1

METHYLENEDIOXY AND METHOXY AMPHETAMINES

OR = OCH_3
R = CH_3
ORO = OCH_2O



N_1	N_2	S_1	S_2	P_2	P_3	P_4	P_5	P_6	m.wt	m.pt (a)	UV (b)	name	references
						OR			151				(2)
		R				OR			165				(2), (1)
R		R						OR	179	126			(1), (2)
		R			OR	R			179	182			(3)
		R				R		OR	179	162			(3)
		R			R	OR	R		193	256			(3)
					OR	OR			181				(2)
R					OR			OR	195				
		R			OR			OR	195	112			(3) (c)
		R				OR	OR		195	148			(3) (c)
		R			OR		OR		195	160			(3) (c)
		R					OR	OR	195	155			(3) (c)
					OR	R		OR	195	212			(4)
		R			OR	R		OR	209	150			(4)
		R				OR	R	OR	209	163			(3)
		R			OR	R		OR	209	190	225 291	STP	(1), (3), (4), (6)
R	R				OR	R		OR	223	168			(4)
R		R			OR	R		OR	223	125			(4)
					OR	OR	OR		211		268	Mescaline	(1), (6), (7)
					OR	OR		OR	211				
						OR	OR	OR	211				
					OR		OR	OR	211				
				OR	OR			OR	211				
				OR		OR		OR	211				
		R			OR	OR	OR		225	216	269	TMA	(1), (3)
		R			OR	OR		OR	225	189			(3)
		R				ORO			179	181	235 286	MDA	(2), (3), (7)
		R						ORO	179				
						ORO	OR		195				
						ORO		OR	195				
							ORO	OR	195				
				OR				ORO	195				
					OR			ORO	195				
						OR		ORO	195				
		R	OH			ORO			195				
R			OH		OR	OH			197	176	272		(1)
		R	OH		OR			OR	211	214	290		(1)

a) reported values of melting point of the hydrochloride salt in °C. (may vary as much as 5 - 15° between various authors.)
b) UV absorption peaks in methanol in nms.
c) similar in formulae to compound A.

consistent with other data, especially those given in the references cited above.

Thus, it seems, more or less, certain that we have correctly obtained the formulae for our unknown compounds. However, we are not yet sure of the phenyl substituent positions. By checking with literature, on the basis of melting points, we will rule out 3,4 or 3,5 or 2,3 dimethoxy amphetamines for compound A. Much more work has to be done on NMR spectra to resolve the positions of phenyl protons. A positive confirmation can only be made when the suggested compound is actually synthesized, followed by comparison of its properties.

The amount of these materials needed to produce certain effects in human beings is not always certain. Various investigators, some of them apparently using substances of questionable purity or employing methods of uncertain statistical variations, have arrived at different dosages (see reference 8 for one of these estimates). But, in most cases, these substances are present in milli-grams or submilligram quantities. All types of impurities can also be expected, including the chemicals used and intermediate reaction products. Once the presence of a particular type of a compound has been inferred, generally by obtaining the UV spectra, further identification can only be made by GC or TLC methods, because of sample size and quality (see reference 9 for one of the latest papers in GC). But, this comparison will not be possible in the absence of available reference standards. Thus, for totally unknown substances, the usefullness of NMR and mass spec is very great, at least in the initial case and provided sufficient sample is available.

Some of the methylenedioxy or methoxy phenylethylamines with which the author is familiar are listed in Table 1.

ACKNOWLEDGEMENTS

The author expresses his appreciation to Jerry Nelson, Jim Done, and their co-workers (in BNDD Lab, Chicago) for many helpful discussions and for use of their facilities. The author also wishes to thank Commander Flannagan and Lt. Haviland of Chicago Police Crime Laboratory for their constant encouragement, and Vick Gironda and Thomas Tatum for their technical help in the field of photocopy.

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