Terry A. Dal Cason,[1] *M.Sc.*

The Characterization of Some 3,4-Methylenedioxyphenylisopropylamine (MDA) Analogs

ABSTRACT: The seizure in 1986 of a large-scale clandestine laboratory producing both the *N*-ethyl and the *N,N*-dimethyl analogs of 3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxyamphetamine [MDA]) and the recent identification of *N*-hydroxy MDA hydrochloride (HCl) indicate an interest by illegal laboratory operators in the synthesis of noncontrolled MDA analogs. Currently, identification of these new analogs may be hampered due to lack of available standards or reference data or both. This potential problem prompted the synthesis of the following *N*-substituted MDA analogs: *N*-methyl, *N*-ethyl, *N*-propyl, *N*-isopropyl, *N*-hydroxy, and *N,N*-dimethyl MDA. Each compound was prepared by reductive amination of 3,4-methylenedioxyphenyl-2-propanone (MDP-2-P) using the appropriate amine hydrochloride and sodium cyanoborohydride. In addition, the acetyl derivatives of MDA, *N*-hydroxy MDA, and MDP-2-P oxime are reported. Spectral and chromatographic data are presented for each of the compounds synthesized.

KEYWORDS: toxicology, 3,4-methylenedioxyphenylisopropylamine, analogs, chemical analysis

3,4-Methylenedioxyphenylisopropylamine (MDA), the parent compound for the analogs examined here, was first reported in 1910 [1]. The drug gained popularity in the San Francisco area in 1967 and was placed under Federal control in 1970. In 1972, the Bureau of Narcotics and Dangerous Drugs identified an unknown MDA analog as 3,4-methylenedioxymethamphetamine hydrochloride (MDMA HCl; *N*-methyl MDA HCl). Until a few years ago, *N*-methyl MDA was infrequently abused. However, in the mid 1980s, this compound enjoyed a resurgence of popularity as a "designer drug" touted as "Ecstasy." Increased abuse of the compound resulted in its temporary scheduling as a controlled substance in July 1985 [2] and final confirmation as a Schedule I drug in March 1988 [3]. In February 1986, a clandestine laboratory was seized which was producing both the *N*-ethyl ("Eve") and *N,N*-dimethyl analogs of MDA. In September 1986, a compound sold as "Fantasy" was identified as *N*-hydroxy MDA HCl.[2]

The proliferation of these analogs has become a source of concern for the forensic science community. These compounds, as well as analogs based on the structure of other controlled substances, are "controlled substance analogs," which refers to potentially physiologically

active derivatives of controlled substances, synthesized in an effort to evade the law. These compounds retain the basic chemical structure of the parent controlled substance but have minor structural alterations giving them a unique chemical identity. These analogs are not delineated by the Federal Controlled Substance Act (CSA) [4] as passed in 1970 and therefore are not proscribed by that statute. This loophole in Federal law has been remedied by amending the CSA through passage of the Controlled Substance Analogue Enforcement Act of 1986 [5]. Briefly, this enactment defines a controlled substance analog as a compound having a chemical structure substantially similar to a controlled substance in Schedule I or II of the CSA.

In addition, for a compound to be a controlled substance analog, it must meet one of two criteria: the compound must have a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS) that is substantially similar to, or greater than, a controlled substance in Schedule I or II (CSA) *or* it must be represented or intended by the seller to have the above attributes. This latter part of the definition will encompass compounds for which CNS activity data are not available but for which there is a putative abuse potential. Under the "Analog Law," compounds which meet the specified criteria and are intended for human consumption are subject to the same penalties as for Schedule I controlled substances (CSA). The human consumption clause is included to permit legitimate researchers to continue to design analogs of controlled substances and to conduct and evaluate animal studies without fear of penalties. Should these new analogs prove effective and safe in such preliminary studies, traditional routes for obtaining approval for human testing may then be followed.

The principle of designing new drugs through molecular modification of existing compounds is an established technique in the pharmaceutical industry. Research aimed at maximizing the desired effect of a parent compound and minimizing the undesirable effects results in the development of new derivatives on a continuing basis. When intended for human consumption, these new drugs are subjected to rigid testing and scrutiny to ensure both effectiveness and safety before marketing.

The history of clandestinely manufactured drugs, and especially those which have achieved notoriety as "designer drugs," is markedly different. Safety of the product has been of minor concern to the clandestine chemist. Overdose deaths related to "China White 'Heroin'" [6] (alpha-methyl fentanyl) and the Parkinson-like state induced from by-product contamination of meperidine analogs [7–9] illustrate this point. In most seized clandestine laboratories, quality control is either of low priority or nonexistent. Simplicity of the synthetic route, availability of the required chemicals, and a profitable market are critical elements for the clandestine laboratory operation.

Rarely do clandestine chemists have the ability to devise novel syntheses. As a consequence, the preparation of controlled substance analogs results primarily from substitution of a single reactant in an established method. Often the synthesis of the targeted analog has already been described in detail in the scientific literature. An exact description of the synthesis procedure is usually obtained through a library search of the scientific literature or through purchase of underground drug manufacturing booklets. These drug booklets are generally an edited composite of literature techniques and provide one or more synthetic methods for each of several different drugs. In general, the simplest synthetic methods are the ones most commonly used by clandestine laboratory operators. The following method is an excellent example of a facile synthesis obtained from recognized scientific literature and applied to clandestine drug manufacture.

Experimental Procedures

The synthesis procedure used in this investigation is based on the work of Borch et al. [10] and elucidated for MDA and some of its analogs by Braun et al. [11]. The CNS activity of the analogs presented here has also been described by Braun et al. [12]. In conformance with

their terminology, the analogs here are referred to as 3,4-methylenedioxyphenylisopropylamines rather than 3,4-methylenedioxyamphetamines. Shulgin [13] has provided a detailed description to the approaches for naming these compounds.

Compounds 2 to 7 (Fig. 1, Table 1) were prepared by mixing 3,4-methylenedioxyphenyl-2-propanone (MDP-2-P) with a methanol solution of the appropriate amine hydrochloride (Fig. 2). Sodium cyanoborohydride was added and the pH of the solution adjusted with hydrochloric acid using methyl red as a visable pH indicator. MDA (Compound 1) was prepared by the same technique but used ammonium acetate as the nitrogen source. In each case the analogs were purified by evaporating the solvent, dissolving the residue in dilute hydrochloric acid and washing with methylene chloride. The aqueous acidic solution containing the analog was made basic with sodium hydroxide, reextracted with methylene chloride, and the solvent evaporated. The crude base which remained was dissolved in isopropyl alcohol and poured into an isopropyl alcohol/hydrochloric acid mixture. Subsequently, ether was added and the precipitated salt collected. Varying amounts of 3,4-methylenedioxyphenyl-2-propanol (MDP-2-Pol) were observed in the reaction mixtures due to reduction of the ketone. The alcohol and any unreacted ketone may be recovered from the methylene chloride washings of the acidic solution described above. Attempts to produce two tertiary amine analogs, N,N-diethyl MDA and N-ethyl, N-methyl MDA, by this procedure were unsuccessful. Application of catalytic hydrogenation for preparation of these two compounds resulted only in trace quantities of the N-ethyl, N-methyl analog sufficient for identification by mass spectrometry. Braun et al. [11] were able to prepare the diethyl homolog through reductive alkylation of MDA with acetaldehyde and sodium cyanoborohydride.

Infrared (IR) spectra were obtained using a Perkin-Elmer Model 1800 Fourier Transform Spectrometer interfaced with a Model 7500 computer. Spectra of the solid compounds listed in Table 2 were prepared using the standard potassium bromide (KBr) matrix technique. For liquids, pure KBr disks were prepared and the liquid coated on the surface of the disk. Gas liquid chromatography (GLC) data were obtained using the instruments, columns, and parameters listed in Table 3. Chloroform solutions (1 to 3 mg/mL) of each compound were
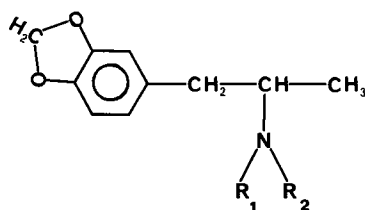

FIG. 1—Structure of MDA and some N-substituted analogs.

TABLE 1—Substitutions on MDA for analogs synthesized.

Chemical Name	Compound Number	R1	R2	MW
3,4-Methylenedioxyphenylisopropylamine	1	H	H	179
N-Methyl-3,4-methylenedioxyphenylisopropylamine	2	H	CH_3	193
N-Ethyl-3,4-methylenedioxyphenylisopropylamine	3	H	C_2H_5	207
N-Propyl-3,4-methylenedioxyphenylisopropylamine	4	H	C_3H_7	221
N-Isopropyl-3,4-methylenedioxyphenylisopropylamine	5	H	$CH(CH_3)_2$	221
N,N-Dimethyl-3,4-methylenedioxyphenylisopropylamine	6	CH_3	CH_3	207
N-Hydroxy-3,4-methylenedioxyphenylisopropylamine	7	H	OH	195

$$\left(R_1 = R_2 = CH_3 \quad OR \quad R_1 = H \ ; \ R_2 = Me, \ Et, \ n\text{-}Pr, \ i\text{-}Pr, \ OH \right)$$
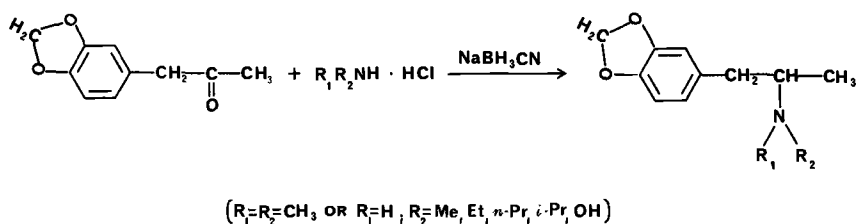
FIG. 2—*Synthesis scheme for* N-*substituted MDA analogs.*

TABLE 2—*List of IR spectra for MDA and related compounds.*

No.	Compound Name
1	3,4-methylenedioxyphenylisopropylamine base (MDA)
1a	3,4-methylenedioxyphenylisopropylamine HCl
2	N-methyl-3,4-methylenedioxyphenylisopropylamine base (N-methyl MDA)
2a	N-methyl-3,4-methylenedioxyphenylisopropylamine HCl
3	N-ethyl-3,4-methylenedioxyphenylisopropylamine base (N-ethyl MDA)
3a	N-ethyl-3,4-methylenedioxyphenylisopropylamine HCl
4	N-propyl-3,4-methylenedioxyphenylisopropylamine base (N-propyl MDA)
4a	N-propyl-3,4-methylenedioxyphenylisopropylamine HCl
5	N-isopropyl-3,4-methylenedioxyphenylisopropylamine base (N-isopropyl MDA)
5a	N-isopropyl-3,4-methylenedioxyphenylisopropylamine HCl
6	N,N-dimethyl-3,4-methylenedioxyphenylisopropylamine base (N,N-dimethyl MDA)
6a	N,N-dimethyl-3,4-methylenedioxyphenylisopropylamine HCl
7	N-hydroxy-3,4-methylenedioxyphenylisopropylamine base (N-hydroxy MDA)
7a	N-hydroxy-3,4-methylenedioxyphenylisopropylamine HCl
8	3,4-methylenedioxyphenyl-2-propanone-2-oxime (MDP-2-P oxime)
9	3,4-methylenedioxyphenyl-2-propanone (MDP-2-P/piperonyl acetone)
10	3,4-methylenedioxyphenyl-2-propanol (MDP-2-Pol)
11	N-acetyl-3,4-methylenedioxyphenylisopropylamine
12	N-acetyl-N-acetoxy-3,4-methylenedioxyphenylisopropylamine
13	O-acetyl-3,4-methylenedioxyphenyl-2-propanone-2-oxime

injected into the gas chromatographs (GC) equipped with flame ionization detectors (FID) by automatic sampling devices. GC columns interfaced to mass spectrometers as the detecting device were manually injected with 1- to 3-mg/mL solutions in methanol. High-performance liquid chromatography (HPLC) employed a Perkin-Elmer Series 4 liquid chromatograph with an LCI 100 laboratory computing integrator. Methanol solutions of the compounds were autoinjected by a Perkin-Elmer ISS-100 automatic sampler. A modified Wheals system [14,15] was used as the mobile phase for each of the columns listed in Table 4. The ultraviolet (UV) detector was set at 254 μ, a commonly used wavelength in fixed wavelength detectors.

Mass spectrometry (MS) employed a Finnigan Model 4530 interfaced to a Model 9600 GC and a Data Control Nova 4 computer. Both electron impact (EI) and chemical ionization (CI/methane) spectra were obtained. EI mass spectra acquired from a Hewlett-Packard Model 5970 mass selective detector (MSD) were essentially the same as those provided by the Finnigan Unit. Proton nuclear magnetic resonance (PNMR) spectra of the title compounds were recorded as the base using a Varian Gemini 300 MHz Fourier Transform NMR. Samples were dissolved in deuterochloroform, which also served as the reference.

TABLE 3—*GLC retention times (in minutes) for MDA and related compounds.*

No.	Compound	Drug One,[a] 125°C	HP-1,[b] 160°C	OV-17,[c] 175°C	OV-101,[d] 170°C	OV-101,[d] 190°C	SPB-1,[e] 160°C
0	ephedrine	0.82	1.90	1.33	1.02	...	0.75
1	MDA	1.30	2.67	2.03	1.43	...	1.10
2	*N*-methyl MDA	1.70	3.23	2.28	1.73	...	...
3	*N*-ethyl MDA	2.17	3.86	2.55	2.07	...	...
4	*N*-propyl MDA	3.37	5.37	3.40	2.87	...	...
5	*N*-isopropyl MDA	2.46	4.26	2.60	2.27	...	...
6	*N,N*-dimethyl MDA	2.35	4.14	2.70	2.20	...	...
7	*N*-hydroxy MDA	1.51	5.15	...	...	...	2.13
	(MDA)[f]	1.29	2.67	2.08	1.43	...	1.03
	(MDP-2-P oxime)[f]	3.40	5.22	4.30	2.80	...	2.22
	(putative dimer)[f]	7.28	10.19	13.05	5.51	...	4.57
8	MDP-2-P oxime	3.39	5.19	4.30	2.81	...	...
9	MDP-2-P	1.24	2.53	2.19	1.35	...	...
10	MDP-2-Pol	1.32	2.69	2.10	1.40	...	...
11	*N*-acetyl MDA	...	...	...	...	2.9	...
12	*N*-acetyl,*N*-acetoxy-MDA	...	...	...	...	5.4	...
13	*O*-acetyl MDP-2-P oxime	...	...	...	...	3.3	...

[a]10M non-pkd Drug One capillary column, 0.53-mm ID, Alltech Associates; HP-5880A GC, FID, He flow rate 10 mL/min, N_2 makeup gas flow rate 20 mL/min; split ratio 4:1.

[b]12M HP-1 capillary column, 0.2-mm ID, Hewlett-Packard Co., 33-μm film; HP-5890 GC, MSD, He flow rate 0.2 mL/min; 1.5-min solvent delay; split ratio 70:1.

[c]Six-foot (1.8-m) glass column. 2-mm ID, Applied Sciences Laboratories, 3% OV-17 on Gas Chrom. Q II 100–120 mesh; HP 5840A GC, FID; N_2 flow rate 61 mL/min.

[d]Six-foot (1.8-m) glass column, 2-mm ID, Applied Sciences Laboratories, 3% OV-101 on Gas Chrom. Q II 100–120 mesh; Finnigan Model 9600 GC interfaced with Finnigan Model 4530 MS, He flow rate 25 mL/min.

[e]5M SPB-1 capillary column, 0.32-mm ID, Supelco, Inc., Finnigan Model 4530 MS, He flow rate 10 mL/min; split ratio 30:1.

[f]Pyrolytic disproportionation products.

TABLE 4—*HPLC retention times (in minutes) for MDA and related compounds.[a]*

No.	Compound	Micro Porasil[b]	C-18[c]	Micro Bondapak Phenyl[d]
0	ephedrine HCl	5.82	3.30	2.74
1	MDA HCl	4.29	2.67	3.05
2	*N*-methyl MDA HCl	7.06	4.78	4.38
3	*N*-ethyl MDA HCl	5.37	3.50	3.78
4	*N*-propyl MDA HCl	3.86	2.74	3.59
5	*N*-isopropyl MDA HCl	4.34	2.82	3.46
6	*N, N*-dimethyl MDA HCl	6.47	4.91	4.93
7	*N*-hydroxy MDA HCl	1.94	1.08	2.07
8	MDP-2-P oxime	1.90	1.07	2.10
9	MDP-2-P	1.93	1.11	2.05
10	MDP-2-Pol	1.93	1.10	2.05

[a]UV Detector 254 nm; Wheals mobile phase (methanol, water, 1N ammonium hydroxide, 1N ammonium nitrate; 27:3:2:1) flow rate 2.0 mL/min.

[b]Waters Associates, 30 cm, micro porasil column, 3.9-mm ID.

[c]Perkin-Elmer, 15 cm, HS-5C-18 column, 4.6-mm ID.

[d]Waters Associates, 30 cm, micro bondapak phenyl column, 3.9-mm ID.

Results and Discussion

Because of the uniqueness of N-hydroxy MDA among the analogs presented here, a separate discussion of this compound is warranted. N-Hydroxy MDA has proven difficult to identify by gas chromatography/mass spectrometry (GC/MS) or to screen using GLC because of its tendency to undergo pyrolytic disproportionation (Fig. 3). This chemical process is initiated by heat and results in one molecule of N-hydroxy MDA oxidizing to 3,4-methylenedioxyphenyl-2-propanone-2-oxime (MDP-2-P oxime), with concomitant reduction of a second molecule to MDA. When pure N-hydroxy MDA HCl is introduced into the high-temperature injection port of the GC or GC/MS, the resulting chromatogram will exhibit at least two peaks. Examination of the corresponding mass spectra will identify these peaks as MDA and MDP-2-P oxime. These data may lead the analyst to postulate that the material at hand is the impure product of a partially successful attempt to produce MDA by reduction of MDP-2-P oxime. What seems to be the obvious conclusion based on GLC and GC/MS, that is, that MDA is an original component of the sample, would be in error. The following information permits unequivocal identification of N-hydroxy MDA as well as the other synthesized analogs.

Purification of "Street" Samples

Solid samples are ground to a powder and dissolved in dilute hydrochloric acid at room temperature. Any insoluble materials are removed by filtration. The aqueous acidic solution is then extracted with chloroform, made basic with sodium hydroxide, and reextracted with chloroform. The chloroform solution of the basic extract is evaporated to yield the analog.

Compounds 1 to 6 (Table 1) are liquids at room temperature, and care should be exercised to prevent volatilization during removal of the extraction solvent. N-hydroxy MDA, although initially recovered as a liquid, solidifies upon standing at room temperature. The recovered bases may be converted to the hydrochloride salts by dissolution in an isopropanol/hydrochloric acid solution and precipitating with ether.

Infrared Spectroscopy

The IR spectra of MDA, its analogs and some related compounds (Table 2) are provided both as the free base (Fig. 4) and, were applicable, as the hydrochloride salt (Fig. 5). With the possible exception of N-ethyl MDA and N-propyl MDA, the IR spectra of the analog bases can be differentiated. The hydrochloride spectra of these two compounds show sufficient difference to make identification by comparison of the salt forms possible. It should be pointed out that polymorphism has been encountered in a number of these hydrochloride salts and that five distinct polymorphs have been identified for MDMA HCl [13].

Gas Liquid Chromatography

Retention times are listed in Table 3 for several different packed and capillary columns. Ephedrine is included as a reference. Repeated injections of MDA or its analogs on the
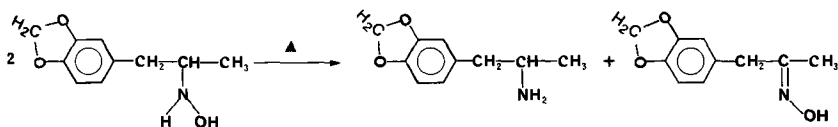

FIG. 3—Pyrolytic disproportionation of N-hydroxy MDA: two molecules of N-hydroxy MDA yield one molecule of MDA and one molecule of MDA oxime.
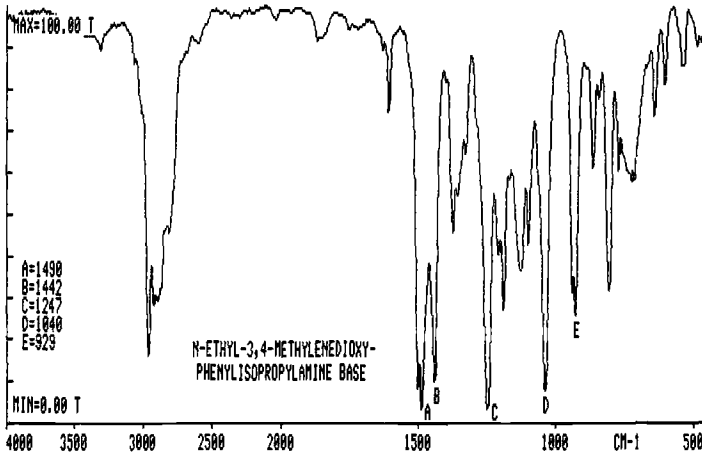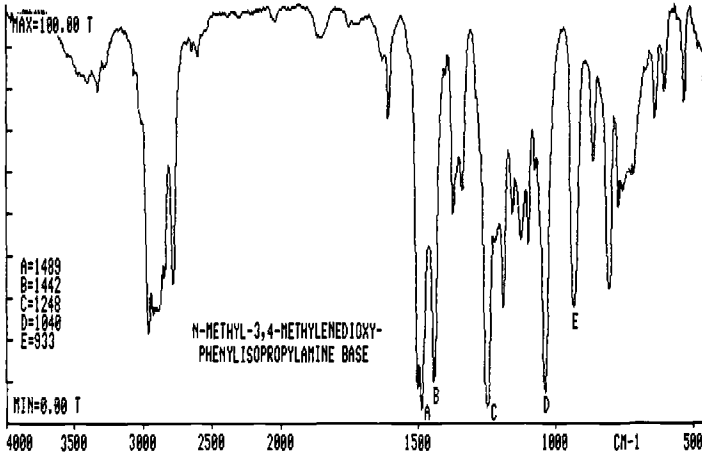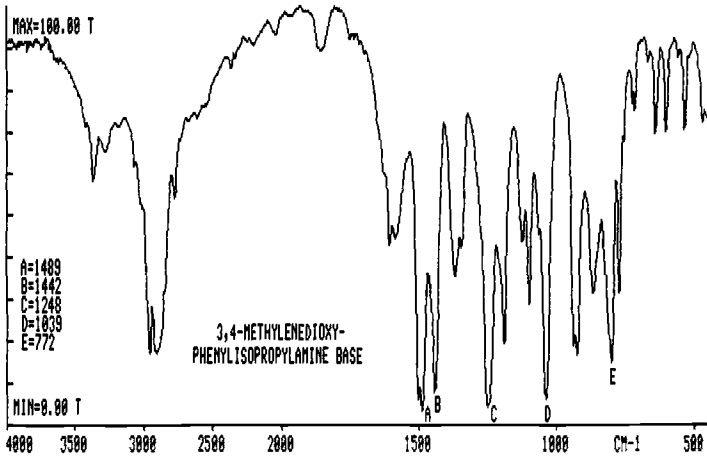
FIG. 4—IR spectra of MDA base, some MDA analogs as bases, and some MDA derivatives.

A=1490
B=1441
C=1247
D=1040
E=940

N-PROPYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE BASE

A=1490
B=1442
C=1247
D=1188
E=1040

N-ISOPROPYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE BASE

A=1490
B=1442
C=1247
D=1040
E=929

N,N-DIMETHYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE BASE

FIG. 4—*Continued.*

MAX=100.00 T

A=1502
B=1490
C=1247
D=1036
E=929

N-HYDROXY-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE BASE

MIN=0.00 T

A B   C   D   E

4000   3500   3000   2500   2000   1500   1000   CM-1   500

MAX=100.00 T

A=1503
B=1487
C=1446
D=1245
E=1040

3,4-METHYLENEDIOXYPHENYL-
2-PROPANONE OXIME

MIN=0.00 T

A B C   D   E

4000   3500   3000   2500   2000   1500   1000   CM-1   500

MAX=100.00 T

A=1712
B=1504
C=1490
D=1249
E=1039

3,4-METHYLENEDIOXYPHENYL-2-PROPANONE

MIN=0.00 T

A   B   D   E
        C

4000   3500   3000   2500   2000   1500   1000   CM-1   500

FIG. 4—Continued.

MAX=100.00 T

A=1503
B=1498
C=1442
D=1248
E=1039

3,4-METHYLENEDIOXYPHENYL-2-PROPANOL

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

A B C   D   E

MAX=100.00 T

A=1632
B=1548
C=1503
D=1489
E=1243

N-ACETYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

A   B C D   E

MAX=100.00 T

A=1789
B=1672
C=1489
D=1246
E=1187

N-ACETYL-N-ACETOXY-
3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

A   B   C   D E

FIG. 4—*Continued.*

MAX=100.00 T

A=1762
B=1504
C=1490
D=1246
E=1206

O-ACETYL-3,4-METHYLENEDIOXY-
PHENYL-2-PROPANONE OXIME

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

FIG. 4—Continued.

evaluated packed columns eventually resulted in degradation of peak symmetry and altera-
tion of observed retention times, but this phenomenon can be avoided by using a tempera-
ture program. The compound is permitted to elute isothermally (see Table 3), and then the
oven temperature is rapidly raised (15°C/min) to 260°C for 2 min before it is returned to the
initial temperature. This approach will permit GC quantitation of all the analogs except
N-hydroxy MDA. As discussed earlier, N-hydroxy MDA undergoes pyrolytic disproportion-
ation in the GC injector port (Fig. 3). Although MDA (171 s) and MDP-2-P oxime (350 s)
provide the primary peaks observed in gas chromatograms of N-hydroxy MDA HCl when
using packed columns (Fig. 6), GCs equipped with capillary columns may provide chro-
matograms with a different appearance (Fig. 7). The additional peaks are believed to be
artifacts of the injection port arising from interaction of the various species available during
volatilization, pyrolysis, and disproportionation. The gas chromatographic peak at 4.57 min

MAX=100.00 T

A=1502
B=1442
C=1257
D=1239
E=1039

3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500
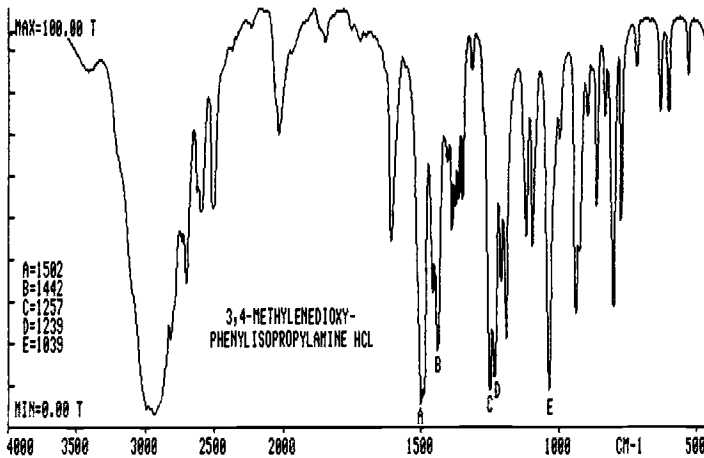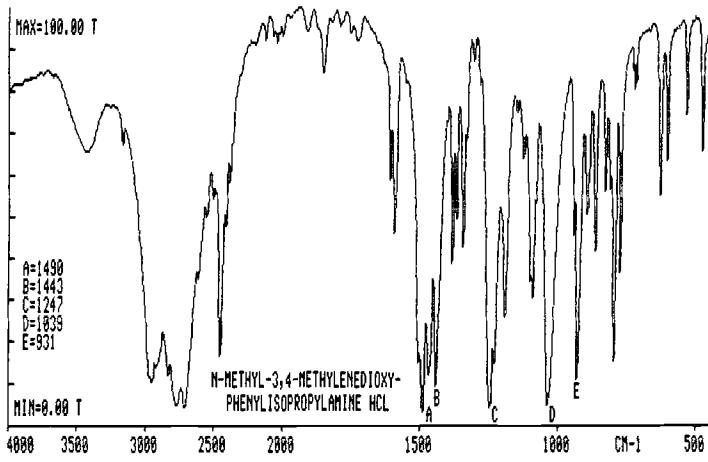
FIG. 5—IR spectra of MDA and some analogs as hydrochloride salts.

MAX=100.00 T

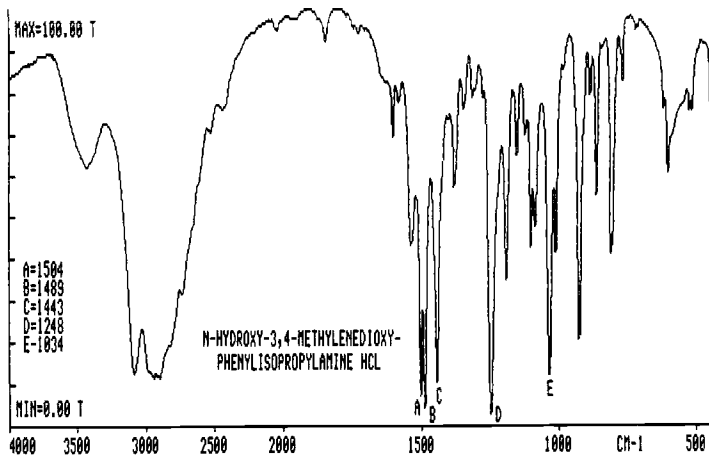A=1490
B=1443
C=1247
D=1039
E=931

MIN=0.00 T

N-METHYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

4000 3500 3000 2500 2000 1500 1000 CM-1 500

MAX=100.00 T

A=1489
B=1444
C=1246
D=1039
E=803

MIN=0.00 T

N-ETHYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

4000 3500 3000 2500 2000 1500 1000 CM-1 500

MAX=100.00 T

A=1491
B=1442
C=1246
D=1039
E=932

MIN=0.00 T

N-PROPYL-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

4000 3500 3000 2500 2000 1500 1000 CM-1 500

FIG. 5—*Continued.*

MAX=100.00 T

A=1484
B=1441
C=1251
D=1041
E=929

N-ISOPROPYL-
3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

MAX=100.00 T

A=1485
B=1443
C=1247
D=1039
E=930

N,N-DIMETHYL-3,4-
METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE HCL

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

MAX=100.00 T

A=1504
B=1489
C=1443
D=1248
E=1034

N-HYDROXY-3,4-METHYLENEDIOXY-
PHENYLISOPROPYLAMINE HCL

MIN=0.00 T

4000   3500   3000   2500   2000   1500   1000   CM-1   500

FIG. 5—*Continued.*

FIG. 6—*Gas chromatogram of* N-*hydroxy MDA HCl on 3% OV-101 packed column.*
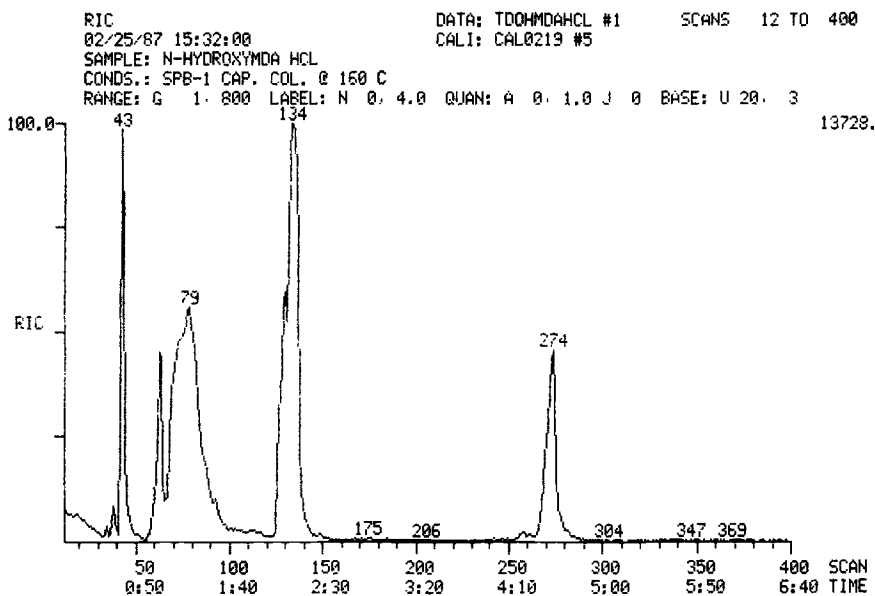
FIG. 7—*Gas chromatogram of* N-*hydroxy MDA HCl on SPB-1 capillary column.*

(274 s) may be a dimer of N-hydroxy MDA (or MDA or both). MDA dimers have previously been reported [16]. Injection of N-hydroxy MDA base (Fig. 8) under identical conditions to those used in Fig. 7 illustrates the effect of hydrogen chloride on the species in the injection port. This comparison also indicates that the additional peaks observed when using the cap-
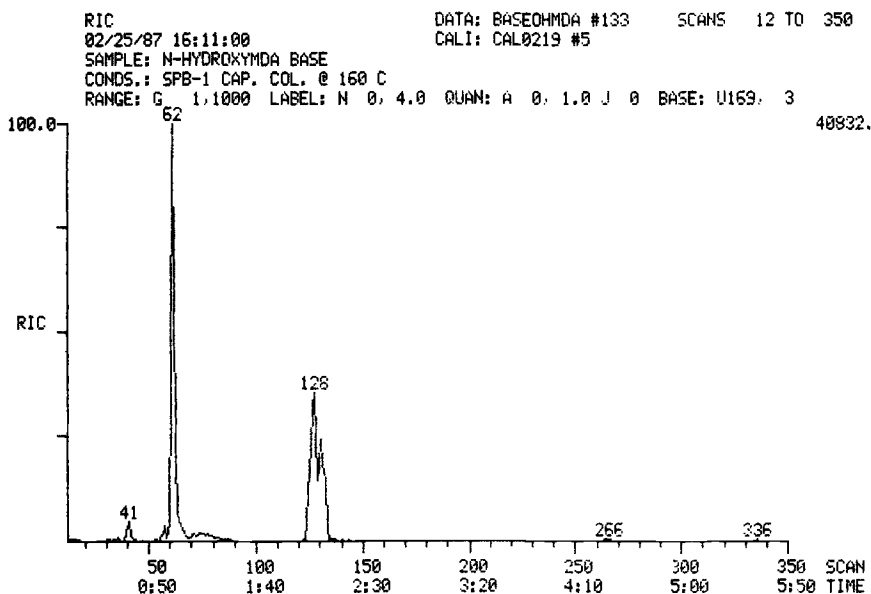
FIG. 8—*Gas chromatogram of* N-*hydroxy MDA base on SPB-1 capillary column.*

illary column (Fig. 7) do not arise from the increased resolving power of this type of column. If such were the case, the same peaks would be evident in both Figs. 7 and 8, but not in Fig. 6. In Fig. 7, N-hydroxy MDA can be identified as the preceding shoulder (unlabeled at 129 s) on the MDP-2-P oxime peak occurring at 134 s. The broad, unsymmetrical peak at 79 s is, at least in part, MDA. In Fig. 8, a significant proportion of N-hydroxy MDA base (128 s) has escaped disporportion into MDA (62 s) and MDP-2-P oxime (unlabeled at 131 s). The EI-GC/MS of these three compounds are presented in Fig. 9.

Unfortunately, packed columns provided essentially identical chromatograms (Fig. 6) whether the base or hydrochloride was injected, and no evidence of N-hydroxy MDA could be found by GC/MS when packed columns were employed.

High-Pressure Liquid Chromatography

Table 4 provides the data for three types of column packings. In each case, modified Wheals [*14,15*] (methanol, water, 1N ammonium hydroxide, 1N ammonium nitrate; 27:3:2:1) was employed as the mobile phase. HPLC is a suitable method for quantitation. Peak degradation does not occur with subsequent injections as it does with packed GC columns. In addition, UV sensitivity [*16*], even at 254 nm, in quite pronounced (MDA HCl max/ethanol: $\lambda = 237$ nm, $\epsilon = 3410$; $\lambda = 287$ nm, $\epsilon = 3580$).

Mass Spectrometry

Mass spectra for MDA, the MDA analogs, and several MDA related compounds were obtained as EI spectra (Fig. 9) and chemical ionization (CI) spectra (Fig. 10). The EI mass spectra for MDA and each of the N-substituted derivatives exhibit weak to extremely weak molecular ions which, in some cases, may not be evident without computer enhancement. Insets in the EI mass spectra (Fig. 9) illustrate an increase of intensity of 10 for mass units of 140 and higher. The base peak in each instance results from alpha cleavage and consists of
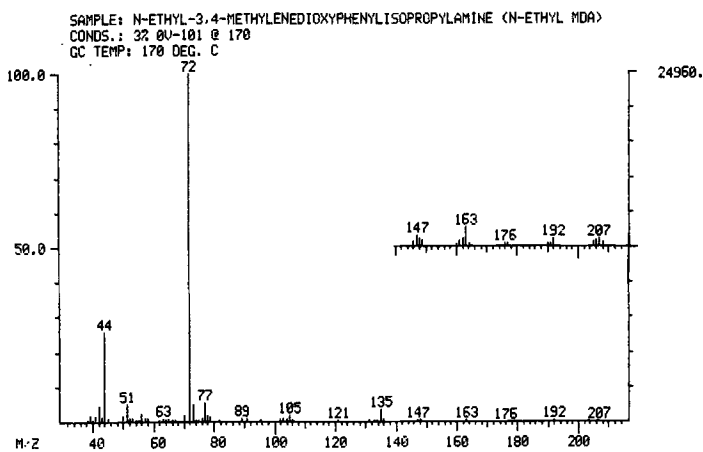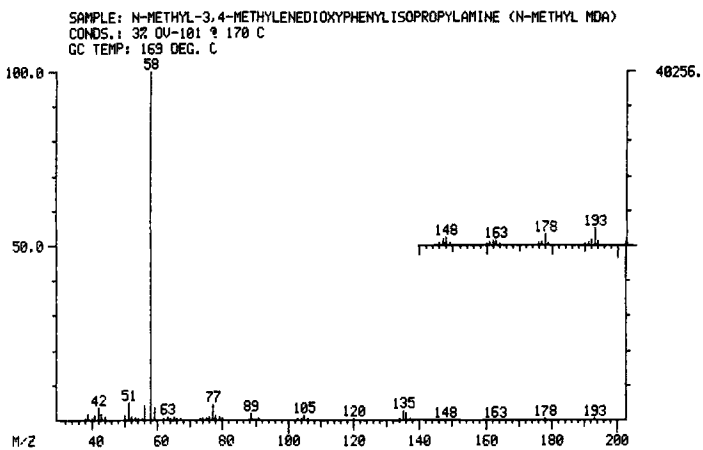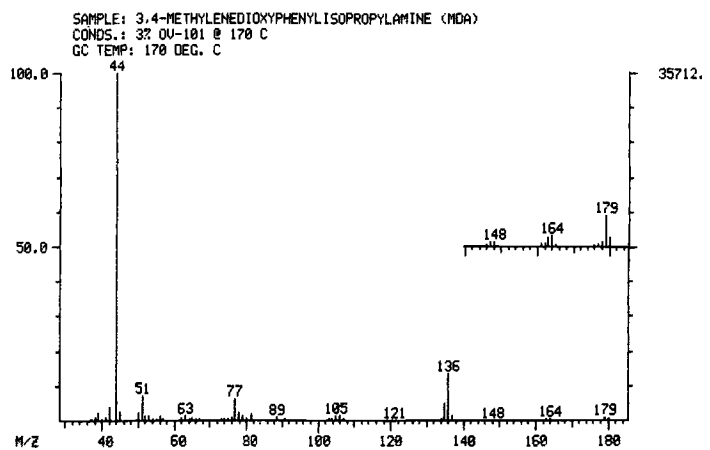
SAMPLE: 3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (MDA)
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 170 DEG. C

SAMPLE: N-METHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-METHYL MDA)
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 169 DEG. C

SAMPLE: N-ETHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-ETHYL MDA)
CONDS.: 3% OV-101 @ 170
GC TEMP: 170 DEG. C

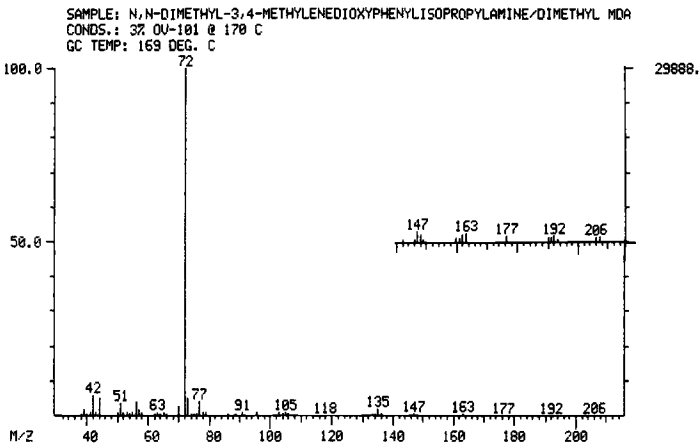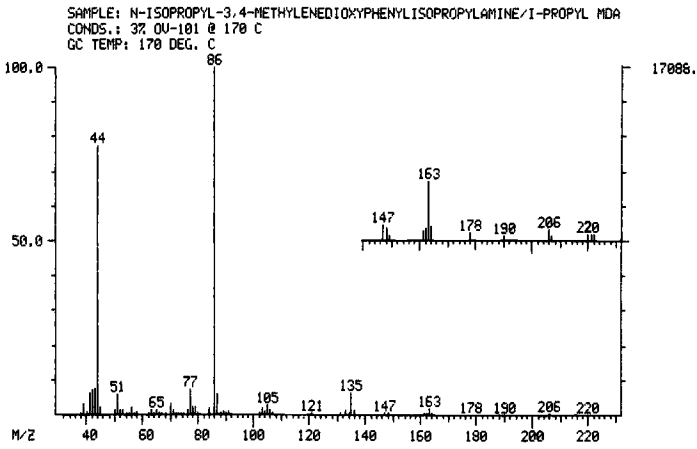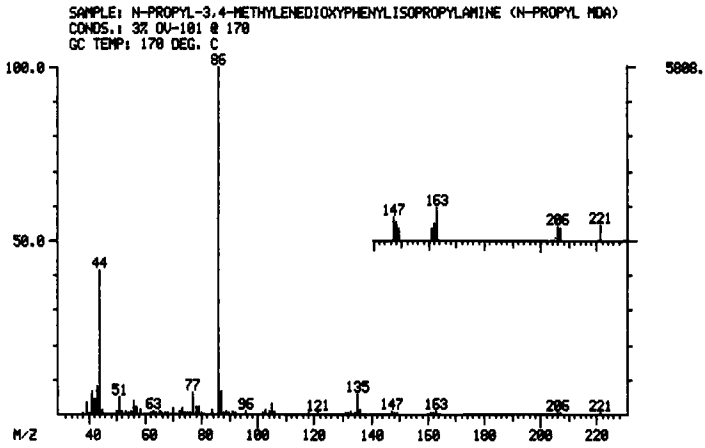FIG. 9—*Electron impact mass spectra for MDA and related compounds.*

SAMPLE: N-PROPYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-PROPYL MDA)
CONDS.: 3% OV-101 @ 170
GC TEMP: 170 DEG. C

SAMPLE: N-ISOPROPYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE/I-PROPYL MDA
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 170 DEG. C

SAMPLE: N,N-DIMETHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE/DIMETHYL MDA
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 169 DEG. C

FIG. 9—*Continued.*

SAMPLE: N-HYDROXY-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-HYDROXY MDA)
CONDS.: SPB-1 CAP. COL. @ 160
GC TEMP: 159 DEG. C

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANONE-2-OXIME
CONDS.: 3% OV-101 @ 170
GC TEMP: 170 DEG. C

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANONE
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 170 DEG. C

FIG. 9—*Continued.*

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANOL
CONDS.: 3% OV-101 @ 170 C
GC TEMP: 170 DEG. C

FIG. 9—*Continued.*

the fragment CH3-CH$=\overset{\oplus}{N}$-R1R2 where R_1 and R_2 represent the appropriate substitutions on the nitrogen atom for that particular analog. Table 5, derived from Lukaszewski [16], shows the major EI mass fragments.

The difficulties encountered with identification of N-hydroxy MDA were previously discussed. To obtain a suitable mass spectrum of N-hydroxy MDA via GC, it is necessary to introduce the compound as the base using a capillary column. This approach minimizes disproportionation and enables mass spectra of unaltered N-hydroxy MDA (along with MDA and MDP-2-P oxime) to be obtained. Alternatively, a solid probe accessory may be used to obtain a "clean" mass spectrum. Mass spectrometer systems having only packed column capabilities may identify N-hydroxy MDA as its acetyl derivative. The acetyl derivatives for MDA (N-acetyl MDA, MW 221), MDP-2-P oxime (O-acetyl MDP-2-P oxime, MW
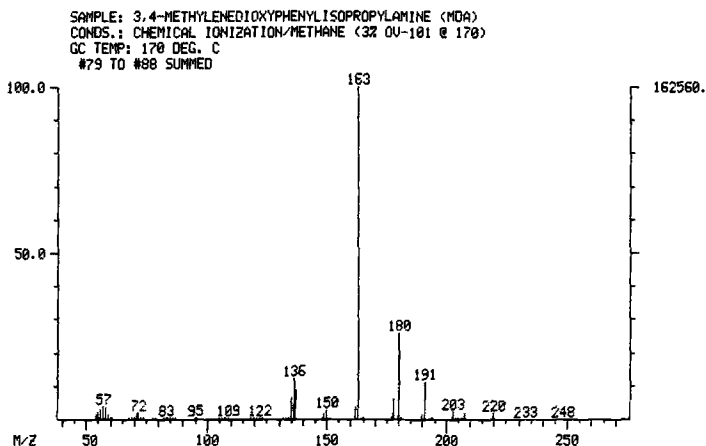
SAMPLE: 3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (MDA)
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170)
GC TEMP: 170 DEG. C
#79 TO #88 SUMMED

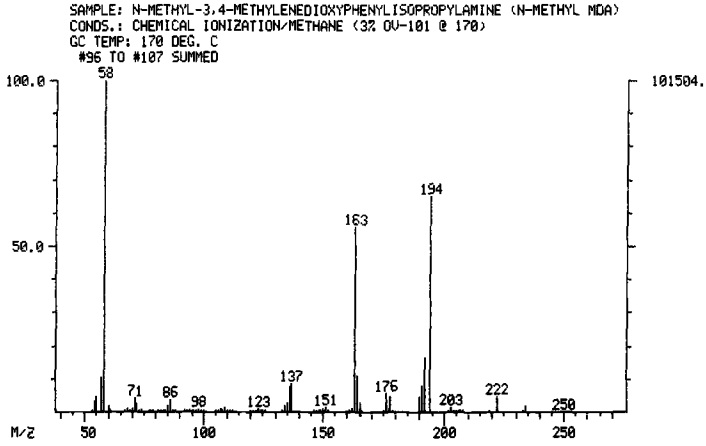FIG. 10—*Chemical ionization mass spectra for MDA and related compounds.*

SAMPLE: N-METHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-METHYL MDA)
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170)
GC TEMP: 170 DEG. C
#96 TO #107 SUMMED

101504.

Peaks labeled: 58, 71, 86, 98, 123, 137, 151, 163, 176, 194, 203, 222, 250

M/Z 50 100 150 200 250

SAMPLE: N-ETHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-ETHYL MDA)
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C)
GC TEMP: 170 DEG. C
#115 TO #125 SUMMED

113280.

Peaks labeled: 57, 72, 79, 100, 123, 137, 149, 163, 178, 192, 208, 222, 236, 248

M/Z 50 100 150 200 250

SAMPLE: N-PROPYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-PROPYL MDA)
CONDS.: CHEMICAL IONIZATION/METHANE (3 % OV-101 @ 170 C)
GC TEMP: 170 DEG. C
#162 TO #172 SUMMED

105088.

Peaks labeled: 56, 69, 86, 100, 114, 137, 149, 163, 177, 206, 222, 236, 250, 262

M/Z 50 100 150 200 250

FIG. 10—*Continued.*

SAMPLE: N-ISOPROPYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE/I-PROPYL MDA
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C)
GC TEMP: 170 DEG. C
 #125 TO #135 SUMMED

SAMPLE: N,N-DIMETHYL-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE/DIMETHYL MDA
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C)
GC TEMP: 170 DEG. C
 #122 TO #132 SUMMED

SAMPLE: N-HYDROXY-3,4-METHYLENEDIOXYPHENYLISOPROPYLAMINE (N-HYDROXY MDA)
CONDS.: CHEMICAL IONIZATION/METHANE (SPB-1 CAP. COL. @ 160 C)
GC TEMP: 159 DEG. C
 #115 TO #120 SUMMED

FIG. 10—*Continued.*

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANONE-2-OXIME
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C.
GC TEMP: 170 DEG. C
#155 TO #165 SUMMED

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANONE (MDP-2-P)
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C)
GC TEMP: 170 DEG. C
#74 TO #84 SUMMED

SAMPLE: 3,4-METHYLENEDIOXYPHENYL-2-PROPANOL (MDP-2-POL)
CONDS.: CHEMICAL IONIZATION/METHANE (3% OV-101 @ 170 C)
GC TEMP: 170 DEG. C
#78 TO #88 SUMMED

FIG. 10—*Continued.*

TABLE 5—*Mass fragments (EI) of MDA analogs.*[a]

Mass Fragment	m/z
	molecular ion
	163
	135
	105
	77
	$42 + (R_1, R_2)$

[a]Where R_1 = hydrogen, methyl, ethyl, propyl, iso-propyl, or hydroxyl and R_2 = hydrogen or methyl.

235), and N-hydroxy MDA (N-acetyl-N-acetoxy-MDA, MW 279) were prepared by dissolving MDA HCl, MDP-2-P oxime and N-hydroxy MDA HCl in acetic anhydride and heating on a steam bath until the acetic anhydride evaporated.

Although all three acetyl compounds were initially recovered as liquids, the two amine derivatives solidified upon standing. Each of the acetyl compounds exhibits the expected molecular ion and provides a mass spectrum suitable for confirmation of identity (Fig. 11).

Compounds 1 to 10 (Table 2) were also subjected to CI-GC/MS (Fig. 9). Base peaks for compounds 2 to 6 remain the same as for the EI discussion. Because masses were recorded from 50 to 270 AMU, the expected base peak of 44 AMU for MDA is not reported as such in Table 6. Normalization of the mass spectrum of MDA (Fig. 10) resulted in m/z 163 registering as the base peak. Table 6 indicates the expected CI fragments represented by M (the molecular weight), $M + 1$, $M + 29$, and $M + 41$ [17,18]. Each of the analogs also has fragments at m/z 163, 191, and 203 arising from $m + 1$, $m + 29$, $m + 41$ where $m = M - NR_1R_2$ (R_1R_2 defined in Table 5).

Proton Nuclear Magnetic Resonance

MDA and its N-substituted analogs can easily, and unequivocally, be differentiated by NMR spectroscopy (Fig. 12). The lower field resonances at approximately 6.5 to 6.8 and 5.8 to 5.9 ppm remain essentially the same from analog to analog and result respectively from benzenoid and methylenedioxy protons. The terminal methyl group produces a doublet between 0.8 and 1.1 ppm and is easily recognized except in the isopropyl analog. Careful inspection of the complex pattern overlapping the 0.8- to 1.1-ppm range will reveal the requiste doublet. Distinguishing characteristics are noted in the 2.2 to 3.2-ppm range, with additional resonance interactions evident between 0.8 and 1.5 ppm for the ethyl, propyl, and isopropyl analogs.
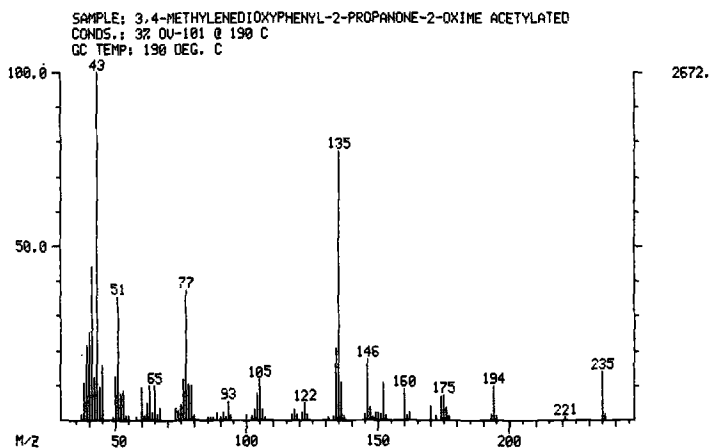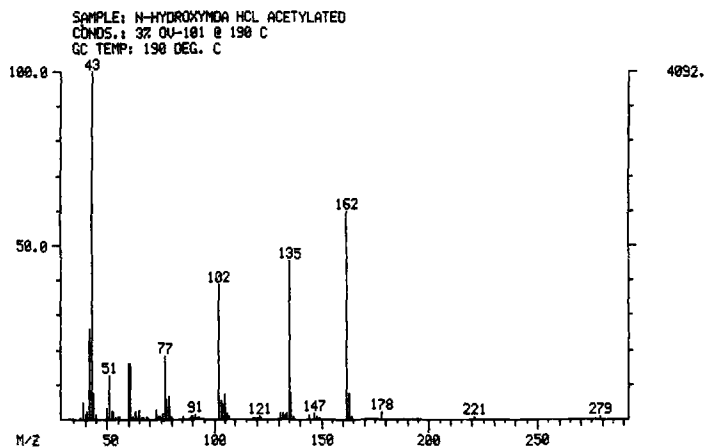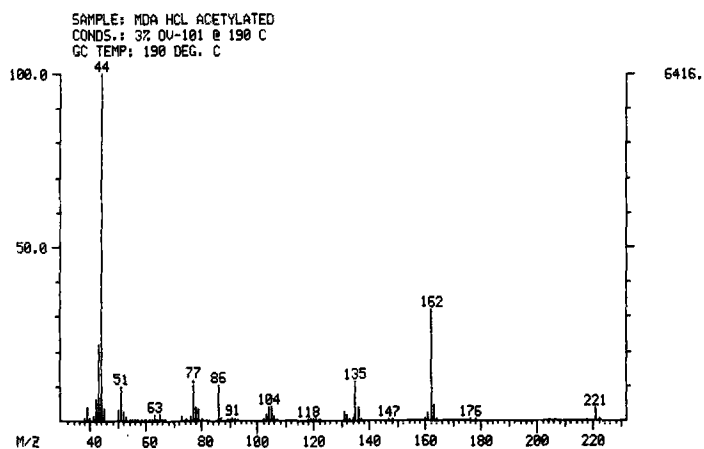
FIG. 11—*Mass spectra of acetylated MDA, acetylated N-hydroxy MDA, and acetylated MDP-2-P-oxime.*

TABLE 6—*Mass fragments (CI) of MDA analogs.*

No.	Compound	Base	M (MW)	$M + 1$	$M + 29$	$M + 41$
1	MDA	163[a]	179	180	208	220
2	N-methyl MDA	58	193	194	222	234
3	N-ethyl MDA	72	207	208	236	248
4	N-propyl MDA	86	221	222	250	262
5	N-isopropyl MDA	86	221	222	250	262
6	N.N-dimethyl MDA	72	207	...	...	...
7	N-hydroxy MDA	163	195	196	224	236
8	MDP-2-P oxime	194	193	194	222	234
9	MDP-2-P	...	178	...	...	...
10	MDP-2-Pol	163	180	181	209	...

[a]This is the observed base peak when spectra are acquired from 50 to 270 AMU. The actual base peak is 44 AMU.

Melting Points

Melting points (Table 7) were recorded using capillary tubes in a Thomas-Hoover "Unimelt" melting point apparatus. MDA HCl and its analogs were purified as described in the experimental procedure. The oxime and the acetylated compounds were purified by dissolving in chloroform and subsequently washing three times with saturated sodium carbonate solution. This was followed by three washings with $3N$ hydrochloric acid and evaporation of the chloroform. The impure residues were dissolved using large quantities of boiling hexanes and, with the exception of the acetylated oxime, were recovered from the cooled solutions by vacuum filtration. O-Acetyl MDP-2-P oxime is a liquid at room temperature and was further purified by vacuum distillation (Table 7).

Conclusion

The analytical data on MDA, six of its N-substituted analogs, and a number of related compounds will enable the analyst to conclusively identify these substances. Analysts using IR, the "workhorse" for identification in many forensic laboratories, should be aware of the polymorphism exhibited by the hydrochloride salts of MDA analogs. Examination of the analogs as the free base, or in solution, eliminates this potential problem. Alternatively, IR identification of the hydrochloride salt in conjunction with GLC or HPLC retention times will permit the analyst to identify correctly the analog at hand. The PNMR spectra of the analogs are distinctive and will permit the rapid identification of these compounds. EI-GC/ MS is less useful for the identification of MDA and the prepared analogs than it is for most classes of illicit drugs. The molecular ions have weak to extremely weak intensities. EI-GC/ MS identification should be supplemented with GLC or HPLC retention times. CI-GC/MS results in mass spectra having substantial $M + 1$ fragments.

N-hydroxy MDA is unique among the studied analogs due to its tendency to undergo pyrolytic disproportionation. GLC and GC/MS identification requires injection of the analog as the base onto capillary columns to minimize disproportionation. Alternatives to the use of capillary columns for GC/MS identification are the solid probe technique or conversion of the analog to N-acetyl, N-acetoxy MDA with acetic anhydride.

Acknowledgment

3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE
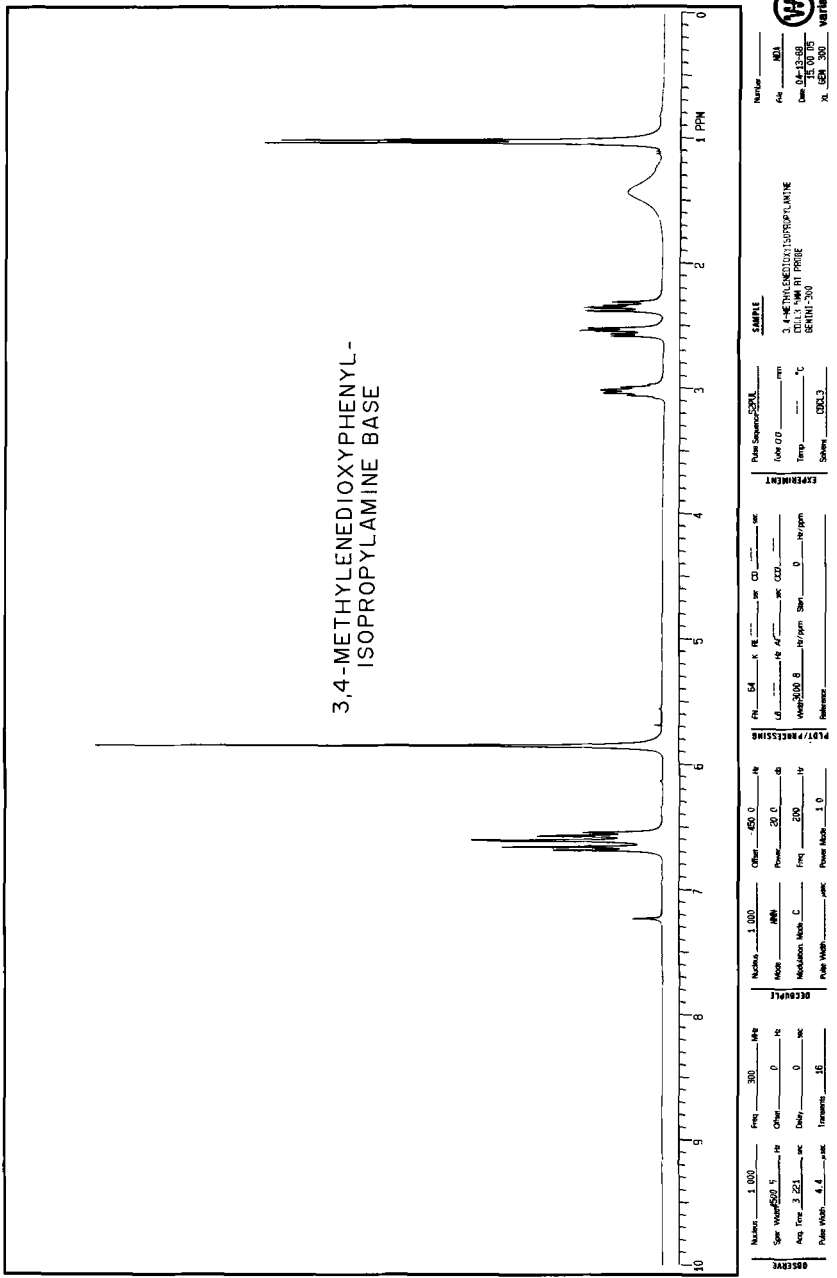
FIG. 12—*PNMR spectra for MDA and analogs.*

N-METHYL-
3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE

FIG. 12—*Continued.*

N-ETHYL-
3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE

FIG. 12—*Continued.*

N-PROPYL-
3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE

FIG. 12—*Continued.*

N-ISOPROPYL-
3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE
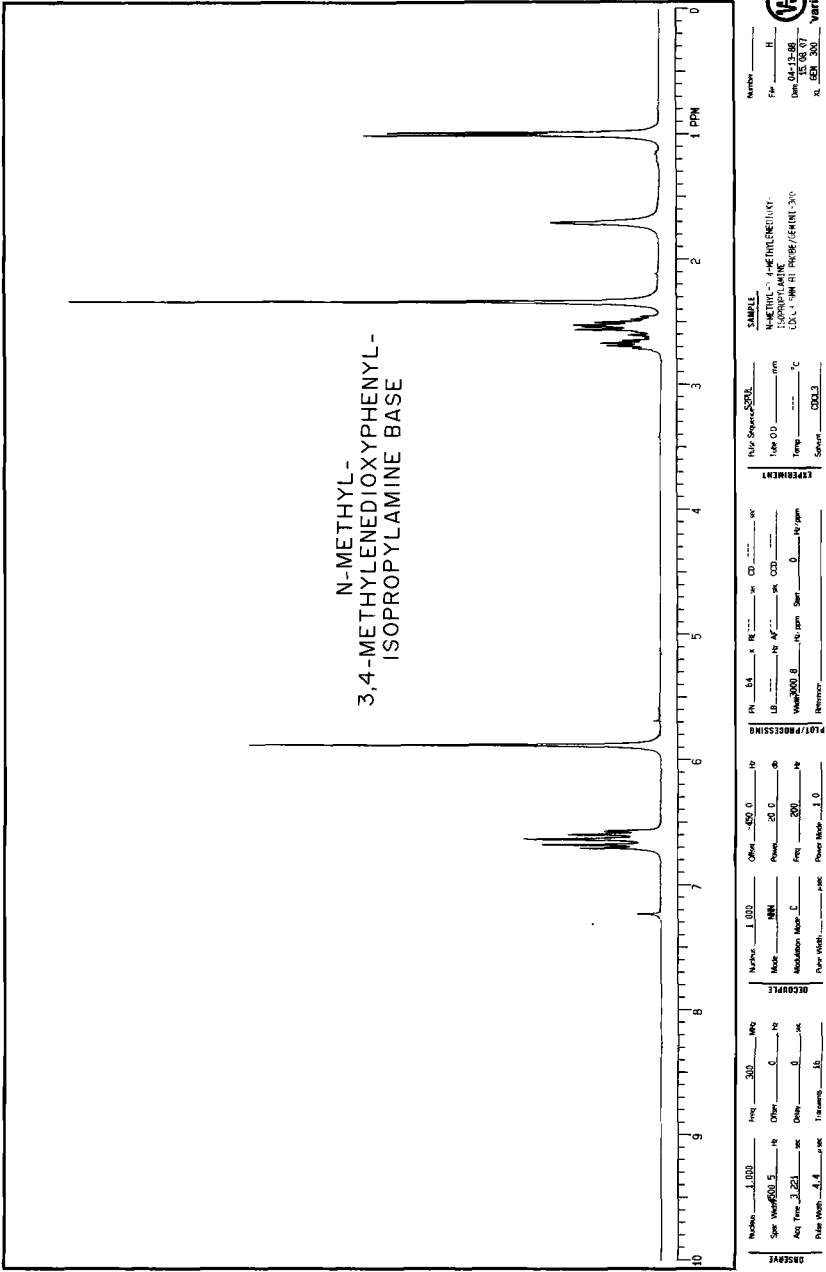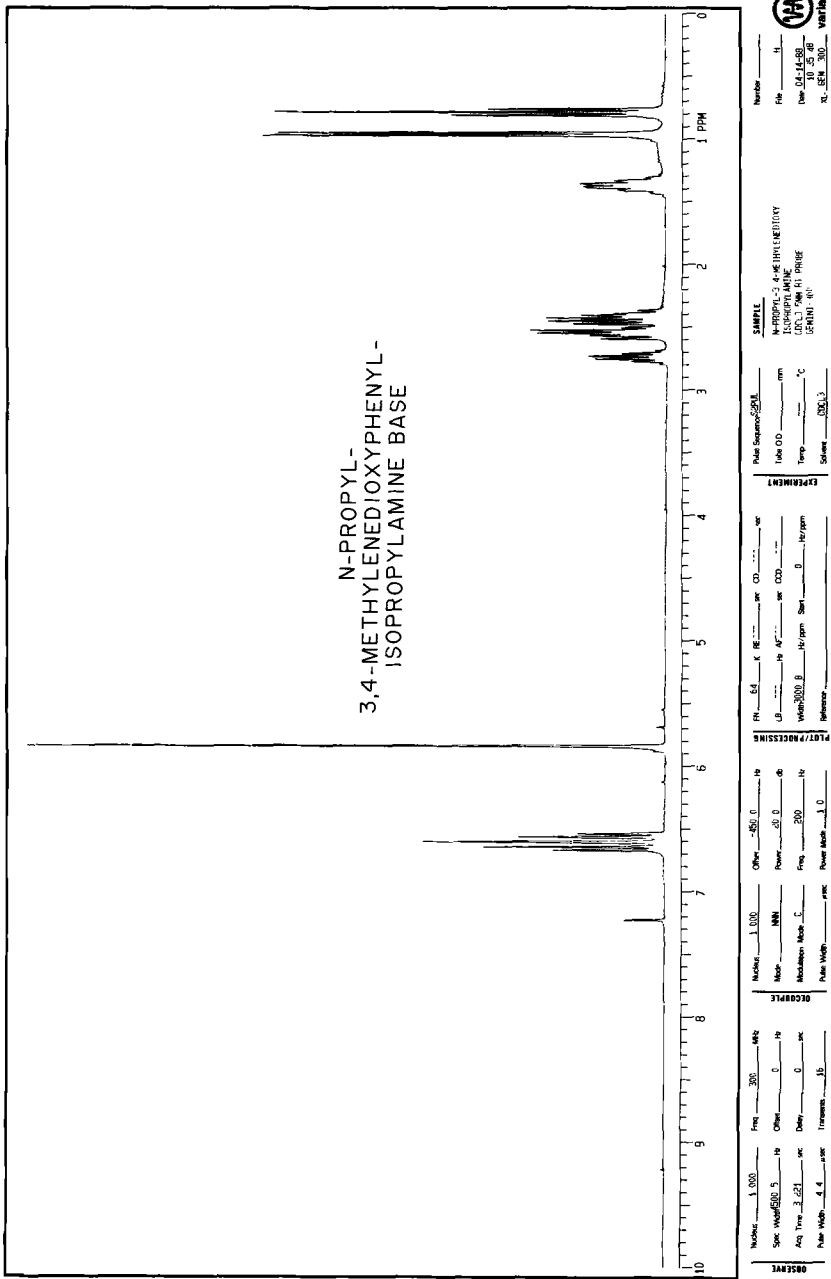
FIG. 12—*Continued.*

FIG. 12—*Continued.*

N-HYDROXY-
3,4-METHYLENEDIOXYPHENYL-
ISOPROPYLAMINE BASE

TABLE 7—*Melting points of MDA HCl and related compounds.*

No.	Compound	Melting Point, °C
1a	MDA HCl	185–186
2a	N-methyl MDA HCl	150–152
3a	N-ethyl MDA HCl	198.5–200.0
4a	N-propyl MDA HCl	191.5–192.5
5a	N-isopropyl MDA HCl	183.5–185.0
6a	N,N-dimethyl MDA HCl	169–170
7a	N-hydroxy MDA HCl	149.5–151.0
8	MDP-2-P oxime	86–88
9	MDP-2-P	a
10	MDP-2-Pol	b
11	N-acetyl MDA	91.5–93.0
12	N-acetyl-N-acetoxy MDA	72.5–74.5
13	O-acetyl MDP-2-P oxime	c

aLiquid at room temperature. Fluka Chemical, Ronkonkoma, New York, lists 120 to 122°C at 0.1 mm.

bLiquid at room temperature. Boiling point of 113 to 116°C recorded at 3 mm.

cLiquid at room temperature. Boiling point of 154 to 157°C recorded at 3 mm.

tion of analytical data. In addition, the author wishes to thank Tina Hellman, Secretary to the Laboratory Chief, for preparation of the manuscript.

References

[1] Mannich, C. and Jacobsohn, W., "Hydroxyphenylalkylamines and Dihydroxyphenylalkylmines," *Berichte,* Vol. 43, 1910, pp. 189-197.

[2] *Federal Register,* Vol. 50, No. 105, 23118, 31 May 1985.

[3] *Federal Register,* Vol. 53, No. 34, 5156-5158, 22 Feb. 1988.

[4] "Comprehensive Drug Abuse Prevention and Control Act of 1970," Public Law 91-513, 91st Congress, 27 Oct. 1970.

[5] "Controlled Substance Analogue Enforcement Act of 1986," Public Law 99-570, Title I, Subtitle E, 99th Congress, 27 Oct. 1986.

[6] Kram, T. C., Cooper, D. A., and Allen, A. C., "Behind the Identification of China White," *Analytical Chemistry,* Vol. 53, No. 12, Oct. 1981, pp. 1379A-1386A.

[7] Heikkila, R. E. and Nicklas, W. J., "Studies on the Mechanism of the Dopaminergic Neurotoxicity of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)," *Current Separations,* Vol. 7, No. 3, Bioanalytical Systems, Aug. 1986, pp. 52-54.

[8] Weingarten, H. L., "1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): One Designer Drug and Serendipity," *Journal of Forensic Sciences,* Vol. 33, No. 2, March 1988, pp. 588-595.

[9] Davis, G. C., Williams, A. C., Markey, S. P., Ebert, M. H., Caine, E. D., Reichert, C. M., and Kopin, I. J., "Chronic Parkinsonism Secondary to Intravenous Injection of Meperidine Analogues," *Psychiatry Research,* Vol. 1, July 1979, pp. 249-254.

[10] Borch, R. F., Bernstein, M. D., and Durst, H. D., "The Cyanohydridoborate Anion as a Selective Reducing Agent," *Journal of the American Chemical Society,* Vol. 93, No. 12, 16 June 1971, pp. 2897-2904.

[11] Braun, U., Shulgin, A. T., and Braun, G., "Centrally Active N-Substituted Analogs of 3,4-Methylenedioxyphenylisopropylamine (3,4-Methylenedioxyamphetamine)," *Journal of Pharmaceutical Sciences,* Vol. 69, No. 2, Feb. 1980, pp. 192-195.

[12] Braun, U., Shulgin, A. T., and Braun, G., "Study of the Central Nervous Activity and Analgesia of the N-Substituted Analogs of the Amphetamine Derivative 3,4-Methylenedioxyphenylisopropylamine," *Arzneimittel Forschung/Drug Research 30(I),* No. 5, 1980, pp. 825-830.

[13] Shulgin, A. T., "The Background and Chemistry of MDMA," *Journal of Psychoactive Drugs,* Vol. 18, No. 4, Oct/Dec. 1986, pp. 291-304.

[14] Wheals, B. B., "Forensic Aspects of High Pressure Liquid Chromatography," *Journal of Chromatography,* Vol. 122, 1976, pp. 85-105.

[15] Jane, I., "The Separation of a Wide Range of Drugs of Abuse by High-Pressure Liquid Chromatography," *Journal of Chromatography*, Vol. 111, 1975, pp. 227-233.

[16] Lukaszewski, T., "Spectroscopic and Chromatographic Identification of Precursors, Intermediates, and Impurities of 3,4-Methylenedioxyamphetamine Synthesis," *Journal of the Association of Official Analytical Chemists*, Vol. 61, No. 4, 1978, pp. 951-967.

[17] Bonelli, E., Story, M., Davis, F., and Squires, R., "Chemical Ionization Mass Spectrometry," *Application Tips*, No. 29, Finnigan Corp., Sunnyvale, CA, 1 April 1971.

[18] Morris, W. J., "Chemical Ionization of Three Amphetamines," *Application Tips*, No. 45, Finnigan Corp., Sunnyvale, CA, 17 July 1972.

Address requests for reprints or additional information to
Terry A. Dal Cason
Drug Enforcement Administration
North Central Laboratory
Rm. 500, 610 S. Canal St.
Chicago, IL 60607