Charles C. Clark,[1] *B.S.*

The Identification of Methoxy-*N*-Methylamphetamines

REFERENCES: Clark, C. C., **"The Identification of Methoxy-*N*-Methylamphetamines,"** *Journal of Forensic Sciences*, JFSCA, Vol. 29, No. 4, Oct. 1984, pp. 1056-1071.

ABSTRACT: Thirteen mono, di, and trimethoxy-*N*-methylamphetamines have been synthesized and characterized. Gas liquid chromatographic data and ultraviolet, infrared, proton magnetic resonance, and mass spectra are presented. The specificity of each technique for the identification of methoxy-*N*-methylamphetamines is discussed.

KEYWORDS: toxicology, methoxy-*N*-methylamphetamines, chromatographic analysis

Compounds that have an amphetamine backbone are seen frequently on the illicit market and have a high potential for abuse. The structure of methamphetamine (*N*-methylamphetamine) is shown in Fig. 1. Amphetamine itself is a sympathomimetic stimulant at normal dosage levels. High dosage levels can lead to a psychotomimetic syndrome [*1*]. The substitution of alkyl groups on the benzene ring produces compounds that cause no obvious stimulation of the central nervous system [*2,3*]. The substitution of methoxyl groups on the benzene ring leads to compounds whose effects are primarily psychotomimetic in nature. Examples of these which have been encountered in forensic science laboratories are 4-methoxyamphetamine (PMA) and 2,5-dimethoxyamphetamine (2,5-DMA). Psychotomimetic activity can be enhanced in methoxyamphetamines by the inclusion of an aryl methyl group, for example, 4-methyl-2,5-dimethoxyamphetamine (STP). Changing the length of the side chain to either two or four carbons decreases the potency but leaves the qualitative nature intact.

Psychotomimetic activity is also related to the number of methoxyl groups present; the more groups present, the greater the activity. The positions of the methoxyl groups on the ring strongly influence the degree of psychotomimetic activity. If only one methoxyl group is present, it must be in the *para* position for the compound to have psychotomimetic properties. Thus, neither 2- nor 3-methoxyamphetamine have psychotomimetic properties. If two or more methoxyl groups are present, one of them must be in the *para* position or two of the methoxyl groups must be *para* to each other. Thus, 2,4-, 3,4-, and 2,5-dimethoxyamphetamines have psychotomimetic properties while 2,3-, 2,6-, and 3,5-dimethoxyamphetamines do not. All six trimethoxyamphetamines are potent psychotomimetics [*4*]. Placing a methylenedioxy bridge on adjacent aryl carbons, either with [*5*] or without [*6,7*] additional methoxyl groups, maintains the psychotomimetic properties. Examples of these are 3,4-methylenedioxyamphetamine (MDA) and 3-methoxy-4, 5-methylenedioxyamphetamine (MMDA).

Much less is known about the effects of *N*-methylation. However, it has been shown that

Presented, in part, at the 35th Annual Meeting of the American Academy of Forensic Sciences, Cincinnati, OH, 15-19 Feb. 1983. Received 12 Nov. 1983; revised manuscript received 13 Jan. 1984; accepted for publication 14 Jan. 1984.

[1]Forensic chemist, Drug Enforcement Administration, Southeast Laboratory, Miami, FL.

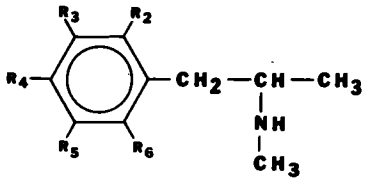

FIG. 1—*Structure of methamphetamine.* $R_2=R_3=R_4=R_5=R_6=H$.

MDA maintains its psychotomimetic properties with both *N*-methyl and *N*-ethyl substitution [*8*]. The *N*-methylation of amphetamine itself gives methamphetamine, whose effects are similar to those of amphetamine.

Methoxy-substituted amphetamines having one, two, or three methoxyl groups are controlled as Schedule I substances in the United States. Methoxy-substituted methamphetamines are not controlled. 2-methoxy-*N*-methylamphetamine, from the above discussion not expected to have psychotomimetic properties, is a sympathomimetic drug having legitimate uses in the treatment of bronchial asthma. Clearly there is a need for methods that will differentiate between closely related controlled and noncontrolled substances and between a legitimate drug and those having possible psychotomimetic properties. Procedures for the differentiation of 2-, 3-, and 4-methoxy-*N*-methylamphetamines have been published [*9*]. The purpose of this paper is to extend these procedures to cover the di and trimethoxy-*N*-methylamphetamines.

Experimental Procedure

The structures of the 13 methoxy-*N*-methylamphetamines used in this study are shown in Table 1. All 13 substituted *N*-methylamphetamines were prepared in this laboratory by the lithium aluminum hydride ($LiAlH_4$) reduction of the corresponding *N*-formylamphetamine obtained by reacting the corresponding amphetamine with formic acid. The amphetamines were obtained by the $LiAlH_4$ reduction of the β-methyl-nitrostyrenes formed by the condensation of nitroethane with the corresponding benzaldehydes. The aldehydes, with the exception of 2,6-dimethoxybenzaldehyde, were purchased from commercial sources. The 2,6-dimethoxybenzaldehyde was prepared by reduction of 2,6-dimethoxybenzoic acid with $LiAlH_4$, followed by oxidation of the resulting alcohol to the aldehyde with chromium trioxide, using the procedure of Poos et al [*10*]. The 2,3,5- and 2,3,6-trimethoxy-*N*-methylamphetamines were

TABLE 1—*Structure of methoxy-*N*-methylamphetamines studied.*

Compound	R_2	R_3	R_4	R_5	R_6
I	OCH_3	H	H	H	H
II	H	OCH_3	H	H	H
III	H	H	OCH_3	H	H
IV	OCH_3	OCH_3	H	H	H
V	OCH_3	H	OCH_3	H	H
VI	OCH_3	H	H	OCH_3	H
VII	OCH_3	H	H	H	OCH_3
VIII	H	OCH_3	OCH_3	H	H
IX	H	OCH_3	H	OCH_3	H
X	OCH_3	OCH_3	OCH_3	H	H
XI	OCH_3	H	OCH_3	OCH_3	H
XII	OCH_3	H	OCH_3	H	OCH_3
XIII	H	OCH_3	OCH_3	OCH_3	H

not prepared because of the lack of a commercial source for suitable starting material. The amines were isolated as their hydrochloride (HCl) salts and purified by recrystallization from an isopropanol-hexane mixture. The free bases were regenerated with sodium carbonate solution and extracted with chloroform. Each compound gave only a single gas liquid chromatographic (GLC) peak, indicating relatively high purity. The phenyl isothiocyanate derivative of each of the 13 methoxy-*N*-methylamphetamines was prepared by extraction of about 50 mg of the free base into chloroform, followed by the addition of 2 drops of phenyl isothiocyanate. This reaction is shown in Fig. 2. After evaporation of the solvent on a steam bath, a small amount of hexane was added to induce crystallization.

Ultraviolet spectra were recorded on a Perkin-Elmer 552A UV/VIS spectrophotometer and infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrophotometer. Gas liquid chromatograms were obtained on a Hewlett-Packard 5790A gas chromatograph. Electron-impact mass spectra were obtained on a Finnigan 4530 mass spectrometer equipped with a Data General Nova 4 data system and operated at an ionization voltage of 70 EV. The underivatized *N*-methylamphetamine bases were introduced into the mass spectrometer via the GLC inlet system, using a 1-mg/mL concentration in methanol. The phenyl isothiocyanate (PIT) derivatives were introduced via the solid probe inlet system. The proton magnetic resonance (PMR) spectra of the 13 methoxy-*N*-methylamphetamine bases in deuterochloroform ($CDCl_3$) were obtained on a Varian EM390 NMR spectrometer. Tetramethylsilane (TMS) was used as the internal reference.

In each instance the spectral data developed are consistent with the assigned structure.

Results and Discussion

Ultraviolet Spectra

The ultraviolet spectra of the 13 compounds, in acidified ethanol, are listed in Table 2. Certain spectra are nearly identical and all spectra closely resemble those of their corresponding non-*N*-methylated counterparts [*11-13*].

Gas Liquid Chromatography

The GLC results obtained using two stationary phases, OV-1 and OV-17, are shown in Table 3. The order of emergence of the compounds is the same for both columns. Separation of the isomers is similar on the two columns and any of the isomers can be distinguished from any of the other isomers on either column. In each instance, the *N*-methylamphetamine elutes after its nonmethylated counterpart.

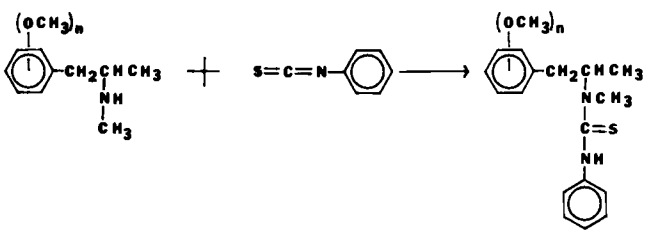

FIG. 2—*Reaction of methoxy-*N*-methylamphetamines with phenyl isothiocyanate to form PIT derivatives.*

TABLE 2—*Ultraviolet data.*[a]

Compound	Wavelength of A_{max}, nm[b]	Wavelength of A_{min}, nm[b]
I	277 270	274 238
II	278 272	275 238
III	280 274	278 241
IV	272	243
V	276	247
VI	291 226	247
VII	278 272	276 243
VIII	277	250
IX	280 274	277 248
X	273	247
XI	290 230	254
XII	267	253
XIII	268	253

[a]All spectra were determined using acidified ethanol as a solvent.
[b]A = absorbance.

TABLE 3—*Gas liquid chromatographic data: retention times relative to 2,5-dimethoxyamphetamine (2,5-DMA).*[a]

Compound	3%OV-1 (150°C)	3% OV-17 (170°C)
I	0.49	0.41
II	0.57	0.48
III	0.60	0.51
IV	0.92	0.82
V	1.29	1.23
VI	1.20	1.13
VII	1.09	1.02
VIII	1.33	1.29
IX	1.44	1.40
X	1.63	1.56
XI	2.59	2.66
XII	2.50	2.49
XIII	2.78	2.99
2,5-DMA	1.00 (5.30 min)	1.00 (5.28 min)

[a]Columns used were 1.8-m (6-ft) by 4-mm inside diameter glass.

Infrared Spectroscopy

The infrared spectra of the di and trimethoxy-*N*-methylamphetamine hydrochlorides (1% in KBr discs) are shown in Figs. 3 through 12. The infrared spectra of the monomethoxy-*N*-methylamphetamine hydrochlorides have been previously published [*14*]. The spectra of the hydrochlorides are all clearly different, both from each other and from those of their non-*N*-methylated counterparts. The HCl salts of the methoxy-*N*-methylamphetamines are very hygroscopic and several were obtained as crystalline solids only with difficulty. Obtaining these salts as crystalline solids from small amounts of amines may not be possible. The spectrum of each phenyl isothiocyanate derivative is also unique and can provide unequivocal identification of the methoxy-*N*-methylamphetamines. This derivative has the advantages of being nonhygroscopic and easily obtained as crystalline solids from small amounts of the amines.

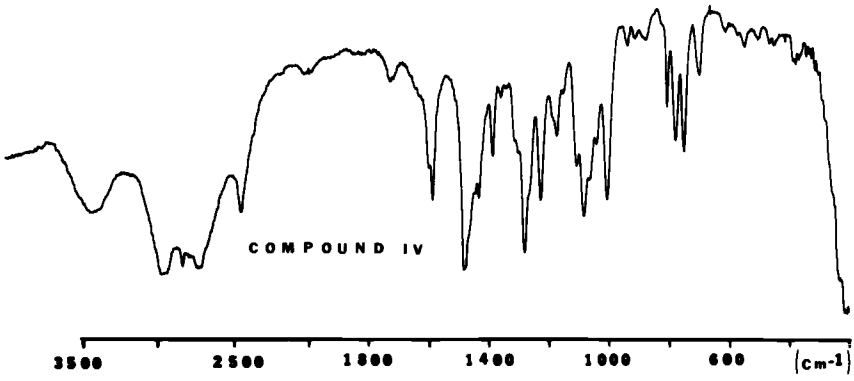

FIG. 3—*IR spectrum of 2,3-dimethoxy-*N*-methylamphetamine HCl in KBr.*

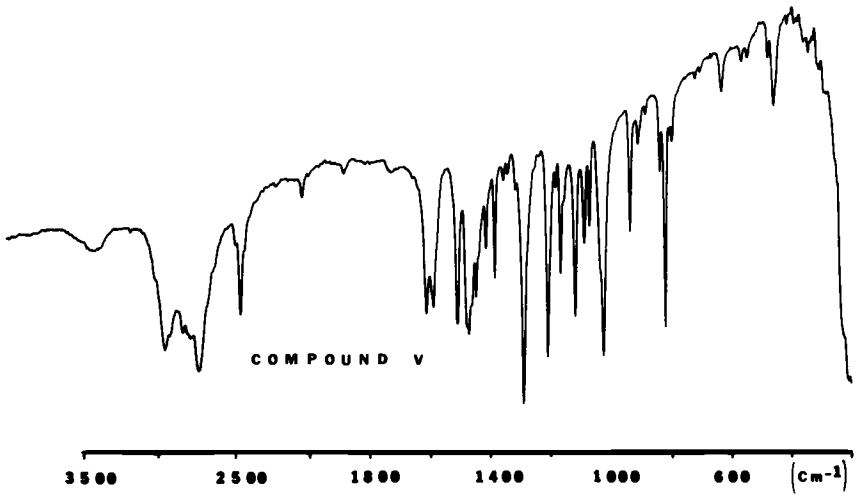

FIG. 4—*IR spectrum of 2,4-dimethoxy-*N*-methylamphetamine HCl in KBr.*

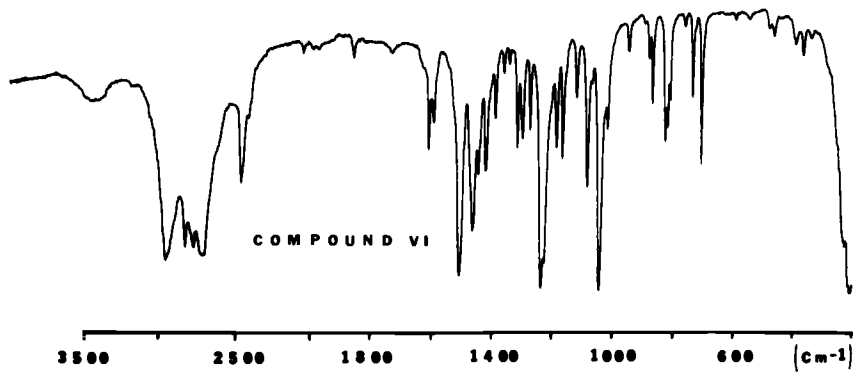

FIG. 5—*IR spectrum of 2,5-dimethoxy-*N*-methylamphetamine HCl in KBr.*

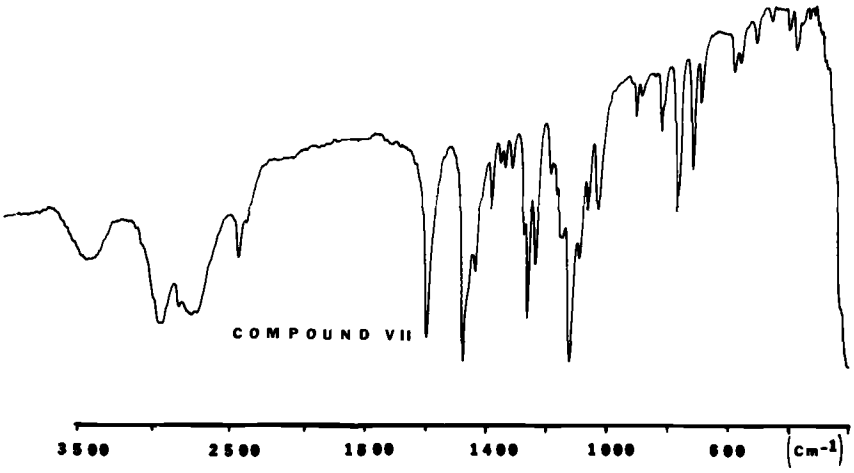

FIG. 6—*IR spectrum of 2,6-dimethoxy-*N*-methylamphetamine HCl in KBr.*

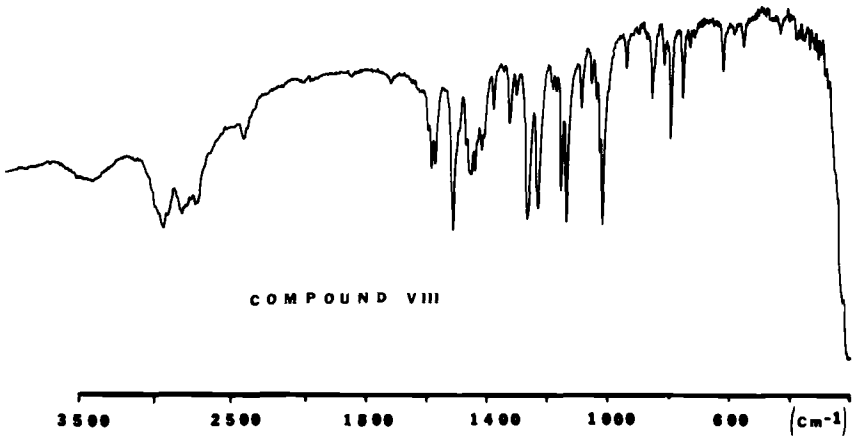

FIG. 7—*IR spectrum of 3,4-dimethoxy-*N*-methylamphetamine HCl in KBr.*

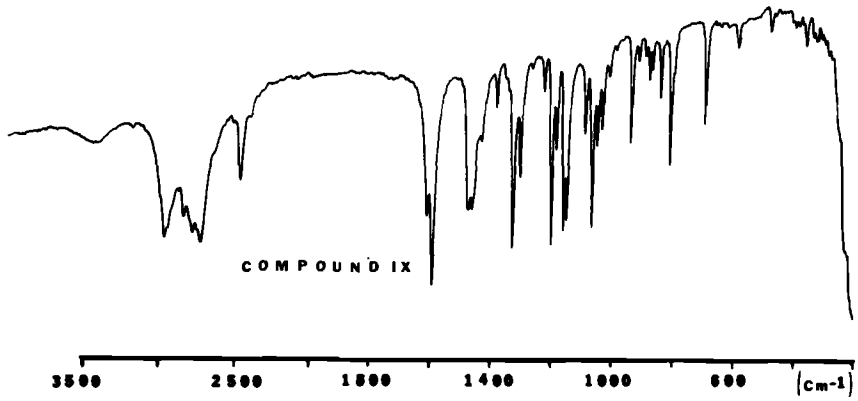

FIG. 8—*IR spectrum of 3,5-dimethoxy-*N*-methylamphetamine HCl in KBr.*

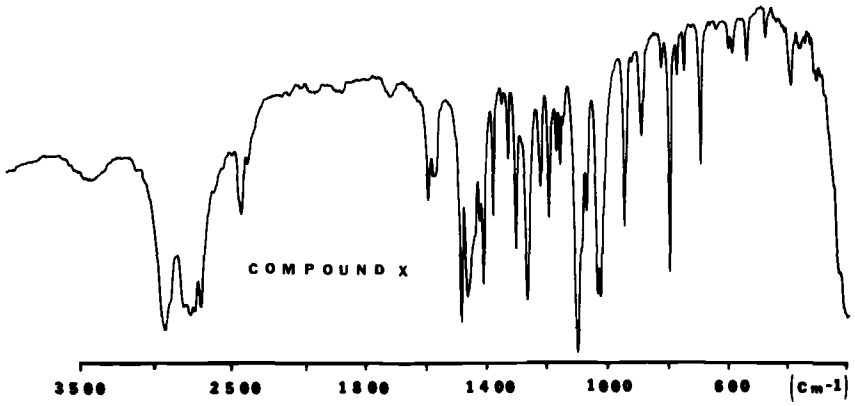

FIG. 9—*IR spectrum of 2,3,4-trimethoxy-*N*-methylamphetamine HCl in KBr.*

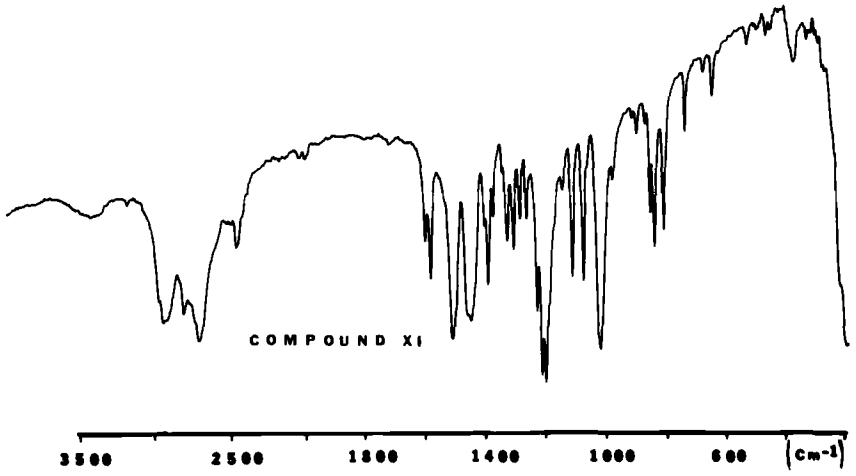

FIG. 10—*IR spectrum of 2,4,5-trimethoxy-*N*-methylamphetamine HCl in KBr.*

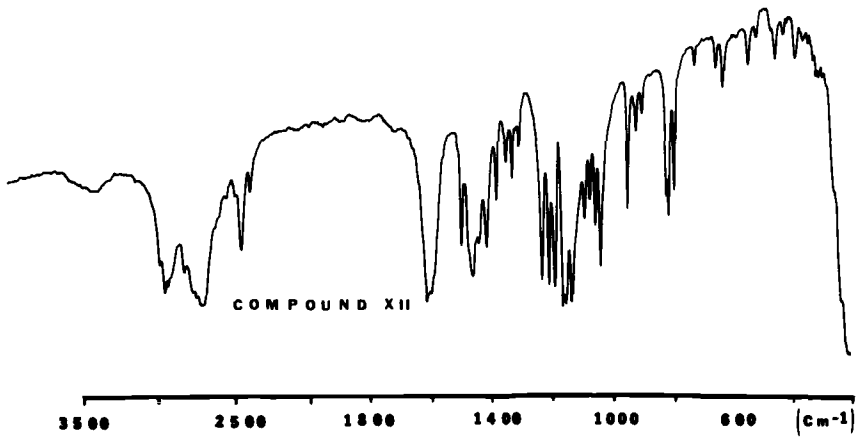

FIG. 11—*IR spectrum of 2,4,6-trimethoxy-*N*-methylamphetamine HCl in KBr.*

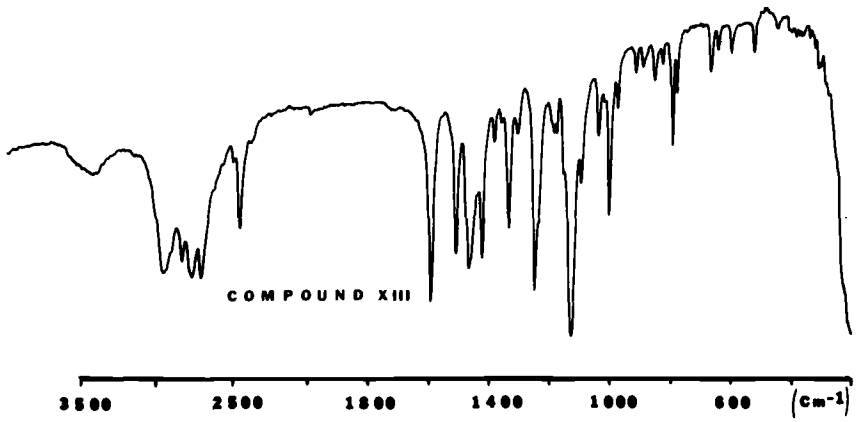

FIG. 12—*IR spectrum of 3,4,5-trimethoxy-*N*-methylamphetamine HCl in KBr.*

Mass Spectroscopy of Bases

All 13 *N*-methylamphetamines follow the established route of fragmentation [*15*] and have a base peak of *m/z* 58 ($CH_3CH-N^+HCH_3$). This base peak distinguishes the *N*-methylamphetamines from their non-*N*-methylated counterparts, which have a base peak of *m/z* 44. The next most intense signal is at *m/z* 122, 152, and 182 for the mono, di, and trimethoxy-*N*-methylamphetamines, respectively. This fragment is thought to arise from amino proton transfer to the benzylic position [*15*]. The intensities of the other peaks are usually less than 5%.

Proton Magnetic Resonance Spectra

The PMR spectra of the bases in $CDCl_3$ are shown in Figs. 13 through 25. The presence of the *N*-methyl singlet at about 2.4 ppm distinguishes *N*-methylamphetamines from the non-methylated counterparts. However, certain pairs of spectra bear very close resemblances: 2-methoxy- and 2,3,4-trimethoxy-*N*-methylamphetamines, 3,5-dimethoxy- and 3,4,5-trimethoxy-*N*-methylamphetamines, and 2,5-dimethoxy- and 2,4,6-trimethoxy-*N*-methylamphetamines. Careful integration of the spectra can, in each case, differentiate between the similar pairs of spectra.

Mass Spectroscopy of PIT Derivatives

All 13 *N*-methylamphetamine PIT derivatives have a base peak at *m/z* 58, distinguishing them from their non-*N*-methylated counterparts which have a base peak at *m/z* 44. All give a discernable molecular ion from which subtraction of 135 mass units reveals the molecular weight of the starting *N*-methylamphetamine. The second most intense peak in all 13 spectra is at M−166. This peak, suspected to be the methoxy-substituted propeneyl benzylic ion, also allows the determination of the substitution group. Addition of 31 mass units to this *m/z* yields the molecular weight of the starting *N*-methylamphetamine. The intensities of other peaks are usually less than 5%.

Conclusion

Data are presented indicating the specificity of some techniques for the differentiation of 13 *N*-methylamphetamines, both from each other and from their non-*N*-methylated counterparts. Ultraviolet spectroscopy is shown to be of limited value because of similar spectra ob-

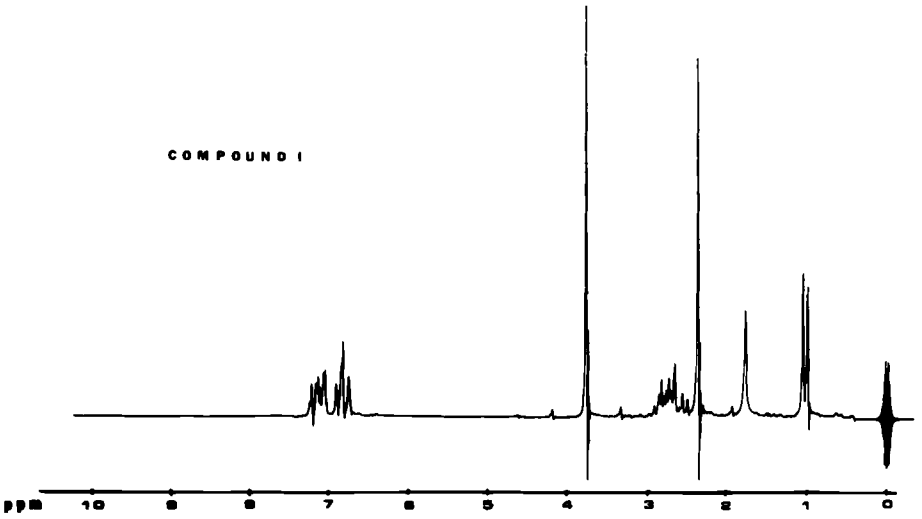

FIG. 13—*NMR spectrum of 2-methoxy-N-methylamphetamine base in* $CDCl_3$.

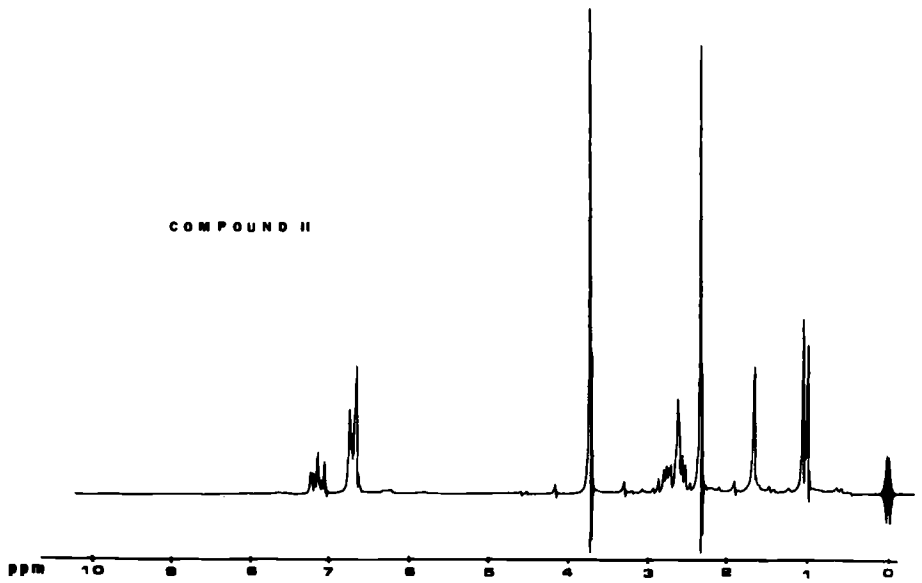

FIG. 14—*NMR spectrum of 3-methoxy-N-methylamphetamine base in* $CDCl_3$.

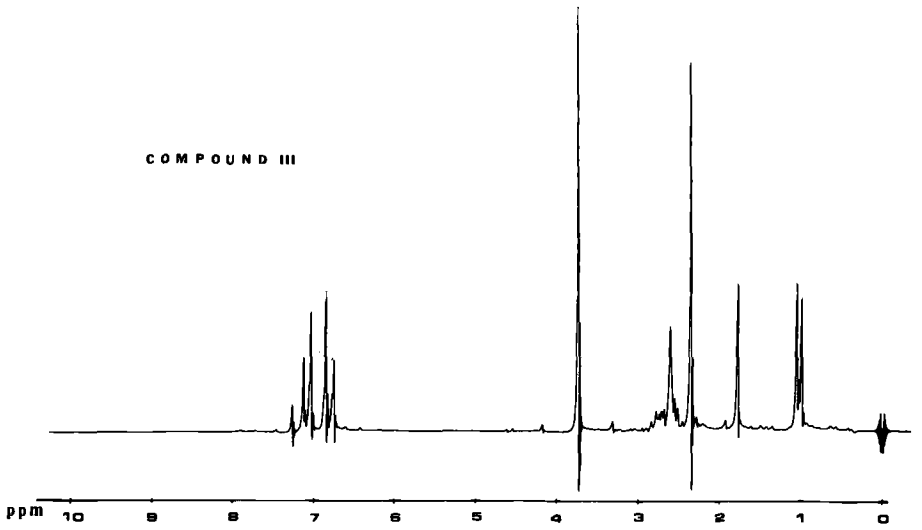

FIG. 15—*NMR spectrum of 4-methoxy-*N*-methylamphetamine base in* $CDCl_3$.

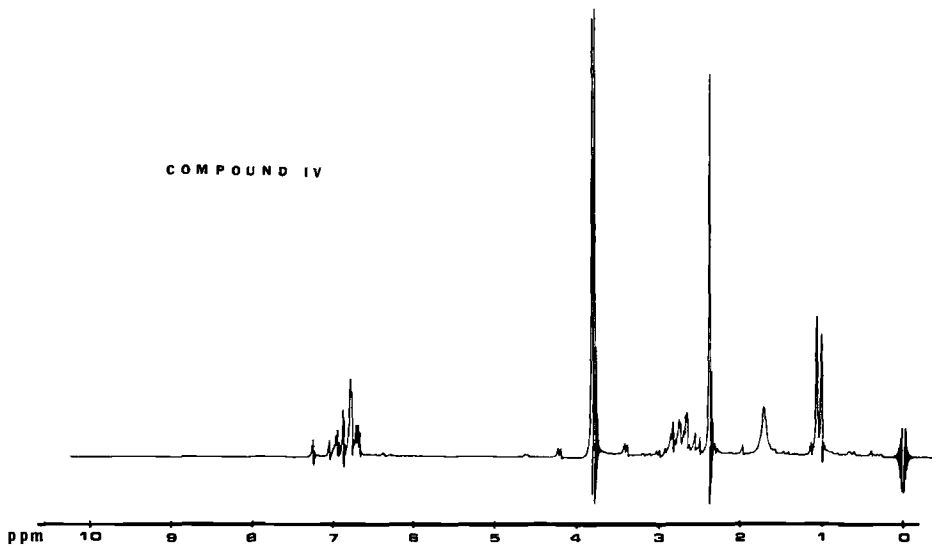

FIG. 16—*NMR spectrum of 2,3-dimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

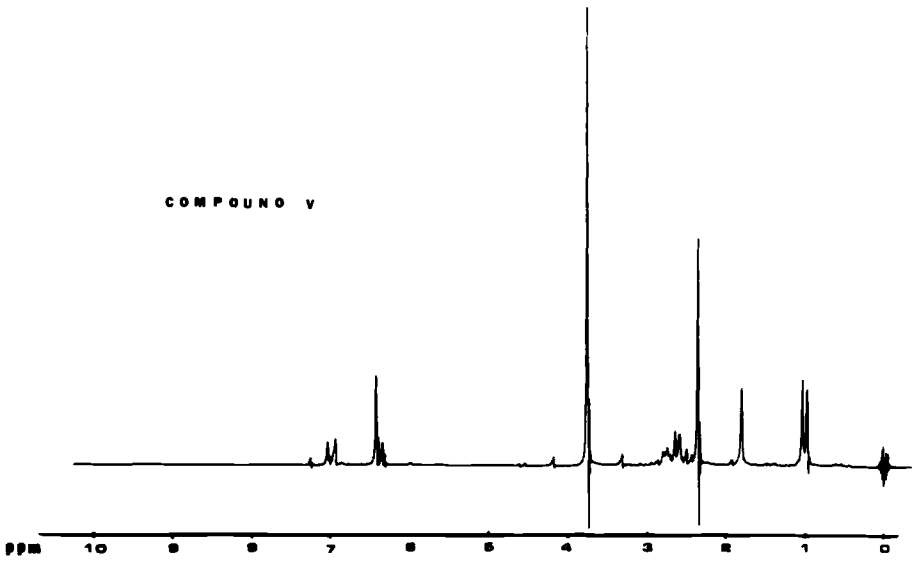

FIG. 17—*NMR spectrum of 2,4-dimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

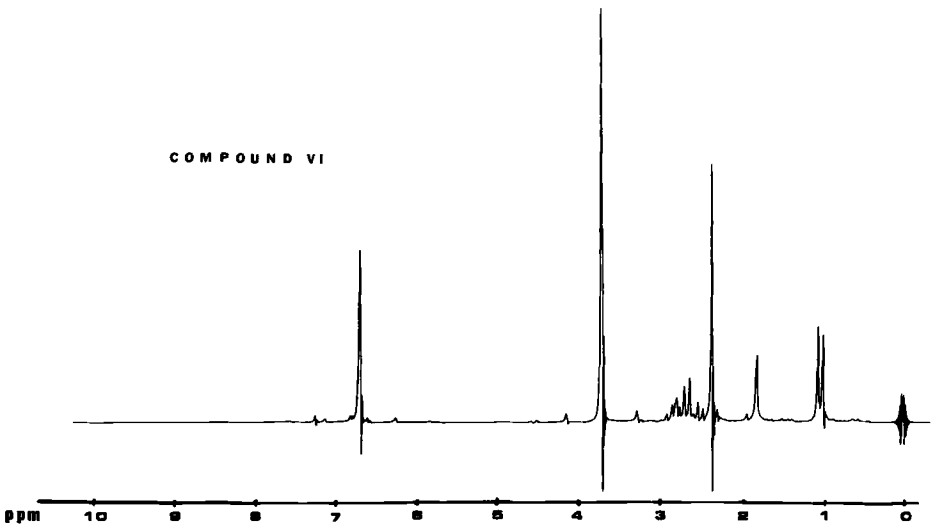

FIG. 18—*NMR spectrum of 2,5-dimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

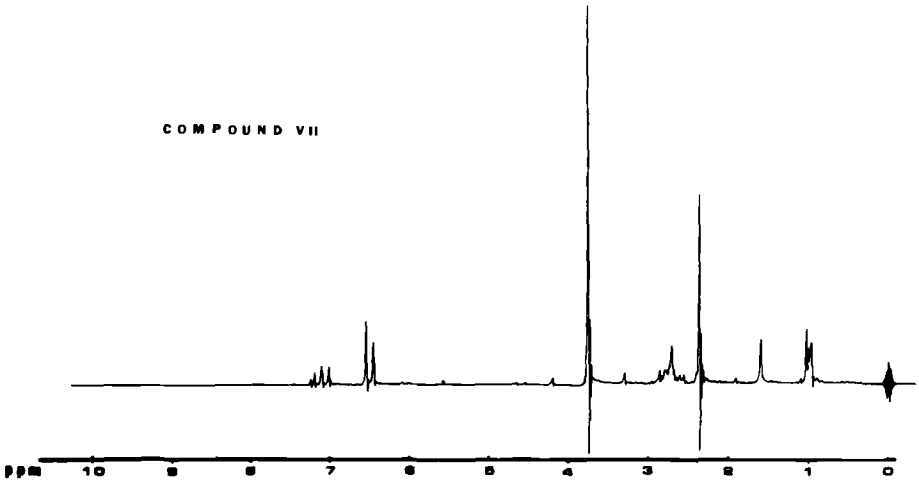

FIG. 19—*NMR spectrum of 2,6-dimethoxy*-N-*methylamphetamine base in* $CDCl_3$.

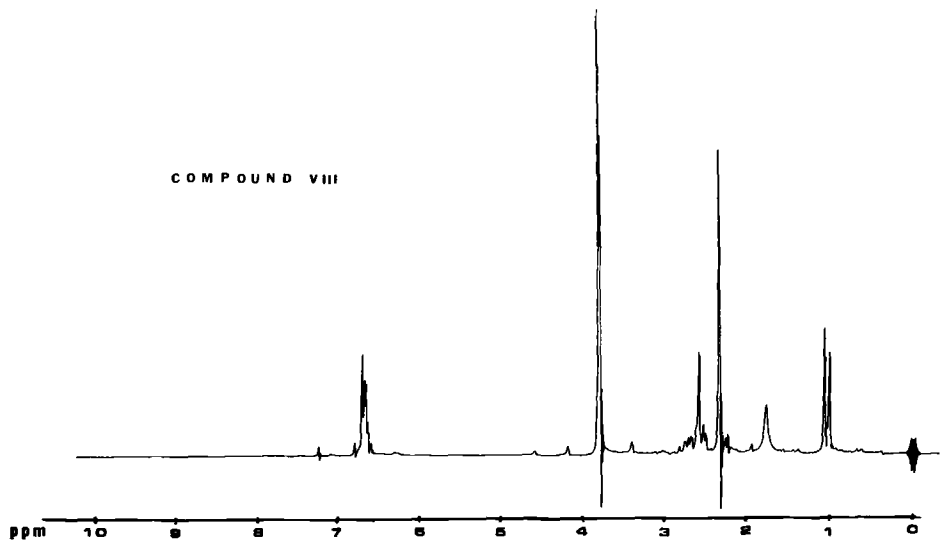

FIG. 20—*NMR spectrum of 3,4-dimethoxy*-N-*methylamphetamine base in* $CDCl_3$.

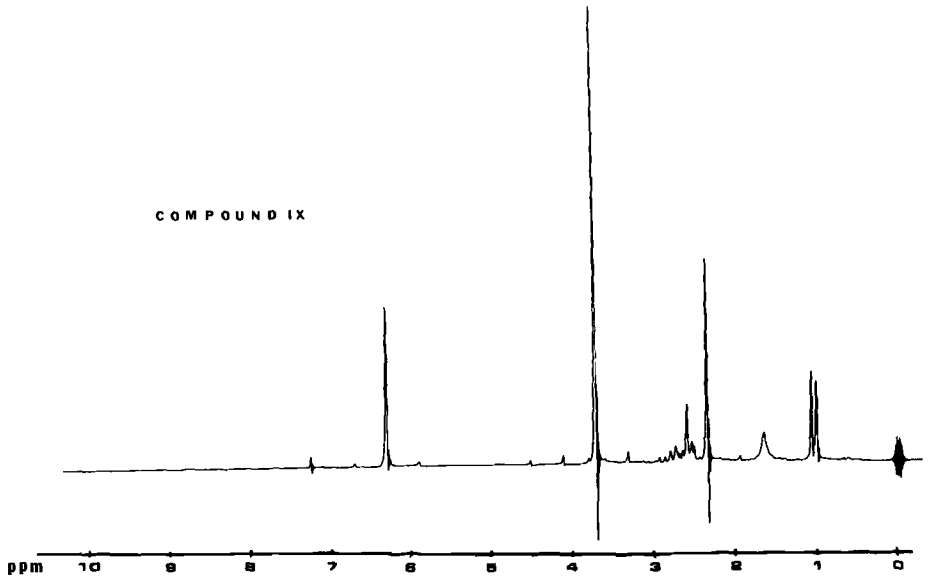

FIG. 21—*NMR spectrum of 3,5-dimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

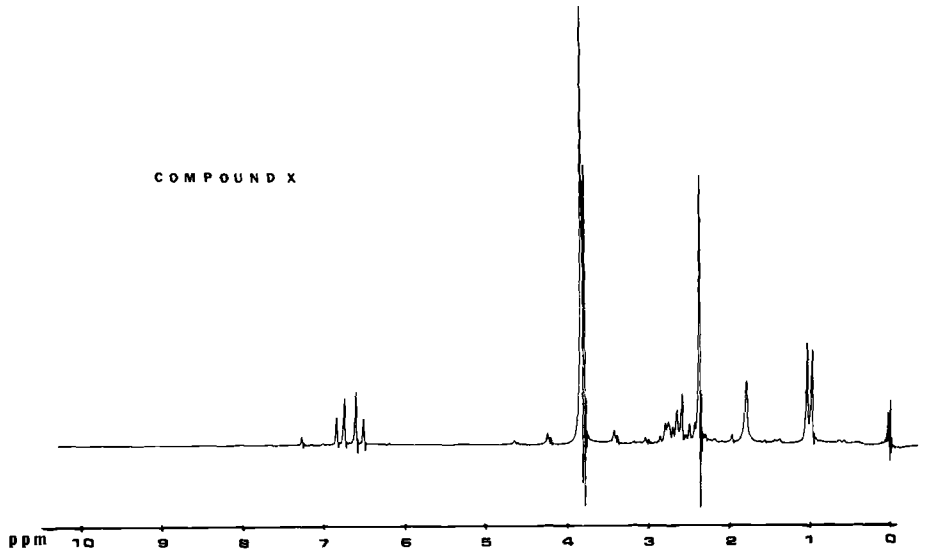

FIG. 22—*NMR spectrum of 2,3,4-trimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

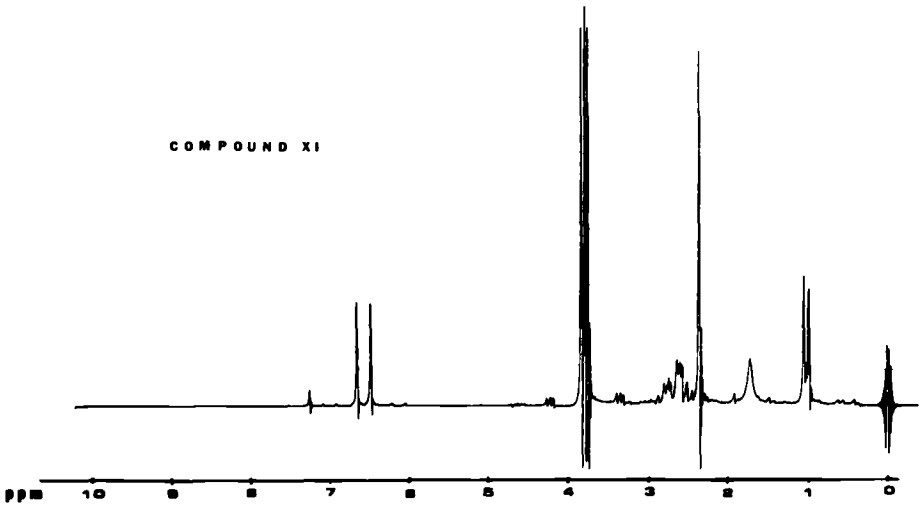

FIG. 23—*NMR spectrum of 2,4,5-trimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

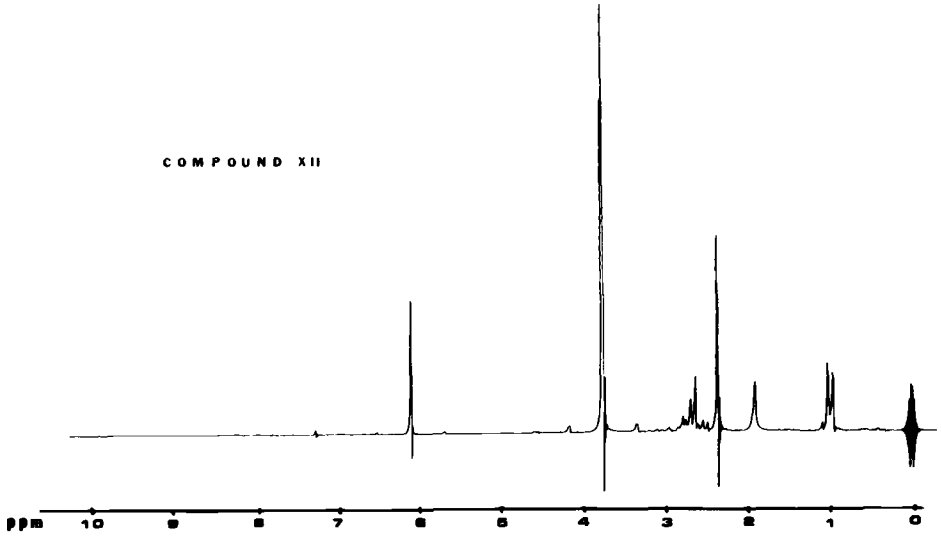

FIG. 24—*NMR spectrum of 2,4,6-trimethoxy-*N*-methylamphetamine base in* $CDCl_3$.

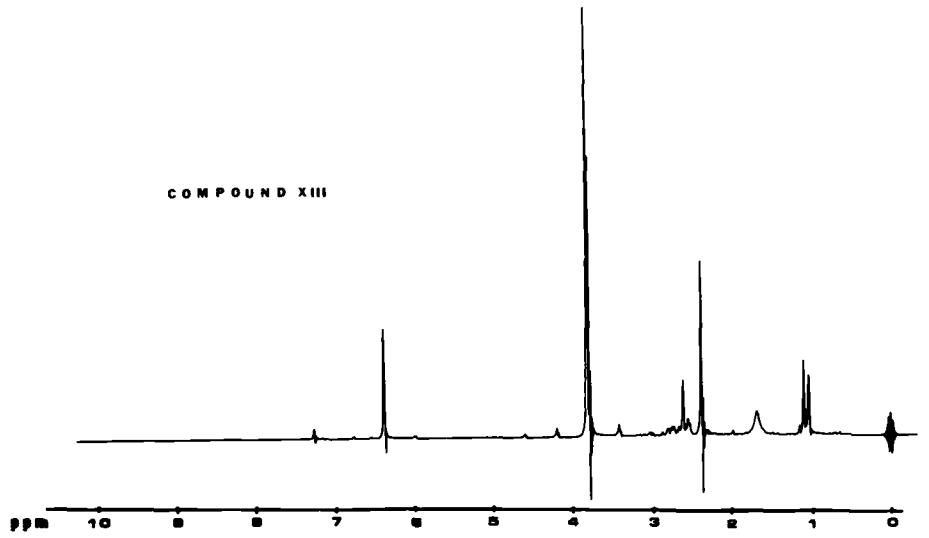

FIG. 25—*NMR spectrum of 3,4,5-trimethoxy*-N-*methylamphetamine base in* $CDCl_3$.

tained from the *N*-methylamphetamines and their non-*N*-methylated analogs. GLC separates all 13 *N*-methylamphetamines from each other and their nonmethylated analogs. Infrared spectroscopy can supply identification of the 13 methoxy-*N*-methylamphetamines, either as their difficult-to-obtain HCl salts or as the phenyl isothiocyanate derivatives. PMR spectroscopy can provide identification of the amines only if the spectrum is carefully integrated. Electron-impact mass spectra of both the unreacted bases and the phenyl isothiocyanate derivatives can indicate the number of methyl groups present. However, the exact determination of their ring positions by this technique is difficult in the absence of standard materials. Combining techniques such as GLC and mass spectroscopy can provide identification of any of the 13 methoxy-*N*-methylamphetamines studied.

References

[1] Connell, P. H., *Maudsley Monographs Number Five*, Oxford University Press, London, England, 1958.

[2] Marsh, D. F. and Herring, D. A., *Journal of Pharmacology and Experimental Therapeutics*, Vol. 100, Nov. 1950, pp. 298-308.

[3] Harris, S. C. and Worley, R. C., *Proceedings of the Society for Experimental Biology and Medicine*, Vol. 95, 1957, pp. 212-220.

[4] Shulgin, A. T., Sargent, C., and Naranjo, C., *Nature*, Vol. 221, 8 Feb. 1969, pp. 537-541.

[5] Shulgin, A. T., *Experimentia*, Vol. 20, No. 7, July 1964, pp. 366-367.

[6] Alles, G. A., in *Neuropharmacology, Transactions of the Fourth Conference*, H. A. Abramson, Ed., Madison Printing Co., Madison, NJ, 1959, p. 181.

[7] Naranjo, C., Shulgin, A. T., and Sargent, T., *Medicina et Pharmacologia Experimentalis*, Vol. 17, July 1967, pp. 359-364.

[8] Braun, U., Shulgin, A. T., and Braun, G., *Journal of Pharmaceutical Sciences*, Vol. 69, No. 2, Feb. 1980, pp. 192-195.

[9] Bailey, K., By, A. W., Legault, D., and Verner, D., *Journal of the Association of Official Analytical Chemists*, Vol. 58, No. 1, Jan. 1975, pp. 62-69.

[10] Poos, G. I., Arth, G. E., Beyler, R. E., and Sarett, L. H., *Journal of the American Chemical Society*, Vol. 75, Jan. 1953, pp. 422-429.

[11] Bailey, K., By, A. W., Legault, D., and Verner, D., *Journal of the Association of Official Analytical Chemists*, Vol. 58, No. 1, Jan. 1975, pp. 62-69.

[12] Bailey, K., Beckstead, H. D., Legault, D., and Verner, D., *Journal of the Association of Official Analytical Chemists*, Vol. 57, Sept. 1974, pp. 1134-1143.

[*13*] Bailey, K., Legault, D., and Verner, D., *Journal of the Association of Official Analytical Chemists*, Vol. 57, No. 1, Jan. 1974, pp. 70–78.
[*14*] Bailey, K., By, A. W., Legault, D., and Verner, D., *Journal of the Association of Official Analytical Chemists*, Vol. 58, No. 1, Jan. 1975, pp. 62–69.
[*15*] Bellman, S. W., *Journal of the Association of Official Analytical Chemists*, Vol. 51, No. 1, Jan. 1968, pp. 164–175.

Address requests for reprints or additional information to
Charles C. Clark
Drug Enforcement Administration
Southeast Laboratory
5205 N.W. 84th Ave.
Miami, FL 33166