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Liquid Chromatographic and Mass Spectral Analysis of 1-(3,4-Methylenedioxyphenyl)-1-propanamines: Regioisomers of the 3,4-Methylenedioxyamphetamines

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Abstract

The title 1-(3,4-methylenedioxyphenyl)-1-propanamines represent positional isomers of the *N*-substituted 3,4-methylenedioxyamphetamines, clandestinely produced drugs frequently encountered by forensic laboratories. These propanamines are prepared by reductive amination of 3,4-methylenedioxypropiophenone with a series of *N*-alkylamines. Analytical methods are developed to distinguish these compounds from the MDA series. The ultraviolet spectra of the propanamines are very similar to those of the MDAs with absorption maxima at 284 and 236 nm. The propanamines are separated under reversed-phase liquid chromatographic conditions by using a C_{18} stationary phase and a mobile phase of acidic (pH 3) acetonitrile containing methanol and triethylamine. The relative retention properties of these compounds parallel those observed in the MDA series. The electron impact mass spectra of the propanamines are determined by GC–MS, and the fragmentation pattern clearly distinguishes these compounds from those of the MDA series having the same molecular weight.

Introduction

3,4-Methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy", or XTC, Figure 1a) continue to be encountered by forensic laboratories in the United States and Canada. The popularity of these illicit drugs appears to be a result of their ability to enhance empathy and reduce the fear and anxiety that accompanies the discussion of emotionally unpleasant events (1,2). Recently, a number of "designer drug" analogues of MDA, including the *N*-ethyl, *N,N*-dimethyl, and *N*-hydroxy derivatives, have been encountered in clandestinely produced drug samples (3–5). These compounds all appear to be prepared from the commercially available 1-(3,4-methylenedioxyphenyl)-2-propanone via reductive amination with the appropriate amine (6). The continued interest in designer analogues of the MDA type suggests the possibility of the appearance of additional derivatives derived by the same synthetic method using alternative available starting ketones. One such commercially available ketone is 3,4-methylenedioxypropiophenone, which upon reductive amination would yield the 1-(3,4-methylenedioxyphenyl)-1-propanamines (Figure 1b), positional isomers of the MDA series. Such a structural modification would be expected to yield compounds with lowered CNS stimulant activity. However, no specific pharmacological data for these propanamines relative to the MDA-type compounds is available. Also, analytical methods to distinguish MDA derivatives from such propanamine positional isomers have not been reported.

Experimental

Instrumentation. The liquid chromatograph consisted of a Waters Associates Model 6000A pump, U6K injector, Model 440 UV detector with a dual wavelength accessory operated at 254 and 280 nm, and a Houston Instruments OmniScribe dual pen recorder. Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier Transform infrared (FTIR) spectrophotometer. Ultraviolet spectra were recorded on a Shimadzu Instruments Model UV-160 spectrophotometer. Nuclear magnetic resonance spectra (^1H) were determined with a Varian T-60A spectrometer.

The electron impact mass spectra were obtained with a Hewlett-Packard 5970B mass selective detector. The ionization voltage was 70 eV and the source temperature was 220°C. The individual amine hydrochlorides were dissolved in methanol (1 mg/mL), and 0.5 μL were introduced into the mass spectrometer via a gas chromatograph equipped with a 12-m × 0.31-mm i.d. fused silica column with a 0.52-μm thickness of OV-1. The column temperature was programmed from 70° to 150°C at a rate of 15°/min and from 150° to 250°C at a rate of 25°/min. The split ratio for the GC was 10:1 and all samples had eluted in approximately 7 min.

Liquid Chromatographic Procedures. The analytical column was 30 cm × 3.9 mm i.d., packed with μBondapak C_{18} (Waters Associates). The analytical column was preceded by a 7-cm × 2.1-mm i.d. guard column packed with CO: Pell ODS (Whatman). The amine hydrochlorides (1 mg/mL) were dissolved in HPLC grade methanol and separated with a mobile phase of pH 3.0 phosphate buffer, HPLC grade acetonitrile, methanol, and triethylamine (600:75:25:1.5). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate (NaH_2PO_4) in 1 L of double-distilled water and adjusting the

pH to 3.0 with H_3PO_4. The mobile phase flow rate was 1.5 mL/min and the detector was operated at 0.2 AUFS. A 15-μL aliquot of each amine solution was injected into the liquid chromatograph.

Synthesis of the 1-(3,4-methylenedioxyphenyl)-1-propanamines. A solution of 3,4-methylenedioxypropiophenone (10 mmol), ammonium acetate or alkyl amine (100 mmol), and sodium cyanoborohydride (25 mmol) in methanol (25 mL) was stirred at room temperature for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and the remaining residue was suspended in dichloromethane (50 mL). The dichloromethane suspension was extracted with 3 N HCl (2 × 75 mL) and the combined acid extracts were made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 × 100 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. Filtration, followed by evaporation of the filtrate solvent under reduced pressure, gave the product amines in the free base form. Treatment of the bases with ethereal HCl afforded the products as hydrochloride salts, which were isolated by filtration and recrystallized from mixtures of anhydrous ether and absolute ethanol. The structures of the hydrochlorides of all products were confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the products was established by GC–MS and the liquid chromatographic analyses.

Results and Discussion

A variety of designer drug analogues of 3,4-methylenedioxyamphetamine (MDA) have become popular drugs of abuse. In recent years several *N*-substituted derivatives of MDA including *N*-methyl, *N,N*-dimethyl, *N*-ethyl, and *N*-hydroxyl MDA have appeared as street drugs. Also, homologues of these compounds, such as the 1-(3,4-methylenedioxyphenyl)-3-butanamines (HMDAs) have been encountered. The appearance of the HMDA series is believed to be the result of selecting the incorrect ketone starting material (3,4-methylenedioxyphenyl-3-butanone) for the synthesis of drugs of this type. The limited pharmacological data available (7) shows that the acute toxicity of the HMDA series is equal to or greater than the MDAs in mice. These results suggest that the HMDAs constitute no less a hazard in humans than MDA. However, little information is available on the hallucinogenic activity of the HMDAs. Based on the appearance of the HMDA series, it is reasonable to suspect that other MDA analogues may emerge in the illicit drug market as a result of syntheses using other available ketones such as 3,4-methylenedioxypropiophenone.

The title 1-(3,4-methylenedioxyphenyl)-1-propanamines were prepared by the reductive amination method reported previously for the synthesis of *N*-substituted derivatives of MDA (5). With this procedure, the commercially available ketone 3,4-methylenedioxypropiophenone is allowed to react with the appropriate amines in the presence of sodium cyanoborohydride (Figure 2). In these syntheses, imine intermediates form initially as a result of reaction between the ketone and the amine. Once formed, the imines are reduced to yield the 1-propanamine products by sodium cyanoborohydride (6). Sodium cyanoborohydride is used as the reducing agent because it, unlike other hydride reducing agents, reduces only the intermediate imine and not the starting ketone. The 1-propanamine products obtained were isolated as the free bases by an extraction sequence, and converted to the hydrochloride salts upon treatment with ethereal HCl. The structures of these products were confirmed by IR and NMR spectroscopic methods. These 1-propanamines are regioisomeric with the MDAs (2-propanamines) and therefore compounds from each of these series having the same *N*-substituent have identical empirical formulas and molecular weights. Thus, it is important to be able to differentiate the 1-propanamines from various controlled drugs of the MDA series.

The ultraviolet absorption spectra of the 1-(3,4-methylenedioxyphenyl)-1-propanamines were determined as 0.5 mM solutions of the amine hydrochlorides in 0.1 N sulfuric acid. The ultraviolet absorption spectra of these compounds are essentially identical to those of the MDA series. This is to be expected since the primary chromophore, the 3,4-methylenedioxyphenyl moiety, is a structural feature shared by both series of compounds. The propanamines show good UV absorbances in both the 284 nm and 236 nm ranges, with almost identical molar absorptivities at the two wavelengths (Table I). The minimum between the two absorption bands is in the 257 nm region.

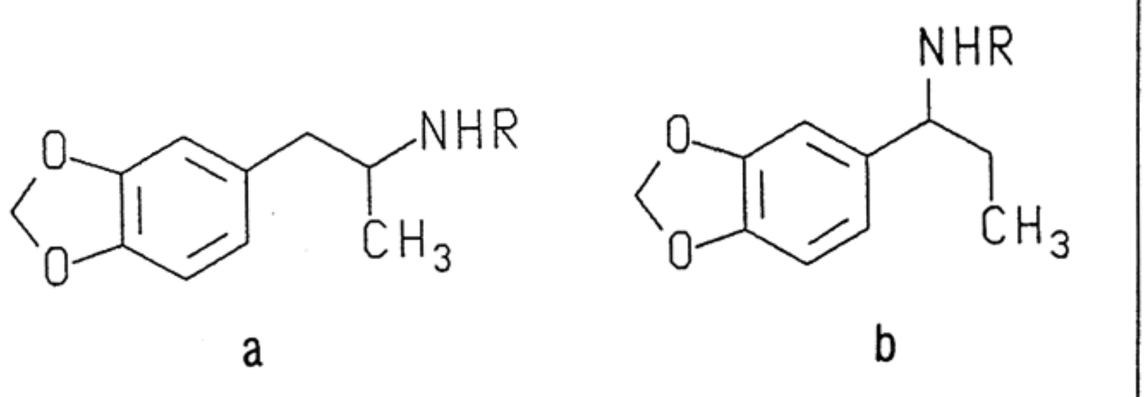


Figure 1. (a) Chemical structure of 3,4-methylenedioxyamphetamine (R=H) and 3,4-methylenedioxymethamphetamine (R=CH_3). (b) Chemical structure of 1-(3,4-methylenedioxyphenyl)-1-propanamines.

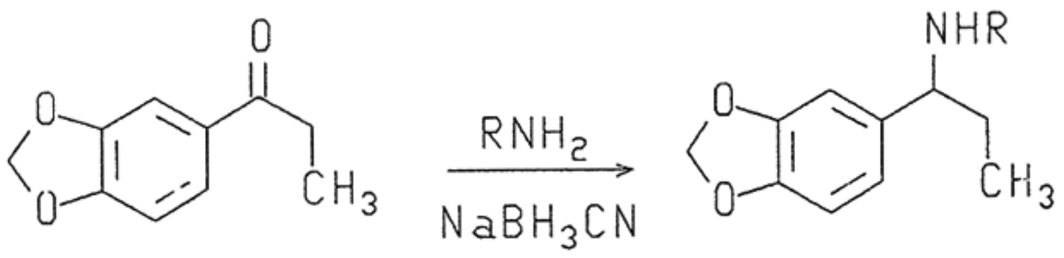
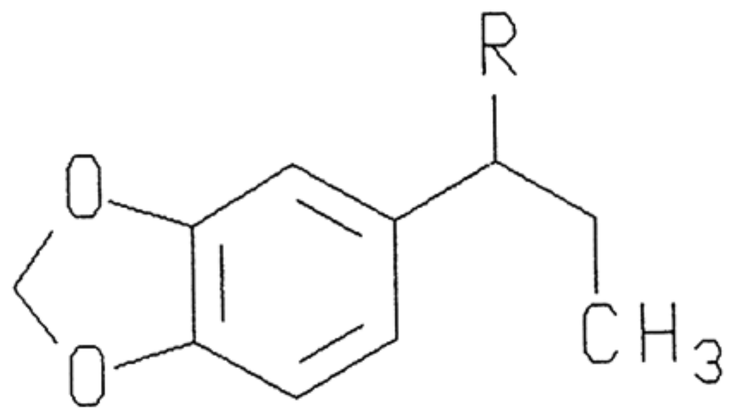


Figure 2. Synthesis of 1-(3,4-methylenedioxyphenyl)-1-propanamines.

Table I. Ultraviolet Absorption Properties of the 1-(3,4-Methylenedioxyphenyl)-1-propanamines*



R	λ_1 (nm)	ε_1	λ_2 (nm)	ε_2
NH_2	283.8	2.1×10^3	235.6	2.2×10^3
$NHCH_3$	285.2	2.1×10^3	236.6	2.2×10^3
$N(CH_3)_2$	284.8	2.0×10^3	239.4	2.1×10^3
$NHCH_2CH_3$	284.8	2.2×10^3	236.8	2.3×10^3
$NHCH_2CH_2CH_3$	284.8	2.1×10^3	236.8	2.2×10^3
$NHCH(CH_3)_2$	284.8	1.9×10^3	237.8	2.0×10^3

* UV spectra were determined with 0.5 mM solutions of the amine hydrochlorides in 0.1 N H_2SO_4.

The liquid chromatographic separation of the 1-(3,4-methylenedioxyphenyl)-1-propanamines is shown in Figure 3. This reversed-phase separation was achieved by using a μBondapak C_{18} stationary phase and a mobile phase consisting of pH 3 phosphate buffer, acetonitrile, methanol, and triethylamine. Addition of triethylamine to the mobile phase significantly improves peak shape and resolution by competing with the solute propanamines for strong adsorption sites on the stationary phase. The chromatogram in Figure 3 was obtained with dual wavelength UV detection at 254 and 280 nm, producing large peak ratios since these wavelengths are very close to the absorbance minima and maxima, respectively, for these compounds. In this chromatographic system, retention of the propanamines on the C_{18} stationary phase increases with the size of the *N*-alkyl substituent. For example, the primary amine has the lowest capacity factor, followed in order by the *N*-methyl, *N,N*-dimethyl, and *N*-ethyl derivatives. Both propyl analogues have higher capacity factors than the *N*-ethyl derivative, and the *N*-isopropyl derivative elutes prior to the *N*-*n*-propyl compound. The elution order observed for these propanamines is consis-

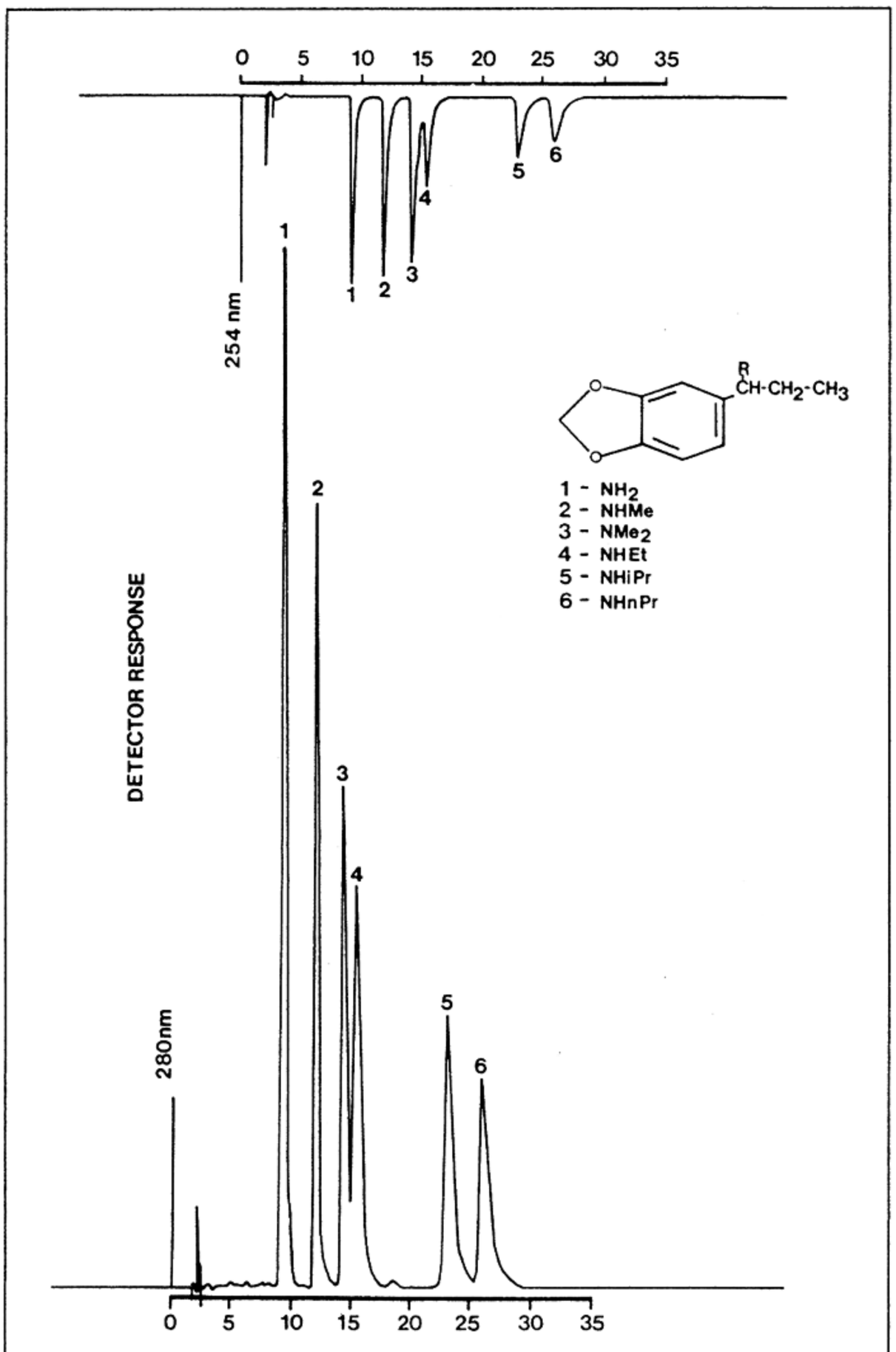


Figure 3. Liquid chromatographic separation of *N*-substituted 1-(3,4-methylenedioxyphenyl)-1-propanamines.

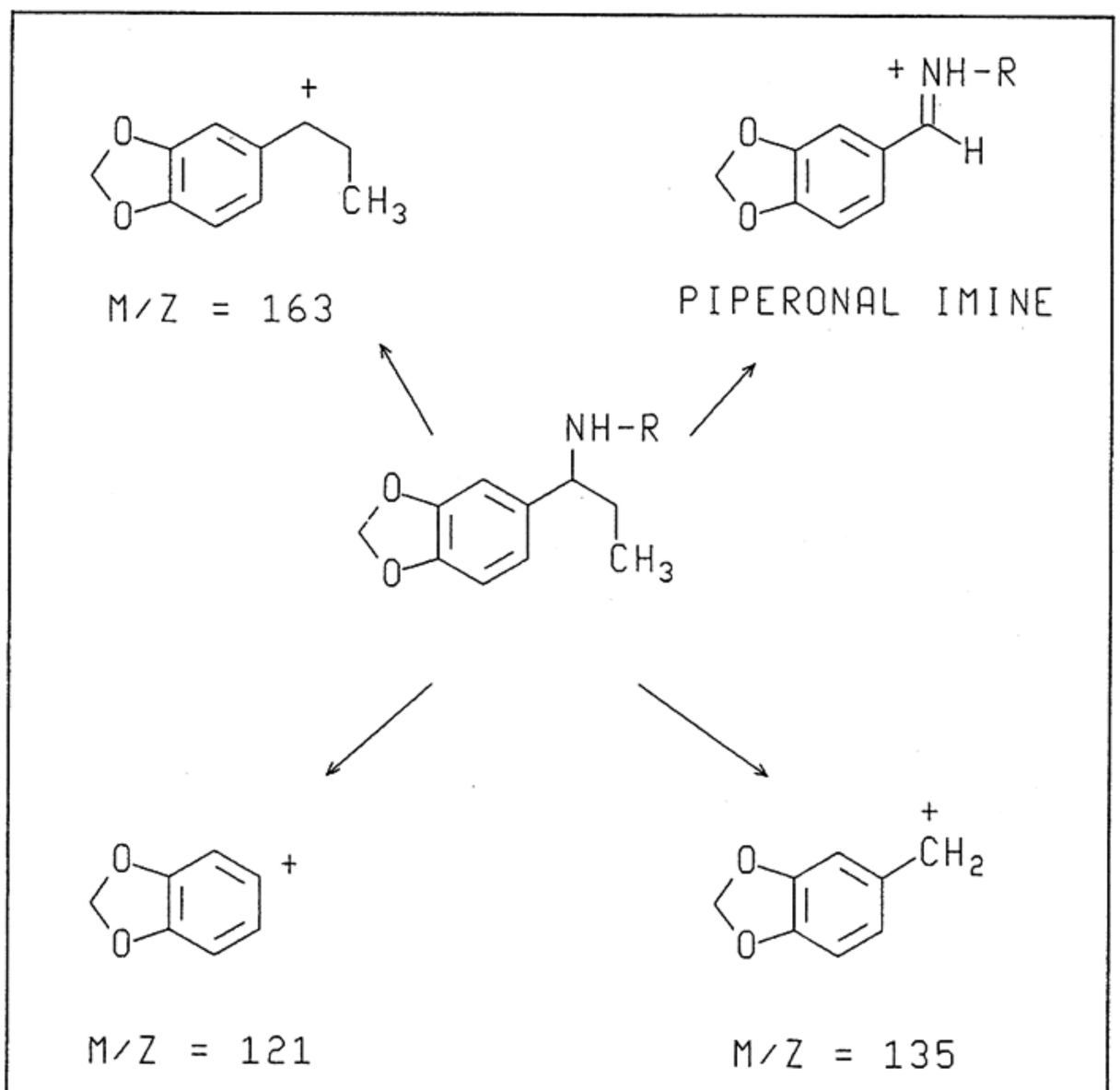


Figure 4. EI mass spectral fragmentation pattern for the 1-(3,4-methylenedioxyphenyl)-1-propanamines.

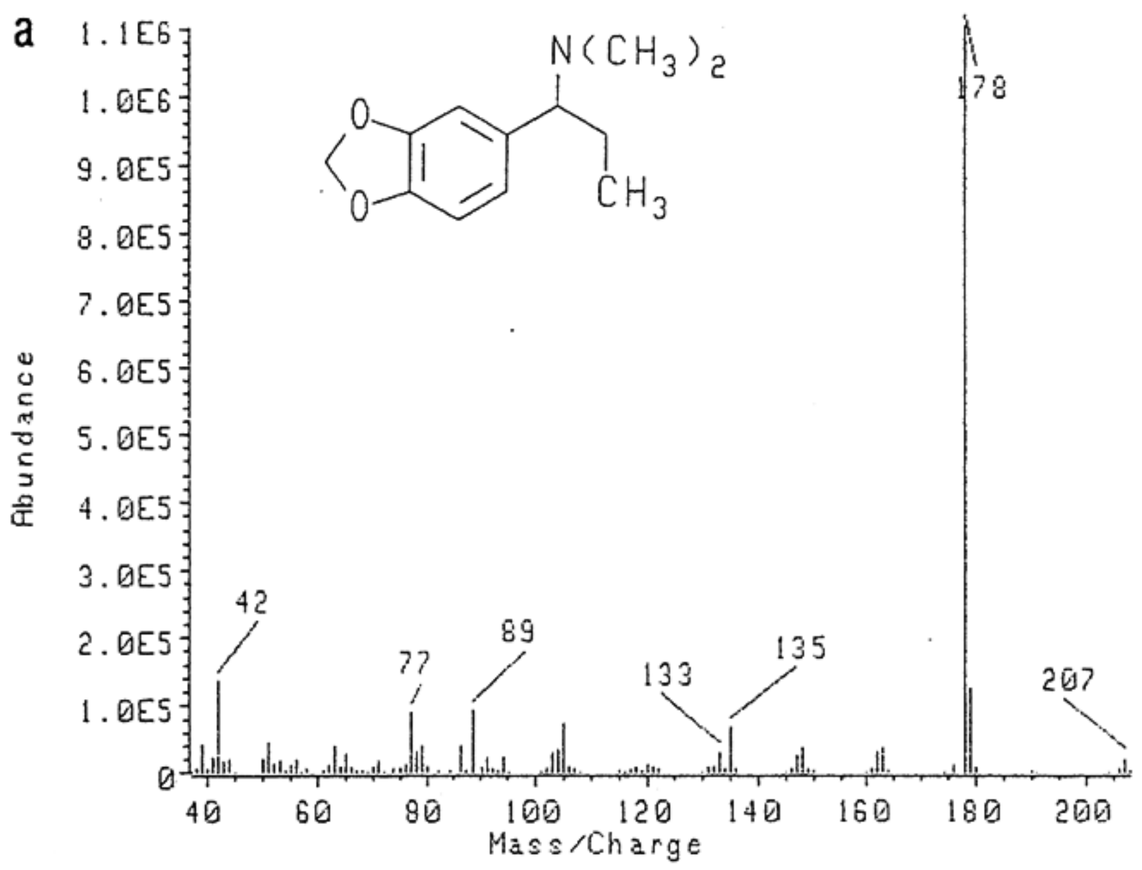


Figure 5. Comparative mass spectra for (a) *N,N*-dimethyl-1-(3,4-methylenedioxyphenyl)-1-propanamine and (b) *N,N*-dimethyl-3,4-methylenedioxyamphetamine.

tent with elution orders observed for both the *N*-alkyl MDA derivatives as well as the *N*-alkyl-1-(3,4-methylenedioxyphenyl)-1-ethanamines reported earlier (8).

The mass spectra of the 1-(3,4-methylenedioxyphenyl)-1-propanamines are distinctly different from those of the isomeric *N*-alkyl MDA derivatives described earlier (5). The mass spectral fragmentation pattern for the propanamines is shown in Figure 4. The base peak in all of these spectra is a relatively high-mass ion resulting from the loss of 29 mass units from the molecular ion. These high-mass ions result from the loss of the α-ethyl group of the side chain yielding the *N*-substituted piperonal imine species. This fragmentation pattern distinguishes the propanamines from the MDA derivatives where the loss of a 3,4-methylenedioxybenzyl radical predominates to afford a low-mass imine as the base peak. Figure 5 shows comparative mass spectra for the *N,N*-dimethyl-1-propanamine and *N,N*-dimethyl MDA regioisomers. These compounds have identical empirical formulas and thus have the same molecular weight. Furthermore, these compounds show similar amine-dominated fragmentation in their mass spectra. However, the difference in the position of the amino moiety in the side chain yields the relatively high mass piperonal imine in the 1-propanamine series and the lower mass acetaldehyde imine for the MDA series. This difference in fragmentation allows for the 1-propanamines to be readily distinguished from compounds of the isomeric MDA series that have the same molecular weight.

In summary, the *N*-substituted 1-(3,4-methylenedioxyphenyl)-1-propanamines were prepared and their analytical profiles compared to the isomeric substituted 3,4-methylenedioxyamphetamines. The compounds were separated by liquid chromatographic methods with a C_{18} stationary phase and an acidic (pH 3) aqueous acetonitrile–methanol mobile phase containing triethylamine. The mass spectra of the propanamines are characterized by fragmentation products that differ significantly from those obtained with the isomeric MDA series.

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