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Technical Note

Liquid Chromatographic and Mass Spectral Analysis of 1-(3,4-Methylenedioxyphenyl)-3-Propanamines: Regioisomers of MDMA

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Abstract

The 1-(3,4-methylenedioxyphenyl)-3-propanamines are prepared from 1-(3,4-methylenedioxyphenyl)propanoic acid via amide formation followed by hydride reduction. The 3-propanamines are regioisomeric with the 1-(3,4-methylenedioxyphenyl)-2-propanamines MDA and MDMA, a series of popular drugs of abuse. The *N*-substituted 3-propanamines were separated via reversed-phase liquid chromatography (LC) using an acidic mobile phase (pH 3). Similar reversed-phase conditions were used to separate the *N*-methyl derivatives of the regioisomeric 1-, 2-, and 3-propanamines. The electron impact (EI) mass spectra for the 3-propanamines show the characteristic amine base peak and can be used to differentiate these compounds from the regioisomeric 2-propanamines.

Introduction

The various *N*-substituted derivatives of 3,4-methylenedioxyamphetamine (MDA) have become popular drugs of abuse in recent years (1–3). Structurally, MDA and its *N*-methyl derivative MDMA resemble both methamphetamine and mescaline (Chart 1) and are reported to act primarily as central nervous system stimulants that may be hallucinogenic in large doses (4,5). MDMA is the most popular derivative of this series and is known by the street names "Ecstasy" or "XTC". MDMA is claimed to have a unique ability to facilitate interpersonal communication by reducing the anxiety or fear that normally accompanies the discussion of emotionally painful events (6).

The continued interest in drugs of the MDA-type is evidenced by numerous literature reports of new derivatives. Several designer analogs of MDA and MDMA, including the *N*-ethyl (MDEA) and *N*-hydroxy (NOHMDA) derivatives (Chart 1), have been encountered in forensic samples and these analogs are reported to have psychotomimetic activity in humans (7). Also, the MDA homologue, 1-(3,4-methylenedioxyphenyl)-3-butanamine (HMDA) has been detected in clandestine drug samples (8). Finally, Nichols et al. (9) recently reported the synthesis and unique pharmacological properties of α-ethyl analogs of MDA, the 1-(3,4-methylenedioxyphenyl)-2-butanamines. Members of this series have been classified as entactogens because they induce a pleasant state of introspection which facilitates the discussion of emotionally painful issues without producing the profound sensory distortions typical of hallucinogens such as LSD.

The continued interest in drugs of the MDMA-type may prompt the clandestine synthesis of additional designer analogs of this general structural class. Furthermore, it is reasonable to expect that new designer analogs of MDMA would be prepared from 3,4-methylenedioxyphenyl starting materials which are readily available. Two such materials, 3,4-methylenedioxycinnamic acid and 1-(3,4-methylenedioxyphenyl)-3-propanoic acid could be converted to 1-(3,4-methylenedioxyphenyl)-3-propanamine regioisomers of MDMA (2-propanamines) using basic synthetic methodology (Scheme 1). The potential for designer analogs such as these creates the need for analytical methodology capable of efficiently differentiating compounds of the 3-propanamine designer class from the traditional 2-propanamine MDA-type compounds.

Experimental

Instrumentation. The liquid chromatograph (LC) 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 Omni-Scribe 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-265 spectrophotometer. Nuclear magnetic resonance (NMR) spectra (1H) were determined using a Varian EM-360 60 MHz spectrometer.

The electron impact (EI) mass spectra were obtained using 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 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 25°/min. The split ratio for the GC was 10:1 and all sample components eluted within approximately 7 min.

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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 chromatographed using a mobile phase of pH 3.0 phosphate buffer, methanol, acetonitrile, and triethylamine (500:100:75:2). 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 5-μL aliquot of each amine solution was injected into the liquid chromatograph.

Synthesis of 1-(3,4-methylenedioxyphenyl)-3-propanamines. The appropriate amine (20 mMol) was added dropwise to a stirred solution of 1-(3,4-methylenedioxyphenyl)-3-propionyl chloride (10 mMol) in chloroform (50 mL) and the mixture stirred at room temperature for 1 h. The mixture was then stirred at reflux for ca. 15 min and the solvent evaporated under reduced pressure to yield an oil. The oil was partitioned between 20% potassium carbonate (50 mL) and chloroform (50 mL) and the chloroform layer separated. The chloroform solution was then washed with 10% HCl (50 mL) and evaporated under reduced pressure to yield the intermediate amide. A solution of the amide in tetrahydrofuran (THF) (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1 g) in THF (10 mL) stirred under a nitrogen atmosphere. After the addition was complete, the mixture was stirred at reflux overnight. The mixture was then cooled to room temperature, filtered, and the filtrate solvent evaporated under reduced pressure to yield the crude amines as oils. The oils were partitioned between 10% HCl (50 mL) and chloroform (50 mL) and the aqueous layer was separated and made basic (pH 12) with aqueous sodium hydroxide. The aqueous base suspension was extracted with chloroform (50 mL) and the chloroform removed under reduced pressure to yield the product amines in free base form. Treatment of the bases with ethereal HCl afforded the desired amine hydrochlorides. The structures of the products were confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the products was established by GC–MS and LC analysis.

Results and Discussion

The 1-(3,4-methylenedioxyphenyl)-3-propanamines are isomers of the 2-propanamines MDA and MDMA. The availability of appropriate precursor chemicals and the increasing interest in designer drug modifications makes the regioisomeric 3-propanamines potential targets for clandestine synthesis. Additionally, these compounds could display similar analytical profiles to comparably substituted MDA derivatives by some analytical techniques. Thus it is critical to establish forensic methods to differentiate between these various regioisomeric compounds.

The 1-(3,4-methylenedioxyphenyl)-3-propanamines can be prepared from 3,4-methylenedioxycinnamic acid or the corresponding propanoic acid, both of which are commercially available. For this study, 3,4-methylenedioxyphenylpropanoic acid was converted to the corresponding acid chloride via treatment with thionyl chloride in methylene chloride (Scheme 1). Reaction of the acid chloride with the appropriate amines yielded the intermediate amides. The amides were then reduced with lithium aluminum hydride in THF to give the desired amines which were converted to the hydrochloride salts and purified by recrystallization.

The liquid chromatographic separation of the primary 3-propnamine and its *N*-methyl, *N,N*-dimethyl, and *N*-ethyl analogs are shown in Figure 1. This separation was achieved in the reversed-phase mode using a mobile phase of pH 3 phosphate buffer, methanol, acetonitrile, and triethylamine (500:100:75:2) with a C_{18} stationary phase. The triethylamine serves to improve peak shape and resolution through its role as a competing base for various stationary phase active sites. Amines are widely recognized as strong silanophiles, often yielding broad bands and severe peak tailing. The use of a substance of similar basicity such as triethylamine, which is transparent to the mode of detection, serves to prevent the analyte silanophilic interactions. The triethylamine is added to the mobile phase in order to continuously saturate these active sites with a competing base.

The elution order for the 3-propanamines essentially parallels the carbon content of the *N*-substituent with the primary amine displaying the lowest capacity factor. The *N*-methyl derivative elutes second, followed by the *N,N*-dimethyl and *N*-ethyl analogs. The tertiary *N,N*-dimethyl derivative displays a higher capacity factor in this system than the isomeric *N*-ethyl analog. The elution order for the isomeric two carbon propanamines has been reversed in other compounds in similar chromatographic systems (10).

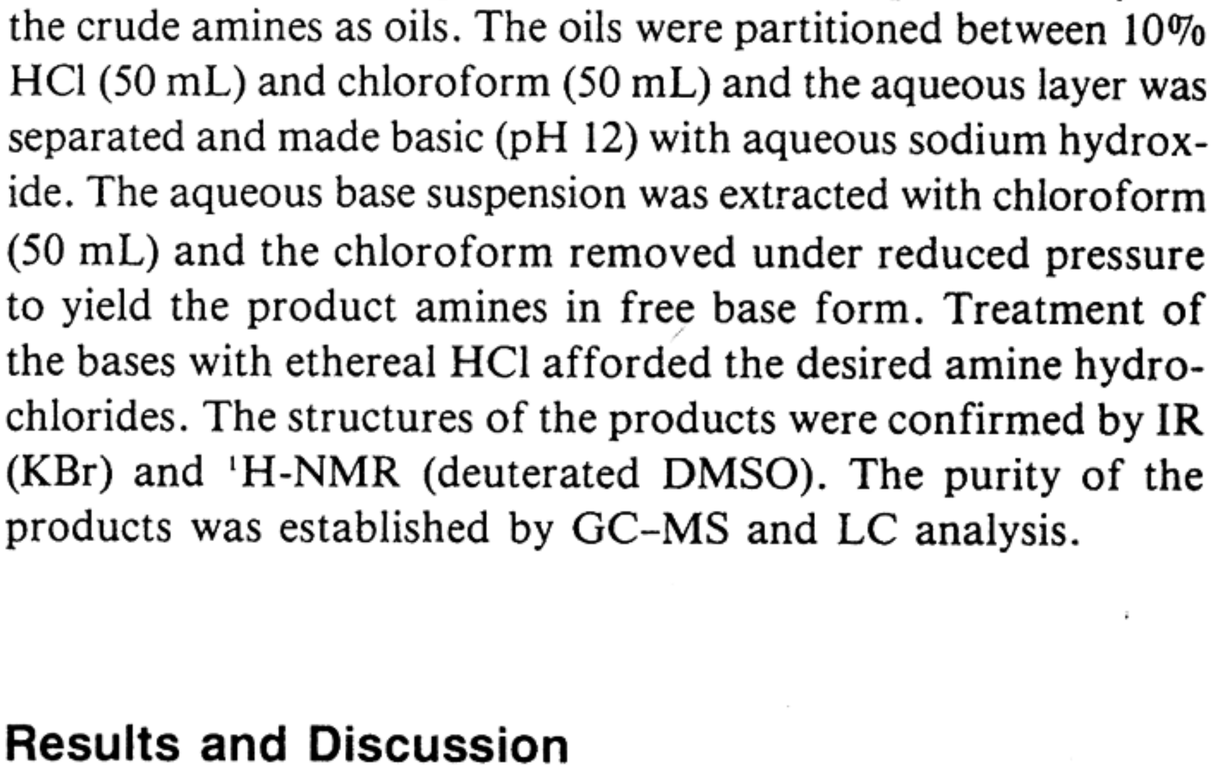
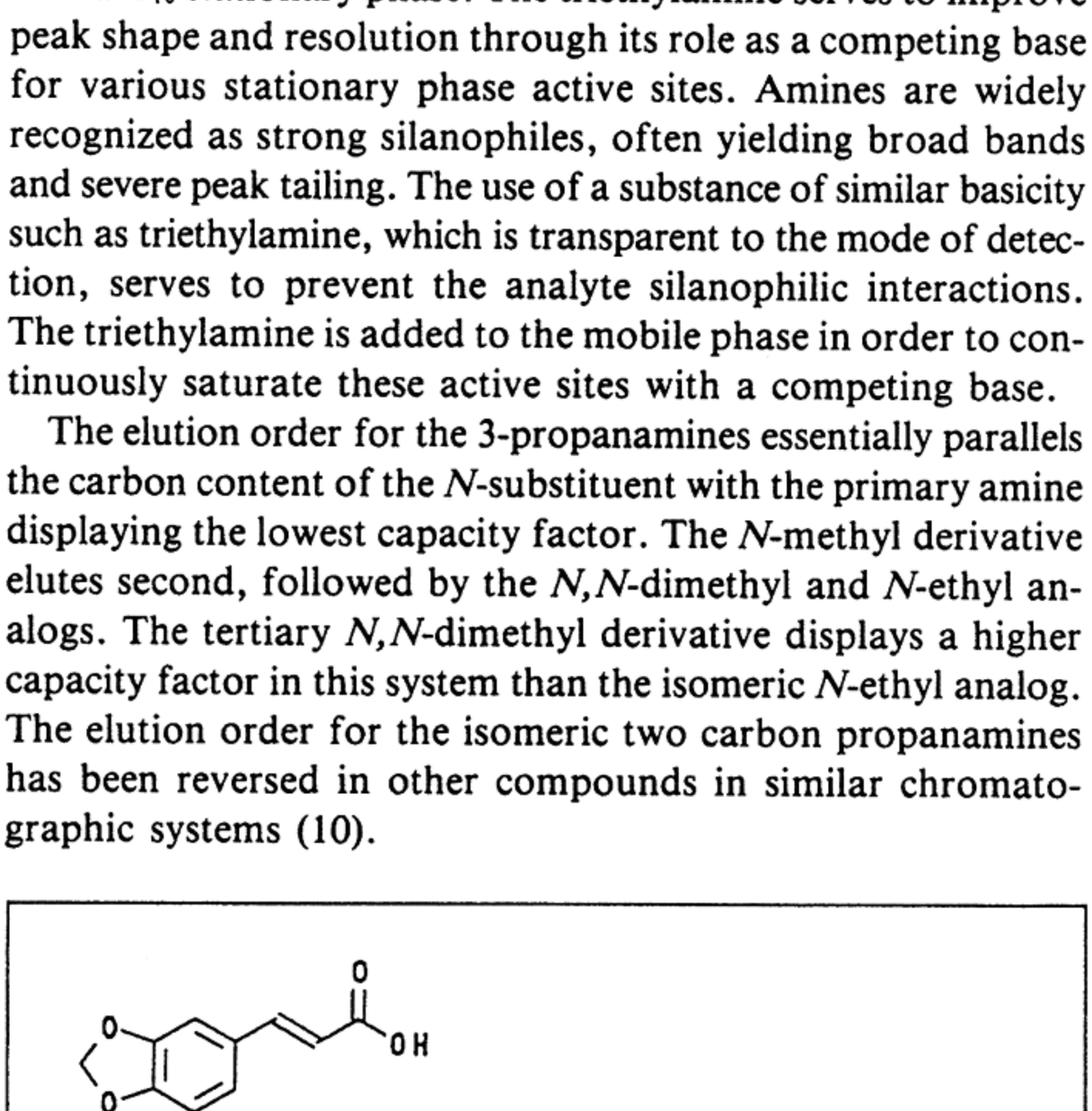


Chart 1. Structures of designer analogs of MDA and MDMA.



Scheme 1. Synthesis of the 1-(3,4-methylenedioxyphenyl)-3-propanamines.

In previous studies, the chromatographic properties of the regioisomeric 1-(3,4-methylenedioxyphenyl)-1-propanamines (10) and the MDA derivatives (1-(3,4-methylenedioxyphenyl)-2-propanamines) (1–3) have been described. Figure 2 shows the separation of the *N*-methyl derivatives of the regioisomeric 1-, 2-, and 3-propanamines. These compounds were separated in a reversed-phase system similar to that described in Figure 1. The mobile phase consisted of pH 3.0 phosphate buffer, methanol, acetonitrile, and triethylamine (600:100:25:1) with a C_{18} stationary phase. Under these conditions, the 2-propanamine MDMA elutes first followed by the 3-propanamine, while the 1-propanamine has the highest capacity factor.

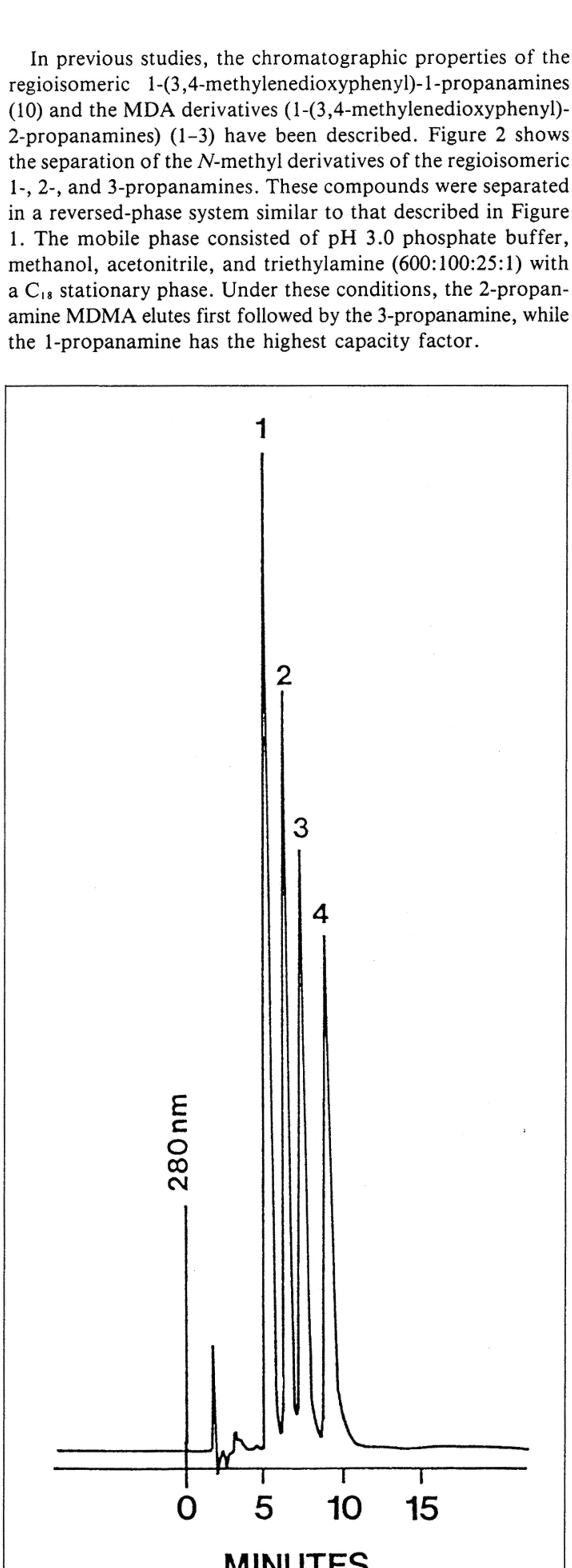


Figure 1. Reversed-phase liquid chromatographic separation of the 1-(3,4-methylenedioxyphenyl)-3-propanamines. Peaks: (1) primary amine, (2) *N*-methyl, (3) *N*-ethyl, and (4) *N*-dimethyl.

The electron impact (EI) mass spectra for the 3-propanamines are shown in Figure 3A–D. These compounds show the low mass base peak resulting from imine formation as illustrated in Scheme 2. The imine from the primary amine has an *m/z* of 30 and the other derivatives show this ion at *m/z* 44 or 58 depending on the nature of the *N*-substitutents. Other major peaks occur at *m/z* 135 and 162 for all compounds and are likely the

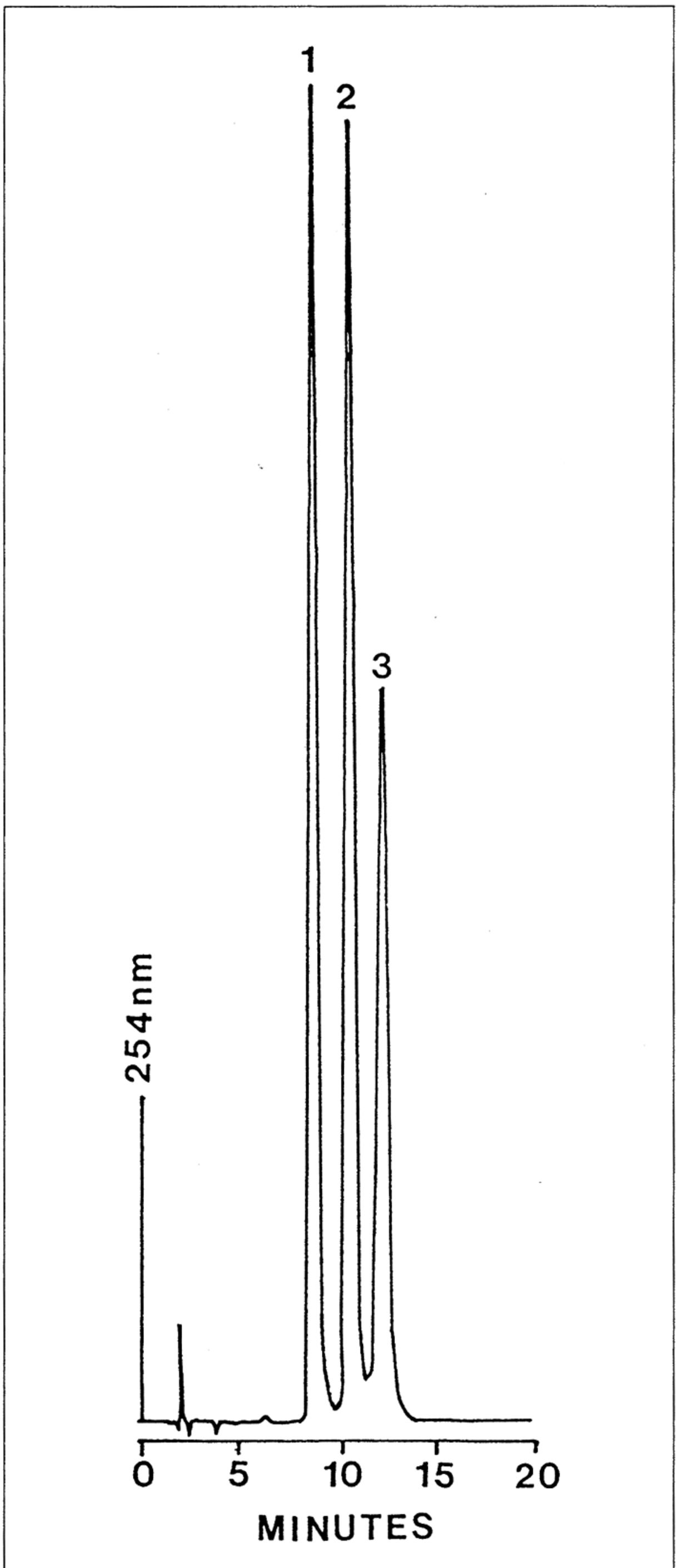
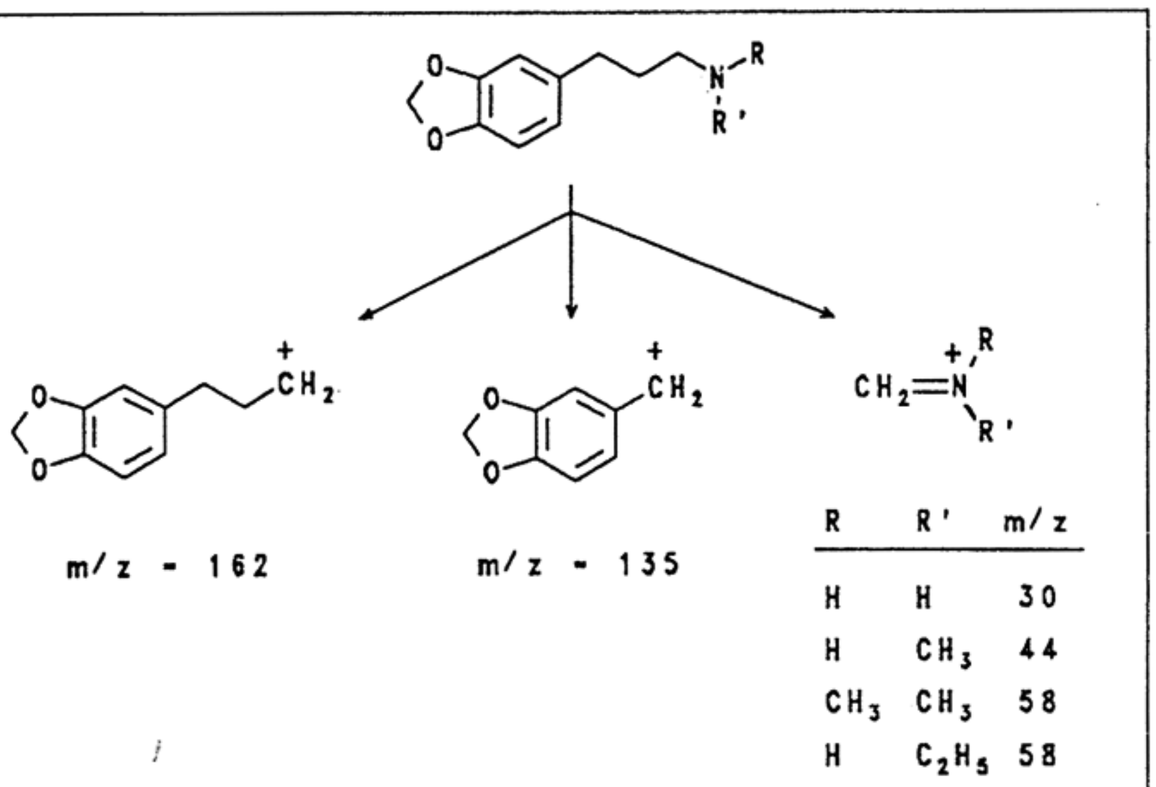


Figure 2, Reversed-phase liquid chromatographic separation of the *N*-methyl derivatives of the regioisomeric 1-(3,4-methylenedioxyphenyl)propanamines. Peaks: (1) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA), (2) *N*-methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine, and (3) *N*-methyl-1-(3,4-methylenedioxyphenyl)-1-propanamine.

result of fragmentation reactions to form the benzyl (tropyllium) ion (135) and the loss of the amino group (162). These mass spectra point out the utility of mass spectrometry in differentiating the 3-propanamines from the 2-propanamines (MDAs).



R	R'	m/z
H	H	30
H	CH_3	44
CH_3	CH_3	58
H	C_2H_5	58

Scheme 2. Mass spectral fragmentation pathway for the 1-(3,4-methylenedioxyphenyl)-3-propanamines.

For example, the *N*-methyl-3-propanamine has the same molecular weight as the corresponding 2-propanamine MDMA, however, the base peak in Figure 3B is *m/z* 44 whereas the base peak for MDMA is *m/z* 58 (see Figure 4). The additional mass in the MDMA base peak results from the α-methyl group in the 2-propanamine series. Additionally, only the straight chain 3-propanamines show a significant peak at *m/z* 162, resulting from a deamination reaction.

In summary, the 1-(3,4-methylenedioxyphenyl)-3-propanamines are regioisomeric with the common street drugs of the 2-propanamine series, MDA, MDMA, etc. The 3-propanamines are potential designer drug analogs of the MDA series because the appropriate starting materials are uncontrolled and available from commercial sources. The various *N*-substituted 3-propanamines were prepared via amide reduction and the resulting amines were separated by reversed-phase liquid chromatography. Additionally, the *N*-methyl derivatives of the 1-, 2-, and 3-propanamine series were separated under similar reversed-phase conditions. Mass spectra of the 3-propanamines show characteristic fragmentation that allows these compounds to be differentiated from the regioisomeric 2-propanamines.

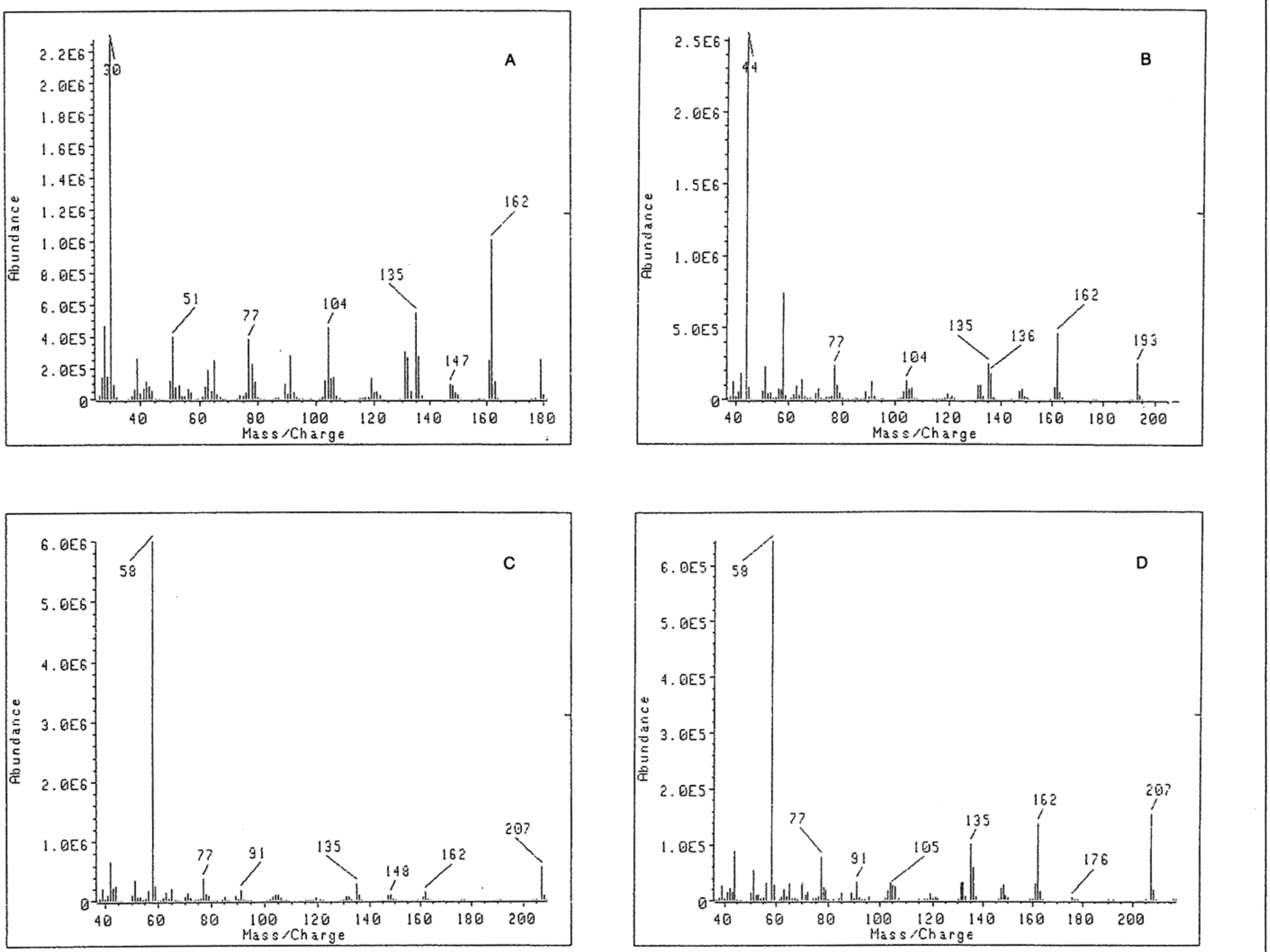


Figure 3. Mass spectra for the 1-(3,4-methylenedioxyphenyl)-3-propanamines; (A) 1-(3,4-methylenedioxyphenyl)-3-propanamine, (B) *N*-methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine, (C) *N,N*-dimethyl-1-(3,4-methylenedioxyphenyl)-3-propanamine, (D) *N*-ethyl-1-(3,4-methylenedioxyphenyl)-3-propanamine.

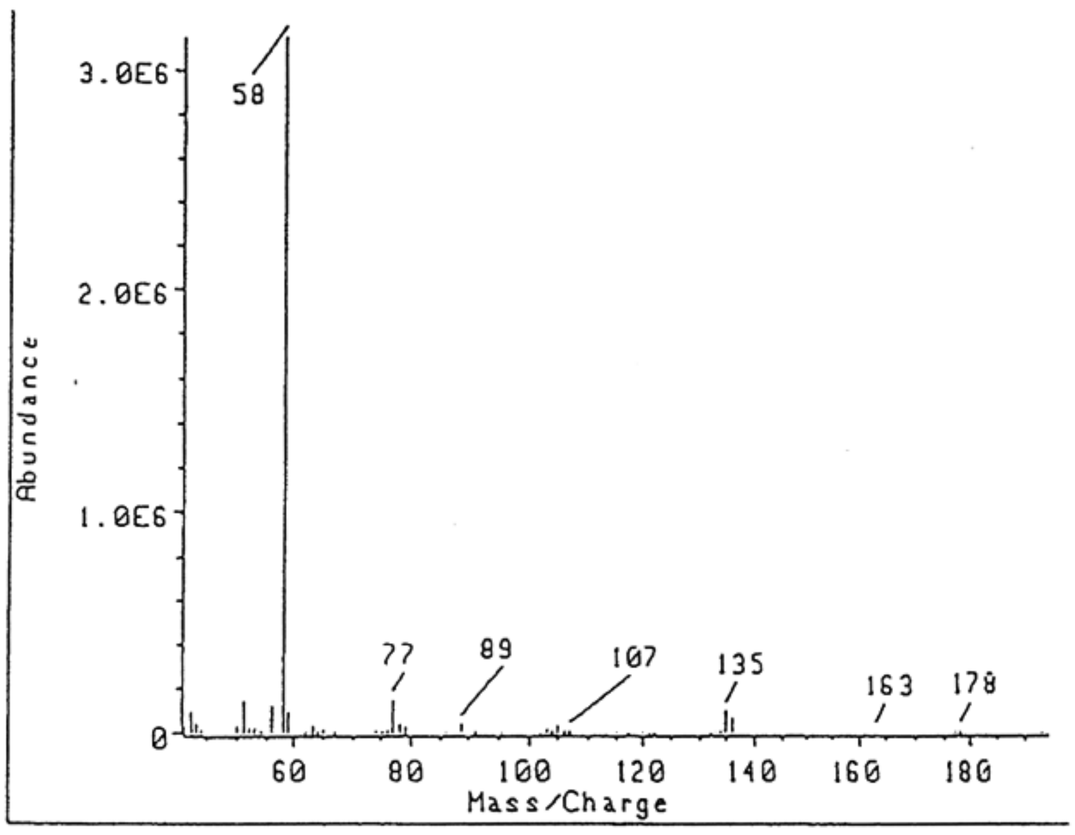


Figure 4. Mass spectrum for MDMA, *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine.

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