Gas Chromatographic–Mass Spectrometric and Liquid Chromatographic Analysis of Designer Butanamines Related to MDMA

C. Randall Clark[1*], **Jack DeRuiter**[1], and **Allen Valaer**[1,2]

[1]Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Alabama 36849 and [2]Alabama Reference Laboratories, 543 South Hull Street, Montgomery, Alabama 36103

F. Taylor Noggle

Department of Forensic Sciences, Wire Road, Auburn, Alabama 36831

Abstract

A series of *N*-substituted, 1-(3,4-methylenedioxyphenyl)-2-butanamines (MDP-2-B) is prepared from piperonal via the 2-butanone intermediate. The analytical properties of these compounds are compared with the structurally similar 3,4-methylenedioxyamphetamine (MDA) derivatives, a popular series of drugs of abuse. The ultraviolet absorption properties of these compounds are determined by the methylenedioxyphenyl ring, which shows major absorption bands in the 285- and 235-nm range. The primary amine (MDP-2-B) and the *N*-substituted derivatives of MDP-2-B are separated by reversed-phase liquid chromatography under acidic mobile-phase conditions. The compounds are not completely resolved by gas chromatography on an HP-1 phase, and the separation is complicated by extensive thermal degradation of the *N*-hydroxy derivative (MDP-2-OHB). The mass spectra for these compounds provide specific structural information for the identification of these compounds. The amines undergo α-cleavage reactions to produce ions at $[M-135]^+$ from the loss of the 3,4-methylenedioxybenzyl radical and $[M-29]^+$ from loss of the other α-group, the ethyl radical.

Introduction

The various *N*-substituted derivatives of 3,4-methylenedioxyamphetamine (MDA) have become popular drugs of abuse in recent years (1–3). These drugs are 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 (4). The continued designer-drug exploration of the MDA series has resulted in legislation to upgrade the penalties associated with the clandestine use of these compounds.

MDA was one of the first hallucinogenic amphetamine derivatives to show popularity as a recreational drug. Structurally, MDA is a phenethylamine resembling both amphetamine and mescaline and is reported to act primarily as a central nervous system stimulant that may be hallucinogenic in large doses (5,6). Although MDA may lack the sensory disruptions commonly recognized with LSD and mescaline, it was reported to be more toxic than mescaline in laboratory animals (7). Several of the *N*-substituted derivatives of MDA have appeared as drugs of abuse, and the *N*-methyl (MDMA), *N*-ethyl (MDEA), and *N*-hydroxy (NOHMDA) analogues were reported to have psychotomimetic activity in humans (8). MDMA is perhaps the most popular of the MDA series and is known by the street names Ecstasy or XTC. This drug was extensively studied in animals via a variety of techniques, including drug discrimination (9) and neurochemical methods (10).

The α-ethyl phenethylamine, 1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-B), was recently reported on by Nichols and co-workers (11), and its pharmacology was compared with the α-methyl homologue, MDA. In rats trained to discriminate between saline and LSD, these effects were generalized by racemic MDA and the racemic butanamine. However, MDP-2-B did not produce complete generalization and was described as a less potent psychoactive drug. In human studies, the *N*-methylated butanamine (MDP-2-MB) was characterized as producing a pleasant state of introspection that facilitates the discussion of emotionally painful issues. Hence, this compound was described as representing a new pharmacological class, the entactogens. The word *entactogen* is derived from the Greek roots *en* for within and *gen* meaning produce and the Latin root *tactus* for touch (11). Entactogens produce their unique behavioral effects without causing profound sensory experiences or distortions as observed with the hallucinogens or psychedelics. Thus entactogens continue to be suggested as potential therapeutic agents in facilitating psychotherapy.

The similarity in the structure and pharmacology of the 2-butanamines and the MDA series of drugs prompted this investigation of analytical methods to distinguish between these series of compounds. The butanamines studied included the primary amine (MDP-2-B) and the *N*-methyl (MDP-2-MB), *N*-ethyl (MDP-2-EB), *N*,*N*-dimethyl (MDP-2-MMB), and

* Author to whom correspondence should be addressed.

N-hydroxy (MDP-2-OHB) analogues of those MDA derivatives reported to have psychotomimetic activity in humans (Chart 1).

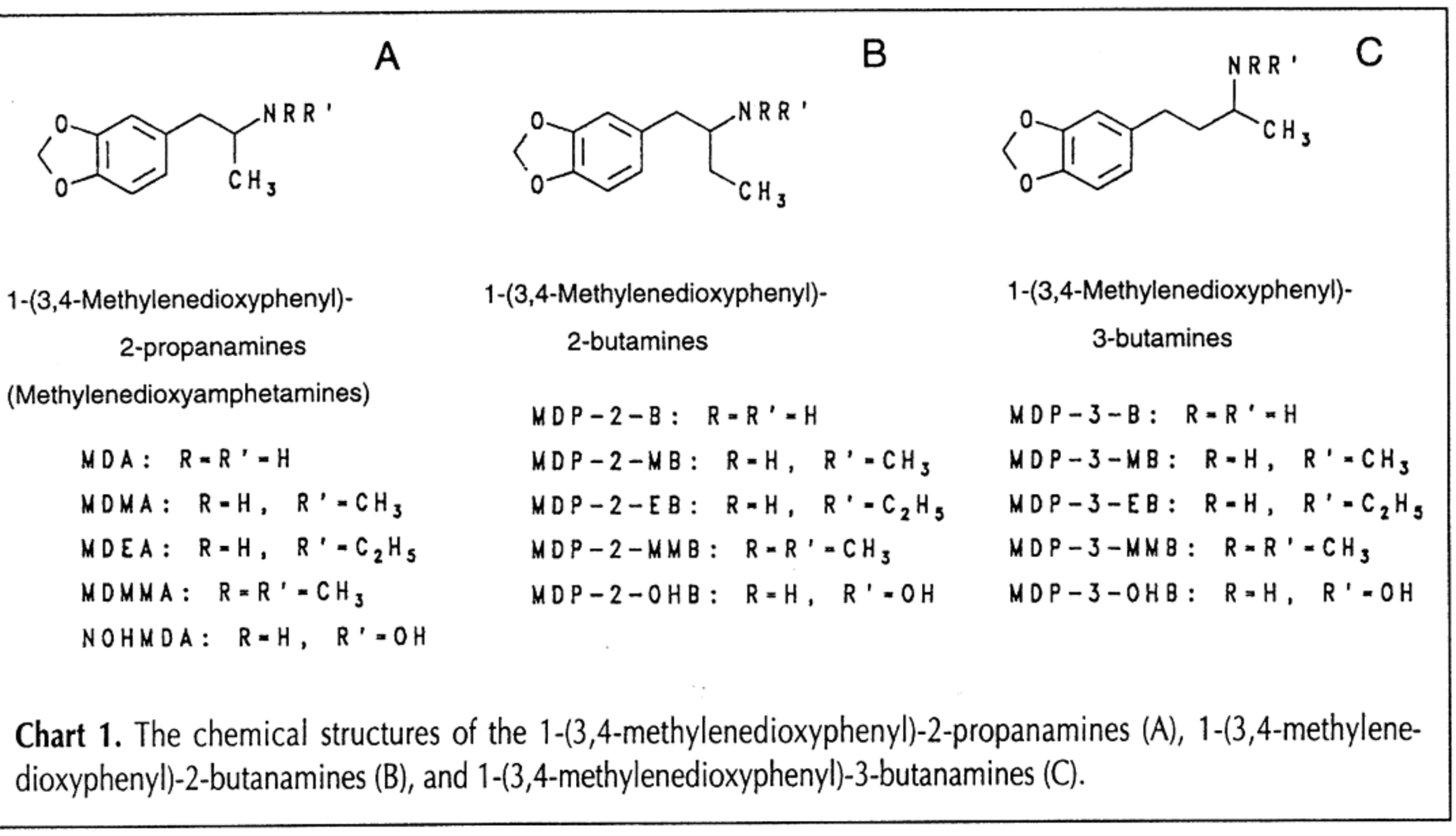
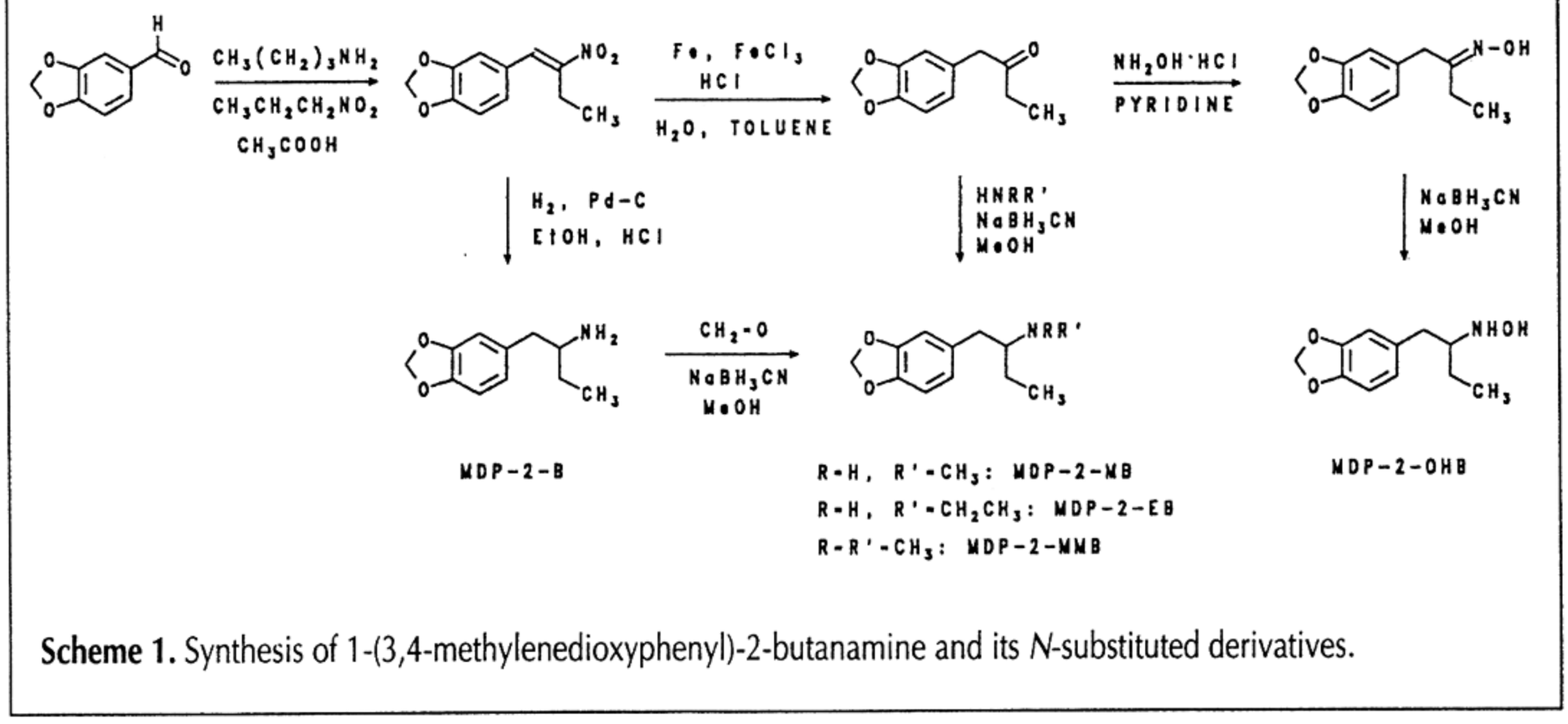


Chart 1. The chemical structures of the 1-(3,4-methylenedioxyphenyl)-2-propanamines (A), 1-(3,4-methylenedioxyphenyl)-2-butanamines (B), and 1-(3,4-methylenedioxyphenyl)-3-butanamines (C).



Scheme 1. Synthesis of 1-(3,4-methylenedioxyphenyl)-2-butanamine and its *N*-substituted derivatives.

Experimental

Instrumentation

The liquid chromatograph (LC) consisted of a Laboratory Data Control Constametric 3000 pump (Riviera Beach, FL), a Model 3100 Spectromonitor ultraviolet (UV) detector, CI 4100 integrator , and a Rheodyne Model 7125 injector (Cotati, CA). Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier-transform infrared (FTIR) spectrophotometer (Norwalk, CT). UV spectra were recorded on a Shimadzu Instruments Model UV-265 spectrophotometer (Columbia, MD).

The electron-impact mass spectra were obtained using a Hewlett-Packard 5970B mass selective detector (Palo Alto, CA). The ionization voltage was 70 eV, and the source temperature was 220°C. The individual samples were dissolved in methanol (1 mg/mL), and 0.5 µL was introduced into the mass spectrometer via the gas chromatograph (GC) equipped with a 12-m × 0.20-mm i.d. fused-silica column (0.33-µm thickness of HP-1). The column temperature was programmed from 70 to 150°C at a rate of 15°C/min and from 150 to 250°C at a rate of 25°C/min with a hold time of 6 min. The split ratio for the GC was 10:1, and the samples eluted in approximately 7 min. The solid-probe, direct-inlet mass spectrum was obtained on a Finnigan Model 3300 spectrometer at 70 eV (Austin, TX).

Liquid chromatographic procedures

The analytical column (30 cm × 3.9-mm i.d.) was packed with Bondclone C_{18} (Phenomenex; Torrance, CA). The analytical column was preceded by a direct-connect guard column (Alltech Associates; State College, PA) packed with CO:Pell ODS (Whatman; Clifton, NJ). The amines (1 mg/mL) were dissolved in HPLC-grade methanol and chromatographed using a mobile phase of pH 3.0 phosphate buffer, HPLC-grade acetonitrile, and triethylamine (600:100:1). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate (NaH_2PO_4) in 1 L double-distilled water and adjusting the pH to 3.0 with H_3PO_4. The mobile phase flow rate

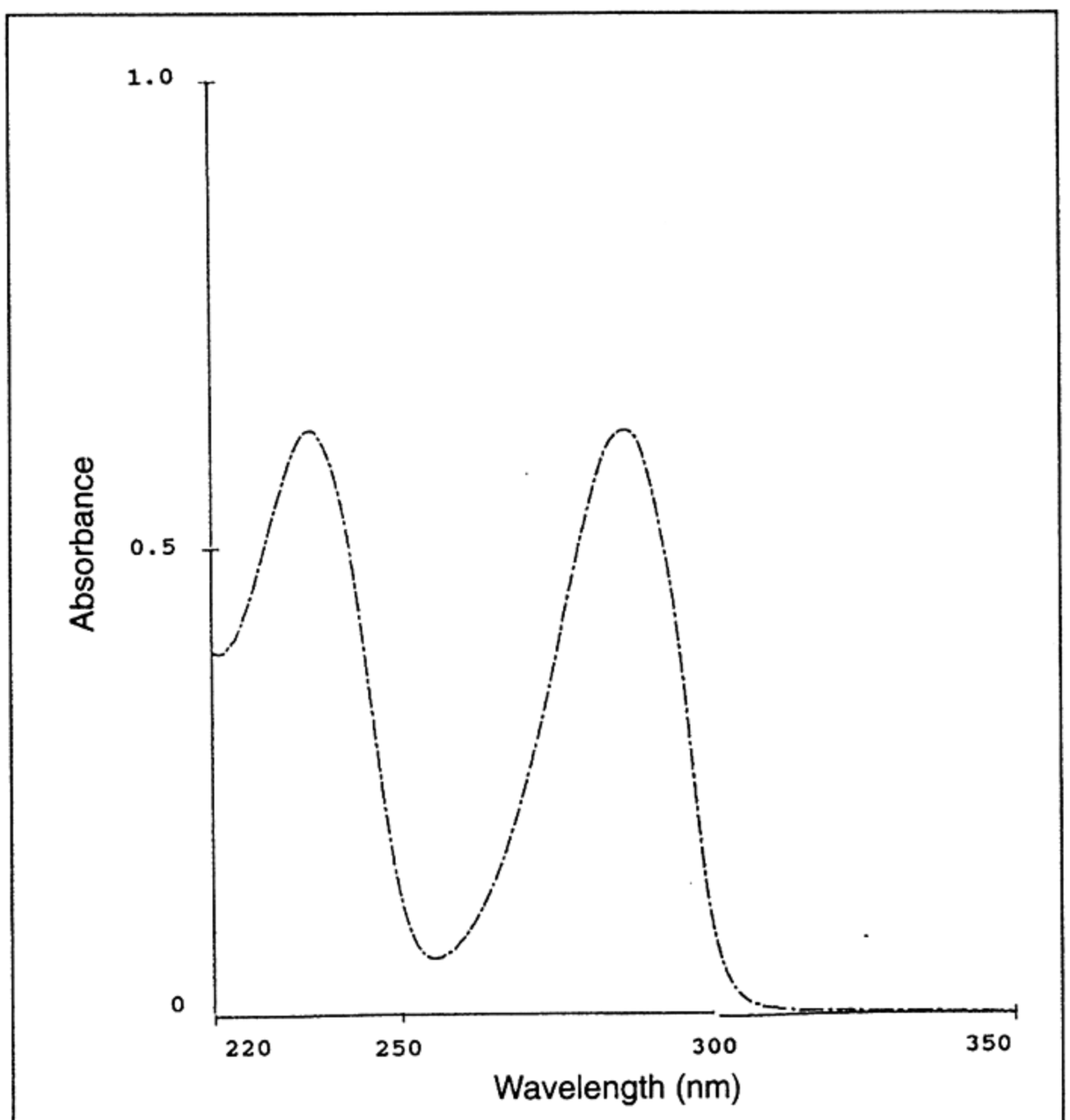


Figure 1. Ultraviolet spectrum of 1-(3,4-methylenedioxyphenyl)-2-butanamine. Methanol was used as the solvent.

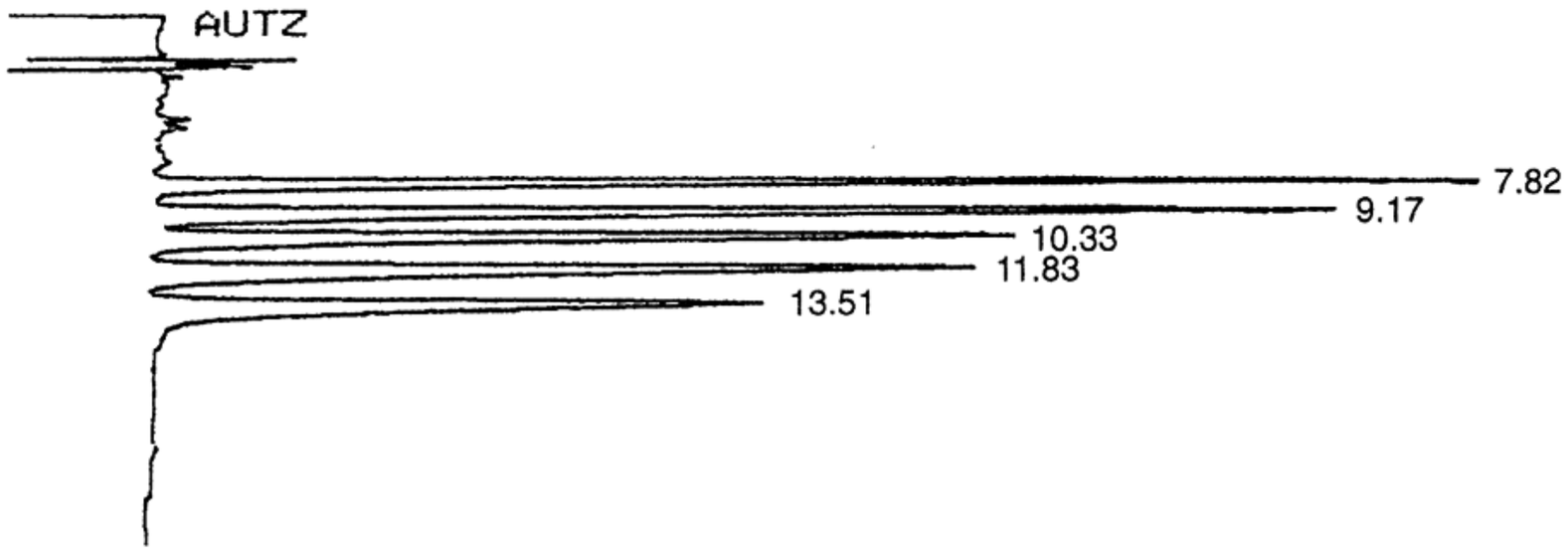


Figure 2. Reversed-phase liquid chromatographic separation of 1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-B) and its *N*-substituted derivatives: MDP-2-B, 7.82 min; *N*-methyl butanamine (MDP-2-MB), 9.17 min; *N*-ethyl butanamine (MDP-2-EB), 10.33 min; *N,N*-dimethyl butanamine (MDP-2-MMB), 11.83 min; and *N*-hydroxy butanamine (MDP-2-OHB), 13.51 min.

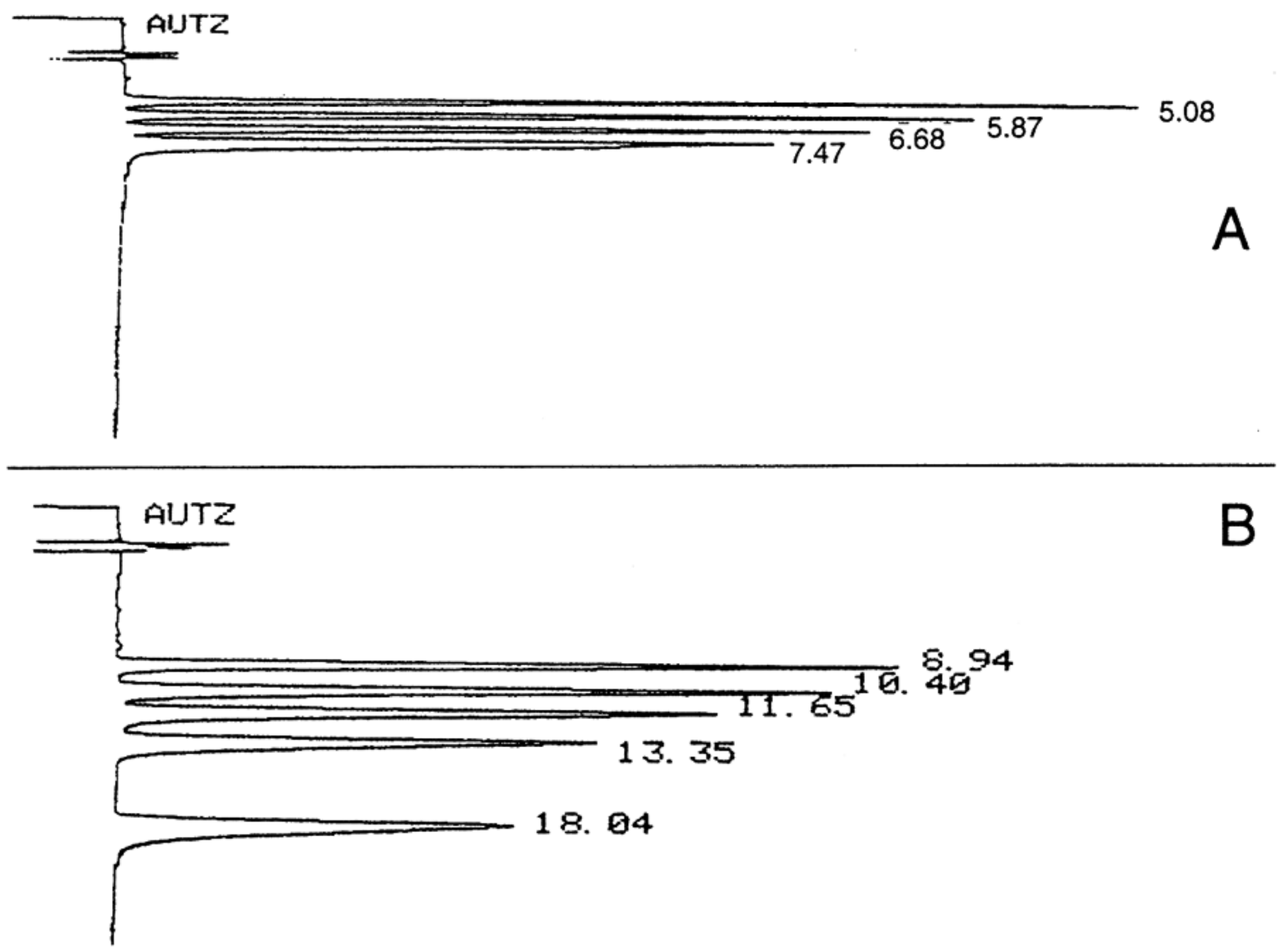


Figure 3. Chromatogram A shows the reversed-phase liquid chromatographic separation of 1-(3,4-methylenedioxyphenyl)-2-propanamine (MDA) and its *N*-substituted derivatives: MDA, 5.08 min; *N*-methyl propanamine (MDMA), 5.87 min; *N*-ethyl propanamine (MDEA), 6.68 min; and *N,N*-dimethyl propanamine (MDMMA), 7.47 min. Chromatogram B shows the reversed-phase liquid chromatographic separation of 1-(3,4-methylenedioxyphenyl)-3-butanamine (MDP-3-B) and its *N*-substituted derivatives: MDP-3-B, 8.94 min; *N*-methyl-3-butanamine (MDP-3-MB), 10.40 min; *N*-ethyl-3-butanamine (MDP-3-EB), 11.65 min; *N,N*-dimethyl-3-butanamine (MDP-2-MMB), 13.35 min; and *N*-hydroxy-3-butanamine (MDP-3-OHB), 18.04 min.

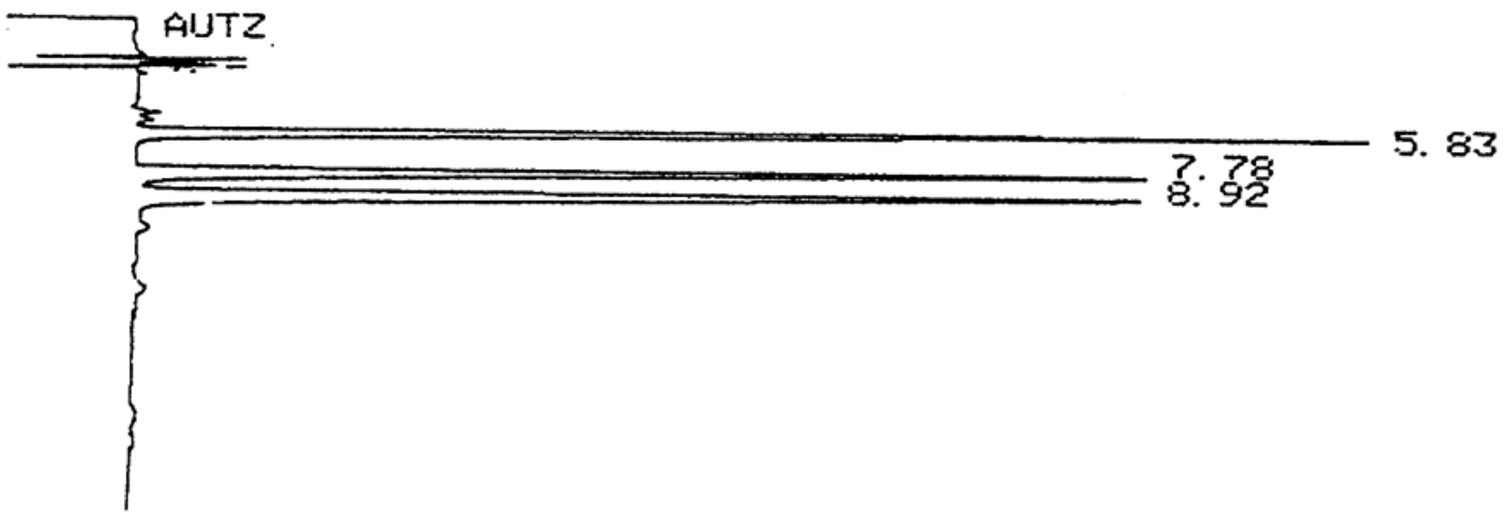


Figure 4. Reversed-phase liquid chromatographic separation of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (5.83 min), 1-(3,4-methylenedioxyphenyl)-2-butanamine (7.78 min), and 1-(3,4-methylenedioxyphenyl)-3-butanamine (8.92 min).

was 1.5 mL/min, and the detector was operated at 280 nm and 0.2 AUFS. A 15-µL aliquot of each amine solution was injected into the LC.

Synthesis of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-butene

A solution of piperonal and *n*-butylamine in benzene was heated at reflux for several hours. The water generated during imine formation was removed with a Dean–Stark trap. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure to yield the intermediate *n*-butylimine as a yellow oil. The imine was dissolved in a solution of nitropropane and glacial acetic acid and stirred at reflux for an hour. The reaction mixture was cooled, poured over crushed ice, and acidified with concentrated HCl to yield the crude nitrobutene as a dark green oil. The product oil was crystallized and recrystallized from 2-propanol (68%).

Catalytic reduction method for the synthesis of MDP-2-B

A solution of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-butene in ethanol containing palladium on carbon was shaken under a hydrogen atmosphere for several hours using a Parr hydrogenator. The reaction mixture was filtered, and the filtered solvent was evaporated under reduced pressure to yield a yellow oil. The oil was dissolved in aqueous acid and washed with ether. The acidic, aqueous solution was made alkaline by the addition of NaOH pellets and was extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and then treated with HCl gas to generate the hydrochloride salt. Recrystallization from a mixture of anhydrous ether and dry acetone afforded the product as white needles (38%; mp, 153–154°C).

Lithium aluminum hydride reduction method for the synthesis of MDP-2-B

A solution of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-butene in dry tetrahydrofuran (THF) was added dropwise over a period of several minutes to a cool, stirred suspension of lithium aluminum hydride in dry THF. After the addition was complete, the reaction mixture was stirred at room temperature for several minutes and then at reflux for 1 h. The reaction mixture was cooled, and the excess lithium alu-

minum hydride and salts were decomposed by the successive addition of water, 5N NaOH, and water. After stirring an additional few minutes, the mixture was filtered, and the filtered solvent was evaporated under reduced pressure to yield a dark oil. The oil was suspended in aqueous acid and washed with methylene chloride. The aqueous solution was made alkaline by the addition of NaOH pellets, and the resulting alkaline suspension was extracted with methylene chloride. The combined methylene chloride extracts were washed with water and evaporated under reduced pressure to yield a yellow oil that was dried under high vacuum. The oil was dissolved in anhydrous ether, and HCl gas was added to yield the hydrochloride salt of the product that was recrystallized as described previously (88%).

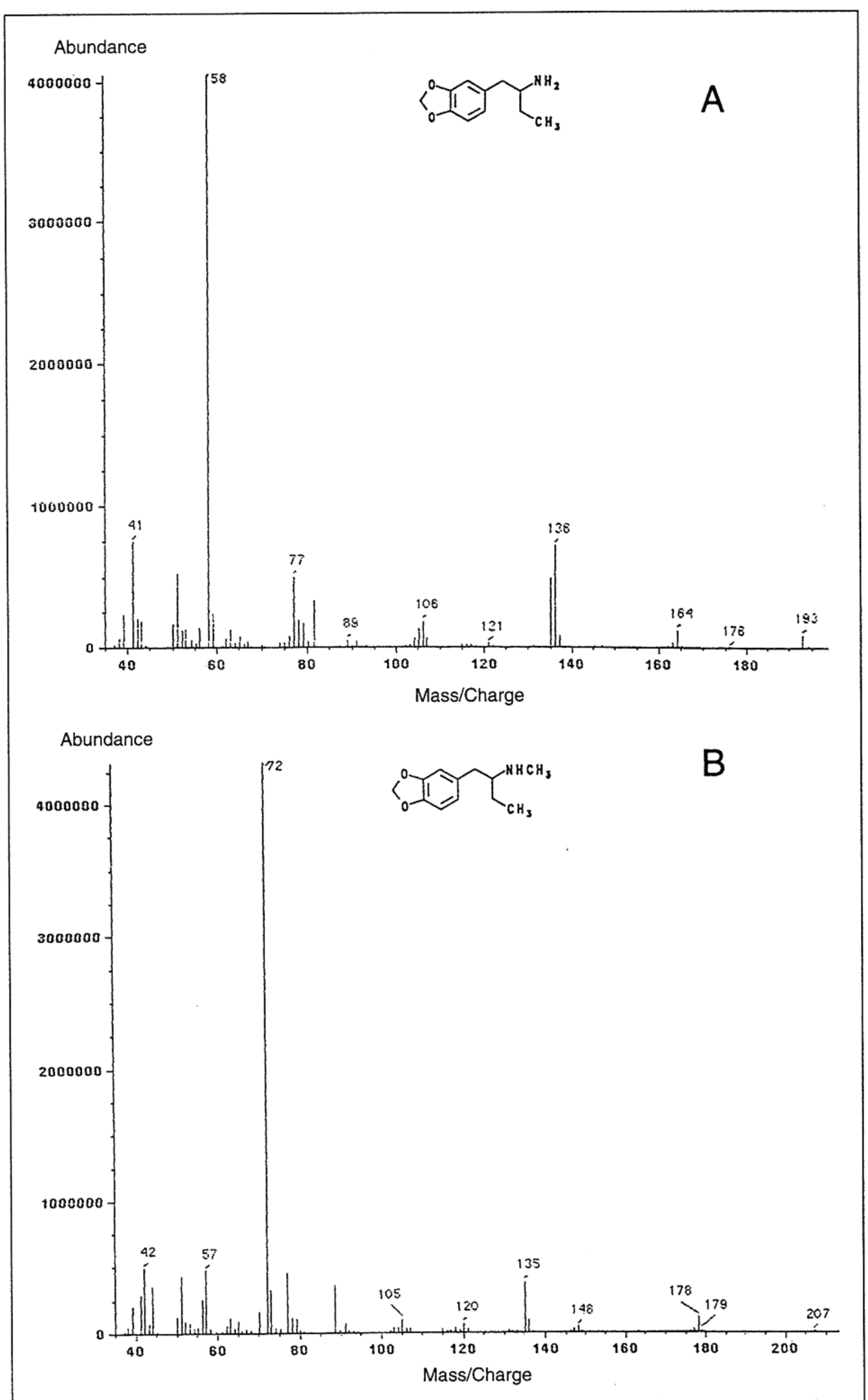


Figure 5. Electron-impact mass spectra for 1-(3,4-methylenedioxyphenyl)-2-butanamine (A) and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (B). *(Continued on page 332.)*

Synthesis of 1-(3,4-methylenedioxyphenyl)-2-butanone

A mixture of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-butene, iron, ferric chloride in toluene, water, and concentrated HCl was stirred vigorously and warmed overnight. The reaction mixture was cooled to room temperature and filtered, and the solid mass was washed with water and toluene. These washings were combined with the original reaction solvents, and the toluene and water layers were allowed to separate. The toluene solution was washed successively with 3N HCl, water, saturated sodium bicarbonate, and water. The toluene solution was filtered and dried over anhydrous potassium carbonate. Filtration followed by evaporation of the filtered solvent gave the crude ketone as a yellow oil. This oil was suspended in 3N HCl and stirred with heating for 1 h to hydrolyze the oxime reduction intermediate. The aqueous suspension was extracted with ether, and the combined ether extracts were evaporated under reduced pressure to yield a yellow oil. Distillation afforded 1-(3,4-methylenedioxyphenyl)-2-butanone as a light-yellow oil (72%).

Reductive amination method for the synthesis of butanamines

A solution of 1-(3,4-methylenedioxyphenyl)-2-butanone, the appropriate amine (ammonium acetate, methylamine, ethylamine, or dimethylamine hydrochloride), and sodium cyanoborohydride in methanol was stirred at room temperature for several days. The reaction mixture was monitored periodically, and concentrated HCl was added to maintain the pH at neutrality. The reaction mixture was evaporated under reduced pressure to yield a white solid. The solid was suspended in water, cooled in an ice bath, and slowly acidified by the addition of concentrated HCl. The aqueous acid was washed with methylene chloride, then made alkaline by the addition of NaOH pellets. The aqueous basic suspension was extracted with methylene chloride, and the extracts were combined and evaporated under reduced pressure to yield a light yellow oil that was dried under high vacuum. The oil was dissolved in anhydrous ether, and HCl gas was added to form the hydrochloride salt. Recrystallization from mixtures of anhydrous ether and absolute ethanol afforded the following products as white needles: MDP-2-B (78%;

mp, 153–154°C); MDP-2-MB (43%; mp, 151–153°C); MDP-2-EB (38%; mp, 177–178°C); and MDP-2-MMB (8%; mp, 97–99°C).

Reductive methylation method for the synthesis of MDP-2-MMB

A solution of MDP-2-B, 37% formaldehyde, and sodium cyanoborohydride in methanol was stirred at room temperature for several days. The reaction mixture was monitored periodically, and concentrated HCl was added to maintain the pH at neutrality. The reaction mixture was evaporated under reduced pressure to yield a white solid. The solid was suspended in water, cooled in an ice bath, and slowly acidified by the addition of concentrated HCl. The aqueous acid was washed with benzene and then made alkaline by the addition of NaOH pellets. The aqueous basic suspension was extracted with methylene chloride, and the extracts were combined and evaporated under reduced pressure to yield a light yellow oil that was dried under high vacuum. The oil was dissolved in anhydrous ether, and HCl gas was added to form the hydrochloride salt. Recrystallization from anhydrous ether afforded the product as white needles (69%).

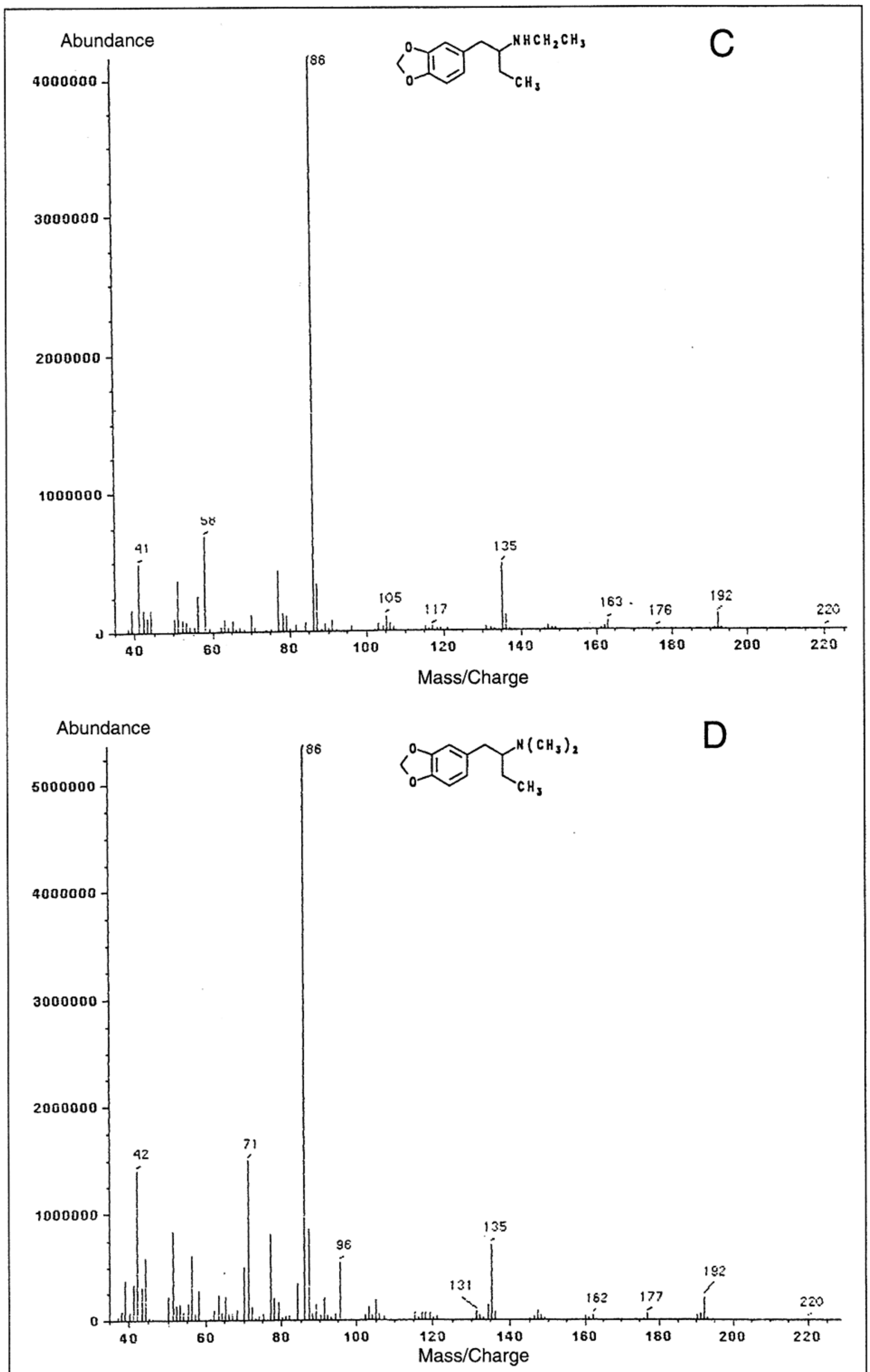


Figure 5. *(Continued from page 331.)* Electron-impact mass spectra for *N*-ethyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (C) and *N,N*-dimethyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (D).

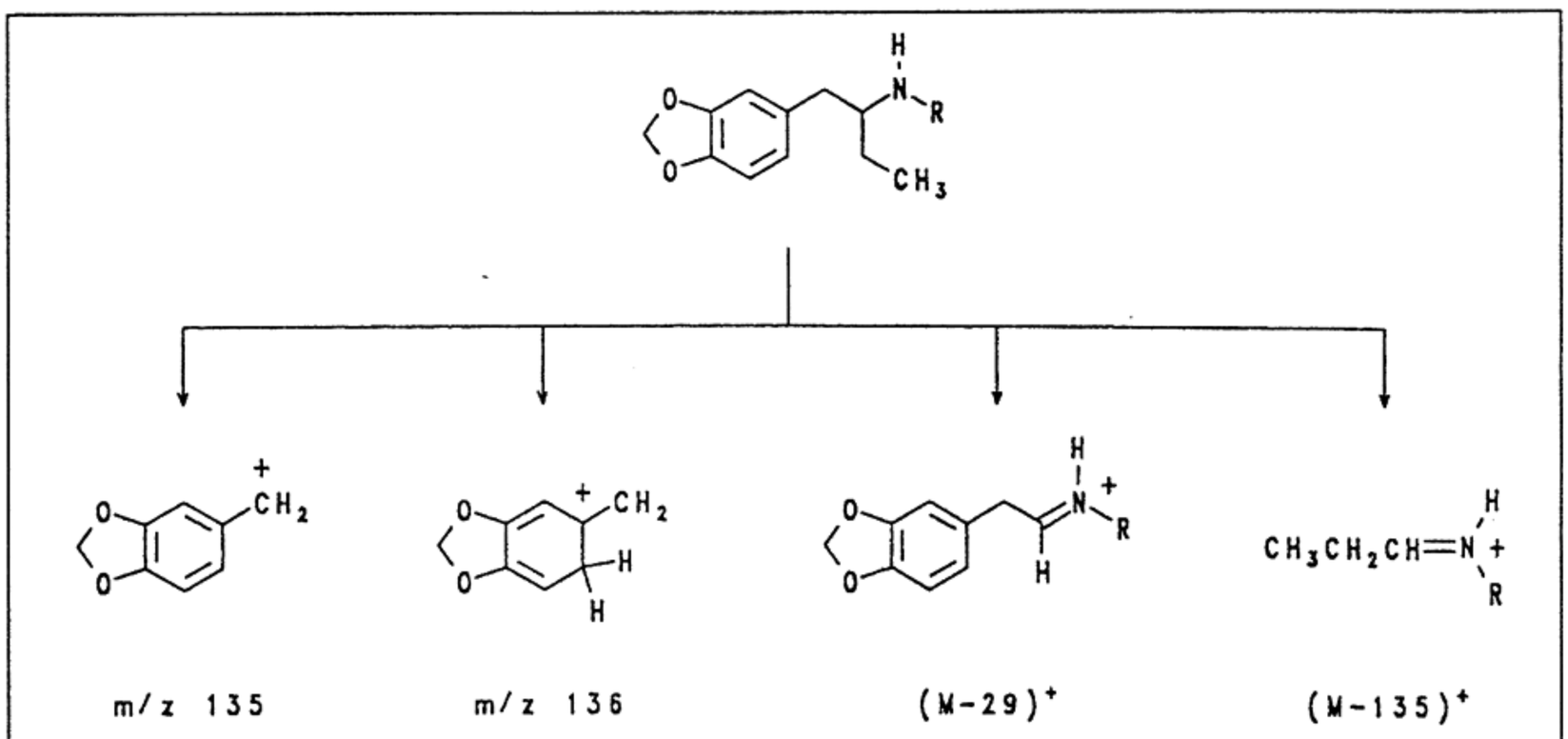
Synthesis of *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine

A solution of 1-(3,4-methylenedioxyphenyl)-2-butanone and hydroxylamine hydrochloride in pyridine and ethanol was stirred at reflux for several hours. The mixture was evaporated under reduced pressure to yield an oil that was dissolved in methylene chloride and washed with 1N HCl. The combined methylene chloride extracts were evaporated under reduced pressure to yield the intermediate oxime as a green oil. A solution of the crude oxime in methanol and sodium cyanoborohydride was stirred at room temperature for several days. The pH of the reaction mixture was maintained at neutrality by the periodic addition of concentrated HCl. The reaction mixture was evaporated to dryness, and the resulting solid was suspended in water and acidified carefully with concentrated HCl. The aqueous acid suspension was washed with methylene chloride and made basic by the addition of NaOH pellets. The aqueous base suspension was extracted with methylene chloride, and the combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. Filtration followed by evaporation of the filtered solvent yielded the product as a yellow oil. The oil was dissolved in anhydrous ether, and HCl gas was added to form the hydrochloride salt. Recrystallization from anhydrous 2-propanol afforded the product as white needles (56%); the melting point was 124–125°C.

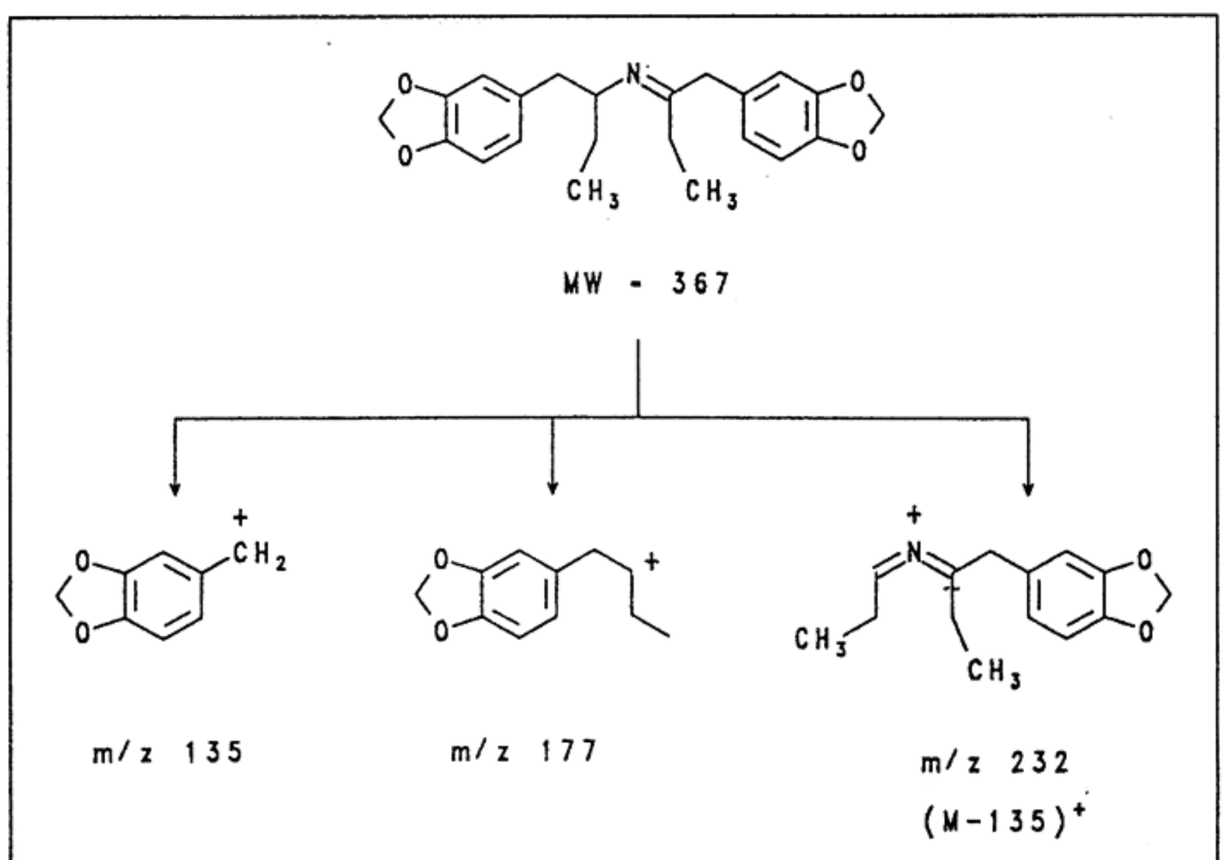
Results and Discussion

The synthesis and unique pharmacological properties of MDP-2-B were first reported by Nichols and co-workers in 1986 (11). They prepared this compound by reductive amination of the corresponding ketone, 1-(3,4-methylenedioxyphenyl)-2-bu-

tanone. The requisite ketone was prepared in a three-step sequence involving treatment of piperonal with propylmagnesium bromide, dehydration of the resulting alcohol, and finally oxidation of the 1-(3,4-methylenedioxyphenyl)-2-butene intermediate. In their paper, Nichols and co-workers also reported that attempts to synthesize MDP-2-B by the more direct nitrobutene method were unsuccessful because of the difficulties encountered in the condensation between piperonal and nitropropane. We found that modification of the initial condensation reaction can provide the key nitrobutene in good yield, and this intermediate can be reduced to MDP-2-B directly (12) or converted to 1-(3,4-methylenedioxyphenyl)-2-butanone. The butanone intermediate can be reductively aminated to afford a variety of MDP-2-B with varying *N*-substituents. Thus, treatment of piperonal with butylamine in benzene at reflux afforded the intermediate imine in quantitative yield (Scheme 1).



Scheme 2. The primary mass spectral fragmentation pathways for the 1-(3,4-methylenedioxyphenyl)-2-butanamines.

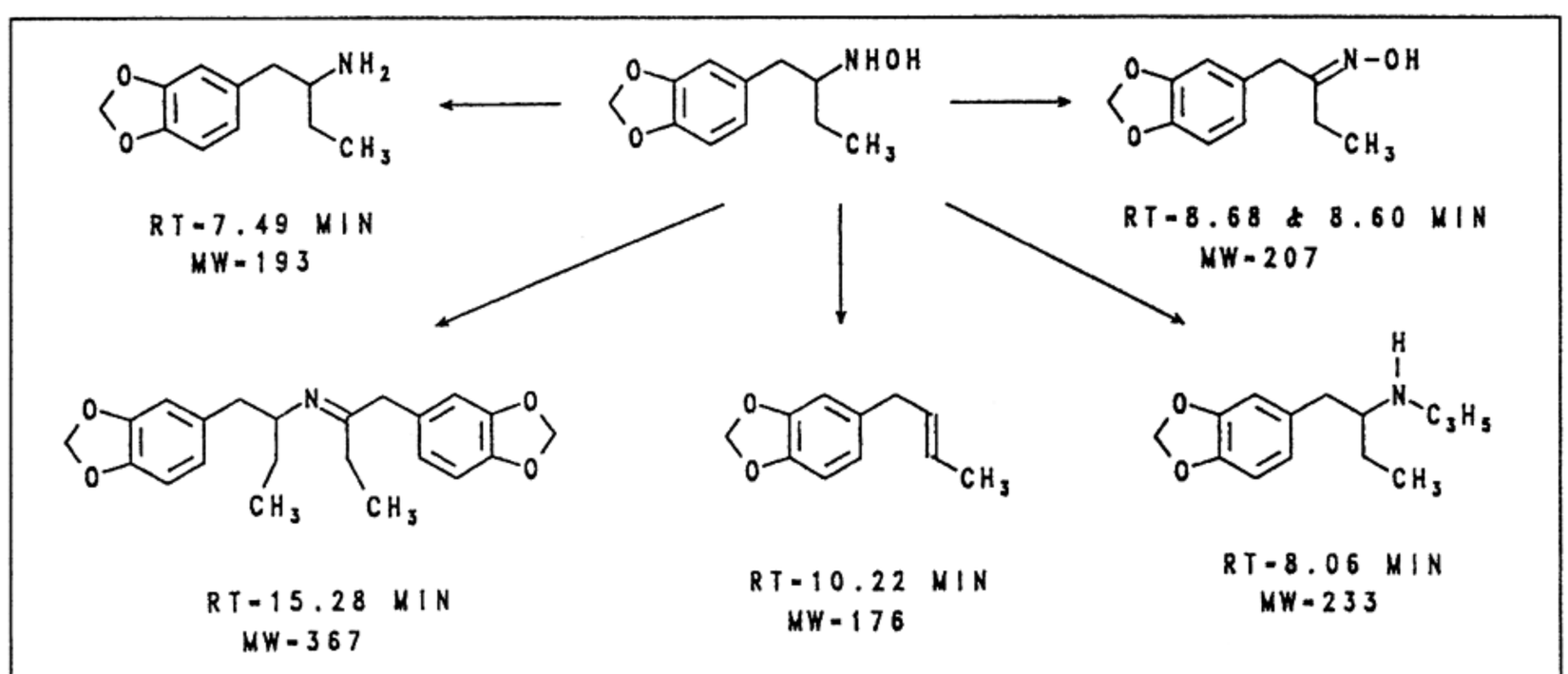


Scheme 3. Mass spectral fragmentation of the imine dimer formed from the decomposition of *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-OHB).

Reaction of the imine with nitropropane in acetic acid then provided the nitrobutene intermediate in yields exceeding 60%. Catalytic or lithium aluminum hydride reduction of the nitrobutene afforded the primary amine. Treatment of the nitrobutene intermediate with iron, ferric chloride, and HCl results in reduction of the nitrobutene to the enamine or imine, which then hydrolyzes to the ketone. Reaction of the ketone with ammonium acetate or alkylamines afforded MDP-2-B and the MDP-2-MB, MDP-2-EB, and MDP-2-MMB analogues. Because the dimethyl analogue was obtained in very low yield by this procedure, an alternate approach involving reductive methylation of MDP-2-B was attempted. The reaction of the primary butanamine with an excess of formaldehyde in the presence of sodium cyanoborohydride yielded the *N,N*-dimethyl analogue in high yield.

An initial objective of this work was to determine the analytical properties of the *N*-substituted MDP-2-B and compare these with various MDMA derivatives. Previous studies (3) showed that the 3,4-methylenedioxyphenyl group is a strong chromophore in the UV range with two major absorption bands in the 285- and 235-nm range. The absorptivity was slightly higher at 285 nm. The MDP-2-B in this study showed similar UV absorption properties and were not significantly different from the MDA derivatives (3). The various *N*-alkyl substituents did not affect the UV absorption, and an example UV spectrum for the primary amine (MDP-2-B) is shown in Figure 1. This spectrum was recorded using methanol as the solvent; however, the spectrum in dilute aqueous acid and base is essentially the same.

The reversed-phase LC separation of MDP-2-B and its *N*-substituted derivatives is shown in Figure 2. These compounds were separated on a C_{18} stationary phase using a mobile phase of pH 3.0 phosphate buffer–acetonitrile–triethylamine (600:100:1). The role of triethylamine in the mobile phase is to serve as a silanol masking agent (13). Triethylamine has basicity in the pK_a 10 range and, as the protonated triethylammonium ion, serves as a continuous displacer for solute–silanol associations. In this system, the primary amine (MDP-2-B) eluted first, followed by the *N*-methyl (MDP-2-MB), then the two C_2 *N*-alkyl derivatives (MDP-2-EB and MDP-2-MMB). The *N*-hydroxy analogue



Scheme 4. Summary of the thermal decomposition pathways for *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine.

(MDP-2-OHB) had the highest capacity factor in this chromatographic system. With the exception of MDP-2-OHB, this series of butanamine derivatives eluted in order of hydrophobic surface area of the *N*-substituent. The low pH of the mobile phase (pH 3.0) was sufficiently acidic to protonate the amine functionality of the butanamine derivatives, allowing these compounds to interact in the chromatographic environment as the more hydrophilic ammonium species. In previous studies (14), *N*-hydroxy MDA (NOHMDA) was found to have a pK_a value of 6.22, whereas MDA and *N*-alkyl derivatives of MDA

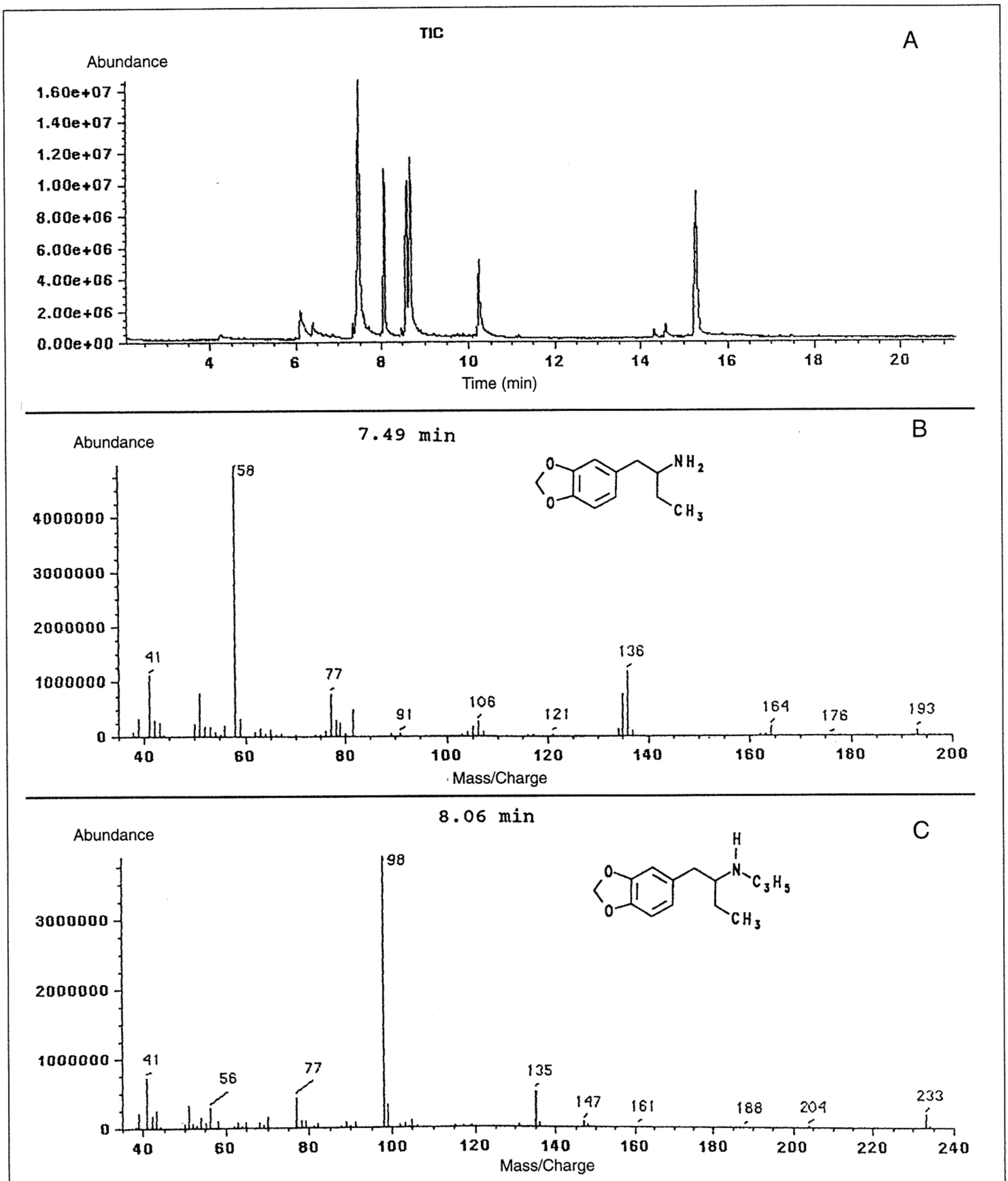


Figure 6. Gas chromatographic–mass spectrometric analysis of *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-OHB): A, chromatogram; B, mass spectrum of MDP-2-B; C, mass spectrum of *N*-propenyl/propylimino-MDP-2B. *(Continued on page 335.)*

showed significantly higher values in the pK_a 10 range. The higher than expected capacity factor for NOHMDA under similar reversed-phase chromatographic conditions (pH 3.0) was accounted for by a lower degree of ionization. The equivalent elution order for *N*-substituted butanamine derivatives and MDA derivatives suggests a similar retention process.

The same chromatographic system consisting of the C_{18} stationary phase and the mobile phase of phosphate buffer (pH 3.0), acetonitrile, and triethylamine was used to separate two other *N*-alkyl series of amines, the MDAs and the 3,4-methylenedioxyphenyl-3-butanamines (MDP-3-B or homomethylenedioxyamphetamines). Figure 3A shows the

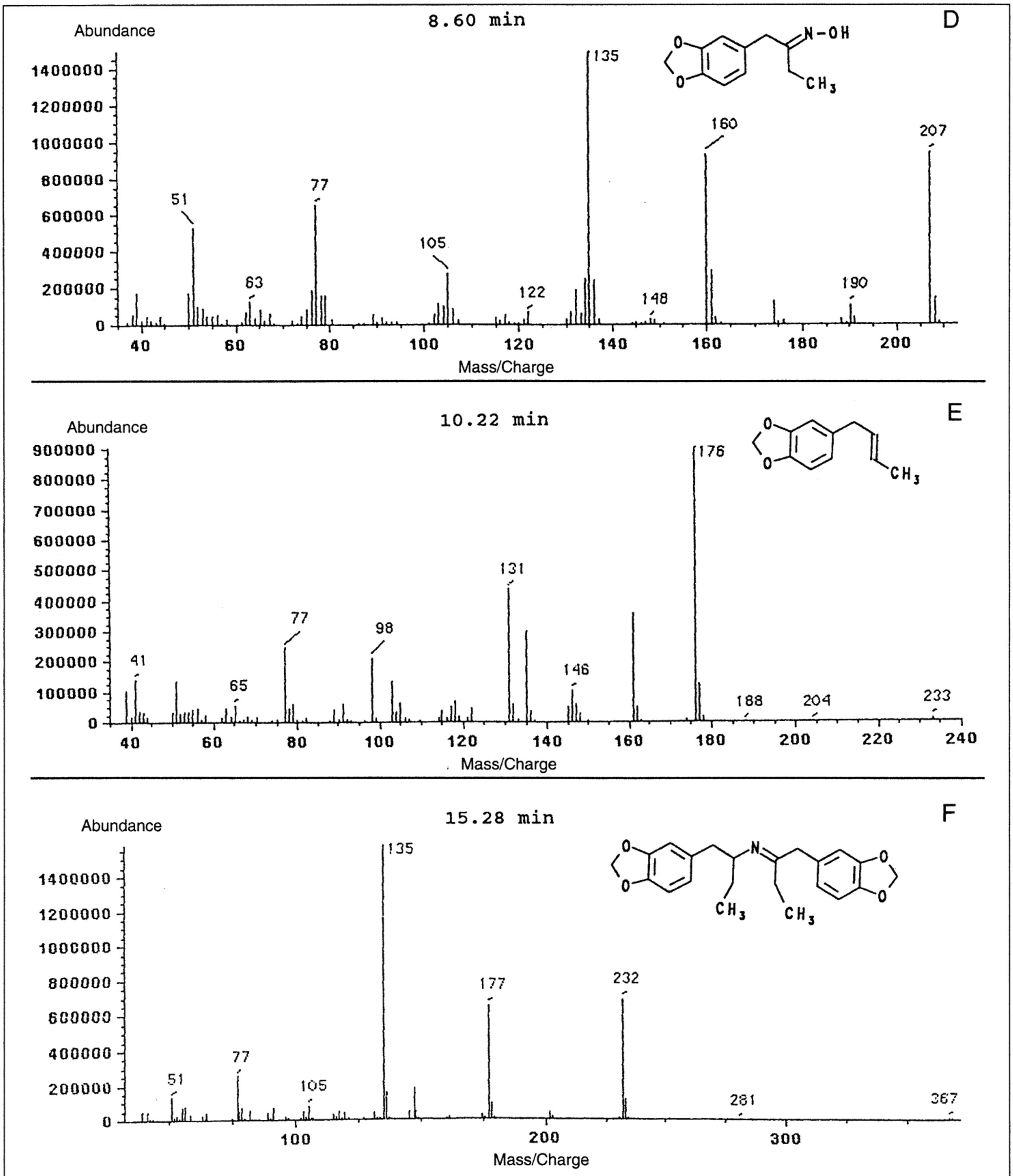


Figure 6. *(Continued from page 334.)* Gas chromatographic–mass spectrometric analysis of *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-OHB): D, mass spectrum of 1-(3,4-methylenedioxyphenyl)-2-butanoxime; E, mass spectrum of 1-(3,4-methylenedioxyphenyl)-1-butene; F, mass spectrum of imine dimer.

separation of the *N*-alkyl MDAs, and Figure 3B shows the separation of *N*-alkyl MDP-3-B. In both cases, the order of elution was according to hydrophobic surface area of the *N*-substituent; H eluted before C_1, and C_1 eluted before the C_2 derivatives. The three-carbon side-chain propanamines (MDAs) had lower capacity factors (eluted earlier) than the 3-butanamines when comparing compounds with identical *N*-substituents. For example, the *N*-methyl-substituted propanamine (MDMA) eluted at 5.87 min, whereas the *N*-methyl-3-butanamine (MDP-3-MB) eluted at 11.65 min. The *N*-methyl-2-butanamine (MDP-2-MB) (Figure 2) eluted between these two at 9.17 min. Furthermore, a comparison of Figures 2 and 3B shows that the 3-butanamines display higher capacity factors than the 2-butanamines of the same *N*-substituent in every case. The equivalent 2-propanamines eluted earlier than either series of butanamines.

Figure 4 shows the separation of MDMA and the two primary amine butanamines (MDP-2-B and MDP-3-B) that have the same molecular weight as this popular drug of abuse. The *N*-methyl-2-propanamine (MDMA) eluted first, followed by the 2-butanamine (MDP-2-B), with the 3-butanamine (MDP-3-B) having the highest capacity factor. Peaks 2 and 3 in Figure 4 again illustrate the increased retention of the 3-butanamines over the corresponding 2-butanamines.

The mass spectra for the *N*-alkyl derivatives of MDP-2-B show ions characteristic of extensive fragmentation usually observed in substituted phenalkylamines (Figure 5 and Scheme 2). The spectra in Figure 5 show a base peak resulting from the amine-dominated loss of the 3,4-methylenedioxybenzyl radical. This base peak appearing at $[M-135]^+$ is the *N*-substituted 1-propanimine shown in Scheme 2. The other α-cleavage product that would appear at $[M-29]^+$ from the loss of the ethyl group is less likely but is apparent in most of the spectra. The ions at *m/z* 135 and 136 are the 3,4-methylenedioxybenzyl cation and the hydrogen-rearranged radical cation, respectively. The radical cation at *m/z* 136 is the more abundant fragment only for the primary amine. In fact, the presence of the more abundant, rearranged, substituted benzyl radical cation is excellent evidence that the compound is a primary amine because two hydrogens on nitrogen increase the probability of the hydrogen-rearrangement product. The mass spectra for MDP-2-B and its *N*-alkyl derivatives were obtained via injection of a solution of each compound onto a GC–MS system using an HP-1 stationary phase film. The retention times were 7.53, 7.76, 8.06, and 8.09 min for MDP-2-B, MDP-2-MB, MDP-2-MMB, and MDP-2-EB, respectively. Thus, the retention properties for the C_2 *N*-substituents are such that resolution of these compounds would be poor. The GC analysis was attempted using various temperature programs without much improvement in resolution. The less than satisfactory resolution of the four compounds by GC illustrates the significance of the excellent reversed-phase LC separation already described.

The GC–MS analysis of the *N*-hydroxy-2-butanamine derivative, MDP-2-OHB, was complicated by its apparent thermal instability and reactivity. Figure 6 shows the GC–MS results of the injection of a sample of MDP-2-OHB. The result was a chromatogram showing several components, six of which were present in relatively significant amounts. Hydroxy-substituted amines were reported (3) to undergo thermal disproportionation reactions to yield the corresponding primary amine and the oxime. The peak at 7.49 min in Figure 6 shows a mass spectrum (Figure 6B) that matches that of the primary amine, MDP-2-B. The two peaks at 8.60 and 8.68 min show the same mass spectrum (Figure 6D), which matches the fragmentation properties of the 1-(3,4-methylenedioxyphenyl)-2-butanoxime isomers. A reference sample of *cis*- and *trans*-oxime was prepared by treating the corresponding ketone, 1-(3,4-methylenedioxyphenyl)-2-butanone, with hydroxylamine hydrochloride in the presence of pyridine. The peak at 8.06 min (Figure 6C) shows a mass spectrum suggestive of an *N*-substituted MDP-2-B derivative. The compound has an apparent molecular weight of 233 and shows an $[M-135]^+$ ion at *m/z* 98 and an $[M-29]^+$

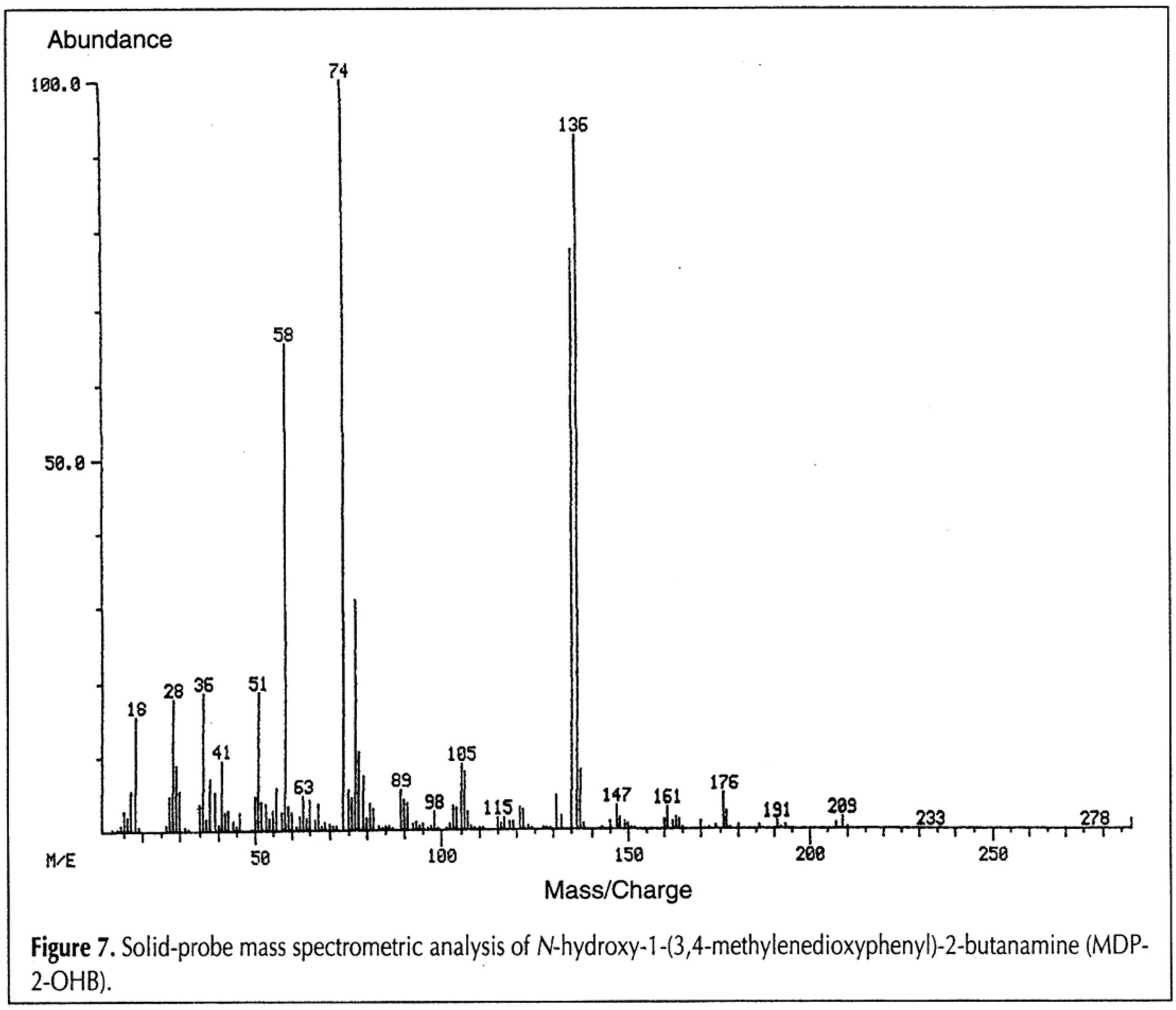


Figure 7. Solid-probe mass spectrometric analysis of *N*-hydroxy-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-OHB).

ion at *m/z* 204. These data suggest the addition of an *N*-substituent having a mass of 41, C_3H_5. This C_3H_5 unit could be present as *N*-allyl, the propylenamine, or the propylimine. The peak at 10.22 min (Figure 6E) appears to have a molecular ion of significant relative abundance (base peak) at *m/z* 176, suggesting the loss of the amino group to yield the C_4 alkene side chain, 1-(3,4-methylenedioxyphenyl)-1-butene, or an isomeric equivalent. However, the major fragment at *m/z* 161 $[M-15]^+$ and a significant *m/z* 135 peak could suggest the 2-butene isomer. The peak at 15.28 min (Figure 6F) shows a molecular ion of low relative abundance at *m/z* 367 whose fragment of highest mass is at *m/z* 232 $[M-135]^+$. This molecular weight suggests an imine dimer formed between MDP-2-B and 1-(3,4-methylenedioxyphenyl)-2-butanone or its equivalent (perhaps the oxime). This imine (Scheme 3) would easily fragment via the nitrogen to yield *m/z* 232 $[M-135]^+$ or the 3,4-methylenedioxyphenylbutane cation at *m/z* 177 and the 3,4-methylenedioxybenzyl cation at *m/z* 135. Scheme 4 is a summary of the compounds that appear to form when MDP-2-OHB is injected into this GC–MS system.

The thermal instability and reactivity of MDP-2-OHB is further illustrated by the mass spectrum in Figure 7. Figure 7 was obtained by solid-probe analysis of a sample of MDP-2-OHB and shows the expected base peak at *m/z* 74 $[M-135]^+$ and a molecular ion at *m/z* 209. However, the ions at *m/z* 58 and 136 suggest some decomposition to yield the primary amine, MDP-2-B, even under lower temperature, solid-probe conditions. It should be pointed out that LC analysis of MDP-2-OHB showed only one peak under conditions that clearly distinguished between MDP-2-B, the butanoxime, and other similar compounds. Thus, the various compounds identified by GC–MS analysis of MDP-2-OHB are formed because of the thermal instability of this compound.

Conclusion

N-Substituted-2-butanamines were separated by reversed-phase LC procedures using an acidic mobile phase. The elution order under these conditions was according to the size of the *N*-substituent with the primary amine (MDP-2-B) having the lowest capacity factor. The reversed-phase retention properties of the 2-butanamines were intermediate between the MDA derivatives (2-propanamines) and the corresponding 3-butanamines. The mass spectra for the 2-butanamines show the characteristic fragments for phenalkylamines and provide for specific identification of these compounds. The *N*-hydroxy butanamine, MDP-2-OHB, undergoes significant decomposition under GC conditions to yield a mixture of at least six compounds.

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Authors note added subsequent to manuscript acceptance: During the past few months, N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MDP-2-MB) has been reported in street drug samples in Europe and the United States (primarily Florida). The samples are in the form of white tablets. The street name for the drug is Fido Dido. The drug is reported to be prepared from the 3,4-methylenedioxyphenyl-2-butanone.