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GC–MS and LC of Addition Products Formed from the Reaction of Allylbenzene and Related Arylpropenes with Acetonitrile and Sulfuric Acid

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Abstract

The synthesis of amphetamine and related compounds from several arylpropenes is investigated using gas chromatography–mass spectrometry and liquid chromatography. Treatment of allylbenzene with acetonitrile and sulfuric acid yields a mixture of 1-phenyl-2-acetamidopropane and 1-phenyl-1-acetamidopropane. Hydrolysis of this product mixture gives the corresponding propanamines, amphetamine and 1-phenyl-1-propanamine. When the isomeric compound *trans*-β-methylstyrene is subjected to this reaction sequence, a single amine product, 1-phenyl-1-propanamine, is obtained. Treatment of the isomeric 3,4-methylenedioxyphenylpropenes (safrole and isosafrole) with acetonitrile and sulfuric acid followed by acid hydrolysis did not result in the formation of 3,4-methylenedioxyamphetamine (MDA). Safrole yields a dihydroisoquinoline derivative, whereas isosafrole gives simple dimers under these reaction conditions. The differences in the products obtained in these studies appear to be determined by differences in the electronic nature of the starting arylpropenes.

Introduction

Several 1-aryl-2-propanamines, including amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine (MDA), and 3,4-methylenedioxymethamphetamine (MDMA), remain popular synthetic drugs of abuse in the United States (Chart 1). Compounds of this structural class are often synthesized in clandestine laboratories by treatment of the appropriate ketones, 1-phenyl-2-propanone (P-2-P) or 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) with an amine under reducing conditions (1–3). Additionally, the amphetamine-type compounds are prepared by hydrogenolysis of commercially available 1-phenyl-1-hydroxy-2-propanamines, including ephedrine, pseudoephedrine, norephedrines, and phenylpropanolamine (3–5). In an attempt to limit the clandestine manufacture of 1-aryl-2-propanamine drugs of abuse, the sale and distribution of a variety of synthetic precursors, including P-2-P, MDP-2-P, the ephedrines, and norephedrines, are now federally regulated (6). This regulation of precursor chemicals has prompted clandestine chemists to pursue alternative methods for the synthesis of amphetamine and MDMA-type compounds. For example, there have been several reports recently of clandestine chemists preparing 1-phenyl-2-nitropropene and converting this intermediate to P-2-P for the manufacture of methamphetamine (7). The MDMA precursor, MDP-2-P, can be prepared from isosafrole in a reaction sequence involving treatment with hydrogen peroxide and formic acid followed by sulfuric acid (8). Also, an alternative method using safrole for the clandestine manufacture of MDMA has been described recently (9). In this approach, safrole is treated with HBr to yield the intermediate bromosafrole that, upon reaction with methylamine, affords MDMA. This latter method, when applied to commercially available allylbenzene instead of safrole, can be used for the synthesis of amphetamine and methamphetamine (Scheme 1). It also has been reported that this same starting material, allylbenzene, may be converted to amphetamine by an alternative method involving treatment with acetonitrile and sulfuric acid, followed by acid hydrolysis of the 2-acetamido intermediate (Scheme 1). In this study, the latter approach for the synthesis of amphetamine was investigated using gas chromatography–mass spectrometry (GC–MS) and liquid chromatography. The scope of this general method and its application for the synthesis of MDA-type drugs of abuse was also studied by analysis of the

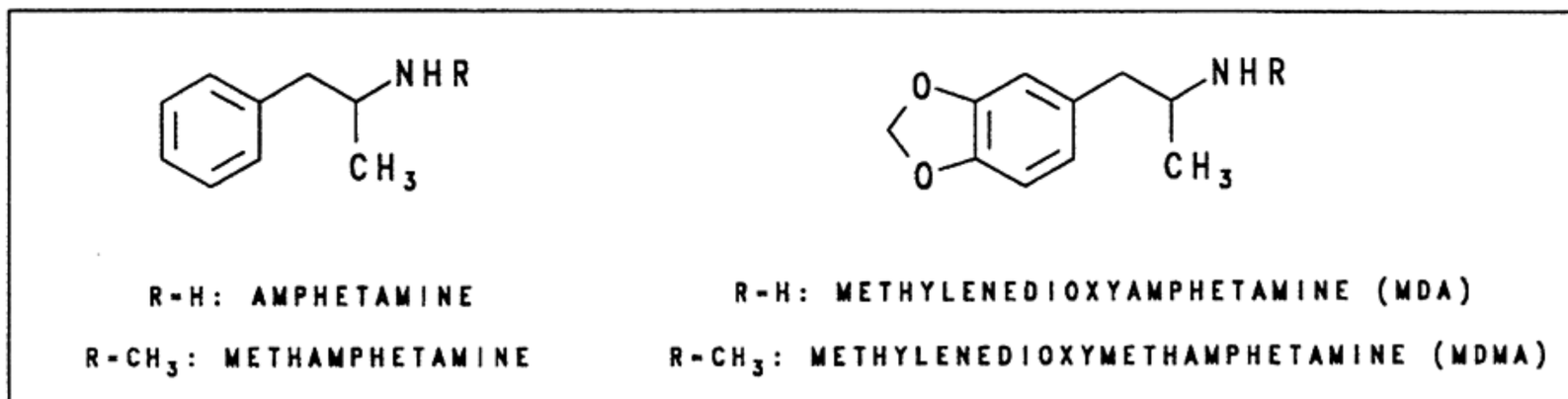

Chart 1. Synthetic drugs of abuse: amphetamine, methamphetamine, methylenedioxyamphetamine, and methylenedioxymethamphetamine.

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amine products formed upon treatment of *trans*-β-methylstyrene, safrole, and isosafrole with acetonitrile and sulfuric acid followed by acid hydrolysis.

Experimental

Gas chromatography–mass spectrometry

GC–MS analyses were performed using a Hewlett-Packard 5970B mass selective detector (Wilmington, DE). The mass spectrometer was operated in the electron impact mode at 70 eV. The source temperature was maintained at 220°C. The samples (1 µL) were introduced into the mass spectrometer with an autoinjector-equipped GC that had a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-µm film thickness of methylsilicone (HP-1). The column temperature was held at 70°C for 2 min and programmed to 170°C at a rate of 10°C/min and from 170°C to 275°C at a rate of 25°C/min with a hold time of 2 min. The injector port temperature was 175°C. The GC was operated in the split mode with a split ratio of 20:1. The carrier gas was ultra-pure helium. On-column acetylation of the amines was accomplished by injection of the amine in an excess of acetic anhydride.

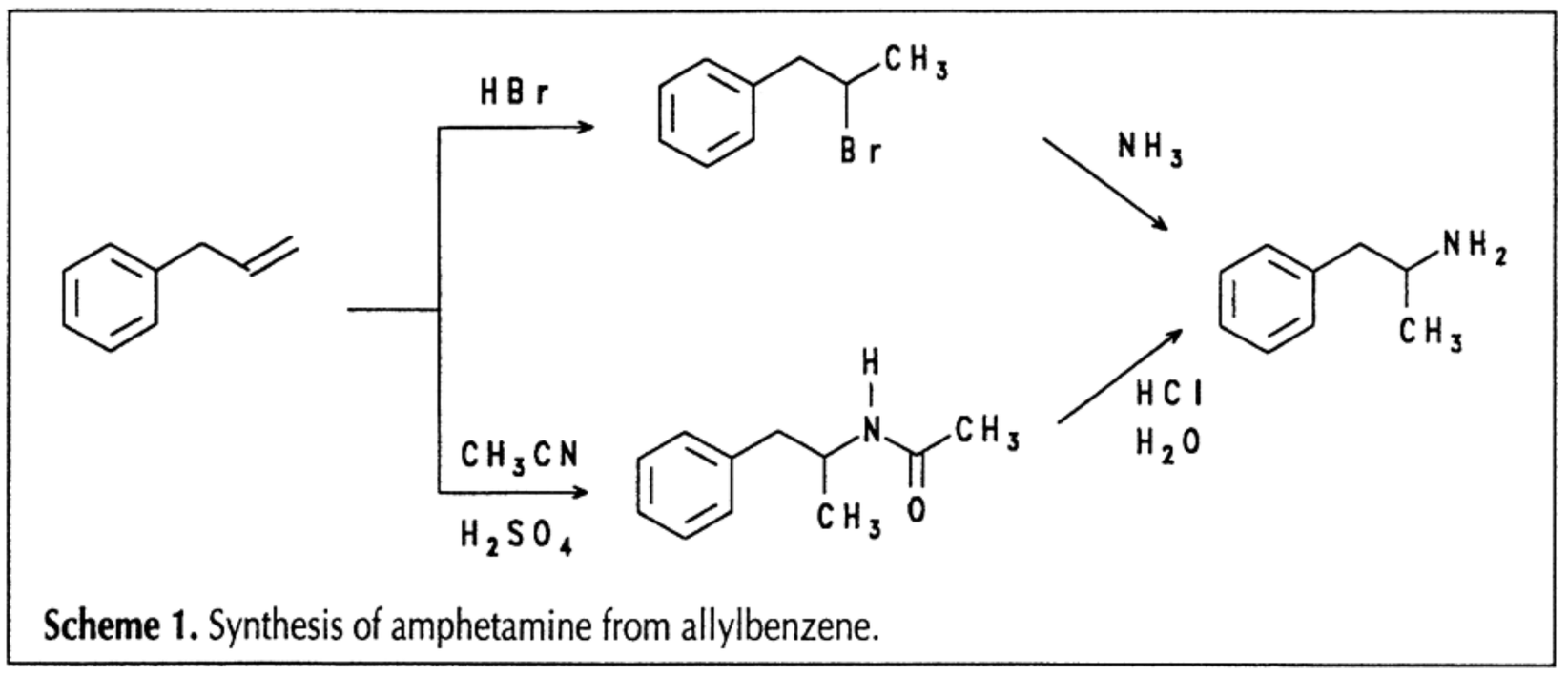
Liquid chromatography

The liquid chromatograph consisted of a Laboratory Data Control Constametric 3000 pump, a 3100 Spectromonitor ultraviolet detector, a CI 4100 integrator (Riviera Beach, FL), and a Rheodyne 7125 injector (Cotati, CA).

The analytical column had dimensions of 30 cm × 3.9-mm i.d. and 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. The samples were dissolved in HPLC-grade methanol, and a 5-µL injection was analyzed using a mobile phase of pH 3.0 phosphate buffer, HPLC-grade methanol, and triethylamine (500:100:1). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate in 1 L 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 240 nm and 0.2 AUFS.

Treatment of arylpropenes with acetonitrile and sulfuric acid

The arylpropenes (allylbenzene, *trans*-β-methylstyrene, safrole, or isosafrole) were added to a mixture of acetonitrile and concentrated sulfuric acid, and the mixture was stirred at room temperature for several hours. The reaction mixture was cooled and made alkaline by the addition of NaOH. The aqueous alkaline suspension was extracted twice with ether, and the combined ether extracts were washed successively with water, saturated $NaHCO_3$, and water. Evaporation of the ether solvent



Scheme 1. Synthesis of amphetamine from allylbenzene.

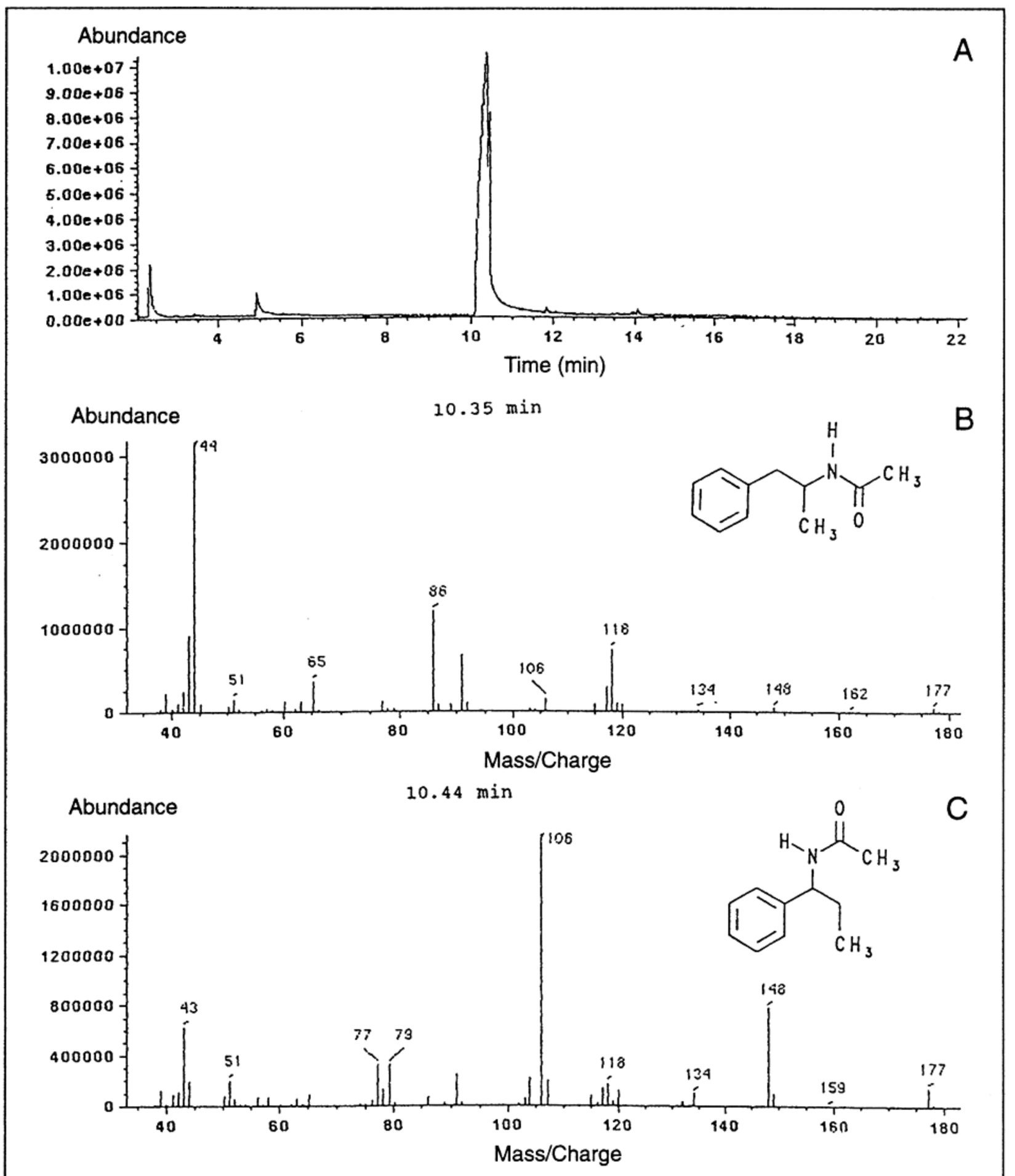
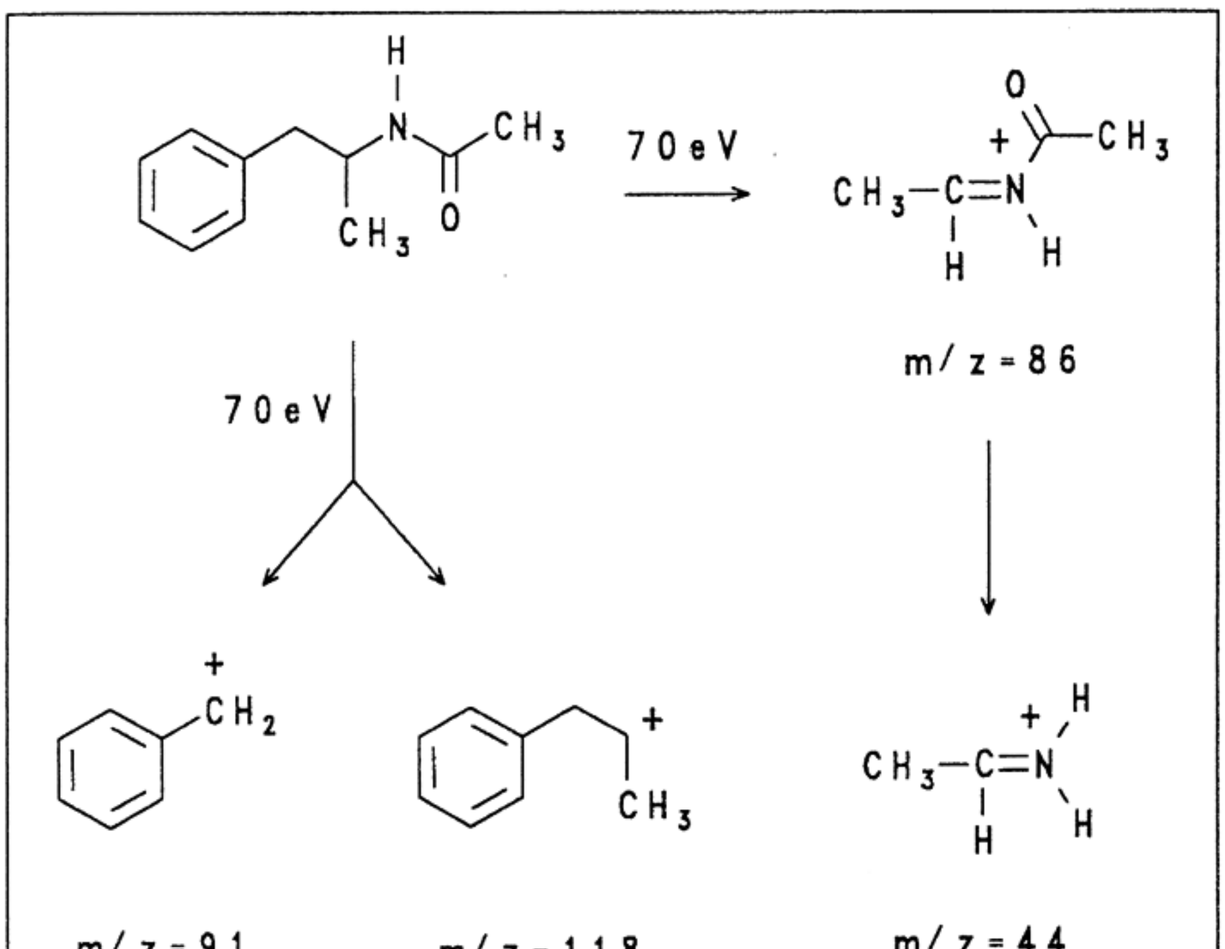


Figure 1. Gas chromatographic and mass spectral analysis of the products formed from treatment of allylbenzene with acetonitrile and sulfuric acid: A, chromatogram; B, mass spectrum of the acetamide of 1-phenyl-2-propanamine; C, mass spectrum of the acetamide of 1-phenyl-1-propanamine.



Scheme 2. Mass spectral fragmentation of the acetamide of 1-phenyl-2-propanamine.

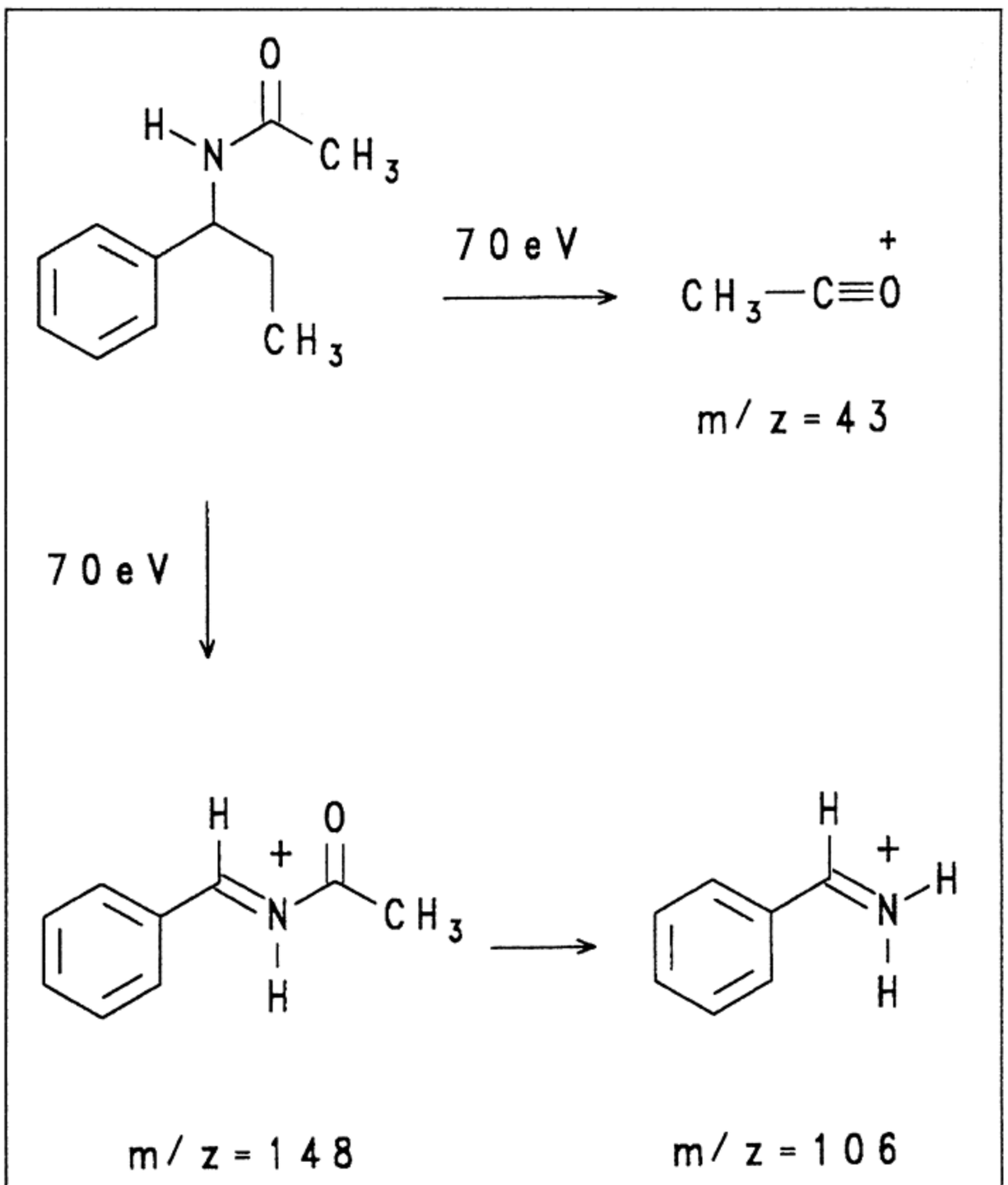
under reduced pressure yielded the product oils, which were analyzed by GC–MS without further purification.

Hydrolysis reactions

The crude oils obtained from treatment of the arylpropenes with acetonitrile and sulfuric acid were stirred at reflux in aqueous HCl for several hours. The reaction mixture was cooled to room temperature and washed with ether. The aqueous acid solution was cooled and made basic by the addition of NaOH pellets. The aqueous base suspension was extracted twice with methylene chloride, and the combined organic extracts were washed with water and dried over anhydrous potassium carbonate. Filtration followed by evaporation of the filtrate solvent yielded the amine fraction, which was analyzed without further purification.

1-Phenyl-1-propanamine

A suspension of propiophenone, ammonium acetate, and sodium cyanoborohydride in methanol was stirred at room temperature for several days. The pH of the reaction mixture was maintained at neutrality by periodic addition of concentrated HCl. The reaction mixture was evaporated to dryness to yield a white solid. The solid was suspended in water and acidified by the addition of concentrated HCl. The acidic suspension was washed with methylene chloride and made basic by the addition of NaOH pellets with cooling. The resultant basic suspension was extracted twice with methylene chloride, and the combined organic extracts were evaporated under reduced pressure to yield a yellow oil. The oil was dried at room temperature under vacuum and dissolved in anhydrous ether. Addition of HCl gas to the ether solution yielded the product amine hydrochloride as a white solid. The product was isolated by filtration and recrystallized from a mixture of ether and ethanol.



Scheme 3. Mass spectral fragmentation of the acetamide of 1-phenyl-1-propanamine.

Results and Discussion

The initial goal of this project was to identify the products, by-products, and contaminants involved in the preparation of amphetamine from allylbenzene (3-phenylpropene). Allylbenzene is a commercially available and uncontrolled precursor substance that contains the carbon skeleton of the amphetamine-type drugs of abuse. It is reported that the unconjugated double bond in allyl-substituted aromatic systems can be functionalized at the 2-position by treatment with acetonitrile and sulfuric acid (9). The resultant 2-acetamido intermediate or *N*-acetylamphetamine is hydrolyzed with aqueous HCl to yield amphetamine, presumably as the major or only amine product (Scheme 1).

The GC–MS analysis of the crude sample obtained following treatment of allylbenzene with acetonitrile in sulfuric acid is

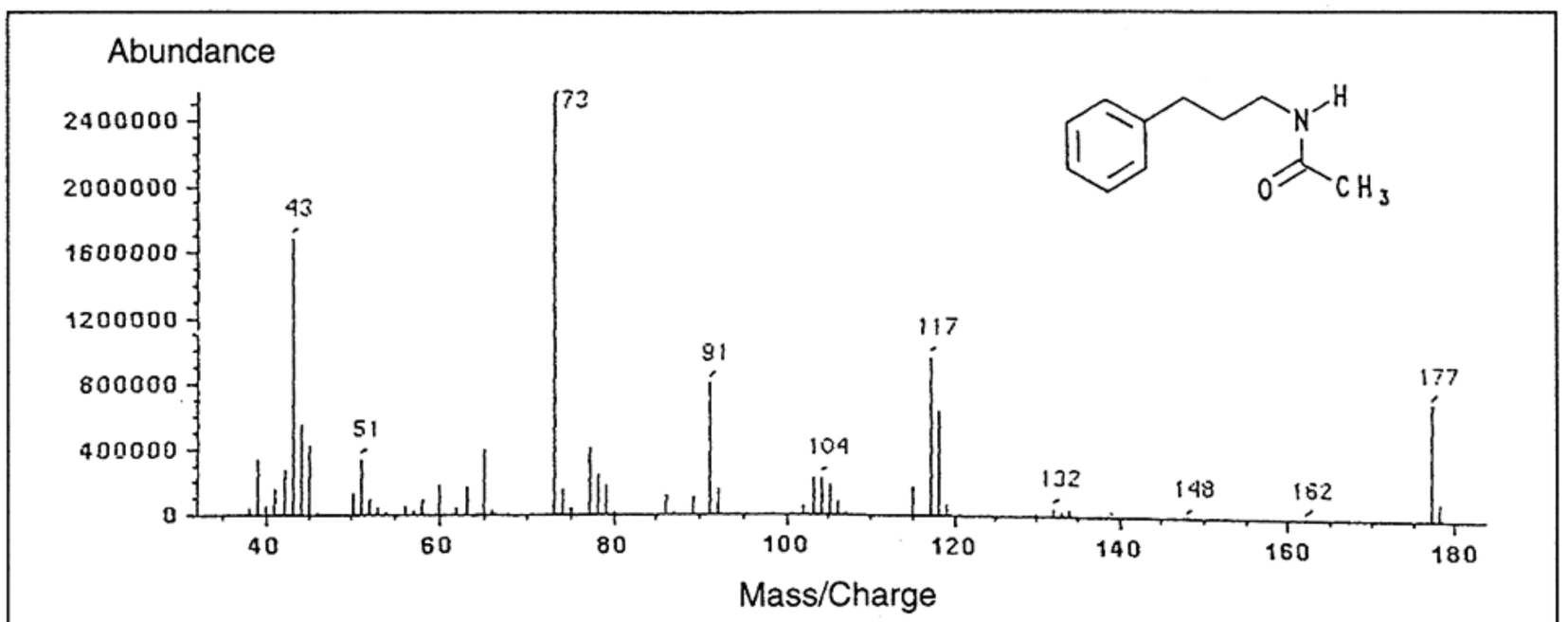
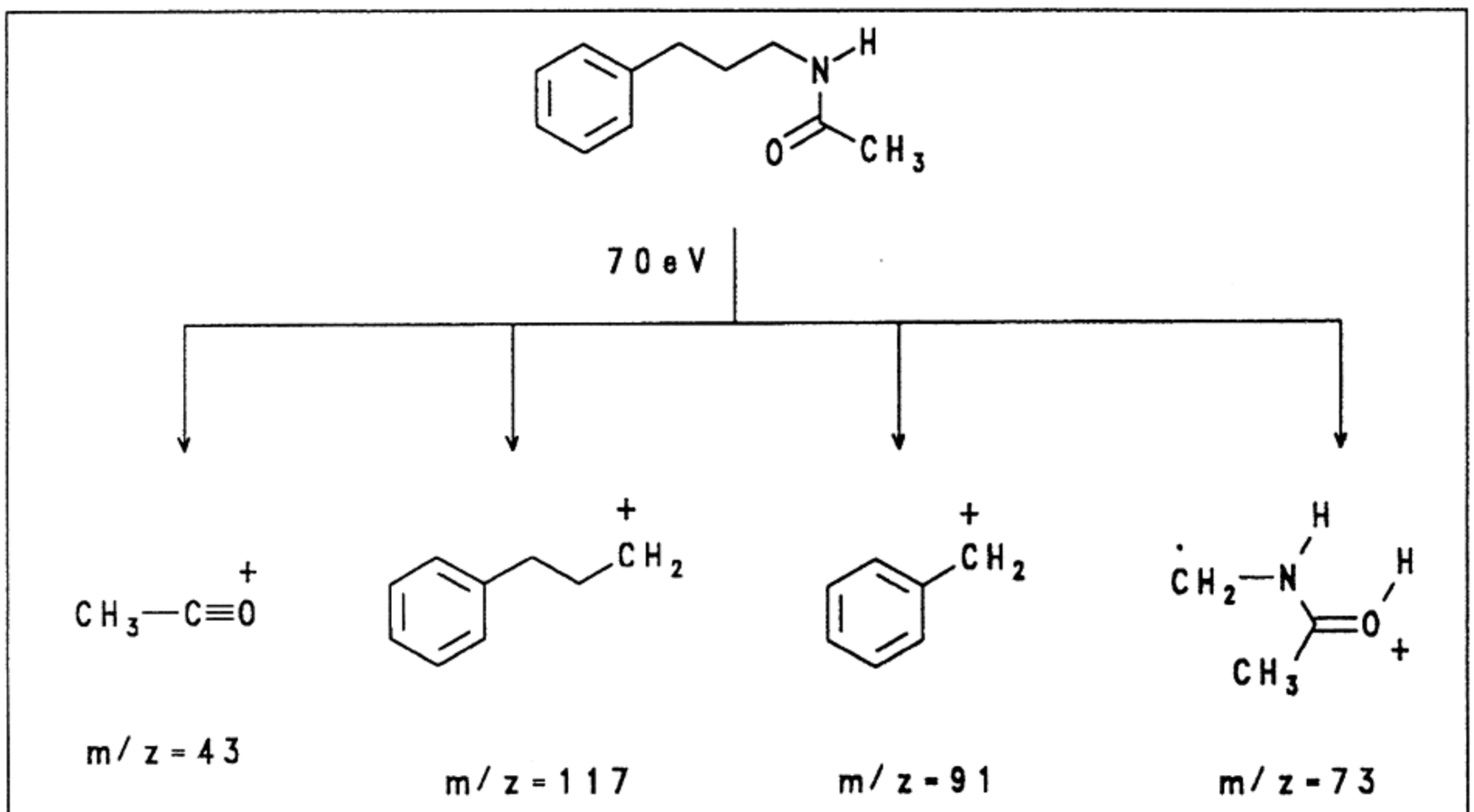


Figure 2. Mass spectrum of the acetamide of 1-phenyl-3-propanamine.

shown in Figure 1. The peak eluting at 2.35 min is the starting material allylbenzene, and the other small peak at 4.92 min is 1-phenyl-2-propanol. The identity of these two minor contaminants was confirmed by GC–MS analysis of the appropriate reference materials. The major fraction eluting at just over 10 min is a mixture of at least two compounds, one band at 10.35 min and a second band at 10.44 min. The major component shows a molecular ion at *m/z* 177 and fragment ions of significant relative abundance at *m/z* 118, 91, 86, and 44 (Figure 1B). A molecular ion at 177 amu is consistent with the addition of acetamide across the double bond of allylbenzene, and the *m/z* 86 and 44 ions suggest the acetamido group is attached at the 2-carbon of the propyl side chain, yielding 1-phenyl-2-acetamidopropane (Scheme 2). The ions at *m/z* 91 and 118 represent the benzyl cation and the phenylpropyl radical cation, respectively. Thus the major component resulting from the treatment of allylbenzene with acetonitrile in the presence of sulfuric acid appears to be the acetamide of amphetamine.



Scheme 4. Mass spectral fragmentation of the acetamide of 1-phenyl-3-propanamine.

The later eluting minor component in Figure 1A gave the mass spectrum shown in Figure 1C. This spectrum also shows a molecular ion at *m/z* 177; however, the major fragment ions occur at 148 and 106 amu. One initial prediction for this component would be the addition of the acetamido group across the double bond of allylbenzene in the opposite manner, resulting in acetamido substitution at the 3-carbon. However, the fragment ion in the mass spectrum at *m/z* 148 indicates a loss of 29 mass units from the molecular ion, and the base peak at *m/z* 106 represents the loss of the acetyl group through a hydrogen rearrangement from the *m/z* 148 ion (Scheme 3). These data suggest addition of the acetamido group at the 1-position of the propyl side chain and not the 3-position. This could be the result of initial carbocation formation at the 2-position as expected, followed by rearrangement to the more stable 1-position (benzylic position) before attack by the reactive nitrogen-containing species.

Reference standards of the acetamides of 1-phenyl-1-propanamine, 1-phenyl-3-propanamine and amphetamine (1-phenyl-2-propanamine), were prepared for comparison with the sample mixture analyzed in Figure 1. A sample of 1-phenyl-1-propanamine was prepared by reductive amination of propiophenone using ammonium acetate and sodium cyanoborohydride. Samples of 1-phenyl-3-propanamine and amphetamine were obtained from commercial sources. The acetamides were prepared by treating each amine with acetic anhydride. Although the three isomeric acetamides were not well resolved under the GC–MS conditions employed in this study, the individual mass spectra clearly allow the identi-

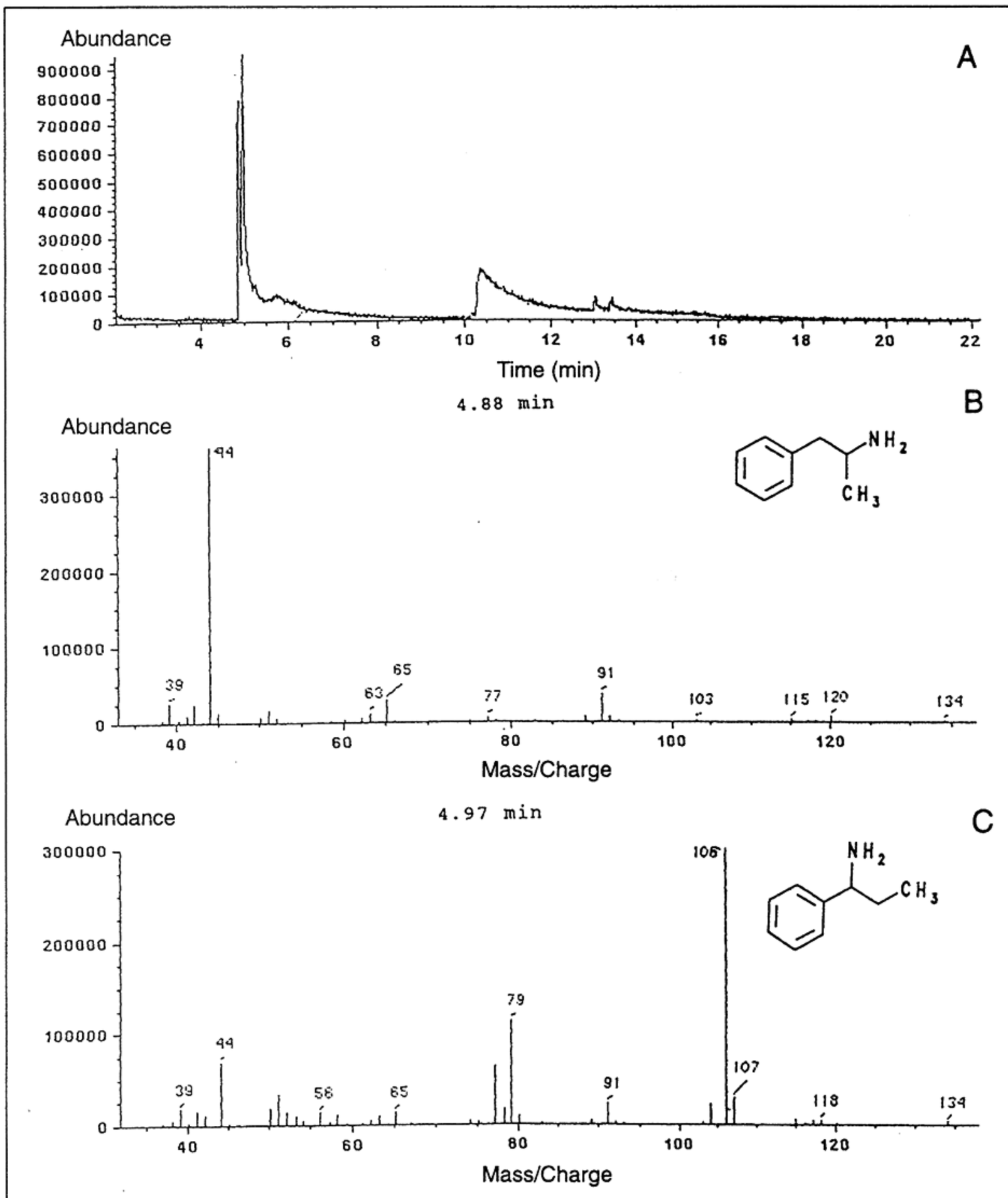


Figure 3. Gas chromatographic and mass spectral analysis of the acetamide hydrolysis product: A, chromatogram; B, mass spectrum of 1-phenyl-2-propanamine (amphetamine); C, mass spectrum of 1-phenyl-1-propanamine.

fication of the components in the original reaction sample. The reference spectra for the acetamides of amphetamine and 1-phenyl-1-propanamine match those of the two major components (Figures 1B and 1C, respectively) obtained following treatment of allylbenzene with acetonitrile in sulfuric acid. The mass spectrum for the acetamide of 1-phenyl-3-propanamine (Figure 2) is significantly different from either of the regioisomeric acetamides found in the product mixture. The fragmentation reactions observed for the three regioisomeric acetamides are shown in Schemes 2–4.

The sample analyzed in Figure 1 subjected to hydrolysis in 15% HCl, and the amine fraction isolated from this reaction produced the data shown in Figure 3, revealing the presence of two peaks eluting in the 5-min range. The component eluting at 4.88 min has a base peak at *m/z* 44 and other fragments consistent with the spectrum for amphetamine. The other component eluting at 4.97 min has a base peak at *m/z* 106 from loss of 29 mass units from the molecular ion and therefore appears to be the positional isomer, 1-phenyl-1-propanamine. The chromatographic properties and mass spectra for authentic samples of amphetamine and 1-phenyl-1-propanamine match those of the two early eluting components in Figure 3.

Figure 4 shows the results of reversed-phase liquid chromatographic analysis of the amine fraction isolated following hydrolysis of the allylbenzene–acetonitrile reaction intermediate. The two major components are well resolved and can be compared with the separation of the three isomeric 1-phenyl-propanamines shown in Figure 5. These data again show the amines obtained from allylbenzene to be a mixture of amphetamine and 1-phenyl-1-propanamine. The reversed-phase separations were accomplished using a C_{18} stationary phase and a mobile phase of pH 3 phosphate buffer, methanol, and triethylamine (500:100:1). These experiments show that significant quantities of amphetamine can be prepared from allylbenzene and that the presence of 1-phenyl-1-propanamine in the samples can serve as an indicator substance for this route of synthesis.

The scope of this synthetic method was investigated further by treating *trans*-β-methylstyrene with acetonitrile and sulfuric acid under reaction conditions identical to those employed in the allylbenzene study. Allylbenzene and *trans*-β-methylstyrene are isomeric, differing only in the position of the double bond in the propene side chain. Treatment of the conjugated double bond in *trans*-β-methylstyrene with acetonitrile and acid followed by hydrolysis gave a basic fraction containing one major component. The liquid chromatographic analysis of this sample showed a single peak, and the retention properties of this component matched those of 1-phenyl-1-propanamine. GC–MS analysis of the intermediate acetamide from this reaction showed one peak whose mass spectrum was identical to that shown in Figure 1C, the acetamide of 1-phenyl-1-propanamine. These results indicate that only the benzylic carbocation is formed via protonation of *trans*-β-methylstyrene, and addition of the acetamido group occurs at the benzylic position. Thus, no amphetamine was obtained from this procedure.

The side chain of (3,4-methylenedioxyphenyl)propenes has been functionalized to produce the methylenedioxyam-

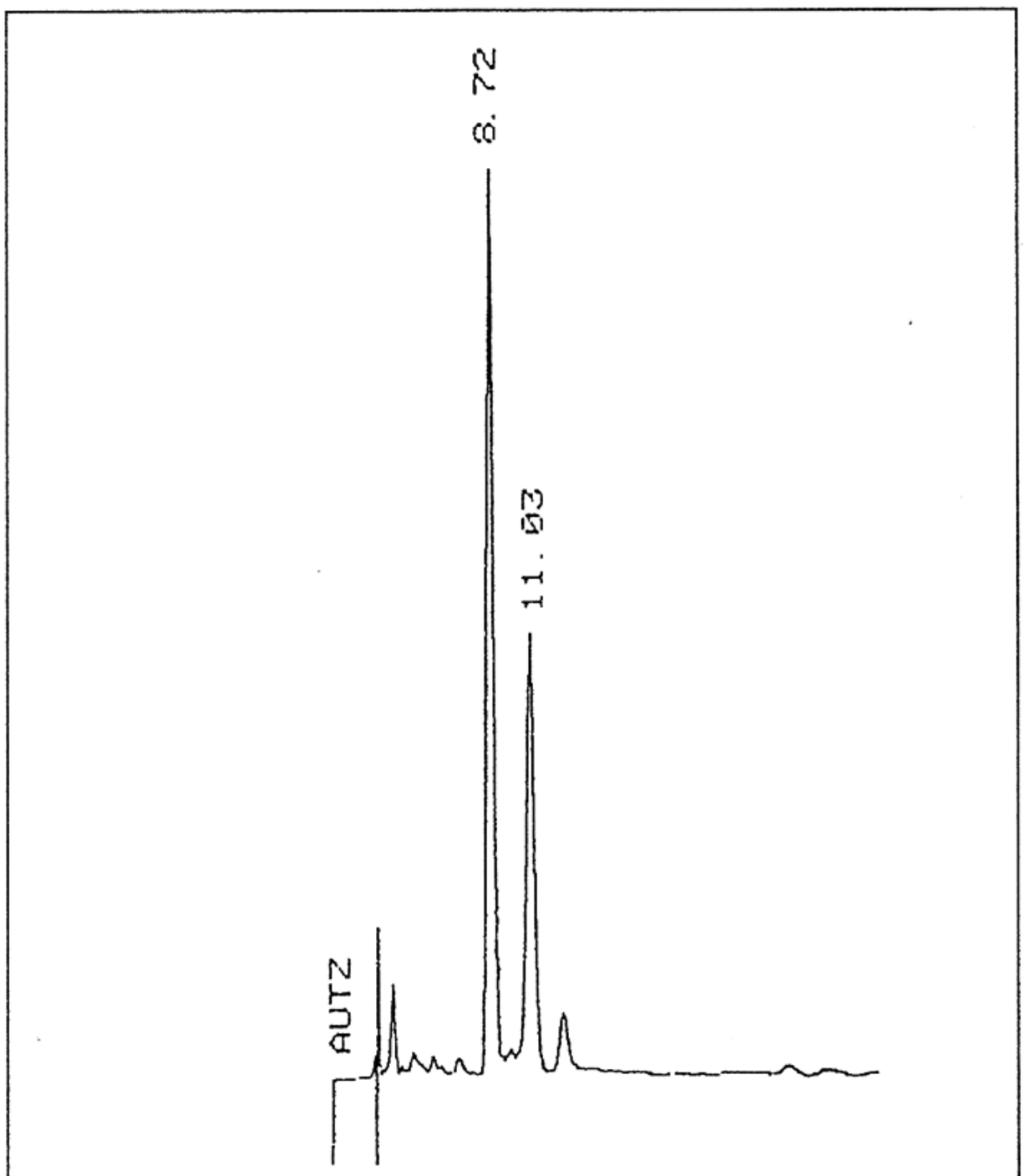


Figure 4. Liquid chromatographic separation of 1-phenyl-2-propanamine (amphetamine, 8.72 min) and 1-phenyl-1-propanamine (11.03 min).

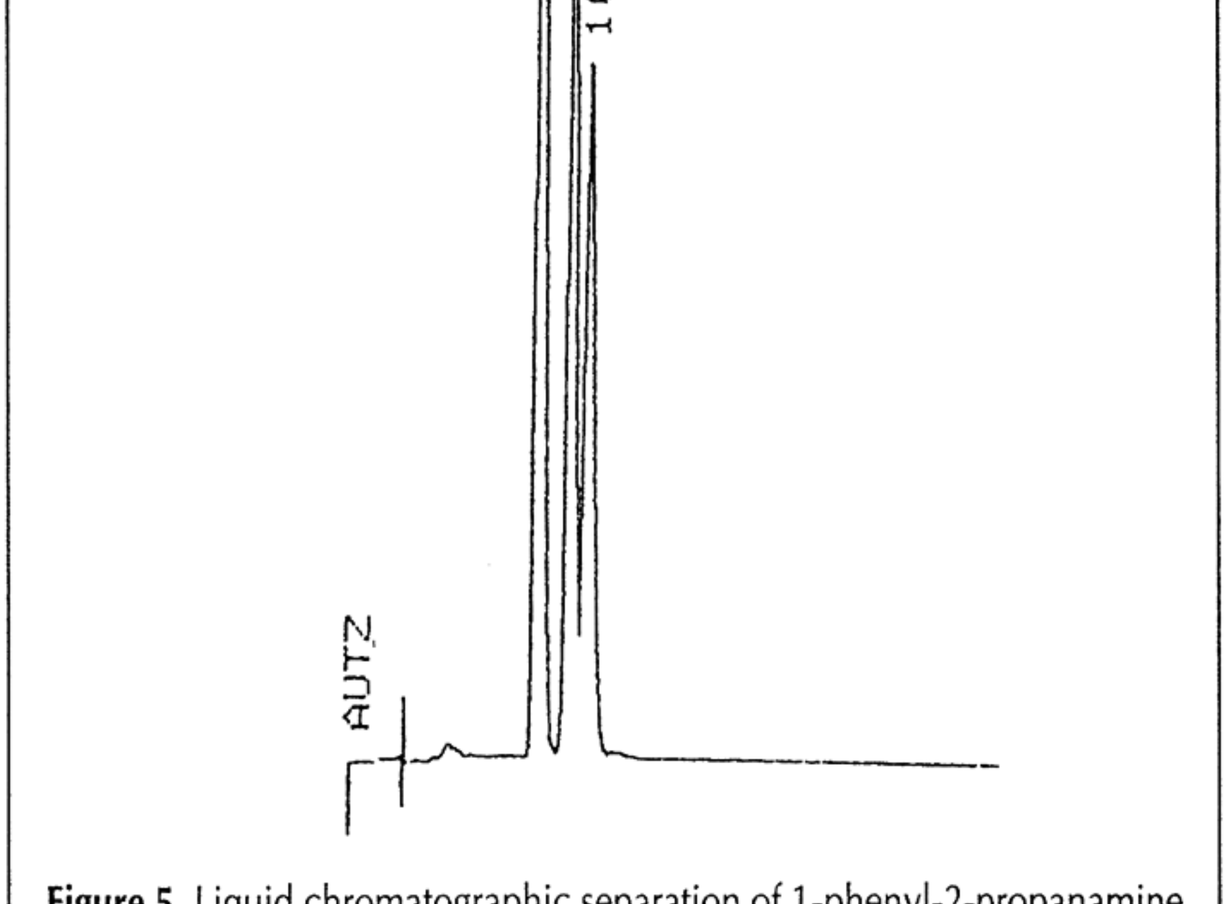


Figure 5. Liquid chromatographic separation of 1-phenyl-2-propanamine (amphetamine, 8.61 min), 1-phenyl-3-propanamine (10.12 min), and 1-phenyl-1-propanamine (10.96 min).

phetamine drugs of abuse, including MDA and MDMA, as described earlier (8,9). Safrole (3-[3,4-methylenedioxyphenyl]-1-propene or 3,4-methylenedioxyallylbenzene) has been converted to MDA and related compounds in a two-step procedure involving activation of the double bond by addition of HBr followed by displacement with an appropriate amine (9). Figure 6 shows the GC–MS analysis of the product obtained following treatment of safrole with acetonitrile and sulfuric acid. This product remained unchanged after hydrolysis in aqueous HCl. The chromatogram suggests one major component, and the mass spectrum suggests a compound with a molecular weight of 203. The high relative abundance (base peak) at *m/z* 203 indicates a very stable molecule that does not readily undergo significant fragmentation. Figure 7 shows the GC–MS analysis of an authentic sample of *N*-acetyl MDA prepared by treating MDA with acetic anhydride. A comparison of the chromatograms in Figures 6 and 7 and the corresponding mass spectra shows that the sample component in Figure 6 is not *N*-acetyl MDA. The molecular ion from the sample occurs at 18 mass units lower than that for *N*-acetyl MDA, suggesting the loss of water (or equivalent). Furthermore, the spectrum in Figure 6 for the sample component contains no *m/z* 135 ion, suggesting extensive substitution or cyclization in this material. One possible structure that fits these observations is a dihydroisoquinoline product that would result from cyclization of the intermediate obtained by attack of the reactive acetonitrile species upon the activated safrole moiety (Scheme 5). Treatment of an authentic sample of *N*-acetyl MDA with sulfuric acid did not, however, produce the suspected dihydroisoquinoline product. This would suggest that the cyclization reactions occur through some intermediate prior to formation of the *N*-acetyl species, perhaps the initial acetonitrile addition product as shown in Scheme 5. These experiments confirm that MDA is not a likely product via this synthetic procedure.

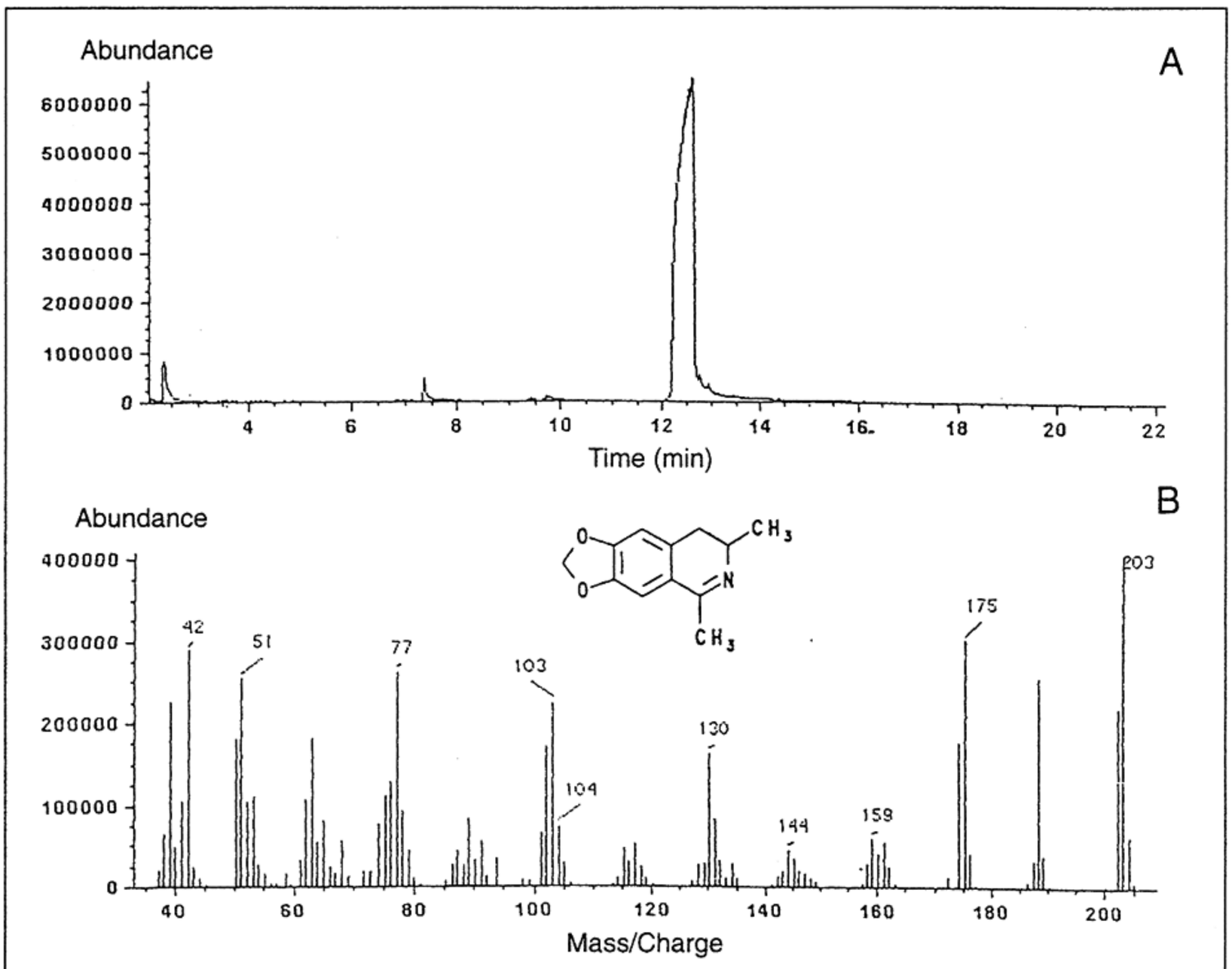


Figure 6. Gas chromatographic and mass spectral analysis of the products formed from treatment of safrole with acetonitrile and sulfuric acid: A, chromatogram; B, mass spectrum of dihydroisoquinoline product.

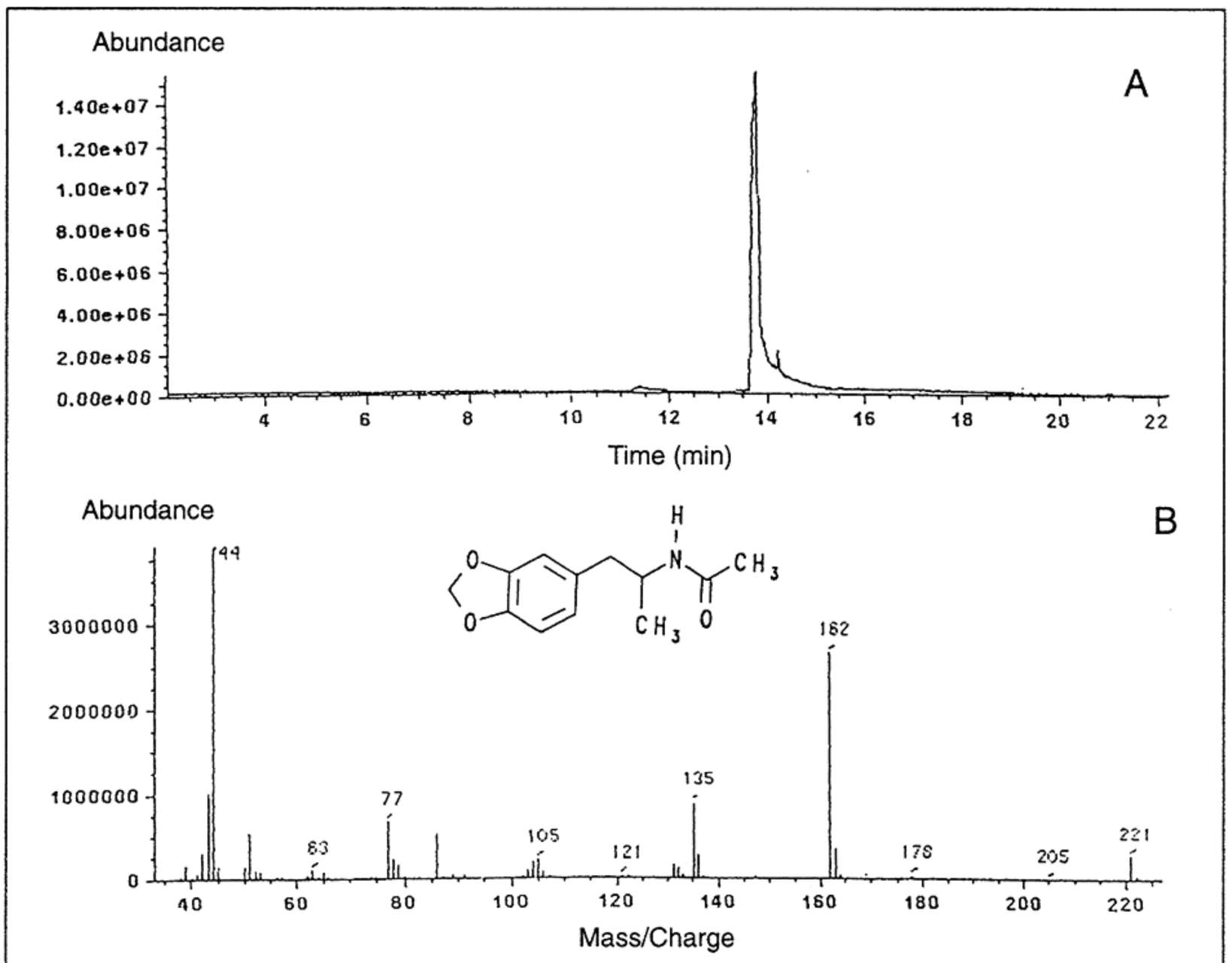
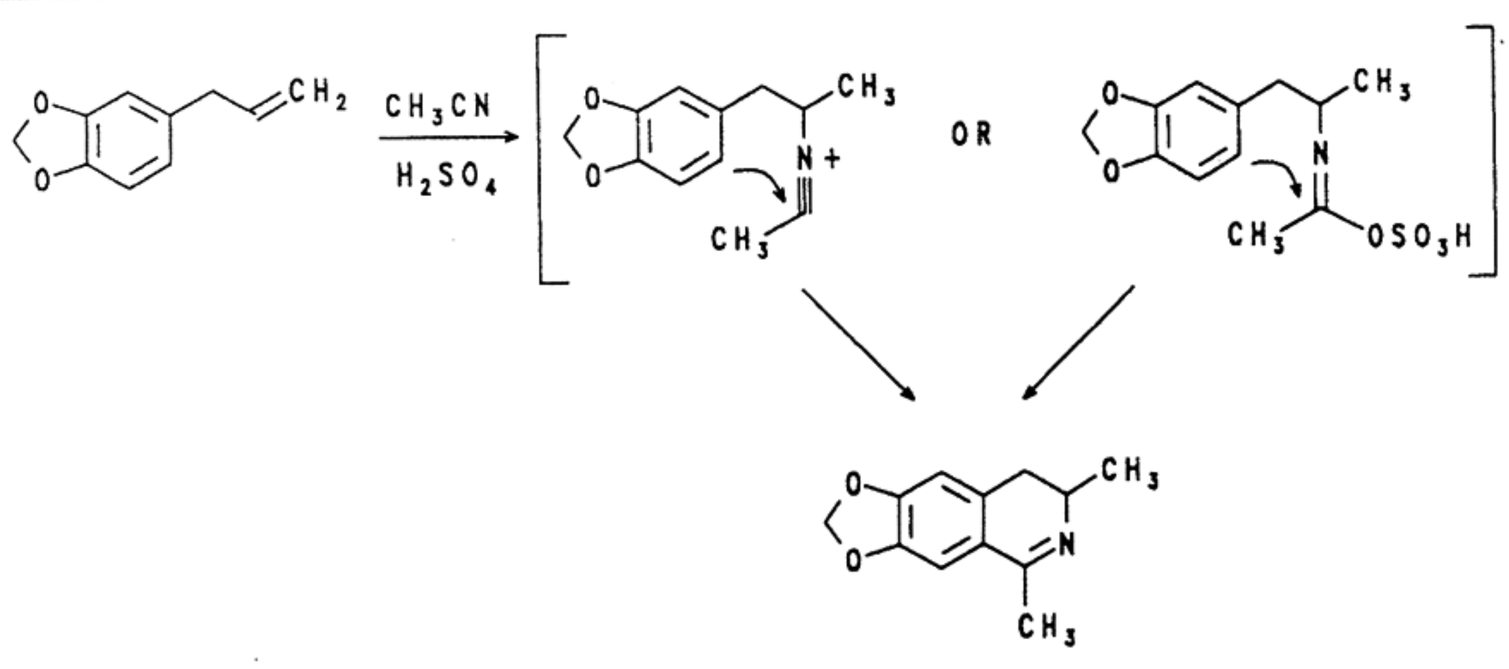


Figure 7. Gas chromatographic and mass spectral analysis of *N*-acetyl MDA: A, chromatogram, B, mass spectrum of *N*-acetyl MDA.

Treatment of isosafrole (1-[3,4-methylenedioxyphenyl]-1-propene) under the same reaction conditions produced only a non-nitrogen containing product. The GC–MS analysis of this product (Figure 8) shows a major product and a minor product that each produce identical mass spectra. These likely isomeric products were also obtained when isosafrole was treated with sulfuric acid in the absence of acetonitrile. The molecular ion at *m/z* 324 suggests a dimer of isosafrole (MW = 162), and this product fragments to yield an ion at $(M-29)^+$ suggesting the loss of an ethyl group. The absence of a significant *m/z* 135 ion again suggests further substitution or cyclization. The structure shown in Figure 8 is an example of one of the possibilities for this compound. This product would result from protonation of isosafrole to yield a benzylic carbocation, followed by attack of a second molecule of isosafrole upon the carbocation, then cyclization of the resulting second benzylic carbocation onto the aromatic ring. The primary fragment



Scheme 5. Mechanism of formation of the dihydroisoquinoline derivative upon treatment of safrole with acetonitrile and sulfuric acid.

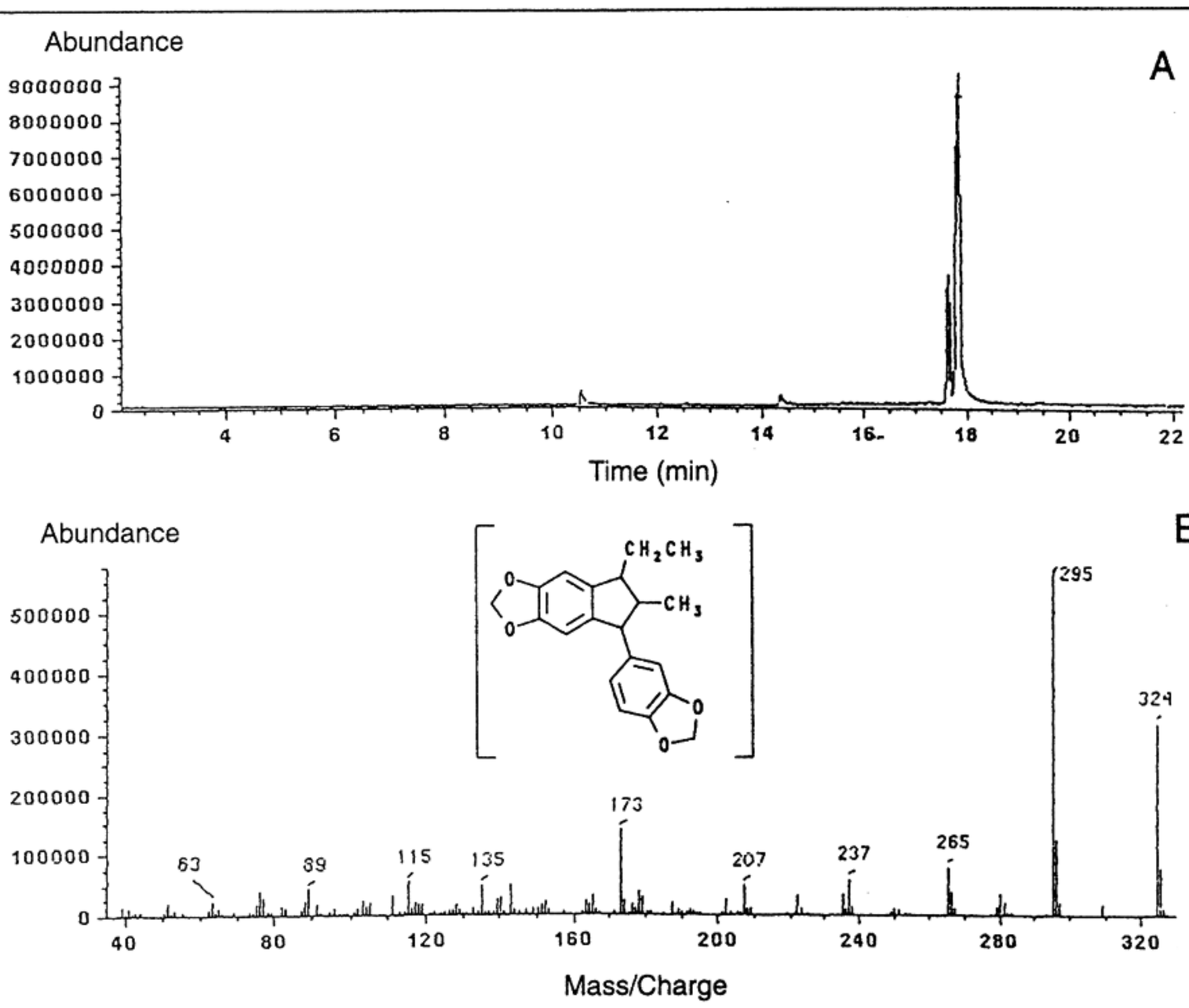


Figure 8. Gas chromatographic and mass spectral analysis of the products formed from treatment of isosafrole with acetonitrile and sulfuric acid: A, chromatogram; B, mass spectrum of the product.

from this compound would be the loss of 29 mass units from the ethyl-substituted indane ring. Although this may not be the exact structure for the isomeric compounds of MW 324, these data clearly show that no MDA was obtained from isosafrole using this procedure.

Conclusion

In summary, treatment of allylbenzene with acetonitrile and sulfuric acid followed by hydrolysis of the intermediate acetamides with aqueous HCl gave a mixture of 1-phenyl-1-propanamine and 1-phenyl-2-propanamine (amphetamine). The isomeric 1-phenyl-1-propene (*trans*-β-methylstyrene) gave only 1-phenyl-1-propanamine under the same reaction conditions. GC–MS and liquid chromatographic methods were used to differentiate between the isomeric 1-phenyl-1-, 2-, and 3-propanamines. These compounds and their acetamides provided characteristic mass spectra, and the compounds were well resolved by reversed-phase liquid chromatographic procedures. The corresponding 3,4-methylenedioxyphenylpropenes (safrole and isosafrole) did not yield the corresponding 1-propanamine and 2-propanamine (3,4-methylenedioxyamphetamine, MDA) products. In this case, the allyl substituted system (safrole) gave a cyclized product likely of the dihydroisoquinoline-type, and isosafrole gave a non-nitrogen dimer.

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