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Gas Chromatographic and Mass Spectral Analysis of Methamphetamine Synthesized From Allylbenzene

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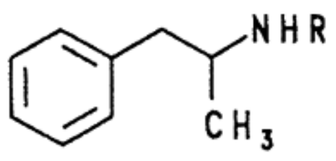
Abstract

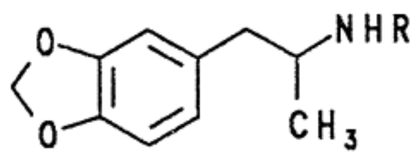
The synthesis of methamphetamine from allylbenzene is investigated using gas chromatography–mass spectrometry. Treatment of allylbenzene with HBr yields 1-phenyl-2-bromopropane as a major product. Smaller amounts of 1-phenyl-3-bromopropane, as well as 2,3-, 1,2-, and 1,3-dibromopropane, are also formed during the course of this reaction; both diastereomeric forms of 1,2-dibromopropane are detected in the product mixture. Amination of the crude bromination product with methylamine yields primarily methamphetamine and other amines characteristic of this synthetic method, including the methamphetamine isomer, *N*-methyl-1-phenyl-1-propanamine.

Introduction

The 1-aryl-2-propanamines, including amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and derivatives, remain popular synthetic drugs of abuse in the United States (Chart 1). Compounds of this structural class are synthesized most commonly 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 often prepared by hydrogenolysis of commercially available 1-phenyl-1-hydroxy-2-propanamines, including the ephedrines, pseudoephedrines, norephedrines, and norpseudoephedrines (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 preparation of MDMA was described recently (9). In this approach, safrole is treated with HBr to yield the intermediate bromosafrole which, upon reaction with methylamine, affords MDMA. This latter method, when applied to commercially available allylbenzene (3-phenylpropene) as the starting material, could also be used for the synthesis of amphetamine and methamphetamine (Scheme 1). In this report, the synthesis of methamphetamine from allylbenzene is studied by gas chromatography–mass spectrometry (GC–MS). Analysis of these reactions allows for complete determination of product composition and provides analytical profiles that may be of value for the identification of methamphetamine synthesized via the bromination of allylbenzene.



R-H: Amphetamine
R-CH_3: Methamphetamine



R-H: Methylenedioxyamphetamine (MDA)
R-CH_3: Methylenedioxymethamphetamine (MDMA)

Chart 1. The 1-aryl-2-propanamines.

Experimental

Gas chromatography–mass spectrometry

GC–MS analyses were performed using a Hewlett-Packard 5970B mass selective de-

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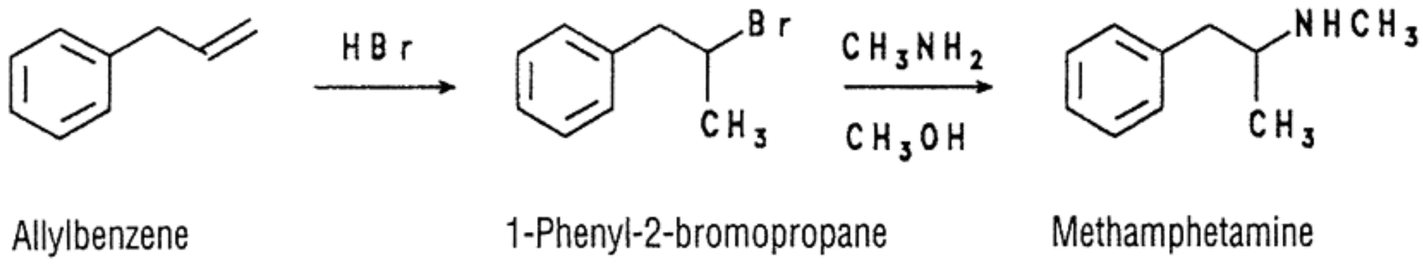


Scheme 1. Synthesis of methamphetamine from allylbenzene.

tector (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 with a 12-m × 0.20-mm i.d. fused-silica column that had 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 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 ultrapure helium.

Treatment of allylbenzene with HBr

A mixture of allylbenzene in 48% HBr was stirred vigorously at room temperature for several days. The reaction was quenched by the addition of water and extracted with ether. The combined ether extracts were washed with water and evaporated under reduced pressure to yield a yellow oil that was analyzed by GC–MS without any further purification.

Amination reaction

Methylamine was added to the unpurified bromination reaction product, and sufficient methanol was added to afford a solution. The reaction mixture was stirred for several days at room temperature and then evaporated under reduced pressure to yield a yellow oil that was analyzed by GC–MS without any further purification.

1-Phenyl-1,2-dibromopropane and 1-phenyl-2,3-dibromopropane

A solution of bromine (0.1 mL, 2.0 mmol) in CCl_4 (10 mL) was added dropwise over a period of 15 min to a solution of *trans*-β-methylstyrene (0.13 mL, 1.0 mmol) or allylbenzene (0.13 mL, 1.0 mmol) in CCl_4 (10 mL). After the addition was complete, the reaction was stirred at room temperature for 12 h and then evaporated to dryness. A yellow oil was obtained from the bromination of *trans*-β-methylstyrene, and a white solid was obtained from allylbenzene. The products were analyzed by GC–MS without further purification.

N-Methyl-1-phenyl-1-propanamine

A suspension of propiophenone (2.0 g, 15 mmol), methylamine hydrochloride (8.8 g, 130 mmol), and sodium cyanoborohydride (1.2 g, 19 mmol) in methanol (100 mL) was stirred at room temperature for 48 h. The pH of the reaction mixture was maintained at neutrality by the addition of concentrated HCl every 12 h. The reaction mixture was evaporated to dryness to yield a white solid. The solid was suspended in water (100 mL) and acidified (pH 1) by the addition of concentrated HCl. The acidic suspension was washed with methylene chloride (2 × 100 mL) and made basic (pH 11) by the addition of NaOH pellets (with cooling). The resultant basic suspension was extracted with methylene chloride (2 × 125 mL), 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 (100 mL). 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.

N-Methyl-1-phenyl-3-propanamine

A solution of 3-phenylpropionyl chloride (1.68 g, 10 mmol) in methylene chloride (50 mL) was added dropwise over a period of 45 min to a stirred solution of methylamine hydrochloride (1.35 g, 20 mmol) and triethylamine (3.04 g, 30 mmol) in methylene chloride (50 mL). After the addition was completed, the reaction mixture was stirred an additional 16 h at room temperature. The reaction mixture was washed successively with 10% HCl (2 × 50 mL), water (50 mL), saturated $NaHCO_3$ (2 × 50 mL), and water (50 mL). Evaporation of the methylene chloride solvent yielded the intermediate amide as a light yellow oil (confirmed by mass spectrometry). A solution of the amide (assume 10 mmol; quantitative yield) in dry THF (15 mL) was added dropwise over a period of 30 min to a stirred suspension of $LiAlH_4$ (3.8 g, 100 mmol) in dry THF (50 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 30 min and then at reflux for 1 h. The reaction mixture was cooled (ice bath), and the excess hydride reagent and lithium salts were decomposed by the successive addition of water (3.8 mL), 2N NaOH (3.4 mL), and water (11 mL). The white suspension was filtered (scintered glass funnel, reduced pressure), and the salts were washed with THF (50 mL). The filtrate and washings were combined and evaporated under reduced pressure to yield a clear oil. The oil was suspended in water (50 mL) and made acidic (pH 1) by the addition of concentrated HCl. The acidic solution was washed with methylene chloride (2 × 50 mL) and then made basic (pH 11) by the addition of NaOH pellets (with cooling). The resultant basic suspension was extracted with methylene chloride (2 × 75 mL), and the combined organic extracts were evaporated under reduced pressure to yield a colorless oil. The oil was dried under high vacuum at room temperature and dissolved in anhydrous ether. Addition of HCl gas to the ether solution yielded the product amine hydrochloride, which was isolated by filtration and recrystallized from a solvent mixture of ether and ethanol.

Results and Discussion

The goal of this project was to identify the products, byproducts, and contaminants involved in the preparation of methamphetamine (and related amines) from allylbenzene

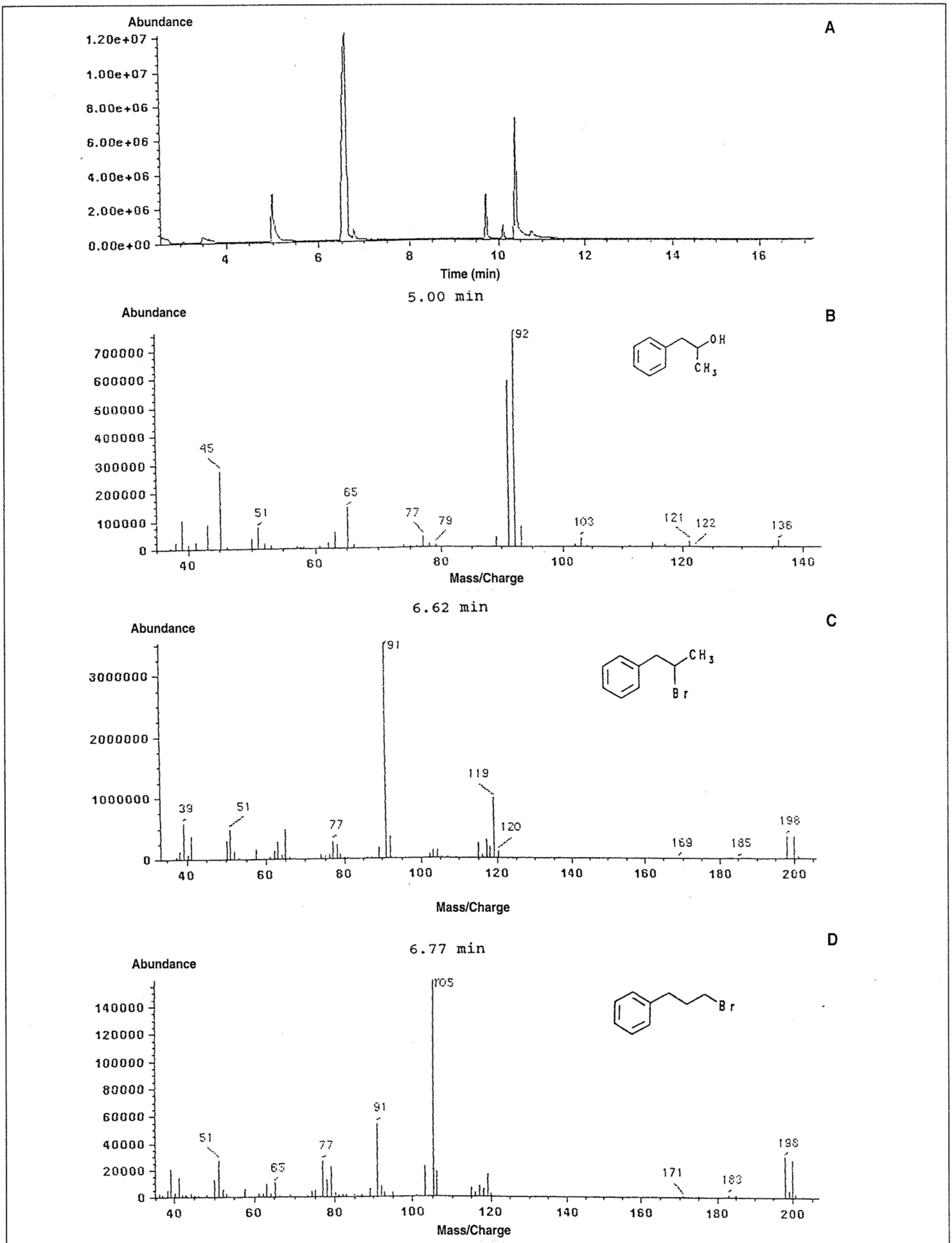


Figure 1. Gas chromatographic and mass spectral analysis of the products formed from treatment of allylbenzene with HBr: A, chromatogram; B, mass spectrum of 1-phenyl-2-propanol; C, mass spectrum of 1-phenyl-2-bromopropane; D, mass spectrum of 1-phenyl-3-bromopropane. *(Figure 1 continued on page 156).*

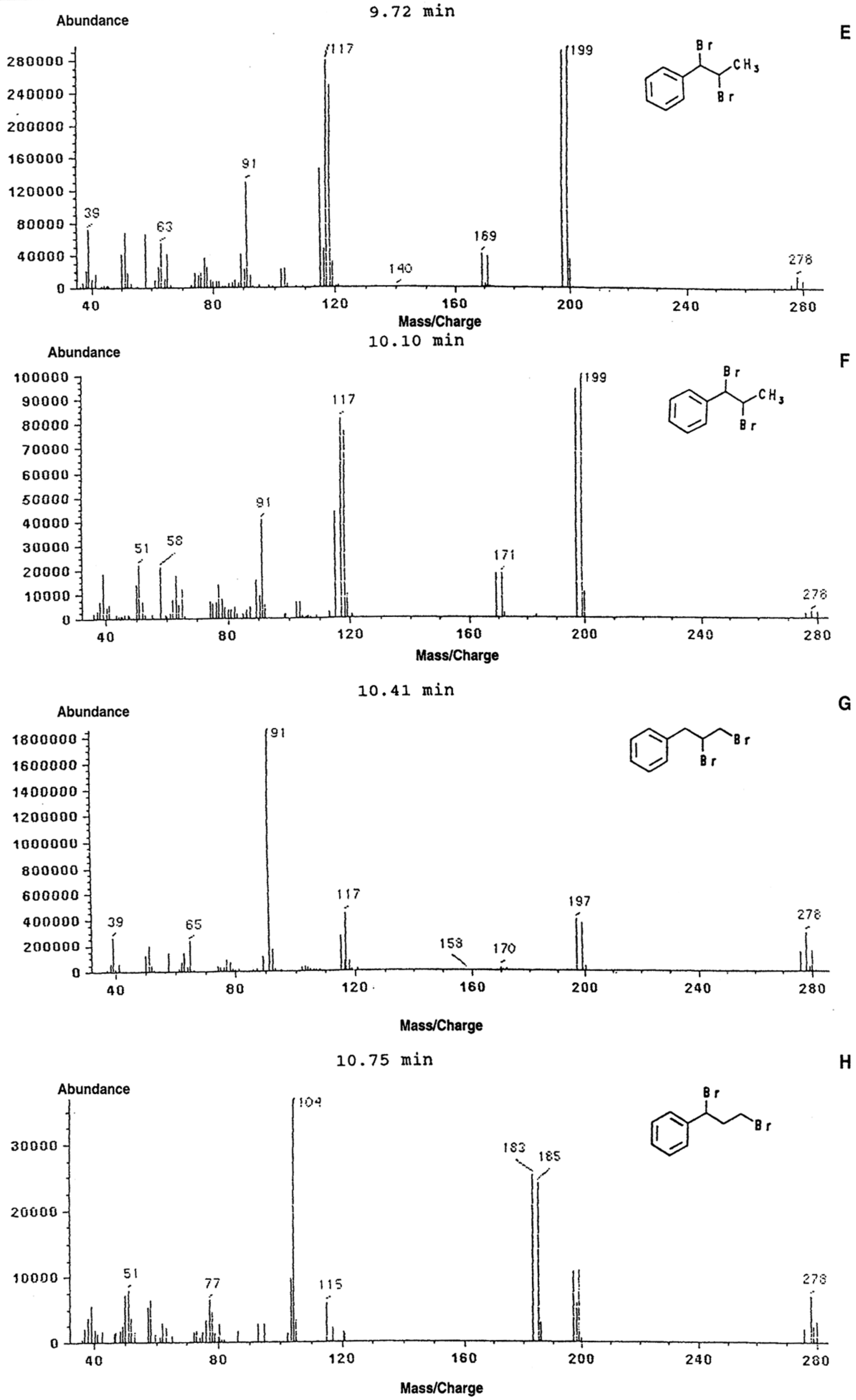
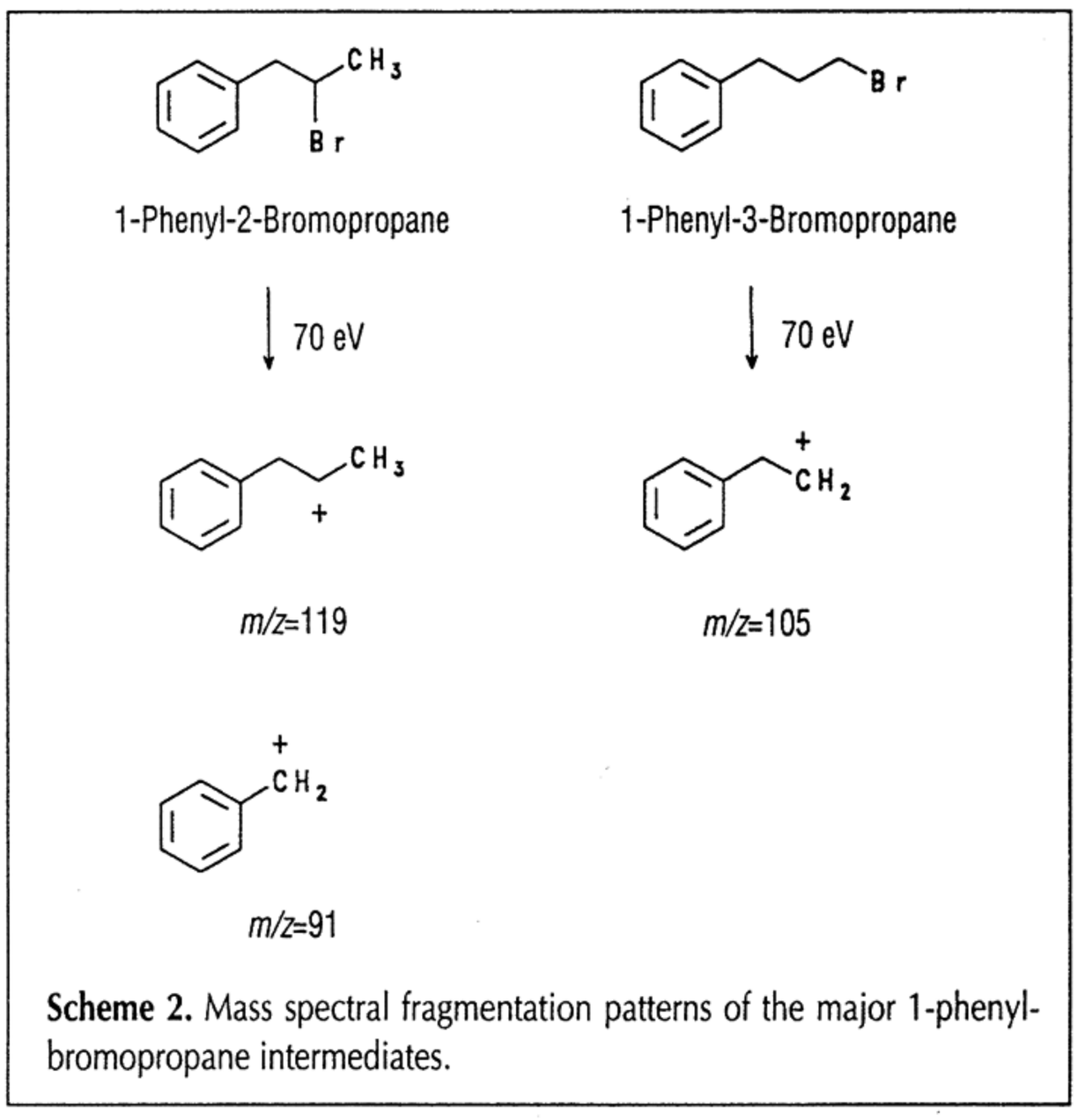


Figure 1. *(continued from page 155)* Gas chromatographic and mass spectral analysis of the products formed from treatment of allylbenzene with HBr: E and F, mass spectra of 1-phenyl-1,2-dibromopropane diastereomers; G, mass spectrum of 1-phenyl-2,3-dibromopropane; H, mass spectrum of 1-phenyl-1,3-dibromopropane.

(3-phenylpropene). Allylbenzene is a commercially available and uncontrolled precursor substance that contains the carbon skeleton of the amphetamine-type drugs of abuse. The unconjugated double bond in allyl substituted aromatic systems can be functionalized at the 2-position by the addition of hydrobromic acid (HBr) (9). Displacement of bromine from the bromoalkane with an amine such as methylamine would yield methamphetamine as the major basic product (Scheme 1).

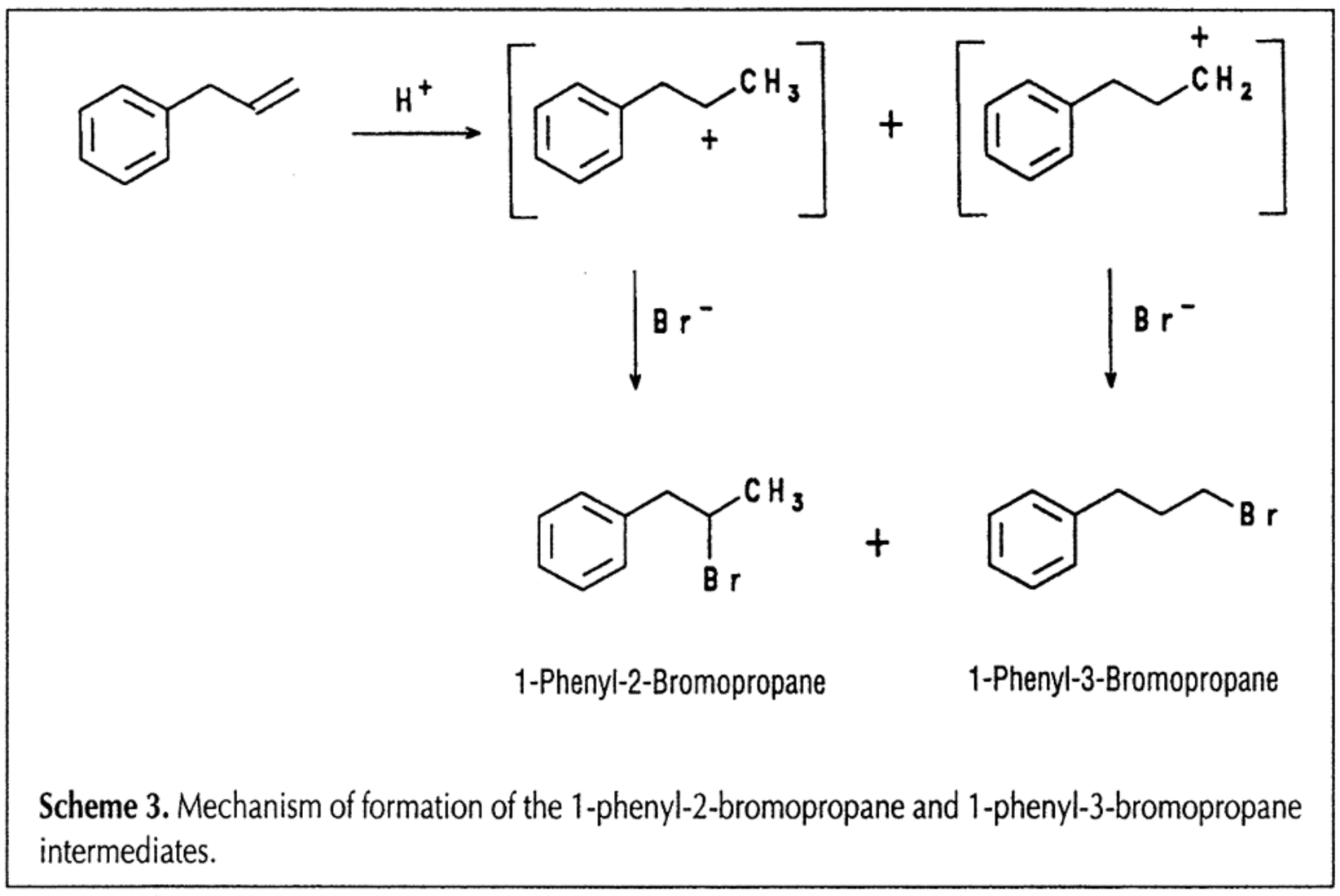
Figure 1 shows the results of GC–MS analysis of the crude product sample obtained following treatment of allylbenzene with 48% HBr at room temperature for 7 days. The first peak in the chromatogram in Figure 1A, which elutes at 5.00 min, corresponds to 1-phenyl-2-propanol and yields the mass spectrum in Figure 1B. A known sample of 1-phenyl-2-propanol prepared by sodium borohydride reduction of phenyl-2-propanone yielded an identical mass spectrum and a coeluting chromatographic peak. This alcohol was likely formed in the reaction mixture by water hydrolysis of the expected major product, 1-phenyl-2-bromopropane.



Scheme 2. Mass spectral fragmentation patterns of the major 1-phenyl-bromopropane intermediates.

The major peak in the chromatogram (6.62 min) in Figure 1 produced the mass spectrum in Figure 1C, indicating a product containing one bromine, a molecular weight of 198, and major fragments at *m/z* 91 and 119. These data are consistent with the expected 1-phenyl-2-bromopropane product of the addition of HBr to allylbenzene. The *m/z* 91 fragment (base peak) corresponds to the benzyl cation, and the *m/z* 119 fragment results from the loss of Br from the parent molecule (Scheme 2). The small peak at 6.77 min in Figure 1A also has a molecular ion at *m/z* 198 and contains one bromine (Figure 1D); however, the base peak is at *m/z* 105, which is consistent with the loss of CH_2Br from the parent molecule (Scheme 2). This fragmentation indicates that the bromine is at the 3-position of the carbon side chain as in 1-phenyl-3-bromopropane. As expected, the 3-bromo derivative is present in much lower concentrations because it is formed from the less stable primary carbocation intermediate (Scheme 3).

The 9.5- to 11.0-min region in the chromatogram in Figure 1A shows four peaks, and each peak has an identical molecular ion region at *m/z* 276–280 amu (Figures 1E–1H). The molecular ion region shows peaks at 276, 278, and 280 amu in a pattern indicating the presence of two bromine atoms in each of these four compounds. The molecular weight at 276 mass units is consistent with the simple addition of two bromines to allylbenzene. Thus, these four compounds represent isomeric dibromophenylpropanes. The first two peaks at 9.72 and 10.10 min show identical mass spectra (Figures 1E and 1F, respectively), and the peak at 9.72 min represents the second largest peak in this region. These two peaks were initially assigned as the two diastereomeric forms of 1-phenyl-1,2-dibromopropane, the only dibromo combination that could yield diastereomeric products. The 1,2-addition of bromine could result from the isomerization of allylbenzene to β-methylstyrene (1-phenyl-propene) or from the presence of this conjugated system in trace quantities in the starting material allylbenzene. To confirm the structural assignment for these two peaks, a sample of 1-phenyl-1,2-dibromopropane was independently synthesized by treating a sample of β-methylstyrene with bromine (Br_2) in carbon tetrachloride. GC–MS analysis of the product mixture from this reaction showed a major component with the lower retention time and a later eluting minor component, each having a mass spectrum that was identical to those shown in Figures 1E and 1F for the peaks at 9.72 and 10.10 min.

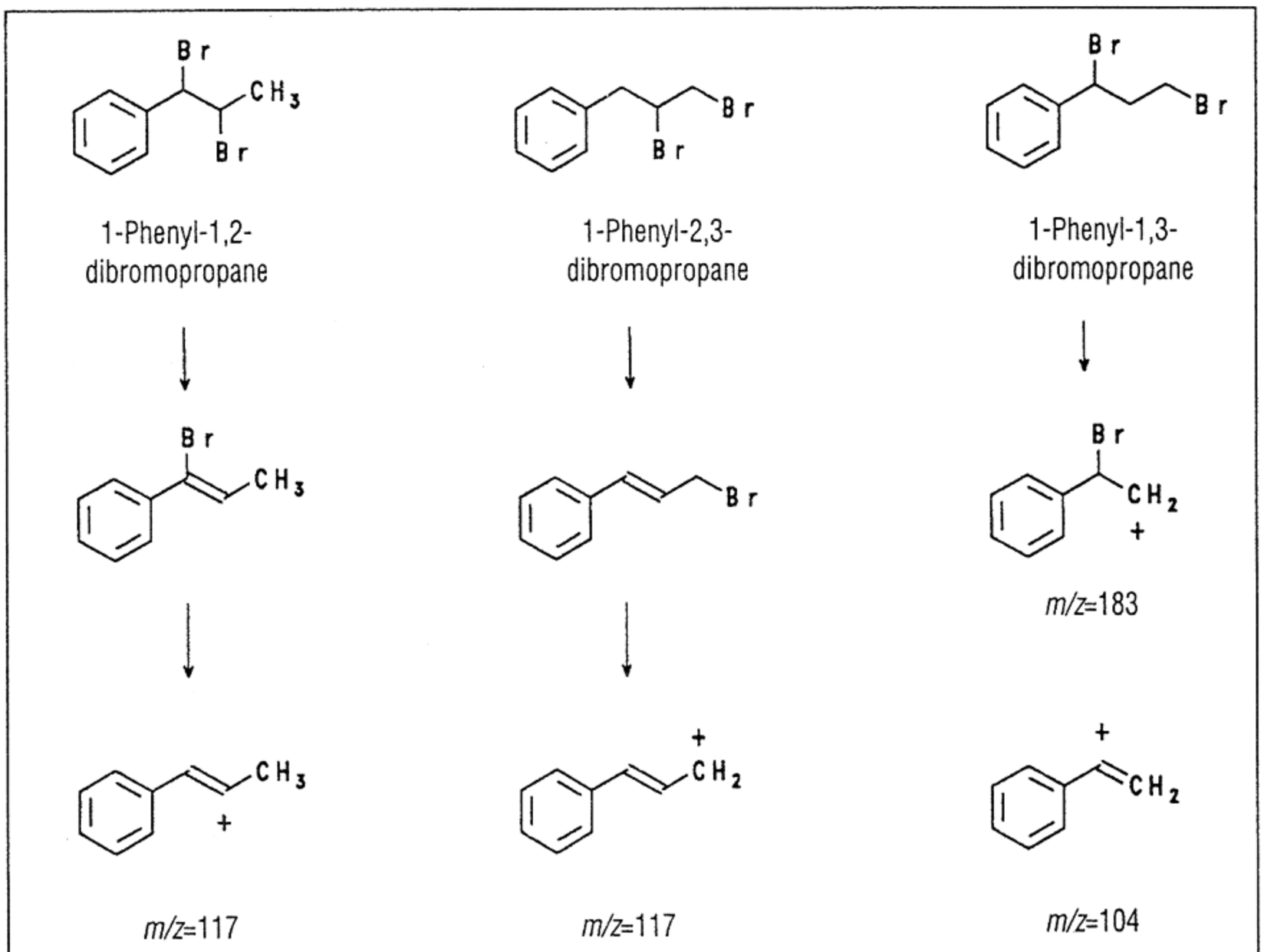


Scheme 3. Mechanism of formation of the 1-phenyl-2-bromopropane and 1-phenyl-3-bromopropane intermediates.

The major dibromo product eluting at 10.41 min shows a mass spectrum (Figure 1G) with a base peak at *m/z* 91, which suggests an unsubstituted benzyl group. This product is likely 1-phenyl-2,3-dibromopropane resulting from the addition of bromine across the double bond of allylbenzene. Confirmation of this assignment was obtained by treatment of allylbenzene with

bromine (Br_2) in carbon tetrachloride. GC–MS analysis of this product showed 1-phenyl-2,3-dibromopropane as the major component eluting in the 10.4-min range with a mass spectrum identical to that of Figure 1G.

The last of the four dibromo products present in the reaction of allylbenzene with HBr elutes at 10.75 min and shows unique major fragment ions at *m/z* 104 containing no bromine and at *m/z* 183 containing one bromine (Scheme 4). The *m/z* 183 ion represents the loss of CH_2Br from the molecular ion and suggests that one of the bromines is attached at the 3-position of the propyl side chain. This information, coupled with the absence of any significant fragment at *m/z* 91, shows that one of the bromines is substituted at the benzylic position. Thus these data suggest that this compound is 1-phenyl-1,3-dibromopropane. The major fragment at *m/z* 104 in this spectrum is likely the result of loss of CH_2Br followed by Br elimination to yield $[C_6H_5CHCH_2]^+$ (*m/z* 104). A similar fragmentation pathway for the other dibromo compounds (Scheme 4) in which the bromines are substituted on adjacent carbons yields the ions at *m/z* 117. The loss of HBr to yield the double bond in both cases (1,2- or 2,3-dibromopropane) is followed by the loss of bromine instead of CH_2Br to give the *m/z* 117 ion from both compounds.



Scheme 4. Mass spectral fragmentation patterns for the dibromo-allylbenzene by-products.

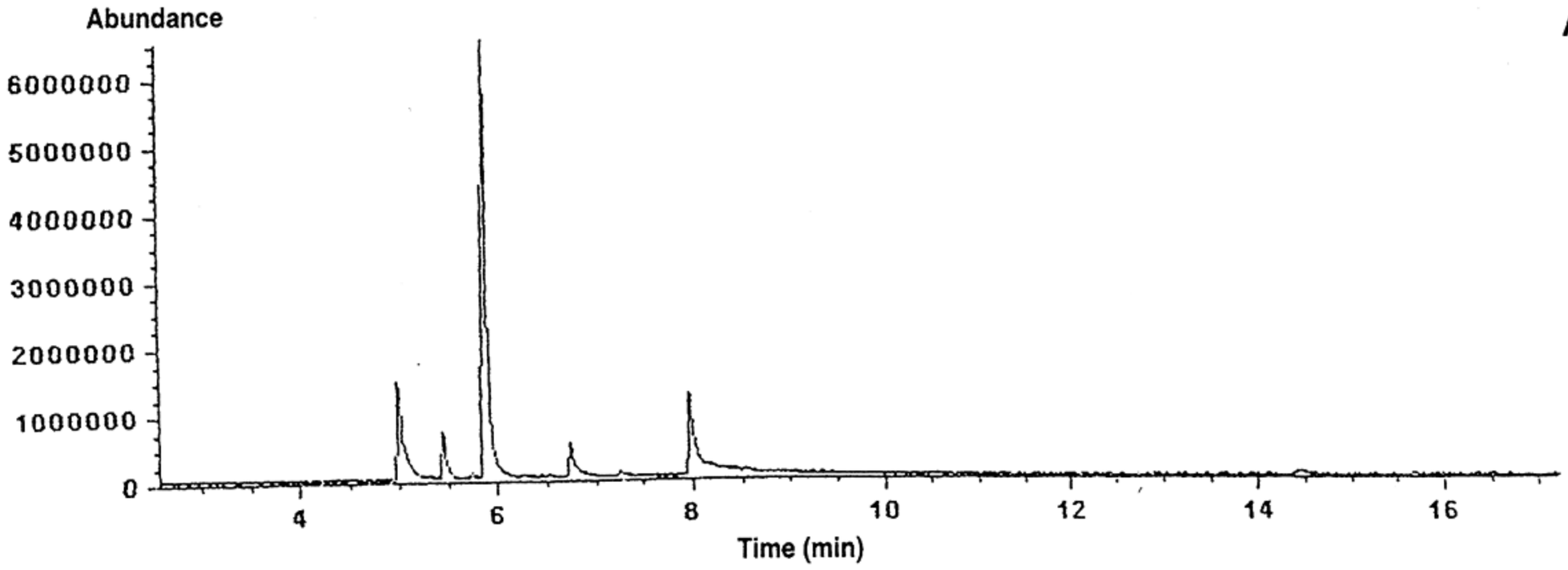
Treatment of the crude product obtained from bromination of allylbenzene (from Figure 1) with aqueous methylamine in methanol produced the product mixture analyzed in Figure 2. The first peak in the chromatogram in Figure 2A at 4.99 min shows a molecular ion at *m/z* 136 and major fragments at 92, 45, and 41 amu (Figure 2B). These data, as well as chromatographic retention, match the properties of 1-phenyl-2-propanol, which would result from water displacement of bromine from 1-phenyl-2-bromopropane. The second peak eluting at 5.44 min shows a molecular ion of very low abundance at *m/z* 149, a base peak at *m/z* 120, and a major fragment at *m/z* 42 (Figure 2C). Because this compound appears to have a molecular weight equivalent to that of the expected product, methamphetamine, it is likely that this compound is a positional isomer of methamphetamine. Based on a relatively high mass base peak (*m/z* 120), the most likely structure for this amine is *N*-methyl-1-phenyl-1-propanamine. Amine-dominated fragmentation of this compound should result in the loss of an ethyl group yielding the *N*-methylbenzylimine fragment (*m/z* 120). Independent synthesis of *N*-methyl-1-phenyl-1-propanamine by reductive amination of propiophenone with methylamine yielded an authentic standard of this compound. GC–MS analysis of the standard produced chromatographic and fragmentation data consistent with the component from the amination reaction that elutes at 5.44 min in Figure 2A and shows a mass spectrum identical to that in Figure 2C.

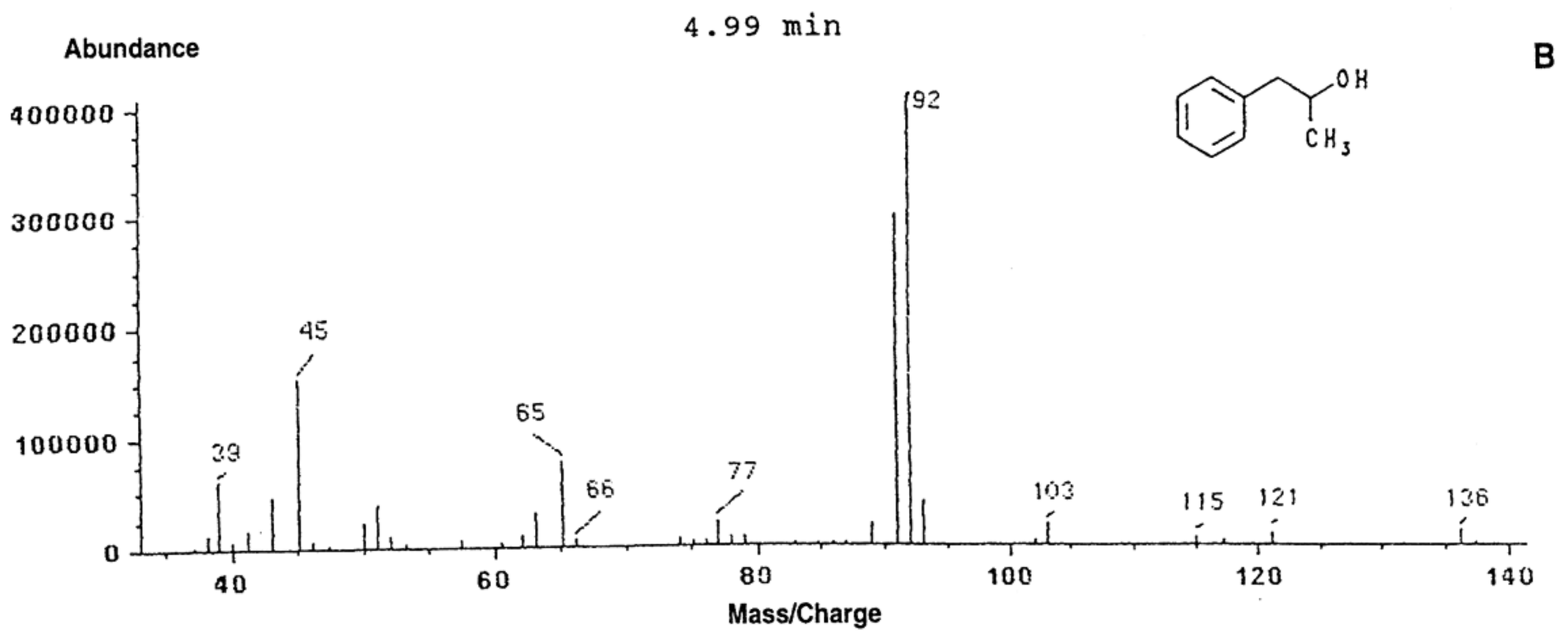
Although no 1-phenyl-1-bromopropane was identified in the allylbenzene bromination product mixture (Figure 1A), the presence of *N*-methyl-1-phenylpropanamine in the amination mixture can be rationalized in several ways. For example, the 1-propanamine could have formed in a reaction sequence involving the initial loss of bromine ion from the major bromo product, 1-phenyl-2-bromopropane, to yield the carbocation at the 2-carbon. This carbocation could then rearrange (isomerize) to the more stable benzylic position (1-carbon), and methylamine attack at the 1-carbon position would yield the observed 1-propanamine product. Alternatively, it is possible that 1-phenyl-1-bromopropane formed during the bromination reaction but coeluted with another component in the product mixture (perhaps the major product, 1-phenyl-2-bromopropane) under the chromatographic conditions used for these analyses.

The major component in the chromatogram in Figure 2A elutes at 5.89 min and produces the mass spectrum in Figure 2D showing a molecular ion at *m/z* 149 and a base peak at *m/z* 58. These data are consistent with methamphetamine, the expected major component of the reaction.

The two later eluting peaks at 6.73 and 7.96 min each show a molecular ion at *m/z* 147 but very different mass spectra. Amines of mass 147 most likely result from methylamine displacement of both bromines from the dibromo-allylbenzenes. These products may appear as imines, enamines, aminoalkenes, or cyclic compounds such as aziridines. The peak at 6.73 min shows a base peak at *m/z* 44 suggestive of the methylamine group attached at the 3-carbon of the side chain. Because no other major fragments occur for this compound, a likely structure is *N*-methyl-3-phenyl-1-propenamine. The later eluting peak at 7.96 min shows a molecular ion (*m/z* 147) of very high abundance suggestive of a cyclic product, perhaps of the aziridine type.

Analysis of the amine fraction clearly shows metham-





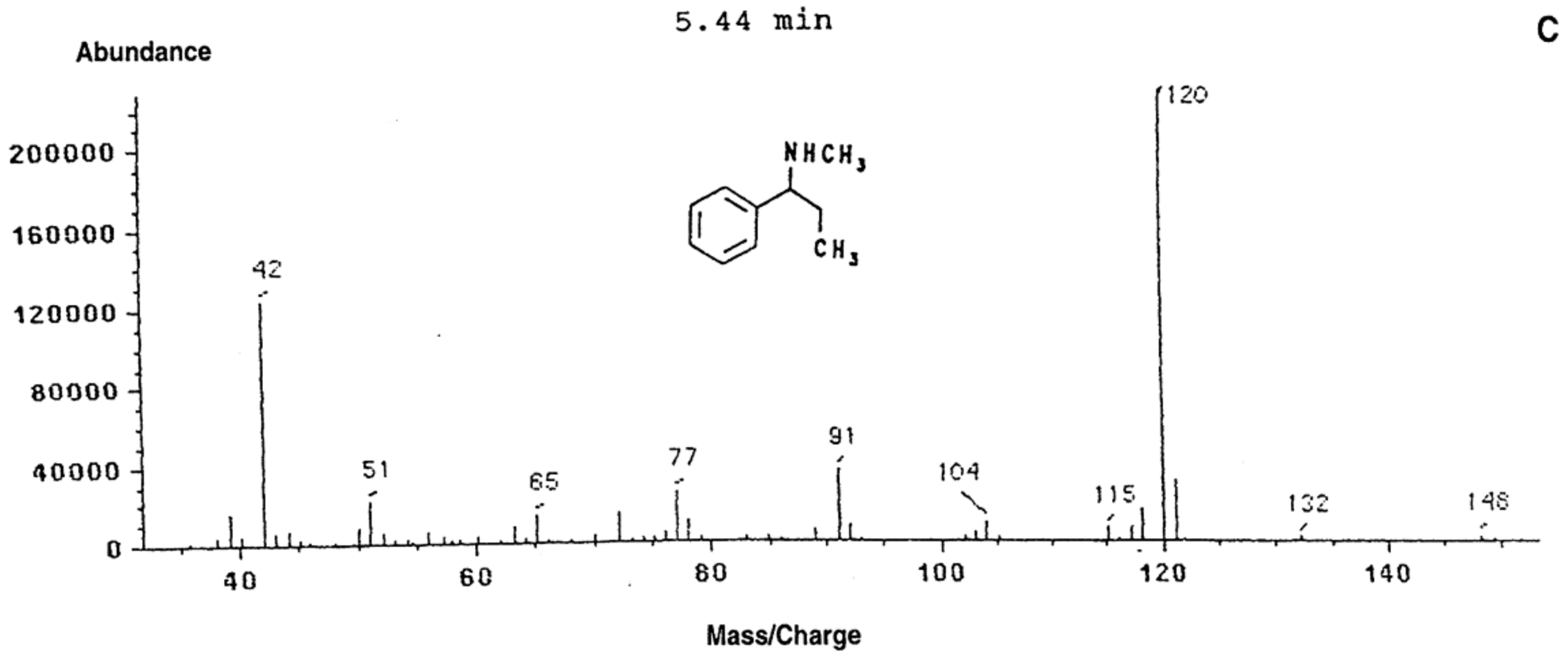


Figure 2. Gas chromatographic and mass spectral analysis of the products formed from treatment of the crude bromination product with methylamine: A, chromatogram; B, mass spectrum of 1-phenyl-2-propanol; C, mass spectrum of *N*-methyl-1-phenyl-1-propanamine; D, mass spectrum of *N*-methyl-1-phenyl-2-propanamine (methamphetamine).

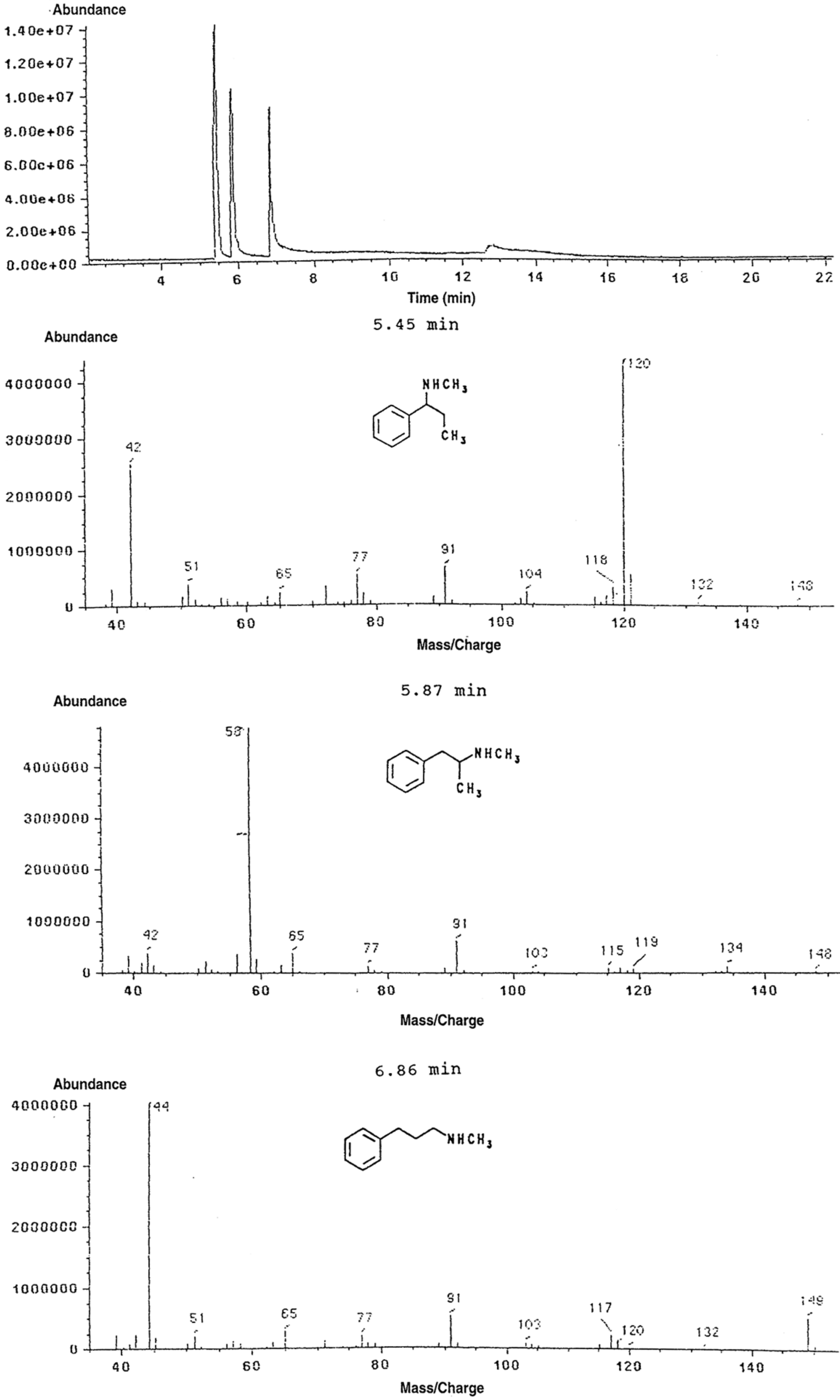
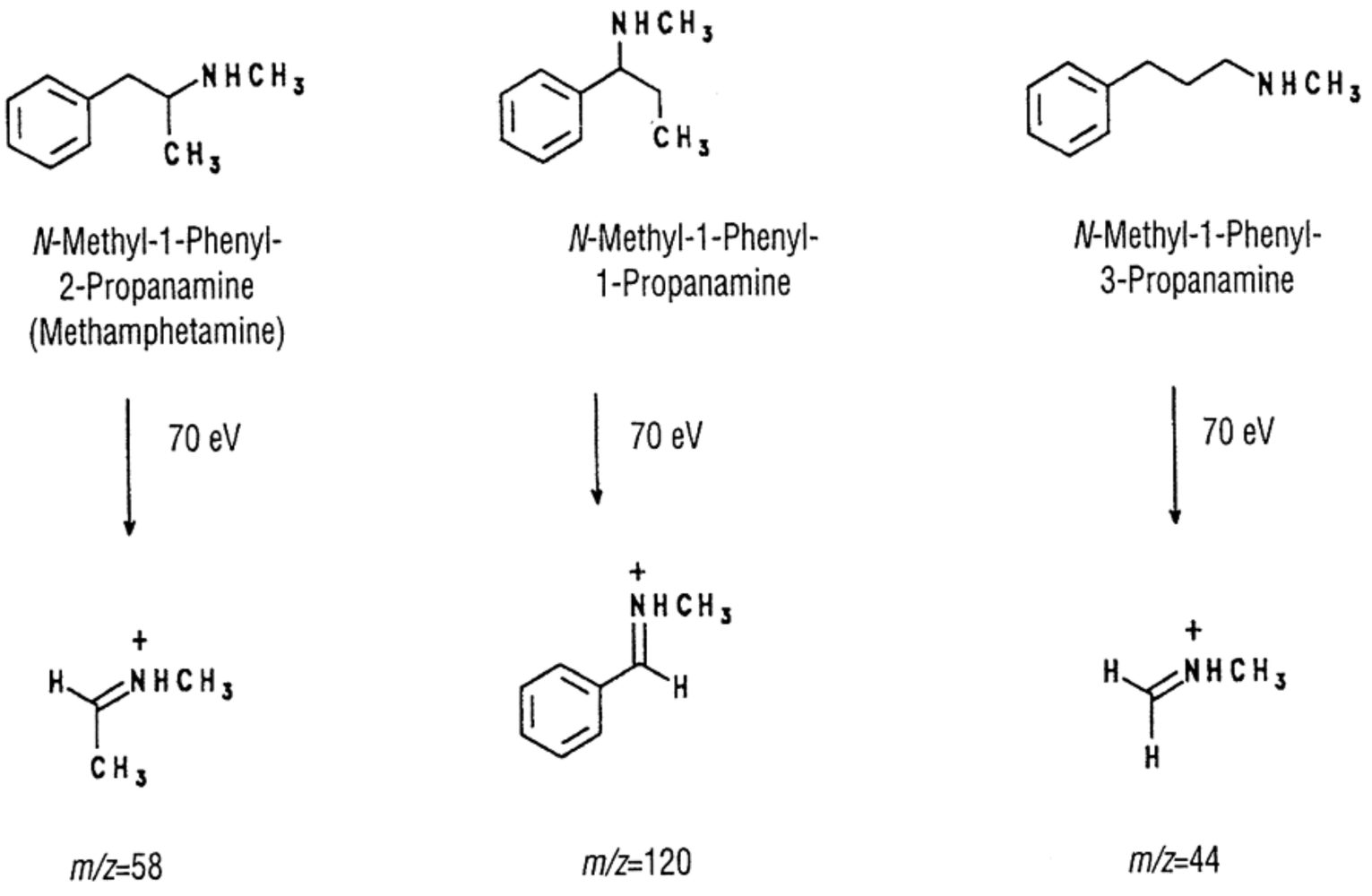


Figure 3. Gas chromatographic and mass spectral analysis of the regioisomeric *N*-methyl-1-phenylpropanamines: A, chromatogram; B, mass spectrum of *N*-methyl-1-phenyl-1-propanamine; C, mass spectrum of *N*-methyl-1-phenyl-2-propanamine (methamphetamine); D, mass spectrum of *N*-methyl-1-phenyl-3-propanamine.



Scheme 5. Mass spectral fragmentation patterns for the propanamine products.

phetamine to be the major component of the amine mixture. This amine forms by a displacement reaction on the major product of the bromination reaction, 1-phenyl-2-bromopropane. However, no *N*-methyl-1-phenyl-3-propanamine was observed in the amine mixture, and furthermore, *N*-methyl-1-phenyl-1-propanamine was found in the amine mixture, whereas no 1-phenyl-1-bromopropane was observed in the bromination mixture. In an effort to substantiate these observations and the structural assignments of the amines in the final product, a sample of *N*-methyl-1-phenyl-3-propanamine was synthesized. This compound was prepared by treatment of 3-phenylpropionyl chloride with methylamine to yield the *N*-methylamide, followed by lithium aluminum hydride reduction to give the desired amine. The GC–MS separation of the three regioisomeric *N*-methylamines that could form from the allylbenzene is shown in Figure 3. The compounds are well resolved chromatographically, and the mass spectral fragmentation (Scheme 5) clearly allows, the differentiation of methamphetamine (base peak *m/z* 58) from the isomeric 1-propanamine (base peak *m/z* 120) or the 3-propanamine (base peak *m/z* 44). These data confirm the structural assignments for the amines observed in Figure 2 and demonstrate that the 3-propanamine is not present in the product mixture.

Conclusion

HBr treatment of allylbenzene yields 1-phenyl-2-bromopropane as a major product and smaller amounts of 1-phenyl-3-bromopropane and 2,3-, 1,2-, and 1,3-dibromopropane. Amination of the crude sample with methylamine yields primarily methamphetamine and other amines characteristic of this synthetic method.

References

1. R.S. Frank. The clandestine drug laboratory situation in the United States. *J. Forensic Sci.* **28:** 18 (1983).
2. F.T. Noggle, C.R. Clark, A.K. Valaer, and J. DeRuiter. Liquid chromatographic and mass spectral analysis of *N*-substituted analogues of 3,4-methylenedioxyamphetamine. *J. Chromatogr. Sci.* **26:** 410–15 (1988).
3. A.M.A. Verweij. Impurities in illicit drug preparations: Amphetamine and methamphetamine. *Forensic Sci. Rev.* **1:** 1–11 (1989).
4. F.T. Noggle, J. DeRuiter, and C.R. Clark. Liquid chromatographic determination of the enantiomeric composition of methamphetamine prepared from ephedrine and pseudoephedrine. *Anal. Chem.* **58:** 1643–48 (1986).
5. F.T. Noggle, J. DeRuiter, and C.R. Clark. Liquid chromatographic determination of the enantiomeric composition of amphetamine prepared from norephedrine and norpseudoephedrine. *J. Chromatogr. Sci.* **25:** 38–42 (1987).
6. Chemical Diversion and Trafficking Act, March, 1989.
7. J.J. Barbato. Identification of 1-phenyl-2-nitropropene. *Microgram.* **23:** 35–36 (1990).
8. C.R. Clark, F.T. Noggle, and J. DeRuiter. Analysis of 3,4-methylenedioxyphenyl-2-propanone and 3,4-methylenedioxyamphetamine prepared from isosafrole. *J. Chromatogr. Sci.* **32:** 393–402 (1994).
9. F.T. Noggle, C.R. Clark, and J. DeRuiter. Gas chromatographic and mass spectrometric analysis of samples from a clandestine laboratory involved in the synthesis of 'Ecstasy' from sassafras oil. *J. Chromatogr. Sci.* **29:** 168–73 (1991).

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