Analysis of 1-(3-Methoxy-4,5-Methylenedioxyphenyl)-2-Propanamine (MMDA) Derivatives Synthesized from Nutmeg Oil and 3-Methoxy-4,5-Methylenedioxybenzaldehyde

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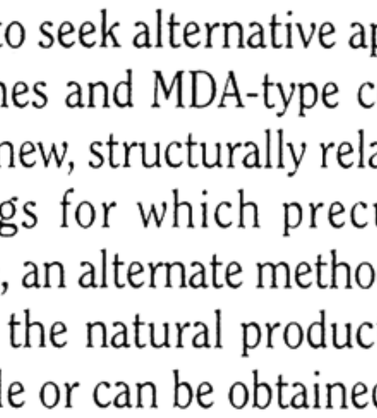
Abstract

Myristicin, a natural product found in nutmeg oil and nutmeg extract, contains the carbon skeleton for a series of drugs of abuse related to the 3,4-methylenedioxyamphetamines (MDAs). Myristicin, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propene, was identified as the major component of commercially available nutmeg oil and in the organic extract of nutmeg powder. The starting materials, intermediates, and products in the synthesis of the drug of abuse *N*-methyl-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine (MMDMA) from myristicin were characterized by gas chromatographic–mass spectrometric analysis. MMDMA and several primary amine derivatives including 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-ethanamine, -propanamine, and -butanamine were also prepared from the commercially available aldehyde, 3-methoxy-4,5-methylenedioxybenzaldehyde. Each of these amine derivatives has a distinct mass spectrum characterized by amine-dominated fragmentation. All four amines in this study were resolved by reversed-phase liquid chromatography using an acidic aqueous mobile phase. Relative retention in this system was determined by differences in the hydrophobic surface area of the four amines.

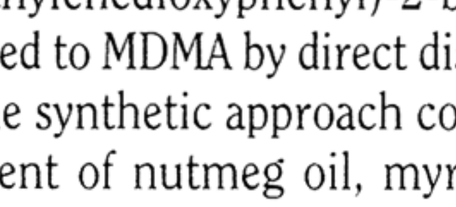
Introduction

A number of phenalkylamines (Chart 1) including the amphetamines (amphetamine and methamphetamine) and 3,4-methylenedioxyamphetamines (MDA, MDMA) remain popular drugs of abuse in the United States and abroad (1). These compounds are synthesized in clandestine laboratories by a variety of methods using commercially available synthetic precursors. For example, methamphetamine is commonly prepared by hydrogenolysis reactions using the ephedrines or pseudoephedrines or by reductive amination of 1-phenyl-2-propanone (P-2-P) (2,3). Similarly, 3,4-methylenedioxymethamphetamine is typically synthesized by reductive amination of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) (4). The synthetic route by which illicit samples of these compounds are produced can frequently be determined by complete characterization and analysis of the sample (2–4).

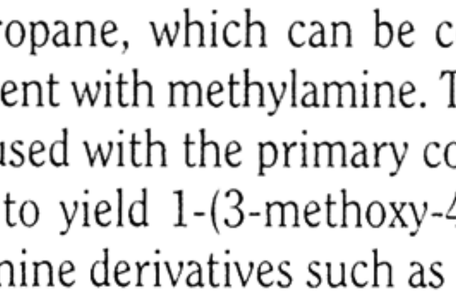
Based on these synthetic strategies, the availability of the precursors and related substances has been controlled by the Drug Enforcement Administration under the Chemical Diversion and Trafficking Act in March of 1989 (5). The restricted availability of these key precursors has prompted clandestine laboratory operators to seek alternative approaches for the synthesis of amphetamines and MDA-type compounds and to explore the synthesis of new, structurally related compounds or so-called designer drugs for which precursor chemicals are available. For example, an alternate method reported for the synthesis of MDMA uses the natural product safrole (6), which is commercially available or can be obtained by extraction or distillation of the sassafras plant, which is native to the United States. Safrole may be used to synthesize the ketone MDP-2-P or may be brominated with hydrobromic acid to yield 1-(3,4-methylenedioxyphenyl)-2-bromopropane, which can be converted to MDMA by direct displacement with methylamine. This same synthetic approach could be used with the primary component of nutmeg oil, myristicin, to yield 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine derivatives such as the *N*-methyl analogue MMDMA and the primary amine MMDA. These compounds are the *m*-methoxy analogues of MDMA and



R = H: Amphetamine
R = CH_3: Methamphetamine



R = H: MDA
R = CH_3: MDMA



R = H: MMDA
R = CH_3: MMDMA

Chart 1. Synthetic drugs of abuse: amphetamine, methamphetamine, MDA, MDMA, MMDA, and MMDMA.

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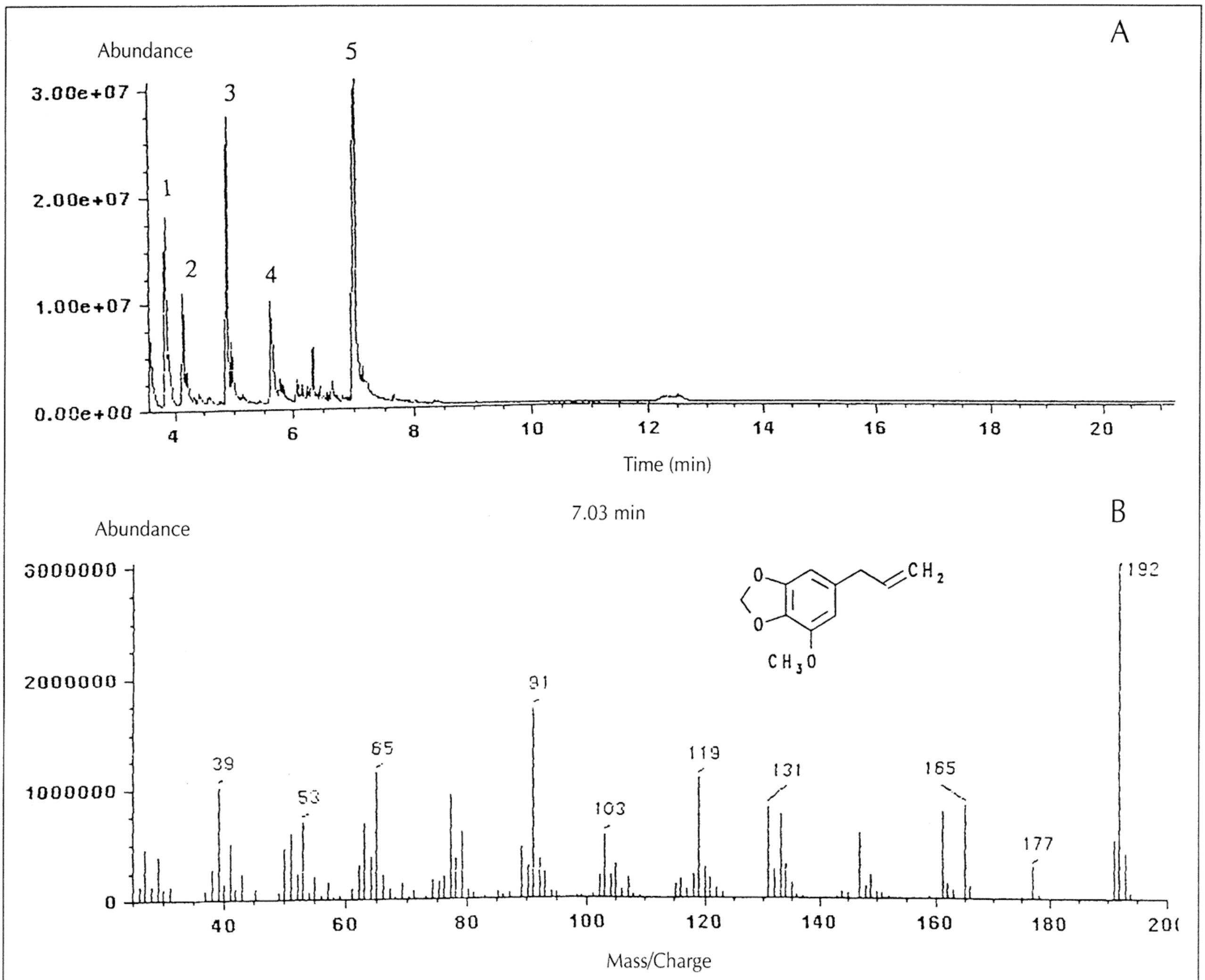


Figure 1. Gas chromatographic–mass spectral analysis of nutmeg oil: A, chromatogram; B, mass spectrum of myristicin (1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propene). Peaks: 1, γ-terpinene (3.84 min); 2, α-terpinolene (4.13 min); 3, terpinen-4-ol (4.87 min); 4, safrole (5.60 min); and 5, myristicin (7.03 min).

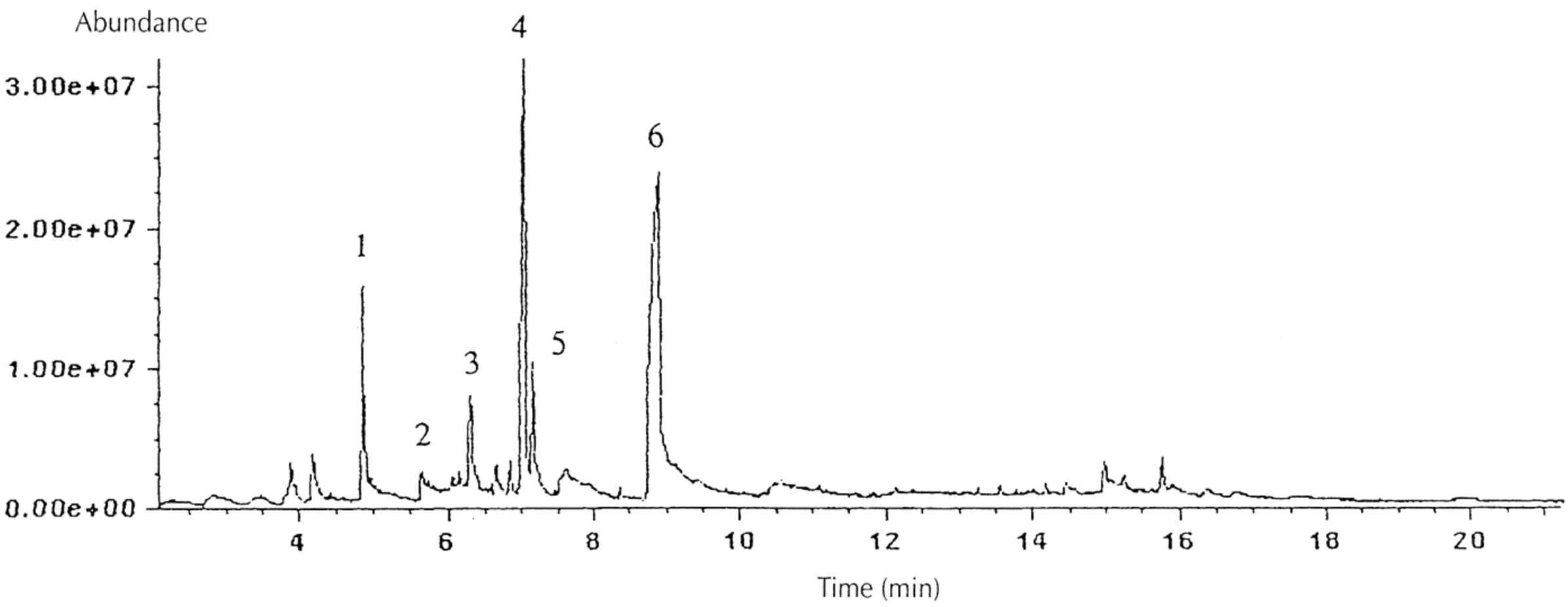
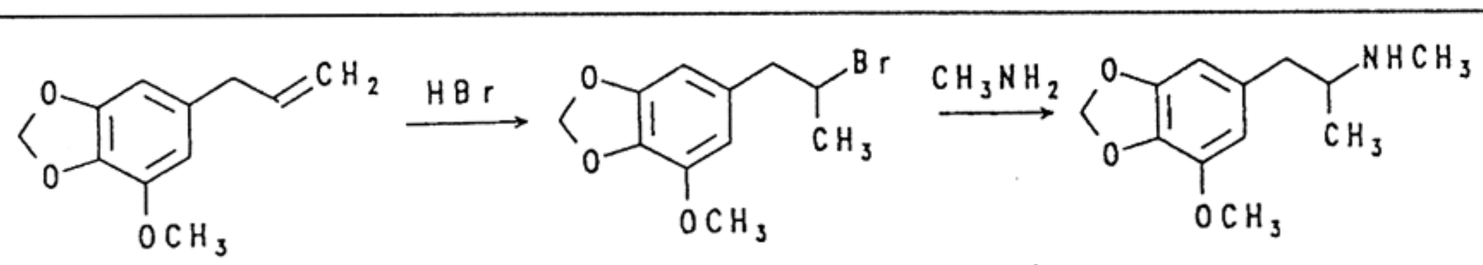


Figure 2. Gas chromatographic analysis of a methanol extract of nutmeg spice. Peaks: 1, terpinen-4-ol (4.87 min); 2, safrole (5.64 min); 3, 1-(3,4-dimethoxyphenyl)-2-propene (6.28 min); 4, myristicin (7.02 min); 5, 1-(3,4,5-trimethoxyphenyl)-2-propene (7.14 min); and 6, tetradecanoic acid.

MDA, respectively. Although less potent, MMDMA and MMDA are reported to possess stimulant and hallucinogenic activity comparable with MDMA (7). Thus, myristicin is another example of a readily available, naturally occurring precursor chemical that may be used in the synthesis of potential drugs of abuse. Additionally, 3-methoxy-4,5-methylenedioxybenzaldehyde is commercially available, and this uncontrolled aldehyde can also be used to prepare MMDA derivatives. We report the results of the gas chromatographic–mass spectrometric (GC–MS) analysis of nutmeg oil and the reaction products obtained from the synthesis of MMDMA from the oil and from the commercially available aldehyde precursor.



Scheme 1. Synthesis of MMDMA from myristicin.

Experimental

GC–MS analysis

These analyses were performed 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 samples were dissolved in methanol (1 mg/mL), and 0.5 µL of each sample was introduced into the mass spectrometer via a gas chromatograph equipped with an HP-1 fused-silica column (12 m × 0.20-mm i.d., 0.33-µm thickness of methylsilicone). The column temperature was programmed from 70°C to 150°C at a rate of 15°C/min and from 150°C 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 9 min.

Liquid chromatographic analysis

Liquid chromatographic analyses were conducted using a Laboratory Data Control Constametric 3000 pump (Riviera Beach,

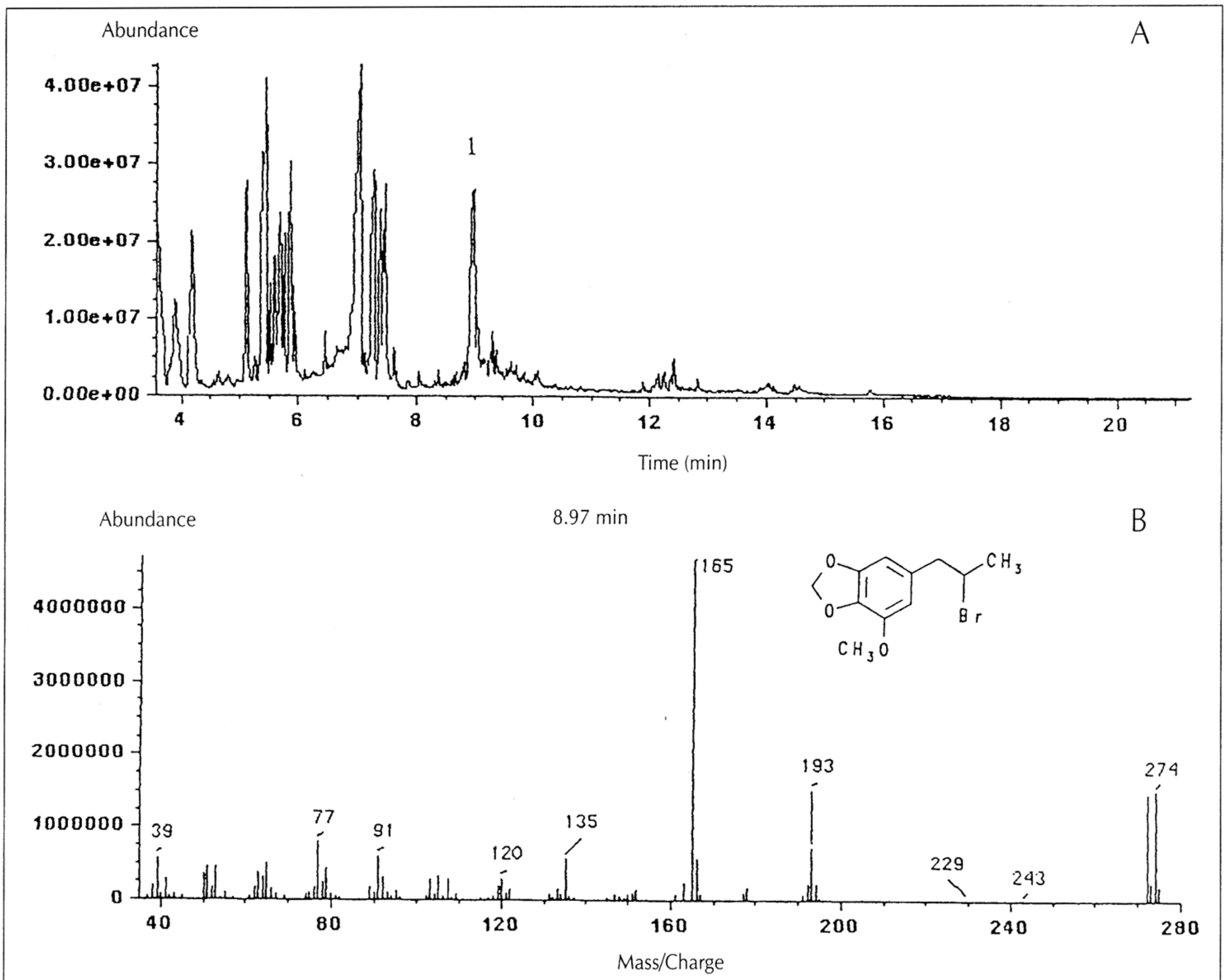
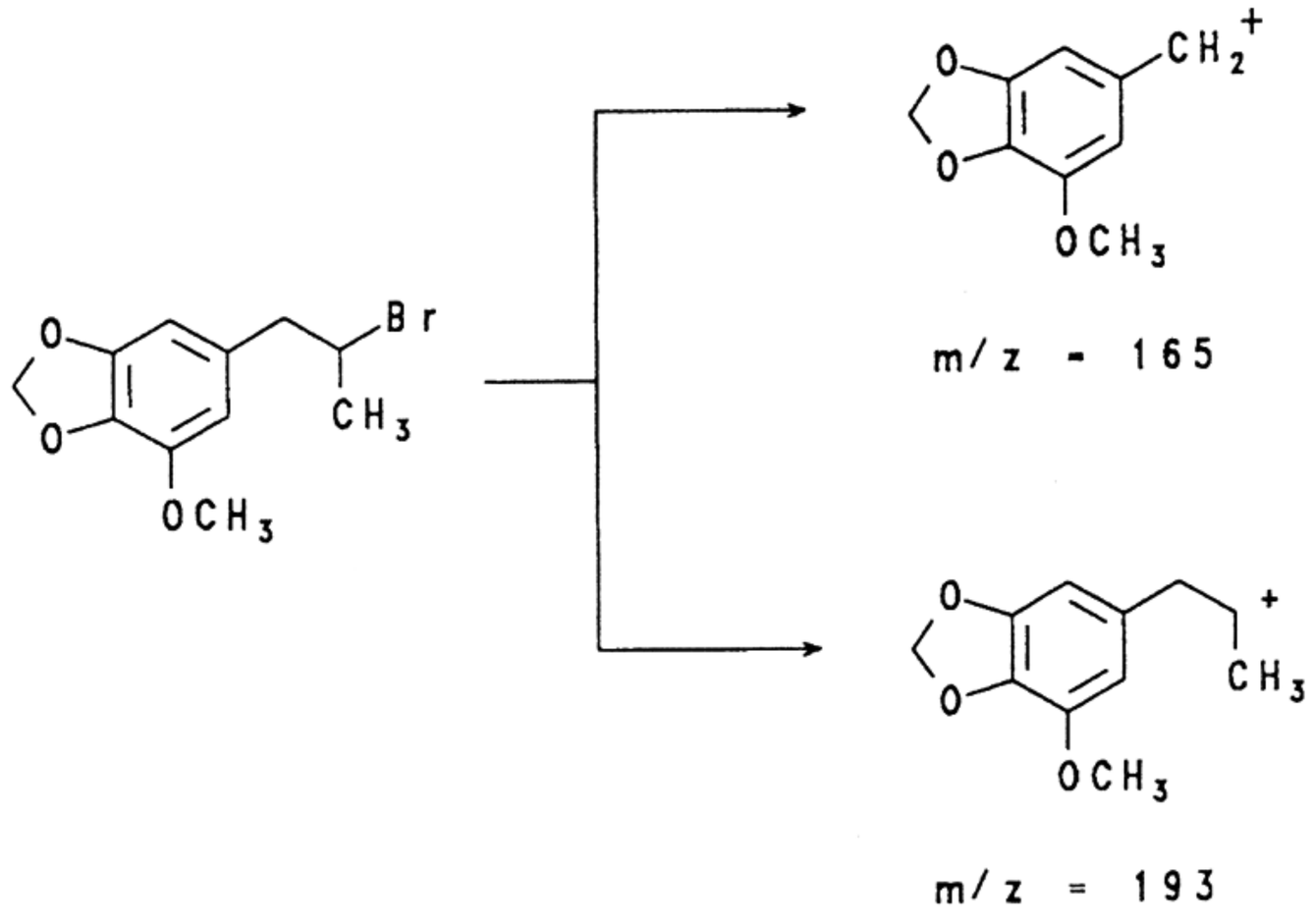


Figure 3. Gas chromatographic–mass spectral analysis of the product obtained on treatment of nutmeg oil with HBr: A, chromatogram; B, mass spectrum of the brominated myristicin product (2-bromo-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propane).



Scheme 2. Mass spectral fragmentation for 2-bromo-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propane.

FL), a 3100 spectromonitor UV detector, a CI 4100 integrator, and a Rheodyne 7125 injector (Cotati, CA). The analytical column (25 cm × 3.9-mm i.d.) was packed with Bondclone C_{18} (Phenomenex; Torrance, CA). The analytical column was preceded by a direct connect (Alltech Associates; State College, PA) guard column packed with CO:Pell ODS (Whatman; Clifton, NJ). The mobile phase consisted of pH 3.0 phosphate buffer–acetonitrile–triethylamine (600:100:1) at a flow rate of 1.25 mL/min. The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate in 1 L of double-distilled water and adjusting the pH to 3.0 with H_3PO_4. The UV absorbance detector was operated at 254 nm and 0.2 AUFS. A 15-µL aliquot of each compound in methanol (1 mg/mL) was injected into the liquid chromatograph.

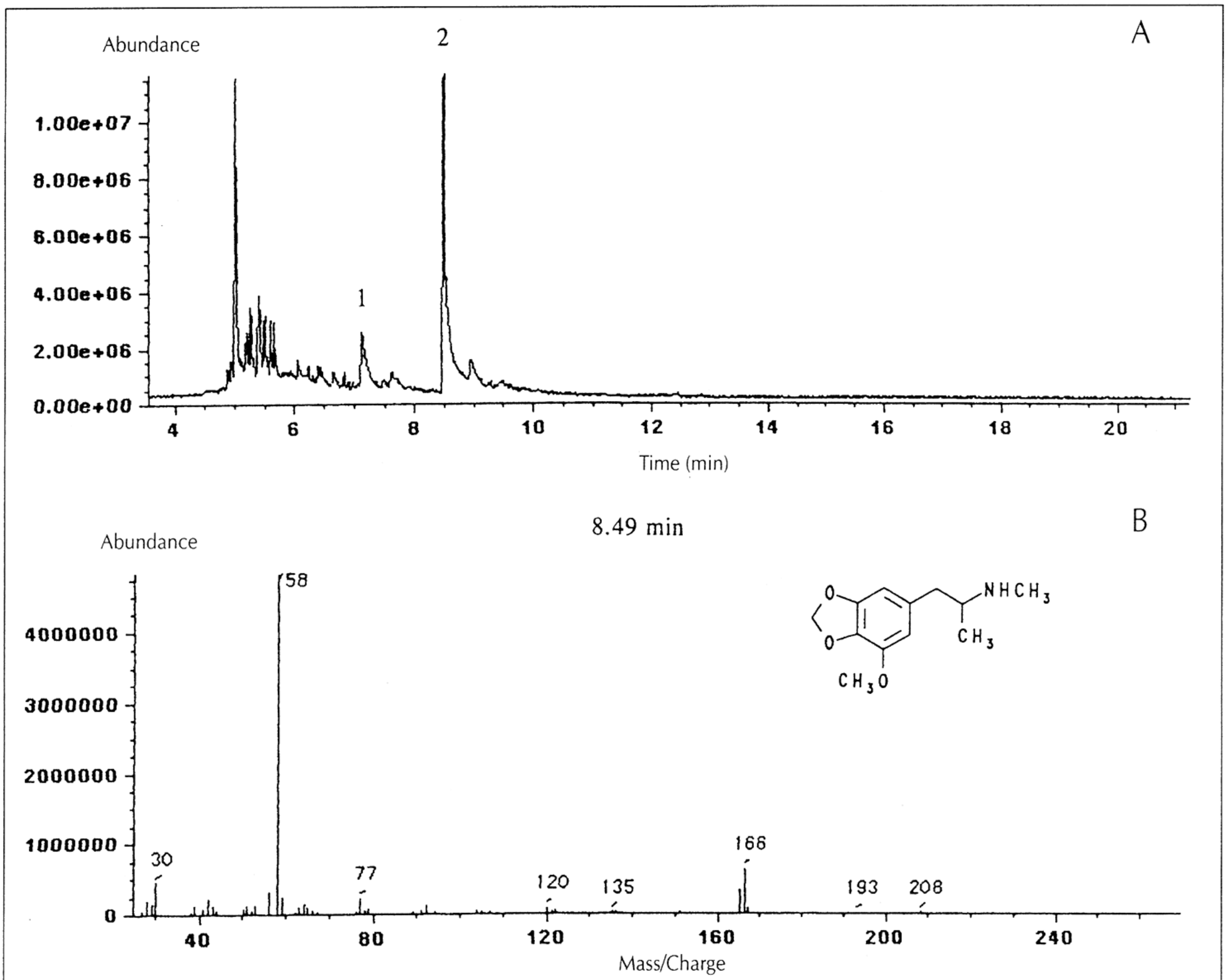


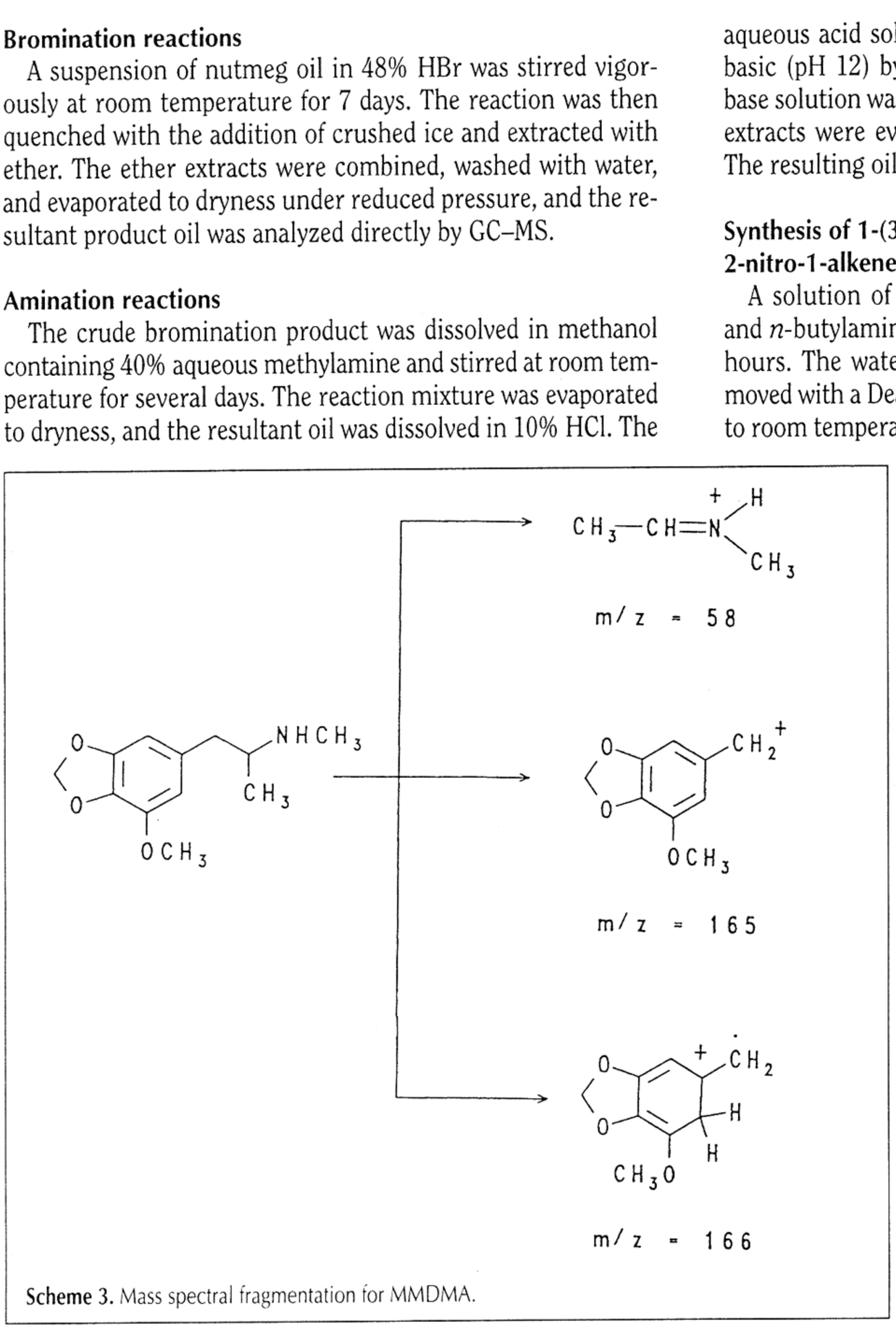
Figure 4. Gas chromatographic–mass spectral analysis of the product obtained on treatment of the brominated nutmeg oil with methylamine: A, chromatogram; B, mass spectrum of MMDMA (*N*-methyl-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine).

Bromination reactions

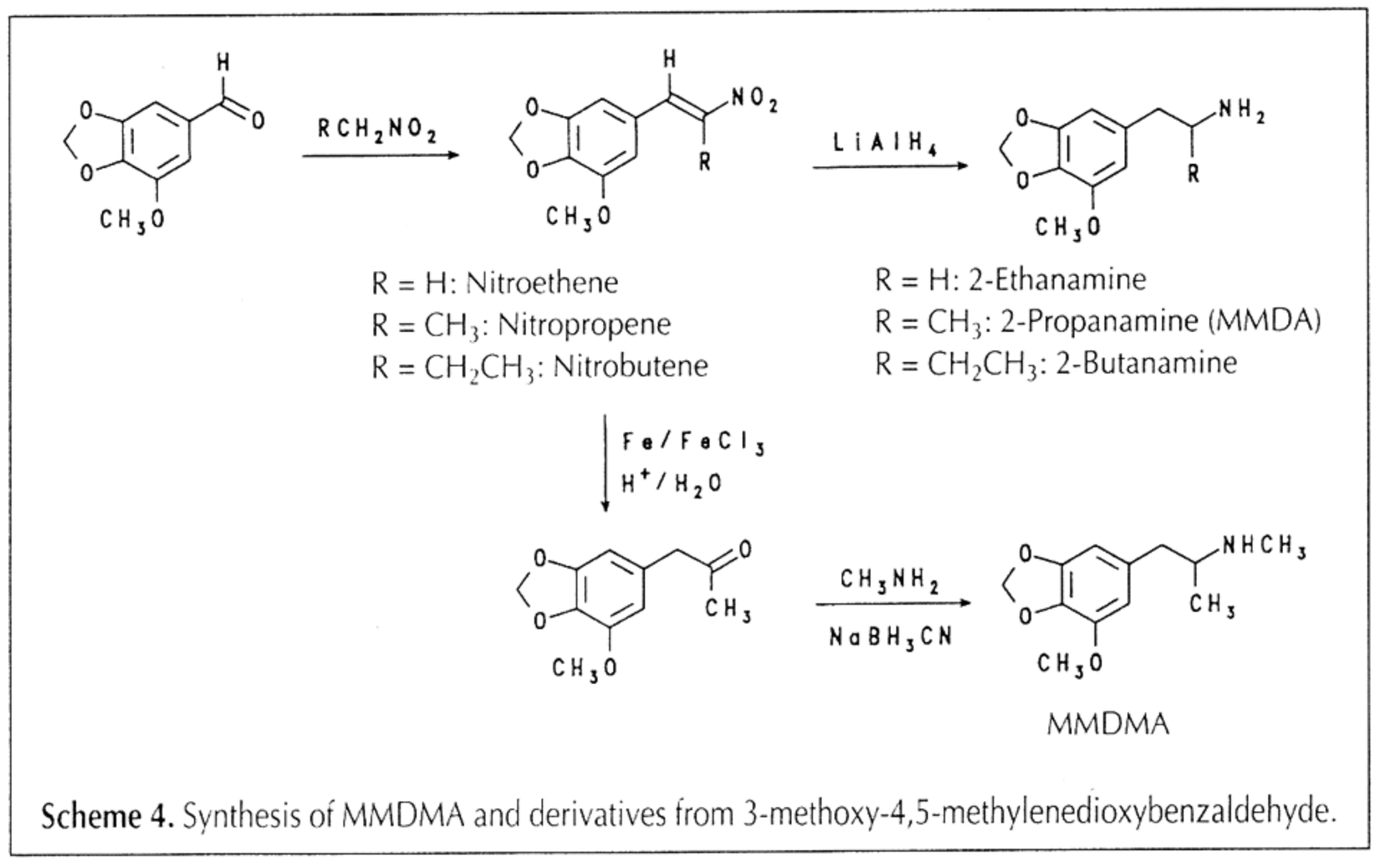
A suspension of nutmeg oil in 48% HBr was stirred vigorously at room temperature for 7 days. The reaction was then quenched with the addition of crushed ice and extracted with ether. The ether extracts were combined, washed with water, and evaporated to dryness under reduced pressure, and the resultant product oil was analyzed directly by GC–MS.

Amination reactions

The crude bromination product was dissolved in methanol containing 40% aqueous methylamine and stirred at room temperature for several days. The reaction mixture was evaporated to dryness, and the resultant oil was dissolved in 10% HCl. The aqueous acid solution was washed with ether and then made basic (pH 12) by the addition of NaOH pellets. The aqueous base solution was extracted with ether, and the combined ether extracts were evaporated to dryness under reduced pressure. The resulting oil was analyzed directly.



Scheme 3. Mass spectral fragmentation for MMDMA.



Scheme 4. Synthesis of MMDMA and derivatives from 3-methoxy-4,5-methylenedioxybenzaldehyde.

Synthesis of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitro-1-alkenes

A solution of 3-methoxy-4,5-methylenedioxybenzaldehyde and *n*-butylamine in benzene was stirred 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 the appropriate nitroalkane and glacial acetic acid and stirred at reflux for several hours. The reaction mixture was cooled, poured over crushed ice, and acidified with concentrated HCl to yield the crude nitroalkenes as dark, highly colored oils. The product oils were crystallized and recrystallized from 2-propanol.

LAH reduction method for the synthesis of the 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-alkylamines

A solution of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitro-1-alkene in dry tetrahydrofuran (THF) was added dropwise over a period of several minutes to a cooled (ice bath), stirred suspension of lithium aluminum hydride (LAH) in dry THF. After the addition was complete, the reaction mixture was stirred at room temperature for several minutes, then at reflux for an hour. The reaction mixture was cooled, and the excess lithium aluminum 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, the solids were washed with THF, and the filtrate and washings were combined and evaporated under reduced pressure to yield a dark oil. The oil was suspended in aqueous acid and washed with benzene. 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 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-alkylamine bases were dissolved in anhydrous ether, and HCl gas was added to yield the hydrochloride salts.

Synthesis of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone

A mixture of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitro-1-propene, 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 filtrate solvent gave the crude ketone as a yellow oil. Distillation under reduced pressure yielded 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone as a light yellow oil.

Reductive amination method for the synthesis of MMDMA

A solution of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone, methylamine, 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 yielded the MMDMA HCl as yellow needles.

Results and Discussion

The GC–MS analysis of commercially available nutmeg oil is shown in Figure 1. The chromatogram in Figure 1A suggests at least five components of relatively significant concentration,

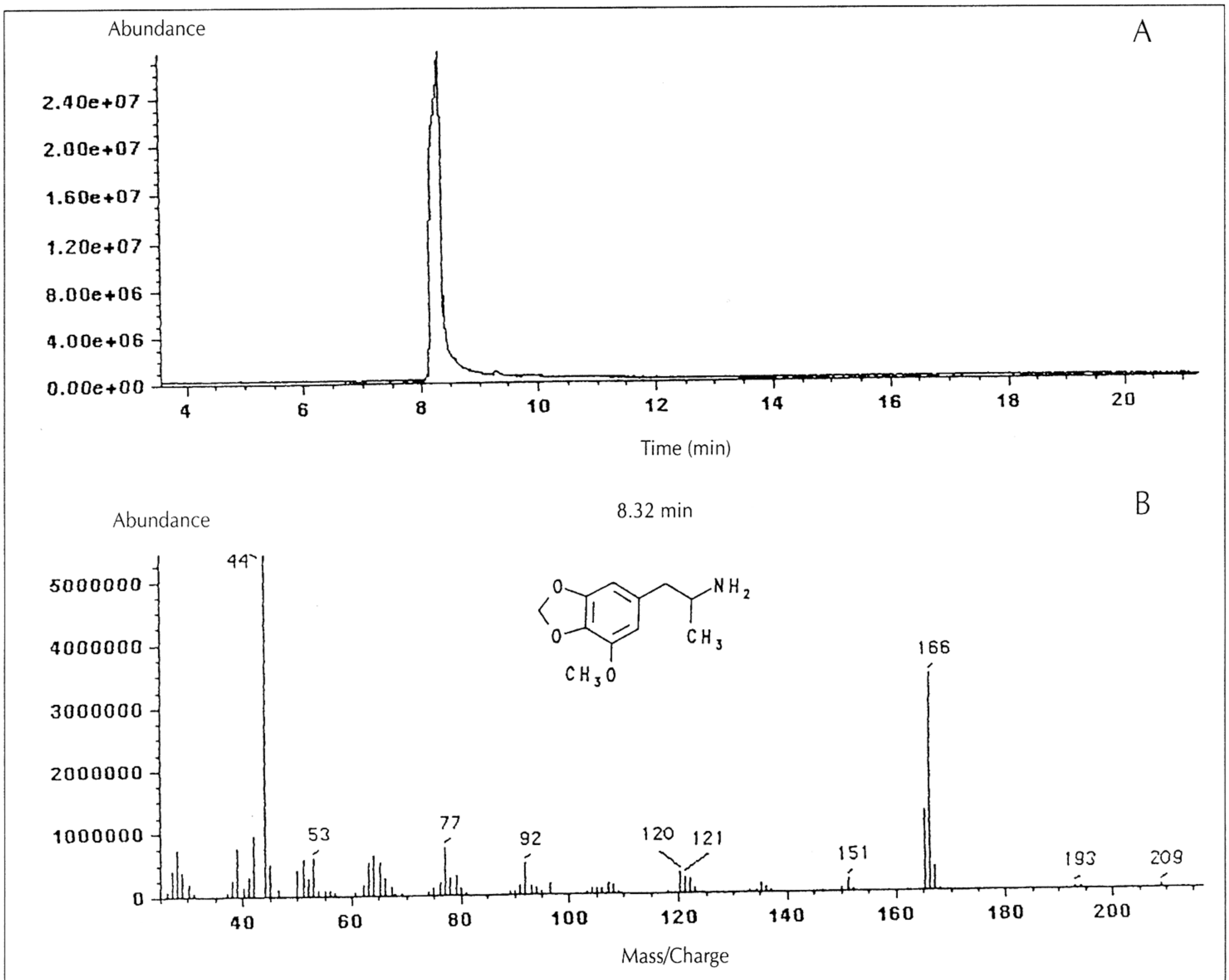


Figure 5. Gas chromatographic–mass spectral analysis of the amine product obtained on reduction of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene with lithium aluminum hydride: A, chromatogram; B, mass spectrum of MMDA (1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine).

and the first three peaks (peaks 1, 2, and 3) are various terpene analogues. The mass spectra obtained for these peaks show matches with a high degree of probability for the spectra of γ-terpinene, α-terpinolene, and terpinen-4-ol. Terpinen-4-ol, which eluted at 4.87 min (peak 3), appears to be the terpene of highest concentration in the nutmeg oil. Peak 4, which eluted at 5.60 min, was identified as safrole (1-(3,4-methylenedioxyphenyl)-2-propene), a common precursor substance bearing the carbon skeleton for the 3,4-methylenedioxyamphetamines. The major component in the nutmeg oil eluting at 7.03 min (peak 5) is a trisubstituted arylpropene, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propene (Figure 1B). The common name for this arylpropene is myristicin, and it is simply the *m*-methoxy derivative of safrole. In previous studies (6) it was shown that the propene side chain of safrole can be functionalized at the 2-position by treatment with HBr, and the resulting bromination product is treated with amines such as methylamine for the preparation of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). The known central nervous system effects of phenethylamines with electron-donating ring substituents, particularly alkoxy groups such as methoxy or methylenedioxy, make myristicin an obvious alternative or designer analogue of safrole (7). When myristicin is substituted for safrole in the bromination–amination synthetic method described previously, the product obtained is *N*-methyl-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine (MMDMA), a known hallucinogenic and stimulant drug (7).

The chromatogram in Figure 2 was obtained from the GC–MS analysis of a methanol extract of nutmeg spice (ground nutmeg). The large peak in the 5-min region (peak 1) is the terpinen-4-ol, and the small peak at 5.64 min (peak 2) is safrole. The larger peak at 6.28 min (peak 3) matches the mass spectrum for 1-(3,4-dimethoxyphenyl)-2-propene, an arylpropene not observed as a significant component in nutmeg oil. The major peak at 7.02 min (peak 4) is myristicin, and the partially resolved secondary peak at 7.14 min (peak 5) yields a mass spectrum corresponding to 1-(3,4,5-trimethoxyphenyl)-2-propene. The later eluting major peak at 8.88 min (peak 6) matches the mass spectrum for tetradecanoic acid. This acid would not be a major component in the nutmeg oil, which is isolated by distillation. Although the

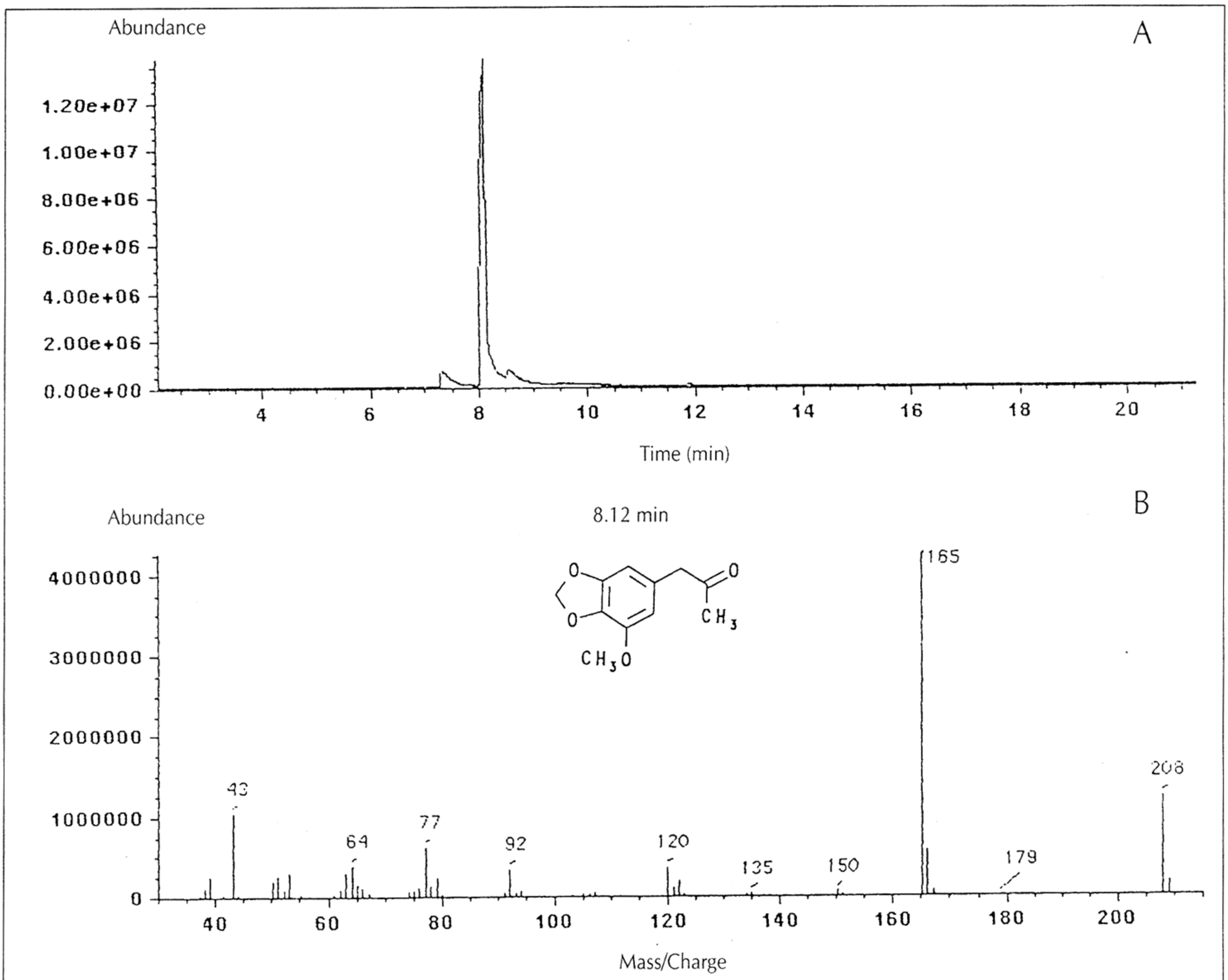


Figure 6. Gas chromatographic–mass spectral analysis of the product obtained on reductive hydrolysis of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene: A, chromatogram; B, mass spectrum of 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone.

extract from ground nutmeg shows some components not found in nutmeg oil, both products are rich in the key precursor substance, myristicin.

The chromatogram and mass spectra in Figure 3 show the analysis of a sample of nutmeg oil treated with HBr. Although the chromatogram in Figure 3A suggests a complex mixture in the crude reaction product, the large peak eluting at 8.97 min yields a mass spectrum (Figure 3B) consistent with the addition of HBr across the side chain double bond of myristicin to yield the 2-bromo derivative (Scheme 1). The major fragments in the mass spectrum in Figure 3B correspond to the loss of bromine from the molecular ion to yield the peak at *m/z* 193 and the 3-methoxy-4,5-methylenedioxybenzyl carbocation base peak at *m/z* 165 (Scheme 2).

The complex series of peaks between 4 and 8 min in the chromatogram in Figure 3A shows quite similar mass spectra indicative of the isomeric products resulting from addition of HBr to the various terpene derivatives. A commercial sample of terpinen-4-ol, a major terpine component identified from nutmeg oil, was treated with HBr under identical reaction conditions. GC–MS analysis of the resulting product showed a complex chromatogram in the 4- to 8-min range yielding similar mass spectra. These spectra are essentially identical to those observed in the chromatogram in Figure 3A and confirm these components as various isomeric bromoterpenes.

Treatment of the brominated nutmeg oil product with methylamine produced a basic fraction (Figure 4) consisting primarily of MMDMA (peak 2 at 8.49 min in Figure 4A) and a detectable amount of MDMA (peak 1 at 7.11 min). These results demonstrate that MMDMA can be obtained from the natural product myristicin in a synthetic procedure involving activation of the propene side chain with HBr, followed by bromine displacement with methylamine. The mass spectrum for the major amine, MMDMA (Figure 4B), shows a molecular ion of low abundance and the expected base peak at *m/z* 58 from the loss of the substituted benzyl radical, which yields the *N*-methylpropylimine cation (Scheme 3). The other high mass fragments at *m/z* 165 and 166 are the substituted benzyl carbocation and radical carbocation, respectively. These latter fragments are observed for aromatic compounds having an alkyl side chain of propyl or larger (8) and are common fragments in phenethylamines, especially those with electron-donating aromatic substituents. Although the mass of these ions varies with the nature and extent of aromatic ring substitution, this fragmentation process is observed in 3,4-methylenedioxyamphetamines (9) and related compounds of forensic interest (10,11).

Scheme 4 illustrates another common approach to the synthesis of phenethylamines and related compounds applied to the preparation of MMDMA and derivatives. The requisite aldehyde, 3-methoxy-4,5-methylenedioxybenzaldehyde, is commercially available and yields the corresponding nitroalkene upon treatment with the appropriate nitroalkane. Reduction of the intermediate nitroalkenes with lithium aluminum hydride yields the corresponding primary amine products, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-ethanamine, -2-propanamine (MMDA), and -2-butanamine. In addition, the nitropropene intermediate (R = CH_3) was subjected to reductive hydrolysis to yield the 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone. Reductive amination of this ketone with methylamine provided MMDMA. The structures of all products were confirmed by standard spectroscopic techniques (i.e., infrared, nuclear magnetic resonance, and mass spectrometric techniques), and the purity of all products was established by chromatography.

Figure 5 shows the analysis of the amine fraction obtained following lithium aluminum hydride reduction of the nitropropene (R = CH_3). The chromatogram in Figure 5A indicates one major component whose mass spectrum (Figure 5B) is consistent with MMDA. The base peak at *m/z* 44 is the primary propylimine, and the peaks at *m/z* 165 and 166 are the substituted benzyl species previously described and illustrated in Scheme 3. Lithium aluminum hydride reduction of the nitroethene (R = H) and nitrobutene (R = CH_2CH_3) intermediates provided the corresponding 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-ethanamine and -2-butanamine products, respectively, in good yield and high purity. These derivatives yielded mass spectra comparable with that obtained for MMDMA with base peaks characteristic of amine-dominated fragmentation (*m/z* = 30 and 58, respectively) and with peaks at *m/z* 165 and 166 representative of the substituted benzyl species.

Figure 6 illustrates the results of analysis of the product from reductive hydrolysis of the nitropropene shown in Scheme

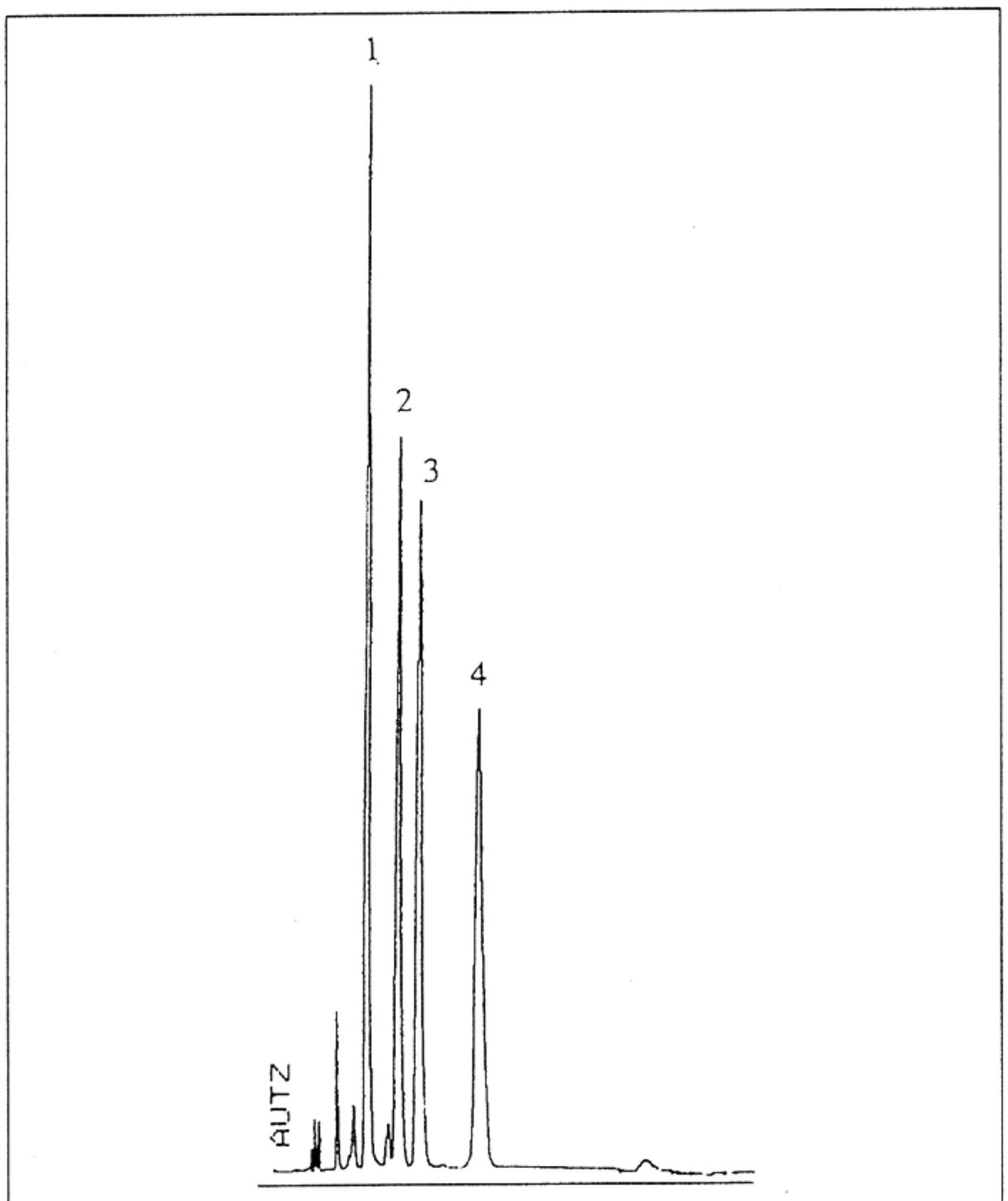


Figure 7. Reversed-phase liquid chromatographic analysis of MMDA and derivatives. Peaks: 1, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-ethanamine (5.02 min); 2, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine (MMDA, 7.80 min); 3, *N*-methyl-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine (MMDMA, 9.05 min); and 4, 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-butanamine (12.69 min).

4. The resulting product mixture is primarily the 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanone eluting at 8.12 min (Figure 6A) and producing the mass spectrum in Figure 6B. The base peak in the spectrum is the substituted benzyl carbocation at *m/z* 165. The remaining high mass fragment is the molecular ion at *m/z* 208. The 2-propanone is a key precursor that can be reductively aminated with various amines to yield a variety of *N*-substituted-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-propanamine derivatives, including the *N*-methyl derivative MMDMA.

The four amines of this study display similar gas chromatographic retention, and complete resolution was not obtained under the conditions investigated. Thus, reversed-phase liquid chromatographic separation was investigated, resulting in the chromatogram shown in Figure 7. In the acidic mobile system used for this separation, the amines are in the protonated form, and the protonated triethylamine in the mobile phase serves as a competitor for silanol sites on the stationary phase. This dynamic saturation of silanol sites prevents the peak tailing commonly observed for amines in reversed-phase liquid chromatography. The four amines are well-resolved in this system, and the unbranched primary amine, the 2-ethanamine, has the lowest capacity factor. The α-methyl-branched primary amine, the 2-propanamine (MMDA), elutes second, and this amphetamine derivative is well-resolved from its *N*-methyl derivative MMDMA, which is the third component to elute in this chromatogram. Peaks 2 and 3 in the chromatogram each represent the addition of a single methyl group to the previously eluting component (peaks 1 and 2, respectively). The enhanced retention observed upon the addition of one methyl group is caused by the increase in solute hydrophobic surface area. The significant resolution of these compounds indicates the sensitivity of hydrocarbon stationary phases to small changes in solute hydrophobicity. Peaks 2 and 3 are baseline-resolved in this system, which has retention differences of more than 1 min. The retention difference for these two compounds was approximately 0.1 min under the gas chromatographic conditions used in this study. Peaks 3 and 4 in Figure 7 further illustrate this point as these two amines differ only in the position of one methyl group. The *N*-methyl-2-propanamine MMDMA and the primary amine 2-butanamine have the same molecular weight and differ only in *N*-methyl versus *C*-methyl substitution. This small difference, however, allows for baseline resolution in this liquid chromatographic system.

Conclusion

GC–MS methods allowed for the specific identification of the starting materials, intermediates, and products involved in the preparation of MMDMA and derivatives from nutmeg oil (myristicin) and commercially available 3-methoxy-4,5-methylenedioxybenzaldehyde. Reversed-phase liquid chromatography separated all MMDMA derivatives, and resolution resulted from relative differences in hydrophobic surface area of the derivatives.

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