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Gas Chromatographic and Mass Spectrometric Analysis of Samples from a Clandestine Laboratory Involved in the Synthesis of Ecstacy from Sassafras Oil

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Abstract

The various samples from a clandestine drug laboratory reported to be involved in the synthesis of 3,4-methylenedioxymethamphetamine (MDMA, Ecstacy, or XTC) are analyzed by gas chromatography–mass spectrometry (GC–MS). Safrole, the starting material for the synthesis, is obtained from the roots of the sassafras plant. GC–MS of the sassafras oil reveals the presence of safrole (4-allyl-1,2-methylenedioxybenzene) as the major component, as well as smaller quantities of camphor, eugenol, a dimethoxyallyl- and trimethoxyallylbenzene. A second sample obtained from the clandestine laboratory is from the treatment of the sassafras oil with HBr. Although this sample contains many brominated and several nonbrominated components, the major constituent is the synthetic precursor for MDMA, 1-(3,4-methylenedioxyphenyl)-2-bromopropane, along with quantities of the regioisomeric 3-bromopropane. The samples from the clandestine laboratory do not reveal the presence of any MDMA. However, upon treatment with methylamine, the brominated sassafras oil gives MDMA as the major amine product.

Introduction

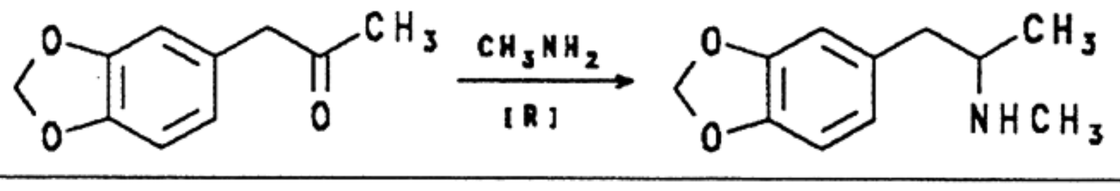
The various *N*-substituted derivatives of 1-(3,4-methylenedioxyphenyl)-2-propanamine (3,4-methylenedioxyamphetamine, MDA) have been popular drugs of abuse in the past decade (1–3). The *N*-methyl derivative, 3,4-methylenedioxymethamphetamine (MDMA, also called Ecstacy or XTC) is perhaps the most widely abused drug of this series. MDMA is reported to have the unique ability to facilitate interpersonal communication by reducing the anxiety and fear that normally accompanies the discussion of emotionally painful events (4). In recent years other so-called designer drug analogs of MDA, including the *N*-ethyl (MDE) and *N*-hydroxy (NOHMDA) analogs, have also been encountered in forensic samples, and appear to possess pharmacological activities comparable to MDA and MDMA. The continued designer drug exploration of the MDA series has resulted in recent legislation to upgrade the penalties associated with the synthesis and abuse of these compounds.

A variety of methods have been reported for the synthesis of MDA, MDMA, and related compounds (5,6). The most direct approach involves treatment of a commercially available ketone, 1-(3,4-methylenedioxyphenyl)-2-propanone (3,4-methylenedioxyphenylacetone) with ammonia or methylamine under reducing conditions as shown in Scheme 1. Based on this synthetic strategy, the availability of the ketone was controlled by the Drug Enforcement Administration (DEA) under the Chemical Diversion and Trafficking Act in March of 1989. The restricted availability of the key ketone precursor has forced clandestine laboratory operators to seek alternative approaches for the synthesis of MDA and MDMA. One such alternate method employs the natural product safrole, which is commercially available or can be obtained by extraction or distillation of the sassafras plant native to the United States. Safrole may be brominated with hydrobromic acid to yield 2-bromosafrole, which can be converted to MDA or MDMA by direct displacement with ammonia or methylamine, respectively (Scheme 2). It appears that this latter approach was being employed by the operator of a clandestine laboratory seized recently. In this laboratory, safrole was obtained by steam distillation of the roots of the sassafras plant and then treated with HBr to generate 2-bromosafrole. In this paper we report the results of the analysis of samples obtained from this laboratory and identification of the key constituents and products in the isolated oil and reaction products by gas chromatography–mass spectrometry (GC–MS).

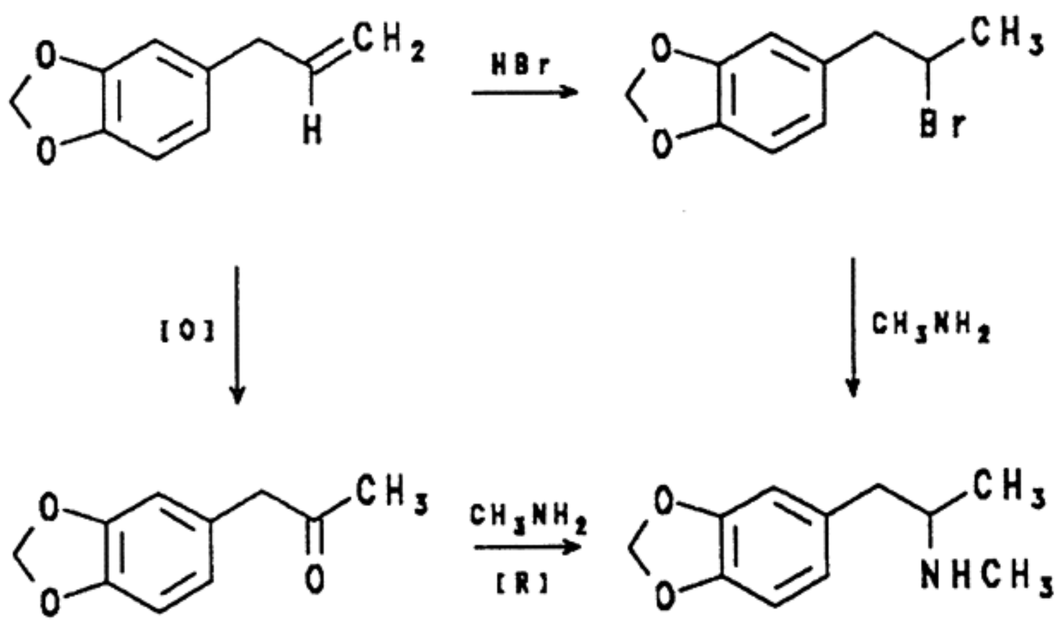
Experimental

Gas chromatographic–mass spectrometric analysis. These analyses were performed using a Hewlett-Packard 5970B mass selective detector. The sample was introduced into the mass spectrometer via a GC equipped with a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-µm thickness of methylsilicone (HP1). The column temperature was programmed from 70° to

SCHEME 1



SCHEME 2



150°C at a rate of 15°/min and from 150° to 250°C at a rate of 25°/min.

Bromination reactions. Samples of sassafras oil or alkenes (5.0 g of safrole, isosafrole, eugenol, isoeugenol, etc.) in 48% HBr (25 mL) were stirred at room temperature for 7 days. The reactions were then quenched with the addition of crushed ice (25 mL) and extracted with ether (2 × 50 mL). The ether extracts were evaporated to dryness under reduced pressure and the resultant product oils analyzed directly.

Amination reactions. The crude bromination products (2.0 g) were dissolved in methanol (100 mL) containing 40% aqueous methylamine (20 mL) and stirred at room temperature for 4 days. The reaction mixture was evaporated to dryness and the resultant oil dissolved in 10% HCl (50 mL). The aqueous acidic solution was washed with ether (2 × 50 mL) and then made basic (pH 12) by the addition of NaOH pellets. The aqueous base solution was extracted with ether (2 × 50 mL) and the combined ether extracts evaporated to dryness under reduced pressure. The resulting oil was analyzed directly.

Results and Discussion

This project originated from the samples obtained from a clandestine laboratory which was reported to be involved in the synthesis of 3,4-methylenedioxymethamphetamine. The initial analysis did not reveal the presence of MDMA or any related amines in the various items obtained from the laboratory. The absence of any MDMA in the sample likely indicates that the laboratory was seized before the synthesis was completed. The starting point for the synthesis appeared to be a plant extract, an oil obtained by steam distillation of roots from the sassafras plant. The oil extract of sassafras bark is reported to consist of about 80% safrole, 4-allyl-1,2-methylenedioxybenzene (7).

The chromatogram in Figure 1 shows the GC analysis of the sassafras oil sample obtained from the clandestine lab. The total ion chromatogram (TIC) trace showed one major component with a retention time of 5.686 min (peak C) and several minor components. Peak A, eluting at 4.567 min, has a molecular ion of $m/z = 152$ and a fragmentation pattern matching that of camphor. The second minor component at 5.016 min (peak B) appeared to be a methylenedioxystyrene, a safrole homologue, but was not identified. The major component in this sample at 5.686 min (peak C) matches both the chromatographic properties and the mass spectrum for safrole (4-allyl-1,2-methylenedioxybenzene). Figure 2A shows the chromatogram and mass spectrum obtained from the analysis of an authentic sample of

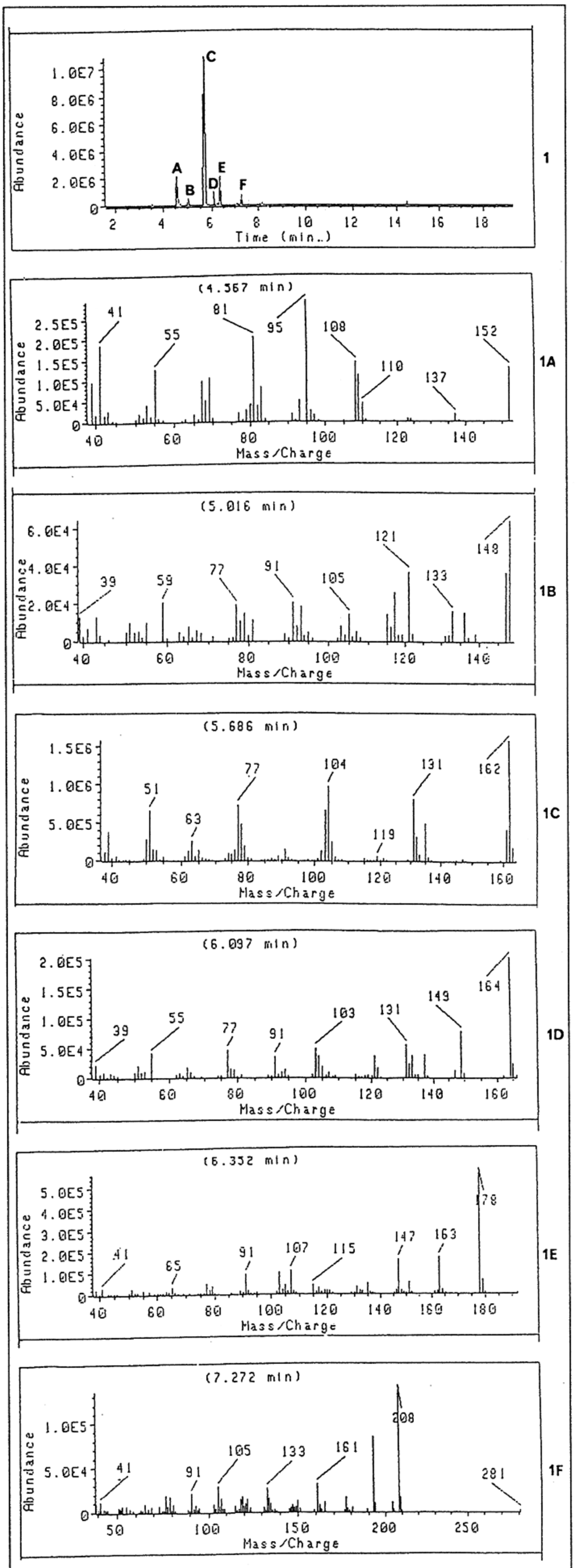


Figure 1. GC–MS analysis of sassafras oil distillate. Chromatogram peaks A, B, C, D, E, and F produced the mass spectra shown in 1A–F.

safrole. These data were obtained under conditions identical to those used for the analysis of the sassafras oil distillate. An additional minor component in the sassafras oil eluting at 6.097 min (peak D in Figure 1) corresponds to eugenol, a hydroxy, methoxy substituted allylbenzene. The chromatogram and mass spectrum in Figure 2B were obtained from the analysis of a known sample of eugenol (4-allyl-1-hydroxy-2-methoxybenzene) under identical analytical conditions. Eugenol may be considered a methylenedioxy ring cleavage product of safrole; however, this compound was not found in the authentic sample of safrole. Thus it appears to be a component of the plant distillate and not an artifact of the analysis.

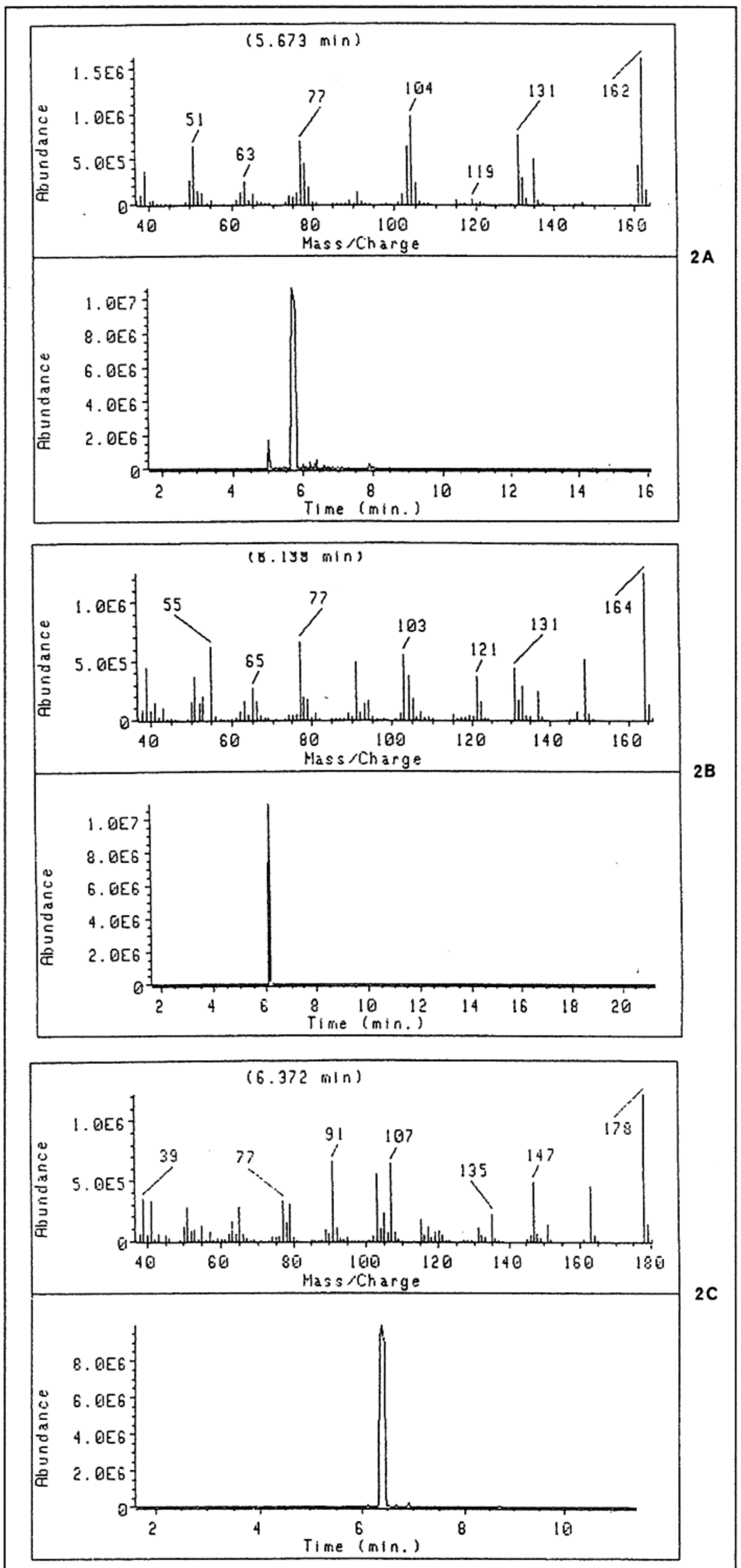


Figure 2. GC–MS analysis of authentic samples of compounds reported to be components of sassafras oil. (2A) safrole, (2B) eugenol, and (2C) 4-allyl-1,2-dimethoxybenzene.

The peak in Figure 1 at 6.352 min (peak E) shows a molecular ion at *m/z* 178 and a mass spectrum which corresponds to 4-allyl-1,2-dimethoxybenzene. Figure 2C shows the chromatographic and mass spectral analysis of a known sample of 4-allyl-1,2-dimethoxybenzene, confirming the identity of peak E in Figure 1. The peak at 7.272 min (peak F) appears to have an MW of 208 and may represent a trimethoxy substituted allylbenzene, although no standard was available for conclusive identification. The assignment of the side chain alkene as an allyl group in the trimethoxy compound rather than the isomeric propenyl moiety having the double bond in conjugation with the aromatic ring is based simply on observations for safrole, eugenol, and 4-allyl-1,2-dimethoxybenzene. However, the allyl moiety was confirmed in these three compounds via comparison with authentic samples of isosafrole, isoeugenol, and 1,2-dimethoxy-4-propenylbenzene. These compounds are the positional isomers of the sample components, each containing the conjugated double bond in the side chain.

Thus, the data shown in Figures 1 and 2 show that the oil obtained from steam distillation of the roots of the sassafras plants contains several aromatic compounds. The major component appears to be safrole (4-allyl-1,2-methylenedioxybenzene). However, this volatile organic fraction contains other substituted allylbenzenes such as eugenol and 4-allyl-1,2-dimethoxybenzene. Several other aromatic compounds were tentatively identified based on mass spectral data. Literature reports (7,8) on the oil of sassafras bark indicate safrole as a major component (approximately 80%) with smaller amounts of pinene, eugenol, camphor, and phellandrene.

A second sample obtained from the clandestine laboratory was reported to be the result of hydrobromic acid (HBr) treatment of the sassafras distillate. The chromatogram obtained from the GC–MS analysis of the HBr-treated sassafras oil is shown in Figure 3. The mass spectra of the individual peaks in this chromatogram indicates the presence of several brominated products as well as other nonbrominated compounds. Peaks A and B in Figure 3 were identified respectively as unreacted camphor and safrole from the sassafras oil distillate. Peaks C and D have mass spectra which are essentially identical to that obtained for safrole. However, the GC properties for both compounds yield higher retentions than safrole (see Figure 2A). Isomerization of the safrole double bond could give rise to isosafrole, which can exist in either *cis*- or *trans*-isosafrole form. The GC–MS analysis of an authentic sample of isosafrole (Figure 4) shows two peaks of similar retention to peaks C and D (Figure 3). The two compounds yield mass spectra identical to each other and very similar to that of safrole. These data confirm the presence of *cis*- and *trans*-isosafrole in the HBr-treated sassafras oil, yet these geometric isomers were not found in the original oil from the plant distillate. It is likely that the source of isosafrole is an acid-catalyzed isomerization of the side chain double bond of safrole or possibly the elimination of HBr from the side chain bromination of safrole to yield the isomeric conjugated olefins (see Scheme 3).

Peaks E (6.738 min) and F (6.844 min) in Figure 3 appear to be the result of the respective additions of methanol and water to the double bond of safrole. The compound of MW 194 is the methanol addition product, and the methoxy group appears to be attached to the side chain at the 2-position in order to yield the *m/z* 59 base peak (CH_3-O=CH-CH_3). Both the methanol and water addition products are likely the result of displacement–hydrolysis reactions from the major safrole bromination product.

Thus, these compounds may be artifacts of the sample workup procedure or the GC analysis process.

The major component in the HBr-treated sassafras oil sample (Peak G) has a retention time of 7.580 min, an MW of 242, and contains one bromine atom. A second peak at 7.781 min (Peak H), which is only partially resolved from the major component, also contains one bromine atom and has a mass of 242. These peaks both give mass spectra consistant with the addition of HBr to safrole. Both compounds have a fragment at *m/z* 163 in the MS which corresponds to the loss of Br from the parent molecule. However, the base peak for the two components differs. The base peak for the major component has an *m/z* of 135 while the base peak for the secondary product has an *m/z* of 149. These peaks are likely the result of fragmentation of the carbon–carbon bond alpha to the bromine atom, with the *m/z* 135 arising from 2-bromosafrole and the *m/z* 149 arising from 3-bromosafrole (Scheme 4). The presence of these two regioisomeric bromo products is reasonable based on the mechanism of the HBr addition reaction (9). Such electrophilic additions are initiated by protonation of the double bond to yield either a primary or secondary carbocation (Scheme 5). Of these, the secondary carbocation forms preferentially because of greater hyperconjugative stabilization. Because the 2-bromosafrole product would form by bromination of the secondary carbocation, it would be expected to form in higher proportion than the 3-bromosafrole product which results from bromine addition to the primary carbocation intermediate. Such a hypothesis accounts for the formation of both bromo regioisomers, with the 2-bromo isomer predominating.

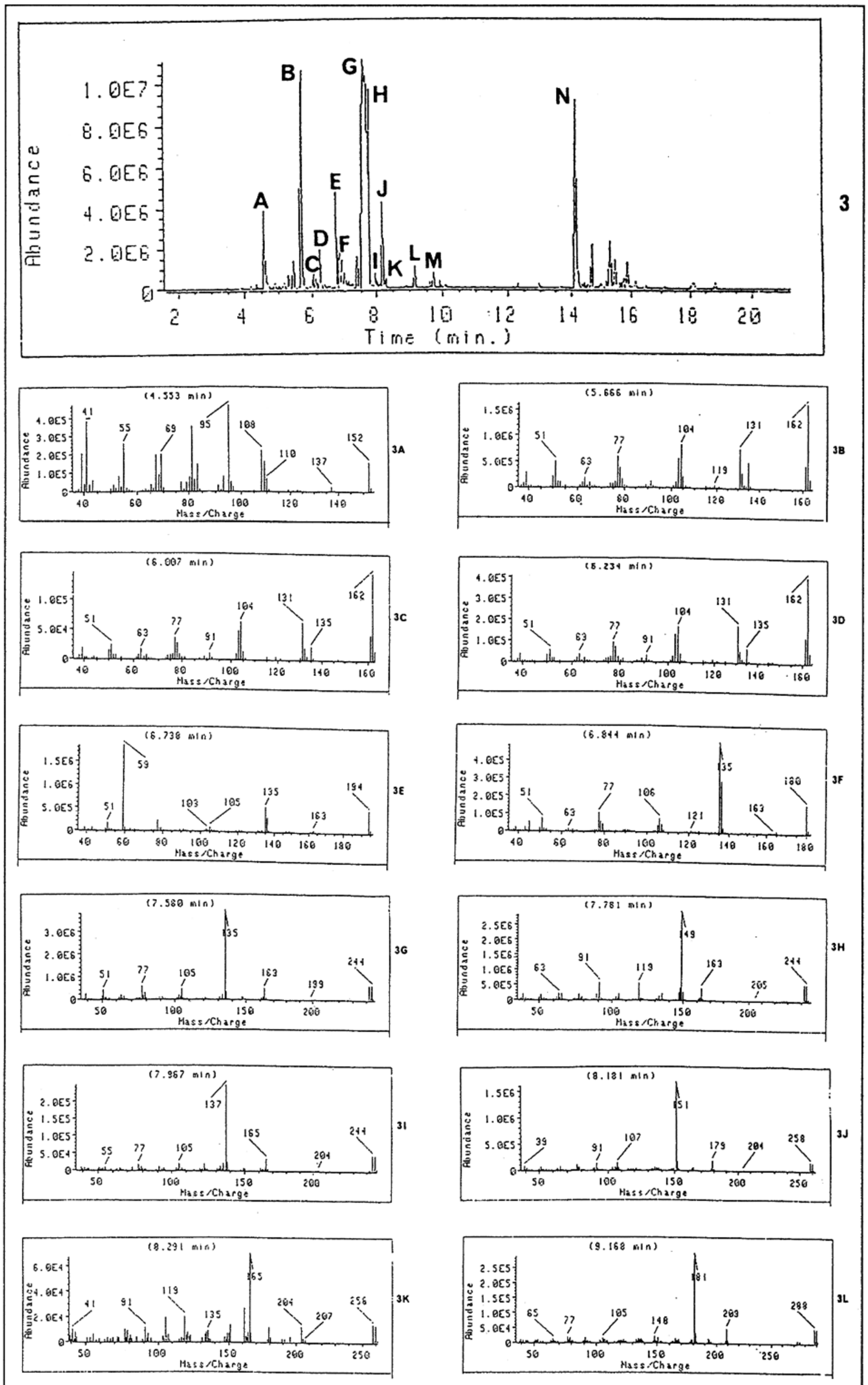


Figure 3. GC–MS analysis of sassafras oil distillate after treatment with 48% HBr.

The chromatogram of the HBr-treated sassafras oil (Figure 3) also has a small peak at 7.967 min (Peak I) for a compound which contains bromine, has an MW of 244, and a base peak at *m/z* 137. These data are consistent with the addition of HBr to eugenol; thus the molecular ion and the base peak should be two mass units higher than the corresponding ions from safrole. Because the base peak occurs at *m/z* 137 and not *m/z* 149, the bromine atom of this compound is at the 2-carbon, which is consistent with the addition of bromine to the more stable carbocation, also observed for safrole. The presence of the minor 3-bromo addition product from eugenol was not detected under these analytical conditions.

The peaks at 8.181 (J) and 8.291 min (K) in the chromatogram shown in Figure 3 have a similar MS fragmentation pattern as was observed for Peaks G and H. Both J and K have an MW of 258 and contain one bromine atom. The base peaks at *m/z* 151 for J and *m/z* 165 for K differ by 14 mass units (a methylene group), with the lower mass base peak being the compound present in higher concentration based on relative peak heights. These data are consistent with HBr addition to the isolated double bond in 4-allyl-1,2-dimethoxybenzene. The major addition product of this pair is the 2-bromo derivative which fragments to yield the lower mass base peak at *m/z* 151. The minor product of this pair fragments to yield the *m/z* 165 ion. Thus, both the 2- and 3-bromo products from the HBr addition to 4-allyl-1,2-dimethoxybenzene were observed in the sample. The peak in Figure 3 at 9.168 min (peak L) corresponds to the bromination of the trimethoxy-substituted allylbenzene at the 2-position in the side chain. This assignment is substantiated by the presence of a molecular ion at *m/z* 288 and a peak at *m/z* 209 resulting from

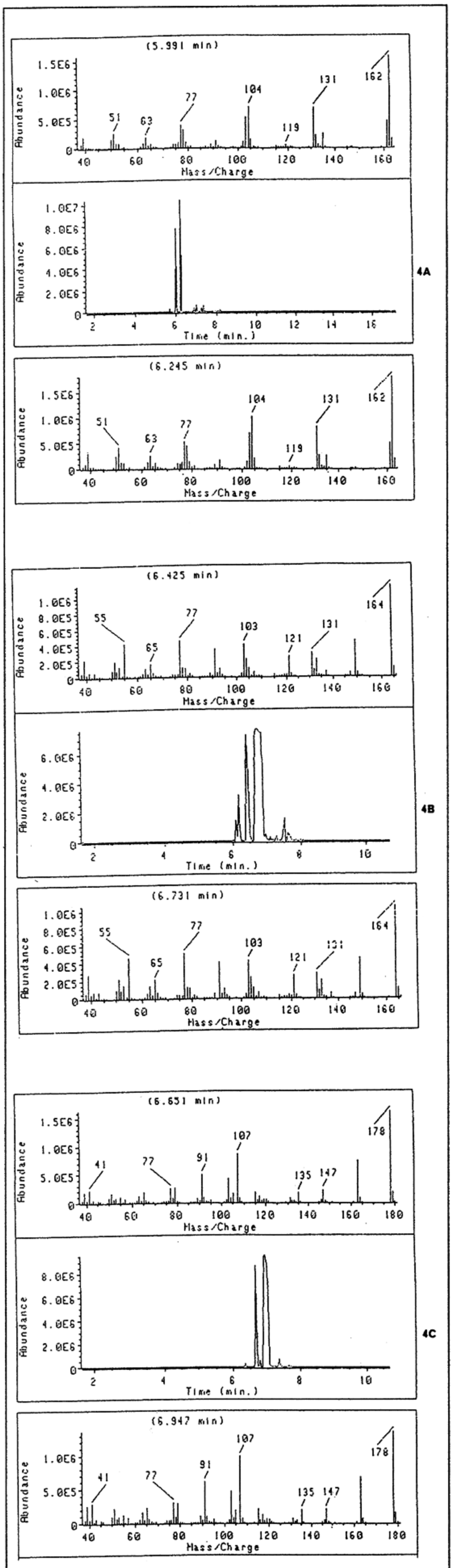
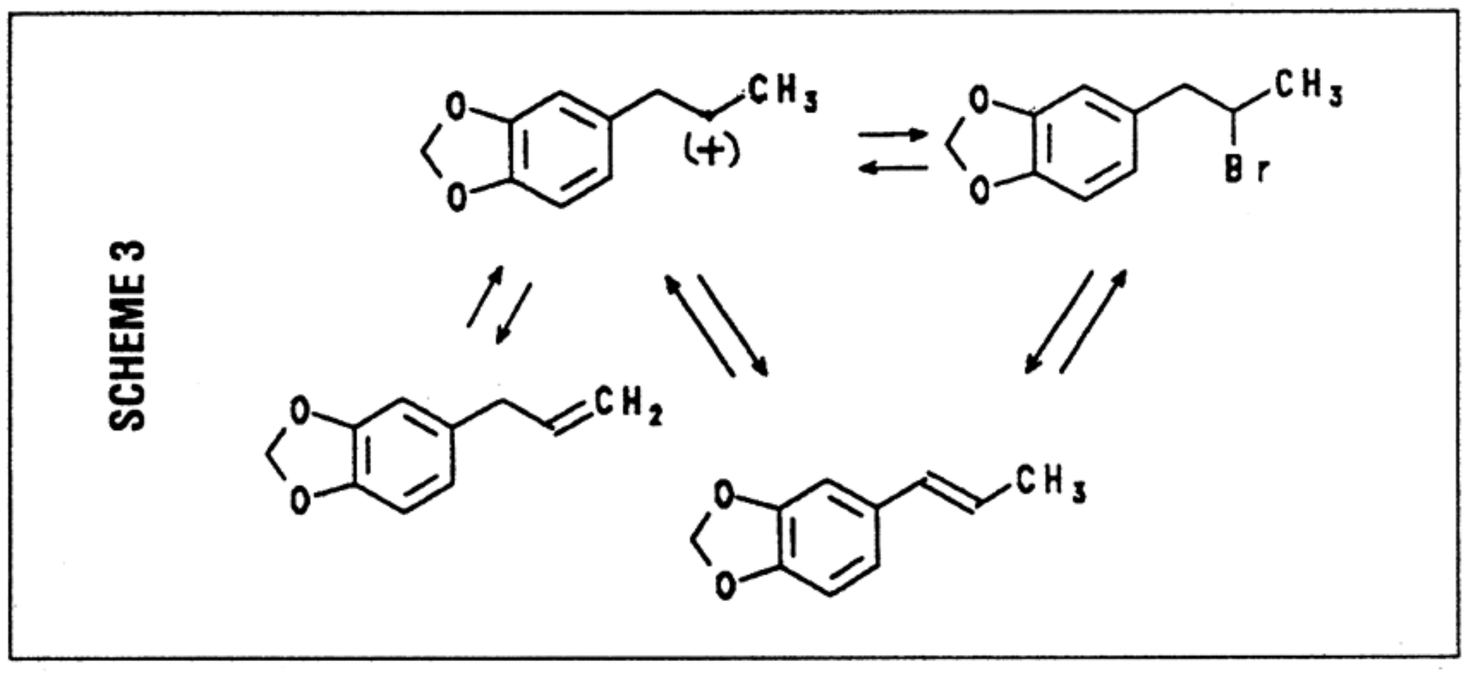
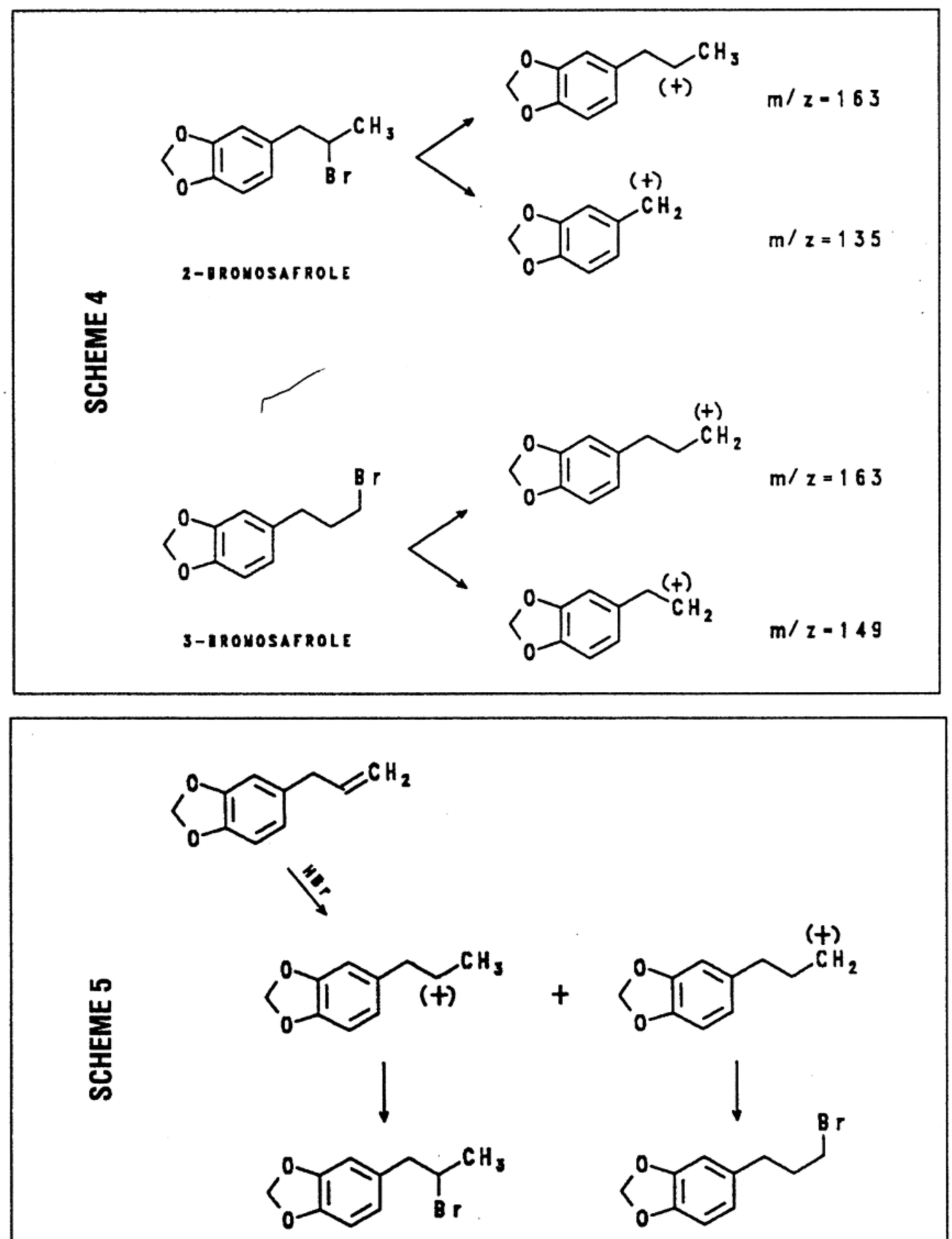


Figure 4. GC-MS analysis of (A) isosafrole, (B) isoeugenol, and (C) 1,2-dimethoxy-4-propenylbenzene.

the loss of bromine. The base peak in this spectrum at *m/z* 181 is from the loss of CH_3CHBr^+ to yield the trimethoxybenzyl fragment, demonstrating that bromination occurred at the 2-position.

The small peaks (region M) in the chromatogram in Figure 3 with retention times between 9.5 and 10.0 min appear to be various dibromination products of safrole and their specific identification was not undertaken. The peaks between 14 and 16 min in the chromatogram of Figure 3 are high molecular weight compounds and may be the result of dimerization of safrole and related olefins in the sassafras oil, as well as bromination of these dimers. The major peak in this region (Peak N) at 14.150 min appears to have an MW of 324 and loses a mass 29 fragment to yield the base peak *m/z* = 295. The specific identification of these compounds is the subject of additional work in our lab.





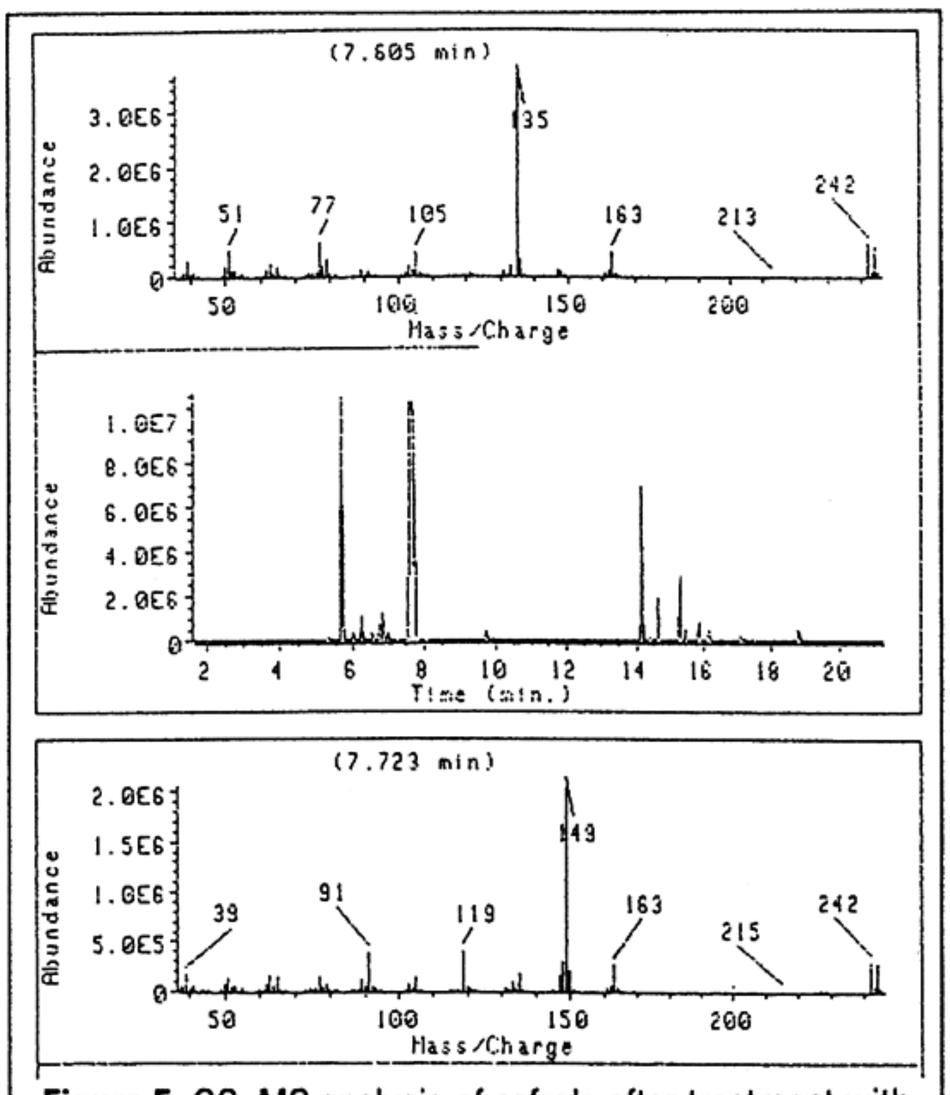


Figure 5. GC–MS analysis of safrole after treatment with 48% HBr.

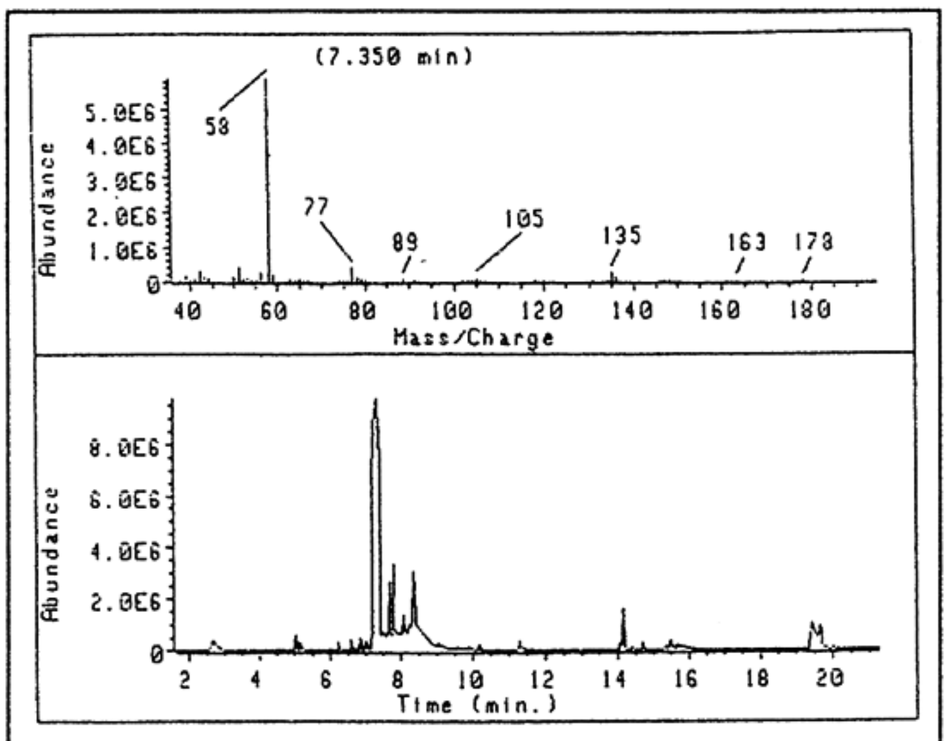


Figure 6. GC–MS analysis of the basic fraction isolated following methylamine treatment of the brominated sassafras oil.

A chromatogram very similar to that shown in Figure 3 was obtained after a sample of sassafras oil was allowed to react with 48% aqueous HBr for 7 days. The mass spectra for the various major peaks were essentially identical to those obtained from the analysis of the sample from the clandestine laboratory. An aliquot of the bromination reaction mixture was removed each day and analysis showed the bromination occurred slowly and require approximately 7 days to consume most of the safrole.

An authentic sample of safrole was subjected to the bromination reaction under the same conditions for 7 days and, after isolation, yielded the chromatogram in Figure 5. The first three peaks in the chromatogram eluting at 5.684, 5.993, and 6.215 min each show a molecular ion at *m/z* 162, and also correspond to safrole (5.684 min) and the *cis* and *trans*-isomers of isosafrole. No attempt was made to distinguish the two geometric isomers of isosafrole. However, based on relative product stability, the *trans*-isomer would be expected to form in greater concentration and can thus be assigned to the larger of the two peaks.

The major component of the safrole bromination reaction (Figure 5) elutes at 7.605 min, and a second, partially resolved component elutes at 7.723 min. As in the case for peaks G and H of the sassafras oil bromination (Figure 3), these compounds have molecular ions at *m/z* 242 with a base peak of *m/z* 135 for the major component and *m/z* 149 for the minor component. These peaks represent the two possible HBr addition products from safrole, and the difference in the base peaks allows the major component to be identified as the 2-bromo isomer, with the minor component identified as the 3-bromo isomer. The trace components between 9 and 10 min appear to be the dibromosafrole compounds and the peaks above 14 min appear to be safrole dimers and brominated dimers. Similar peaks and spectra were observed in the analysis of the brominated sassafras oil.

The brominated sassafras oil was treated with methylamine in an attempt to show that *N*-methyl-1-(3,4-methylenedioxy-phenyl)-2-propanamine (3,4-methylenedioxymethamphetamine, MDMA) could be synthesized by this method. The chromatogram in Figure 6 was obtained following isolation of the basic fraction from the reaction mixture. The major component in the chromatogram has a retention time of 7.350 min and its mass spectrum shows a molecular ion at 193 and a base peak at *m/z* 58. These data are consistent with the profile for MDMA under identical analysis conditions. Thus, this synthetic procedure can be used to prepare MDMA in significant quantities from the constituents of a plant material native to the U.S. The various other amine components in the chromatogram in Figure 6 were not identified in this work. However, amine displacement reactions with the various brominated compounds identified in Figure 3 would yield a number of products. These amine products are the subject of current work in our laboratory. The results of the present study clearly show that MDMA and related designer drug analogues of MDA can be prepared by amine displacement of bromosafrole obtained via bromination of the organic steam distillate of the roots of the sassafras plant.

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