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Gas Chromatographic and Mass Spectrometric Analysis of *N*-Methyl-1-aryl-2-propanamines Synthesized from the Substituted Allylbenzenes Present in Sassafras Oil

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Abstract

One method used for the synthesis of the illicit drug *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (methylenedioxymethamphetamine, MDMA) involves the treatment of safrole with HBr to form the intermediate 2-bromosafrole, followed by bromide displacement with methylamine. The starting material required for this synthesis, safrole, may be obtained from sassafras oil which is isolated from the roots of the sassafras plant. In addition to safrole, sassafras oil contains other allylbenzenes such as eugenol and 4-allyl-1,2-dimethoxybenzene. Gas chromatography–mass spectrometric (GC–MS) studies show that these allylbenzenes may also be brominated and undergo amine displacement to yield the corresponding *N*-methyl-1-aryl-2-propanamines. These studies also show that the regioisomeric 3-bromosafrole intermediate and 3-propanamine are not formed during this synthesis. Furthermore, the isomeric allylbenzenes isosafrole and isoeugenol that are generated in these reactions do not form stable bromo products and therefore no *N*-methyl-1-aryl-1-propanamine products are produced during the course of the bromination and amine displacement reactions.

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, 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 designer drug analogs of MDA including the *N*-ethyl (MDE) and *N*-hydroxy (NOHMDA) derivatives have also been encountered in forensic samples and appear to possess pharmacological activities comparable to MDA and MDMA (5). The continued designer drug exploration of the MDA series has resulted in legislation in recent years to upgrade the penalties associated with the clandestine 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 the 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 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 an earlier study we found that in addition to safrole, sassafras oil contains other allylbenzenes such as eugenol (4-allyl-2-methoxyphenol) and 4-allyl-1,2-dimethoxybenzene (Scheme 3). In the present study, gas chromatographic–mass spectral (GC–MS) methods were used to determine if the other allylbenzenes present in sassafras oil also undergo the bromination and amine displacement reactions to yield the corresponding *N*-methyl-1-aryl-2-propanamines.

Experimental

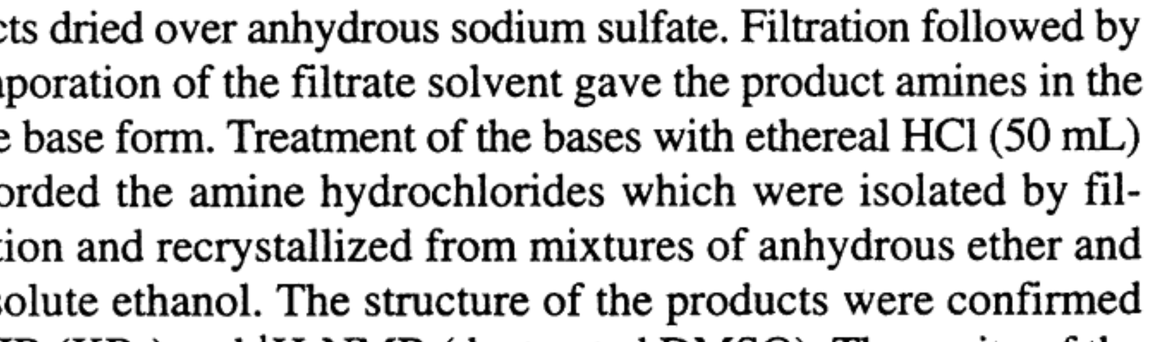
Gas chromatographic–mass spectrometric analysis. These analyses were performed using a Hewlett-Packard 5970B mass selective detector with sample introduction into the mass spectrometer via a gas chromatograph equipped with a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-µm thickness of methylsilicone (HP1). The column temperature was programmed from 70° to 150°C at a rate of 15°/min and from 150° to 250° at a rate of 25°/min.

Bromination reactions. Samples of the individual substituted allylbenzenes (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.

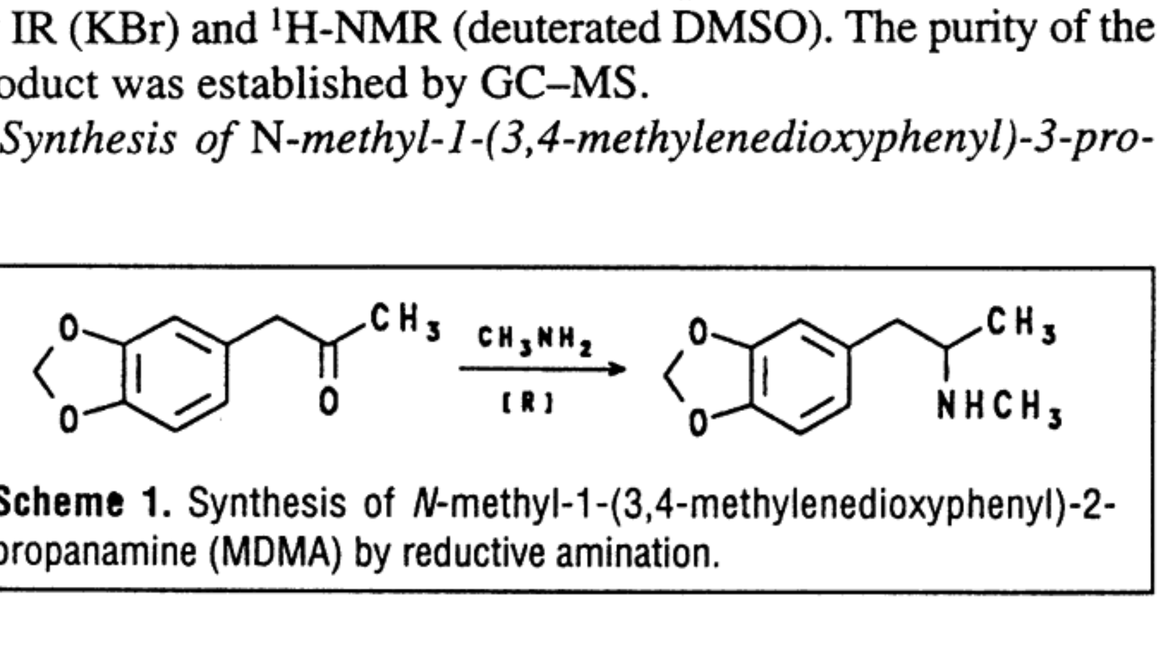
Amination reactions. The crude bromination products (2.0 g) were dissolved in methanol (100 mL) containing 40% aqueous methylamine (20 mL) and stirred at room temperature for 4 days. The reaction mixture was evaporated to dryness and the resultant oil dissolved in 10% HCl (50 mL). The aqueous acidic 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.

Synthesis of the standard N-*methylaryl-2-propanamines.* A solution of the appropriate ketone (10 mMol), 1-(3,4-methylenedioxyphenyl)-2-propanone or 1-(3,4-dimethoxyphenyl)-2-propanone, aqueous methylamine (100 mMol), and sodium cyanoborohydride (25 mMol) in methanol (25 mL) was stirred at room temperature for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and the residue suspended in dichloromethane (50 mL). The dichloromethane suspension was extracted with 3 N HCl (2 × 75 mL) and the combined acid extracts made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 × 100 mL) and the combined organic extracts dried over anhydrous sodium sulfate. Filtration followed by evaporation of the filtrate solvent gave the product amines in the free base form. Treatment of the bases with ethereal HCl (50 mL) afforded the amine hydrochlorides which were isolated by filtration and recrystallized from mixtures of anhydrous ether and absolute ethanol. The structure of the products were confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the product was established by GC–MS.

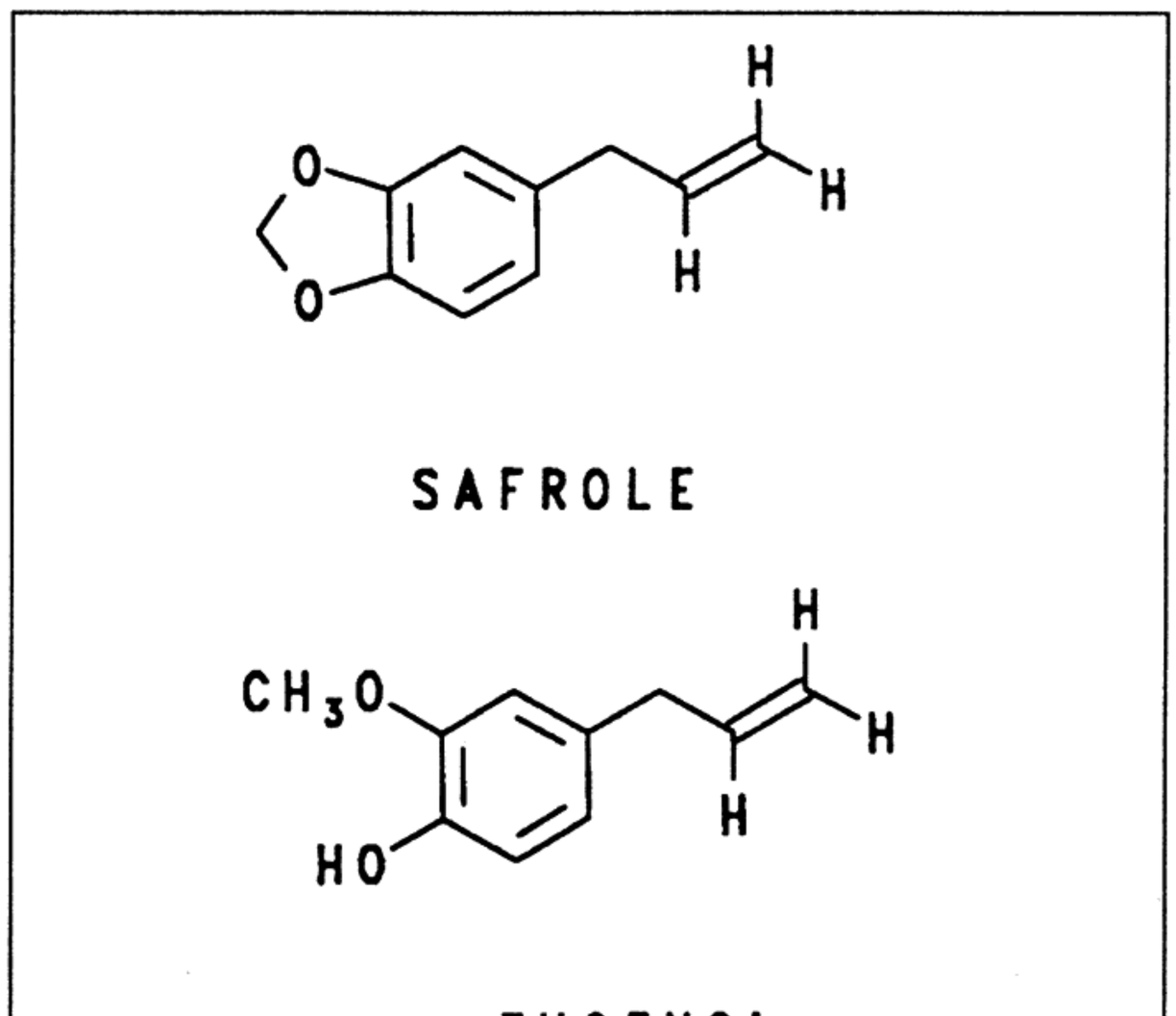
Synthesis of N-*methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine.* Aqueous methylamine (20 mMol) was added dropwise to a stirred solution of 1-(3,4-methylenedioxyphenyl)-3-propionyl chloride (10 mMol) in chloroform (50 mL) and the mixture stirred at room temperature for 1 h. The mixture was then stirred at reflux for ca. 15 min and the solvent evaporated under reduced pressure to yield an oil. The oil was partitioned between 20% potassium carbonate (50 mL) and chloroform (50 mL), and the chloroform layer separated. The chloroform solution was then washed with 10% HCl (50 mL) and evaporated under reduced pressure to yield the intermediate amide. A solution of the amide in THF (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1 g) in THF (10 mL) stirred under a nitrogen atmosphere. After the addition was complete, the mixture was stirred at reflux overnight. The mixture was then cooled to room temperature, filtered, and the filtrate solvent evaporated under reduced pressure to yield the crude amine as an oil. The oil was partitioned between 10% HCl (50 mL) and chloroform (50 mL) and the aqueous layer separated and made basic (pH 12) with aqueous sodium hydroxide. The aqueous base suspension was extracted with chloroform (50 mL) and the chloroform removed under reduced pressure to yield the product amine in free base form. Treatment of the base with ethereal HCl afforded the desired amine hydrochloride. The structure of the product was confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the product was established by GC–MS.



Scheme 1. Synthesis of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA) by reductive amination.



Scheme 2. Synthesis of 1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA) from safrole.



Scheme 3. Allylbenzenes present in sassafras oil.

Results and Discussion

In a recent report (7), three allyl-substituted benzenes were identified as components of the volatile organic fraction from the steam distillation of the roots of the sassafras plant. The major component was safrole (4-allyl-1,2-methylenedioxybenzene); however, appreciable quantities of eugenol (4-allyl-2-methoxyphenol) and 4-allyl-1,2-dimethoxybenzene were also identified (Scheme 3). This mixture of allylbenzenes was obtained from a clandestine laboratory involved in the synthesis of aryl-2-propanamines via the addition of HBr to the double bond of the allyl group followed by amine displacement of the bromide. The major aryl-2-propanamine obtained from treating the brominated sassafras oil with methylamine would be 3,4-methylenedioxymethamphetamine (MDMA, Ecstacy, or XTC). This method for the preparation of MDMA circumvents the need for controlled precursor chemicals by obtaining the key intermediate, safrole, from the plant material.

In this study, authentic samples of each of the three allyl-substituted benzenes found in the sassafras distillate were subjected to the bromination–amination procedure. The goal of this work was to determine if these allyl benzenes would yield amine products similar to MDMA. The amine product from the treatment of safrole in this manner would be 3,4-methylenedioxymethamphetamine, MDMA (Scheme 2). The chromatogram resulting from the GC analysis of the amine from safrole is shown in Figure 1. The chromatogram shows one major component eluting at 7.2 min and displaying a base peak at *m/z* 58 and a molecular weight of 193. The chromatogram does not show any other major components in the amine product prepared from safrole. This mass spectrum is consistent with that obtained from an authentic sample of MDMA prepared from 3,4-methylenedioxyphenyl-2-propanone and methylamine via reductive amination with sodium cyanoborohydride (Scheme 1).

The bromination of the isolated double bond in safrole could yield the 3-bromo intermediate as well as the 2-bromo regioisomer. The bromination at the terminal carbon to give 1-(3,4-methylenedioxyphenyl)-3-bromopropane, followed by displacement of bromide by methylamine, would yield the 3-methylaminopropane regioisomer of MDMA. Although no 3-methylamino isomer was observed in the GC–MS analysis of the amination product from safrole following treatment with HBr, an authentic sample of *N*-methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine was prepared to validate the specificity of the analytical method. This amine was prepared from 1-(3,4-methylenedioxyphenyl)propionic acid via methylamide formation followed by amide reduction with lithium aluminum hydride to yield the corresponding amine (Scheme 4). These two amines were subjected to GC–MS analysis yielding the chromatograms and spectra in Figure 2. This analysis was done under the same con-

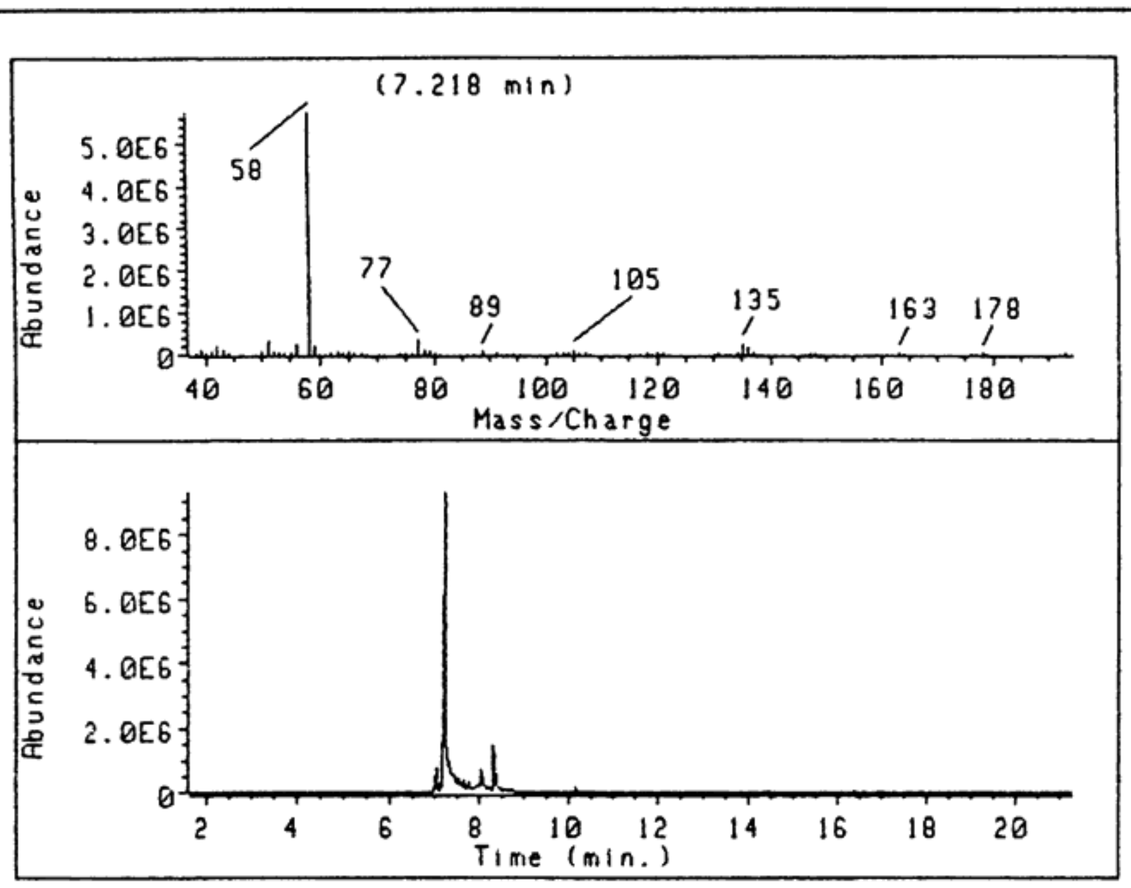


Figure 1. GC–MS analysis of the amines isolated after treatment of bromosafrole with methylamine.

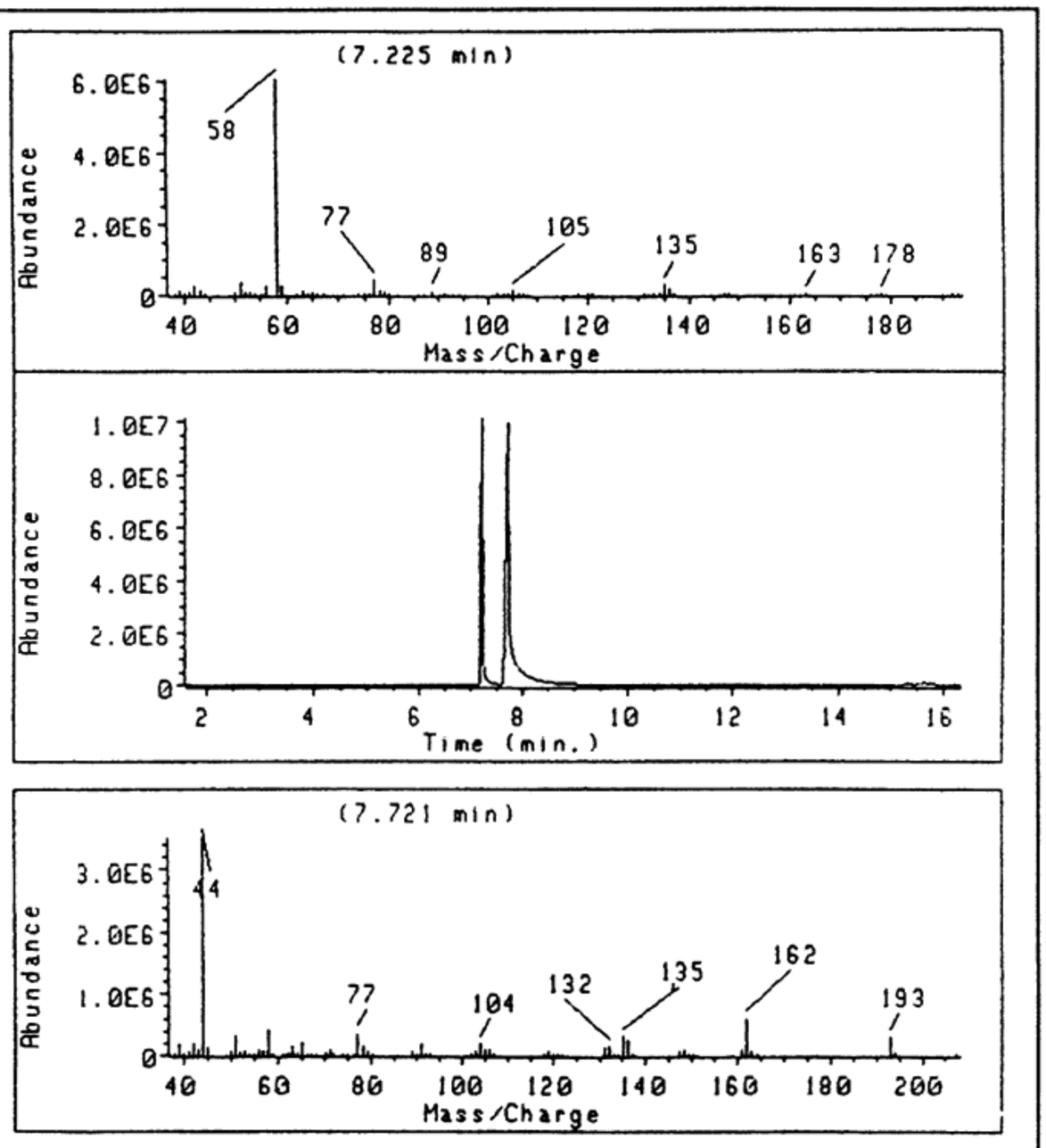
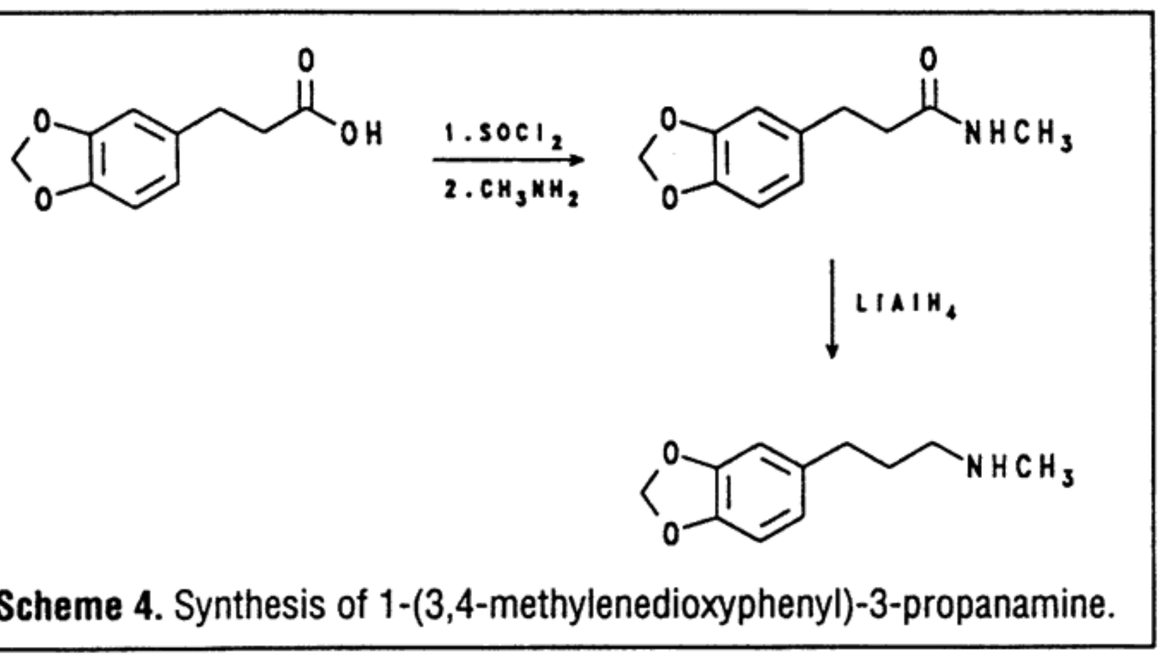
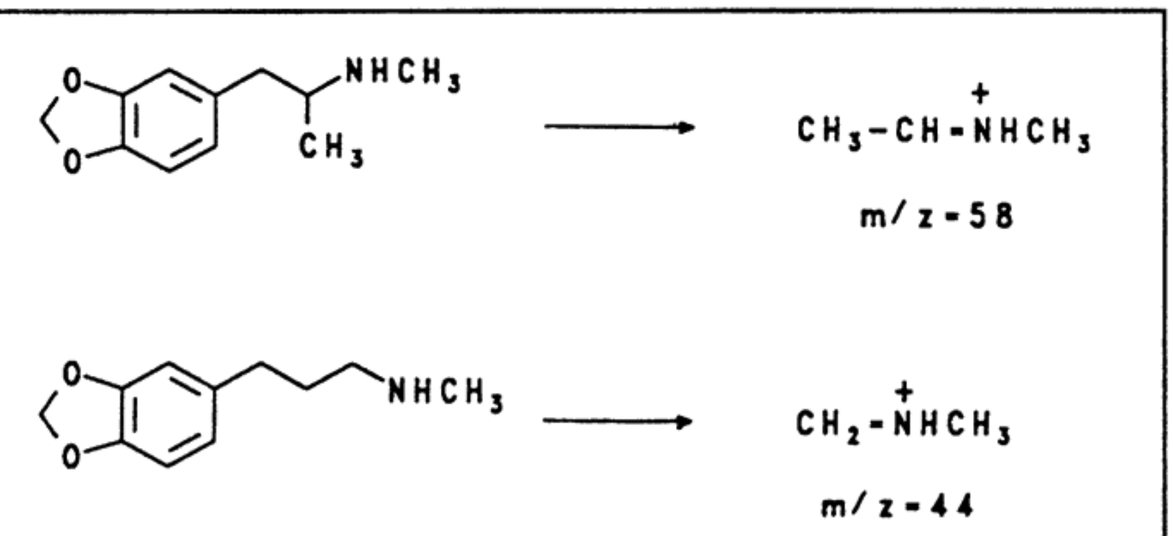


Figure 2. GC–MS analysis of the regioisomeric *N*-methyl-1-(3,4-methylenedioxyphenyl)-2- and 3-propanamines.



Scheme 4. Synthesis of 1-(3,4-methylenedioxyphenyl)-3-propanamine.



Scheme 5. EI mass spectral fragmentation pattern for the *N*-methyl-1-aryl-2-propanamines.

ditions as described for the chromatogram in Figure 1. The two regioisomeric amines are well resolved in the chromatogram (Figure 2) and the peak at 7.225 min for MDMA matches the elution properties for the major component in the safrole-derived amines in Figure 1. The base peak in this spectrum at *m/z* 58 is consistent with the 2-methylaminopropane side chain and is likely the result of the amine-dominated fragmentation illustrated in Scheme 5. The peak eluting at 7.721 min and yielding a base peak at *m/z* 44 is the 3-methylaminopropane isomer. The *m/z* 44 fragment arises from a similar fragmentation reaction from the 3-methylaminopropane as shown in Scheme 5.

The results of this experiment show that only the 2-aminopropane (MDMA) is produced in significant quantities via the treatment of safrole with HBr followed by methylamine as in Scheme 2. Furthermore, the gas chromatographic conditions used for the analysis of amines (as in Figure 1) are clearly capable of resolving the regioisomeric 2- and 3-propanamines (Figure 2).

The second allyl-substituted benzene identified in the plant distillate was eugenol. This compound was subjected to the same analogous reaction conditions as safrole, i.e., treatment with HBr followed by methylamine. The amine fraction from the reaction mixture was subjected to GC–MS analysis to yield the chromatogram and accompanying spectrum in Figure 3. Again, one

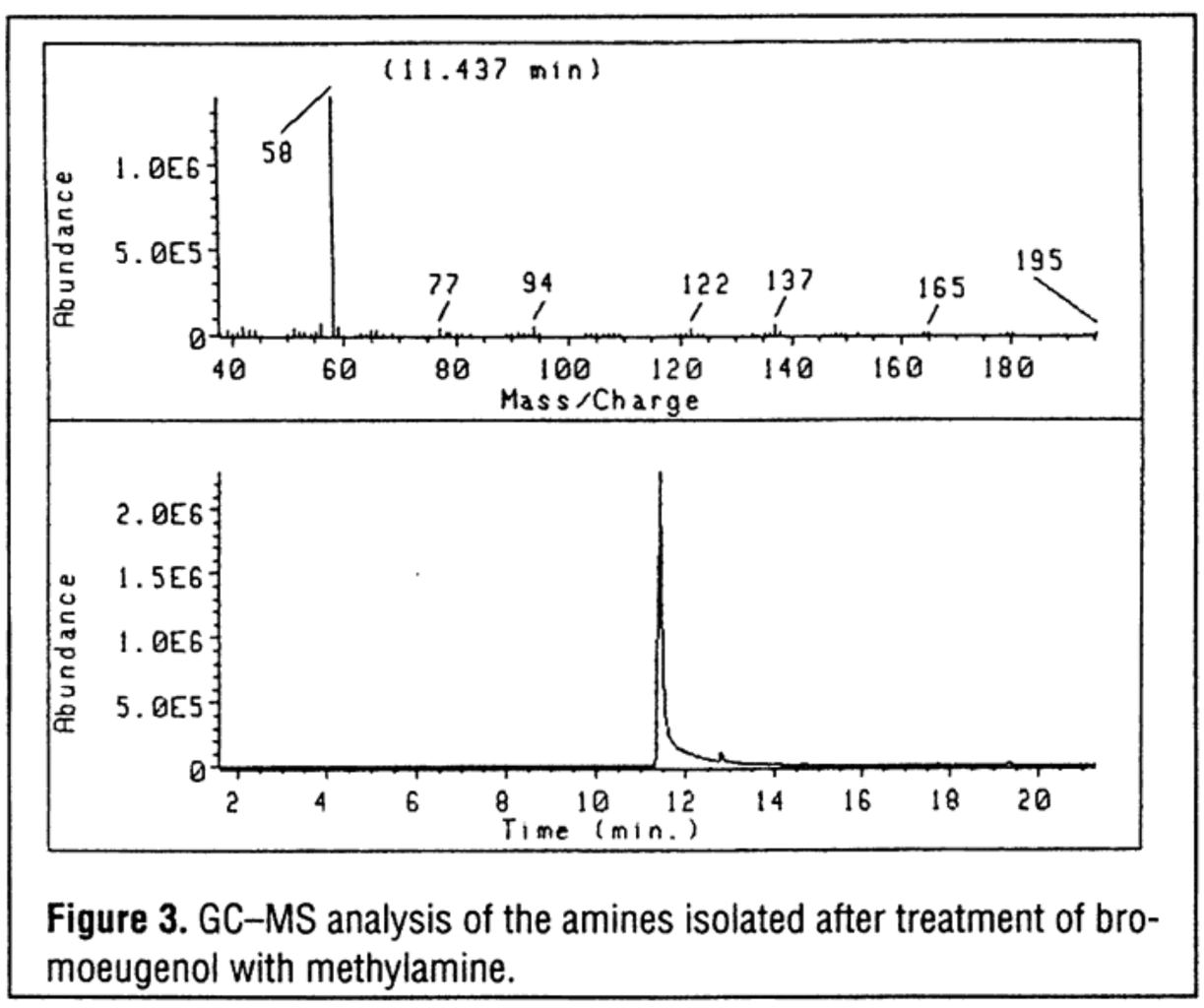


Figure 3. GC–MS analysis of the amines isolated after treatment of bromoeugenol with methylamine.

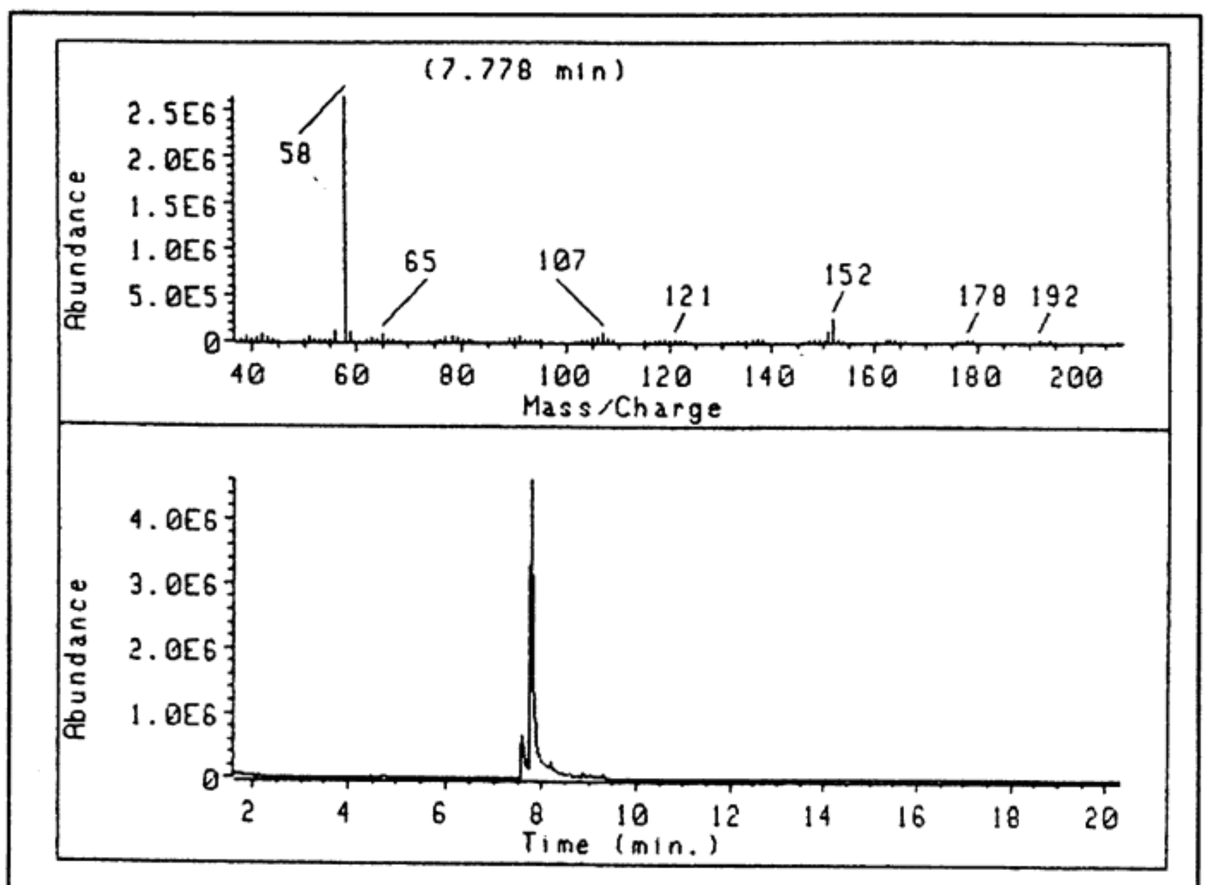


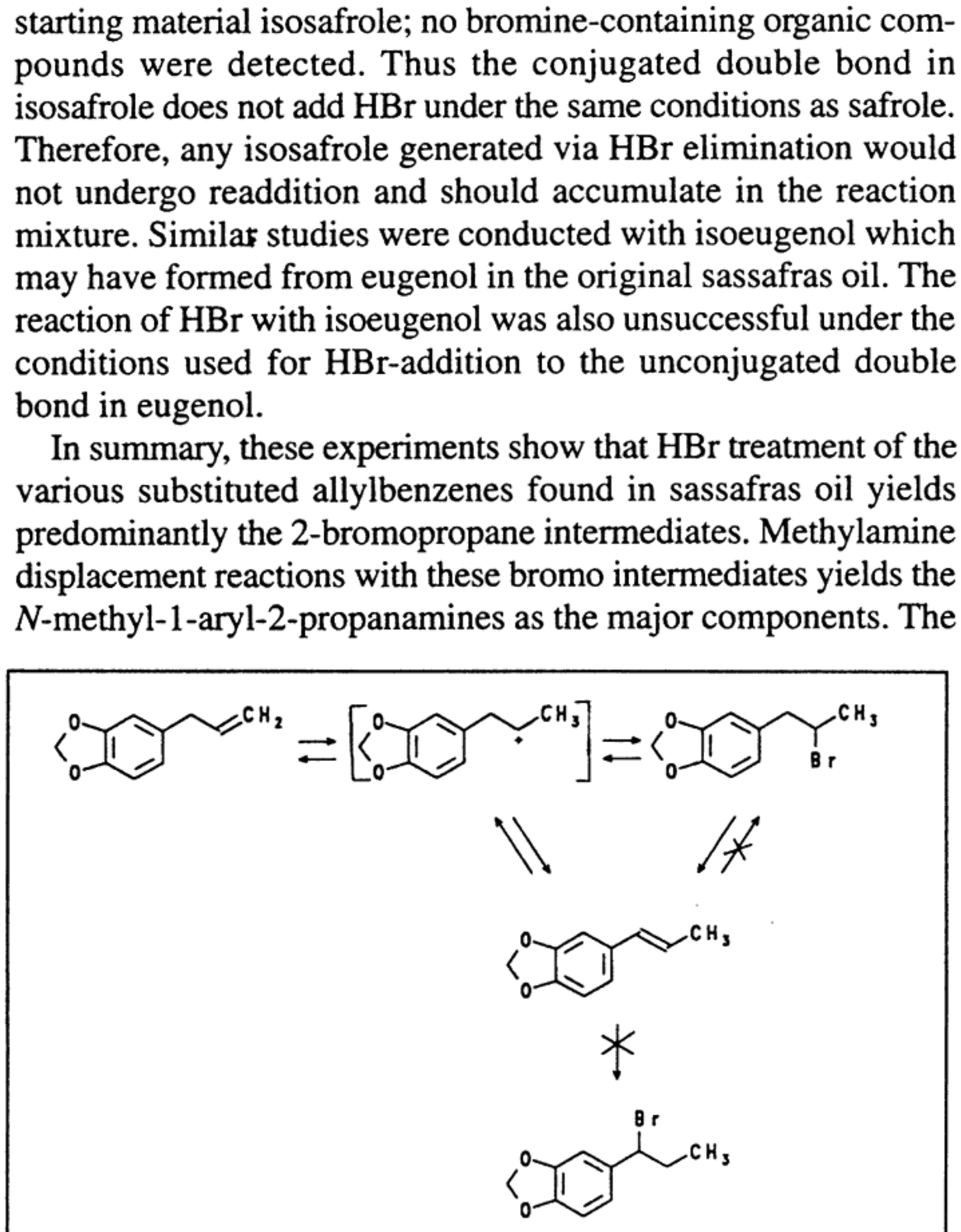
Figure 4. GC–MS analysis of the amines isolated after treatment of brominated 4-allyl-1,2-dimethoxybenzene with methylamine.

major amine component was identified which, based upon the fragmentation data, is the 2-propanamine (*m/z* 58) product. This 2-propanamine is the result of bromide ion displacement from the major bromine addition site, the 2-position. Thus, this experiment shows that the 2-propanamine product of eugenol is a likely component of the amine fraction obtained from HBr and methylamine treatment of sassafras oil

The third substituted allylbenzene, 4-allyl-1,2-dimethoxybenzene, was subjected to the same synthetic procedure as described previously. Analysis of the amine fraction yielded the chromatogram and spectrum in Figure 4. The product is composed primarily of one amine which appears to be the *N*-methyl-2-propanamine based on the characteristic amine dominated fragmentation pattern with a base peak of *m/z* 58. Independent synthesis of this amine from 3,4-dimethoxyphenylacetone via reductive amination confirmed the identity of the major component in Figure 4 as *N*-methyl-1-(3,4-dimethoxyphenyl)-2-propanamine.

In a previous report (7), the analysis of HBr-treated sassafras oil showed the presence of isosafrole, which was not identified in the original oil prior to HBr treatment. It was theorized that this product formed from elimination of HBr from 2-bromosafrole as shown in Scheme 6. The readdition of HBr to this compound could yield the 1-bromosafrole intermediate and the 1-propanamine product upon treatment with methylamine. Although this product was not identified in the amine fraction from sassafras oil, the failure to identify such a product could be because of a lack of necessary instrument sensitivity or of the complexity of the sample. In a effort to determine the reactivity of this isomeric olefin, isosafrole was subjected to treatment with HBr under the reaction conditions outlined in Scheme 2. Analysis of the product solution showed only the presence of the starting material isosafrole; no bromine-containing organic compounds were detected. Thus the conjugated double bond in isosafrole does not add HBr under the same conditions as safrole. Therefore, any isosafrole generated via HBr elimination would not undergo readdition and should accumulate in the reaction mixture. Similar studies were conducted with isoeugenol which may have formed from eugenol in the original sassafras oil. The reaction of HBr with isoeugenol was also unsuccessful under the conditions used for HBr-addition to the unconjugated double bond in eugenol.

In summary, these experiments show that HBr treatment of the various substituted allylbenzenes found in sassafras oil yields predominantly the 2-bromopropane intermediates. Methylamine displacement reactions with these bromo intermediates yields the *N*-methyl-1-aryl-2-propanamines as the major components. The



Scheme 6. Formation of isofarole from safrole.

2-propanamines of eugenol and 1-allyl-3, 4-dimethoxybenzene are likely components of MDMA samples prepared from sassafras oil.

References

1. F.T. Noggle, Jr., J. DeRuiter, S.T. Coker, and C.R. Clark. Synthesis, identification and acute toxicity of some *N*-alkyl derivatives of 3,4-methylenedioxyamphetamine, *J. Assoc. Off. Anal. Chem.* **70:** 981–86 (1987).
2. F.T. Noggle, Jr., J. DeRuiter, C.L. McMillian, C.R. Clark. Liquid chromatographic analysis of some *N*-alkyl-3,4-methylenedioxyamphetamines, *J. Liq. Chromatogr.* **10:** 2497–2504 (1987).
3. F.T. Noggle, Jr., C.R. Clark, A.K. Valaer, and J. DeRuiter. Liquid chromatographic and mass spectral analysis of *N*-alkyl analogues of 3,4-methylenedioxyamphetamine, *J. Chromatogr. Sci.* **26:** 410–15 (1988).
4. A.T. Shulgin and D.E. Nichols. *The Psychopharmacology of Hallucinogens,* R.C. Stillman and R.E. Willette, Eds., Pergamon Press, New York, p. 74 (1987).
5. U. Braun, A.T. Shulgin, and G. Braun. Centrally active *N*-substituted analogs of 3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxyamphetamine), *J. Pharm. Sci.* **69:** 192–95 (1980).
6. T.A. Dal Cason. An evaluation of the potential for clandestine manufacture of 3,4-methylenedioxyamphetamine (MDA) analogs and homologs, *J. Forensic Sci.* **35:** 675–97 (1990).
7. F.T. Noggle, Jr., C.R. Clark, and J. DeRuiter. Gas chromatographic and mass spectrometric analysis of samples from a clandestine laboratory involved in the synthesis of Ecstacy from sassafras oil, *J. Chromatogr. Sci.* **29:** 168–73 (1991).

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