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 (methylene-dioxymethamphetamine, 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-methylenedioxyamphetamine (MDMA) 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.

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 x 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 x 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 x 50 mL) and then made basic (pH 12) by the addition of NaOH pellets. The aqueous base solution was extracted with ether (2 x 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 x 75 mL) and the combined acid extracts made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 x 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 afforded the desired amine hydrochlorides. The structure of the product was confirmed by IR (KBr) and 1H-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 allyl benzenes 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-methylenedioxyamphetamine (MDMA, Ecstasy, 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-methylenedioxyamphetamine, 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 regiosomer. 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 regiosomer 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-
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 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 isoasafrole, 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 an effort to determine the reactivity of this isomeric olefin, isoasafrole 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 isoasafrole; no bromine-containing organic compounds were detected. Thus the conjugated double bond in isoasafrole does not add HBr under the same conditions as safrole. Therefore, any isoasafrole 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
2-propanamines of eugenol and 1-allyl-3,4-dimethoxybenzene are likely components of MDMA samples prepared from sassafras oil.

References


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