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Analysis of 3,4-Methylenedioxyphenyl-2-Propanone and 3,4-Methylenedioxyamphetamine Prepared From Isosafrole

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Abstract

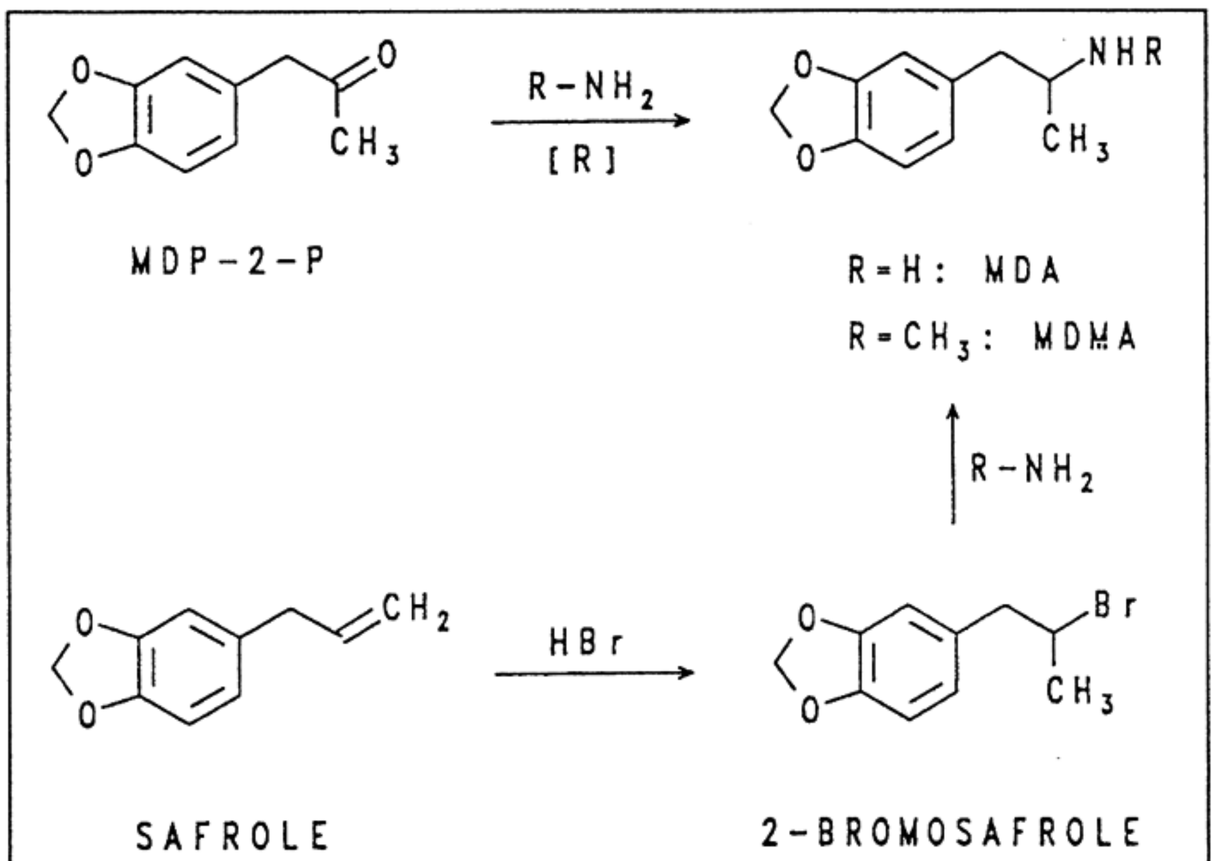
The intermediates, products, and by-products obtained in the synthesis of MDA from isosafrole are identified by gas chromatography–mass spectrometry. The initial oxygenation of the conjugated double bond in isosafrole produces a number of products, and the product distribution varies with the reaction solvent. If acetone is used as a cosolvent, the major product is the diol acetonide, while without acetone the product mixture contains the diol, the ketone (methylenedioxyphenyl-2-propanone, MDP-2-P), and mono- and diformates of the diol. These oxygenated products, upon treatment with sulfuric acid, are all converted to the expected ketone, MDP-2-P. Amination of MDP-2-P with formamide (Leuckart conditions) yields the desired amine, MDA, and a pyrimidine by-product, 4-methyl-5-(3,4-methylenedioxyphenyl)pyrimidine, which is characteristic of these reaction conditions.

Introduction

MDA (3,4-methylenedioxyamphetamine or 1-[3,4-methylenedioxyphenyl]-2-propanamine) and MDMA (3,4-methylenedioxymethamphetamine or *N*-methyl-1-[3,4-methylenedioxyphenyl]-2-propanamine) have been popular drugs of abuse over the past decade (1–3). MDA and MDMA exhibit pharmacological profiles similar to stimulants such as amphetamine and display some properties characteristic of hallucinogens such as LSD. Yet these drugs have properties that differ from the stimulants and hallucinogens, and therefore they represent a distinct pharmacological class (4–6). Perhaps the most noteworthy activity unique to this structural class is their "entactogenic" potential evidenced by their ability to facilitate interpersonal communication by reducing the anxiety and fear that normally accompanies the discussion of emotionally painful events (6). It is this property that is believed to contribute most significantly to the abuse potential of the MDA/MDMA-type drugs.

In recent years, other "designer drug" analogues of MDA, including *N*-ethyl (MDE) and *N*-hydroxy (NOHMDA), have also been encountered in forensic samples and appear to possess pharmacological activities comparable with MDA and MDMA. 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 (7–9). The most direct approach involves treatment of the commercially available ketone, 1-(3,4-methylenedioxyphenyl)-2-propanone (3,4-methylenedioxyphenylacetone or MDP-2-P), with ammonia or methylamine under reducing conditions as shown in Scheme 1 (8). Based on this synthetic strategy, the availability of the key precursor, MDP-2-P, was controlled by the Drug Enforcement Administration under the Chemical Diversion and Trafficking Act in March 1989. The restricted availability of MDP-2-P has forced clandestine laboratory operators to seek methods for the synthesis of the ketone, or explore alternative approaches for the synthesis of MDA and MDMA. In one alternative approach encountered recently, a clandestine chemist used safrole as a starting material for the synthesis of MDMA (9). Although a method has been reported (10) as a possible procedure for the



Scheme 1. Synthesis of MDA/MDMA from 3,4-methylenedioxyphenyl-2-propanone (MDP-2-P) or from safrole.

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synthesis of MDP-2-P from isosafrole, a comprehensive study of the composition of the intermediates and MDA products obtained from this approach is not available. In the present study, we investigated each step of this synthetic procedure using gas chromatography–mass spectroscopy (GC–MS) to determine the major products and characteristic side-products that might be used as diagnostic markers for MDA samples prepared by this method.

Experimental

Synthesis

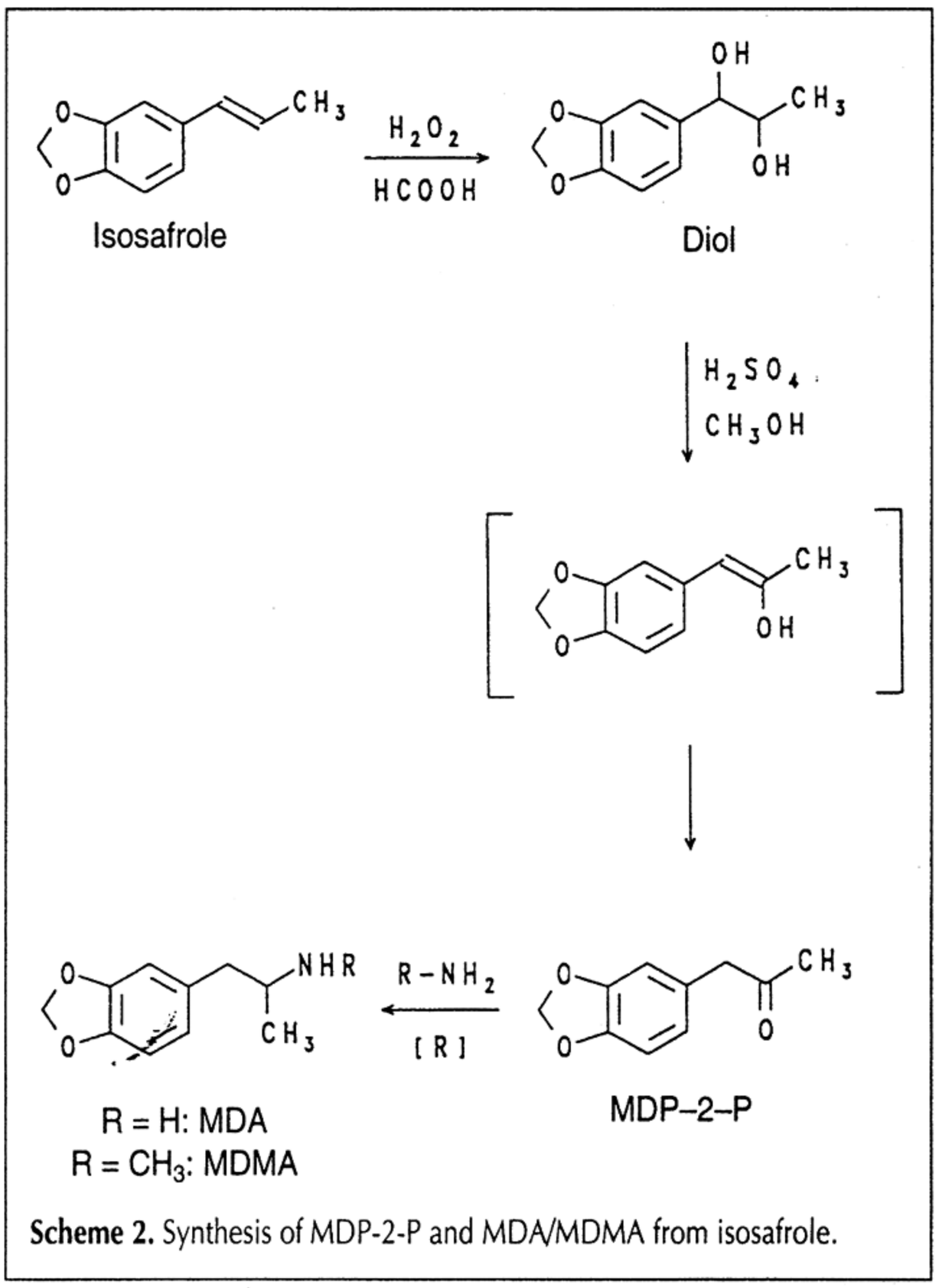
Isosafrole (5 g) was dissolved in acetone (19 mL), and the solution was cooled in an ice bath. To this solution a mixture of 30% hydrogen peroxide (4.7 mL) and 96% formic acid (15.9 mL) was added dropwise with stirring. The reaction mixture was stirred an additional 2 h and then allowed to stand at room temperature for 16 h. The solvent was removed under reduced pressure without applying heat, and a sample of the resulting residue was analyzed by GC–MS. To evaluate the effect of solvent on the course of this reaction, the reaction was repeated using tetrahydrofuran instead of acetone (all other conditions were the same).

The residue from the first reaction (run in acetone) was dissolved in a solution of methanol (15 mL) and 15% v/v sulfuric acid (75 mL) and warmed at approximately 90°C for 3 h. The reaction mixture was then extracted with diethyl ether (2 × 75 mL), and the combined ether extracts were washed carefully with 5% NaOH. Evaporation of the solvent yielded a brown oily residue, a sample of which was analyzed by GC–MS. This reaction was repeated under the same conditions except that the methanol solvent was replaced with ethanol.

A sample (1.22 g) of the residue obtained after treatment with sulfuric acid and methanol was stirred at 190°C (oil bath) for 5 h in 3.5 g formamide. The mixture was cooled to room temperature, and hydrogen peroxide (5.5 mL) was added. After stirring for 10 min, the mixture was extracted with benzene (2 × 25 mL), and the combined benzene extracts were evaporated under reduced pressure with no heating. A solution of methanol (0.5 mL) and 15% HCl (2.5 mL) was then added to the residue, and the mixture was heated on a water bath with stirring for 2 h. After cooling to room temperature, the methanol was evaporated under reduced pressure, and the aqueous acid was made basic (pH 12) with KOH and transferred to a separatory funnel. The basic solution was extracted with ether (2 × 25 mL). The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to obtain MDA as a dark yellow oil.

Gas chromatography–mass spectrometry

GC–MS analyses were performed using a Hewlett-Packard 5970B mass selective detector (Wilmington, DE), and the sample was introduced into the MS via a GC equipped with a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-µm thickness of methylsilicone (HP-1). The column temperature was held at 70°C for 2.5 min and then programmed to 175°C at a rate of 25°C/min and from 175 to 275°C at a rate of 12°C/min with a hold time of 6 min. The injection port temperature was 230°C.



Scheme 2. Synthesis of MDP-2-P and MDA/MDMA from isosafrole.

Results and Discussion

The goal of this work was to identify the products and by-products formed during the synthesis of 3,4-methylenedioxyamphetamine and related compounds from isosafrole. Isosafrole or 1,2-(methylenedioxy)-4-propenylbenzene is readily available from commercial sources and contains the appropriate carbon skeleton for conversion to MDA-type compounds. Isosafrole and safrole differ in the position of the double bond in the three-carbon side chain; isosafrole has a conjugated double bond, and the double bond is isolated in safrole. The conversion of safrole to MDA involves addition of HBr across the isolated double bond to yield the 2-bromo intermediate as the major product (Scheme 1). In previous work (9), however, it was shown that isosafrole is resistant to the addition of HBr across the conjugated double bond under the same reaction conditions.

The reported method (10) for the activation of the double bond in isosafrole involves preparation of the 1,2-diol followed by dehydration in acid to yield the enol, which upon tautomerization yields 3,4-methylenedioxyphenyl-2-propanone (3,4-methylenedioxyphenylacetone or MDP-2-P) (Scheme 2). The initial synthetic step involves treatment of isosafrole with hydrogen peroxide and formic acid in acetone. Figure 1 shows the GC–MS analysis of the reaction mixture obtained following treatment of isosafrole under those conditions for 18 h. The

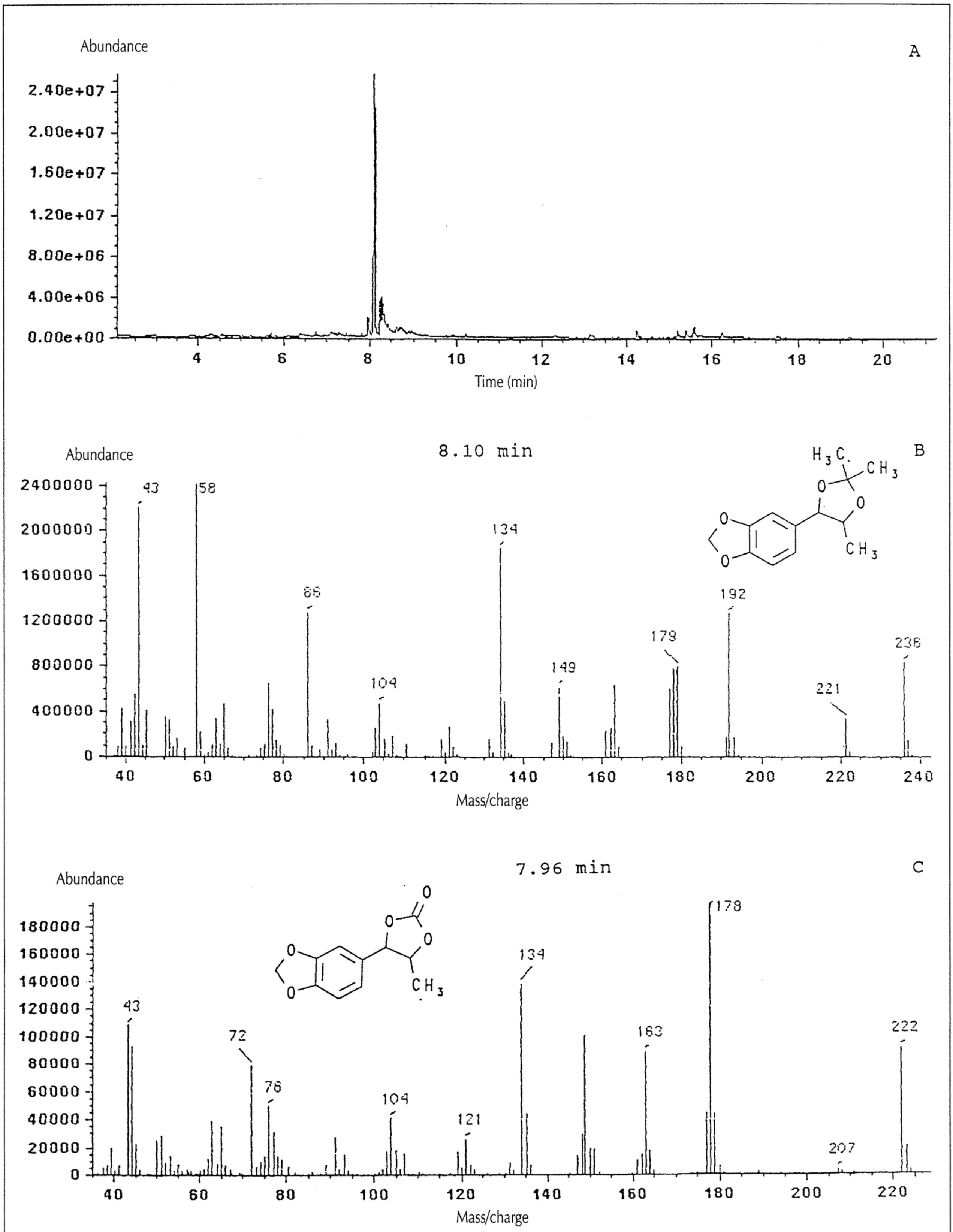
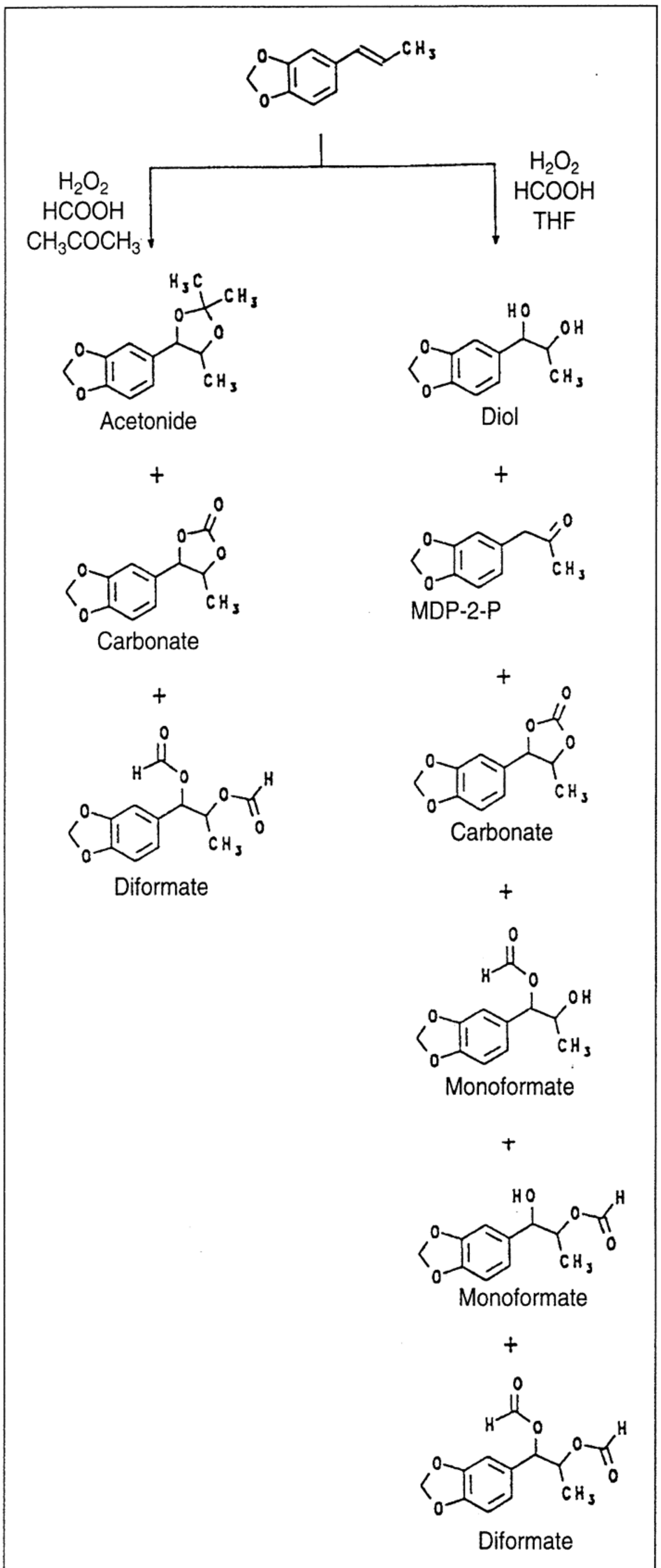


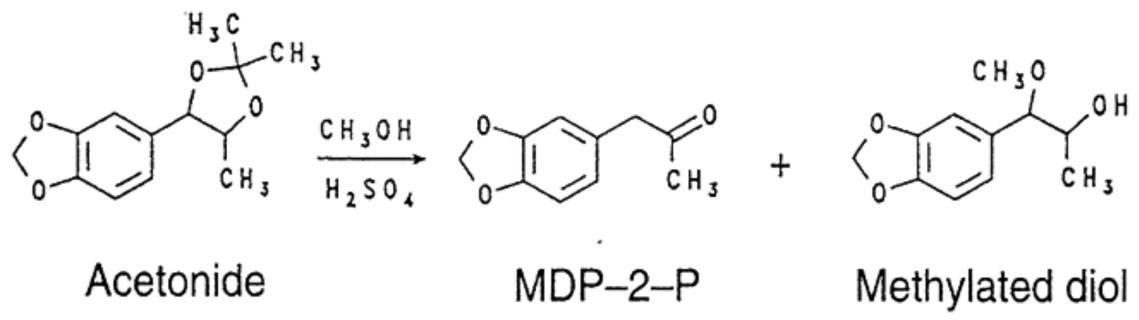
Figure 1. GC–MS analysis of isosafrole oxygenation products synthesized with acetone as the cosolvent: A, chromatogram; B, mass spectrum of the acetonide ketal; C, mass spectrum of the cyclic carbonate.

chromatogram shows one major component with a retention time of 8.10 min and a molecular ion at 236 amu that does not correspond to the expected diol product. The major low mass fragments at 58 and 43 suggest the incorporation of acetone into the compound, and all of these data are consistent with the production of the acetonide of the diol (Scheme 3). Further evidence of the acetonide ketal as the major product in the initial reaction was obtained by repeating the reaction without acetone as a cosolvent. The chromatogram and mass spectra obtained from the analysis of this product mixture are shown in Figure 2. The mass spectra for the major components show a variety of oxygenated products resulting from addition reactions. The peak at 7.04 min corresponds to 3,4-methylenedioxyphenylacetone, and the peak at 8.01 has a molecular ion at 222 amu suggestive of the cyclic carbonate of the diol. The peak at 8.43 min has a mass spectrum consistent with the diol, and the later eluting peaks at 8.85 and 9.05 min correspond to the monoformate and diformate esters of the diol, respectively. This product mixture does not show any trace of the mass 236 compound which was the major component in the product mixture obtained in the presence of acetone (Figure 1). Thus, the mass 236 product appears to be the acetonide ketal. The variety of oxygenated products obtained in the absence of acetone as a cosolvent (including the diol, the diol carbonate, diol formate, and diol diformate) should all yield the expected 3,4-methylenedioxyphenylacetone intermediate upon treatment with strong acid. It should be pointed out that two of these oxygenated products, the diol carbonate and diol diformate, occur in small quantities in the acetone-solvent reaction shown in Figure 1. Scheme 3 shows the complete list of products obtained from the oxygenation of isosafrole both in the presence of acetone and in its absence.

The crude product obtained from the oxygenation of isosafrole in the presence of acetone cosolvent (Figure 1) was subjected to hydrolysis conditions using sulfuric acid in methanol (Scheme 4). The crude product obtained from this reaction was analyzed by GC–MS, and the results are shown in Figure 3. The major product eluting at 7.01 min has chromatographic and mass spectral properties identical to 3,4-methylenedioxyphenylacetone, and the peak eluting at 8.08 min corresponds to the starting diol acetonide (spectrum not shown). Thus, the major product of the hydrolysis is the expected 3,4-methylenedioxyphenylacetone. However, two additional products with the same molecular weight and essentially the same mass spectra eluted at 7.63 and 7.72 min. These compounds have a molecular weight of 210 and show major fragments at 165 and 150 amu. The mass spectral fragmentation corresponds to a methylated diol, which is likely the result of methanol hydrolysis of the acetonide. The two diastereomeric forms of this compound would account for the two separate chromatographic zones. The major fragment at *m/z* 165 suggests that the methoxy group is on the benzylic carbon as



Scheme 3. Products formed from oxygenation of isosafrole with acetone or THF as cosolvents.



Scheme 4. Formation of MDP-2-P and the methylated diols from treatment of the diol acetonide with sulfuric acid in methanol.

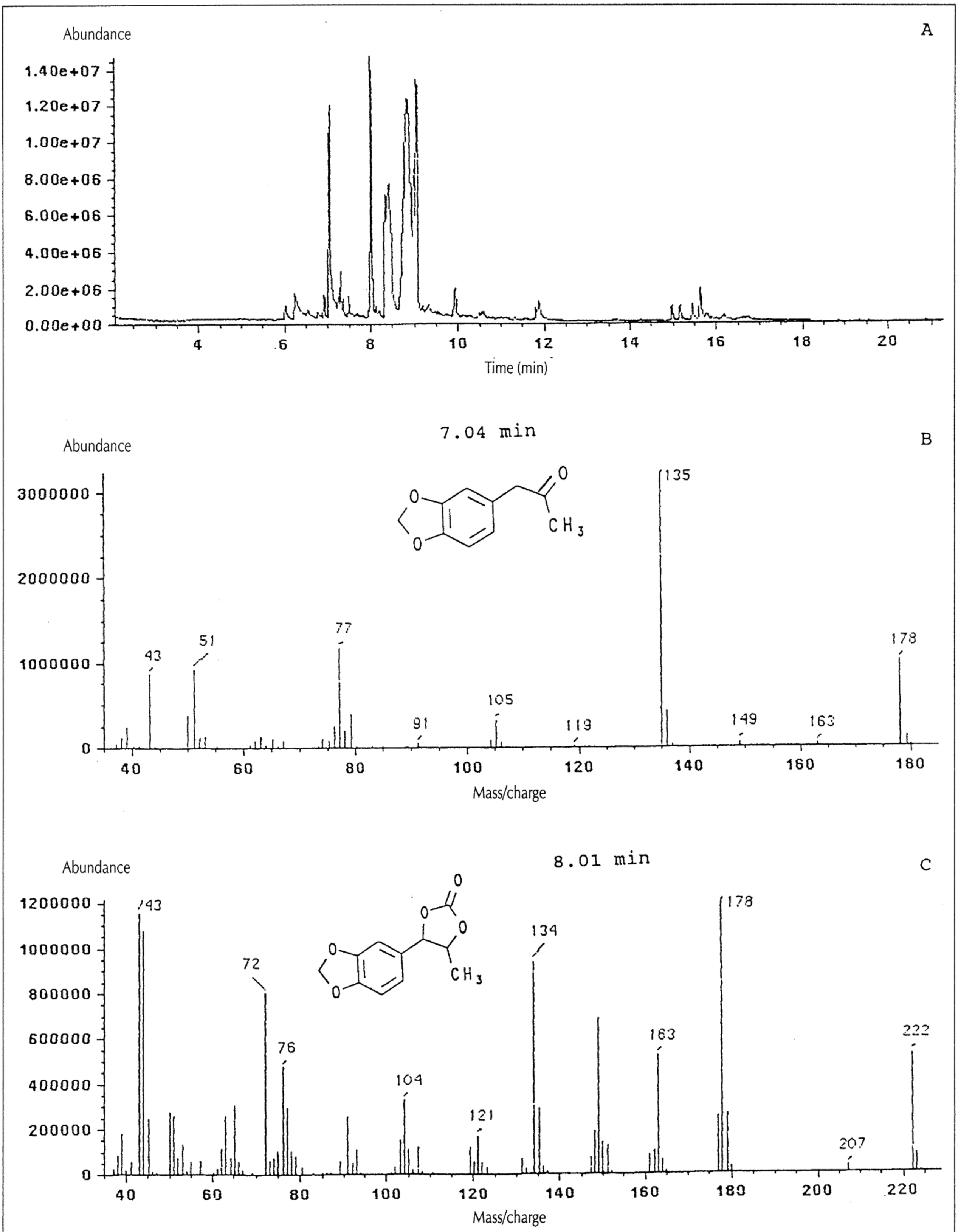


Figure 2. GC–MS analysis of isosafrole oxygenation products synthesized without acetone as the cosolvent: A, chromatogram; B, mass spectrum of MDP-2-P; C, mass spectrum of cyclic carbonate; D, mass spectrum of the diol; E, mass spectrum of monoformate; F, mass spectrum of diformate. *Figure 2 continued on page 398.*

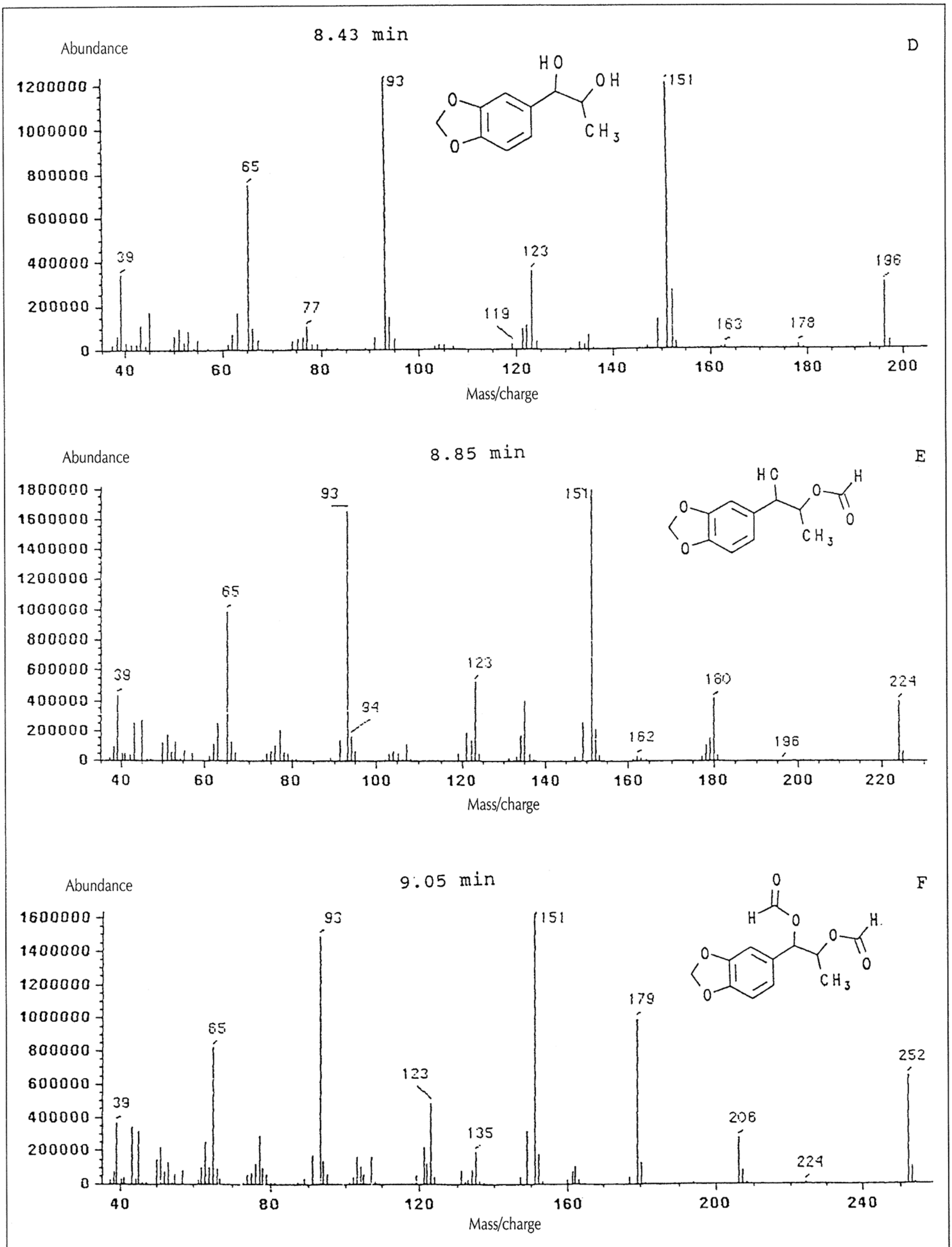


Figure 2 *(Continued).* GC–MS analysis of isosafrole oxygenation products synthesized without acetone as the cosolvent: A, chromatogram; B, mass spectrum of MDP-2-P; C, mass spectrum of cyclic carbonate; D, mass spectrum of the diol; E, mass spectrum of monoformate; F, mass spectrum of diformate.

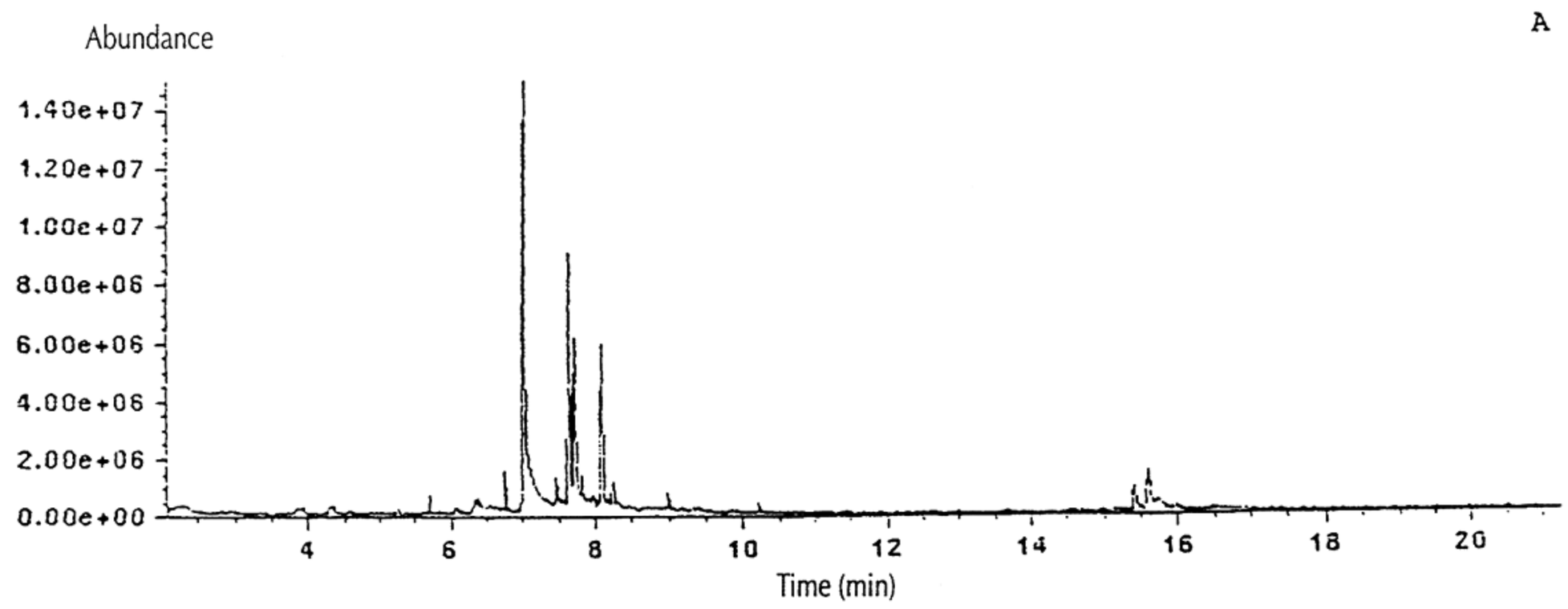


Figure 3. GC–MS analysis of the crude product from acid hydrolysis of the diol acetonide: A, chromatogram; B, mass spectrum of MDP-2-P; C, mass spectrum of a methylated diol; D, mass spectrum of a methylated diol.

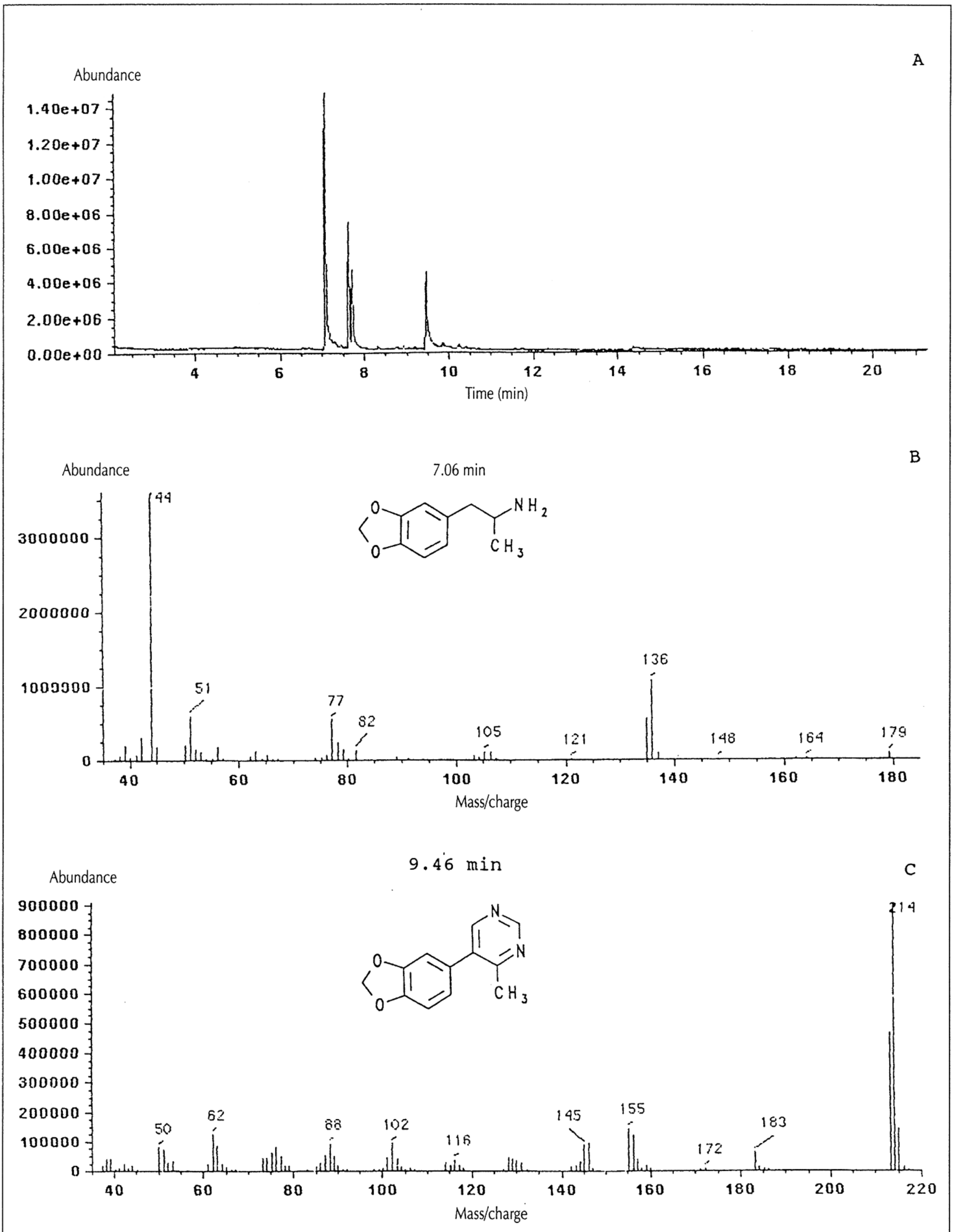
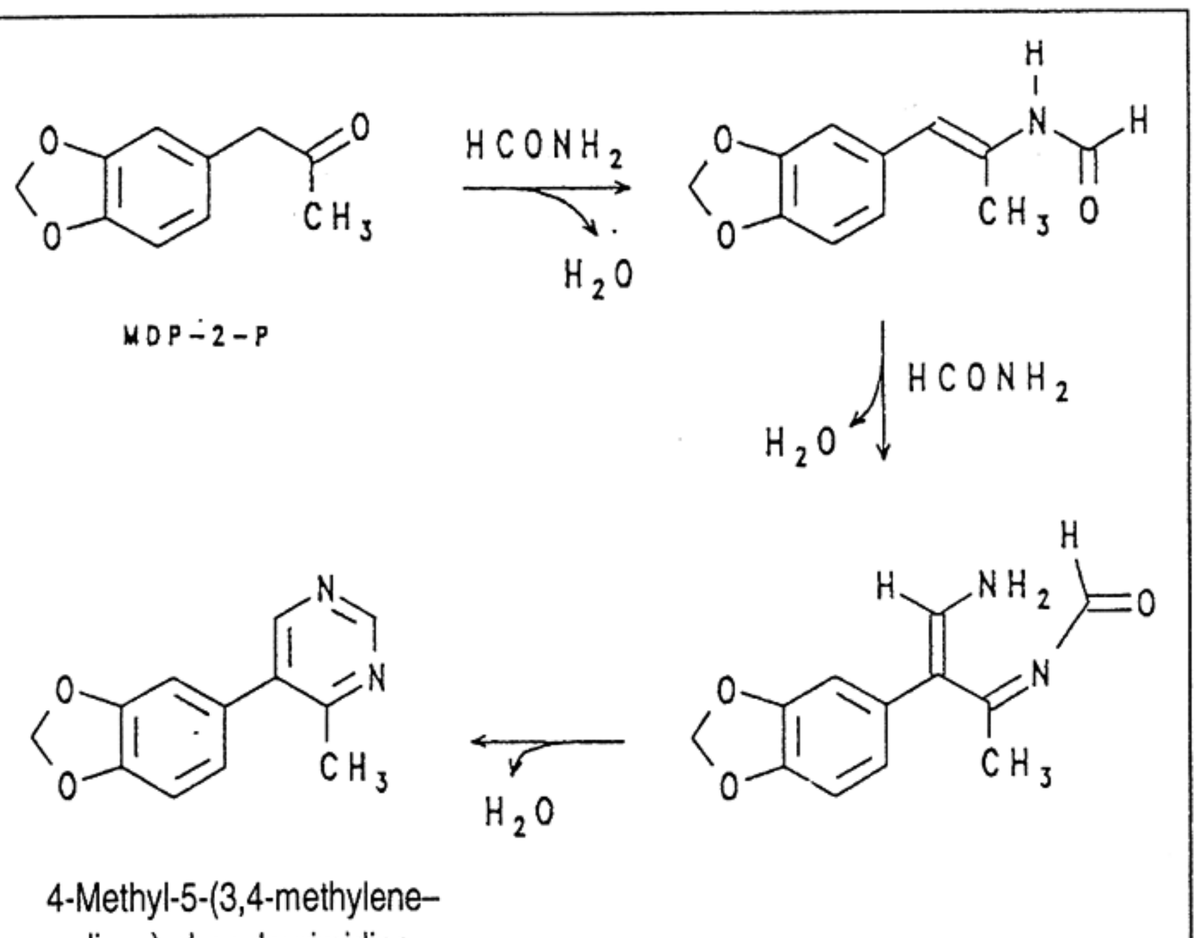


Figure 4. GC–MS analysis of the amine product from Leuckart amination of MDP-2-P: A, chromatogram; B, mass spectrum of MDA; C, mass spectrum of 4-methyl-5-(3,4-methylenedioxy)phenylpyrimidine.



Scheme 5. Formation of 4-methyl-5-(3,4-methylenedioxy)phenylpyrimidine during the Leuckart reaction with MDP-2-P.

would be expected based on the chemical stability of the benzylic carbocation precursor. One additional experiment that lends support to the theory that the methylated diol is the source of the two compounds of mass 210 was treatment of the acetonide with sulfuric acid in ethanol instead of methanol. As expected, two chromatographic peaks that had molecular ions at 224 mass units and identical major fragments with a base peak at *m/z* 179 were obtained.

The crude 3,4-methylenedioxyphenyl-2-propanone was heated to 180°C in formamide for approximately 5 hours (Leuckart conditions), cooled, and treated with hydrogen peroxide and hydrochloric acid. The residue obtained following evaporation of the solvent was analyzed by GC–MS, yielding the chromatogram and spectra in Figure 4. The first peak to elute (7.06 min) produced the mass spectrum in Figure 4B, which corresponds to that of 3,4-methylenedioxyamphetamine (MDA). The base peak in the spectrum at *m/z* 44 is the imine ($CH_3CH{=}NH_2$) resulting from the α-cleavage reaction. The *m/z* 135 and 136 fragments are the 3,4-methylenedioxybenzyl carbocation and radical cation, respectively. As expected for primary phenethylamines, the rearrangement product (*m/z* 136) is the more abundant benzylic fragment.

The two chromatographic peaks between 7.5 and 8.0 min are the two diastereomeric monomethylated diols of molecular weight 210 described previously and shown in Figure 3. These compounds do not undergo amination under Leuckart conditions and remain in the crude final product mixture. However, solvent extraction of this mixture for basic compounds eliminates these two diastereomers from the mixture.

The fourth peak in the chromatogram (9.46 min) in Figure 4A produced the mass spectrum shown in Figure 4C. This spectrum shows a base peak at *m/z* 214 and few other significant fragments. The lack of an abundant low mass fragment suggests that this compound is not a simple methylenedioxyphenylalkylamine. Furthermore, the absence of any peaks in the 135–136 mass range suggests extensive substitution of the benzylic carbon of the starting ketone. The most likely structure for this component is 4-methyl-5-(3,4-methylenedioxy)phenylpyrimidine. This compound would be formed by the reaction of the formamide imine of 3,4-methylenedioxyphenyl-2-propanone with a second molecule of formamide, followed by cyclization and dehydration (see Scheme 5). This fully aromatic system would be resistant to major fragmentation reactions and likely yield an abundant molecular ion. Because the mass spectrum for this product is quite different from any other side products identified, it could be argued that this peak is a result of the solvent (formamide) or other reactant polymerization under Leuckart conditions. The exact Leuckart reaction conditions were repeated without the substrate 3,4-methylenedioxyphenyl-2-propanone, and following workup and GC–MS analysis, no compound of mass 214 was detected in the sample. Thus the compound of mass 214 is produced from the reaction of 3,4-methylenedioxyphenyl-2-propanone (or a compound derived from MDP-2-P) and the other reactants.

Further evidence for the assignment of the mass 214 compound as the disubstituted pyridimine comes from the literature on the preparation of amphetamine by the Leuckart method (11). One of the side products in the preparation of amphetamine from phenyl-2-propanone (P-2-P) and formamide is 4-methyl-5-phenylpyrimidine. Thus the analogous product from MDP-2-P is the 4-methyl-5-(3,4-methylenedioxy) phenylpyrimidine.

Conclusion

In summary, MDA can be prepared from commercially available isosafrole in a three-step synthetic procedure, and each of these reactions produces by-products that may serve as indicators of the synthetic origin of the sample. Oxygenation of the conjugated double bond in isosafrole followed by dehydration/hydrolysis to yield MDP-2-P and amination under Leuckart conditions produces MDA.

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