Spectroscopic and Chromatographic Identification of Precursors, Intermediates, and Impurities of 3,4-Methylenedioxyamphetamine Synthesis

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The ultraviolet, infrared, nuclear magnetic resonance, and mass spectra of a number of precursors, intermediates, and impurities of 3,4-methylenedioxyamphetamine (MDA) synthesis are presented as well as gas-liquid and thin layer chromatographic data. Test results are given on the precursors safrole, isosafrole, and piperonal; the intermediates isosafrole glycol, *N*-formyl-MDA, and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene; the impurities di[1-(3,4-methylenedioxyphenyl)-2-propyl] amine, di[1-(3,4-methylenedioxyphenyl)-2-propyl] methylamine, and 3,4-methylenedioxyphenylpropane; and the product MDA. The data are discussed and 2 methods of MDA synthesis are summarized, in which the precursors, intermediates, and impurities are encountered.

In Canada, 3,4-methylenedioxyamphetamine (MDA) continues to be a popular illicit drug. Because no legitimate therapeutic use exists for this amphetamine, MDA is produced almost exclusively by illicit or clandestine laboratories. Chemicals seized from such laboratories often contain precursors, intermediates, or impurities in addition to, or in the absence of, MDA. Presence of impurities in illicit MDA samples can interfere with some methods of analysis. The identification of these impurities can, however, assist in establishing the method of MDA synthesis being used and can be used in the comparison of samples of diverse origin. Identification of precursors and intermediates helps to establish the synthetic route employed and the potential quantity of MDA that could be produced.

Experimental

Mass spectra were obtained with a Finnigan 3100 quadrupole mass spectrometer interfaced to a Finnigan 9500 gas chromatograph by a glass jet separator. The mass spectrometer was operated at 70 ev potential. The gas chromatograph contained a 6 ft × ¼ in. id glass column packed with 3% OV-1 on 80–100 mesh Chromosorb W (HP). Helium was used as the carrier gas.

Ultraviolet (UV) spectra were obtained with a Beckman Acta C III spectrophotometer as absolute ethanol solutions in 1 cm quartz cells.

Infrared (IR) spectra were obtained with a Perkin-Elmer 457 spectrophotometer. The liquids safrole, isosafrole, isosafrole glycol, 3,4-methylenedioxyphenyl-2-propanone, and 3,4-methylenedioxyphenylpropane were determined as films sandwiched between 25 × 4 mm AgCl cells. Spectra of *N*-formyl-MDA and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene were obtained as KBr disks. Piperonal, which melts at 37°C, was dissolved in ether and spotted on a blank KBr disk.

All nuclear magnetic resonance (NMR) spectra, with the exception of that for *N*-formyl-MDA, were obtained with a Varian HA 100 spectrometer. The spectrum of *N*-formyl-MDA was obtained with a Varian XL 100 spectrometer. All samples were dissolved in $CDCl_3$ and determined at a probe temperature of 28.5°C.

Gas chromatograms were obtained on a Hewlett-Packard 5700 gas chromatograph with flame ionization detection, containing a 6 ft × ⅛ in. id stainless steel column packed with 3% OV-1 on 80–100 mesh Chromosorb W (HP). Nitrogen was used as the carrier gas at a flow rate of 30 ml/min.

Isosafrole, safrole, and piperonal were purchased from Matheson Coleman and Bell Chemicals, Norwood, OH; 3,4-methylenedioxyphenylpropane and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene from Alfred Bader Chemicals, Milwaukee, WI; and 3,4-methylenedioxyphenyl-2-propanone from Terochem Laboratories, Edmonton, Alberta, Canada. MDA hydrochloride was obtained from the Health Protection Branch, Department of Health and Welfare, Ottawa, Ontario, Canada.

Isosafrole glycol was synthesized by the method of Fujisawa and Deguchi (1). Following the completion of the reaction, the reaction mixture was divided into 2 portions. One portion was evaporated under vacuum to remove the acetone; the residue was taken up in ether and washed with 5% $NaHCO_3$ to remove excess formic acid. The ether was evaporated on a steam bath, and the residue was taken up in a small volume of methanol and hydrolyzed with 10% aqueous NaOH.

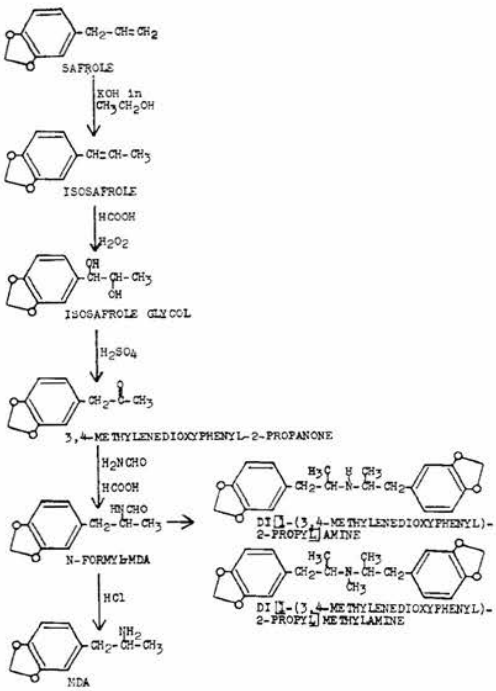

FIG. 1—Synthesis of MDA from safrole.

Isosafrole glycol was extracted into ether and purified by preparative thin layer chromatography (TLC) on silica gel G plates, using benzene as the solvent and Marquis reagent (H_2SO_4 and formaldehyde) as the visualizing agent. The second portion was prepared according to the method of Fujisawa and Deguchi (1), treated with 15% H_2SO_4, and extracted with ether to yield 3,4-methylenedioxyphenyl-2-propanone.

N-Formyl-MDA was synthesized from 3,4-methylenedioxyphenyl-2-propanone, formic acid, and formamide in a molar ratio of 1:2.5:5, by heating 7 hr at 160–170°C on an oil bath (2). The reaction solution was diluted with water and extracted with ether which was washed with water and 5% $NaHCO_3$. The ether was evaporated on a steam bath and the *N*-formyl-MDA was purified by preparative TLC using silica gel C plates and the solvent *n*-butyl ether-ethyl ether-diethylamine (45+45+5). The visualizing agent was acidified iodoplatinate.

Di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine and di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine were isolated from the *N*-formyl-MDA reaction solution by diluting the solution with water and extracting it with ether. The ether solution was extracted with 0.5*N* H_2SO_4, the acidic solution was made basic with 3*N* NH_3 and back-extracted into ether. The ether was evaporated on a steam bath and the di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine and di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine were purified by preparative TLC using silica gel G plates and *n*-butyl ether-ethyl ether-diethylamine (45+45+5). The R_f values of *N*-formyl-MDA, di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine, and di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine in this solvent system are 0.21, 0.62, and 0.75, respectively. The visualizing agent was acidified iodoplatinate.

Results and Discussion

Synthesis of MDA from Safrole via the Leuckart Reaction

Safrole is a naturally occurring compound found in oil of sassafras. The treatment of safrole with an ethanol-potassium hydroxide solution causes isomerization of the double bond (3) resulting in the conversion of safrole into isosafrole (Fig. 1). Although the mass spectra of safrole and isosafrole (Fig. 2) are similar due to the facile isomerization of the double bond, the compounds can easily be distinguished by UV (Table 1) or IR spectrophotometry (Fig. 3). The compounds can also be distinguished by gas-liquid chromatography (GLC) (Table 2). Gas chromatograms of isosafrole formed by the base-catalyzed isomerization of safrole or of practical grades of isosafrole show 2 peaks due to the

Table 1. Ultraviolet data for MDA, precursors, and intermediates[a]

Compound	λ max., nm	ε
MDA hydrochloride	237	3,410
	287	3,580
Piperonal	230	16,815
	272	6,905
	312	8,710
Safrole	235	3,930
	287	3,700
Isosafrole	260	11,420
	304	4,990
1-(3,4-Methylenedioxyphenyl)-2-nitro-1-propene	254	8,495
	354	7,875
3,4-Methylenedioxyphenyl-2-propanone	235	2,710
	287	2,675
N-Formyl-MDA	235	4,725
	287	3,815

[a] Solutions in absolute ethanol.

Table 2. Retention times relative to MDA for GLC separation[a] of precursors, intermediates, and MDA on a 3% OV-1 column

Compound	Rel. retention time
Safrole	0.48
3,4-Methylenedioxyphenylpropane	0.50
Piperonal	0.56
cis-Isosafrole	0.57
trans-Isosafrole	0.66
3,4-Methylenedioxyphenyl-2-propanone	0.94
MDA[b]	1.0
Isosafrole glycol	2.2
1-(3,4-Methylenedioxyphenyl)-2-nitro-1-propene	2.4
N-Formyl-MDA	2.6

[a] See text for GLC conditions.
[b] Absolute retention time of 126 sec at 150°C.

resolution of the *cis* and *trans* isomers. The *cis* isomer elutes from an SE-30 column before the *trans* isomer (4).

Reaction of isosafrole with formic acid and hydrogen peroxide followed by treatment with sulfuric acid yields 3,4-methylenedioxyphenyl-2-propanone (1, 5). Oxidation of an olefinic compound with formic acid and hydrogen peroxide results in the formation of the *trans* glycol (6). The IR, NMR, and mass spectra of isosafrole glycol are illustrated in Figs 4, 5, and 6, respectively. Figure 6 shows that although the methyl resonance signal at 1 ppm appears as a triplet, expansion of this signal reveals that it actually consists of 2 doublets. This phenomenon is likely

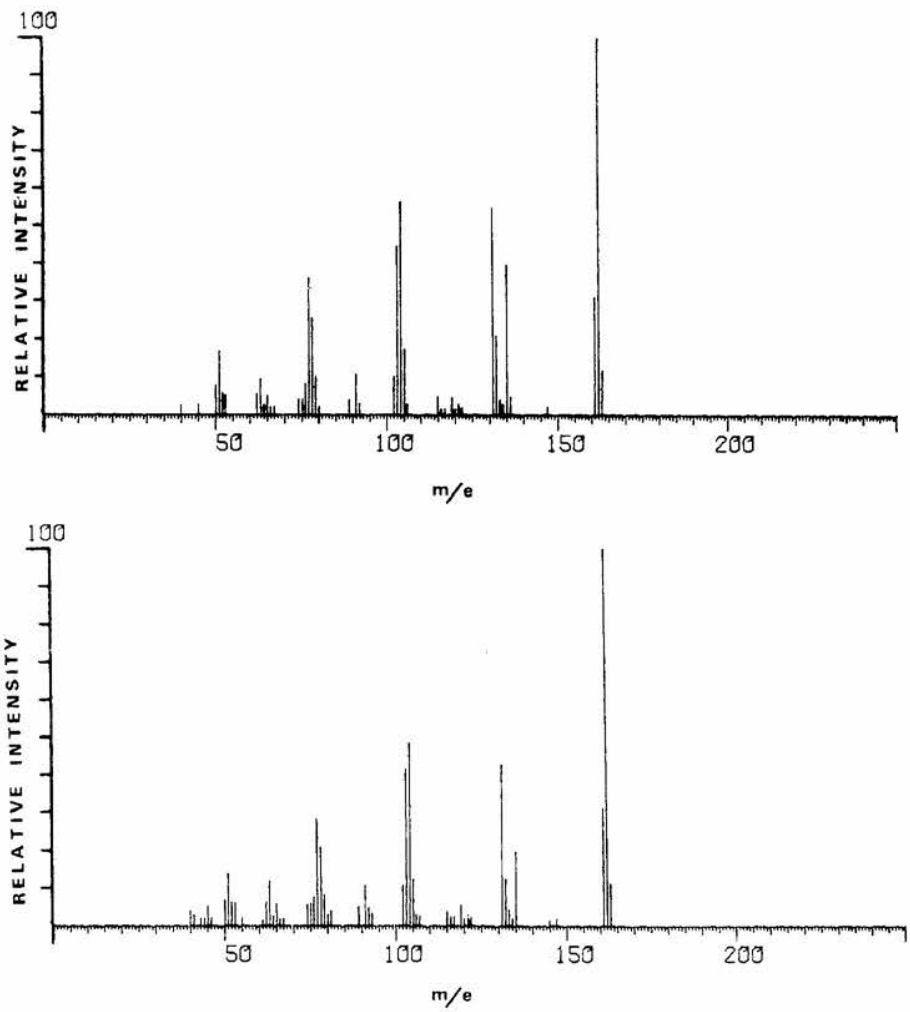

FIG. 2—Mass spectra of safrole (top) and isosafrole (bottom).

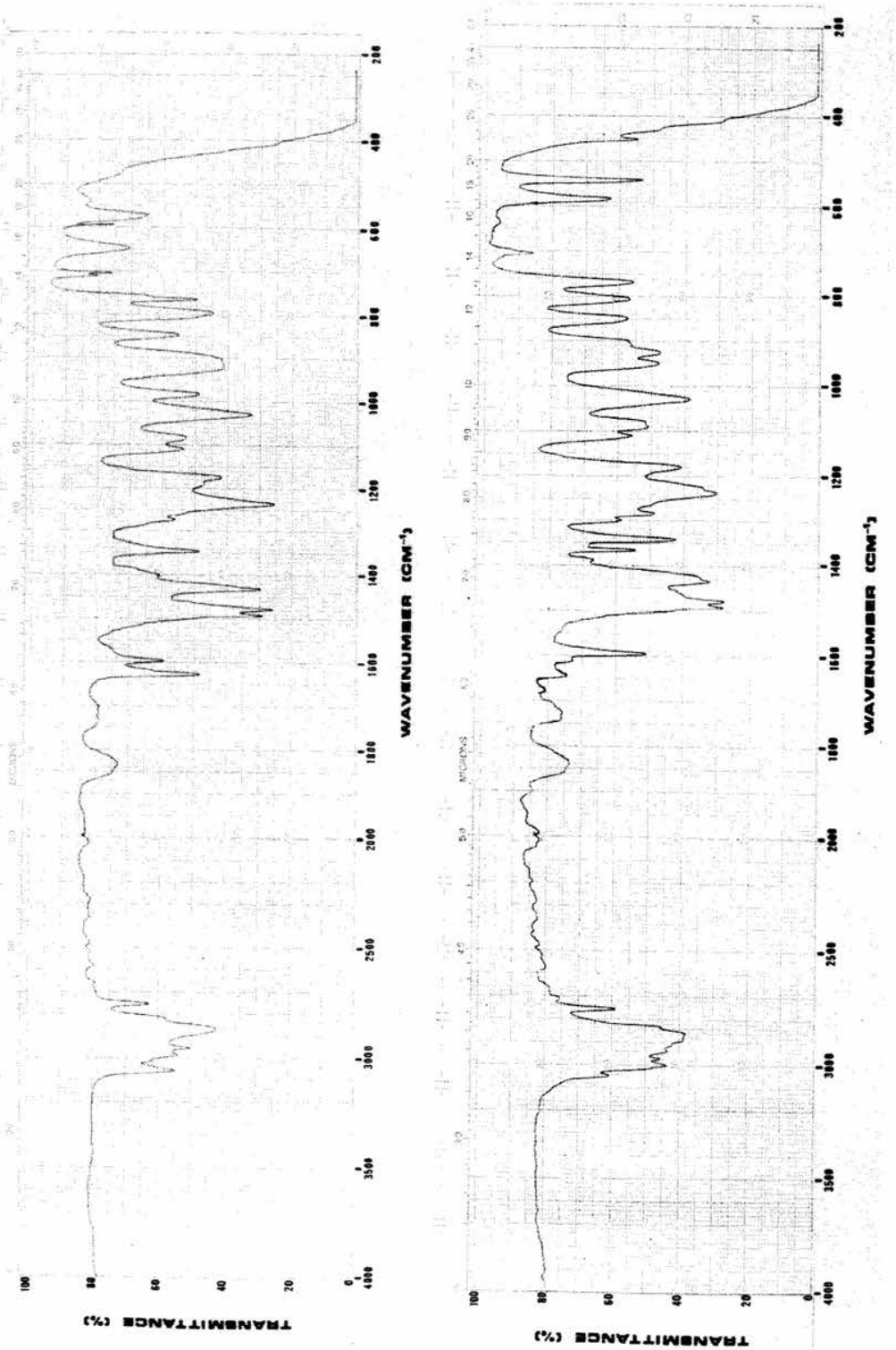

FIG. 3—IR spectra of safrole (top) and isosafrole (bottom).

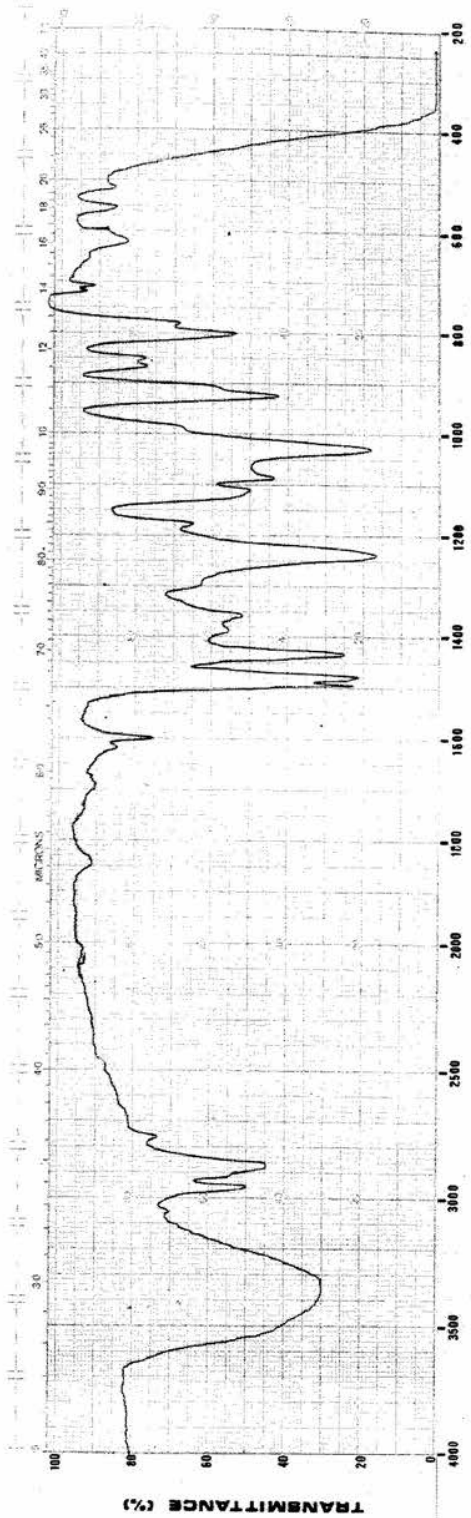

FIG. 4—IR spectrum of isosafrole glycol.

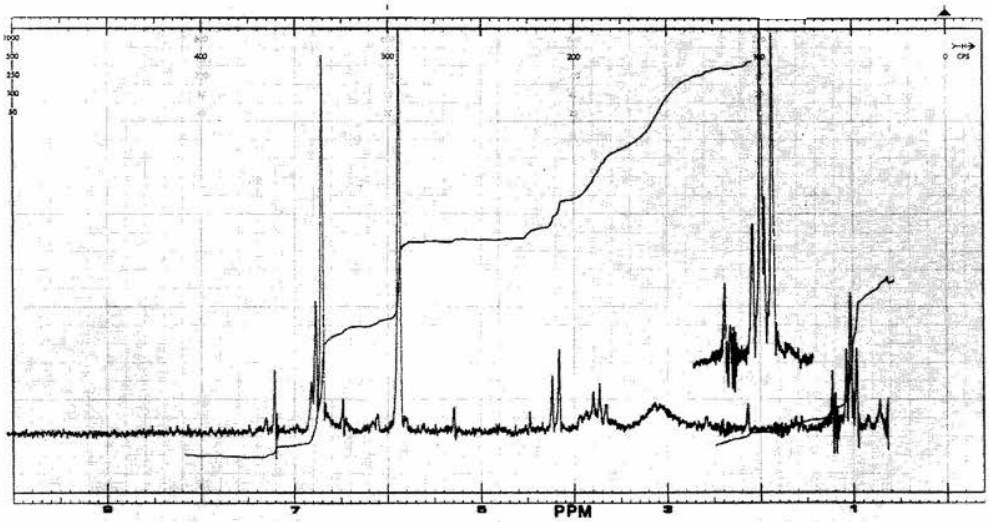

FIG. 5—NMR spectrum of isosafrole glycol.

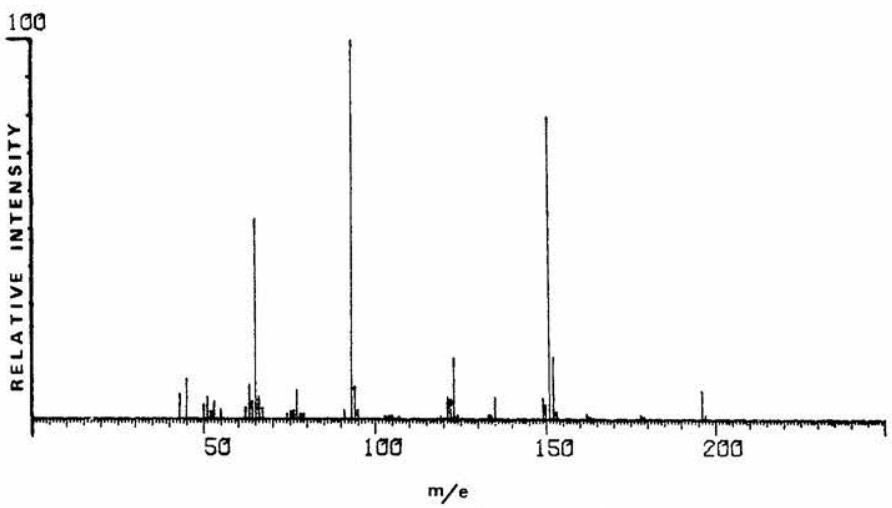

FIG. 6—Mass spectrum of isosafrole glycol.

caused by the presence of both the threo and erythro forms of the glycol.

Gas chromatographic-mass spectral analysis of the reaction products of the glycolation reaction prior to treatment with sulfuric acid shows the presence of piperonal, 3,4-methylenedioxyphenyl-2-propanone, isosafrole glycol, the monoformate ester of isosafrole glycol, and the diformate ester of isosafrole glycol. Treatment of the reaction mixture with sulfuric acid will result in the hydrolysis of the esters and dehydration of the glycol to yield 3,4-methylenedioxyphenyl-2-propanone, whereas treatment with sodium hydroxide simply results in the hydrolysis of the esters to yield isosafrole glycol. The mass spectra of the monoformate and diformate esters of isosafrole glycol are similar to isosafrole glycol itself except that the parent peak at m/e 196 is replaced by a parent peak at m/e 224 in the case of the monoformate ester and at m/e 252 for the diformate ester.

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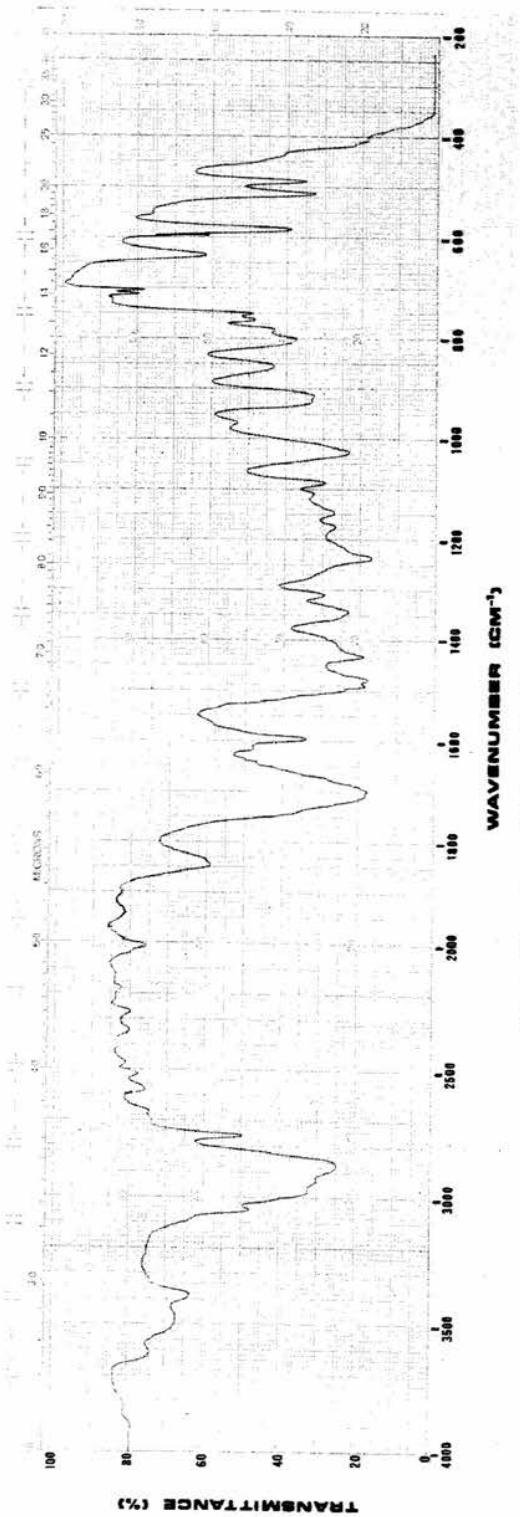

FIG. 7—IR spectrum of 3,4-methylenedioxyphenyl-2-propanone.

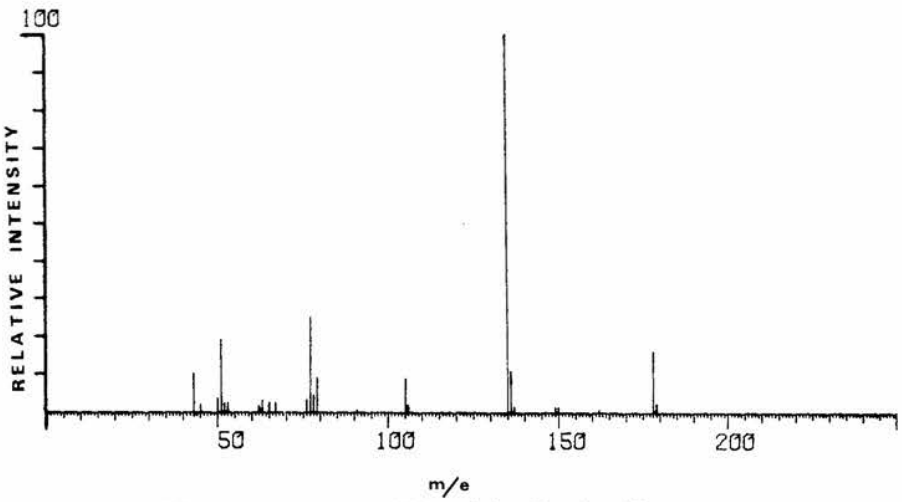

FIG. 8—Mass spectrum of 3,4-methylenedioxyphenyl-2-propanone.

Although isosafrole glycol is converted to 3,4-methylenedioxyphenyl-2-propanone by treatment with sulfuric acid, it can also be converted to piperonal by reaction with paraperiodic acid (7). This reaction results in the cleavage of the glycol and the formation of piperonal and acetaldehyde. Also, although 3,4-methylenedioxyphenyl-2-propanone is most easily synthesized from isosafrole, it can be prepared from piperonal (8). The IR and mass spectra of 3,4-methylenedioxyphenyl-2-propanone are illustrated in Figs 7 and 8.

The Leuckart reaction is a convenient method for synthesizing amines from ketones and aldehydes. Although numerous reactants and reaction conditions have been used (9), good yields have been reported using a ketone, formic acid, and either ammonia or formamide (2). Reaction of 3,4-methylenedioxyphenyl-2-propanone under reflux conditions results in the formation of *N*-formyl-MDA (Fig. 1). Hydrolysis of *N*-formyl-MDA with hydrochloric acid yields MDA. Incomplete hydrolysis can result in the presence of *N*-formyl-MDA as an impurity of MDA synthesized by the Leuckart reaction. The IR and mass spectra of *N*-formyl-MDA and MDA are presented in Figs 9 and 10. The NMR spectrum of *N*-formyl-MDA is shown in Fig. 11.

Examination of the *N*-formyl-MDA reaction solution prior to hydrolysis with hydrochloric acid revealed the presence of 2 amine impurities. Because amine by-products have recently been reported in illicit methamphetamine (10, 11) and amphetamine samples (12), the impurities were isolated and purified by preparative TLC. The amine by-products have been identified as di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine and di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine. The proposed mass spectral fragmentation pattern of the latter compound is illustrated in Fig. 12 while the NMR and mass spectra of both amines are presented in Figs 13–15. The mass spectrum of di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine contains a parent peak at m/e 341 with a relative abundance of $<1\%$. The mass spectrum of di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine contains a peak at m/e 355, also with a relative abundance of $<1\%$. Figures 13 and 14 show that whereas the NMR of di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine contains the expected methyl doublet at 1.1 ppm, the methyl resonance signal of di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine at 1.1 ppm consists of a triplet. This phenomenon is likely caused by a restricted rotation about the nitrogen, resulting in the occurance of rotational isomers (13, 14). The presence of these amines, formed by the condensation of *N*-formyl-MDA with 3,4-methylenedioxyphenyl-2-propanone, in a sample of illicit MDA indicates the route of synthesis to be the Leuckart reaction.

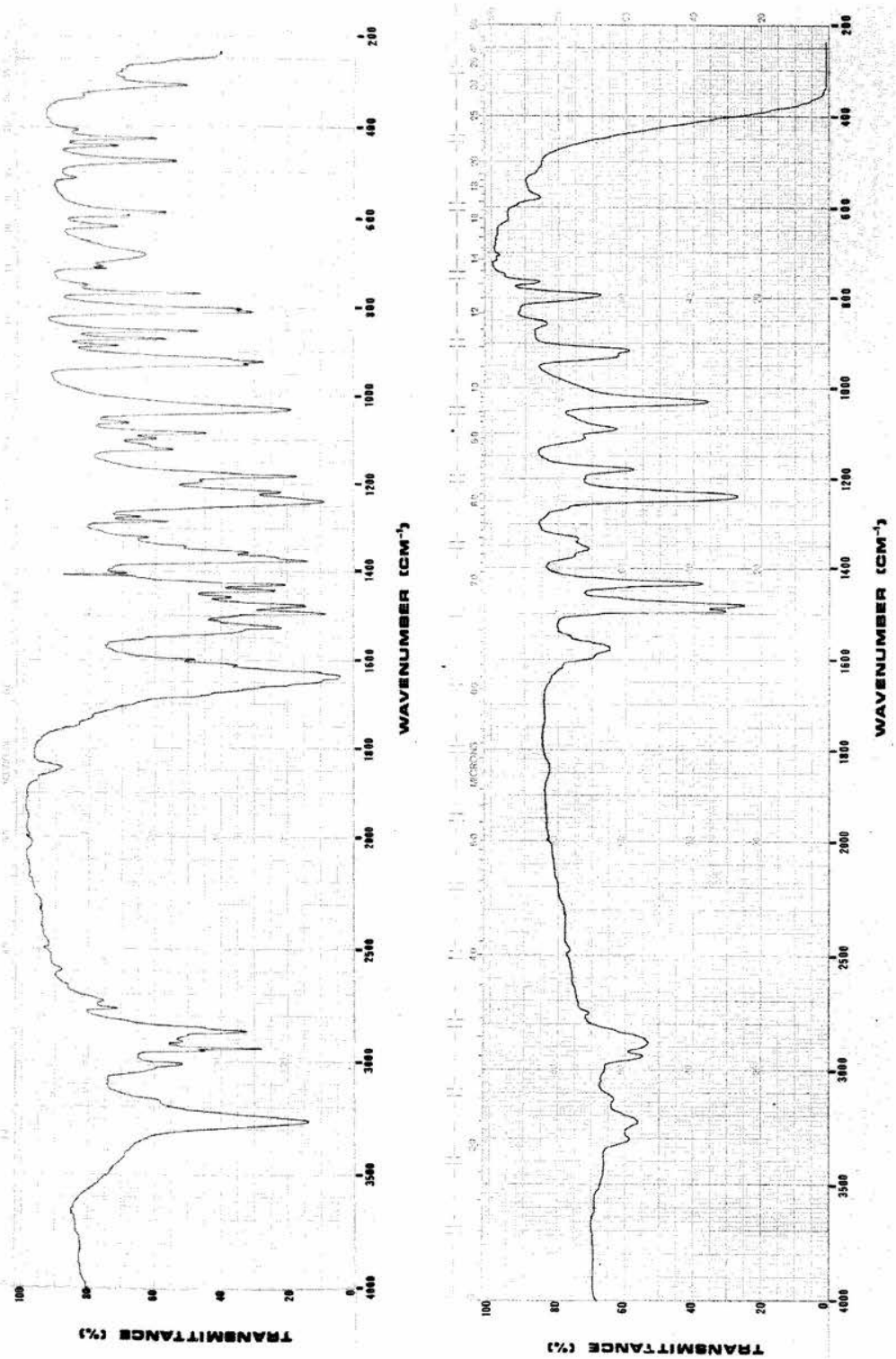

FIG. 9—IR spectra of *N*-formyl-MDA (top) and MDA (bottom).

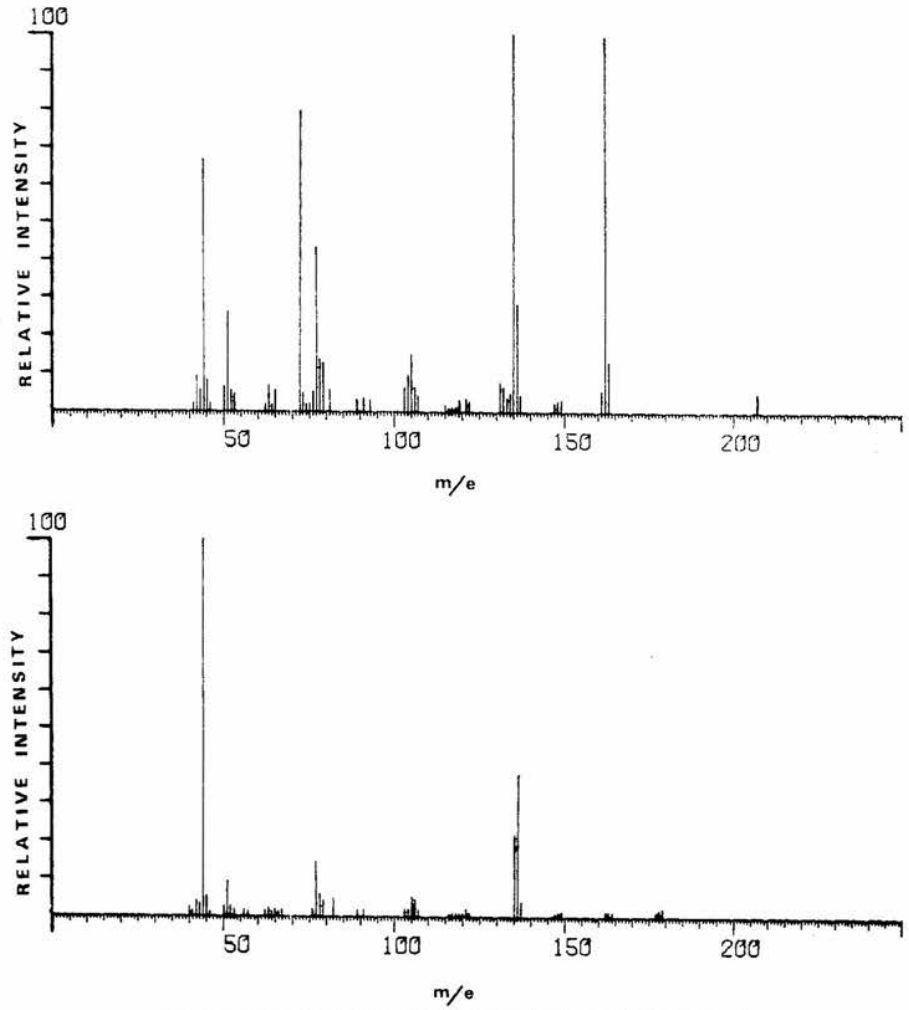

FIG. 10—Mass spectra of *N*-formyl-MDA (top) and MDA (bottom).

Synthesis of MDA from Piperonal

Piperonal, also known as heliotropin, is another common precursor used in the synthesis of MDA. Reaction of piperonal with nitroethane in the presence of a suitable catalyst results in the formation of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene. Condensation of aromatic aldehydes with nitromethane or nitroethane is a common method of preparing nitrostyrenes or nitropropenes (15–19). Subsequent reduction of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene with lithium aluminum hydride (20) or by hydrogenation (21) yields MDA. Incomplete reduction of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene can cause this compound to be present as an impurity of illicit MDA. The IR and mass spectra of piperonal and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene are illustrated in Figs 16 and 17.

Aromatic aldehydes can also be synthesized from corresponding aromatic propenes by treatment with ozone (22–24). Hydrogenation of the resultant ozonide gives the best yields of the aromatic aldehyde (25). Recently, this laboratory has identified 3,4-methylenedioxyphenylpropane in solutions of isosafrole, piperonal, and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene seized at a clandestine laboratory. This compound was

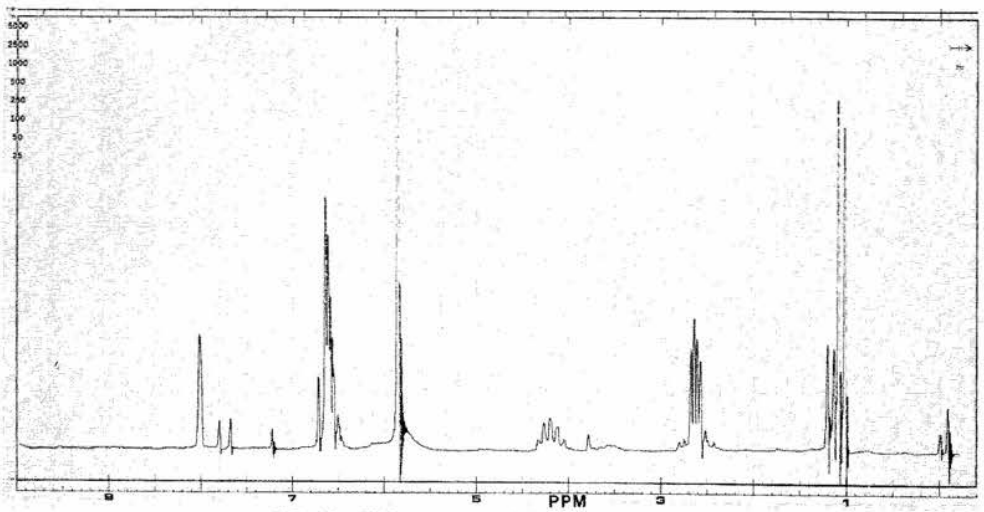

FIG. 11—NMR spectrum of *N*-formyl-MDA.

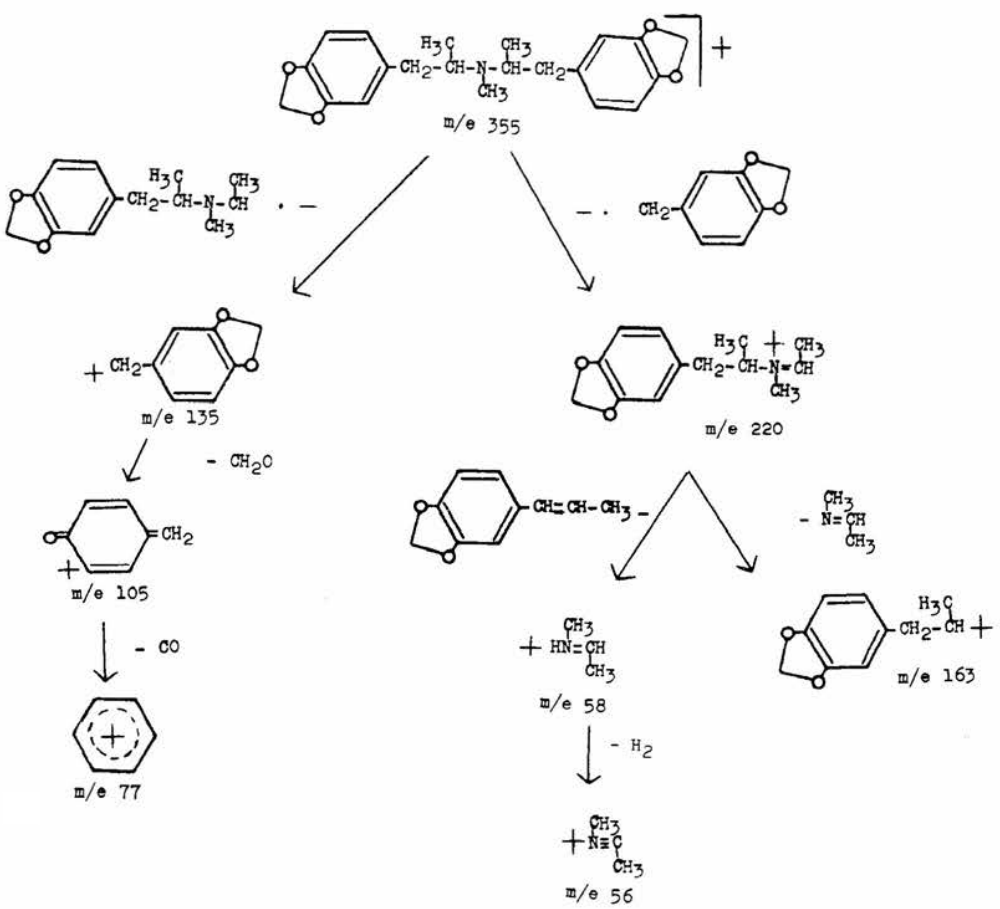

FIG. 12—Proposed fragmentation pattern of di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine.

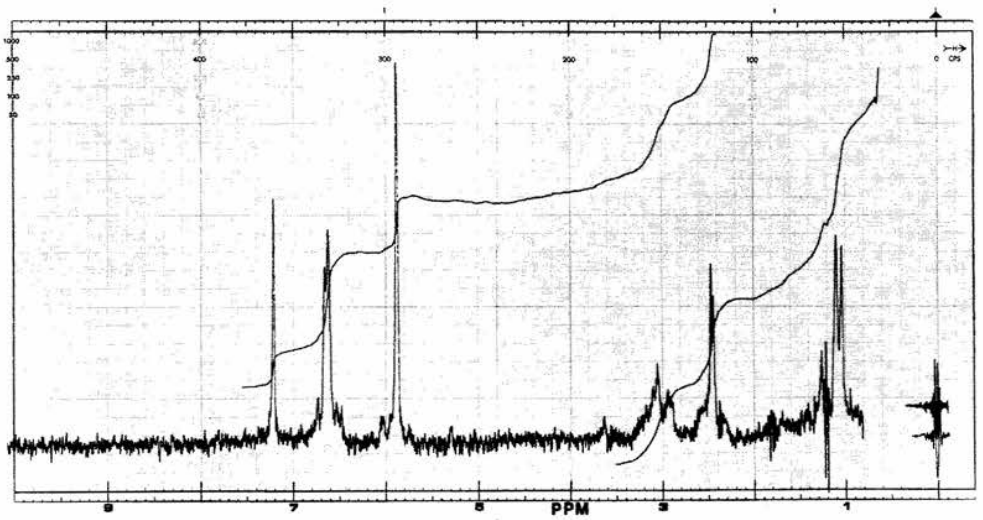

FIG. 13—NMR spectrum of di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine.

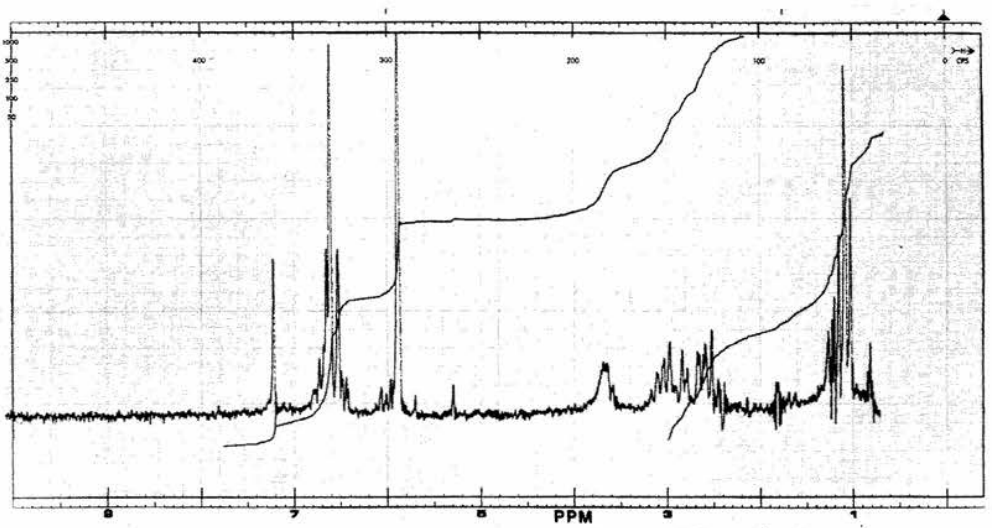

FIG. 14—NMR spectrum of di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine.

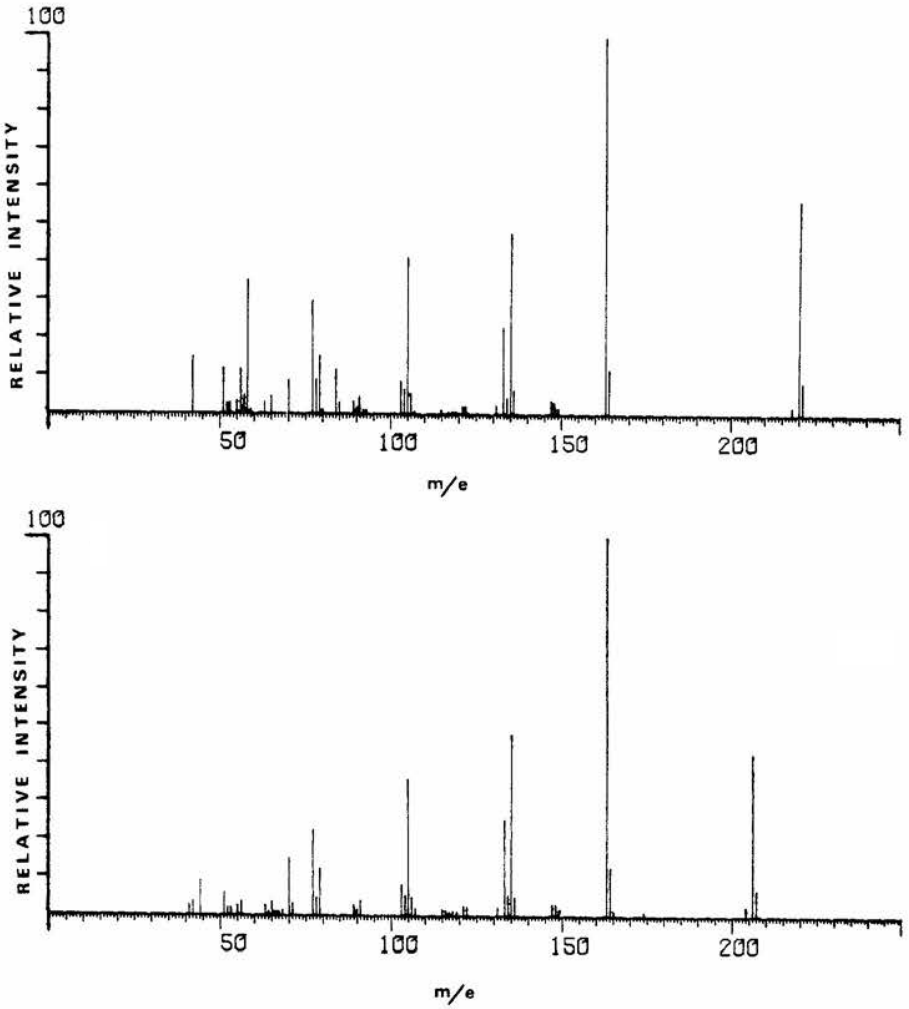

FIG. 15—Mass spectra of di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine (top) and di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine (bottom).

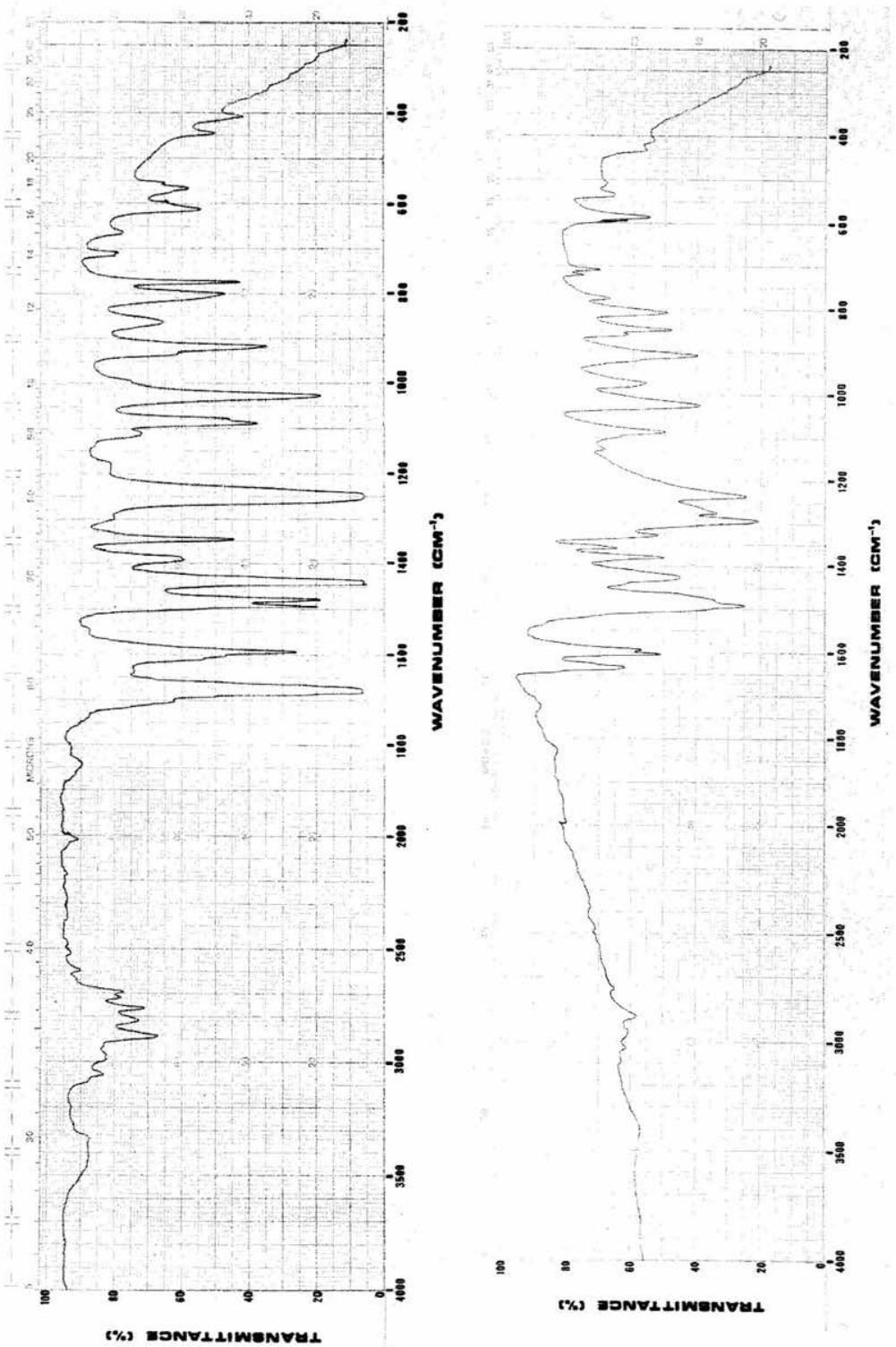

FIG. 16—IR spectra of A, piperonal and B, 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene.

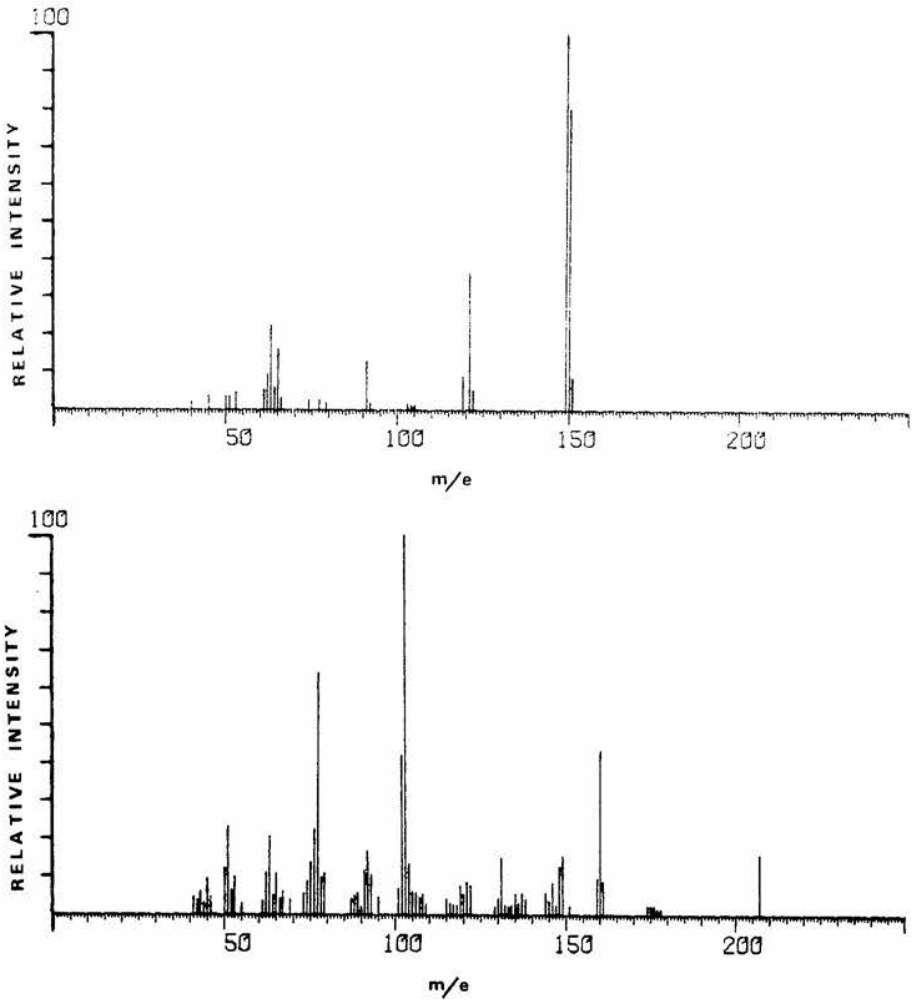

FIG. 17—Mass spectra of piperonal (top) and 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene (bottom).

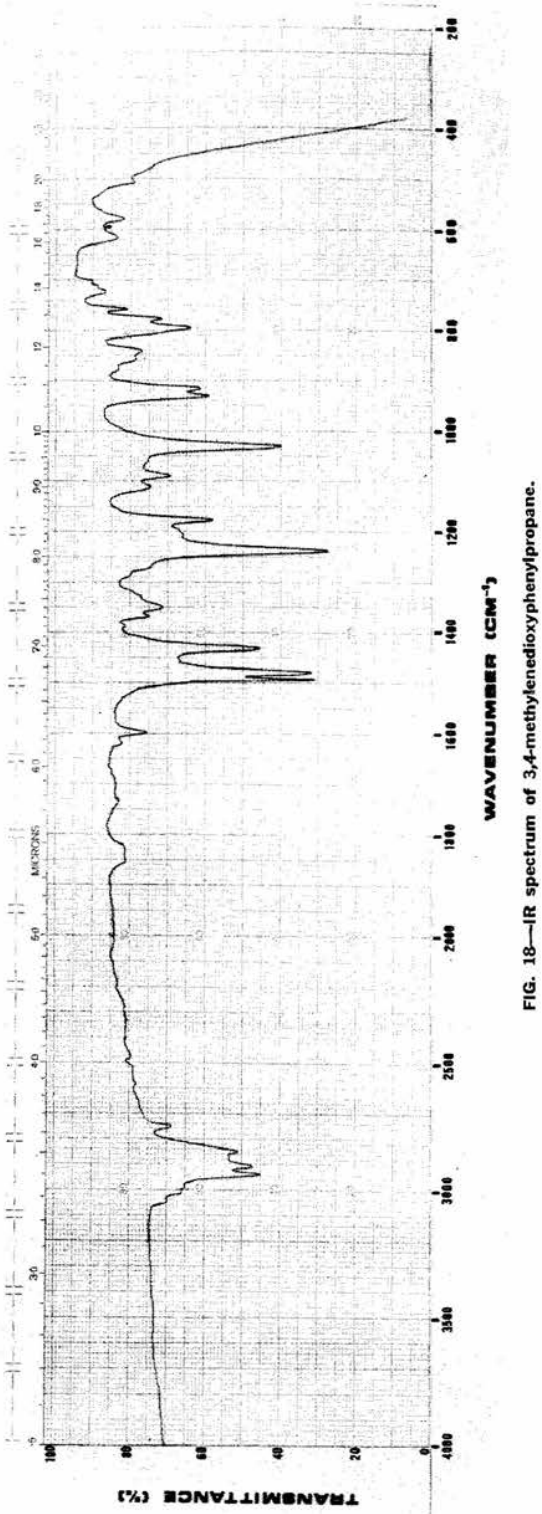

FIG. 18—IR spectrum of 3,4-methylenedioxyphenylpropane.

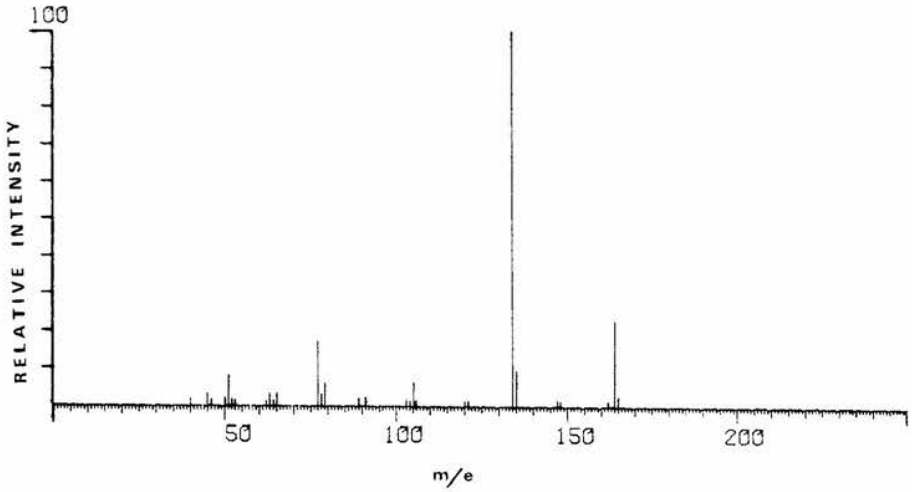

FIG. 19—Mass spectrum of 3,4-methylenedioxyphenylpropane.

probably formed as a result of incomplete ozonolysis of isosafrole. Subsequent hydrogenation of the mixture of isosafrole and isosafrole ozonide resulted in the formation of 3,4-methylenedioxyphenylpropane and piperonal. The IR and mass spectra of 3,4-methylenedioxyphenylpropane are illustrated in Figs 18 and 19.

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