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Synthesis and Characterization of the 2,3-Methylenedioxyamphetamines

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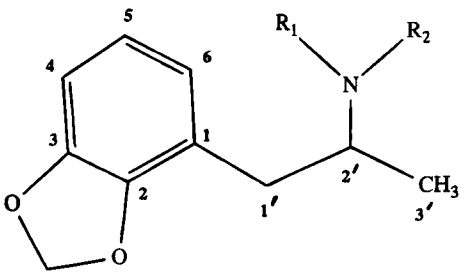
ABSTRACT: Synthetic methods and spectroscopic and chromatographic data are provided for four 2,3-methylenedioxyamphetamines (2,3-MDA, N-methyl-2,3-MDA, N-ethyl-2,3-MDA and N,N-dimethyl-2,3-MDA). These compounds are aromatic positional isomers of the corresponding 3,4-methylenedioxyamphetamines, which are well known, widely abused central nervous system stimulants with euphoric properties. Direct spectroscopic and chromatographic comparisons of the two isomeric series indicate that the 2,3-MDA's may be easily and unambiguously differentiated from the corresponding 3,4-MDA's via standard analytical methodologies.

KEYWORDS: toxicology, 2,3-methylenedioxyamphetamine, analogs, positional isomers, designer drugs, synthesis, chemical analysis

3,4-Methylenedioxyamphetamine (3,4-MDA) is a well known and widely abused central nervous system (CNS) stimulant with euphoric properties [*1*]. It was formally placed under Federal Control (Schedule I) in 1970 [*2*]. Soon after being scheduled, however, various N-substituted analogs (for example, N-methyl (3,4-MDMA), N-ethyl (3,4-MDEA) and N,N-dimethyl (3,4-MDDMA)) began circulating in the clandestine market. These so-called "designer" drugs were synthesized by clandestine laboratory operators attempting to exploit a legal loophole in the Federal Controlled Substance Act, that is, to create non-controlled analogs of 3,4-MDA with similar/identical physiological properties. Many of these analogs were eventually scheduled in turn [*3–5*], and the legal loophole itself was effectively eliminated with the passage of the Controlled Substance Analogue Enforcement Act of 1986, which specifically addressed all such attempts to circumvent existing statutes with "designed" analog drugs [*6*]. Nonetheless, new analogs of controlled substances are still occasionally identified by forensic chemists, and clandestine laboratory operators caught synthesizing such analogs predictably (and erroneously) claim that their products are "not controlled." Despite many legal challenges, the Analogue Enforcement Act remains in effect and has been utilized as a model statute for similar international controls.

More recently, a new variation of this still developing legal defense strategy is based on tasking forensic chemists to "prove" that an identified controlled substance is not in fact a closely related analogue. Although the Analogue Enforcement Act would invariably cover all such analogs, the legal situation may nonetheless be made so unclear as to confuse chemically unsophisticated jurors and result in acquittal(s) of the defendant(s). This latter strategy was recently attempted by defendants in a very large seizure of 3,4-MDMA; to whit: had the forensic chemists involved "proved" that the seized material was *not* in fact 2,3-MDMA, the aromatic positional isomer of 3,4-MDMA [*7*].

The 2,3-MDAs (Fig. 1) are chemically viable compounds, and it is conceivable that 2,3-MDMA could be clandestinely produced for illicit use. However, it has been previously reported that 2,3-MDA has only one-fifth the CNS stimulant activity of 3,4-MDA [*8*], and additionally that the N-substituted homologs of 3,4-MDA each have significantly lower CNS stimulant activity than 3,4-MDA itself [*9*]. Thus, *a priori,* it is expected that quite high doses of 2,3-MDMA would be required by abusers to achieve the desired physiological effects (that is, equivalent to 3,4-MDA). With the total absence of either scientific or "underground" literature reporting unexpected, unusual potency, it appears that the 2,3-MDAs have only a very low abuse potential, and the relative probability of their clandestine manufacture is therefore quite low.



Chemical Name	R_1	R_2
2,3-MDA	H	H
2,3-MDMA	H	CH_3
2,3-MDEA	H	C_2H_5
2,3-MDDMA	CH_3	CH_3

FIG. 1—*Structural formulas.*

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To our knowledge, none of the 2,3-MDAs have ever been identified in an illicit drug exhibit. Nonetheless, the ability to unambiguously differentiate 2,3- versus 3,4-MDAs remains of importance to forensic chemists. Herein, we present synthetic methodologies and analytical data for four of the 2,3-methylenedioxyamphetamines (2,3-MDA, 2,3-MDMA, 2,3-MDEA and 2,3-DMMDA), along with comparative data for the corresponding 3,4- substituted positional isomers.

Experimental Procedures

Materials and Methods

Authentic samples of 3,4-MDA, 3,4-MDMA, 3,4-MDEA, 3,4-MDP-2-P and 3,4-methylenedioxy-β-methyl-β-nitrostyrene were obtained from the reference collection of this laboratory. A sample of 3,4-MDDMA was provided by Mr. Terry Dal Cason of the U.S. Drug Enforcement Administration's North Central Regional Laboratory (Chicago, IL). 2,3-Methylenedioxybenzaldehyde was obtained from Aldrich Chemical Co., Inc., and was used without further purification. All other reagents were of reagent grade or better quality.

Melting points were taken on a Perkin-Elmer Model DSC-7 Differential Scanning Calorimeter. GC/Mass spectra were obtained on a Hewlett-Packard Model 5972 Mass Selective Detector (MSD) interfaced with a Hewlett-Packard 5890 Series II Gas Chromatograph. The MSD, column and oven temperature parameters were as follows: The MSD operated under electron ionization (EI) conditions at 70 eV and in full scan mode. The injection port (20:1 split) and source were maintained at 250°C and 180°C, respectively. A 30 m × 0.25 mm i.d. fused-silica capillary column coated with 0.25 μm DB-1 (J & W Scientific) was employed with a pressure programmed constant linear velocity of 36.1 cm/s. The oven temperature was programmed as follows: initial temperature, 90°C; initial hold, 1.0 min; program rate, 6.0°C/min; final temperature, 300°C; final hold, 4.0 min. Infrared spectra were obtained on a Nicolet Model 710 FT-IR using potassium bromide disks. ^{1}H-NMR spectra were obtained at 500 MHz on a Varian Unity 500 FT-NMR with a 5 mm indirect detection probe and Sun SPARC Station 300 computer system; a 45° pulse was used for all spectra. Tetramethylsilane (TMS) was utilized as an internal reference standard.

Synthesis

2,3-methylenedioxy-β-methyl-β-nitrostyrene—Nitroethane (12.0 g, 1.6×10^{-2} mol), 2,3-methylenedioxybenzaldehyde (11.0 g, 7.3×10^{-2} mol) and cyclohexylamine (7.3 g, 7.4×10^{-2} mol) were dissolved in 50 mL glacial acetic acid in a 250 mL round-bottom flask equipped with a reflux condenser and heated to 90 to 100°C. After 6 h, the hot, dark brown-green solution was transferred to a separate flask, diluted with 15 mL of cold water and allowed to cool to room temperature, whereby the crude product precipitated. The product was collected via suction filtration and recrystallized from acetic acid to provide 10.6 g (70% yield) of the nitrostyrene as bright yellow crystals.

2,3-methylenedioxyamphetamine Hydrochloride (2,3-MDAHCl)—A solution of 2,3-Methylenedioxy-β-methyl-β-nitrostyrene (3.6 g, 1.7×10^{-2} mol) in 20 mL tetrahydrofuran (THF) was added dropwise over 30 minutes to lithium aluminum hydride (LAH, 4.2 g, 1.1×10^{-1} mol) in 50 mL THF and then heated to reflux. After 5 h, the excess LAH was quenched [*10*] with dropwise water and the precipitated inorganic salts were removed via suction filtration. The filtrate was evaporated *in vacuo* to a light yellow oil that was in turn dissolved into 15 mL isopropanol, acidified with concentrated HCl and diluted with 200 mL diethyl ether. The precipitated product was recrystallized from methanol/diethyl ether to provide 3.03 g (81% yield) of 2,3-MDA·HCl as white crystals.

N-Formyl-2,3-Methylenedioxyamphetamine (N-Formyl-2,3-MDA)—A solution of 2,3-MDA (2.07 g, 1.16×10^{-2} mol) and 1.0 mL of 88% formic acid were added to 100 mL dry benzene in a 250 mL round-bottom flask fitted with a Dean-Stark trap containing four Å molecular sieves and refluxed. After four days, the resulting solution was evaporated *in vacuo* to give an amber colored oil, which was in turn dissolved into 100 mL methylene chloride and washed with dilute HCl (4 × 25 mL) to remove unreacted 2,3-MDA. The organic phase was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 1.86 g (77% yield) of N-formyl-2,3-MDA as a clear oil.

N-Methyl-2,3-Methylenedioxyamphetamine Hydrochloride (2,3-MDMA·HCl)—A solution of N-formyl-2,3-MDA (1.86 g, 9.0×10^{-3} mol) in 10 mL THF was added dropwise over 15 minutes to 60 mL of 1.0 M LAH (6.0×10^{-2} mol) in THF and then heated to reflux. After 4.5 h, the excess LAH was quenched in the usual manner and the inorganic salts were removed via suction filtration. The filtrate was evaporated *in vacuo* to a colorless oil which was in turn dissolved into 10 mL isopropanol, acidified with concentrated HCl and diluted with 200 mL diethyl ether. The precipitated product was recrystallized from methanol/diethyl ether and then again from methylene chloride/diethyl ether to provide 1.16 g (56% yield) of 2,3-MDMA·HCl as white crystals.

N-Acetyl-2,3-Methylenedioxyamphetamine (N-Acetyl-2,3-MDA)—Approximately 1.0 mL of acetic anhydride and 2,3-MDA (0.460 g, 2.57×10^{-3} mol) was mixed in a 13 mL Teflon-capped glass tube and heated at 75°C. After 20 h, the excess acetic anhydride was evaporated under a stream of nitrogen and the resulting residue dissolved into 10 mL methylene chloride, washed with dilute HCl (5 × 4 mL), dilute NaOH (3 × 4 mL), water (2 × 4 mL) and finally dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.414 g of N-acetyl-2,3-MDA (73% yield) as an amber oil.

N-Ethyl-2,3-Methylenedioxyamphetamine Hydrochloride (2,3-MDEA·HCl)—A solution of N-acetyl-2,3-MDA (0.414 g, 1.87×10^{-3} mol) in 2 mL THF was added dropwise over 5 minutes to 15 mL of 1.0 M LAH (1.5×10^{-2} mol) in THF and then heated to reflux. After 3.5 h, the excess LAH was quenched in the usual manner and the inorganic salts were removed via suction filtration. The resulting filtrate was evaporated *in vacuo* to a colorless oil which was in turn dissolved into 5 mL isopropanol, acidified with concentrated HCl and diluted with 150 mL diethyl ether. The precipitated product was recrystallized from methanol/diethyl ether to provide 114 mg (25% yield) of 2,3-MDEA·HCl as white crystals.

2,3-Methylenedioxyphenyl-2-propanone (2,3-MDP-2-P)—Under N_2, 3,5-di-*tert*-butyl-1,2-benzoquinone (1.67 g, 7.57×10^{-2} mol) was added to a solution of 2,3-MDA (1.40 g, 7.82×10^{-3} mol) in 50 mL degassed methanol with stirring. After 3 h, 10 mL of degassed water was added and stirred for 5 min, followed by oxalic acid (1.19 g, 9.46×10^{-3} mol) and finally an additional 100 mL of degassed water. The resulting yellowish solution was extracted

with diethyl ether (4 × 100 mL); the combined extracts were washed well with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to a yellow oil containing the crude ketone. Elution with diethyl ether on a neutral alumina column gave 0.245 g (18% yield) of analytically pure 2,3-MDP-2-P as a yellow oil.

N,N-Dimethyl-2,3-Methylenedioxyamphetamine Hydrochloride (2,3-MDDMA·HCl)—A trace of mercuric chloride, 2,3-MDP-2-P (0.245 g, 1.37×10^{-3} mol), 40% dimethylamine in H_2O (0.20 g, 1.77×10^{-2} mol) and aluminum foil (0.4 g) were added to 40 mL methanol in a 100 mL flask. The reductive animation was allowed to proceed overnight with stirring. The reaction mixture was then diluted with 100 mL water and filtered. The resulting filtrate was acidified with 0.36 N sulfuric acid and washed with diethyl ether (2 × 75 mL). The aqueous phase was then brought to pH 8 to 10 with 15% aqueous sodium hydroxide and extracted with methylene chloride (20 mL). The extract was dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo* to give an oil. The hydrochloride salt was prepared via addition of ethereal HCl and the resulting crystals were washed with additional diethyl ether to provide 6 mg (<2% yield) of 75% pure, hygroscopic crystalline material.

Results and Discussion

The 3,4-MDAs may be readily prepared via a large number of synthetic routes due to the wide availability of a variety of 3,4-methylenedioxyphenyl substituted precursors [*11*]. However, routine synthetic routes to the 2,3-MDAs are sharply limited because of the commercial availability of only a single precursor compound, that is, 2,3-methylenedioxybenzaldehyde. The preparation of 2,3-MDA has been previously reported [*12*]; however, to our knowledge, 2,3-MDMA, 2,3-MDEA and 2,3-MDDMA have never been previously synthesized.

The general synthetic scheme used in this study is presented in Fig. 2. In summary, 2,3-methylenedioxybenzaldehyde was condensed with nitroethane to give 2,3-methylenedioxy-β-methyl-β-nitrostyrene, which was in turn directly reduced to 2,3-MDA [*10*]. Formylation and acetylation of 2,3-MDA followed by reduction gave 2,3-MDMA and 2,3-MDEA, respectively. Repeated attempts to prepare 2,3-MDP-2-P (the precursor for 2,3-MDDMA) via reductive hydrolysis of the nitrostyrene failed; 2,3-MDP-2-P was therefore prepared in low yield via oxidative deamination of 2,3-MDA with 3,5-di-*tert*-butyl-1,2-benzoquinone [*13*]. Reductive amination of 2,3-MDP-2-P with dimethylamine gave 2,3-MDDMA. It is noted that this unusual synthetic route would almost certainly never be used by a clandestine laboratory operator, since the precursor (2,3-MDA) is significantly more physiologically active than the end product (2,3-MDDMA). The preparation of larger amine substituents followed a trend of decreasing yields: 2,3-MDA = 81%, 2,3-MDMA = 56%, 2,3-MDEA = 25% and 2,3-MDDMA = <2%); even taking the disparate number of synthetic steps into account, the results suggest that steric hindrance plays a significant role in the overall stabilities of the N-substituted compounds. Dal Cason also reported very poor yields in his attempted syntheses of two tertiary amine analogues of 3,4-MDA [*14*]. The extremely low yield of 2,3-MDDMA upon reductive amination with dimethylamine was primarily due to preferential reduction of 2,3-MDP-2-P to 2,3-methylenedioxyphenyl-2-propanol, even in reactions where large excesses of dimethylamine were utilized. Formal preparation and isolation of the intermediate 2,3-MDP-2-P/dimethylamine enamine (for independent reduction to 2,3-MDDMA) was not attempted.

All four 2,3-MDAs were isolated as their hydrochloride salts; with the exception of 2,3-MDDMA·HCl, the purity of each synthesized 2,3-MDA·HCl exceeded 97%. 2,3-MDDMA·HCl was both impure and hygroscopic.

Melting Points

Melting points for the respective 2,3- and 3,4- isomeric nitrostyrenes and MDAs are presented in Table 1. 2,3- and 3,4-MDP-2-P, N-formyl-2,3-MDA and N-acetyl-2,3-MDA were all oils. No melting point was obtained for 2,3-MDDMA HCl.

Capillary Gas Chromatography

GC retention data for the respective 2,3- and 3,4- substituted isomers are presented in Table 2. For the MDAs, it was observed that the hydrochloride salts underwent thermally induced decomposition and chromatographed poorly, whereas the corresponding free bases gave excellent chromatography. Excellent peak symmetry was observed for all compounds under the conditions used. All four 2,3-MDAs were baseline resolved upon co-injection and each was also easily resolved from its respective 3,4-positional isomer, with an average 42 second difference in retention time (at approximately a 14 minute run time, using the column and oven temperature program as specified in the Experimental Section.)

Infrared Spectroscopy

The IR spectra of the respective 2,3- and 3,4- nitrostyrenes, MDP-2-Ps and MDA hydrochlorides are illustrated in Figs. 3–7.The spectrum for 2,3-MDDMA HCl is not shown. Comparison of the respective analog pairs reveals substantial absorption differences in the phenyl ring CH out-of-plane bending frequencies between 700–900 cm^{-1}, with more subtle differences between 900–1700 cm^{-1}. The spectra of the isomeric nitrostyrenes (Fig. 6) and propanones (Fig. 7) are easily distinguishable. The spectra of the isomeric MDAs could be likewise differentiated; however, the spectra of 2,3-MDMA HCl and 2,3-MDEA HCl were rather similar. As an additional cautionary note, however, it is known that 3,4-MDMA HCl can have several polymorphic forms [*1*], and it is reasonable to expect analogous behavior in the 2,3-MDAs.

Mass Spectrometry

GC/Mass spectra for the respective 2,3- and 3,4- substituted isomers are presented in Figs. 8 to 14. Note that the ion abundances for the entire spectra in Figs. 8 to 11 have been enhanced 5X due to extremely weak molecular and fragment ions. 2,3- and 3,4-MDA (Fig. 8) each gave a base peak at m/z 44, but were easily distinguished by the relative abundances of ions at m/z 135 and m/z 136 [*12*]. Both 2,3- and 3,4-MDMA (Fig. 9) gave a base peak at m/z 58, but were also easily distinguished by the relative abundances of ions at m/z 135 and m/z 136. 2,3- and 3,4-MDEA (Fig. 10) each gave virtually identical spectra with a base peak at m/z 72. 2,3- and 3,4-MDDMA (Fig. 11) also gave virtually identical spectra with a base peak at m/z 72. Both the 2,3- and 3,4-nitrostyrenes (Fig. 12) gave a base peak at m/z 103, but were easily distinguished by the relative abundances of ions m/z 91, 92, 119, 147 and 160. 2,3- and 3,4-MDP-2-P (Fig. 13) each gave a base peak at m/z 135, but were easily distinguished by the relative abundances of ions m/z 43 and m/z 51. Finally, the intermediates N-formyl-2,3-MDA and N-acetyl-2,3-MDA (Fig. 14) are presented; the spectra of 2,3- and 3,4-N-acetyl-MDA (the latter as published by Dal Cason [*14*]) are virtually identical.

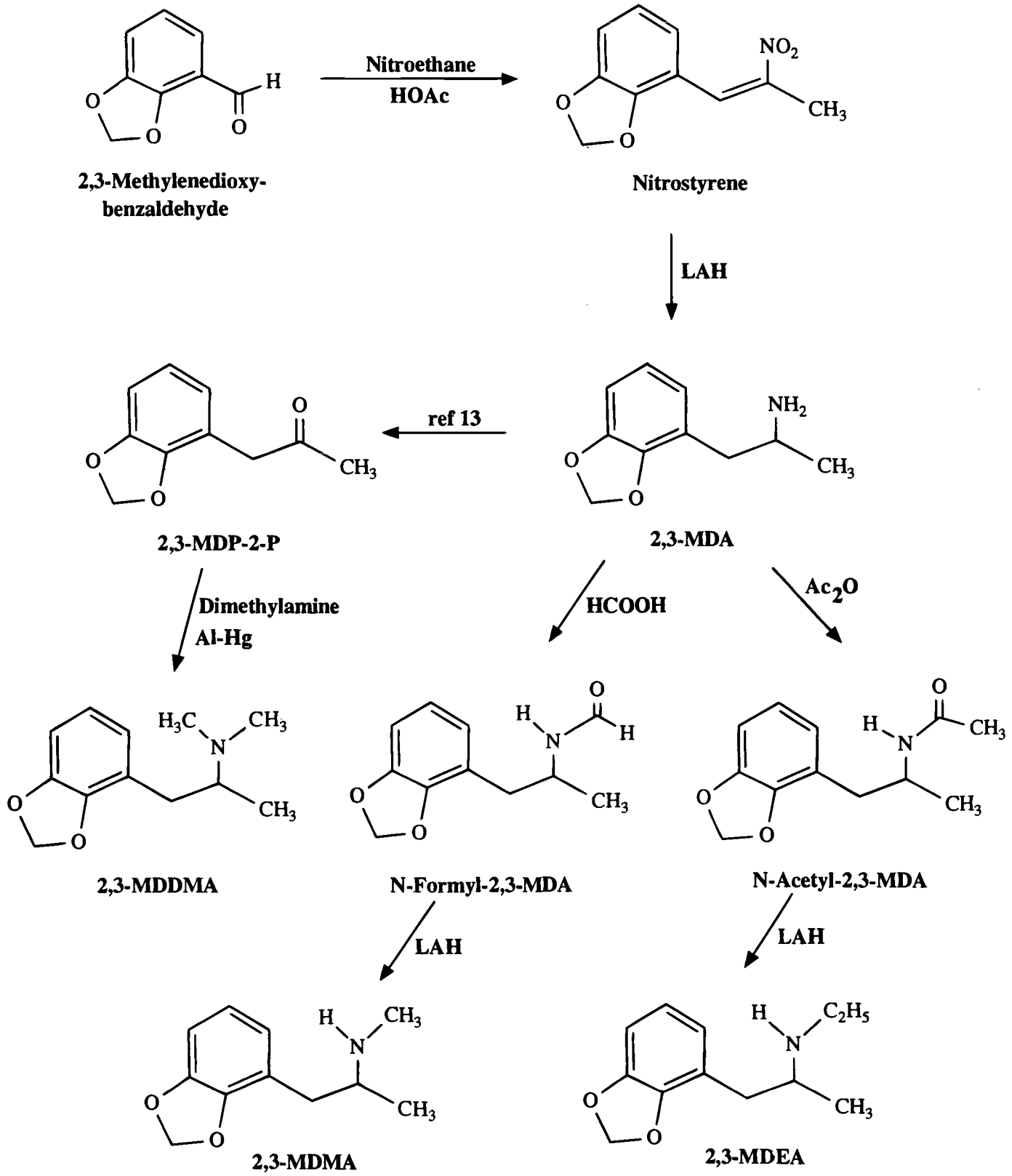

FIG. 2—*Synthetic routes to the 2,3-MDAs.*

TABLE 1—*Melting points (°C) of N-substituted methylenedioxyamphetamines and related compounds.*

Compound	2,3-Substitution	3,4-Substitution
Styrene	74.9	97–98[a]
MDA HCl	158	185–186[b]
MDMA HCl	145	150–152[b]
MDEA HCl	155	198.5–200[b]
MDDMA HCl	...[c]	169–170[b]

[a]Reference 10.
[b]Reference 14.
[c]An analytically pure sample was not obtained.

TABLE 2—*Retention times (min) for methylenedioxyamphetamines and related compounds.*[a]

Compound	2,3-Substitution	3,4-Substitution
Nitrostyrene	17.95	18.84
MDP-2-P	11.59	12.32
MDA	11.61	12.25
MDMA	12.68	13.37
MDEA	13.64	14.32
MDDMA	13.95	14.72

[a]Conditions given in Experimental Section.

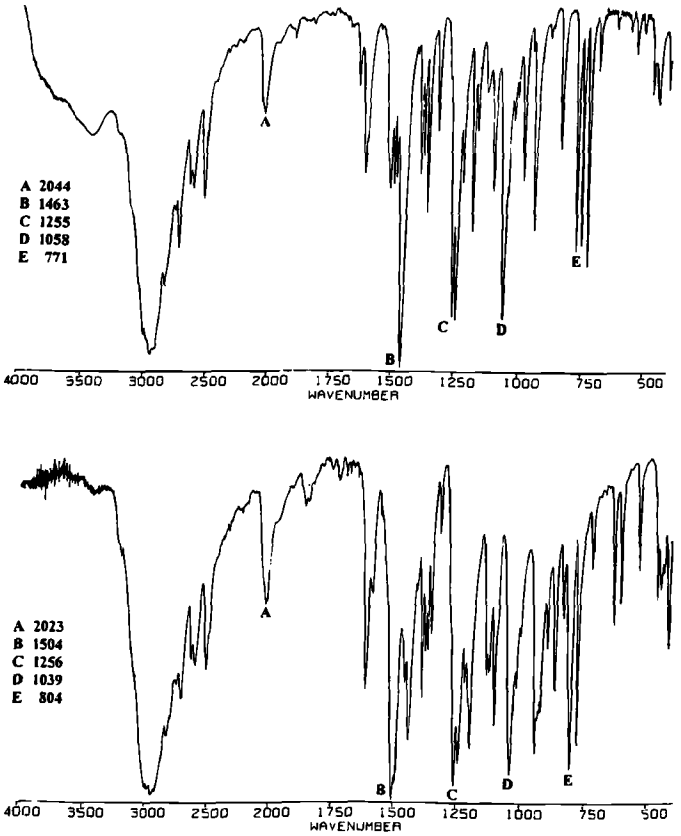

FIG. 3—*Infrared spectra of* (upper) *2,3-MDA HCl and* (lower) *3,4-MDA HCl.*

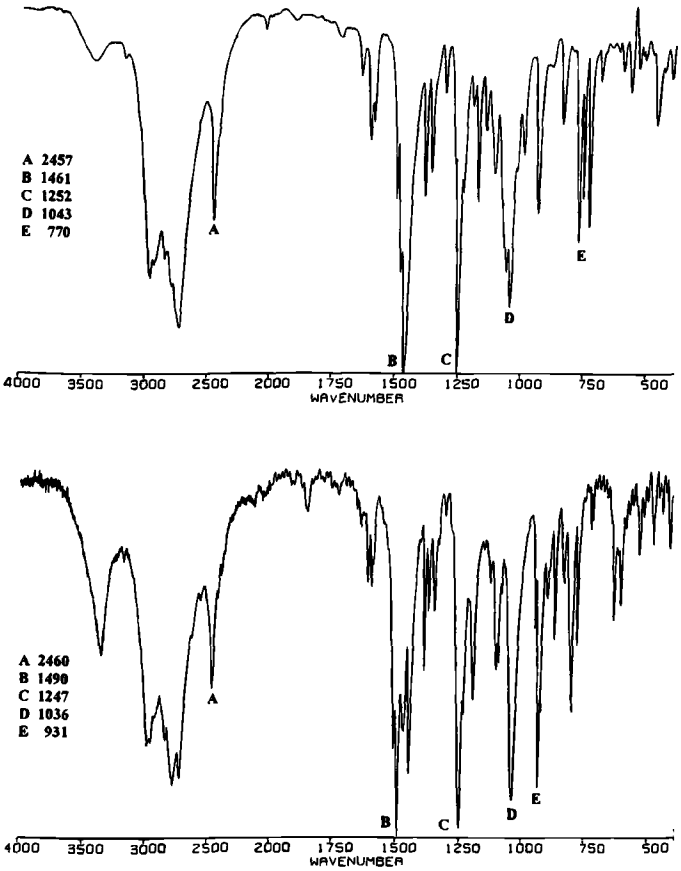

FIG. 4—*Infrared spectra of* (upper) *2,3-MDMA HCl and* (lower) *3,4-MDMA HCl.*

^{1}H-NMR Spectroscopy

The ^{1}H chemical shifts for the respective 2,3- and 3,4- substituted isomers are presented in Table 3. The isomeric MDAs could each be differentiated via variances in both chemical shifts and overall peak patterns.[2] The most definitive differences are in the aromatic region, as shown in Fig. 15 for MDMA. The 2,3-MDMA aromatic protons are all either *ortho* or *meta* to each other while the 3,4-MDMA protons are *ortho, meta* or *para.* This yields differing peak patterns due to different coupling constants; *ortho* at about 7 Hz, *meta* at about 1.5 Hz and *para* between 0–1 Hz. The apparent triplet[3] for H-5 in 2,3-MDMA at 6.78 ppm is actually composed of two *ortho* couplings (7.4 and 7.8 Hz) while its 3,4-MDMA counterpart (H-5 at 6.75 ppm) is a doublet of broad peaks made up of an *ortho* coupling (7.7 Hz) and a *para* coupling (less than 1 Hz). H-4 in 2,3-MDMA (6.75 ppm) is composed of a doublet of doublets (*ortho* coupling 7.8 Hz and *meta* coupling 1.5 Hz) and H-2 in the 3,4-MDMA (6.71 ppm) appears as a doublet (*meta*

[2]Magnets with a lower field strength may not be able to distinguish 2,3- vs 3,4-MDAs based on the aromatic region peak patterns. In addition, the nearly coincident chemical shifts may augment second order effects at lower field strengths, resulting in a further loss in resolution.

[3]Doublet of doublets with similar coupling constants that cause overlapping in the middle peak.

TABLE 3—*Chemical shift (ppm) and splitting patterns from ^1H NMR spectra of the methylenedioxyamphetamine hydrochlorides.*

Proton(s)	2,3-MDA	3,4-MDA	2,3-MDMA	3,4-MDMA	2,3-MDEA	3,4-MDEA	2,3-MDDMA	3,4-MDDMA
H-2	...	6.73d	...	6.71d	...	6.70d	...	6.72d
H-4	6.75dd	...	6.75dd	...	6.74dd	...	6.77dd	...
H-5	6.77dd[b]	6.76d	6.78dd[b]	6.75d[c]	6.78dd[b]	6.74d	6.81dd[b]	6.76d
H-6	6.70dd	6.68dd	6.69dd	6.68dd	6.69dd	6.67dd	6.71dd	6.68dd
H-1'a	2.90dd	2.79dd	2.89dd	2.77dd	2.91dd	2.78dd	2.68dd	2.52dd
H-1'b	3.12dd	3.08dd	3.36dd	3.39dd	3.44dd	3.47dd	3.36dd	3.51dd
H-2'	3.71m	3.49m	3.46m	3.27m	3.58m	3.30m	3.61m	3.40m
H-3'	1.40d	1.40d	1.40d	1.35d	1.41d	1.36d	1.35d	1.27d
$-OCH_2O-$	5.97d 5.98d	5.93d 5.94d	5.94d 5.95d	5.95bs	5.92[a]	5.94[a]	5.96[a]	5.96bs
$-^+\underline{NH}R$	8.46bs	8.41bs	9.70bs	9.68bs	9.68bs	9.66bs	12.40bs	12.72bs
$-^+NH_2\underline{CH_3}$	...	...	2.73t	2.70bs	...	...	...	...
$-^+NH_2\underline{CH_a}H_bCH^3$	...	...	...	...	3.14m	3.05dddd	...	...
$-^+NH_2CH_a\underline{H_b}CH_3$	...	...	...	...	...	3.12dddd		
$-^+NH_2CH_2\underline{CH_3}$	...	...	...	...	1.55t	1.54t	...	...
$-^+NH(\underline{CH_3})_2$	...	...	...	...	...	...	2.82bs	2.75d 2.79d

d = doublet s = singlet t = triplet bs = broad singlet m = multiplet

[a]Peaks distorted by second order effects.
[b]Apparent triplet distorted by second order effects.
[c]Peaks broad due to *para* coupling < 1 hz.

coupling 1.4 Hz and *para* coupling less than 1 Hz). H-6 (6.69 ppm for 2,3-MDMA and 6.68 ppm for 3,4-MDMA) is a doublet of doublets in both cases with *ortho* (about 7.5 Hz) and *meta* (about 1.5 Hz) coupling. Various other differences in the spectra were also noted (Table 3).

The proton chemical shifts for the 2,3- and 3,4-methylenedioxy-phenyl-2-propanones and methylenedioxyphenyl-β-methyl-β-nitrostyrenes are given in Table 4. The aromatic region for these compounds gave the only obvious differences between the 2,3- and 3,4-isomers. The MDP-2-Ps could be distinguished using the same method described above for the MDAs. The 2,3-nitrostyrene aromatic protons had the same or nearly the

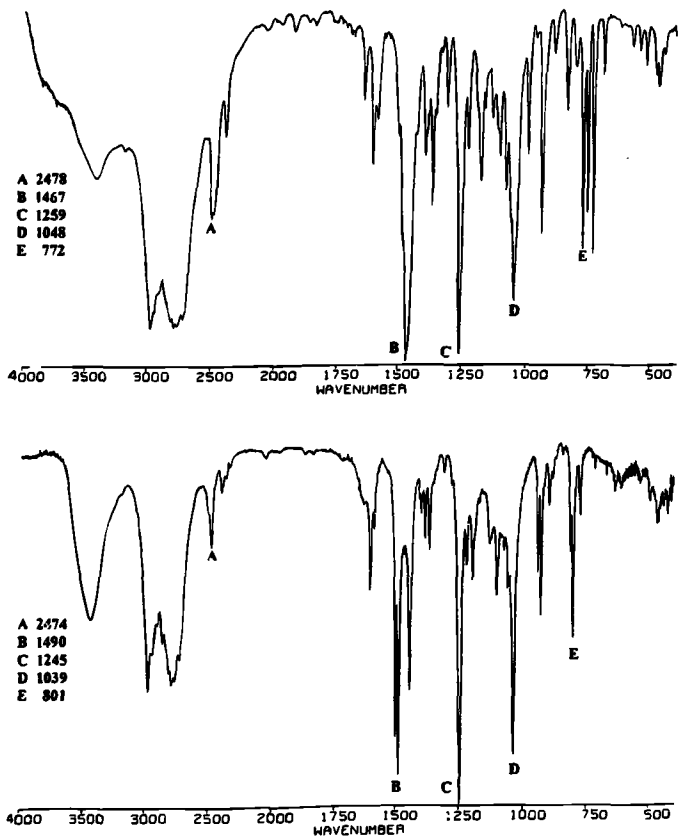

FIG. 5—*Infrared spectra of* (upper) *2,3-MDEA HCl and* (lower) *3,4-MDEA HCl.*

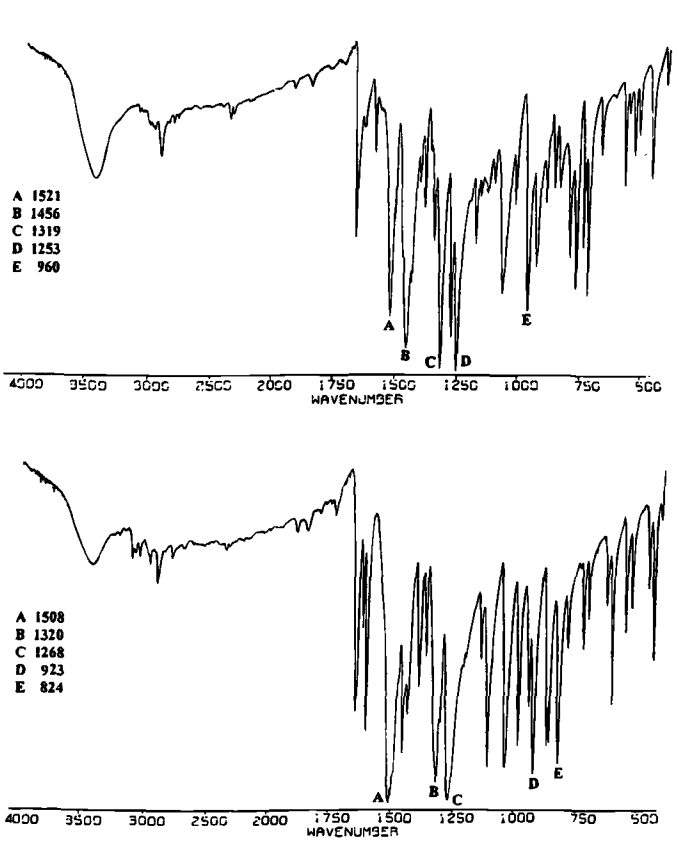

FIG. 6—*Infrared spectra of* (upper) *2,3-methylenedioxy-β-methyl-β-nitrostyrene and* (lower) *3,4-methylenedioxy-β-methyl-β-nitrostyrene.*

same chemical shifts, resulting in a complex multiplet with pronounced second order effects. In contrast, the 3,4-nitrostyrene displayed the typical splitting pattern for a 1,3,4-trisubstituted benzene, as shown in the 3,4-MDA analogs above (however, the H-5 and H-6 placement in the spectrum are switched).

Conclusions

The significantly reduced physiological activity levels, lack of synthetic precursors and only poor to fair overall synthetic yields all suggest that the 2,3-MDAs are unlikely to ever be identified on the clandestine market. Nonetheless, their identification is of importance to forensic chemists. In this study, analytical data is presented for four 2,3-MDAs and several related compounds to assist delineating them from the 3,4-positional isomers. Salient differences in their combined spectroscopic and chromatographic analyses allow for routine differentiation of isomers. The possible occurance of polymorphism may inhibit conclusive identification by IR alone; the isomers are best differentiated by either high field NMR or the combination of mass spectra and retention time. Other techniques such as IR may be utilized in conjunction with either GC, GC/MS or NMR. The "red-flag" marker for a possible 2,3-MDA is its GC retention time, which for every MDA examined in this study was significantly less than the corresponding 3,4-substituted MDA.

TABLE 4—*Chemical shift (ppm) and splitting patterns from ^1H NMR spectra of the methylenedioxy-β-methyl-β nitrostyrenes and methylenedioxyphenyl-2-propanones.*

Proton(s)	2,3-MDP-2-P	3,4-MDP-2-P	2,3-styrene	3,4-styrene
H-2	...	6.68d	...	6.95d
H-4	6.77dd	...	6.88m	...
H-5	6.80dd[a]	6.77d	6.88m	6.90d
H-6	6.66dd	6.65dd	6.88m	6.99dd
H-1′	3.67s	3.61s	8.04bs	8.03bs
H-3′	2.20s	2.15s	2.41d	2.47d
$-OCH_2O-$	5.96s	5.95s	6.04s	6.05s

[a]Apparent triplet distorted by second order effects.

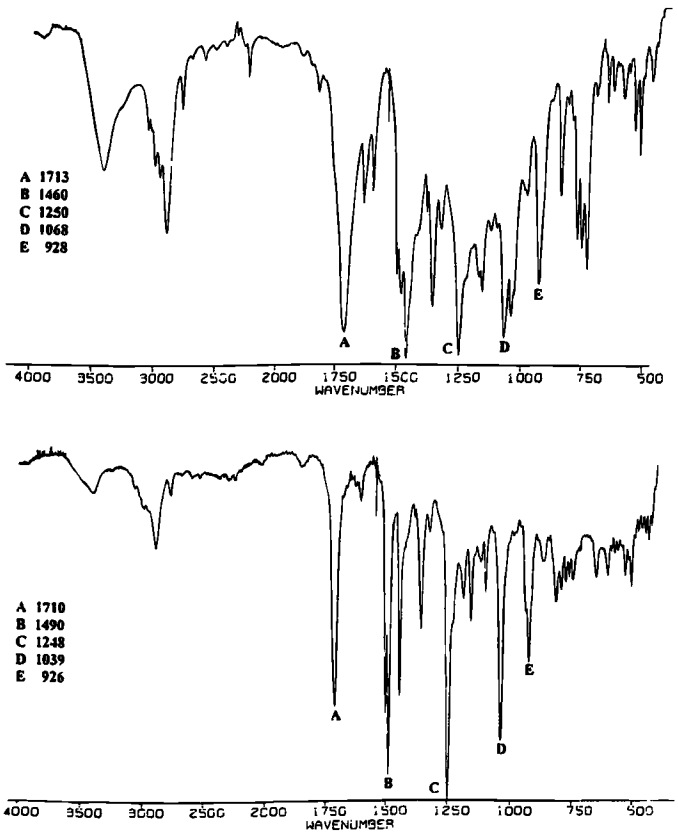

FIG. 7—*Infrared spectra of* (upper) *2,3-MDP-2-P and* (lower) *3,4-MDP-2-P.*

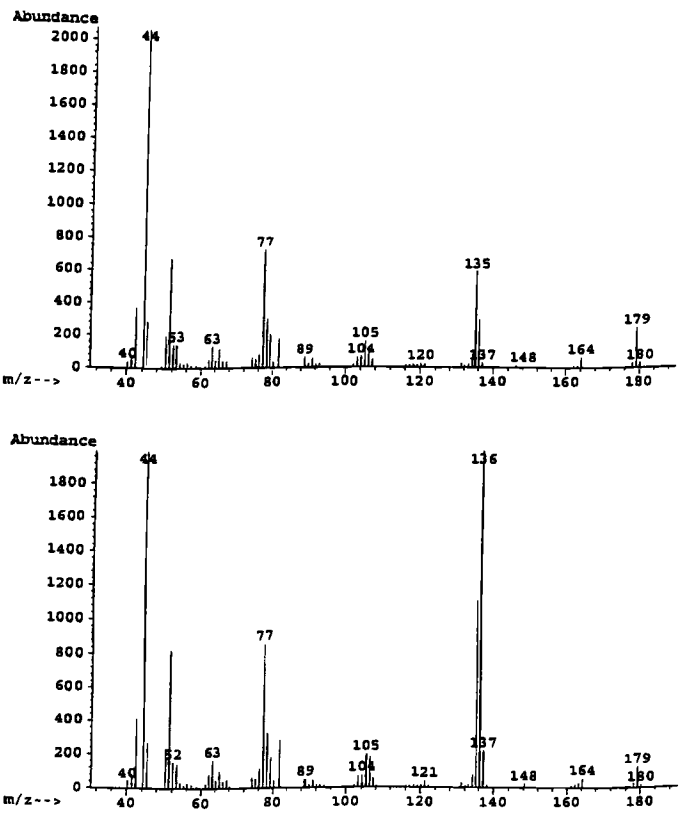

FIG. 8—*Mass spectra of* (upper) *2,3-MDA and* (lower) *3,4-MDA. Ion abundances enhanced 5X.*

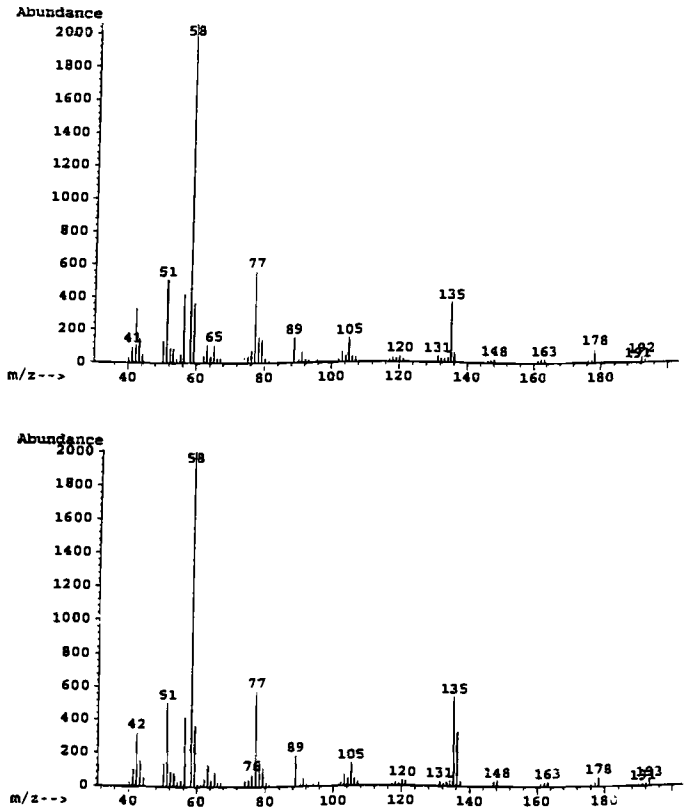

FIG. 9—*Mass spectra of* (upper) *2,3-MDMA and* (lower) *3,4-MDMA. Ion abundances enhanced 5X.*

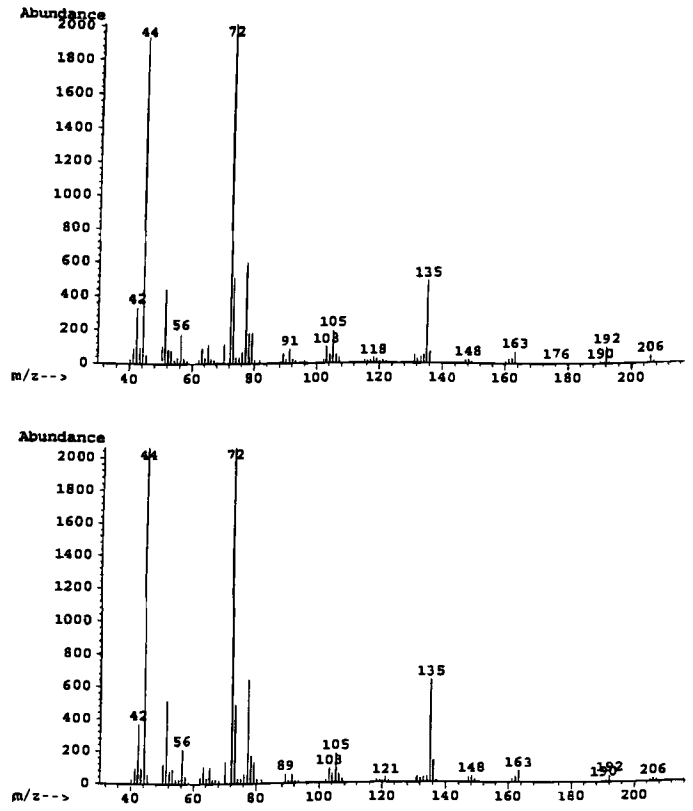

FIG. 10—*Mass spectra of* (upper) *2,3-MDEA and* (lower) *3,4-MDEA. Ion abundances enhanced 5X.*

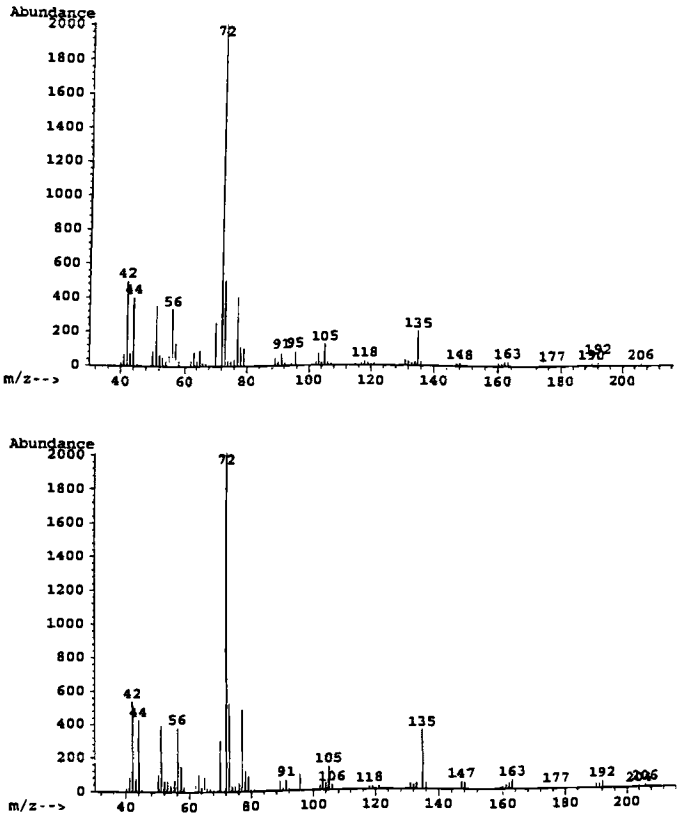

FIG. 11—*Mass spectra of* (upper) *2,3-MDDMA and* (lower) *3,4-MDDMA. Ion abundances enhanced 5X.*

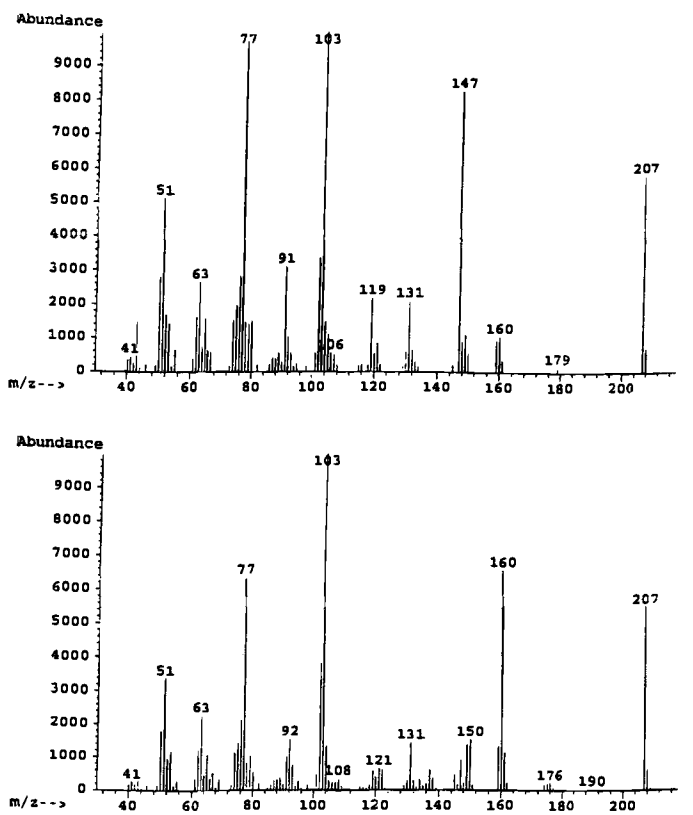

FIG. 12—*Mass spectra of* (upper) *2,3-methylenedioxy-β-methyl-β-nitrostyrene and* (lower) *3,4-methylenedioxy-β-methyl-β-nitrostyrene.*

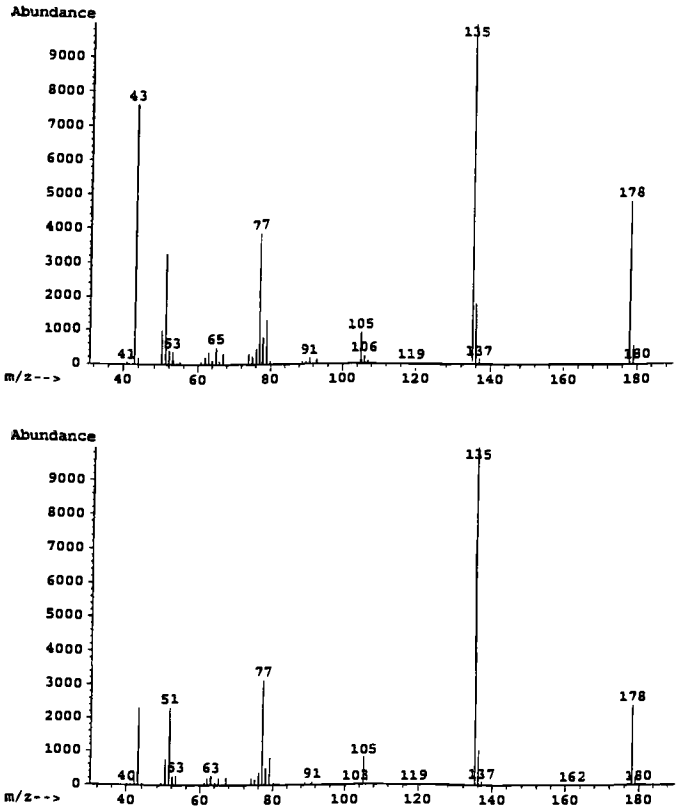

FIG. 13—*Mass spectra of* (upper) *2,3-MDP-2-P and* (lower) *3,4-MDP-2-P.*

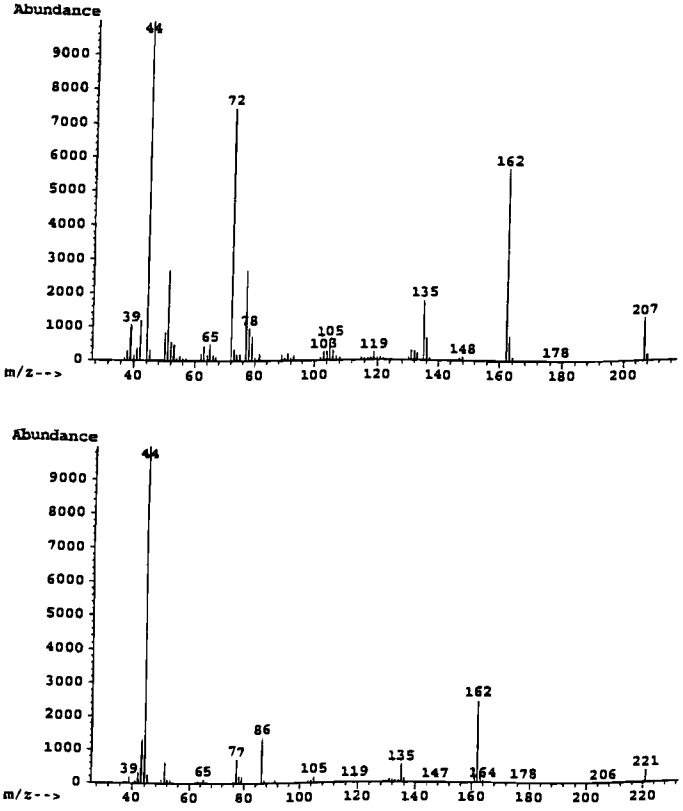

FIG. 14—*Mass spectra of* (upper) *N-formyl-2,3-MDA and* (lower) *N-acetyl-2,3-MDA.*

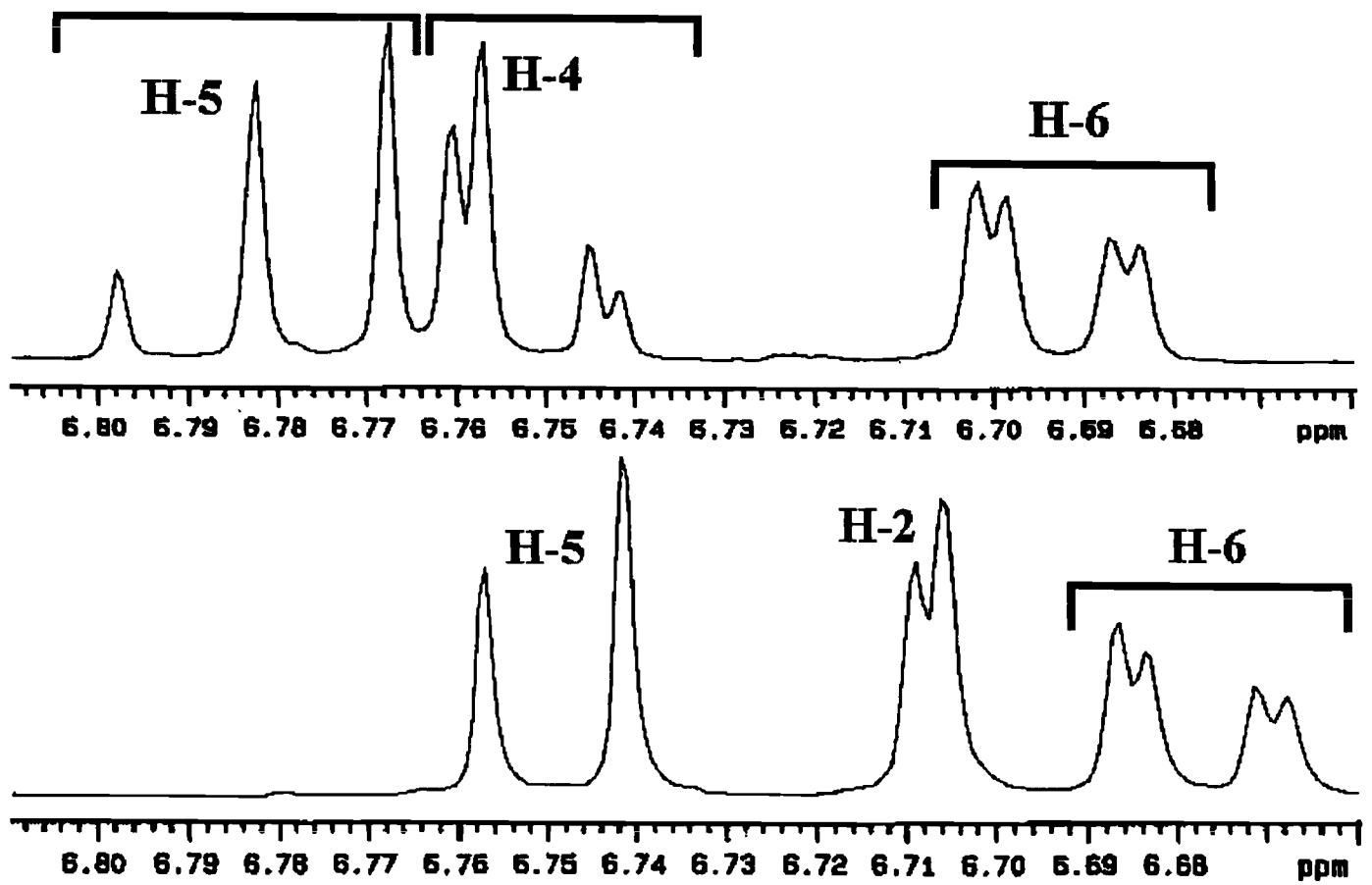

FIG. 15—*500 mHz H^1-NMR spectrum of aromatic region for* (upper) *2,3-MDMA HCl and* (lower) *3,4-MDMA HCl.*

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