# Characterization of the "Methylenedioxy-2-aminoindans"

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**ABSTRACT:** Spectroscopic and chromatographic data are provided for 5,6-(methylenedioxy)-2-aminoindan (commonly referred to as MDAI), 4,5-(methylenedioxy)-2-aminoindan (a positional isomer of MDAI), and their respective synthetic intermediates. Direct comparisons of the analytical data are made to assist forensic chemists in correctly differentiating between these isomers in illicit drug exhibits.

**KEYWORDS:** 5,6-(methylenedioxy)-2-aminoindan, 4,5-(methylenedioxy)-2-aminoindan, MDA analogs, designer drugs, chemical analysis, forensic chemistry.

5,6-(Methylenedioxy)-2-aminoindan, commonly referred to as "MDAI" (henceforth 5,6-MDAI) is a popular "research chemical" for sale over the internet at quantities of 1 gram to 10 kg. Currently, it is not specifically scheduled as a controlled substance in the United States, nor listed by the U.S. Drug Enforcement Administration as an analog of 3,4-methylene-dioxyamphetamine (MDA) [1]. 5,6-MDAI **1**, and its positional isomer 4,5-(methylenedioxy)-2-aminoindan (4,5-MDAI) **2**, were synthesized by the Nichols group [2] in 1990 to compare their pharmacological/neurotoxological properties with 3,4-methylenedioxymethamphetamine (MDMA) **3** (Figure 1). That study found that 5,6-MDAI did substitute for MDMA in MDMA-trained rats. Although 4,5-MDAI did not show significant CNS activity, its close structural association with 5,6-MDAI merits analytical delineation of the two positional isomers. Direct comparisons of the spectroscopic and chromatographic data are presented to assist forensic chemists in correctly differentiating these positional isomers in suspected drug seizures.

## Experimental

*Chemical, Materials, and Reagents*

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI, USA). All other chemicals were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI).

*Gas Chromatography/Mass Spectrometry (GC/MS)*

Mass spectra were obtained on an Agilent Model 5975C quadrupole mass-selective detector (MSD) that was interfaced with an Agilent Model 7890A gas chromatograph (GC). The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 34-600 amu, and at a scan rate of 2.59 scans/s. The GC was fitted with a 30 m x 0.25 mm ID fused-silica capillary column coated with 0.25 μm 100% dimethylpolysiloxane, DB-1 (J & W Scientific, Rancho Cordova, CA). The oven temperature was programmed as follows: initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1) at 280°C. The MSD source was operated at 230°C.

*Infrared Spectroscopy (FTIR)*

Infrared spectra were obtained on a Thermo-Nicolet Nexus 670 FTIR equipped with a single bounce attenuated total reflectance (ATR) accessory. Instrument parameters were: resolution = 4 $cm^{-1}$; gain = 8; optical velocity = 0.4747; aperture = 150; and scans/sample = 16.

*Nuclear Magnetic Resonance Spectroscopy (NMR)*

Proton ($^{1}H$), carbon ($^{13}C$), and 2-dimensional NMR spectra were obtained on an Agilent VNMRS 600 MHz NMR using a 5 mm Protune broad band detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). All compounds were dissolved in deuterochloroform ($CDCl_3$) containing 0.03% v/v tetramethylsilane (TMS) as the 0 ppm reference compound. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to acquire $^{1}H$, proton-

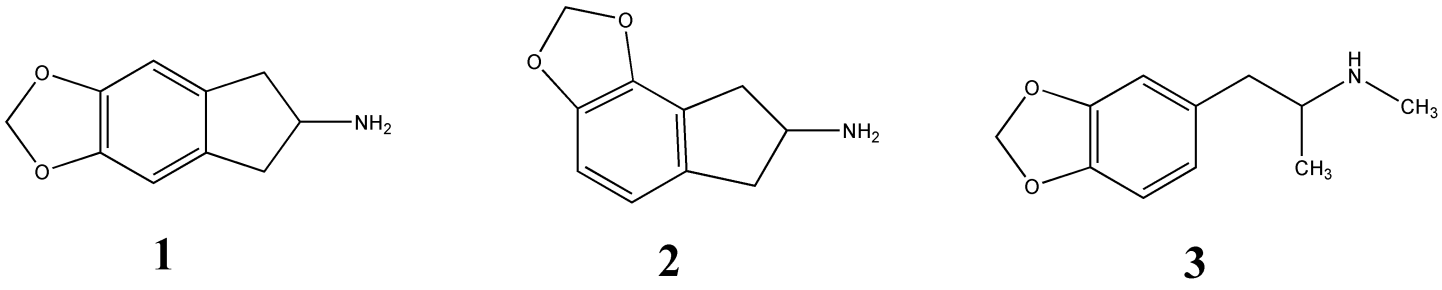


Figure 1 - Structural formulas of (**1**) 5,6-MDAI, (**2**) 4,5-MDAI, and (**3**) MDMA.

decoupled $^{13}C$, and gradient versions of HSQC, HMBC, and 1D-NOESY spectra. Data processing was performed using software from Agilent and Applied Chemistry Development (ACD/Labs, Toronto, Canada). Structure elucidation and the prediction of $^{1}H$ and $^{13}C$ spectra was accomplished using ACD/Labs software.

*Synthesis*

The procedures of Nichols *et al*. [2] were followed (Figures 2 and 3) for the preparation of 5,6-MDAI and 4,5-MDAI. Synthetic details and yield values are not reported.

**Results and Discussion**

GC retention time data for the respective compounds (Figures 2 and 3) are presented in Table 1. The amines were injected as the free bases since the hydrochloride ion-pairs of some phenethylamines undergo thermally induced degradation and chromatograph poorly [3]. 5,6-MDAI and 4,5-MDAI gave identical retention times and could not be resolved under the conditions utilized. The intermediate oximes **6** and **11** would not chromatograph as underivatized; however, each displayed excellent chromatographic properties as their trimethylsilyl (TMS) derivatives.

The FTIR spectra for 5,6-MDAI and 4,5-MDAI hydrochlorides are illustrated in Figure 4. Comparison of the hydrochloride ion pairs reveals similar absorption patterns with the most prominent differences being in the "fingerprint region" of 750-1750 $cm^{-1}$, and presence/absence differences in the C-H out-of-plane bending frequencies between 500-800 $cm^{-1}$. Since the spectra are somewhat similar, we recommend that additional or supplementary spectroscopic methods should be utilized for identification.

Mass spectra for the respective 5,6- and 4,5- substituted isomers and their intermediates are presented in Figures 5-8. Spectra produced from 5,6-MDAI and 4,5-MDAI gave an intense molecular ion at *m/z* 177 (Figure 5), however 4,5-MDAI's molecular ion is also the base peak for that compound (*m/z* 160 is the base peak for 5,6-MDAI). The relative abundances for the remaining ions are quite similar. Therefore, care must be taken in differentiating 5,6-MDAI from

Table 1 - Gas chromatographic retention times ($R_t$) for the methylenedioxy-2-aminoindans and related compounds[a].

| Compound | $R_t$ (min) |
|---|---|
| 1 | 11.53 |
| 1-TMS Derivative | 15.36 |
| 2 | 11.53 |
| 2-TMS Derivative | 15.27 |
| 3 | 10.77 |
| 4 | 13.33 |
| 5 | 13.01 |
| 6-TMS Derivative | 21.28 |
| 7 | 6.86 |
| 8 | 15.02 |
| 9 | 12.73 |
| 10 | 12.55 |
| 11-TMS Derivative | 20.89 |

[a]Conditions given in the experimental section.

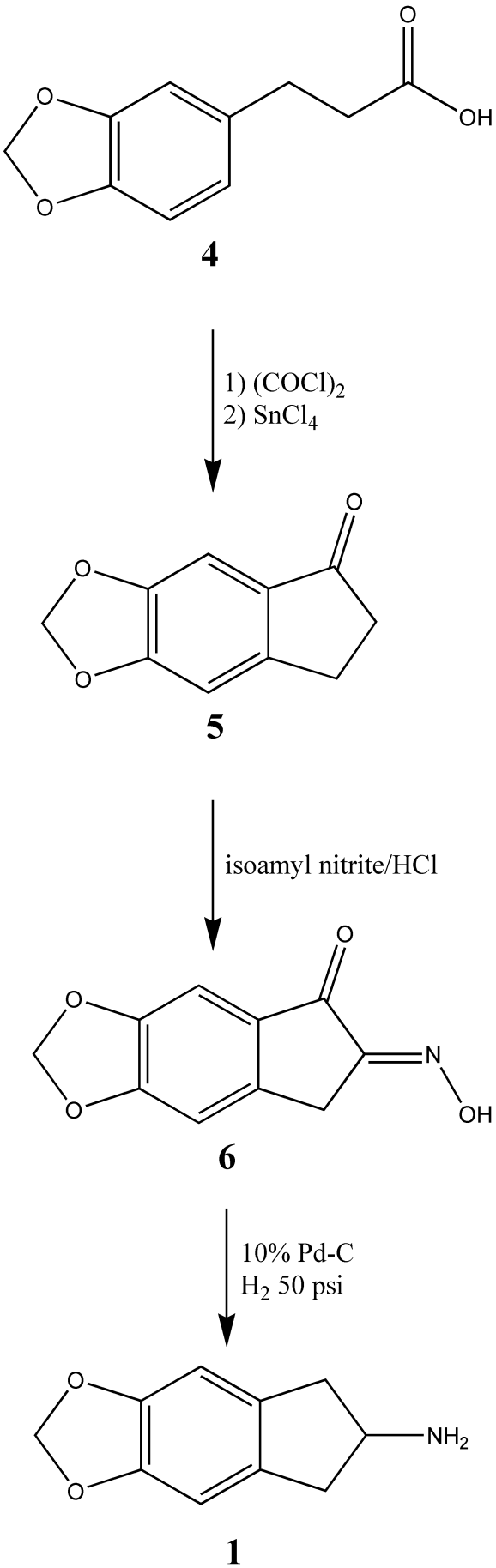


Figure 2 - Synthetic route to 5,6-MDAI.

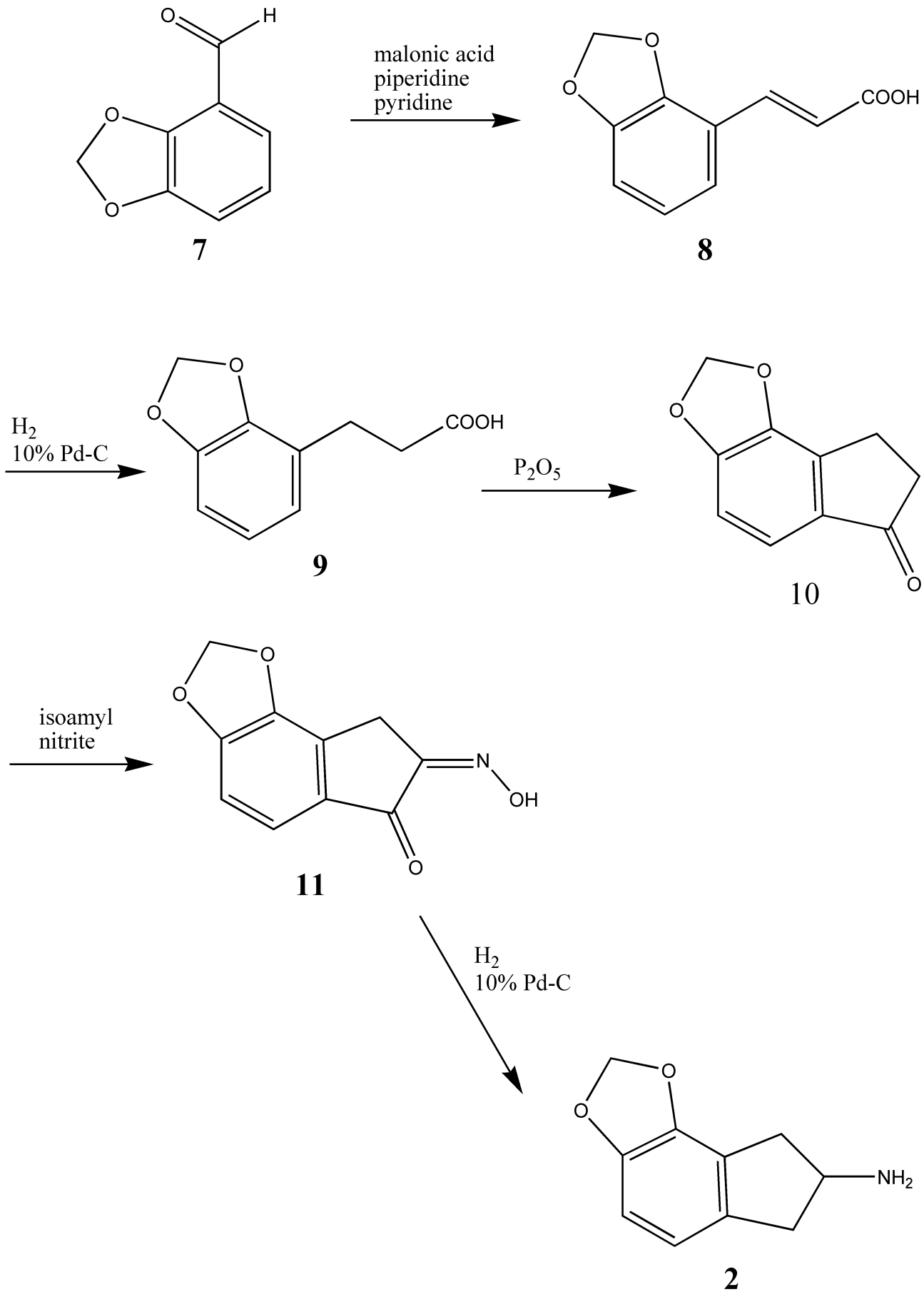


Figure 3 - Synthetic route to 4,5-MDAI.

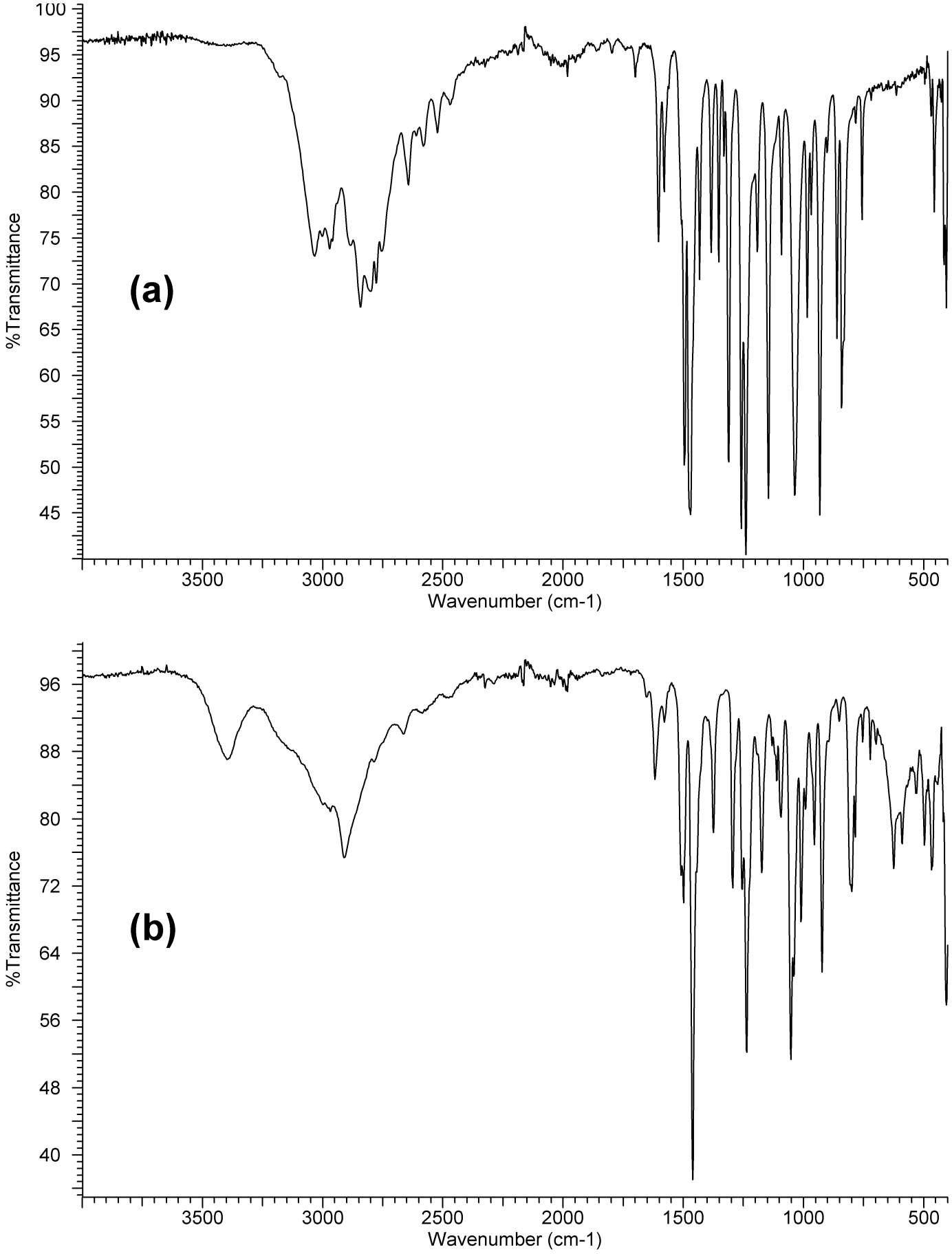


Figure 4 - Infrared spectra of (a) 5,6-MDAI HCl and (b) 4,5-MDAI HCl.

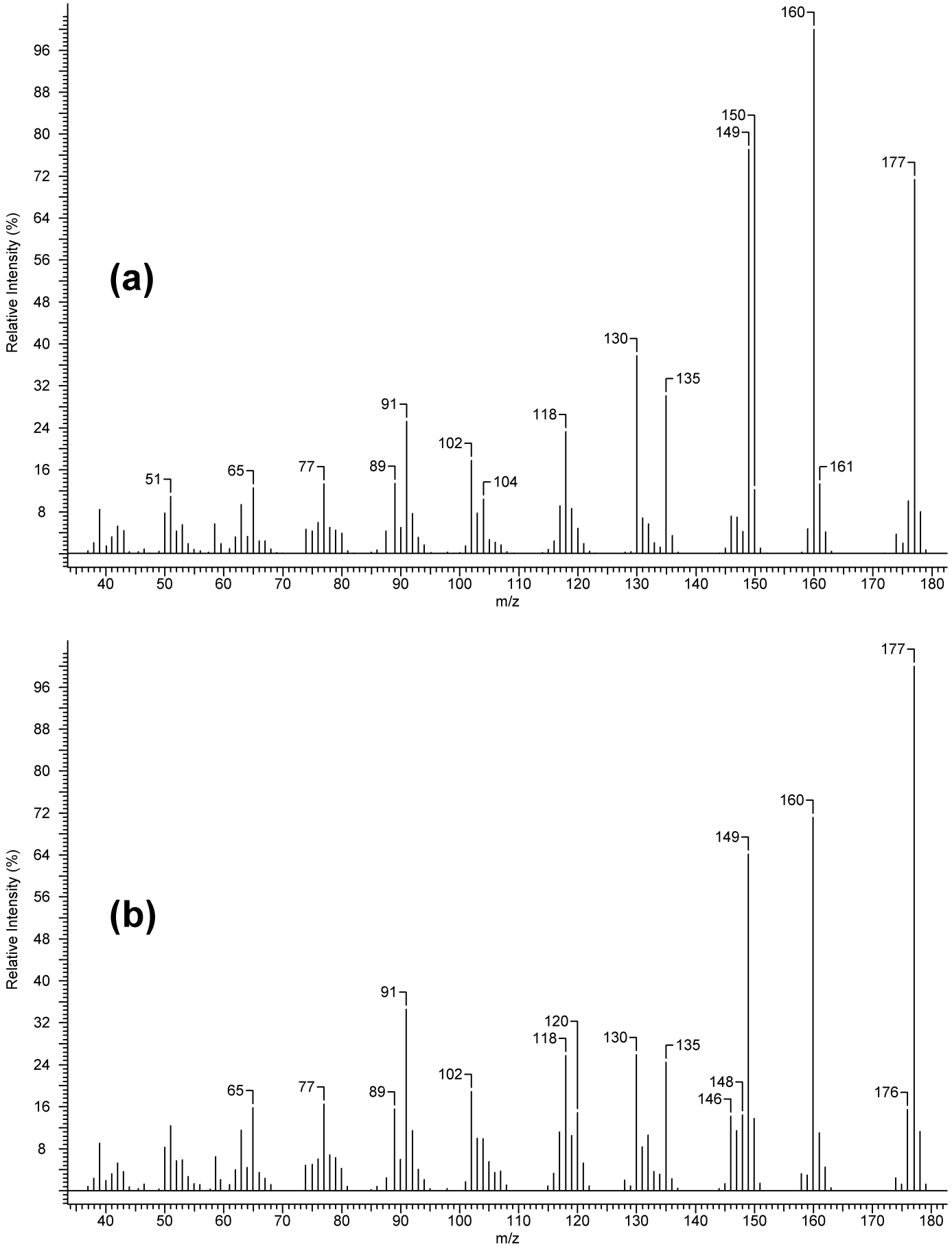


Figure 5 - Electron ionization mass spectra of (a) 5,6-MDAI and (b) 4,5-MDAI.

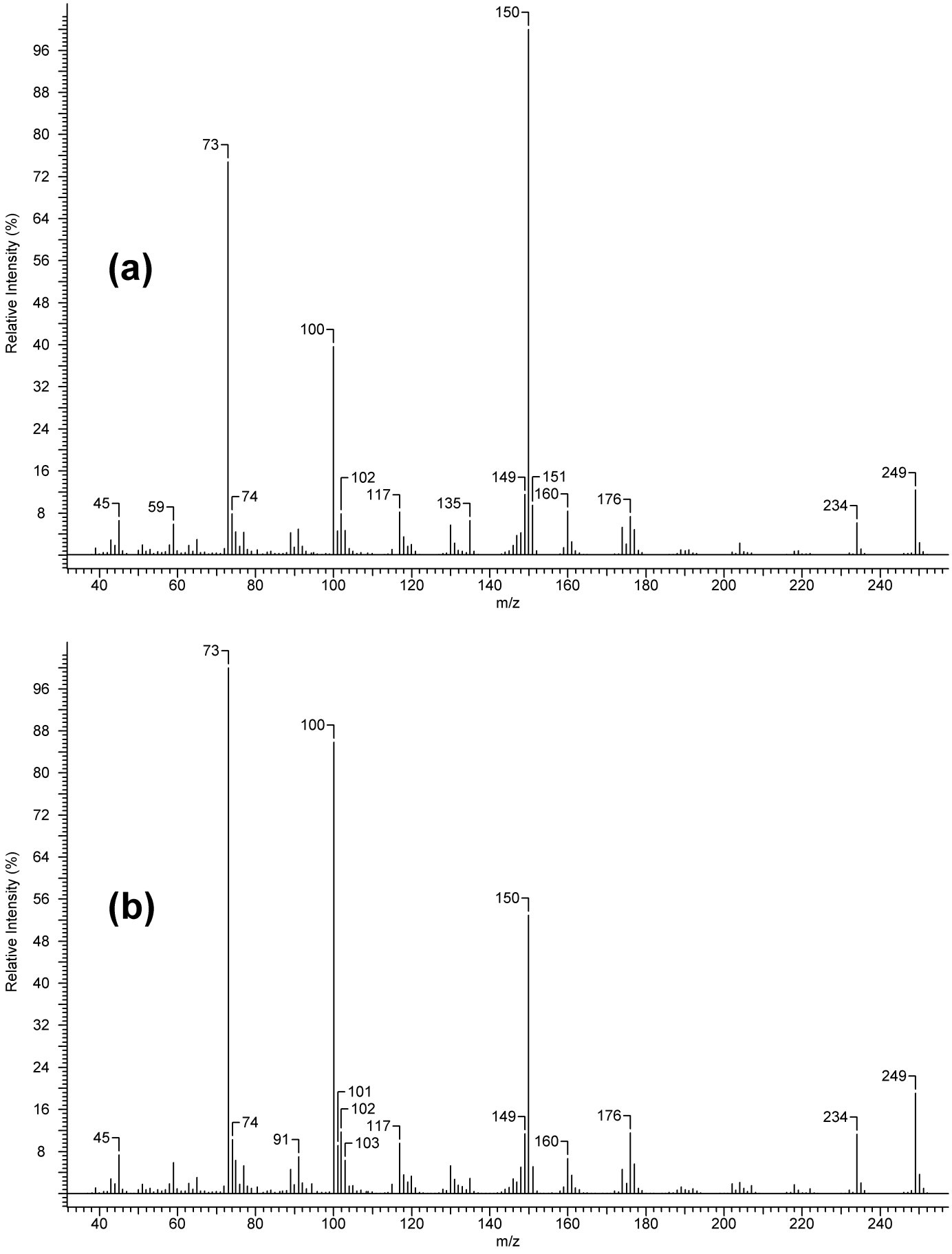


Figure 6 - Electron ionization mass spectra of (a) 5,6-MDAI-TMS and (b) 4,5-MDAI-TMS.

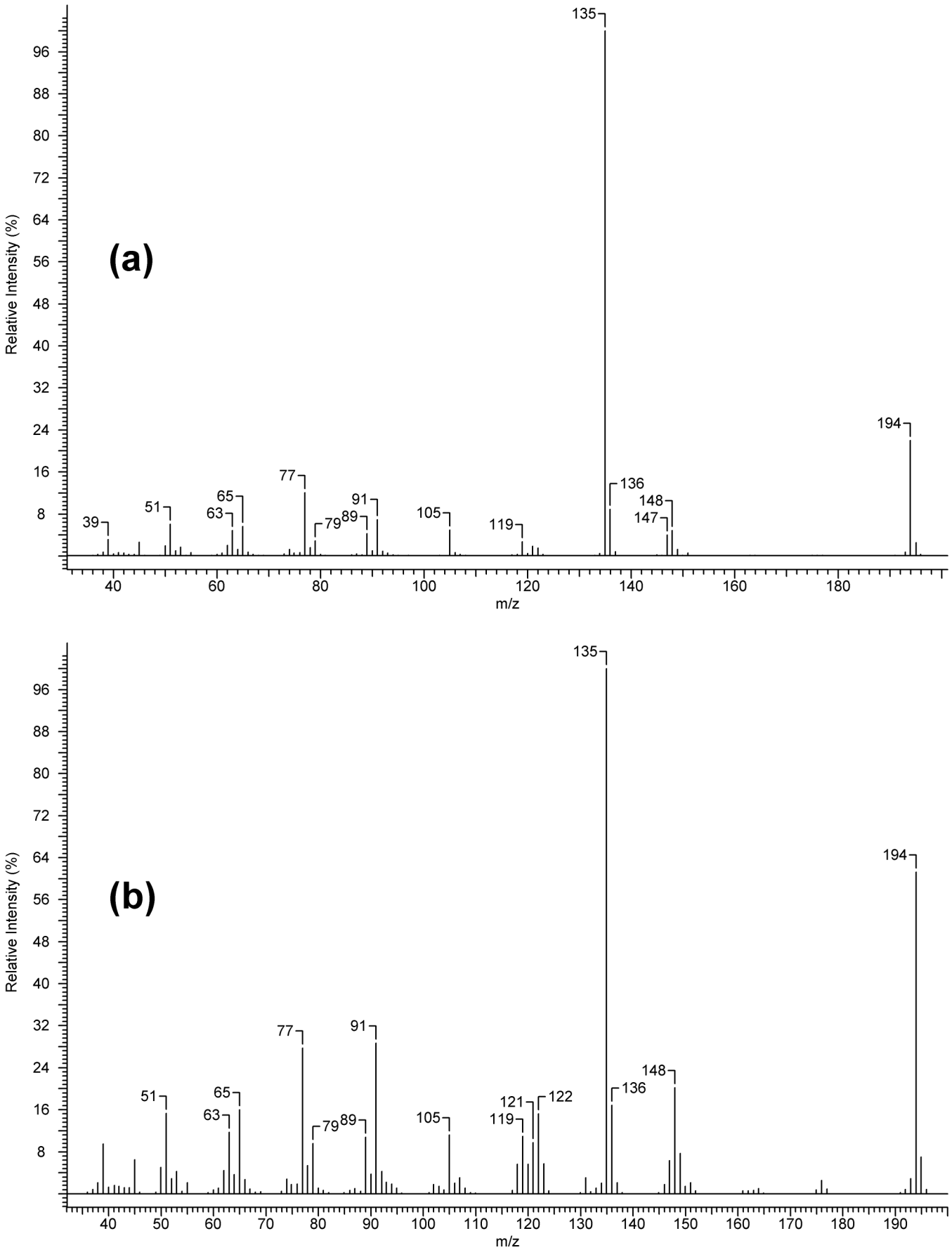


Figure 7 - Electron ionization mass spectra of (a) 3-[3,4-(methylenedioxy)phenyl]propanoic acid and (b) 3-[2,3-(methylenedioxy)-phenyl]propanoic acid.

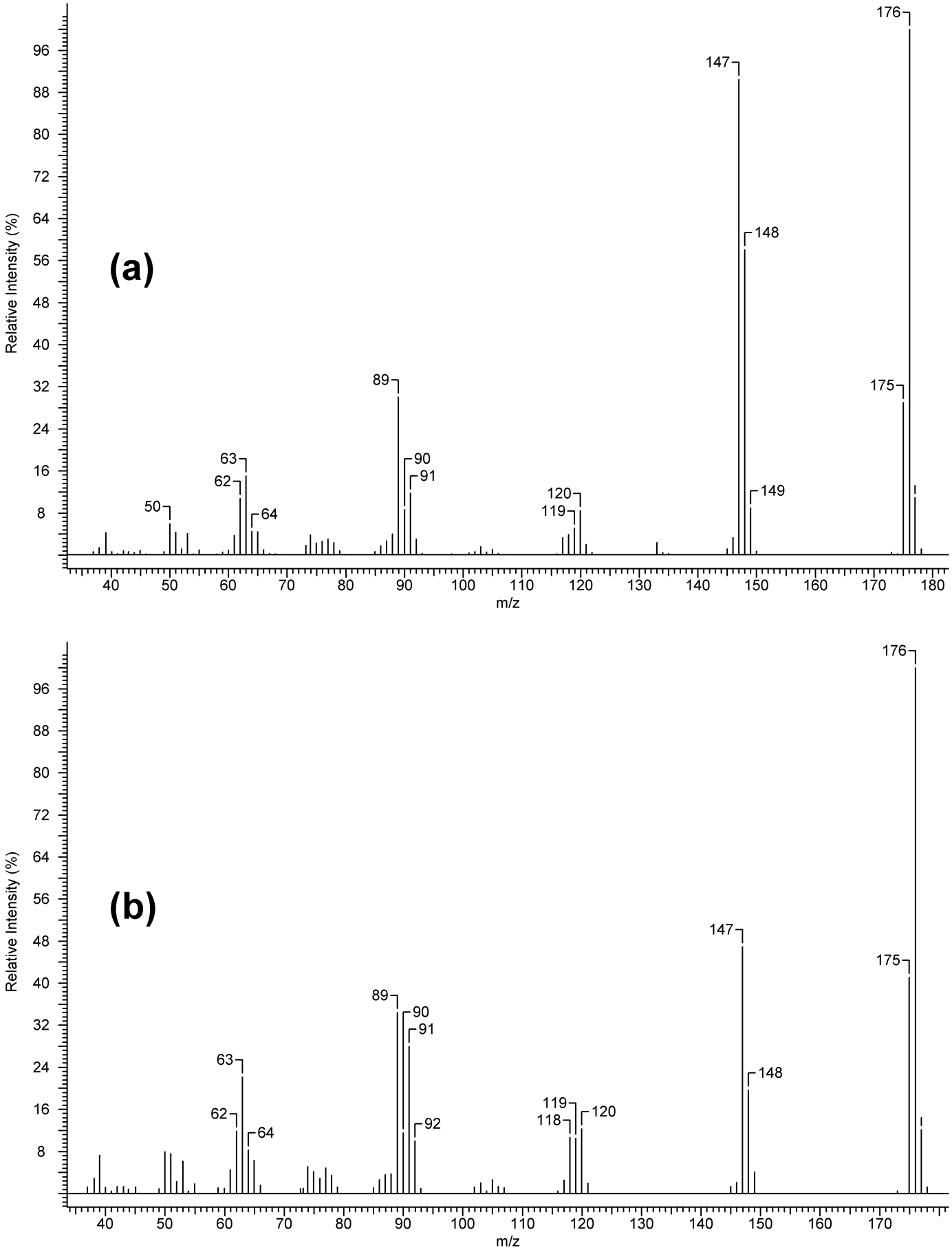


Figure 8 - Electron ionization mass spectra of (a) 5,6-(methylenedioxy)-1-indanone and (b) 4,5-(methylenedioxy)-1-indanone.

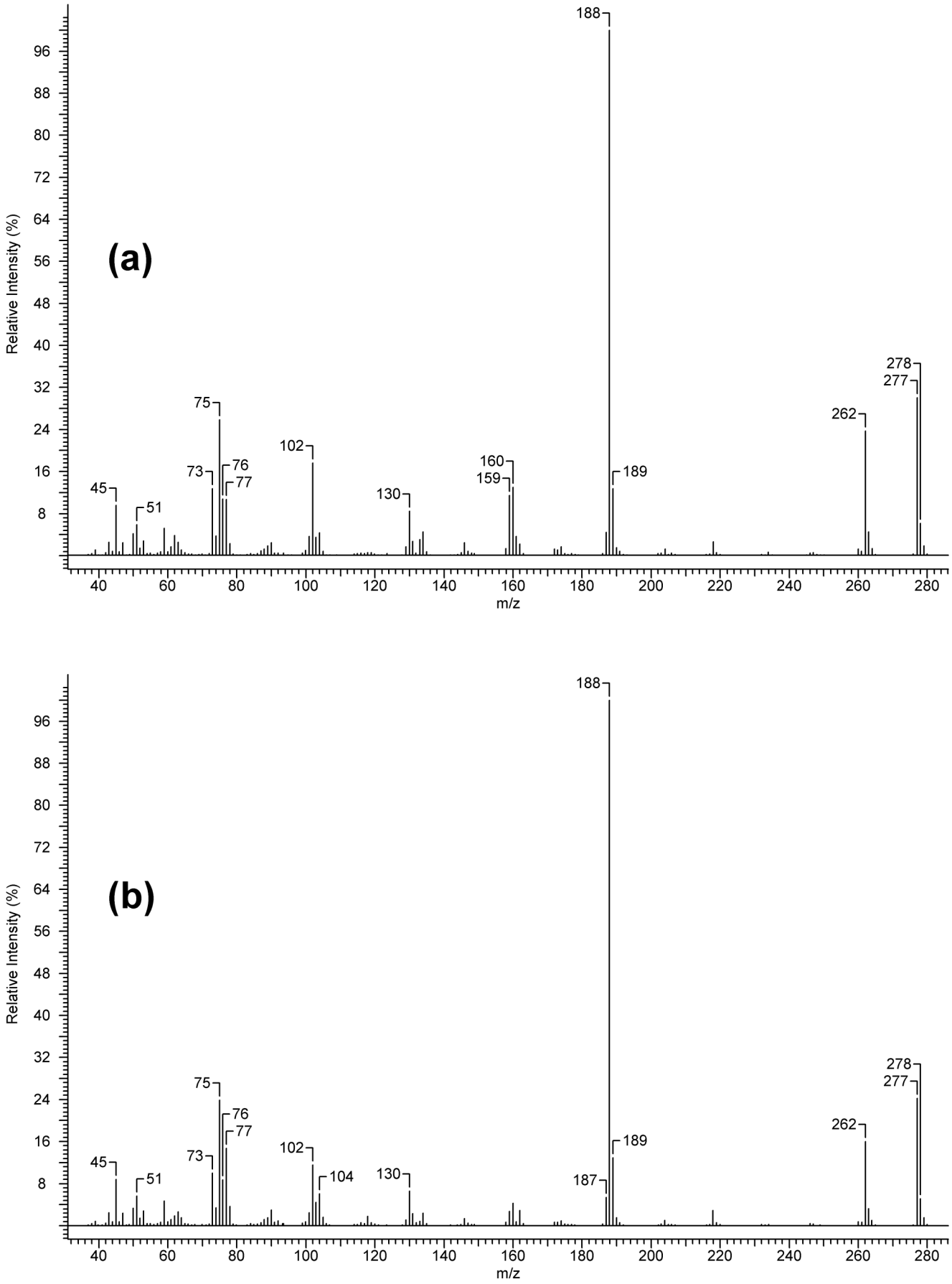


Figure 9 - Electron ionization mass spectra of (a) 2-(hydroxyimino)-5,6-(methylenedioxy)-1-indanone-TMS and (b) 2-(hydroxyimino)-4,5-(methylenedioxy)-1-indanone-TMS.

Table 2 - NMR carbon and proton chemical shifts (in ppm) and splitting patterns of the methylenedioxy-2-aminoindans and related compounds. Samples run in $CDCl_3$ with TMS as the reference compound for 0 ppm.

| | Compound **1** | | Compound **2** | |
|---|---|---|---|---|
| | carbon | proton | carbon | Proton |
| 1 | 43.1 | 2.56 dd (15.3, 4.7 Hz, 1H), 3.07 dd (15.3, 7.0 Hz, 1H) | 42.6 | 2.60 dd (15.8, 5.0 Hz, 1H), 3.13 dd (15.8, 6.5 Hz, 1H) |
| 2 | 53.6 | 3.81 tt (7.0, 4.7 Hz, 1H) | 53.9 | 3.86 ddt (6.7, 6.5, 5.0, 1H) |
| 3 | 43.1 | 2.56 dd (15.3, 4.7 Hz, 1H), 3.07 dd (15.3, 7.0 Hz, 1H) | 39.0 | 2.63 dd (15.6, 5.0 Hz, 1H), 3.10 dd (15.6, 6.7 Hz, 1H) |
| 3a | 134.2 | - | 122.2 | - |
| 4 | 105.5 | 6.66 s (1H) | 143.5 | - |
| 5 | 146.4 | - | 146.3 | - |
| 6 | 146.4 | - | 106.7 | 6.65 d (7.7 Hz, 1H) |
| 7 | 105.5 | 6.66 s (1H) | 116.9 | 6.67 d (7.7 Hz, 1H) |
| 7a | 134.2 | - | 137.1 | - |
| 8 | 100.7 | 5.88 s (2H) | 100.7 | 5.91 s (2H) |

its positional isomer (underivatized) via GC/MS, especially since both compounds elute at the same retention time. However, the mass spectra of 5,6-MDAI and 4,5-MDAI were easily differentiated as their TMS derivatives (Figure 6). Each produced a molecular ion at *m/z* 249, but the relative intensities of ions at *m/z* 73, *m/z* 100, and *m/z* 150 provided clear delineation of the two compounds. The propanoic acids **4** and **9** (Figure 7) each gave base peak at *m/z* 135, and were easily distinguished by the relative abundances of ions at *m/z* 147 and *m/z* 148 and also the relative abundances of the molecular ions at *m/z* 194 (*m/z* 194 for **9** was 2x more intense than for **4**). The indanone intermediates **5** and **10** (Figure 8) each gave a base peak and molecular ion at *m/z* 176, and were easily distinguished by the relative abundances of ions at *m/z's* 147/148 relative to *m/z's* 176/175. Finally, the intermediate oximes **6** and **11** (Figure 9) produced similar spectra, but could be distinguished by the relative abundances of ions at *m/z* 102 and *m/z* 104, and at *m/z* 159 and *m/z* 160.

The proton and carbon chemical shifts and proton splitting patterns for 5,6-MDAI and 4,5-MDAI, are presented in Table 2. Assignments were based on proton and carbon chemical shift values, proton splitting patterns and coupling constants, and correlations between proton and carbon using the HSQC (directly bonded carbon to proton) and HMBC (2, 3, or 4 bond correlation between carbon and proton) experiments. Both 5,6-MDAI and 4,5-MDAI had the following characteristics: 6 aromatic carbons (of which 2 were protonated), plus 3 methylene carbons, and 1 methine. The methylene with carbon at 100.7 ppm with HMBC correlated aromatic carbons indicated a methylenedioxyphenyl moiety was present. The remaining alkyl carbons formed a $CH_2$-CH-$CH_2$ group, with the methine likely bonded to nitrogen (based on its carbon and proton chemical shifts and the presence of a nitrogen based on the mass spectrum data), and the two methylenes bonded to the phenyl (based on HMBC correlations).

5,6-MDAI NMR proton and carbon spectra indicated a symmetric molecule with chemical equivalence for carbons and protons down the axis of symmetry; i.e., 1 and 3, 3a and 7a, 4 and 7, as well as 5 and 6 are chemically equivalent. The singlet at 6.66 ppm integrating to 2 hydrogens indicated that these protons were *para* to each other.

4,5-MDAI NMR proton and carbon spectra showed no chemical equivalence; all of the carbons and protons having unique chemical shifts. The 7.7 Hz doublets at 6.65 and 6.67 ppm indicated that these aromatic protons were adjacent to each other. While only one structure for this compound is possible based on the NMR data, assignments for positions 1, 3, 6, and 7 required confirmation using a NOESY-1D experiment (showing spatially near protons). Excitation of the 3.10 ppm proton resulted in an NOE peak at 6.67 ppm indicating these were near each other (positions 1 and 7, respectively), while excitation of the 3.13 ppm proton did not result in an NOE effect on any other aromatic proton.

**Conclusions**

Analytical data is presented to assist delineating 5,6-MDAI and 4,5-MDAI, as well as their respective synthetic intermediates. Characterization is achieved by either IR, NMR, or mass spectrometry.

**References**


1. Code of Federal Regulations. 21 U.S.C. § 802(32)(A).
2. Nichols DE, Brewster WK, Johnson MP, Oberlender R, Riggs RM. Nonneurotoxic tetralin and indan analogues of 3,4-(methylenedioxy)amphetamine (MDA). J. Med. Chem. 1990;33:703-10.
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