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An unusual clandestine laboratory synthesis of 3,4-methylenedioxyamphetamine (MDA)

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MDA
MMDPPA

ABSTRACT

An unknown compound from a putative clandestine laboratory was analyzed by GC–MS, GC-IRD, IR (ATR), and NMR and found to be α-methyl-3,4-methylenedioxyphenylpropionamide (MMDPPA), an unusual precursor for the synthesis of 3,4-methylenedioxyamphetamine (MDA), a Schedule I controlled substance. A portion of this precursor was subjected to the Hofmann Degradation (i.e., Hofmann Rearrangement) reaction using a sodium hypochlorite solution (bleach) to produce the expected compound, MDA. When excess hypochlorite was used in the reaction, a second, unexpected, compound was formed. Use of the listed instrumentation identified the new material as 2-chloro-4,5-methylenedioxyamphetamine, a compound not previously identified in the forensic literature.

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1. Introduction

In mid-June 2010, the Drug Enforcement Administration (DEA) North Central Laboratory (NCL) was asked to assist in the identification of a substance seized from a putative clandestine laboratory. Instrumental analysis (GC–MS, IR (ATR), GC-IRD, NMR) identified the unknown as α-methyl-3,4-methylenedioxyphenyl-propionamide (MMDPPA). The synthesis of this compound, as well as the synthesis of MDA, has previously been reported by both Ide and Buck [1] and Hey and Williams [2]. The synthesis of MDA was further detailed in a 1990 article [3] that attempted to evaluate the potential for clandestine manufacture of MDA and its analogs based on a number of factors including the ease of synthesis and the commercial availability of the precursors and required chemicals. Of the nine procedures examined in that article, Scheme 9 (Fig. 1), based on the use of a substituted cinnamic acid, was judged the least likely approach. In that scheme, α-methyl-3,4-methylenedioxycinnamic acid (MMDCA) served as the initial precursor while MMDPPA was the final precursor in the five step synthesis. At the time of the evaluation, no legitimate domestic sources could be found either for MMDCA or for the three precursors leading to MMDCA in the manufacture of MDA. The original evaluation was based on the assumption that MMDCA would be the logical starting material for the sequence since relatively simple procedures for the synthesis of compounds of similar structure had been published some years before [4,5]. Since that time, the Internet has become an indispensable tool in many areas, including international commerce. Many chemicals, including MMDPPA, that were previously unavailable or inaccessible in the domestic market are now available for "on-line" purchase.

Prior to 1989, MDA and its structural analogs were conveniently synthesized using readily available 3,4-methylenedioxyphenyl-2-propanone (MDP-2-P) as the primary precursor. In mid-March of that year, MDP-2-P was federally regulated as a List I chemical under Public Law 100-690 (see 21 USC 802) [6a,b], greatly reducing its availability to clandestine laboratory chemists. Because of this, clandestine laboratory operators were forced to synthesize MDP-2-P, primarily from safrole, isosafrole or piperonal, or to use synthesis procedures requiring different precursors such as MMDPPA. In February of 1991, safrole, isosafrole and piperonal

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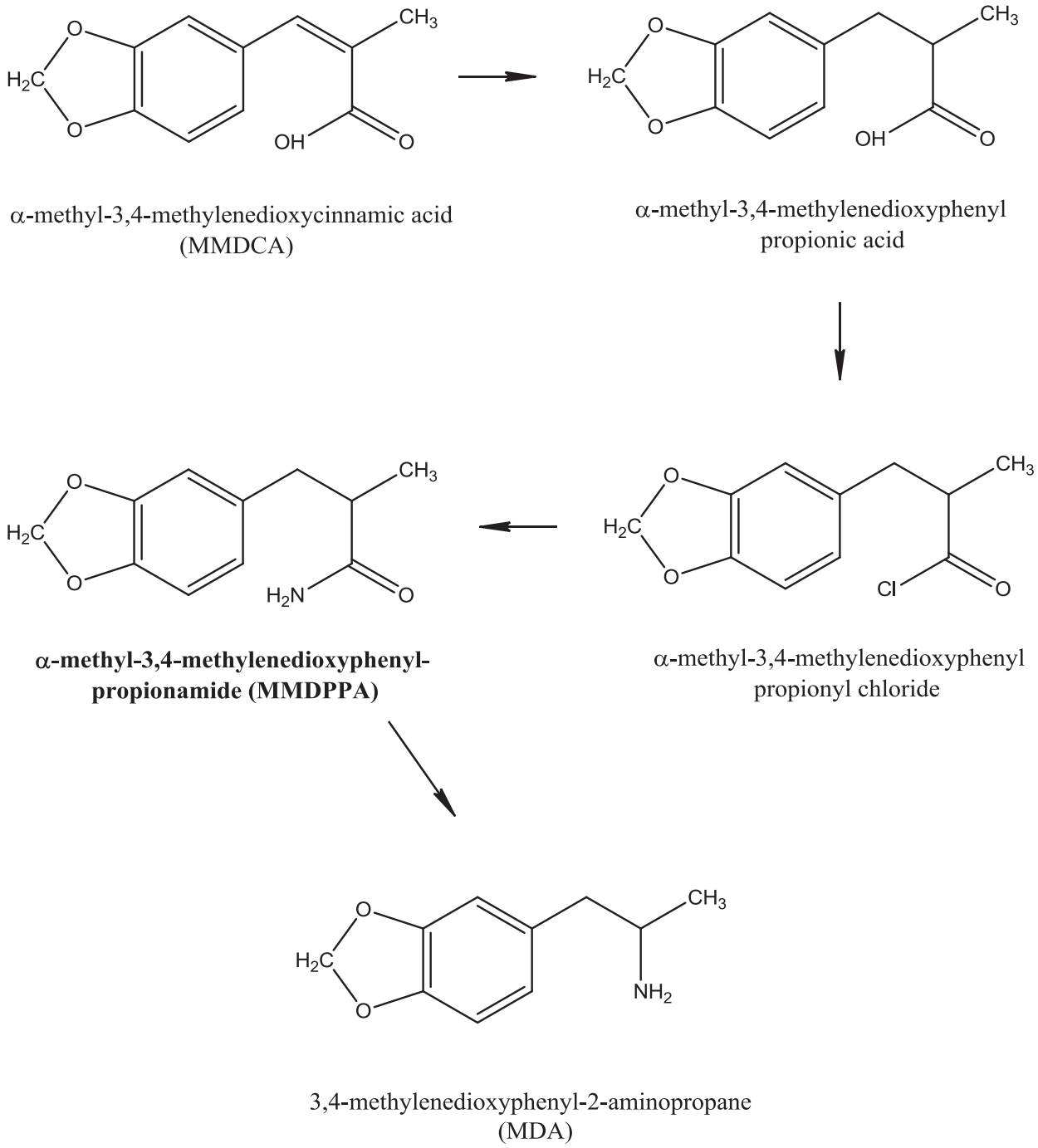

Fig. 1. Original synthesis scheme for production of MDA.
From Ref. [3], Scheme 9.

were also made List I chemicals, further reducing the availability of MDP-2-P. Currently, it is extremely difficult to legitimately obtain MDP-2-P domestically.

MDA first gained popularity in the San Francisco, CA area around 1967 and was listed in the original scheduling of the "Comprehensive Drug Abuse Prevention and Control Act of 1970" [7], as the first entry of Schedule I subtitle "Hallucinogenic Substances". This law is often referred to as the Controlled Substances Act, or CSA. The first report of the synthesis of MDA was published in Berichte in 1910 [8] and later appeared in a 1912 German Patent [9] describing its synthesis from 1-(3,4-methylenedioxyphenyl)-2-bromopropane.

Although MDA appears to be substantially less popular with the drug subculture than its N-methyl analog, 3,4-methylenedioxymethamphetamine (MDMA), it is, however, a unique drug from a pharmacological perspective. Racemic MDA has been shown to have both stimulant and hallucinogenic properties. MDA possesses a chiral center and can exist as [*R*]-(−), [*S*]-(+), or [*R*,*S*]-(−,+) configurations. The [*S*] enantiomer appears to be responsible for the stimulant effect of racemic (i.e., [*R*,*S*]) MDA, whereas

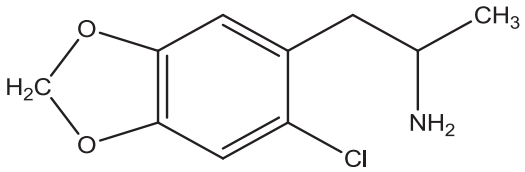

Fig. 2. 2-Chloro-4,5-methylenedioxyamphetamine (2-Cl-4,5-MDA) MW 213.

hallucinogenic activity is attributed to the [*R*] enantiomer [10–12]. With these unique features, MDA still retains a level of popularity for recreational drug users.

Initial analysis of the unknown by mass spectrometry led to the belief that the material contained a methylenedioxy-bridge, and was, therefore, probably a precursor for a MDA analog. Inspection of the infrared spectrum (ATR) indicated that an amide was likely present in the molecule. Piecing together the information provided by these two analytical procedures, MMDPPA became the putative identification of the material. Subsequent proton and carbon 1D and 2D NMR spectra confirmed this hypothesis. For forensic purposes [13], and in order to explore the efficacy of using the analytically identified MMDPPA in a clandestine laboratory setting, several trials of the Hofmann Rearrangement were conducted [2]. Two of these syntheses used an excess of sodium hypochlorite and produced an unexpected compound. Instrumental analysis identified the material as 1-(2-chloro-4,5-methylenedioxyphenyl)-2-aminopropane (2-chloro-4,5-methylenedioxyamphetamine; 2-Cl-4,5-MDA) (Fig. 2). Previous literature describing the calcium hypochlorite oxidation of aldehydes to acids noted instances of aromatic aldehyde chlorination with electron donating substituents on the phenyl ring [14]. Although there have been previous reports of the identification and synthesis of 1-(2-chloro-4,5-methylenedioxy-phenyl)-2-methylaminopropane (2-chloro-4,5-methylenedioxymethamphetamine; 2-Cl-MDMA) [15–17], this is the first reported identification of 2-Cl-MDA in the forensic literature.

2. Materials and methods

2.1. Synthesis

The following syntheses used the general procedure of Hey and Williams [2]. MMDPPA, as received, was recrystallized several times from aqueous ethanol. In the initial trial synthesis, a portion of the powder was added to an excess of sodium hypochlorite (an old generic bleach solution, nominally 5.25% sodium hypochlorite) at 0 °C, and allowed to come to room temperature. The temperature of the mixture was slowly brought to 50 °C and an aqueous solution of potassium hydroxide was slowly added. After the amide had completely dissolved, the reaction temperature was raised to between 75 °C and 80 °C and held for 30 min. At the end of this time, the solution was cooled, extracted with ether, dried with sodium sulfate, and isopropanolic HCl was added. The mixture was evaporated and the solid washed with a small amount of cold acetone producing a small quantity of off-white colored powder. Analysis of this powder showed the material not to be the expected MDA, but a chloro analog determined by MS and NMR to be 2-Cl-4,5-MDA HCl. Repeating the above reaction using stoichiometric quantities of the reactants and a new container of bleach of known concentration (Clorox®, 6.0% sodium hypochlorite) resulted in the formation of MDA HCl in approximately 10–15% greater yield than previously reported [1,2] with no 2-Cl-MDA noted. Additional reactions using excesses of Clorox® produced mixtures of MDA and 2-Cl-MDA. Using a 10-fold excess of sodium hypochlorite led to the destruction of both compounds.

2.2. Instrumentation

2.2.1. GC–MS

GC–MS (EI) analyses were performed on an Agilent 7890A gas chromatograph coupled with an EI mass selective detector Model 5975C fitted with an Agilent HP-5MS column 30 m × 0.25 mm I.D. × 0.25 μm film thickness. Analytical conditions: He carrier gas at a constant flow rate of 1.2 mL/min (41 cm/s) and split ratio of 50:1; oven temperature program 140 °C (2 min) then ramped at 20 °C/min to 320 °C with

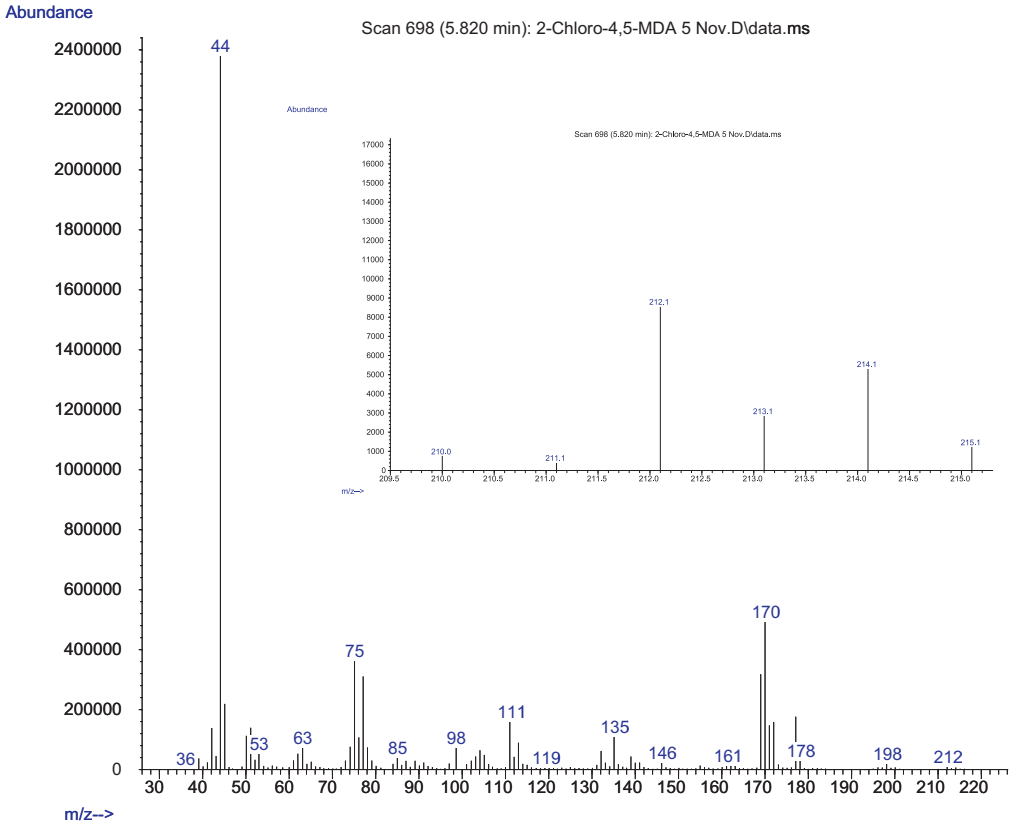

Fig. 3. Mass spectrum of 2-chloro-4,5-methylenedioxyamphetamine (2-Cl-4,5-MDA) with high masses inset.

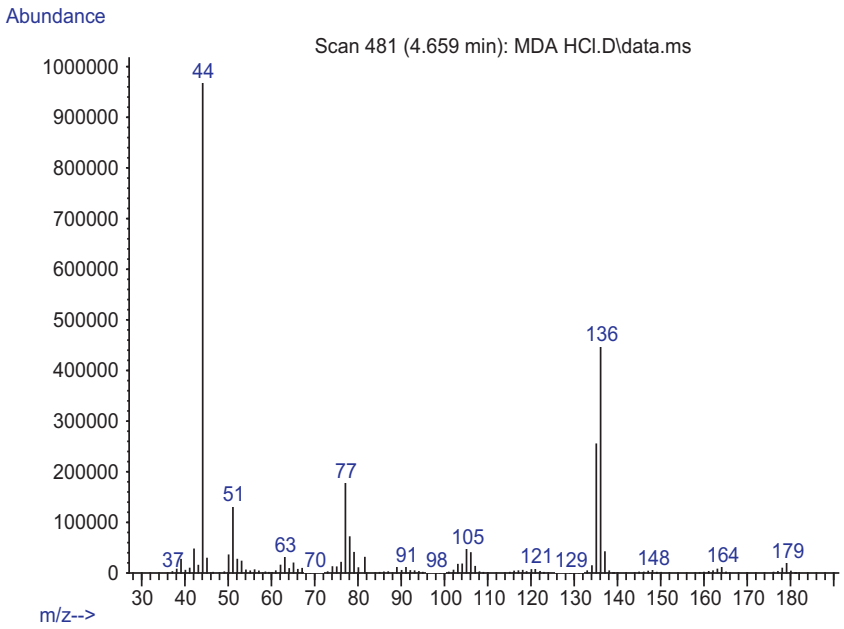

Fig. 4. Mass spectrum of 3,4-methylenedioxyamphetamine (MDA).

a 1 min hold time; injection port: 275 °C; transfer line: 280 °C; source temperature: 230 °C; electron impact mode: 70 eV.

2.2.2. IR (ATR)

Solid phase infrared (IR) spectra were acquired using attenuated total reflection (ATR) with a Nicolet 6700 FT-IR having a Smart DuraScope ATR attachment (single bounce) from 4000 to 600 cm^{-1}. Sixteen scans were collected at a resolution of 2 cm^{-1}.

2.2.3. IR (IRD)

The gas phase infrared (GC-IRD) spectra were obtained from a Bio-Rad IRD II detector interfaced with an Agilent 6890 GC using a 7683 automatic sample injector. Data were acquired in splitless mode on a HP-5 column 30 m × 0.32 mm I.D. × 0.25 μm film thickness. The GC oven was programmed from 80 °C (2 min) and ramped at 20 °C/min to 320 °C with a 3 min hold. Flow cell temperature was 280 °C and the transfer line temperature was 300 °C. Initial flow was 3.0 mL/min in a constant flow mode with a nominal inlet pressure of 14.56 psi.

2.2.4. NMR

NMR spectra were collected using a 400 MHz Varian 400-MR spectrometer and referenced to internal TMS or TSP at 0 ppm. MMDPPA was prepared in deuterochloroform containing TMS, and 2-Cl-4,5-MDA HCl was prepared in deuterium oxide containing TSP. All solvents were obtained from Sigma–Aldrich. The following spectra were obtained of each sample: ^{1}H (proton), ^{13}C (carbon), Distortionless Enhancement by Polarization Transfer (DEPT), Correlation Spectroscopy (COSY), Nuclear Overhauser Enhancement and Exchange Spectroscopy (NOESY), Heteronuclear Single Quantum Coherence (HSQC) and Heteronuclear Multiple Bond Coherence (HMBC).

3. Results and discussion

3.1. GC–MS results

The 2-Cl-4,5-MDA and MDA were analyzed both as the free amine (Figs. 3 and 4) and as the acetylated derivatives (Figs. 5 and 6). The MS of MMDPPA is shown in Fig. 7. GC–MS spectra for all compounds show the characteristic ion at *m/z* 135 typical of the 3,4-methylenedioxybenzyl fragment. 2-Cl-4,5-MDA showed a molecular ion $M^{+\bullet}$ at *m/z* 213 with a $M^{+}/(M+2)^{+}$ cluster in a ratio

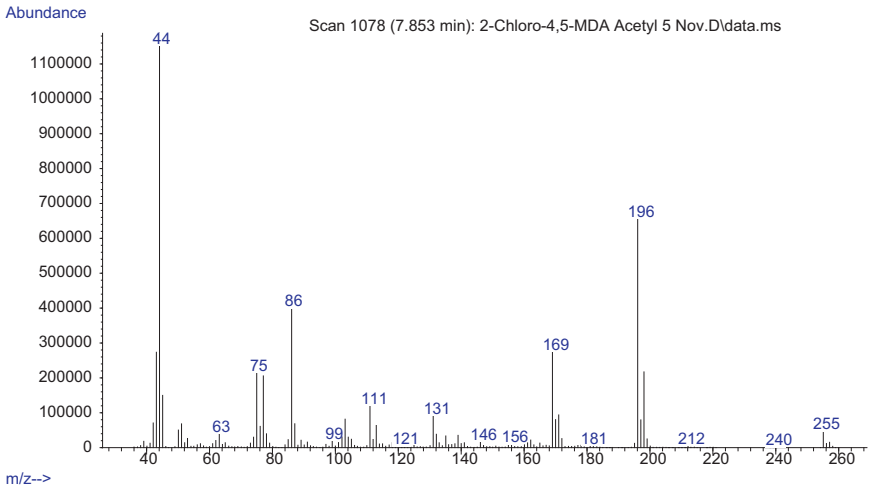

Fig. 5. Mass spectrum of N-acetyl-2-chloro-4,5-methylenedioxyamphetamine (Ac-2-Cl-4,5-MDA).

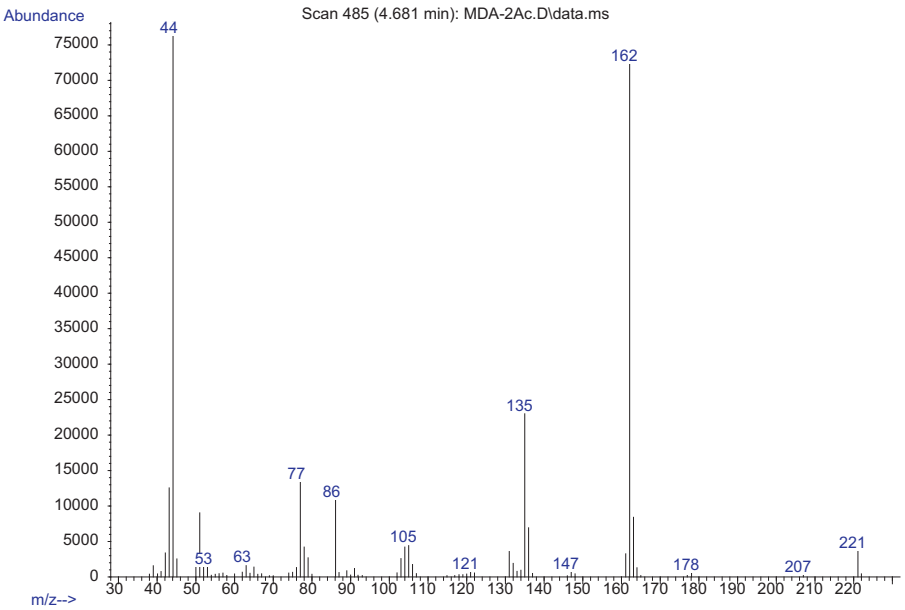

Fig. 6. Mass spectrum of N-acetyl-3,4-methylenedioxyamphetamine (Ac-MDA).

of 100:39, suggestive of mono chlorine substitution. The $(M-1)^+$ ion at *m/z* 212 is significantly higher (3×) than the parent ion. The prominent ion *m/z* 44 was a result of α-fission of the amine side chain $[CH_3CH{=}NH_2]^+$. The ions at *m/z* 198 (M−15) and *m/z* 177 (M−36) are consistent with the loss of a methyl radical and expulsion of chlorine as HCl, respectively. The ion cluster at *m/z* 169/170 is consistent with a chlorinated 3,4-methylenedioxybenzyl fragment with and without hydrogen transfer. The *m/z* 111/113 ions are indicative of $[C_6H_4Cl]^+$.

Acetylated 2-Cl-4,5-MDA shows a molecular ion $M^{+\bullet}$ at *m/z* 255 with the $(M+2)^+$ ion at *m/z* 257 in a ratio of 3:1. Additional ion fragments containing the chlorine atom are found at *m/z* 196/198 $(M-59)^+$, *m/z* 169/171 (chlorinated 3,4-methylenedioxybenzyl)$^+$, and *m/z* 111/113 $[C_6H_4Cl]^+$. The ion *m/z* 86 is a result of α-fission of the acetylated amine side chain $[CH_3CONH{=}CHCH_3]^+$, with the prominent ion *m/z* 44 arising as a result of secondary α-fission and expulsion of a ketene $[CH_2C{=}O]$ from the *m/z* 86 fragment [18,19]. Analogous fragments from the acetylated MDA are found at *m/z* 221 $(M^{+\bullet})$, *m/z* 162 $(M-59)^+$, *m/z* 135 (3,4-methylenedioxybenzyl)$^+$, *m/z* 77 $[C_6H_5]^+$, in addition to the *m/z* 86 and *m/z* 44 ions common to both acetylated compounds.

The $(M-59)^+$ ion in the acetylated derivatives of both chlorinated MDA and MDA is most likely a result of the loss of a neutral acetamide $[CH_3CONH_2]$ with charge migration away from the amide functionality [18,19] (Fig. 8).

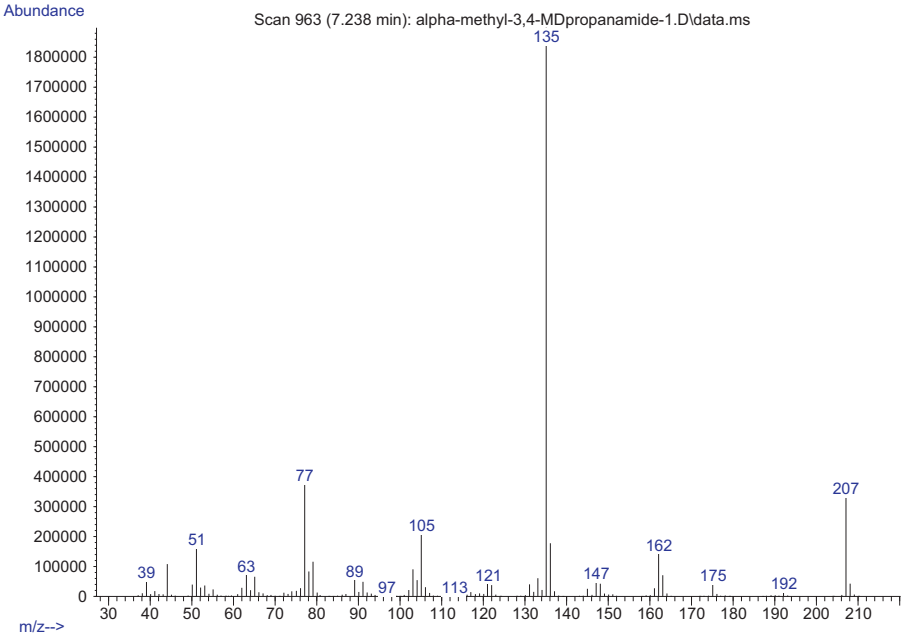

Fig. 7. Mass spectrum of α-methyl-3,4-methylenedioxyphenylpropionamide (MMDPPA).

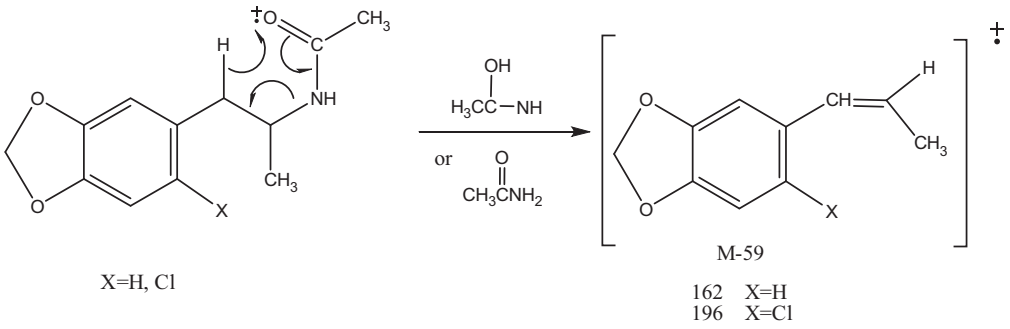

Fig. 8. Origin of the M-59 ion in N-acetyl derivatives of MDA and 2-chloro-4,5-methylenedioxyamphetamine [18].

The EI-MS for the MMDPPA (Fig. 7) shows a molecular ion $M^{+\bullet}$ at m/z 207, a $(M-CH_3)^+$ peak at m/z 192, and a weak α-cleavage of the amide moiety $[O{=}CNH_2]^+$ at m/z 44. The loss of a neutral amide $[HCONH_2]$ from the parent ion is most likely the origin of the $(M-45)^+$ fragment at m/z 162. The characteristic 3,4-methylenedioxybenzyl fragment (as the tropylium ion) at m/z 135 with subsequent loss of formaldehyde gives rise to a suspected troponium ion at m/z 105. Loss of CO from the troponium ion gives rise to the phenyl ion at m/z 77 [20] (Fig. 9).

3.2. GC-IRD results

Figs. 10–14 provide the GC-IRD spectra of MMDPPA, MDA, 2-Cl-4,5-MDA, and the N-acetyl derivatives of MDA and 2-Cl-4,5-MDA, respectively. As with all GC-IRD spectra, bands are broadened and shifted with respect to the condensed phase spectra of the same samples. The shifts result from the elevated temperatures of the samples that lead to different transition energies. Broadening is a result of the elevated temperature and more populated vibrational states around a fundamental vibration than found at room temperature. The vibrational states convolve and this leads to much broader bands. Observed band assignments for GC-IRD spectra were confirmed with the use of the EPA Vapor Phase Library [21]. Assignments for the GC-IRD spectra are summarized in Table 1.

The spectrum of MMDPPA as shown in Fig. 10 exhibits the anti-symmetric and symmetric N–H stretching modes at 3549 and 3430 cm^{-1}, respectively. The amide group shows the typical GC-IRD Amide I C=O stretch (1728 cm^{-1}) at a higher wavenumber than condensed phase spectra, and similarly the Amide II N–H wag (1589 cm^{-1}) is found at a lower wavenumber than in the condensed phase. Other characteristic bands are the phenyl ring mode (semicircle stretch) at 1489 cm^{-1} and phenyl ether C–O stretch at1246 cm^{-1}. At 1443 cm^{-1} there is the methylene scissor; however, this may be overlapped with the methyl anti-symmetric deformation. The methyl symmetric deformation (umbrella mode) is lowered compared to the condensed phase to 1354. It would be expected to find an out-of-plane C–H aromatic C–H wag for this sample and the band at 810 cm^{-1} is consistent with 1,2,4-trisubstitution (i.e., 1,3,4-trisubstitution) on the phenyl ring.

Fig. 11 is the spectrum of MDA, and the N–H stretching bands at ~3400 cm^{-1} are missing, but this is common for amines and amides in GC-IRD spectra. Other bands are consistent with those found in Fig. 10 and are summarized in Table 1, but the amide bands are absent as anticipated. The aromatic C–H wag is most likely hidden by the band at 795 cm^{-1}. The spectrum of 2-chloro-4,5-methylenedioxyamphetamine (Fig. 12) is complicated by the presence of the strong electronegative chlorine on the phenyl. Electronic interactions between the phenyl ring and chlorine lead to shifts in the band positions. The aromatic semicircle stretch appears to be lowered to 1477 cm^{-1}. The aromatic ether C–O stretch at 1227 cm^{-1} is also lower. It would be expected that the methyl symmetric deformation would not be affected by the presence of the chlorine, but no appropriate band is discernible. The remaining bands are consistent with those found in Fig. 10, except that the aromatic wag is raised to 841 cm^{-1}, which is consistent with 1,2,4,5-tetrasubstitution.

The spectrum of N-acetyl-MDA is presented in Fig. 13. The assignments are shown in Table 1. A new band is present, the carbonyl stretch that is found at 1713 cm^{-1}. It would be expected to see an additional methyl deformation from the acetyl functional group, and it should be lowered by the attachment to the carbonyl. It may be present as the lower shoulder on the band at 1369 cm^{-1}. The last GC-IRD spectrum (Fig. 14) is of N-acetyl-2-chloro-4,5-methylenedioxyamphetamine. Comparison of the assignments for Figs. 12 and 13 shows the assignments are consistent with the structure.

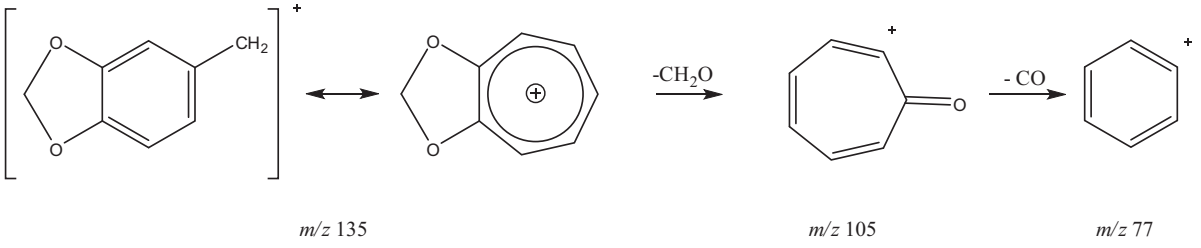

Fig. 9. Formation of m/z 105 and m/z 77 from 3,4-methylenedioxybenzyl fragment (m/z 135) [20].

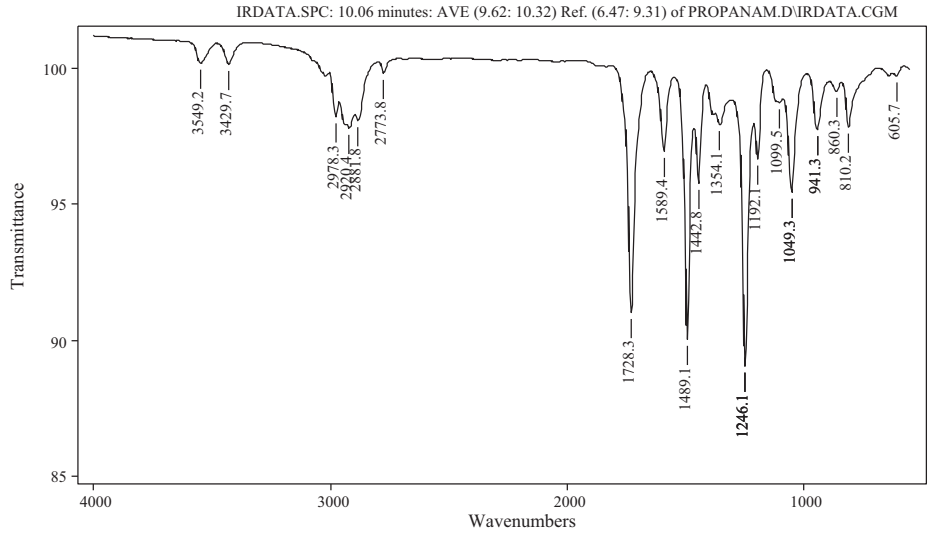

Fig. 10. GC-IRD of α-methyl-3,4-methylenedioxyphenylpropionamide (MMDPPA).

3.3. IR (ATR) results

An attenuated total reflection infrared (ATR IR) spectrum of MMDPPA is shown in Fig. 15. The overall appearance of the spectrum suggests a constrained molecule, probably aromatic in nature. The bands at 3369 and 3179 cm^{-1} are the anti-symmetric and symmetric N–H stretches of a primary amine or amide, respectively. The presence of a primary amide is confirmed by the presence of the Amide I band (1654 cm^{-1}, C═O stretch) and the Amide II (1631 cm^{-1}, NH_2 bend, i.e., "scissors deformation"). The relative intensity of these four bands indicates a phenyl-amide structure. A weak band at 1608 cm^{-1} is indicative of an aromatic quadrant stretching mode and the semicircle stretching mode is found as a degenerate pair of bands at 1501 and 1440 cm^{-1}. At 1242 cm^{-1} is the C–O stretch for aromatic ethers. The band at 1042 cm^{-1} is associated with an aromatic ring stretching mode, however, this band is often variable in position and intensity. Nonetheless, it appears to be present in this spectrum. Substitutions on the aromatic ring can often be determined from the C–H out-of-plane wagging mode and the ring pucker mode. The band at 811 cm^{-1} represents the wagging mode, but no ring puckering mode is present, which is consistent with a number of substitutions on the ring, including 1,2,4-trisubstitution (i.e., 1,3,4-trisubstitution). A band at 858 cm^{-1} confirms 1,2,4-trisubstitution. The bands in the 2900–2750 cm^{-1} region show that a portion of the sample is protonated as those bands are due to the presence of a hydrogen coordinate covalent bond stretch. The N–H stretching region around 3400 cm^{-1} indicates that the majority of the sample is not protonated.

Fig. 16 is the ATR IR spectrum of MDA HCl. Many of the bands are the same as those found in Fig. 15, with small wavenumber shifts, but clearly the amide bands at 3369, 3179, 1654, and 1631 cm^{-1} are not present. The amino group is fully protonated and the characteristic primary ammonium pattern is seen in the 3000–2500 cm^{-1} region. There is an interesting pattern of bands from 1390 to 1350 cm^{-1}. This is the methyl deformation region and a band is expected at 1378 cm^{-1} and one is found at 1377 cm^{-1}. Unfortunately C–Cl stretches are unreliable in infrared

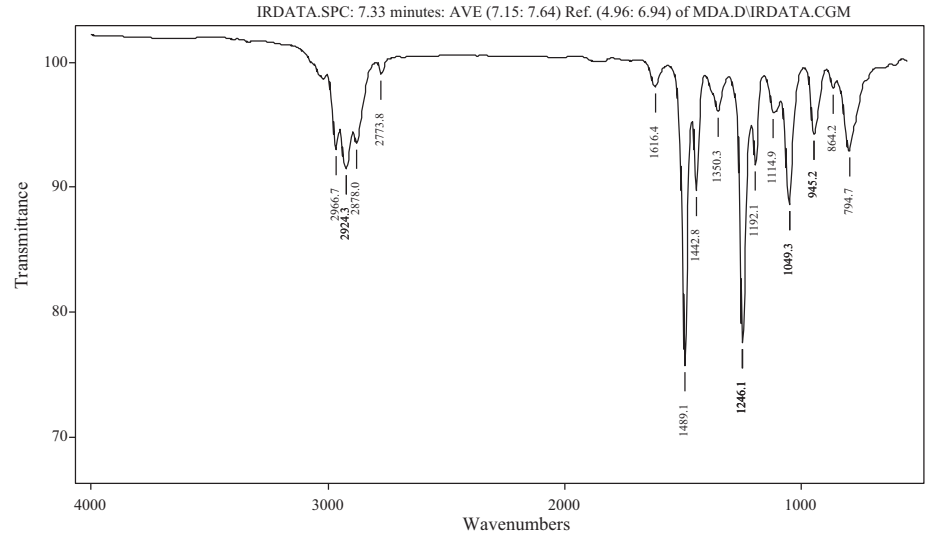

Fig. 11. GC-IRD of 3,4-methylenedioxyamphetamine (MDA).

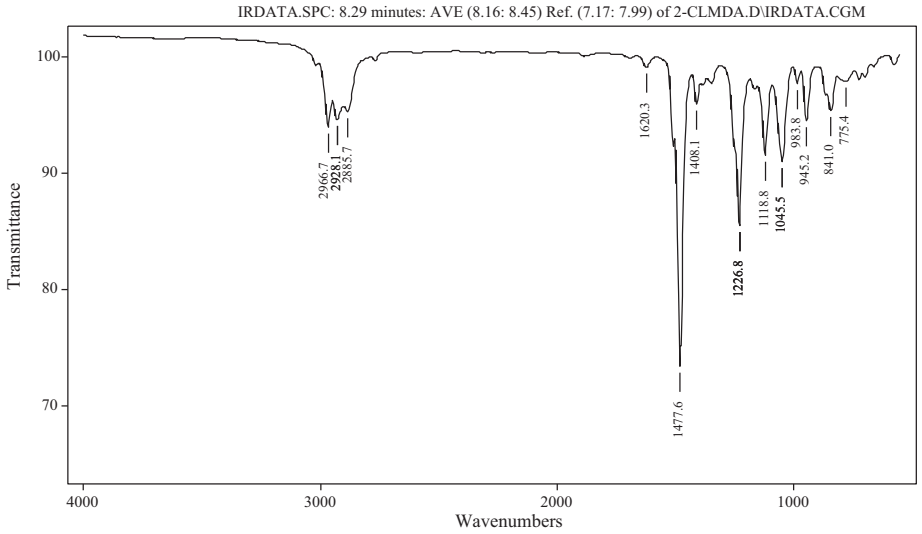

Fig. 12. GC-IRD of 2-chloro-4,5-methylenedioxyamphetamine (2-Cl-4,5-MDA).

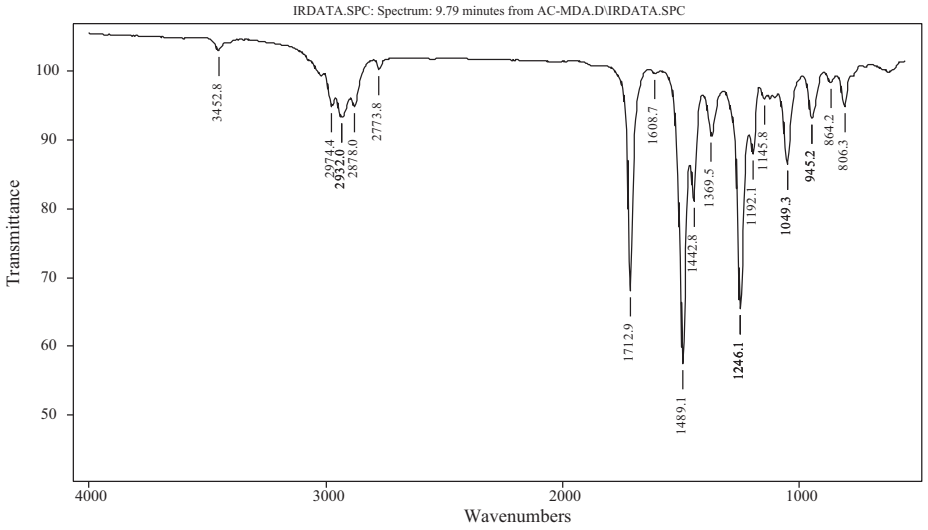

Fig. 13. GC-IRD of N-acetyl-3,4-methylenedioxyamphetamine (Ac-MDA).

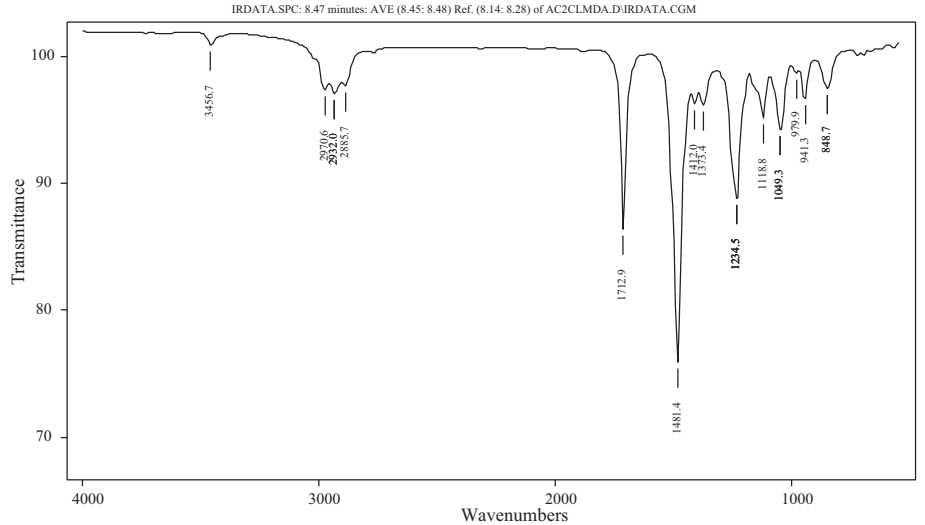

Fig. 14. GC-IRD of N-acetyl-2-chloro-4,5-methylenedioxyamphetamine (Ac-2-Cl-4,5-MDA).

Table 1
Functional group assignments for Figs. 10–14 in cm^{-1}.

Functional group	Fig. 10	Fig. 11	Fig. 12	Fig. 13	Fig. 14
NH_2 antisymm stretch	3549				
N–H stretch				3453	3457
NH_2 symm stretch	3430				
Amide I	1728				
C=O stretch				1713	1713
Amide II	1589				
NH_2 scissor		1616	1620		
Aromatic semicircle stretch	1489	1489	1477	1489	1481
CH_2 scissor	1443	1443		1443	
CH_3 symm deformation	1354	1350		1369	1373
Aromatic ether C–O stretch	1246	1246	1227	1246	1235
Aromatic ring stretch	1049	1049	1045	1049	1049
Aromatic C–H wag	810		841		849

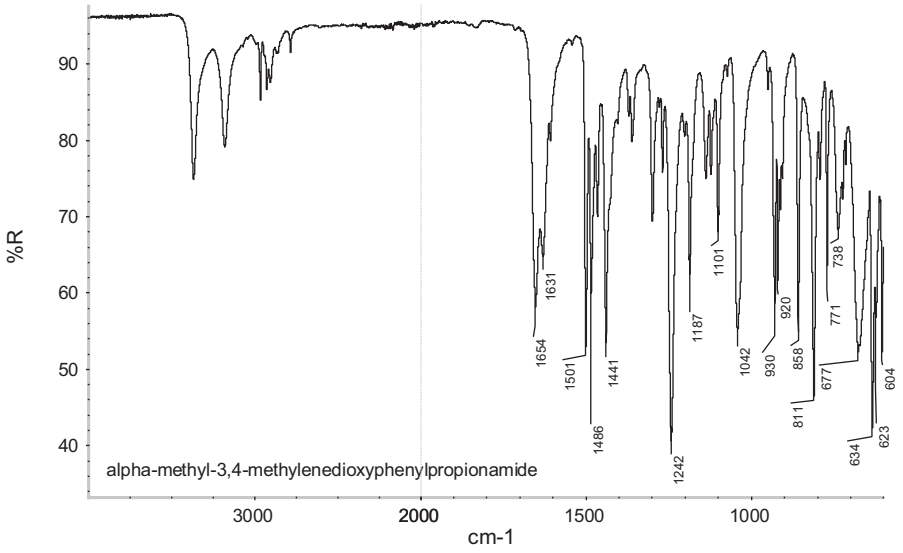

Fig. 15. IR (ATR) of α-methyl-3,4-methylenedioxyphenylpropionamide (MMDPPA).

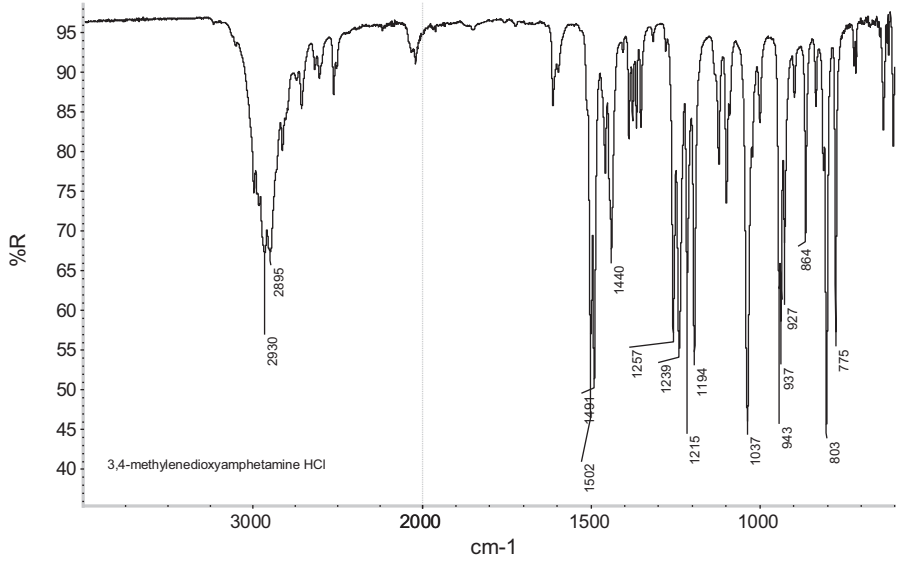

Fig. 16. IR (ATR) of 3,4-methylenedioxyamphetamine HCl (MDA HCl).

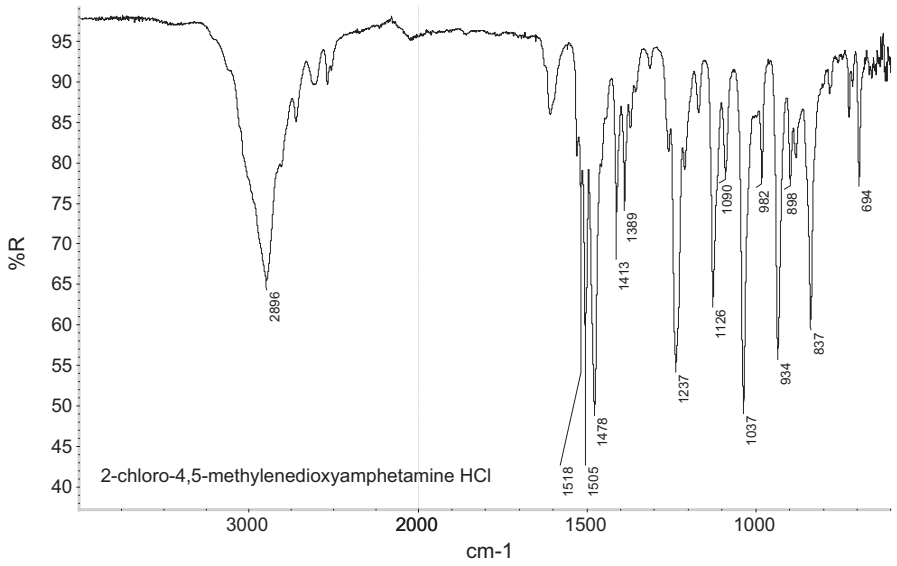

Fig. 17. IR (ATR) 2-chloro-4,5-methylenedioxyamphetamine HCl (2-Cl-4,5-MDA HCl).

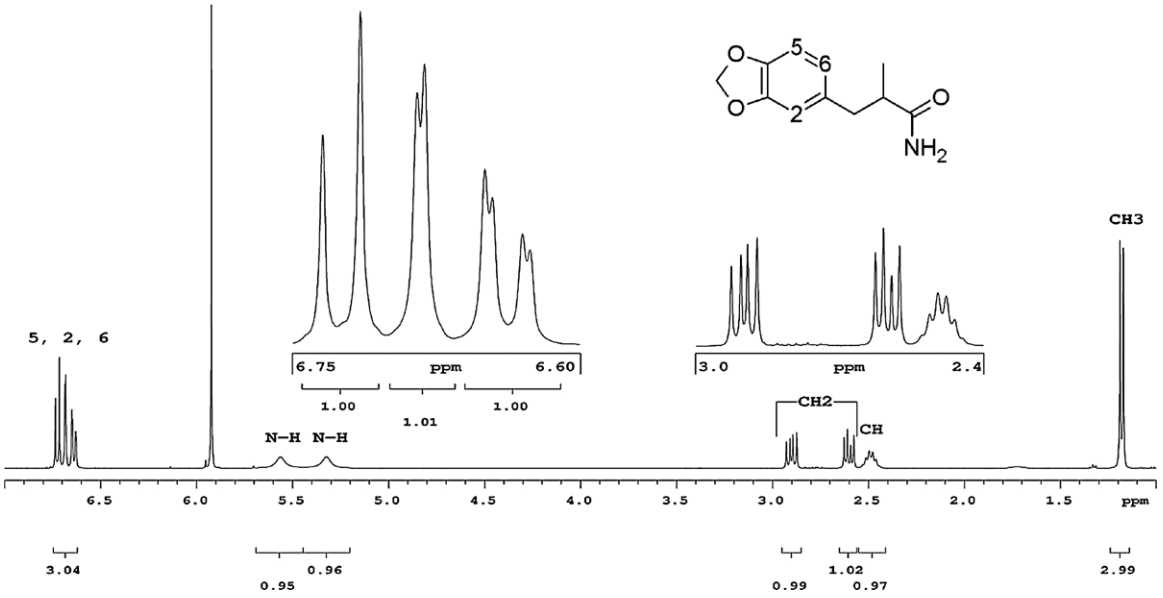

Fig. 18. Proton NMR of α-methyl-3,4-methylenedioxypropionamide (MMDPPA).

spectra. They occur in the 800–600 cm^{-1} range, and while they are strong bands, their positions are highly variable. The assignment of such a band in the spectrum of 2-Cl-MDA (Fig. 17) would be speculative. The spectral assignments are very similar to those for Fig. 16, except the aromatic ether C–O stretch is shifted slightly to 1237 cm^{-1} and the symmetric band of the aromatic semicircle stretch is missing, or much weaker and hidden by the band at 1478 cm^{-1}. The methyl deformation is found at 1371 cm^{-1}. 1,2,4,5-Tetrasubstitution is indicated by the band at 837 cm^{-1}.

Table 2
Proton NMR chemical shifts (ppm), peak shape and coupling constants (Hz) of α-methyl-3,4-methylenedioxphenylpropionamide (MMDPPA) prepared in $CDCl_3$ and referenced to TMS at zero ppm. d, doublet; dd, doublet of doublets; s, singlet; br s, broad singlet; ddq, doublet of doublet of quartets.

2	6.68 (d 1.6)
5	6.72 (d, 7.9)
6	6.63 (dd, 7.8, 1.6)
$O–CH_2–O$	5.92 (s)
NH_2	5.32 (br s), 5.56 (br s)
CH_2	2.90 (dd, 8.0, 13.6)
	2.60 (dd, 6.7, 13.6)
CH	2.49 (ddq, 8.0, 6.7, 6.7)
CH_3	1.179 (d, 6.7)

3.4. NMR results

The proton spectrum of MMDPPA (Fig. 18) demonstrates a spectrum similar to MDA, except for an observed shifting of the CH and CH_2 groups. The aromatic protons can be assigned based upon their splitting patterns (Table 2). Protons five and six demonstrate a larger coupling, and protons two and six have a smaller long-range coupling. The aliphatic protons can be assigned via peak integration. Their connectivity is demonstrated with the COSY spectrum. The NOESY spectrum confirms that the two N–H protons are attached to the same nitrogen atom. The carbon spectrum (Fig. 19) is also similar to MDA, except for the additional peak at

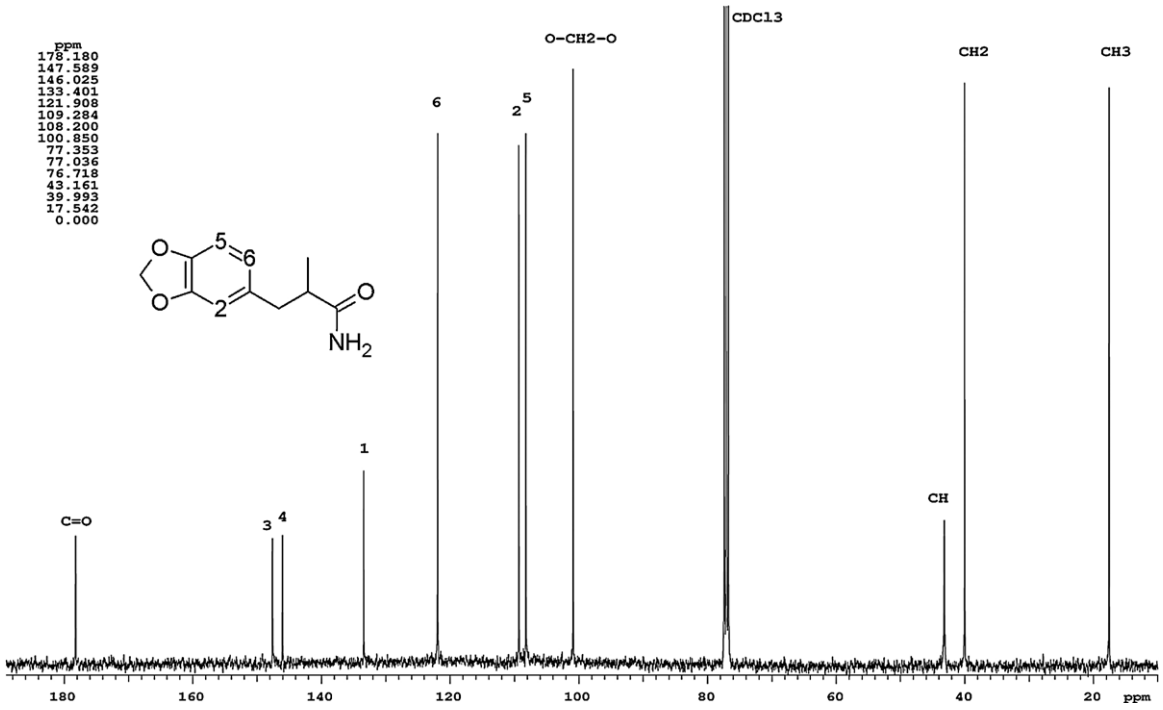

Fig. 19. Carbon NMR of α-methyl-3,4-methylenedioxypropionamide (MMDPPA).

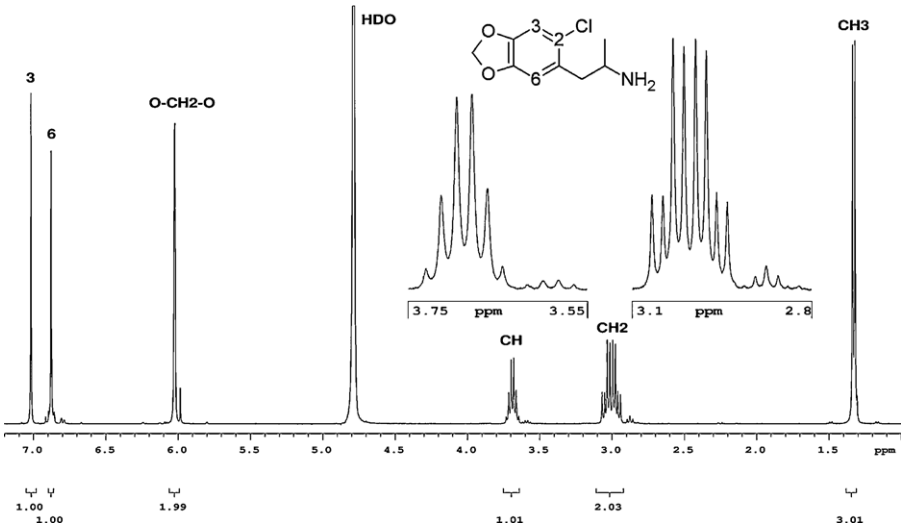

Fig. 20. Proton NMR of 2-chloro-4,5-methylenedioxyamphetamine (2-Cl-4,5-MDA) HCl.

178 ppm, which is consistent with a carbonyl from an amide group. Based on the proton spectrum assignment, the corresponding carbon atoms were assigned using the proton–carbon single bond correlations demonstrated with the HSQC experiment. The DEPT spectrum confirmed the aliphatic carbon designations. A limitation of the DEPT experiment is highlighted with the peak in the quaternary region at 101 ppm, which is due to incomplete subtraction of the large methylene carbon peak at this chemical shift. The quaternary carbon lines were assigned using the HMBC experiment. Proton five demonstrates interaction with carbons one and three, while proton two has correlation with carbons four and six. The carbonyl exhibits interaction with one of the CH_2 protons as well as the CH_3 protons, indicating that it is attached to the carbon of the CH group. The NMR spectra verify the unknown substance to be MMDPPA.

NMR spectra of the putative chloro-MDA were obtained for structural confirmation, especially pertaining to the position of the chlorine on the aromatic ring. The proton and carbon spectra (Figs. 20 and 21) do indicate a small amount of MDA; however the majority of the product has a structure with only two aromatic protons that are both singlets, indicating that a chlorine atom is attached to the two position, since neither ortho nor meta coupling between the aromatic protons is indicated. Chlorine has also been found to preferably substitute at the two position on the ring of MDMA [15,16]. The chemical shift and coupling information can be found in Table 3. The carbon spectrum indicates the loss of the

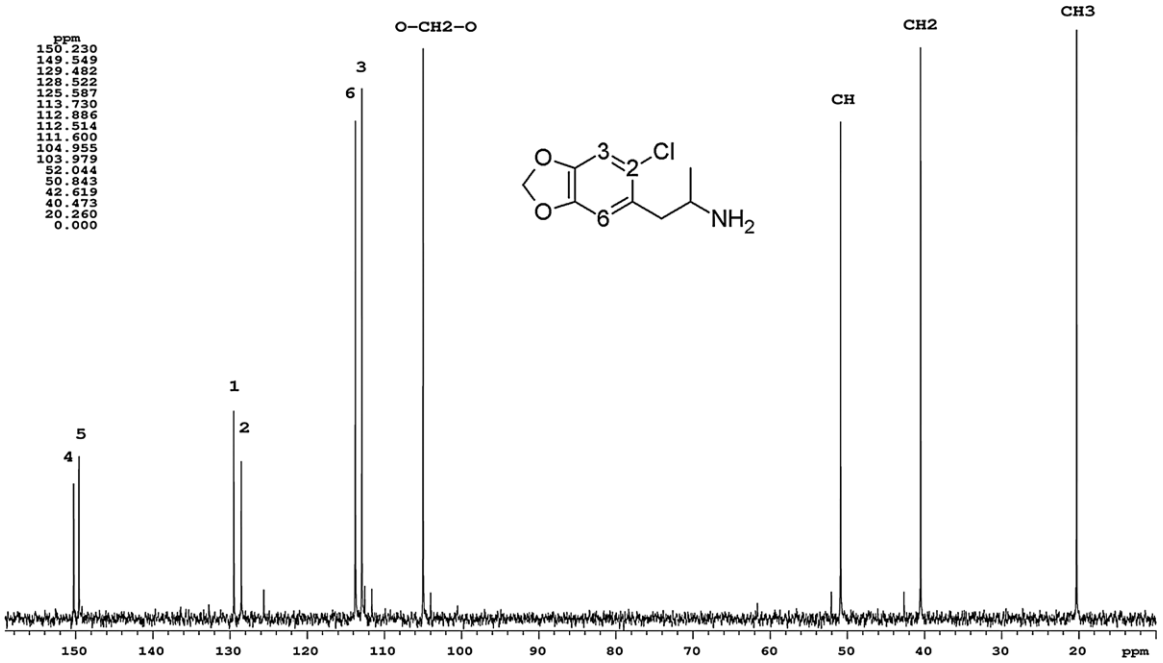

Fig. 21. Carbon NMR of 2-chloro-4,5-methylenedioxyamphetamine (2-Cl-4,5-MDA) HCl.

Table 3
Proton NMR chemical shifts (ppm), peak shape and coupling constants (Hz) of reaction by-product 2-chloro-4,5-methylenedioxymethamphetamine HCl (2-Cl-4,5-MDA HCl) prepared in D_2O and referenced to TSP at 0 ppm. d, doublet; dd, doublet of doublets; s, singlet; ddq, doublet of doublet of quartets.

3	7.02 (s)
6	6.88 (s)
O–CH_2–O	6.02 (s)
CH_2	2.97 (dd, 7.2, 14.1)
	3.04 (dd, 7.3, 14.1)
CH	3.69 (ddq, 7.2, 7.3 and 6.6)
CH_3	1.33 (d, 6.6)

carbonyl. The DEPT and HSQC experiments identify the aliphatic portions. The NOESY and HMBC spectra demonstrate a correlation between the methylene moiety and only one proton on the aromatic ring, so chlorine is confirmed to be at position two, and the correlated aromatic proton can be assigned to proton six. The assignment of the quaternary carbon lines is determined through the HMBC spectrum by using the following correlations: the methoxy protons to carbons four and five, proton six to carbons two and four, and proton three to carbons one and five. This assignment confirms the compound to be 2-chloro-4,5-MDA.

4. Conclusions

Clandestine laboratory chemists are assumed to have explored using an unusual precursor for the synthesis of MDA. The unknown material was initially received by the Las Vegas Metropolitan Police Department during the investigation of a putative clandestine laboratory.Alpha-methyl-3,4-methylenedioxyphenylpropionamide's structure was elucidated using GC–MS, IR (ATR) and NMR. This precursor is known to produce MDA when used in the Hofmann Degradation reaction. An initial Hofmann synthesis using this material unexpectedly resulted in the formation of a new compound. The structure for this compound was determined to be 2-Cl-4,5-MDA using GC–MS, IR (ATR) and NMR. Additional analytical data was acquired in the form of the N-acetylated mass spectra of the amines and gas phase infrared spectra for each compound.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.forsciint.2012.10.002.

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