

A STUDY OF THE PRECURSORS, INTERMEDIATES AND REACTION BY-PRODUCTS IN THE SYNTHESIS OF 3,4-METHYLENEDIOXY-METHYLAMPHETAMINE AND ITS APPLICATION TO FORENSIC DRUG ANALYSIS

R.J. RENTON, J.S. COWIE and M.C.H. OON

Metropolitan Police Forensic Science Laboratory, 109 Lambeth Road, London SE1 7LP (UK)

(Received December 18th, 1992)

(Accepted March 8th, 1993)

Summary

3,4-Methylenedioxyamphetamine (MDMA) was prepared by three synthetic routes. Analytical data from thin-layer chromatography, gas chromatography and gas chromatography-mass spectrometry of the precursors (safrole and isosafrole), intermediates (isosafrole glycol, piperonylmethylketone, *N*-formyl-3,4-methylenedioxyamphetamine, *N*-formyl-3,4-methylenedioxyamphetamine and 1-(3,4-methylenedioxyphenyl)-2-bromopropane), reaction by-products and the product MDMA were obtained. Further analyses of MDMA using other techniques including ^1H - and ^{13}C -nuclear magnetic resonance spectroscopy, X-ray diffraction, infrared spectroscopy, ultraviolet spectroscopy and high performance liquid chromatography were also carried out. The results were then used as reference data for the identification of MDMA in case samples and also to establish the route of synthesis of illicitly prepared MDMA by the study of trace impurities.

Key words: MDMA; 3,4-Methylenedioxyamphetamine; Impurities; Synthesis; Analysis

Introduction

Although patented in 1914 as an appetite suppressant [1], 1-(3,4-methylenedioxyphenyl)-2-(*N*-methylamino)-propane, more commonly known as 3,4-methylenedioxyamphetamine (MDMA or Ecstasy), is a relatively new drug of abuse in the UK. Over the last 4 years, the number of seizures of the drug has increased and already, illicit laboratories for the production of MDMA have been uncovered. There is no current therapeutic use for MDMA in the UK and under British legislation, it is controlled as a class 'A' drug by the Misuse of Drugs Act, 1971, as amended by the Misuse of Drugs Act, 1971 (Modification) Order, 1977.

MDMA in illicit preparations was first observed in 1972 (Gaston, T.R. and Rasmussen, G.T. pers. commun.) and various aspects of this drug have been reviewed [2,3]. However, there is only limited information on the forensic examination of the various methods of illicit manufacture. Vermeij [4] examined the reaction mixtures of MDMA prepared by low pressure reductive amination. A number of impurities were identified by gas chromatography-mass spectrometry

(GC-MS). The analyses by GC-MS of samples from a clandestine laboratory involved in the synthesis of MDMA from sassafras oil was carried out by Noggle et al. [5]. Lukaszewski [6] made a study of the various syntheses of 3,4-methylenedioxyamphetamine (MDA) where the precursors, intermediates and reaction by-products were characterised by chromatographic and spectroscopic techniques.

This study was designed to obtain analytical data pertaining to the identification of precursors, intermediates and reaction by-products encountered in certain synthetic routes as well as obtaining further analytical information to assist in the laboratory identification of MDMA.

Experimental

Materials

Safrole (97%), *N*-methylformamide (NMF, 99%) and trifluoroacetic anhydride (TFAA) were purchased from Aldrich Chemical Co. (Gillingham, Dorset, UK); isosafrole (*cis* and *trans*, 95%) and methylamine (33% in ethanol) were obtained from Fluka Chemical Co. (Glossop, UK); formamide and lithium aluminium hydride (LAH) were from Cambrian Gases (Croydon, UK). Other reagents, solvents (general purpose reagent grade) and methanol (Analar grade) for high-performance liquid chromatography (HPLC) were obtained from BDH Ltd (Poole, UK).

Syntheses

Figure 1 shows a summary of the syntheses of which routes I and II involve the Leuckart reaction [7,8]. The original synthesis of MDMA [1] was carried out by route III.

Piperonylmethylketone (PMK) was synthesized from isosafrole through the intermediate isosafrole glycol [6].

Route I. Formic acid (3.66 g), NMF (7.6 g) and PMK (9.0 g) were refluxed at 150–170°C for 7 h with additional formic acid (7.32 g) added periodically. On cooling, a clear yellow solution of *N*-formyl-3,4-methylenedioxyamphetamine (*N*-formylMDMA) was obtained.

Concentrated hydrochloric acid (30 ml) was added to this solution which was refluxed for a further 3 h. The reaction mixture was made basic with sodium hydroxide and the crude MDMA extracted into diethyl ether. After the volume of the organic solvent was decreased, the remaining residue was treated with hydrogen chloride gas to yield a gelatinous brown precipitate of impure MDMA hydrochloride. The crude salt, dissolved in boiling methanol, was added to chilled acetone to form a crystalline product. This was recrystallized to yield fawn crystals with a melting point of 147–148°C [9].

Route II. Formamide (65 g) and PMK (23 g) were refluxed at 190°C for 5 h. The solution was made basic and extracted with diethyl ether. The ethereal solution was first washed with dilute sulphuric acid, rinsed with water and finally dried over anhydrous sodium sulphate. The diethyl ether volume was reduced to yield a clear yellow solution of *N*-formyl-3,4-methylenedioxyamphetamine (*N*-

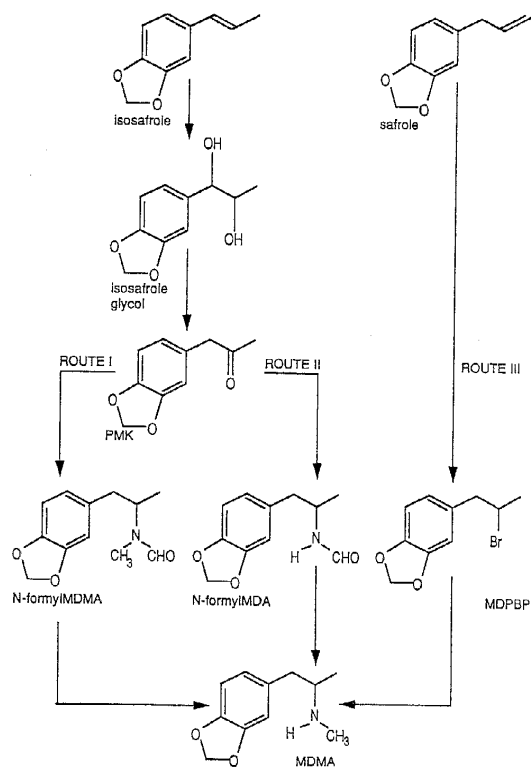


Fig. 1. Flow diagram of the synthetic routes investigated. Route I: PMK - *N*-formylMDMA - MDMA; Route II: PMK - *N*-formylMDA - MDMA; Route III: safrole - MDPBP - MDMA.

formylMDA). This was added drop-wise to LAH (2.5 g in 100 ml of sodium-dried diethyl ether) and refluxed for 3 h. The excess LAH was decomposed by the addition of water and the resulting mixture was filtered and the precipitate washed with diethyl ether. The washings and the filtrate were combined and extracted with dilute sulphuric acid. The aqueous solution was made alkaline with dilute sodium hydroxide and extracted with diethyl ether. The solvent was evaporated leaving an amber oil of crude MDMA.

Route III. The reactions described in the Merck patent [1] involve the formation of 1(3,4-methylenedioxyphenyl)-2-bromopropane (MDPBP) from safrole followed by reaction with methylamine. This was the method followed.

Extraction of intermediates and reaction by-products

Route I. An aliquot of the acidic *N*-formylMDMA reaction mixture was washed with diethyl ether, made basic with dilute sodium hydroxide and extracted with diethyl ether. This sample was analysed by thin-layer chromatography (TLC), gas chromatography (GC) and GC-MS.

Route II. A sample of the *N*-formylMDA reaction mixture was made acidic with tartaric acid [10] and extracted with diethyl ether. The organic layer was separated and extracted with dilute hydrochloric acid. The acidic extract was then made basic with dilute sodium hydroxide and extracted with chloroform. This sample was analysed by the above-mentioned methods.

Route III. A sample of the chloroform used to extract the brominated intermediate from the safrole/hydrobromic acid reaction mixture was analysed by the techniques described above.

Preparation of the trifluoroacetyl (TFA) derivative

Ethyl acetate (1.0 ml) and TFAA (0.1 ml) were added to a 10-ml screw-topped tube containing the dried extract. The reaction mixture was heated at 60°C for 20 min, evaporated to dryness and methanol (0.1 ml) was added to the tube prior to GC-MS analysis.

Extraction of impurities from case samples

Powder or crushed tablet (5 mg), known to contain the MDMA salt, was vortex-mixed with redistilled diethyl ether (1 ml) and centrifuged. The supernatant was taken off, evaporated to dryness and methanol (0.1 ml) was added prior to GC-MS analysis.

Analytical techniques

HPLC

The two HPLC systems used 12.5 cm by 4.9 mm (i.d.) stainless steel columns with slurry packed 5 μ m Spherisorb silica (Phase Separations, Queensferry, UK) and an eluent flow rate of 2 ml/min.

System I. A reciprocating pump, type HM (Metering Pumps, London, UK), delivered the eluent of methanol/30% hydrochloric acid/ammonium hydroxide (sp. gr. 0.880) 2000:5.8:18.4. The sample in 0.02 M methanolic hydrochloric acid was introduced to a Rheodyne model 7125 injection valve (Berkeley, CA, USA) fitted with a 5- μ l loop. A Cecil CE212 UV detector (Cecil Instruments, Cambridge, UK) monitored the eluant by absorption at 284 nm.

System II. An Applied Chromatography Systems model 400 pump (ACS Ltd., Macclesfield, UK) delivered the eluent of 0.01 M ammonium perchlorate in methanol adjusted to pH 6.7 by the addition of 1 ml/l of 0.1 M sodium hydroxide in methanol. The sample in methanol was introduced to a Rheodyne injection valve, model 7125, fitted with a 20- μ l loop. A LDC spectromonitor III (LDC Analytical Ltd., Stone, UK) monitored the eluant by UV absorption at 284 nm.

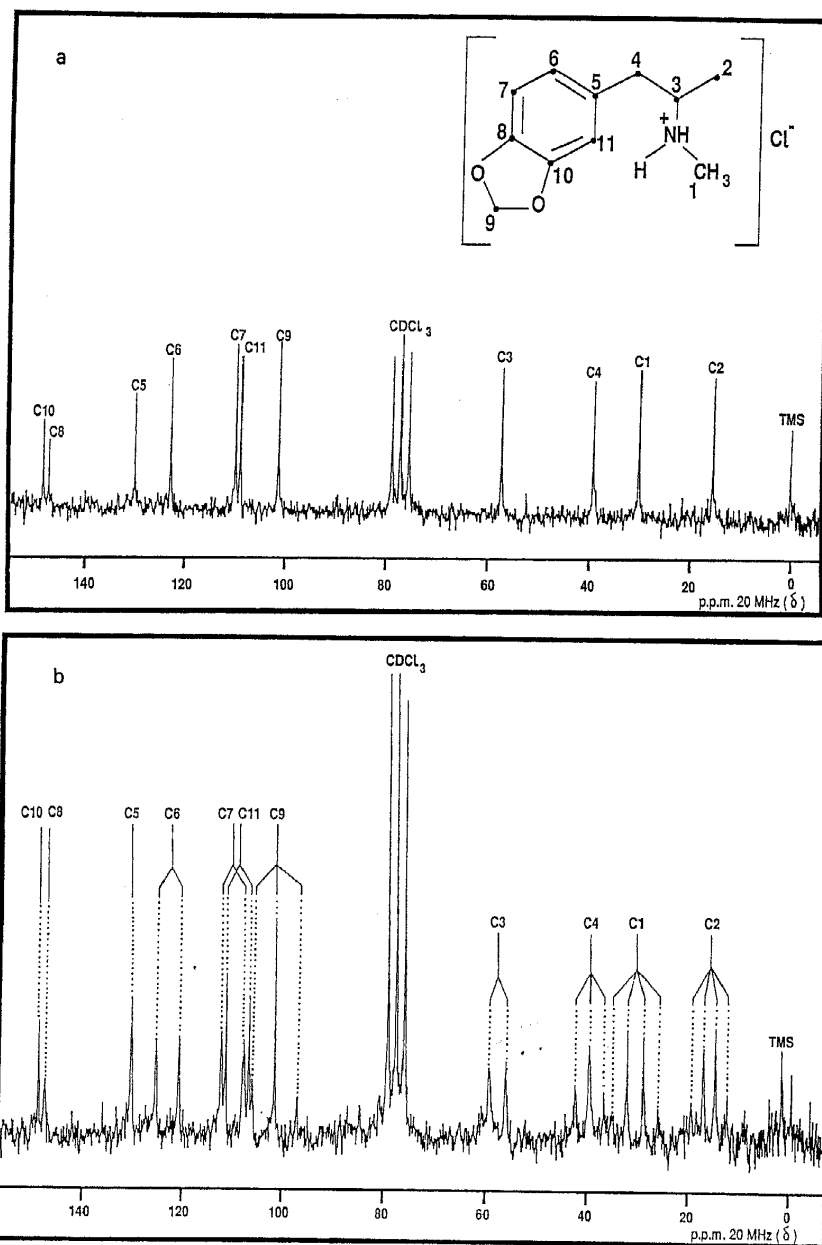


Fig. 2. The ^{13}C NMR spectra of MDMA.HCl. (a) BBPD and (b) SFORD.

GC-MS

A VG 12-12F quadrupole mass spectrometer (VG Biotech, Altrincham, UK) was used in combination with a Carlo Erba model 4160 gas chromatograph (Fisons Instruments, Crawley, UK). The inlet of a fused-silica capillary column of bonded dimethyl silicone (15 m by 0.22 mm i.d., 0.25 μm film thickness; Thames Chromatography, Maidenhead, UK) was connected to a split/splitless injector. The column outlet was inserted directly into the ion source of the mass spectrometer. A splitless injection was made with the GC oven temperature held at 100°C for 1 min. The temperature was ramped at 30°C/min to 280°C where it was maintained for 5 min. The temperature of the injection port and the transfer line was 270°C. The inlet pressure for the helium carrier gas was 1.0 kg/cm⁻². The mass spectrometer was used in the EI mode, the source temperature was 200°C and electron energy was 70 eV. Mass spectra were obtained by scanning from 35 to 535 amu at 1 s/scan and the data was processed on a VG DS2050 Data System (VG Analytical, Manchester, UK). Isobutane was the reagent gas in the chemical ionization (CI) mode and the source temperature was 200°C. The vacuum in the source housing was 10⁻⁴ Torr and the mass spectrometer scanned from 100 to 400 amu at 1 s/scan.

Other techniques

Ultraviolet (UV) spectra were recorded on a Uvikon UV/visible spectrophotometer, model 810 (Kontron Scientific Instruments Ltd., St Albans, UK). Infrared (IR) spectra were obtained as potassium bromide discs on a Perkin Elmer IR spectrophotometer, model 298, used in conjunction with a Perkin Elmer IR data station 3600 (Perkin Elmer Instruments, Beaconsfield, UK).

The other techniques are detailed with their tabulated data.

Results and Discussion

MDMA and intermediate compounds

There is a large number of potential synthetic routes to MDMA [2] but the choice of this study was restricted to three. From the information available, it appears that the Leuckart reaction (routes I and II) is the most commonly used reaction in the illicit production of amphetamine type drugs. This reaction can be easily adapted to the manufacture of methylenedioxy-substituted analogues. The reactions (route III) described in the Merck patent [1] could be used for those in search of a published method.

The IR, UV and ¹H-MMR spectra were all consistent with those published previously [9,13]. The ¹³C-NMR spectra (both broad-band proton decoupled (BBPD) and single frequency off-resonance decoupled (SFORD) spectra) and the XRD pattern of MDMA.HCl are presented in Fig. 2 and Tables 1 and 2 respectively. Figures 3 and 4 show the mass spectra of *N*-formylMDMA and MDPBP. The mass spectra of safrole, isosafrole, isosafrole glycol, PMK, *N*-formylMDA and MDMA have been reported previously [6,9]. The mass spectrum of MDMA is not highly characteristic. It has a base peak of mass 58 with minor ions of mass 135 and 136 [14]. A highly characteristic mass spectrum can be obtained with the

TABLE 1

DATA FROM ^{13}C -NMR SPECTRA OF MDMA · HCL

A Bruker model WP-80 nuclear magnetic resonance (NMR) spectrometer ^1H at 80 MHz and ^{13}C at 20.12 MHz (Bruker Spectrospin Ltd., Coventry, UK) was used.

<i>Chemical shift/p.p.m.</i> (BBPD, Fig. 2a)	<i>Multiplicity</i> (SFORD, Fig. 2b)	<i>Assignment</i>
15.4	quartet	C 2
30.2	quartet	C 1
39.1	triplet	C 4
57.3	doublet	C 3
101.2	triplet	C 9
108.7	doublet	C 11
109.6	doublet	C 7
122.6	doublet	C 6
129.8	singlet	C 5
146.9	singlet	C 8
148.1	singlet	C 10

TABLE 2

XRD PATTERN OF MDMA · HCL

A Debye-Scherrer powder camera (Philips Scientific Ltd., Cambridge, UK, 114.6 mm diameter) with a 2.5-h exposure of Agfa Gevaert OSRAY M3 film (Agfa Gevaert Ltd., Brentford, UK) to iron-filtered $\text{Co K}\alpha$ X-rays ($\lambda = 1.79026 \text{ \AA}$) generated at 35 kV, 25 mA was used. The sample was contained in a 0.5-mm diameter capillary tube. The intensities quoted are approximate.

$d(\text{\AA})$	II°	$d(\text{\AA})$	II°	$d(\text{\AA})$	II°
9.2	5	3.53	20	2.24	5
7.1	10	3.30	40	2.10	5
5.6	25	3.12	15	2.05	5
5.4	20	3.06	15	1.99	5
4.80	60	2.87	15	1.92	5
4.55	50	2.83	15	1.86	5
4.18	100	2.73	10	1.745	5
3.90	10	2.67	10	1.635	5
3.82	10	2.59	10	1.600	5
3.72	15	2.43	10	1.575	5
3.59	20	2.29	10	—	—

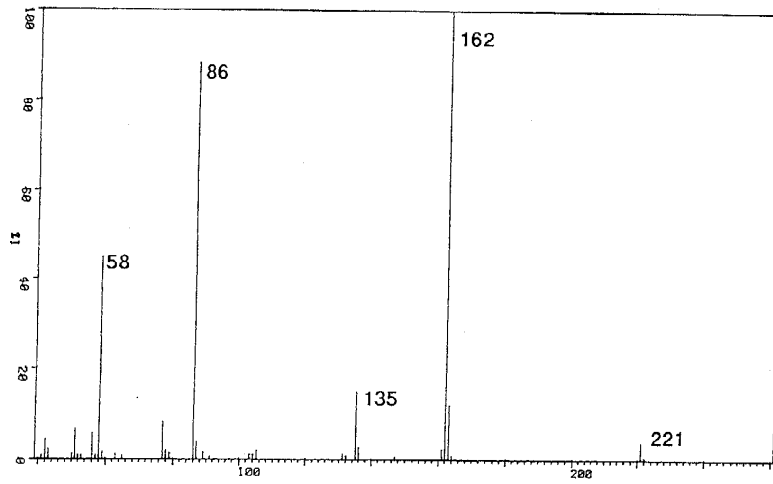


Fig. 3. The mass spectrum of *N*-formylMDMA.

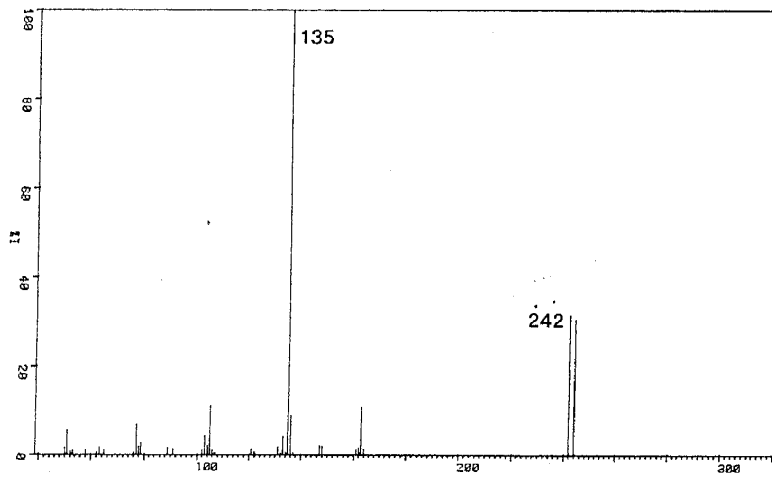


Fig. 4. The mass spectrum of MDPBP.

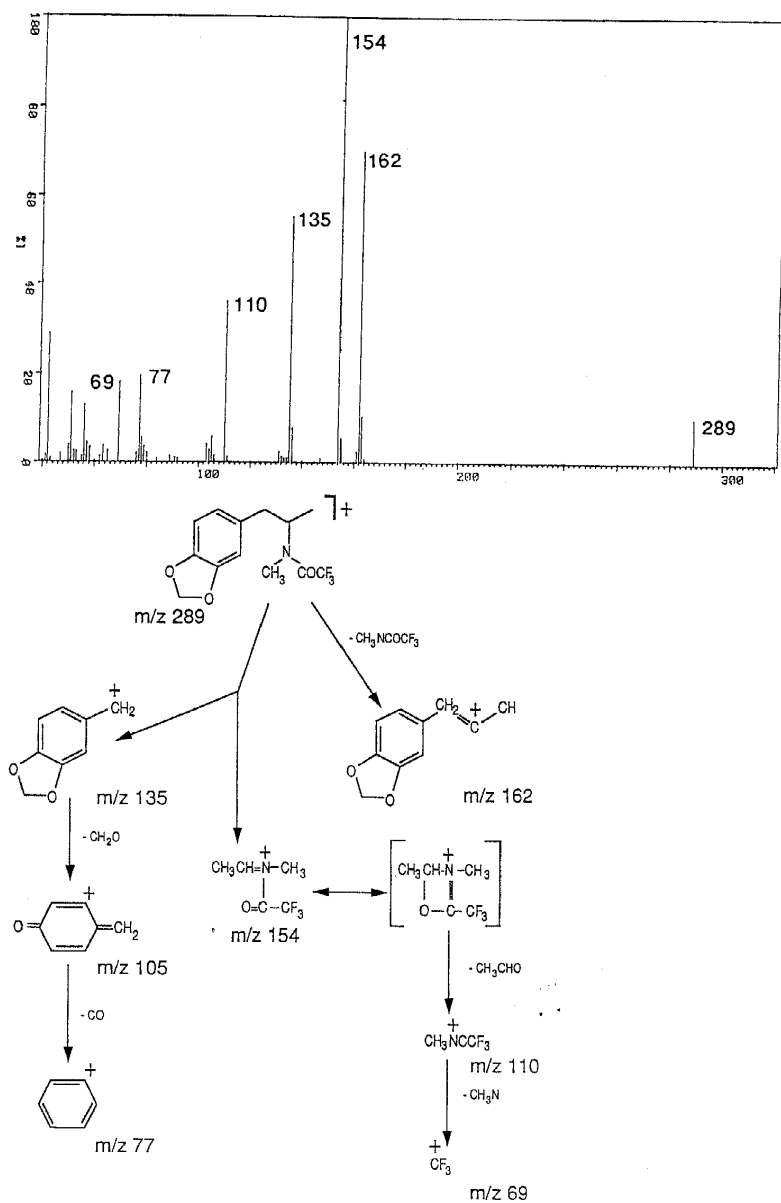


Fig. 5. The mass spectrum of the MDMA TFA derivative and the proposed fragmentation pathway.

TABLE 3

TLC DATA FOR MDMA AND RELATED COMPOUNDS

TLC was carried out on glass plates coated with Kieselguhr 60 F₂₅₄ (Merck TLC plates, BDH Ltd., Poole, UK) that had been dipped in a methanolic solution of 0.01 M sodium hydroxide [16]. The plates were developed in a methanol/acetone (3:1) solvent system, visualised in ultraviolet light at 254 nm and sprayed with acidified iodoplatinate solution.

<i>Compound</i>	<i>Relative retention distance</i>
MDMA	0.27
DMMDA	0.38
<i>N</i> -formylMDA	0.75
<i>N</i> -formylMDMA	0.78

TABLE 4

GC DATA FOR MDMA AND RELATED COMPOUNDS

GC was performed using a glass column (2 m by 6 mm o.d.) packed with 3% OV17 coated on Gas Chrom Q (Phase Separations, Queensferry, UK) with a nitrogen carrier gas flow rate of 30 ml/min. The Philips PU4500 gas chromatograph (Philips Scientific Ltd., Cambridge, UK) was fitted with a flame ionization detector. The oven temperature was 200°C isothermal, injector temperature was 200°C and the detector temperature was 280°C.

<i>Compound</i> (MDMA = 1.0)	<i>Relative retention time</i>
Safrole	0.35
Isosafrole (<i>trans</i>)	0.44
Isosafrole (<i>cis</i>)	0.53
PMK	0.97
DMMDA	1.21
MDPBP	1.44
Isosafrole glycol	2.24
<i>N</i> -formylMDA	5.77
<i>N</i> -formylMDMA	6.45

TABLE 5

HPLC DATA FOR MDMA · HCL

<i>System</i>	<i>Reference compound</i>	<i>Relative retention time</i>
I	Morphine	1.35
II	Imipramine	0.63

TFA derivative. Figure 5 shows the mass spectrum and proposed fragmentation route. The chromatographic data for MDMA and related compounds by TLC, GC and HPLC are shown in Tables 3, 4 and 5, respectively.

Reaction by-products

Route I. A reaction by-product *N,N*-dimethyl-3,4-methylenedioxyamphetamine (DMMDA) was identified. This assignment was based on the mass spectrum shown in Fig. 6 together with a molecular weight of 207 (from the CI mass spectrum) and by analogy with the corresponding amphetamine synthesis [11,12]. However, DMMDA (a tertiary amine) has the same mass spectrum as its isomer *N*-ethyl-3,4-methylene-dioxyamphetamine (a secondary amine) [13,14]. The compound did not, however, form a derivative with TFAA, showing it to be a tertiary amine and not a secondary amine. This compound could be the product of the reaction of dimethylformamide (DMF) and PMK where DMF is an impurity of NMF [12]. Vermeij [4] has identified DMMDA as an impurity in illicit MDMA manufactured by low pressure reductive amination.

Route II. Reaction by-products such as [1-(3,4-methylene-dioxyphenyl)-2-propyl]amine and [1-(3,4-methylene-dioxyphenyl)-2-propyl]methylamine which have been identified in the synthesis of MDA [6] using the Leuckart reaction were not observed in this study. However, GC-MS provides some evidence to suggest the presence of methylenedioxy substituted pyrimidines and pyridines analogous to those observed in the cognate synthesis of amphetamine [10,15]. The mass spectrum of the tentatively substituted pyrimidine (Fig. 7a) is characterized by its two major ions of mass 213 and 214. The molecular ion of

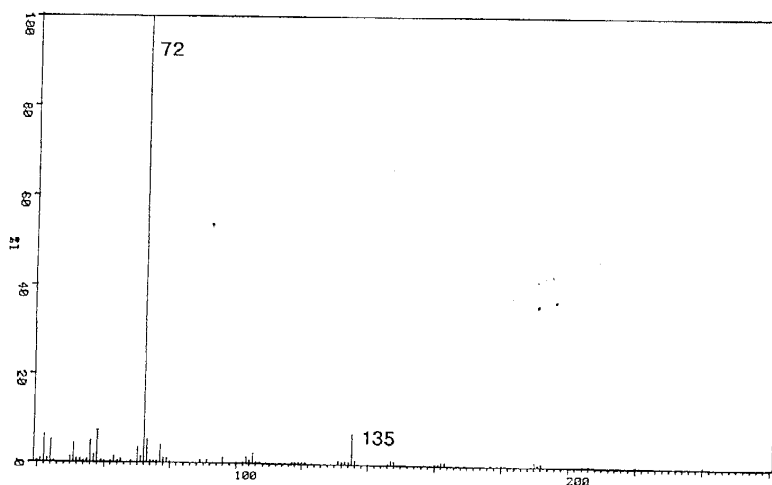


Fig. 6. The mass spectrum of DMMDA.

mass 214 exhibits a mass shift of 44 from that observed in the mass spectrum of the cognate amphetamine impurity [15], suggesting a methylenedioxy substituted analogue. Similarly, the molecular ion of mass 348 (Fig. 7b) of the tentatively identified substituted pyridine impurity [10] exhibits a mass shift of 88 with respect to similar compounds observed in amphetamine synthesis. This sug-

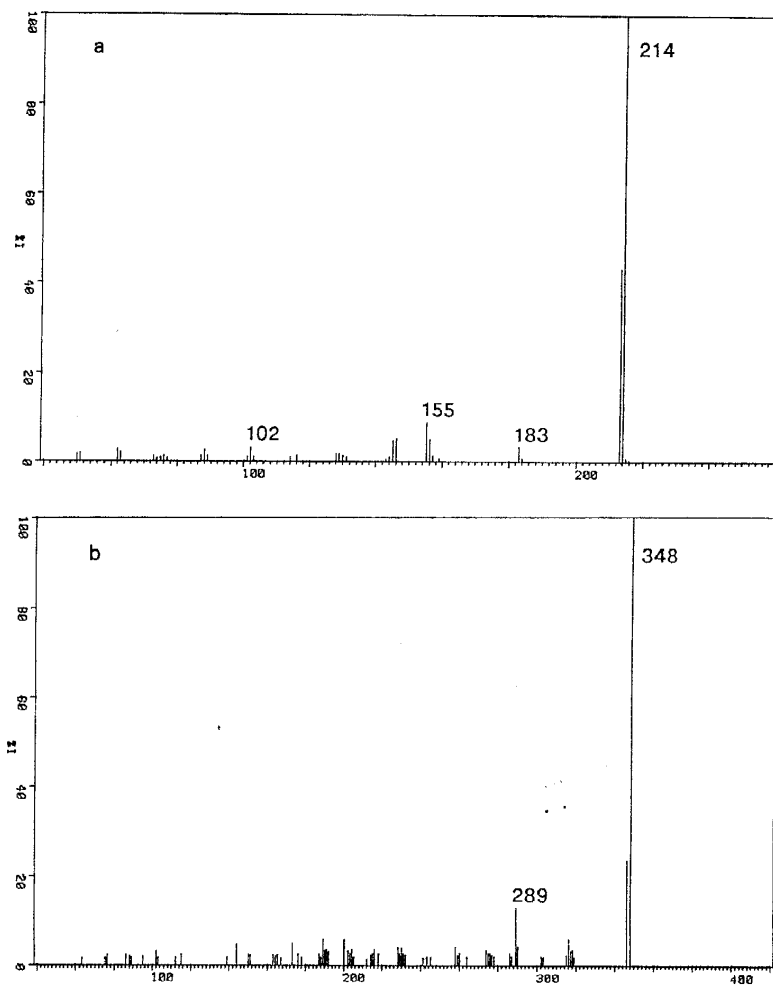


Fig. 7. Mass spectra of (a) substituted pyrimidine and (b) substituted pyridine.

gests a methylenedioxy doubly substituted pyridine analogue which is consistent with the structure of the known impurity.

No significant reaction by-products were identified in route III which involves the formation of the intermediate MDPBP.

Applications

Impurities are often observed in illicitly prepared drugs samples as they are not usually purified to any great degree after manufacture. In the case of illicitly prepared amphetamine, the presence of 'route specific' impurities is used to establish the manufacturing process [11]. Applying this analogy to MDMA, the identification of the reaction intermediates in the illicit sample can be used to establish the synthetic route used. Figure 8 shows the chromatogram of an extract of a typical sample. The reaction intermediates isosafrole glycol, PMK and *N*-formylMDMA were observed together with the reaction by-product DMMDA. This demonstrates that route I was used in the manufacture.

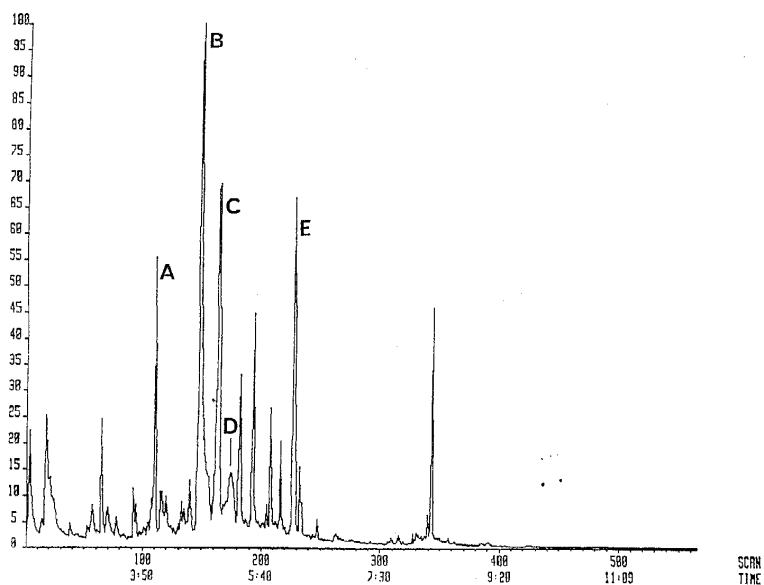


Fig. 8. Total ion chromatogram of illicitly prepared MDMA and impurities. A: PMK; B: MDMA; C: DMMDA; D: isosafrole glycol; E: *N*-formylMDMA. A VG 15-250 quadrupole mass spectrometer, fitted with a Hewlett Packard 5980 gas chromatograph (Hewlett Packard Analytical, Winnersh, UK), was used in the analysis of extracts of case samples. The operating conditions were in the EI mode as described earlier.

mass 214 exhibits a mass shift of 44 from that observed in the mass spectrum of the cognate amphetamine impurity [15], suggesting a methylenedioxy substituted analogue. Similarly, the molecular ion of mass 348 (Fig. 7b) of the tentatively identified substituted pyridine impurity [10] exhibits a mass shift of 88 with respect to similar compounds observed in amphetamine synthesis. This sug-

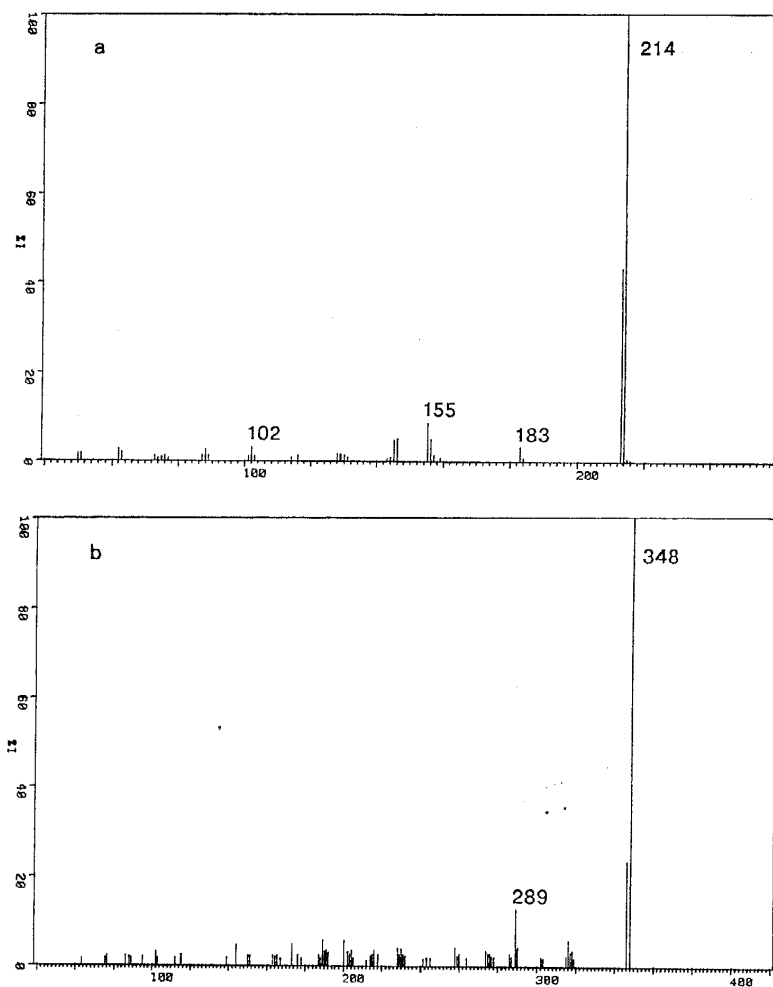


Fig. 7. Mass spectra of (a) substituted pyrimidine and (b) substituted pyridine.

gests a methylenedioxy doubly substituted pyridine analogue which is consistent with the structure of the known impurity.

No significant reaction by-products were identified in route III which involves the formation of the intermediate MDPBP.

Applications

Impurities are often observed in illicitly prepared drugs samples as they are not usually purified to any great degree after manufacture. In the case of illicitly prepared amphetamine, the presence of 'route specific' impurities is used to establish the manufacturing process [11]. Applying this analogy to MDMA, the identification of the reaction intermediates in the illicit sample can be used to establish the synthetic route used. Figure 8 shows the chromatogram of an extract of a typical sample. The reaction intermediates isosafrole glycol, PMK and *N*-formylMDMA were observed together with the reaction by-product DMMDA. This demonstrates that route I was used in the manufacture.

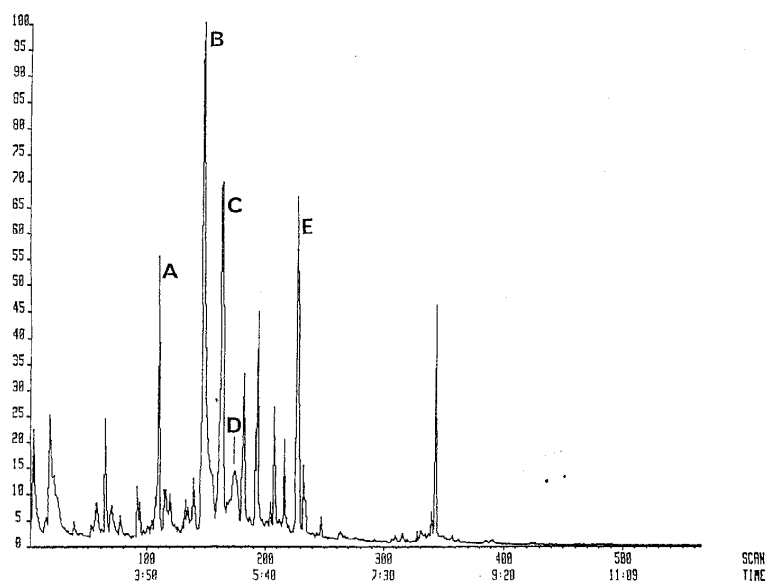


Fig. 8. Total ion chromatogram of illicitly prepared MDMA and impurities. A: PMK; B: MDMA; C: DMMDA; D: isosafrole glycol; E: *N*-formylMDMA. A VG 15-250 quadrupole mass spectrometer, fitted with a Hewlett Packard 5980 gas chromatograph (Hewlett Packard Analytical, Winnersh, UK), was used in the analysis of extracts of case samples. The operating conditions were in the EI mode as described earlier.

Conclusion

In addition to providing reference data for the identification of MDMA in case samples, the analytical data from this study can be used to determine the synthetic route used in the illicit manufacture of MDMA, and may also help in the discrimination of sources of origin in the comparison of illicit samples.

Acknowledgements

The authors would like to thank Dr. W.D.C. Wilson for useful discussions and the Chemistry Department of the Polytechnic of North London for the use of the NMR instrument.

References

- 1 E. Merck, Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylenedioxyarylamino-propanen bzw. deren Amstickstoff Monoalkylierten Derivaten. *German Patent, No. 274 350*, 1914.
- 2 A.T. Shulgin, The background and chemistry of MDMA. *J. Psychoactive Drugs*, 18 (1986) 291-304.
- 3 G.N. Hayner and H. McKinnon, MDMA. The dark side of Ecstasy. *J. Psychoactive Drugs*, 18 (1986) 341-347.
- 4 A.M.A. Vermeij, Clandestine manufacture of 3,4-methylenedioxy-methylamphetamine (MDMA) by low pressure reductive amination. A mass spectrometric study of some reaction mixtures. *Forensic Sci. Int.*, 45 (1990) 91-96.
- 5 F.T. Noggle, C.R. Clark and J. DeRuiter, Gas chromatographic and mass spectrometric analysis of samples from a clandestine laboratory involved in the synthesis of Ecstasy from Sassafras oil. *J. Chromatogr. Sci.*, 29 (1991) 168-173.
- 6 T. Lukaszewski, Spectroscopic and chromatographic identification of precursors, intermediates and impurities of 3,4-methylenedioxyamphetamine synthesis. *J. Assoc. Off. Anal. Chem.*, 61 (1982) 951-967.
- 7 M.L. Moore, The Leuckart reaction. *Organic Reactions*, 5 (1949) 301-330.
- 8 E. Merck, Verfahren zur Gewinnung von Formylderivaten sekundärer Basen. *German Patent, No. 334 555*, 1920.
- 9 K. Bailey, A.W. By, D. Legault and D. Verner, Identification of the *N*-methylated analogs of the hallucinogenic amphetamines and some isomers. *J. Assoc. Off. Anal. Chem.*, 58 (1975) 62-69.
- 10 A.M. van der Ark, A.M.A. Vermeij and A. Sinnema, Weakly basic impurities in illicit amphetamine. *J. Forensic Sci.*, 23 (1978) 693-700.
- 11 A.M.A. Verweij, Impurities in illicit drug preparations: amphetamine and methamphetamine. *Forensic Sci. Rev.*, 1 (1989) 1-14.
- 12 T.C. Kram and A.V. Kruegel, The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy. *J. Forensic Sci.*, 22 (1977) 40-52.
- 13 T.A. Del Cason, The characterization of some 3,4-methylenedioxyisophenylpropylamine (MDA) analogs. *J. Forensic Sci.*, 34 (1989) 928-961.
- 14 F.T. Noggle, C.R. Clark, A.K. Valaer and J. DeRuiter, Liquid chromatographic and mass spectral analysis of *N*-substituted analogues of 3,4-methylenedioxyamphetamines. *J. Chromatogr. Sci.*, 26 (1988) 410-415.
- 15 A.M. van der Ark, A.B.E. Theuwen and A.M.A. Vermeij, Impurities in illicit amphetamine; isolation and identification of some pyrimidines. *Pharm. Weekbl.*, 112 (1977) 977-982.
- 16 J.V. Jackson and A.J. Clatworthy, Toxicological applications of chromatography. In I. Smith and J.W.T. Seakins (eds.), *Chromatography and Electrophoretic Techniques*, Vol. 1, Paper and Thin Layer Chromatography, William Heinemann Medical Books Ltd, 1976, pp. 380-455.