

Case report

Analytical profile of 4-methylthioamphetamine (4-MTA), a new street drug

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Abstract

The analytical properties for a new street drug, 4-methylthioamphetamine (4-MTA), are presented. This new compound was found in tablets sold on the illicit market in the Netherlands and Switzerland in 1997 and 1998. The intermediate 1-(4-methylthiophenyl)-2-nitropropene was also found in a clandestine laboratory in the Netherlands in January 1997.

In this study, reference standards were prepared and characterized. The ultraviolet, infrared and nuclear magnetic resonance spectral properties as well as the chromatographic and mass spectrometric (MS) data are reported.

1. Introduction

In January 1997, the Forensic Science Laboratory of the Netherlands received three unrelated cases concerning a new ring-substituted amphetamine derivative. The first case concerned unidentified yellow crystals found in a clandestine laboratory where 3,4-(methylenedioxy)amphetamine (MDA) was prepared via the nitropropene route [1]. The second case included white single scored tablets (average weight, 0.693 g; diameter, 13.1 mm), containing an unknown compound as well as caffeine. The third case was analyzed by the toxicology department. In addition to amphetamine, the same compound as in case 2 was found in the blood sample of a drug-related death.

In the summer of 1998, the IPSC (Institut de Police Scientifique et de Criminologie, University of Lausanne, Switzerland) received two unrelated cases where an unknown

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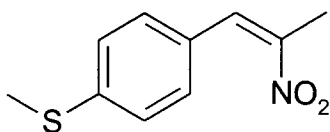


Fig. 1. Structure of 1-(4-methylthiophenyl)-2-nitropropene.

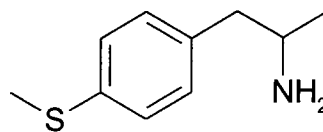


Fig. 2. Structure of 4-methylthioamphetamine (4-MTA).

compound as well as lactose were found in tablets sold as ecstasy. The first case consisted of pink tablets (average weight, 400 mg; diameter, 11.1 mm), which had a star with five branches as a logo (white and pink tablets with the same logo were seized in the Netherlands during the same year).

The second case consisted of white–yellowish single scored tablets without any logo (average weight, 300 mg; diameter, 9 mm).

The yellow crystals in the first Dutch case were later identified as 1-(4-methylthiophenyl)-2-nitropropene (see Fig. 1) and the unknown compound in all of the other cases was identified as 4-methylthioamphetamine (see Fig. 2).

In this study, reference standards were prepared and characterized. The ultraviolet, infrared and nuclear magnetic resonance spectral properties as well as the chromatographic and mass spectrometric (MS) data are reported.

2. Experimental

2.1. Synthesis

The method of synthesis used for 4-methylthioamphetamine was the same as encountered for MDA in the clandestine laboratory. The nitropropene intermediate was prepared from 4-methylthiobenzaldehyde (7 g), nitroethane (3.5 g) and *n*-butylamine (300 μ l). After five days, the yellow crystals were collected and washed with cold methanol. A solution of 1-(4-methylthiophenyl)-2-nitropropene in ether was added dropwise to a suspension of lithium aluminium hydride (LAH) in ether and then heated to reflux. Water was added to decompose the excess LAH and the precipitated inorganic salts were removed by filtration. Basic extraction with ether and evaporation of the solvent yielded 4-methylthioamphetamine base, a white solid. Treatment of the base with ethereal HCl provided the hydrochloric salt as a white powder, which was isolated by filtration.

At IPSC, 4-methylthioamphetamine hydrochloride was prepared in a similar way via the nitropropene route according to Mourad et al. [2].

2.2. Spot tests and thin-layer chromatography

Marquis reagent was prepared according to Moffat et al. [3] and thin layer chromatography was carried out using precoated Silicagel 60 GF 254 plates (Merck,

Darmstadt, Germany). Two solvent systems were used and consisted of: (a) cyclohexane/toluene/diethylamine (75:15:10, v/v), plates previously sprayed with KOH, 0.1 M and (b) methanol [4]. Detection was achieved under UV light at 254 nm and after spraying with acidified iodoplatinate [3].

Samples were dissolved in a mixture of dichloromethane/methanol (1:1, v/v).

2.3. Instrumental analysis

Chromatographic and MS data were obtained on two different instruments and under two sets of conditions:

1. A Hewlett Packard 5890 gas chromatograph coupled to a 5971 mass selective detector. Split ratio, 50:1. Injector temperature, 275°C; detector temperature, 280°C and the oven temperature was programmed from 100°C at 10°C/min to 280°C. An HP Ultra-1 column (12 m×0.22 mm I.D.×0.25 µm film thickness) was used.
2. A Hewlett-Packard GCD G1800A series. Split ratio, 50:1. Injector temperature, 250°C; detector temperature, 330°C. The oven temperature programme was: 150°C for 1 min; 8°C/min to 250°C; 6°C/min to 320°C. A DB-1 column (30 m×0.25 mm I.D.×0.25 µm film thickness) was used.

Reference samples were dissolved in methanol (1 mg/ml) and 1.0 µl was introduced into the gas chromatography (GC)–MS system.

Infrared spectra were recorded on a Perkin Elmer Spectrum 1000 Fourier transform infrared spectrometer, equipped with a Golden Gate single reflection diamond ATR.

Capillary electrophoresis was performed on a Hewlett-Packard C1600A system using a HP fused-silica column (total length, 64.5 cm; effective length, 56 cm; internal diameter, 50 µm). Introduction of the sample was via pressure injection, for a duration of 1 s at 50 mbar. Separation was achieved by application of 30 KV (current, 30 µA; total field strength, 465 V/cm) at 30°C, in a buffer containing 50 mM H₂PO₄ and 50 mM H₃PO₄, at pH 2.35, with UV detection at 214 nm, with the UV/Vis spectrum of the eluted compound being recorded between 190 and 600 nm using the HP-CE Chemstation software (DOS series, 1993) [5].

¹H-NMR was performed on a Bruker DPX 400 apparatus operating at room temperature at 400 MHz. Samples were dissolved in deuterated chloroform in 5 mm NMR tubes.

3. Results

3.1. General

In both countries, 4-(methylthio)amphetamine was encountered as the hydrochloride salt. Pictures of the Dutch and Swiss tablets that had the star logo were compared. It was

found that the logo of the respective tablets superimposed perfectly, although the colour, thickness and average weight did not match.

Following personal communications, it appears that this new derivative has been identified in other European countries such as Germany and especially the United Kingdom (personal communication with Dr Les King, Forensic Science Service, UK), as well as in Australia (personal communication with Dr P. Pigou, Adelaide, Australia).

3.2. Spot tests and thin-layer chromatography (TLC)

With the Marquis reagent, both the illicit tablets and the prepared 4-methylthioamphetamine gave no coloration.

With the two solvent systems used for TLC, the exhibits and the prepared reference standard gave the same R_f values and could be separated from 3,4-(methyl-

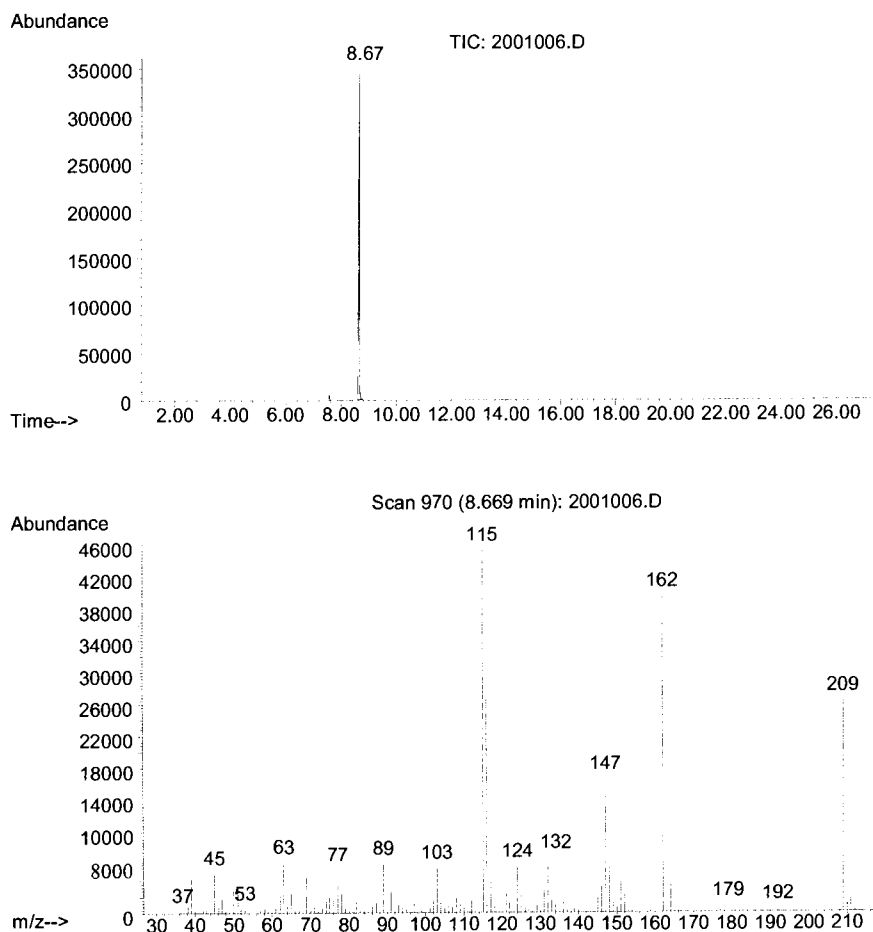


Fig. 3. Total Ion Chromatogram (TIC) and mass spectrum of unknown yellow crystals from Dutch case 1.

enedioxy)methylamphetamine (MDMA), 3,4-(methylenedioxy)ethylamphetamine (MDEA) and N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) but could not be separated from MDA. 4-Methylthioamphetamine and MDA indeed gave the same R_f values with the two solvent systems.

4-Methylthioamphetamine reacted positively with the acidified iodoplatinate spray, giving a purple colour.

3.3. Pharmacology

Although the effects of 4-methylthioamphetamine on humans is not known, a pharmacological study, where the synthesis was described, has shown that this compound has anorexic properties [6]. Two other studies have reported that 4-MTA is a potent serotonin-releasing agent [7,8].

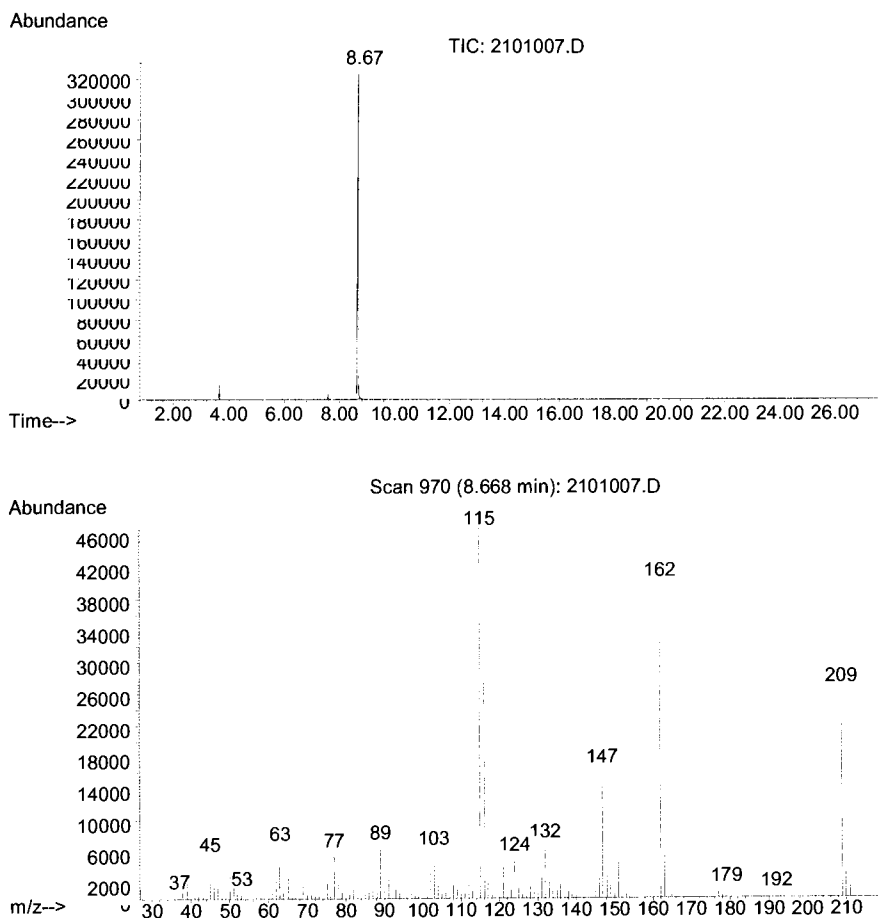


Fig. 4. TIC and mass spectrum of 1-(4-methylthiophenyl)-2-nitropropene.

3.4. Gas-chromatography–mass spectroscopy

GC–MS analysis (GC–MSD instrument) of the unknown yellow crystals from case 1 showed a peak with a retention time of 8.67 min and a molecular ion at 209 m/e (Fig. 3). The peak had the same retention time as 1-(4-methylthiophenyl)–2-nitropropene and its mass spectrum was similar to that of the prepared standard (Fig. 4).

GC–MS analysis of the tablets in case 2 showed a peak with a retention time of 5.11 min; the peak at 7.61 min is caffeine. The mass spectrum of the peak at 5.11 min had a small molecular ion at m/e 181 and a base peak at m/e 44 (Fig. 5). The retention time and mass spectrum were the same as for the prepared 4-methylthioamphetamine standard (Fig. 6).

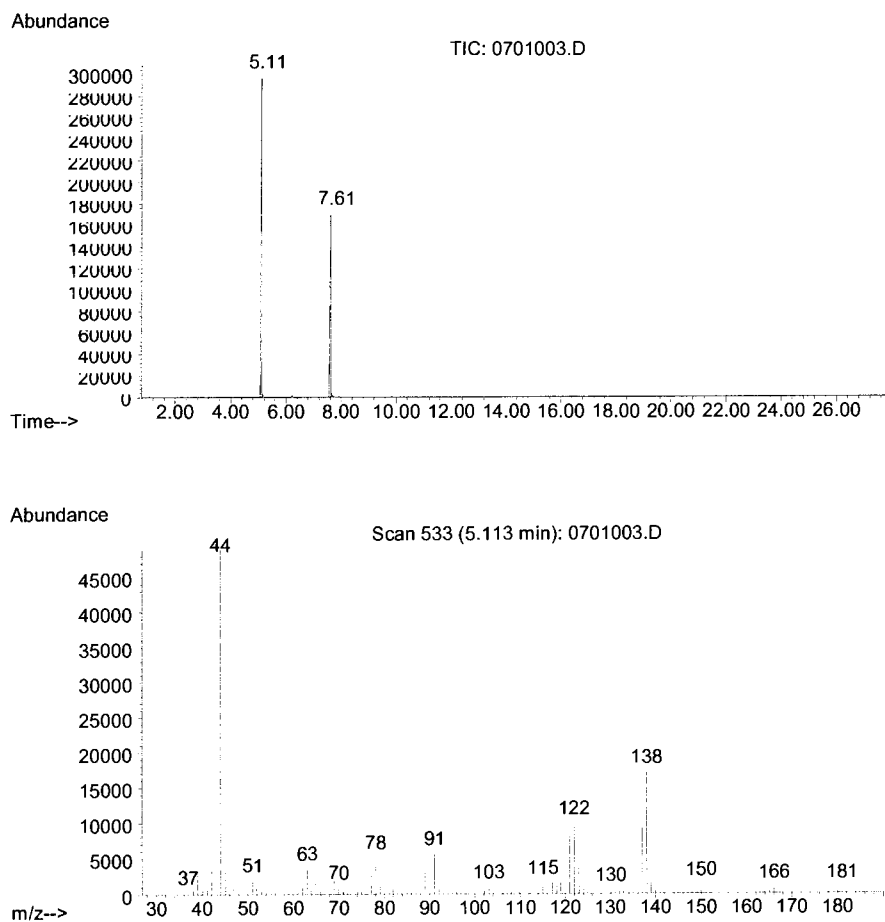


Fig. 5. TIC and mass spectrum of the tablets from Dutch case 2.

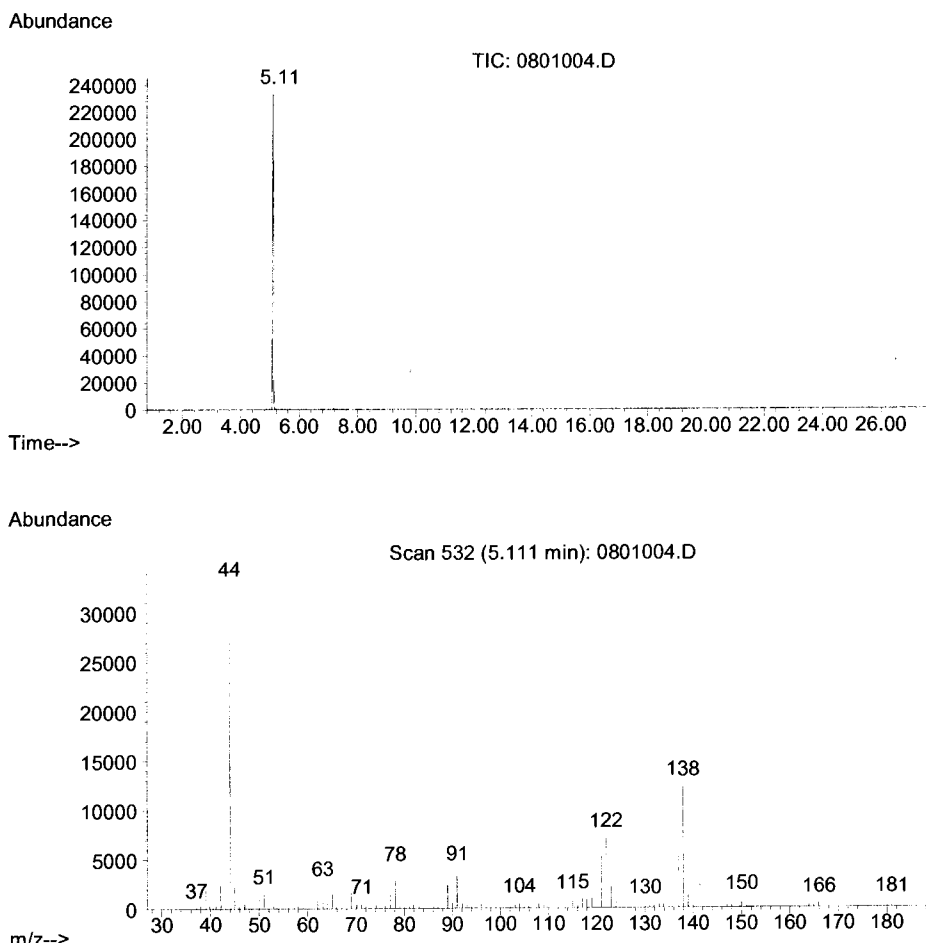


Fig. 6. TIC and mass spectrum of 4-methylthioamphetamine.

The same results were found for the Swiss tablets, although lactose was the cutting agent instead of caffeine.

Fig. 7 shows the separation of five amphetamine derivatives including 4-methylthioamphetamine on a DB-1 column (GCD instrument). It can be seen that MDA, MDMA, MDEA, MBDB and 4-methylthioamphetamine are well separated, with 4-methylthioamphetamine eluting between MDMA and MDEA.

Figs. 8 and 9 show the mass spectra of the unknown compound after derivatization with MSTFA and acetic anhydride, respectively.

The retention times and mass spectra of the unknown compound matched perfectly with the 4-methylthioamphetamine trimethylsilyl derivative and the 4-methylthioamphetamine acetyl derivative, respectively.

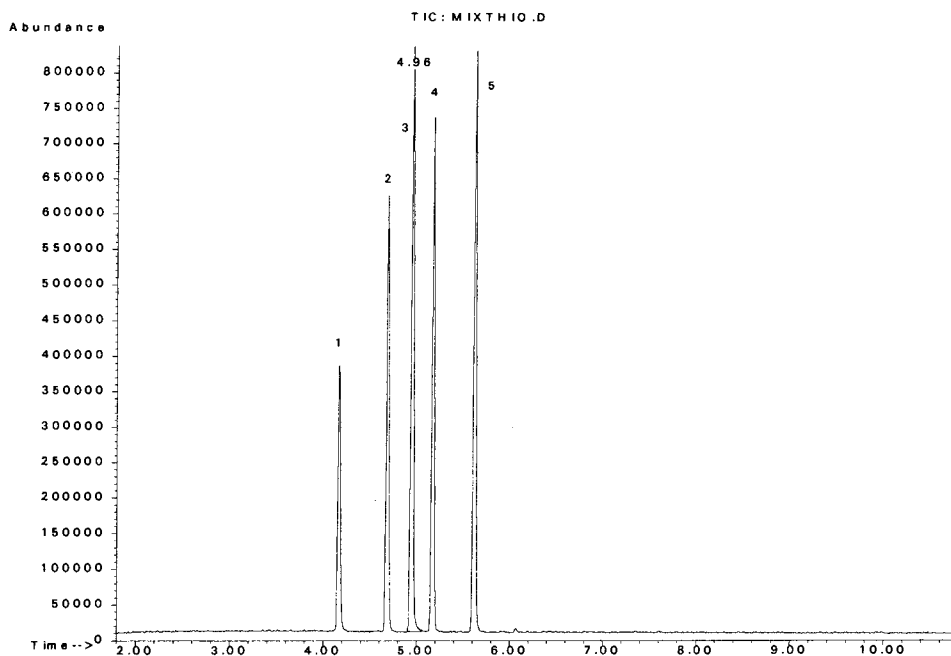


Fig. 7. GC-MS analysis of a mixture of (1) MDA, (2) MDMA, (3) 4-methylthioamphetamine, (4) MDEA and (5) MBDB.

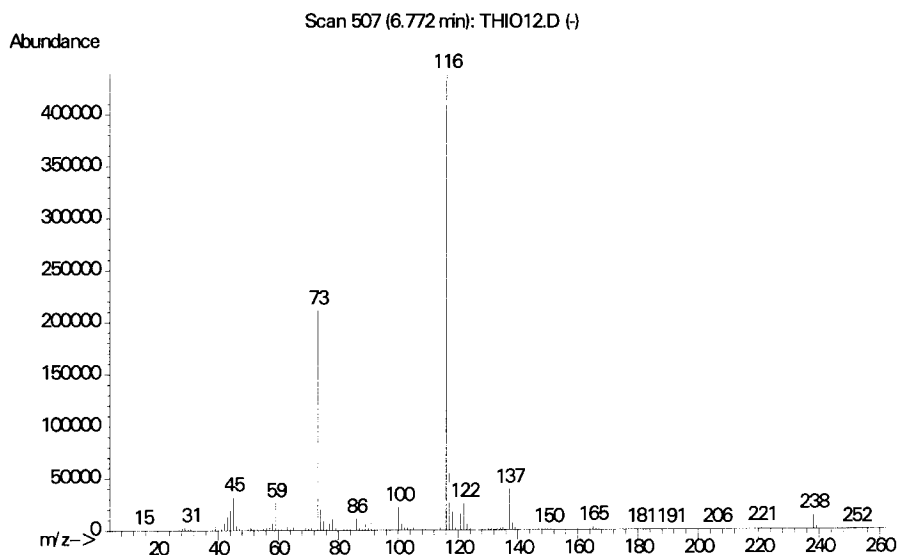


Fig. 8. Mass spectrum of 4-methylthioamphetamine after derivatization with N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA).

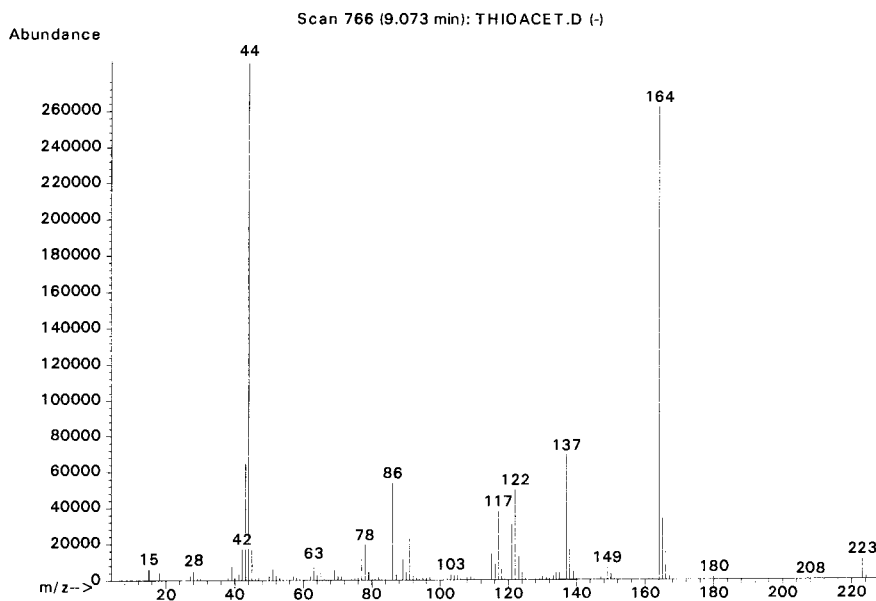


Fig. 9. Mass spectrum of 4-methylthioamphetamine after acetylation.

3.5. Infrared spectroscopy

The IR spectra of the synthesized nitropropene intermediate and 4-methylthioamphetamine hydrochloride are shown in Figs. 10 and 11.

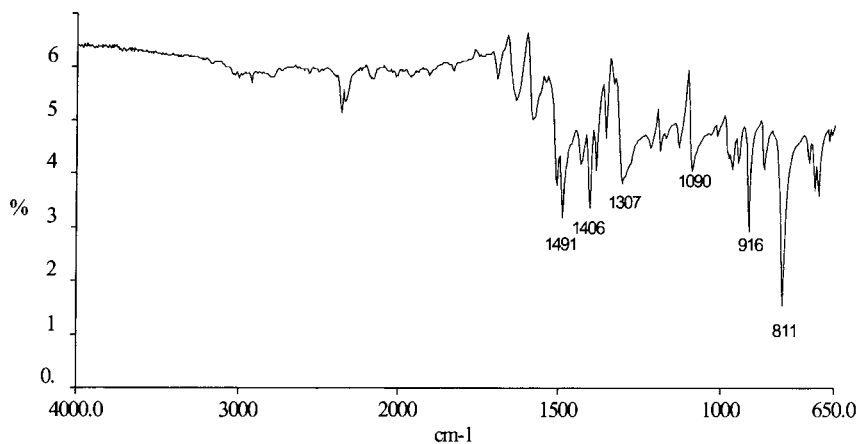


Fig. 10. IR spectrum of 1-(4-methylthiophenyl)-2-nitropropene.

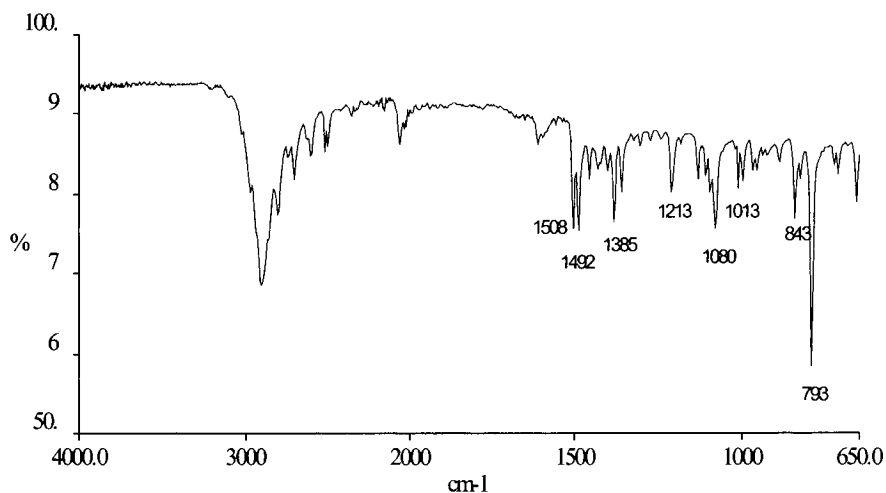


Fig. 11. IR spectrum of 4-methylthioamphetamine hydrochloride.

3.6. Capillary electrophoresis

Fig. 12 shows the UV spectra of the unknown compound, with a maximum absorption at 255 nm. Analysis of the prepared 4-methylthioamphetamine showed the same

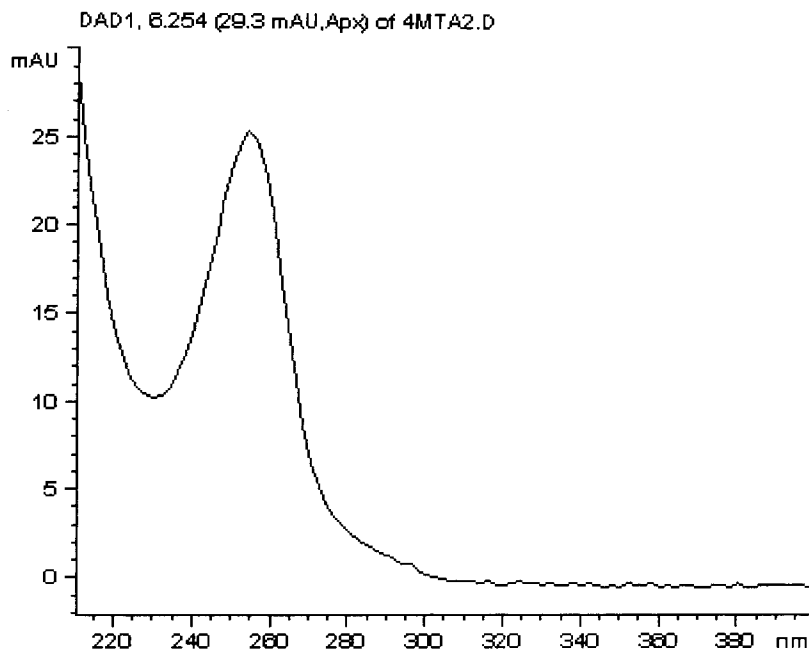


Fig. 12. UV spectra of 4-methylthioamphetamine.

retention time and UV spectra. Although this method enables the separation of the most common amphetamine derivatives, separation could not be achieved between MDMA and 4-MTA. Nevertheless, these two compounds can easily be differentiated by their UV spectra (MDMA showing two maxima absorption peaks at 235 and 285 nm).

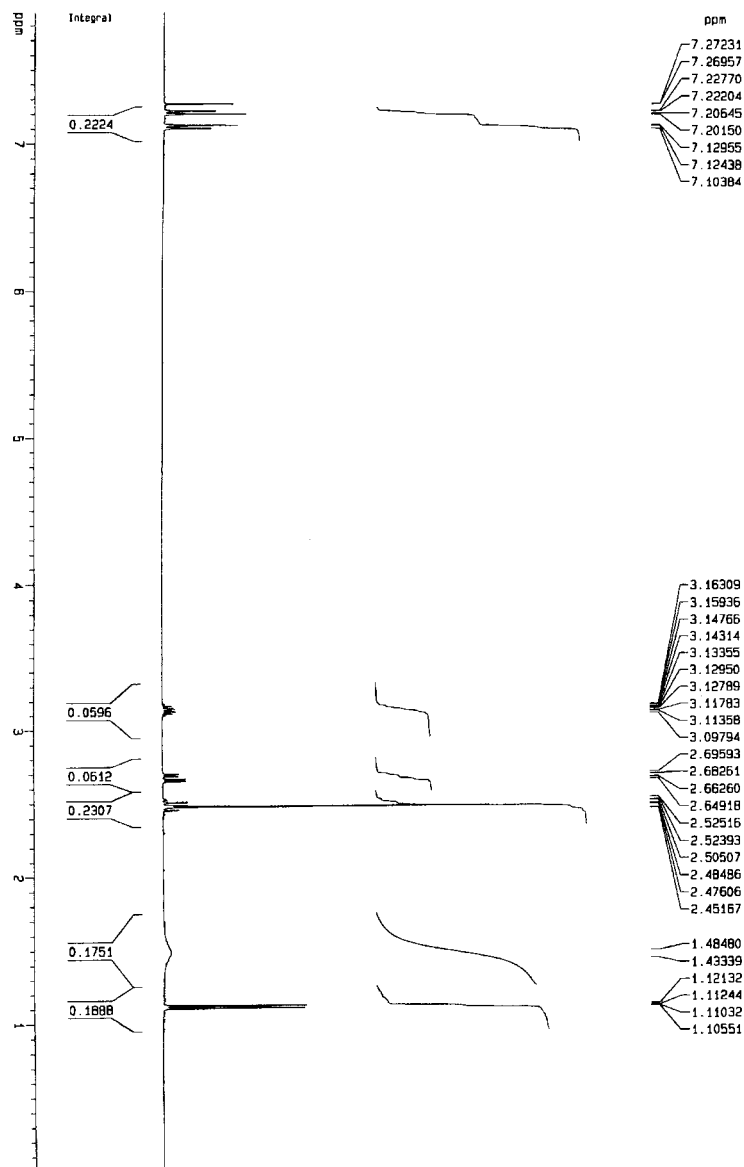


Fig. 13. ^1H -NMR spectra of 4-methylhioamphetamine base.

3.7. Quantitation

The 4-methylthioamphetamine HCl content of the tablets in the second Dutch case was approximately 140 mg/tablet. Levels of both the title compound and amphetamine in the blood sample in case 3 were 1.5 µg/ml.

3.8. ¹H-NMR

The proton nuclear magnetic resonance spectra is shown in Fig. 13. About 10 mg of 4-methylthioamphetamine base was dissolved in deuterated chloroform prior to analysis.

4. Discussion

Although 4-methylthioamphetamine is a known compound that has been synthesized previously and used particularly for pharmacological studies on animals, it appears that this compound is now appearing in illicit tablets. It has been reported in the United Kingdom, the Netherlands, Germany, Switzerland and even in Australia and it would not be surprising if this compound was found in other countries.

The purpose of selling this substance on the street market is not known as the effects on humans are not yet defined to the knowledge of the authors.

Currently, identification of this new compound may be hampered due to the lack of available standards or reference data or both. Therefore, it is hoped that the data reported here will help to overcome this problem.

As far as is known, 4-methylthioamphetamine is not currently treated as a controlled drug by legislation and 4-methylthiobenzaldehyde (which is the more obvious precursor) is commercially available.

Further studies on the toxicity and pharmacological effects on humans are necessary as the abuse and spreading of this compound seem to be increasing.

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