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Synthesis of 4-methyl-5-arylpyrimidines and 4-arylpyrimidines: route specific markers for the Leuckardt preparation of amphetamine, 4-methoxyamphetamine, and 4-methylthioamphetamine

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Abstract

General synthetic routes to 4-methyl-5-arylpyrimidines and 5-arylpyrimidines are described. 4-Benzylpyrimidine, 4-methyl-5-phenylpyrimidine, 4-(4-methoxybenzyl)pyrimidine, and 4-methyl-5-(4-methoxyphenyl)pyrimidine have been positively identified as route-specific by-products in the Leuckardt preparations of amphetamine and 4-methoxyamphetamine.

Using headspace solid phase microextraction (SPME) 4-(4-methoxybenzyl)pyrimidine and 4-methyl-5-(4-methoxyphenyl)pyrimidine have been identified in illicit tablets containing 4-methoxyamphetamine. This is an indication that illicit laboratories use the Leuckardt method for the preparation of 4-methoxyamphetamine.

Flatliner tablets containing 4-methylthioamphetamine have been screened for the presence of 4-(4-methylthiobenzyl)pyrimidine and 4-methyl-5-(4-methylthiophenyl)pyrimidine using both headspace and aqueous phase SPME. As these pyrimidines were not detected it would appear likely that illicit laboratories are not using the Leuckardt method for the preparation of 4-methylthioamphetamine.

Keywords: Designer drugs; Leuckardt reaction; Solid phase microextraction; 4-Benzylpyrimidine; 4-Methyl-5-phenylpyrimidine; 4-(4-Methoxybenzyl)pyrimidine; 4-Methyl-5-(4-methoxyphenyl)pyrimidine; 4-(4-Methylthiobenzyl)pyrimidine; 4-Methyl-5-(4-methylthiophenyl)pyrimidine; Amphetamine; 4-Methoxyamphetamine; 4-Methylthioamphetamine

1. Introduction

In certain circumstances a forensic drug chemist can be called upon to indicate the exact method by which a synthetic illicit drug might have been manufactured. For example, it can be of critical forensic importance to indicate whether or not a chemical collection in the possession of a suspect could have been used to prepare a batch of drugs. Manufacturing information also gives law enforcement agencies an indication as to which chemicals should be subject to sales control and monitoring, or even prohibited.

Two features of illicit drug synthesis make it possible to predict the route used. Firstly, as different synthetic schemes utilise different raw materials, then

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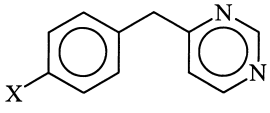
different schemes can give rise to characteristic profiles of chemical by-products. Secondly, for a given synthetic scheme, minor variations in the parameters associated with the reaction (e.g. temperature, molar ratio of the reagents) might give rise to variations in the yields of characteristic chemical by-products. Of great interest to forensic drug chemists are the so-called route-specific markers, these are by-products that are unique to a specific synthetic method. If such markers are detected in an illicit drug, then the forensic drug chemist can confidently predict the method by which the material has been manufactured.

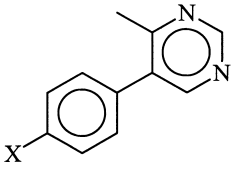
In the late 1970s two compounds that appeared to be present only in amphetamine prepared from phenyl-2-propanone via the Leuckardt synthesis were detected by van der Ark et al. [1]. These two compounds were identified as 4-benzylpyrimidine (1) and 4-methyl-5-phenylpyrimidine (2). Unfortunately, it would appear that the early work did not include the unambiguous synthesis of these compounds followed by the comparison of this authentic material with the by-products from the Leuckardt reaction. As a consequence, the assignment of identity must be considered tentative. One of the goals of the work described in this article was to synthesise authentic (1) and (2) and thereby confirm (or disprove) the identifications arrived at by van der Ark.

As described elsewhere [2–4], illicit 4-methoxyamphetamine (PMA) preparations have been the cause of fatalities in Australia; in the past they have been the cause of deaths in other countries [5,6]. Recent analysis of PMA tablets by us [4] led to the suggestion that aryl pyrimidines were present. If this were true, then by extension of the work of van der Ark it indicates that the illicit material was prepared from 4-methoxyphenyl-2-propanone via the Leuckardt reaction. Another goal of the work described herein was to synthesise 4-(4-methoxybenzyl)pyrimidine (3) and 4-methyl-5-(4-methoxyphenyl)pyrimidine (4) so that intelligence relating to the illicit manufacture of PMA might be gathered.

4-Methylthioamphetamine (MTA) is a relatively new designer drug that emerged in Europe [7–10]. Similar to PMA, it appears to be a dangerous drug; there have been fatal overdose outcomes in the Netherlands and UK [11]. It has recently turned up in seizures in Australia, but as yet there have been no deaths attributed to its abuse. Currently the exact route by which MTA is produced in illicit laboratories is not known. Other goals of this work were to prepare the Leuckardt-specific by-products 4-(4-methylthiobenzyl)pyrimidine (5) and 4-methyl-5-(4-methylthiophenyl)pyrimidine (6), and screen illicit preparations for the presence of these compounds.

This paper describes synthetic routes to 4-arylpyrimidines and 4-methyl-5-arylpyrimidines, and presents characteristic analytical data for them. The synthetic methodology presented is potentially applicable to the synthesis of a wide variety of other pyrimidines characteristic of the Leuckardt synthesis of many designer amphetamine drugs.





(1) X = H
(3) X = CH_3O
(5) X = CH_3S

(2) X = H
(4) X = CH_3O
(6) X = CH_3S

2. Methods and techniques

2.1. Materials and instrumental methods

Two gas chromatograph–mass spectrometers were used in this study, a Hewlett-Packard 5890 equipped with a 5972 MSD and electronic pressure programming, and a Hewlett-Packard 6890 equipped with a 5973 MSD and electronic pressure programming. For SPME a glass liner of 0.75 mm i.d. was used in the injector, while a standard split/splitless liner was used for liquid injections.

Helium was used as carrier gas at a constant linear flow rate of 62 cm/s for SPME and 55 cm/s for liquid injection; the column was a 15 m×0.257 mm× 0.25 μm DB-1 fused silica capillary; for SPME the oven program went from 50°C (2 min delay) to 300°C at a rate of 30°C/min; for liquid injection the oven program started at 90°C (3 min delay) and went to 300°C at 45°C/min, the injector was kept at 290°C (for SPME) or 300°C for liquid injection; for SPME the injector was run in the splitless mode for 30 s with a pressure pulse of 20 psig for 30 s; for liquid injections

the instrument was run in split mode using a 1 μl injection and a split flow of 50 ml/min; the mass spectrometer operated from 40 to 400 Da in electron impact mode, 70 eV, 3.6 scans per second.

The SPME 'syringe' used was a Supelco manual fibre holder equipped with a fibre coated with an 85 μm thick polyacrylate solid phase.

^{1}H and ^{13}C NMR data were collected using a Varian Gemini 200 spectrometer with deuterochloroform as solvent. Resonances were measured in parts per million relative to tetramethylsilane (δ=0.0) for hydrogen, and chloroform (δ=77.0) for carbon. Accurate mass measurements were performed by the Organic Mass Spectrometer Facility, Central Science Laboratory, University of Tasmania, while microanalyses were performed by the Chemistry Department, University of Otago, New Zealand. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh) and redistilled solvents.

Melting points were recorded using a Reichert hot stage melting point apparatus and are uncorrected.

2.2. Solid-phase microextraction of illicit preparations

2.2.1. Headspace SPME

The illicit preparations (crushed if tablet form) were placed into a 2 ml glass GC autosampler phial and capped with a teflon backed septum cap. After placing the phial on its side, the septum was carefully pierced with the SPME needle; it was allowed to protrude only about 5 mm into the phial. The fibre was then exposed to the headspace at the appropriate temperature while taking care not to allow the fibre to touch powder. Upon completion of headspace extraction the fibre was withdrawn into the needle, and then placed into the injector of the gas chromatograph. The fibre was then exposed immediately to the hot interior of the chromatographic injector and data acquisition commenced; the fibre was left in place, exposed to the hot environment, until required for the next extraction.

2.2.2. Aqueous SPME

A Flatliner (1/2 tablet) was dissolved in distilled water (10 ml) and filtered through a 0.45 μm Nylon filter into a small beaker. The fibre of an SPME device was dipped into the liquid for 30 min while it was stirred rapidly with the aid of a magnetic stirrer. After this time the fibre was rinsed with a few millilitre of distilled water and exposed to the gas chromatograph in the usual fashion.

2.2.3. Synthesis of trisformaminomethane

A mixture of diethyl sulphate (30.6 g) and formamide (51 g) was heated with stirring at 70–80°C for 2 h. The mixture was allowed to cool and the ethyl formate that had formed was distilled off under reduced pressure. The crystals that formed on cooling were collected, washed with cold absolute methanol (5 ml) and dried under vacuum to yield trisformaminomethane (7.8 g) as white crystals (Lit. mp 164–165°C [12], 163–164°C).

2.2.4. Synthesis of 4-methyl-5-phenylpyrimidine (2)

4-Methyl-5-phenylpyrimidine was prepared using the method of Koyama et al. [13]. A mixture of phenyl-2-propanone (2.21 g), trisformaminomethane (5 g), *p*-toluenesulphonic acid (0.2 g), and formamide (3.5 ml) was heated at 150–160°C with stirring for 8 h. The mixture was allowed to stand at room temperature overnight whereupon it was made alkaline with sodium hydroxide (2 M, 4 ml) and extracted with dichloromethane (4×20 ml). The combined organic extracts were dried over anhydrous sodium sulphate and then concentrated in vacuo to yield an oil. The oil was dissolved in a minimum quantity of hot hexane that, on cooling, yielded the pyrimidine as yellow crystals (0.91 g, 32%, Lit. mp 75–75.5°C [13], 76–76.5°C).

^{1}H NMR δ: 2.52 singlet (3H), 7.4 multiplet (5H), 8.54 singlet (1H), 9.08 singlet (1H). ^{13}C NMR: δ: 22.83, 128.33, 128.77, 128.98, 134.85, 135.83, 156.32, 157.17, 164.42. Mass spectrum 170 Da (M^{+}, 80%), 169 (64%), 115 (50%), 102 (100%) (Fig. 1).

2.3. Synthesis of 4-methylthiophenyl-2-propanone (8) via 1-(4-methylthiophenyl)-2-nitropropene (11)

A mixture of 4-methylthiobenzaldehyde (30.5 g), nitroethane (15 g), ethanol (35 ml) and butylamine (4 ml) was heated under reflux for 8 h. The mixture was then cooled to 0°C and the crystals that formed were collected and washed with cold ethanol. Concentration of the mother liquor afforded another crop of crystals. Recrystallisation from ethanol yielded

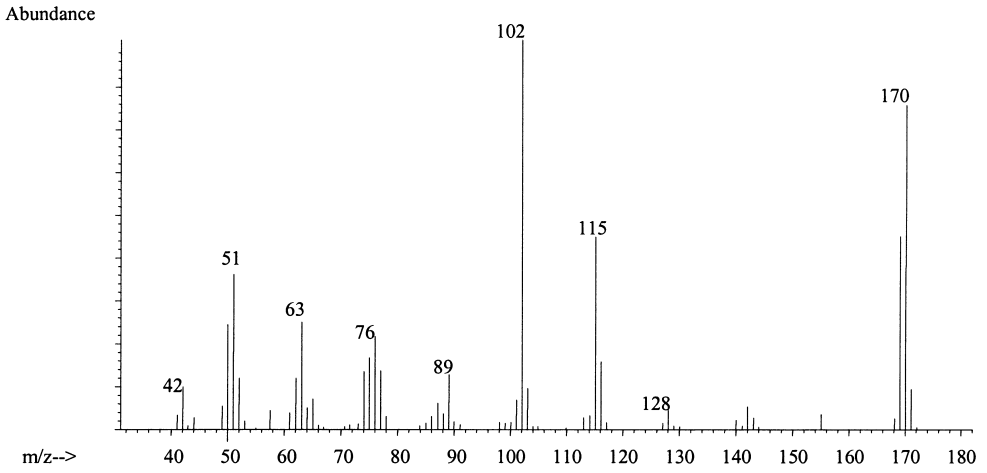


Fig. 1. Mass spectrum for 4-methyl-5-phenylpyrimidine (2).

1-(4-methylthiophenyl)-2-nitropropene (32.75 g, 78%) as bright yellow crystals, melting point 71–73°C. Microanalysis: found: C, 57.52%; H, 5.32%; N, 6.69%. $C_{10}H_{10}NO_2S$ requires C, 57.40%; H, 5.30%; N, 6.69%. ^{1}H NMR δ: 2.51 singlet (3H), 2.56 singlet (3H), 7.40 multiplet (4H), 8.13 singlet (1H). ^{13}C NMR δ: 14.15, 15.05, 125.94, 128.63, 130.48, 133.17, 142.16, 146.92. Mass spectral data agreed well with those published by Poortman-van der Meer [8], 209 Da (M^+, 26%), 162 (46%), 115 (100%); see Fig. 2. Concentrated hydrochloric acid (10 ml) was added dropwise over 1 h to a refluxing mixture of iron filings (20.75 g), ferric chloride (5 g), and 1-(4-methylthiophenyl)-2-nitropropene (10.8 g) in water (75 ml). After addition of the acid was complete the mixture was heated under reflux for an additional 7 h whereupon it was cooled and subjected to steam distillation (500 ml distillate collected). The distillate was extracted with diethyl ether (4×80 ml), the combined organic extracts were dried over anhydrous sodium sulphate, then concentrated in vacuo to yield 4-methylthiophenyl-2-propanone as a yellow oil (2 g, 22%).

^{1}H NMR δ: 2.15 singlet (3H), 2.47 singlet (3H), 3.65 singlet (2H), 7.17 multiplet (4H). ^{13}C NMR δ:

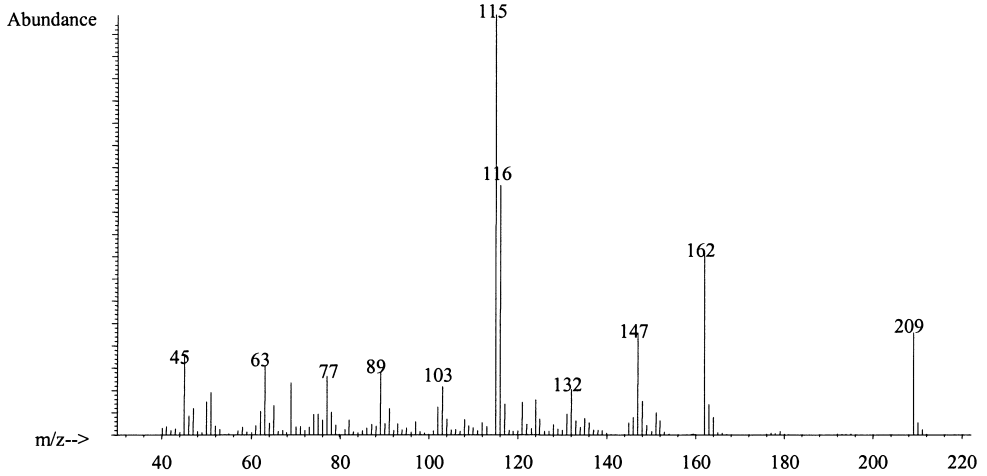


Fig. 2. Mass spectrum for 1-(4-methylthiophenyl)-2-nitropropene (11).

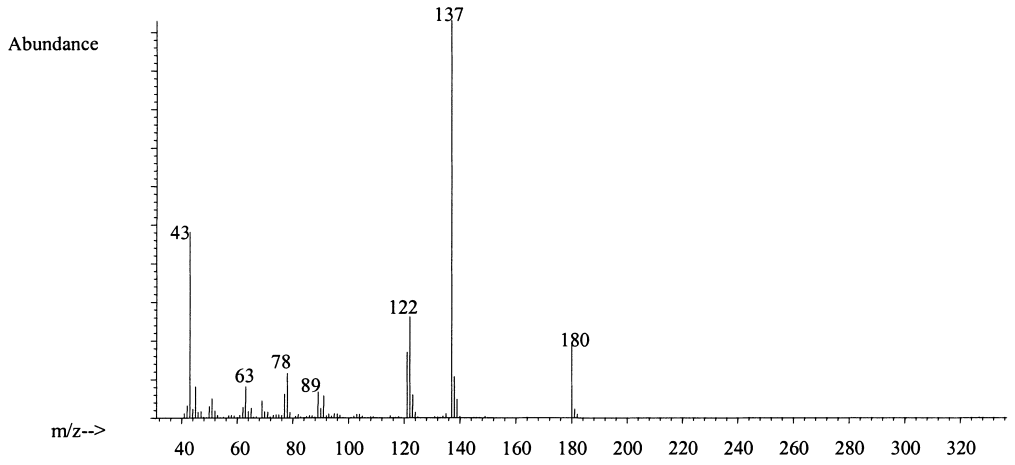


Fig. 3. Mass spectrum for 4-methylthiophenyl-2-propanone (8).

15.88, 29.17, 50.31, 127.04, 129.80, 131.02, 137.19, 205.99. Mass spectrum 180 Da (M^+, 18%), 137 (100%), 122 (25%); see Fig. 3. Accurate mass, found 180.0609 Da, $C_{10}H_{12}OS$ requires 180.0609.

2.4. Synthesis of 4-methyl-5-(4-methoxyphenyl)pyrimidine (4)

A mixture of 4-methoxyphenyl-2-propanone (2 g), trisformaminomethane (3.7 g), *p*-toluenesulphonic acid (0.15 g), and formamide (2.5 ml) was heated under reflux at 150–160°C for 8 h then allowed to cool to room temperature overnight. The resulting mixture was made alkaline with sodium hydroxide (2 M, 2 ml) then extracted with dichloromethane (3×25 ml). The combined organic extracts were washed with water (3×20 ml), dried over anhydrous magnesium sulphate, and concentrated in vacuo to yield an oil. The oil was taken up in a minimum quantity of hot hexane which, when cooled, afforded 4-methyl-5-(4-methoxyphenyl)pyrimidine (0.6 g, 25%) as yellow crystals, melting point 56–58°C. Microanalysis: found: C 71.76%, H 6.08%, N 13.72%, $C_{12}H_{12}N_2O$ requires C 71.97%, H 6.04%, N 13.99%. ^{1}H NMR δ: 2.53 singlet (3H), 3.88 singlet (3H), 7.02 multiplet (2H), 7.23 multiplet (2H), 8.52 singlet (1H), 9.05 singlet (1H). ^{13}C NMR δ: 22.83, 55.31, 114.22, 127.94, 130.14, 150.67, 156.29, 156.77, 159.67, 164.43. Mass spectrum 200 Da (M^+, 100%), 185 (17%), 132 (19%), 117 (25%), 89 (14%); see Fig. 4.

2.5. Synthesis of 4-methyl-5-(4-methylthiophenyl)pyrimidine (6)

A mixture of 4-methythiophenyl-2-propanone (2.4 g), trisformaminomethane (3.98 g), *p*-toluenesulphonic acid (0.2 g), and formamide (4.8 ml) was heated under reflux at 130°C for 6 h then allowed to cool to room temperature overnight. The resulting mixture was made alkaline with sodium hydroxide (1.25 M, 2 ml) then extracted with dichloromethane (2×50 ml). The combined organic extracts were washed with water (2×20 ml), dried over anhydrous sodium sulphate, and concentrated in vacuo to yield an oil. Flash chromatography of the oil on silica gel using ethyl acetate/dichloromethane (1:1) afforded 4-methyl-5-(4-methythiophenyl)pyrimidine (0.66 g, 23%) as yellow oil.

^{1}H NMR δ: 2.53 singlet (3H), 2.55 singlet (3H), 7.31 multiplet (4H), 8.52 singlet (1H), 9.07 singlet (1H). ^{13}C NMR δ: 22.86, 55.64, 126.51, 129.36, 129.71, 134.35, 156.29, 157.11, 158.77, 164.44. Mass spectrum 216 Da (M^+, 100%), 201 (14%), 168 (20%), 133 (43%); see Fig. 5. Accurate mass, found 216.0717 Da, $C_{12}H_{12}N_2S$ requires 216.0721.

2.6. Synthesis of 4-benzylpyrimidine (1)

This method, and those described below for other 4-arylpyrimidines, is based on that reported by Brederek et al. [12]. Benzyl chloride (1.95 g) in anhydrous diethyl ether (8 ml) was added dropwise over a period of 10 min to a stirred mixture of magnesium turnings

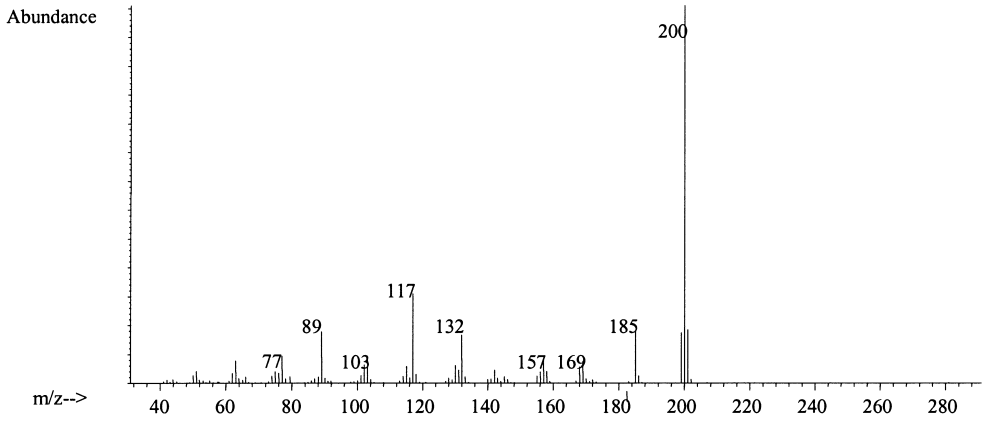


Fig. 4. Mass spectrum for 4-methyl-5-(4-methoxyphenyl)pyrimidine (3).

(0.31 g), diethyl ether (20 ml), and a small crystal of iodine under a nitrogen atmosphere. The mixture was heated under reflux until all of the magnesium had been consumed, cooled to 10°C, then treated dropwise with a solution of pyrimidine (1.0 g) in diethyl ether (8 ml) at such a rate that the mixture did not boil. After addition of pyrimidine the mixture was stirred at room temperature overnight then treated with a solution of aqueous ammonium chloride (saturated, 2 ml). The two phases were separated, the organic phase washed with water (20 ml), and the aqueous phase extracted with chloroform (2×20 ml). The combined organic phases were dried over anhydrous sodium sulphate and concentrated in vacuo to yield an oil. The oil was taken up in a few ml of acetone then treated with a saturated solution of potassium permanganate in acetone until no more manganese dioxide formed. The resulting solution was filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (elution with ethyl acetate/hexane, 1:3) to yield 4-benzylpyrimidine as a pale brown oil (0.6 g, 25%).

^{1}H NMR δ: 4.12 singlet (2H), 7.10 doublet (1H, 5.2 Hz), 7.3 multiplet (5H), 8.59 doublet (1H, 5.2 Hz), 9.15 singlet (1H). ^{13}C NMR δ: 44.15, 120.50, 126.94, 128.79, 129.19, 137.29, 156.94, 158.71, 169.33. Mass spectrum 170 Da (M^{+}, 32%), 169 (100%), 115 (25%), 91 (30%); see Fig. 6. Accurate mass, found 170.0839 Da, $C_{11}H_{10}N_2$ requires 170.0844.

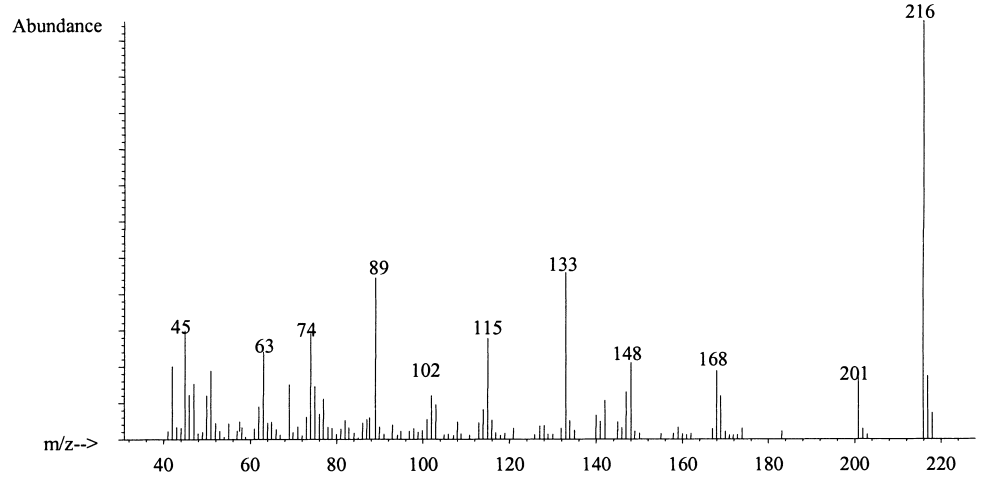


Fig. 5. Mass spectrum for 4-methyl-5-(4-methylthiophenyl)pyrimidine (5).

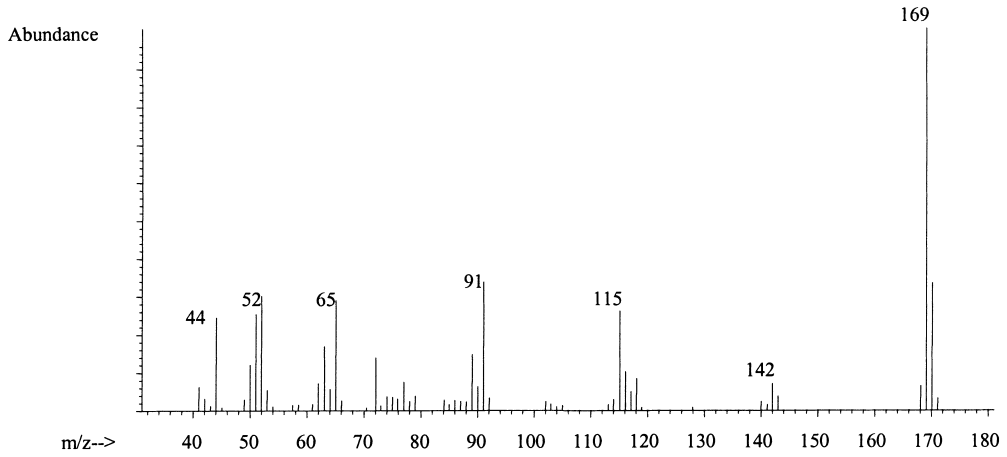


Fig. 6. Mass spectrum for 4-benzylpyrimidine (1).

2.7. Synthesis of 4-(4-methoxybenzyl)pyrimidine (3)

4-Methoxylbenzyl chloride was prepared from 4-methoxybenzyl alcohol using the method of Koyama et al. [13]. 4-Methoxylbenzyl chloride (1.96 g) in anhydrous tetrahydrofuran (8 ml) was added dropwise under nitrogen to a stirred mixture of magnesium turnings (0.31 g), tetrahydrofuran (8 ml) and a crystal of iodine at such a rate that gentle reflux was maintained. The mixture was heated under reflux until all of the magnesium had been consumed, cooled to 10°C, then treated dropwise with pyrimidine (1.0 g) at such a rate that the mixture did not exceed 30°C. After addition of pyrimidine the mixture was stirred at room temperature overnight then treated with a solution of aqueous ammonium chloride (saturated, 2 ml). The two phases were separated, the organic phase washed with water (4×50 ml), and the aqueous phase extracted with diethyl ether (2×50 ml). The combined organic phases were dried over anhydrous sodium sulphate and concentrated in vacuo to yield an oil. The oil was taken up in a few ml of acetone then treated with a saturated solution of potassium permanganate in acetone until no more manganese dioxide formed. The resulting solution was filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (elution with ethyl acetate/hexane, 1:4) to yield 4-(4-methoxybenzyl)pyrimidine as a pale yellow oil (0.4 g, 16%).

^{1}H NMR δ: 3.80 singlet (3H), 4.06 singlet (2H), 6.87 AA′ of AA′XX′ (2H), 7.10 doublet (1H, 5 Hz), 7.18 XX′ of AA′XX′ (2H), 8.58 doublet (1H, 5 Hz), 9.14 singlet (1H). ^{13}C NMR δ: 43.31, 55.25, 114.28, 120.42, 129.35, 130.23, 156.93, 158.68, 169.81 (signal due to quarternary carbon not detected). Mass spectrum 200 Da (M^+, 100%), 199 (65%), 185 (55%), 157 (18%), 121 (62%), 77 (14%); see Fig. 7. Accurate mass, found 200.0949 Da, $C_{12}H_{12}N_2O$ requires 200.0950.

2.8. Synthesis of 4-(4-methylthiobenzyl)pyrimidine (5)

4-Methylthiobenzyl chloride was prepared from thioanisole using the method of Pines et al. [15]. 4-Methylthiobenzyl chloride (3.0 g) in anhydrous diethyl ether (10 ml) was added dropwise under a nitrogen atmosphere to a stirred mixture of magnesium turnings (0.41 g), diethyl ether (20 ml), and a small crystal of iodine at such a rate that gentle reflux was maintained. The mixture was heated under reflux until all of the magnesium had been consumed, cooled to 10°C, then treated dropwise with a solution of pyrimidine (0.6 g) at such a rate that the mixture did not boil. After addition of pyrimidine the mixture was stirred at room temperature overnight then treated with water (30 ml). The organic phase was removed, the aqueous phase extracted with diethyl ether (2×20 ml), then the combined organic phases were washed with water (3×50 ml) and dried over anhydrous sodium sulphate. Concentration of the organic phase in vacuo yielded an oil. The oil was taken up in

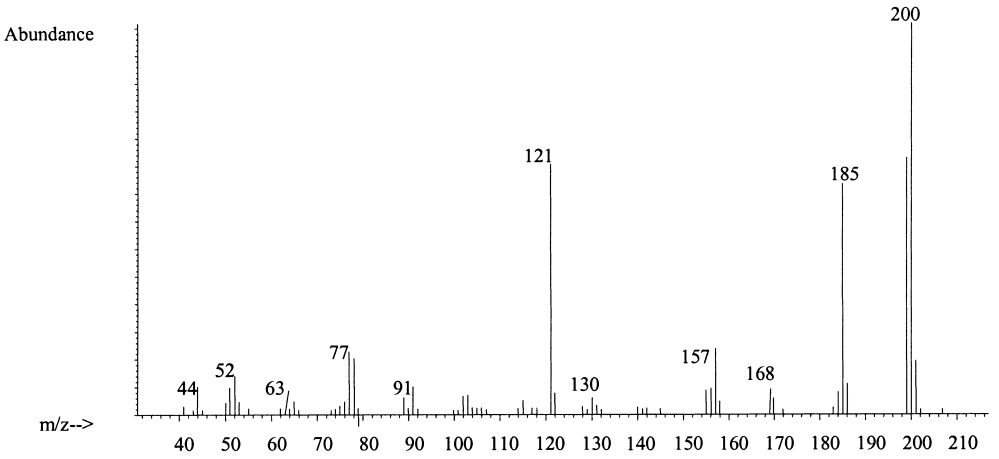


Fig. 7. Mass spectrum for 4-(4-methoxybenzyl)pyrimidine (3).

chloroform and oxygen was bubbled through for 3 days. Concentration of the mixture in vacuo followed by purification of the resulting oil by flash chromatography on silica gel (elution with ethyl acetate/hexane, 1:3) yielded 4-(4-methylthiobenzyl)pyrimidine as a pale yellow oil (0.3 g, 20%).

^{1}H NMR δ: 2.47 singlet (3H), 4.10 singlet (2H), 7.11 doublet (1H, 4.6 Hz), 7.17 multiplet (4H), 8.59 doublet (1H, 4.6 Hz), 9.13 singlet (1H). ^{13}C NMR δ: 15.97, 43.63, 120.49, 127.21, 129.01, 129.71, 134.18, 157.03, 158.77 (signal due to quarternary carbon not detected). Mass spectrum 216 Da (M^{+}, 100%), 201 (32%), 168 (58%), 137 (60%), 122 (33%); see Fig. 8. Accurate mass, found 216.0717 Da, $C_{12}H_{12}N_2S$ requires 216.0721.

3. Results and discussion

3.1. Synthesis of pyrimidines

A search of the chemical literature indicated that of the six pyrimidines listed above, only 4-methyl-5-phenylpyrimidine (2) has been synthesised. Koyama et al. [13] treated phenyl-2-propanone with trisformaminomethane ($CH(NHCHO)_3$, TFM) in formamide

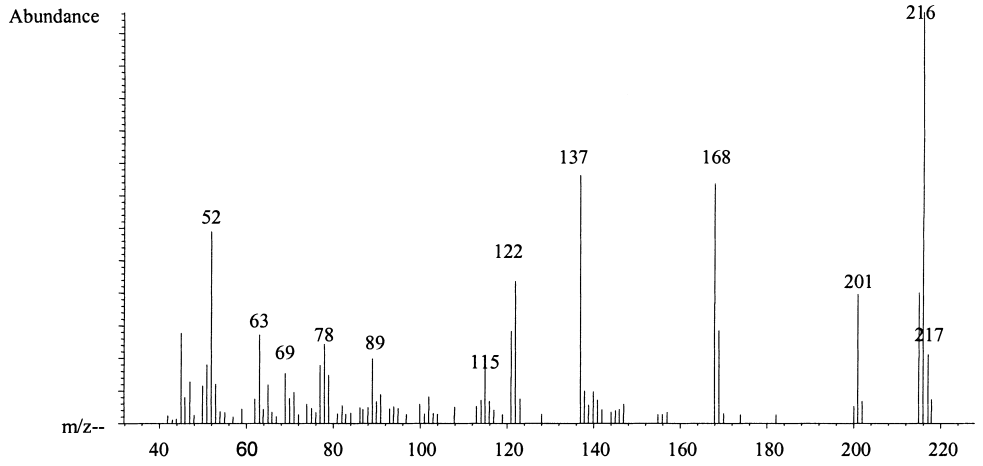
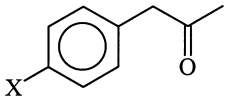


Fig. 8. Mass spectrum for 4-(4-methylthiobenzyl)pyrimidine (5).

with an acid catalyst to form (2). In our hands, the method of Koyama et al. readily yielded (2) and, by extension, was directly applicable to the synthesis of (4) and (6) from 4-methoxyphenyl-2-propanone (7) and 4-methylthiophenyl-2-propanone (8), respectively.



(7) X = CH_3O
(8) X = CH_3S

As there was no literature precedent for the syntheses of 4-arylpyrimidines such as (1), (3), and (5), a synthetic route had to be devised. There were indications, however, that other 4-substituted pyrimidines had been prepared by nucleophilic displacement reactions upon 4-chloropyrimidine [16], or by addition of Grignard reagents to pyrimidine followed by oxidation [12]. The action of benzylmagnesium chloride upon 4-chloropyrimidine failed to yield any 4-benzylpyrimidine; a complex mixture of compounds was produced. However, benzylmagnesium chloride did add readily to pyrimidine to yield 4-benzyl-3,4-dihydropyrimidine (9), which was readily oxidised to (1) using potassium permanganate (Scheme 1). Similarly, (3) and (5) were prepared by treating pyrimidine with 4-methoxybenzylmagnesium chloride and 4-thiomethylbenzylmagnesium chloride, respectively, followed by oxidation. As it was felt that the use of potassium permanganate in the preparation of (5) might lead to concomitant oxidation of the methylthio moeity, oxygen gas was used instead. The position of attack by the Grignard reagent upon pyrimidine was readily determined from ^1H NMR data, in particular all products clearly showed a singlet resonance at approximately δ=9.15 and doublets near 7.1 and 8.6.

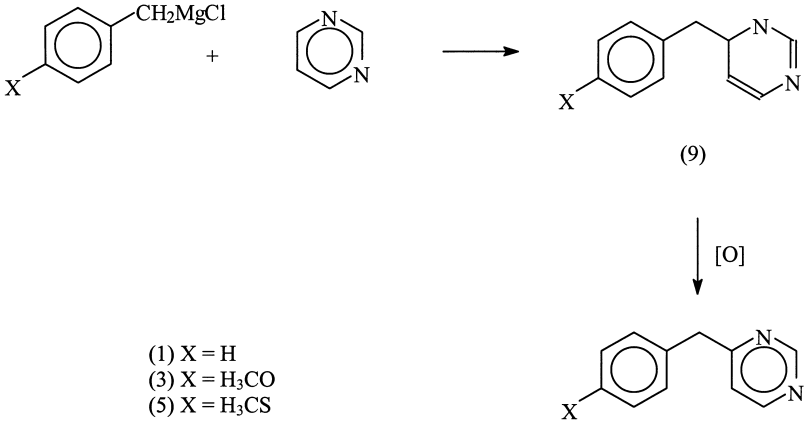
3.2. Pyrimidines as markers for the Leuckardt reaction

A trial preparation of amphetamine using the Leuckardt reaction was performed. The crude reaction mixture (after acid hydrolysis) was examined by GC–MS (see Fig. 9). Using retention time and mass spectral data obtained from the synthesised authentic (1) and (2) as a guide, both of these compounds were confirmed as by-products in the Leuckardt reaction product. The suggestions put forward by van der Ark [1] that (1) and (2) are markers for the Leuckardt reaction have therefore been confirmed.

A trial preparation of PMA via the Leuckardt reaction was also conducted. GC–MS (see Fig. 10) indicated that both (3) and (4) were present as by-products in this reaction.

In both Leuckardt reaction trials it was found that the 4-methyl-5-arylpyrimidines were produced in much greater abundance (about 5:1 ratio) than the 4-arylpyrimidines.

It should also be pointed out that using the gas chromatographic conditions as described in Section 2, we found that the pyrimidines virtually co-elute with their related formylamphetamine, forming a convoluted envelope. Therefore, in Leuckardt reaction



(9)

(1) X = H
(3) X = H_3CO
(5) X = H_3CS

Scheme 1.

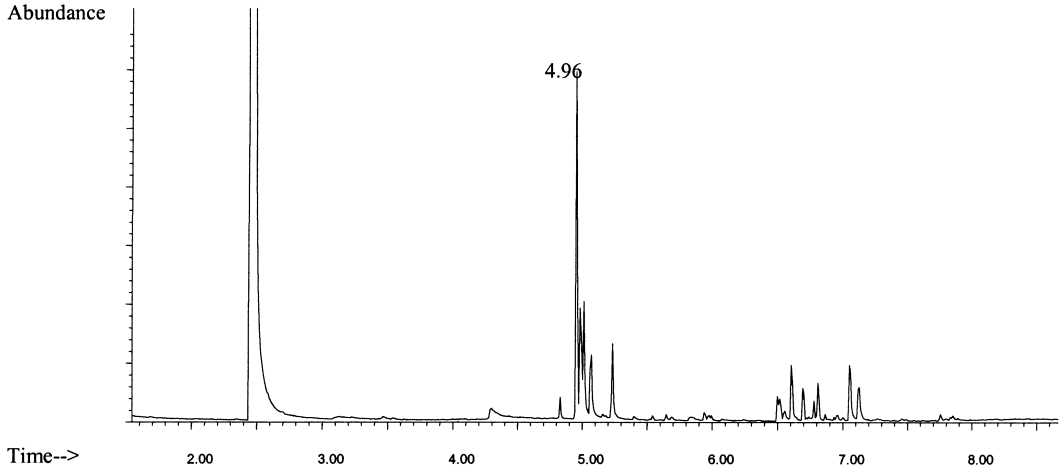


Fig. 9. GC–MS data for trial Leuckardt preparation of amphetamine (after hydrolysis). Crude reaction extract in dichloromethane was injected as a liquid sample into the chromatograph. The compounds eluting at 5.01 and 4.96 min, respectively, were identified as 4-benzylpyrimidine (1) and 4-methyl-5-phenylpyrimidine (2) on the basis of their retention time and mass spectral data (see Figs. 6 and 1, respectively). The over-range peak at 2.5 min is due to amphetamine, while the peak eluting between (1) and (2) was residual *N*-formylamphetamine.

product that has not been completely hydrolysed, the formyl amphetamine might mask the presence of pyrimidines. This finding indicates that careful control of the chromatographic conditions is required for drug profiling, or careful inspection of chromatographic data should be performed.

3.3. Pyrimidines in illicit preparations

Earlier work by us [4] and others [17] has indicated that solid-phase micro-extraction (SPME) is a valuable technique that is complimentary to liquid–liquid extraction for the generation of manufacturing by-

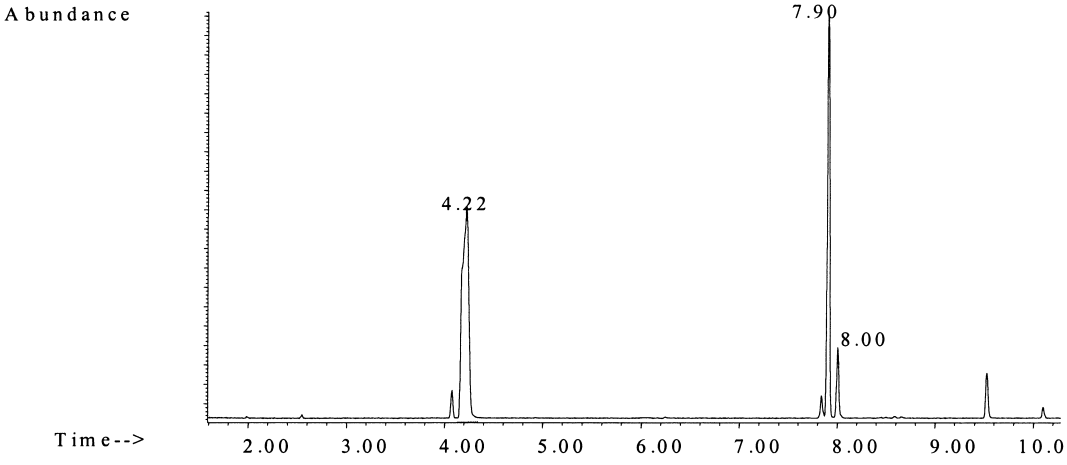


Fig. 10. GC–MS data for trial Leuckardt preparation of 4-methoxyamphetamine (after hydrolysis). Crude reaction extract in dichloromethane was injected as a liquid sample in the instrument. The compounds eluting at 7.90 and 8.00 min were identified as 4-methoxybenzylpyrimidine (3) and 4-methyl-5-(4-methoxyphenyl)pyrimidine (4), respectively, on the basis of their retention time and mass spectral data (see Figs. 4 and 7). The distorted peak at 4.22 min is due to 4-methoxyamphetamine, while the peak eluting very close to (3) and (4) was residual *N*-formyl-4-methoxyamphetamine.

product profiles of illicit tablets and powders. In particular the method is rapid, simple, and offers repeatability comparable to liquid–liquid extraction. Under the SPME conditions described [4,17], extraction of tablet excipients and the active drug was minimal. As a consequence extracts were relatively rich in manufacturing by-products, but deficient with respect to the active drug and excipients, even though these compounds are usually present in relatively high abundance in illicit tablets and powders. Compared to analysis of liquid extracts derived from illicit preparations, gas chromatography of 'clean' SPME extracts did not suffer from problems arising from injection of high concentrations of drug and excipients.

In the current study headspace SPME in conjunction with GC–MS was used to screen several illicit PMA preparations. A typical chromatogram is presented in Fig. 11. As demonstrated in our previous work, the impurity profile is free from contributions arising from PMA as the drug is present in the illicit preparations as its involatile salt. In all the pills examined both (3) and (4) were detected, an indication

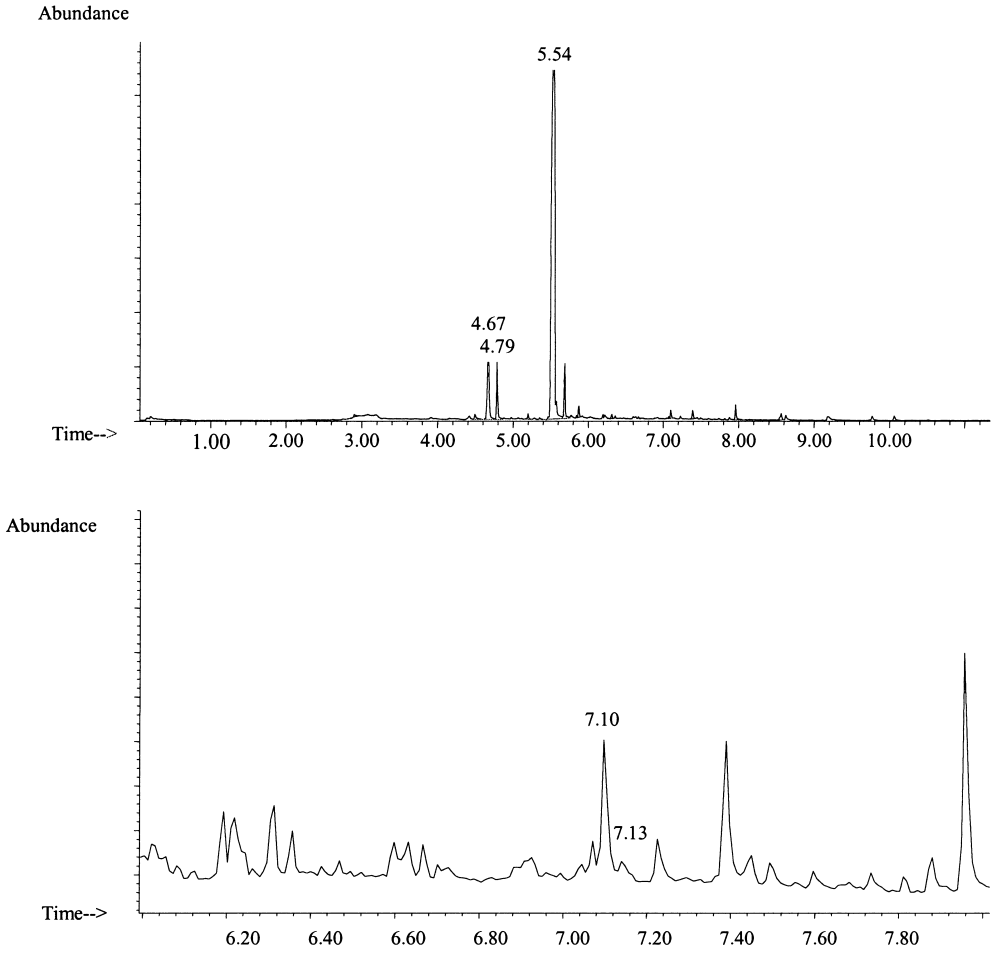


Fig. 11. GC–MS data for headspace SPME performed at 65°C for 30 min over one-half of an illicit tablet containing 4-methoxyamphetamine; bottom trace is an expansion of the data between 6 and 8 min. The identity of the compound eluting at 7.10 min was confirmed using retention time and mass spectral data as 4-(4-methoxybenzyl)pyrimidine (3), while the compound eluting at 7.13 min was confirmed as 4-methyl-5-(4-methoxyphenyl)pyrimidine (4). The compound eluting at 5.54 min was identified as 4-methoxyphenyl-2-propanone (7), that at 4.79 min was identified as 4-methoxybenzaldehyde, and that at 4.67 min was identified as 4-methoxyphenol.

that local PMA is manufactured using the Leuckardt reaction. As reported previously [4] it would appear that the 4-methoxyphenyl-2-propanone used in the illicit manufacture of the drug was itself of illicit manufacture, presumably originating from 4-methoxybenzaldehyde. However, it is still unclear as to the exact conditions under which the ketone was produced.

Several illicit tablets containing 4-methylthioamphetamine were screened for the presence of pyrimidines using headspace SPME-GC–MS. The tablets used weighed about 0.3 g, and were white, half-scored; the only active compound present appeared to be methylthioamphetamine. Such preparations are the only type to be encountered so far in Australia, and they appear to be identical to some preparations encountered in UK [9,11]. Other tablets reported in Europe have been heavier and larger than local specimens, and caffeine has been present as well as the active drug [7,8,10,11]. Except for seizures in Germany and Switzerland, where the tablets featured a five pointed star design, all other tablets encountered in Europe and Australia have been flat, half-scored and white, characteristics that have led to the nickname 'Flatliners' being adopted [11].

A seizure of 1-(4-methylthiophenyl)-2-nitropropene (11) in Europe [10] suggests that illicit 4-methylthioamphetamine might be derived from this compound. However, there is no evidence to indicate exactly how this transformation was brought about; (11) might have been reduced directly to 4-methylthioamphetamine, or it might have been converted into 4-methylthiophenyl-2-propanone which in turn was elaborated into 4-methylthioamphetamine using, for example, the Leuckardt reaction. In order to investigate the question of the intermediacy of the Leuckardt reaction, it was decided to screen 'Flatliners' for the presence of pyrimidines (5) and (6). Headspace SPME experiments on 'Flatliners' were carried out both at room temperature for short periods (about 5 min) and elevated temperatures (60 and 80°C) for 30 min. Using these extraction conditions, and with the mass spectrometer operating under full scan acquisition, neither (5) nor (6) was detected (see Fig. 12). In case the concentration of (5) or (6) was too low in the headspace for reliable detection, SPME was also carried out on an aqueous solution of a Flatliner tablet. As can be seen in Fig. 13, SPME from the aqueous phase did result in an increase in abundance of high molecular weight compounds extracted, but

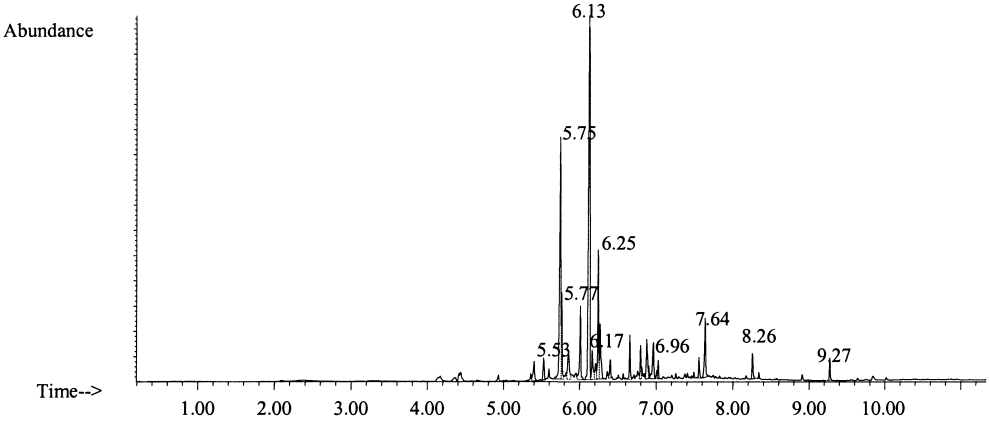


Fig. 12. GC–MS data for headspace SPME performed at 80°C for 30 min over one-half of an illicit tablet containing 4-methylthioamphetamine. Under the chromatographic conditions used, 4-(4-methylthiobenzyl)pyrimidine (5) and 4-methyl-5-(4-methylthiophenyl)pyrimidine (6) elute at close to 8 min. Compounds with mass spectral data corresponding to those for (5) and (6) were not detected. 1-(4-Methythiophenyl)-2-nitropropene (11) was not detected. The compound eluting at 5.53 min was identified as 4-methylthiobenzaldehyde (10), at 5.75 min 4-methythiobenzyl alcohol (13) was tentatively identified, at 6.13 min 4-methylthiophenyl-2-propanone (8) was identified, and at 6.17 min 4-methylthiophenyl-2-propanol (12) was tentatively identified. The mass spectral data for these compounds are given in Figs. 3 and 14–16. The large peaks at 6.96, 7.64, and 8.26 min were tentatively identified as fatty acids, while the peak at 9.27 min was tentatively identified as a phthalate ester.

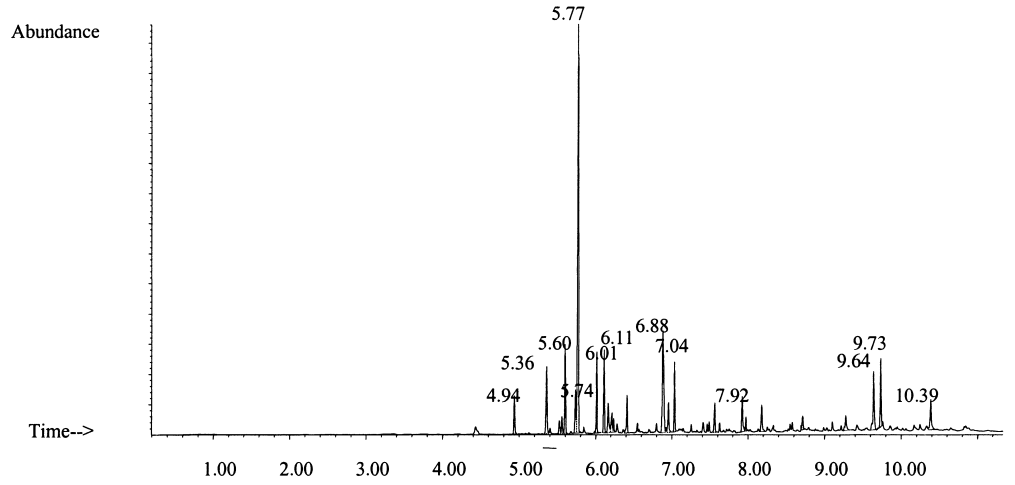


Fig. 13. GC–MS data for SPME performed on an aqueous solution of one half of an illicit tablet containing 4-methylthioamphetamine. Under the conditions used neither (5) nor (6) nor (11) were detected. 4-Methylthiobenzaldehyde (10) was identified at 5.53 min, 4-methylthiobenzyl alcohol (13) was tentatively identified at 5.74 min, and 4-methylthiophenyl-2-propanone (8) was identified at 6.11 min. Compared to headspace extraction for the same illicit preparation (see Fig. 12), three differences were noted using extraction from aqueous solution. Firstly, the abundance of the substance eluting at 5.77 min is greatly enhanced; this compound is as yet unidentified, but it appears to be either 1-(4-methylthiophenyl)propene or 1-(4-methylthiophenyl)-2-propene on the basis of its mass spectral data (see Fig. 17). Secondly, a trace of 4-methylthioamphetamine was detected at 6.16 min. Finally, compounds at higher molecular weight were recovered, but the level of fatty acid extraction is relatively low.

again neither (5) nor (6) was detected. It would therefore appear likely that 4-methylthioamphetamine, or at least that available locally, is not produced via the Leuckardt method.

As a result of the synthetic work towards 4-methyl-5-(4-methylthiophenyl)pyrimidine (6), authentic specimens of 4-methylthiophenyl-2-propanone (8), 4-methylthiobenzaldehyde (10), and 1-(4-methylthiophenyl)-2-nitropropene (11) were at hand. It was possible to confirm the presence of both (8) and (10) in the headspace SPME extract of the Flatliner tablets; nitropropene (11) was not detected however.

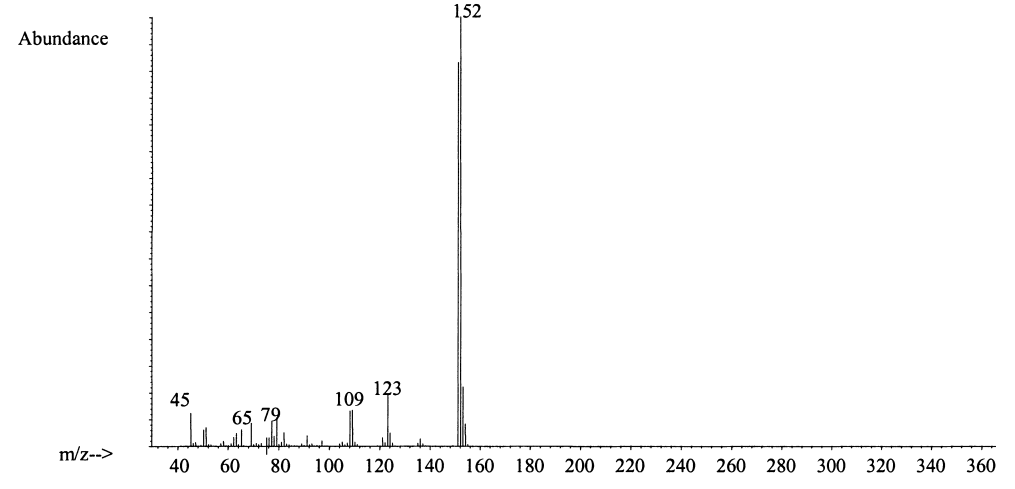


Fig. 14. Mass spectrum for compound eluting at 5.53 min in Fig. 12, identified as 4-methylthiobenzaldehyde (10).

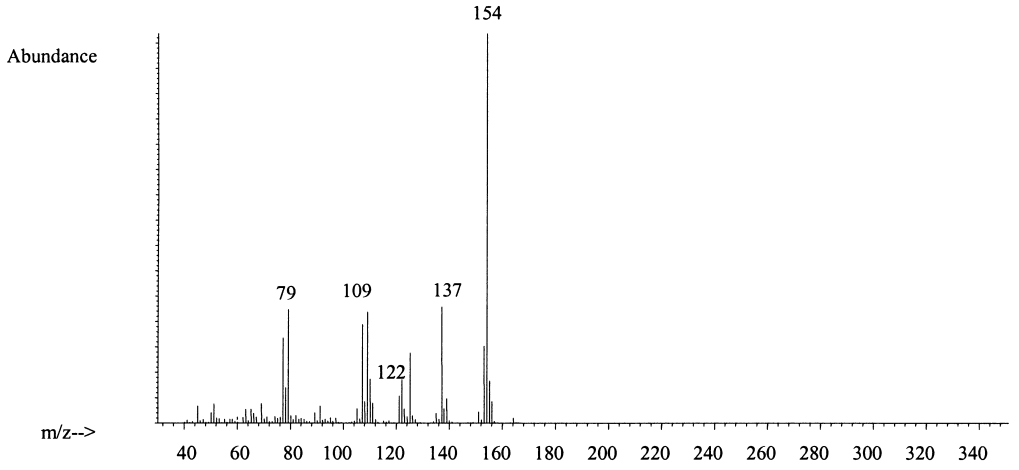


Fig. 15. Mass spectrum for compound eluting at 5.77 min in Fig. 12, tentatively identified as 4-methylthiobenzyl alcohol (13).

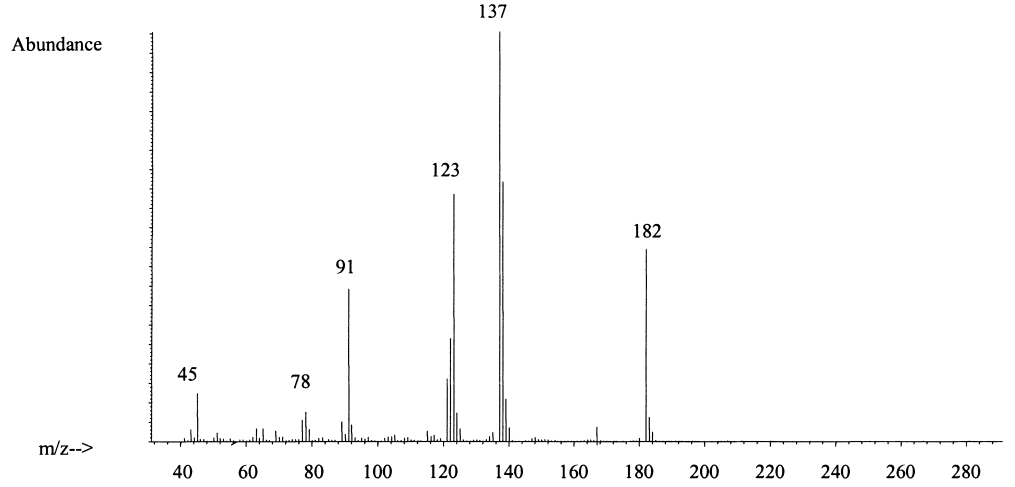


Fig. 16. Mass spectrum for compound eluting at 6.17 min in Fig. 12, tentatively identified as 4-methylthiophenyl-2-propanol (12).

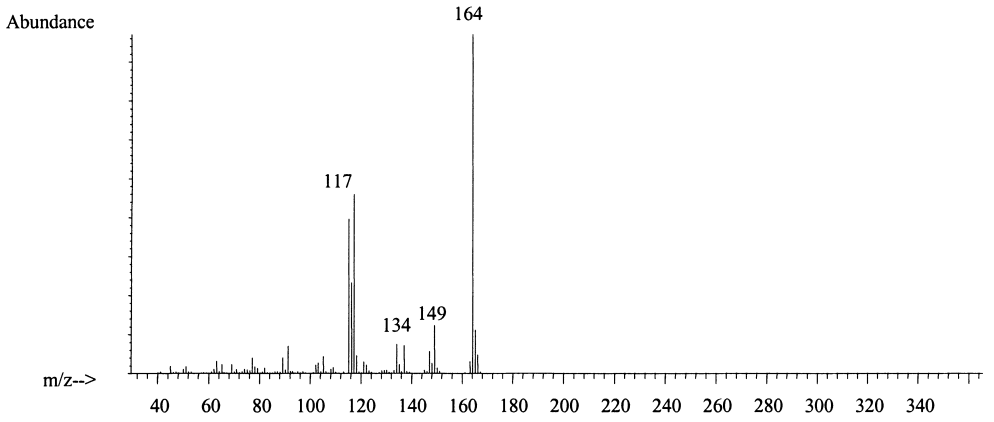
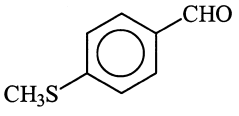


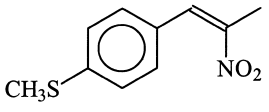
Fig. 17. Mass spectrum for unknown compound (possibly 1-(4-methylthiophenyl)propene or 1-(4-methylthiophenyl)-2-propene) eluting at 5.77 min as extracted from an aqueous solution of a 'Flatliner' tablet (see Fig. 13).

In addition, a tentative identification of 4-methylthiophenyl-2-propanol (12) and 4-methylthiobenzyl alcohol (13) in the extract was made. Mass spectral data for these compounds are presented (Figs. 14–17). The presence of (8) and (13) in other Flatliners has been reported elsewhere [9,14].

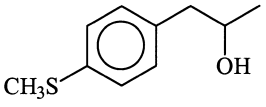
Although it would appear that the illicit route to MTA involves a reductive step, the exact pathway is still unclear.



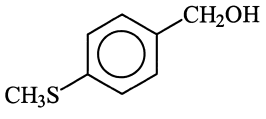
(10)



(11)



(12)



(13)

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