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The syntheses of 1-(2-thienyl)-2-(methylamino) propane (methiopropamine) and its 3-thienyl isomer for use as reference standards

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1-(2-Thienyl)-2-(methylamino)propane (methiopropamine, MPA), the thiophene analogue of methamphetamine, has recently appeared on a number of websites offering 'legal highs' for sale and has also been reported as a new psychoactive substance by the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) Early Warning System. The drug is currently not controlled in the European Union (EU) but it would be expected that forensic laboratories will encounter it during routine analysis. As no reference standard was available, we have established a three-step protocol for its synthesis. We have also synthesized its 3-thienyl isomer and have established that this is separable from methiopropamine by gas chromatography using one of our routine protocols. The synthetic methodology presented here could be readily extended to the syntheses of analogous compounds. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: methiopropamine; MPA; synthesis; mass spectrum; forensic; separation

Introduction

1-(2-Thienyl)-2-(methylamino)propane (methiopropamine, MPA) (**1a**) (Figure 1) has recently appeared on a number of websites offering recreational drugs/'legal highs' for sale.[1–3] Its preparation was first reported in 1942[4] but it remained in obscurity until January 2011 when its presence in a drug seizure was reported by Finnish authorities *via* the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) Early Warning System.[5] Methiopropamine is the thiophene equivalent of methamphetamine; personal possession is currently legal in Ireland as it is not covered by the Misuse of Drugs Acts but its sale through Head Shop outlets and websites could be prevented by the Criminal Justice (Psychoactive Substances) Act 2010.[6,7] The appearance of methiopropamine in the recreational drugs marketplace is an example of an attempt to circumvent laws controlling amphetamines by substituting heterocyclic moiety for a phenyl group. Such a replacement with a thiophene is a classic example of *bio*-isosterism and is a common molecular substitution in drug development.[8,9] Users discussing methiopropamine on popular drugs forums have anecdotally described its effects as a combination of mephedrone and amphetamine and it is referred to as 'legal methamphetamine'. A number of users have also reported adverse effects such as tightening of the chest and increased heart rate, which may be due to its pressor properties.[10,11]

The formal pharmacology of methiopropamine has not been well studied. However, the *N-des*-methyl derivative was found not to have any central nervous system (CNS) stimulant activity following oral administration to humans (maximum dose 20 mg, body weights not specified).[11] It would be expected that the presence of the *N*-methyl group in methiopropamine would increase its lipophilicity (and log P) thus enhancing its penetrability through the blood-brain barrier and possibly its activity. Recreational drug users discussing the effects of methiopropamine on Internet drugs forums have reported that it does indeed possess stimulant properties.[10] Also, recently it has been reported that *N-des*-methyl derivative possesses some MAO inhibitory properties.[12] It is probable that this may be metabolite of methiopropamine in humans as *N*-dealkylation is a common metabolic pathway. This is of some concern as it may lead to drug-drug interactions in instances where recreational drugs users 'experiment' with 'cocktails' of drugs.

Considering the likelihood that methiopropamine will gain some popularity amongst users, we required a reference standard for forensic drugs analysis in our laboratory. Our approach to the synthesis was that it should be straightforward and adaptable enough to facilitate the preparation of analogous heterocyclic 'amphetamines'. As standard 'amphetamine chemistry' is well established and we chose to utilize this.[13] The overall reaction pathway is shown in Figure 2. We also extended the synthetic protocol to its 3-thienyl isomer (**1b**) (Figure 1)[14] to establish if they were separable by gas chromatography (GC), a point which may be crucial in future forensic cases.

Experimental

Chemicals

Thiophene-2-carboxaldehyde, nitroethane, n-butylamine, acetic acid, iron powder, 8 M ethanolic methylamine solution, methanol and sodium cyanoborohydride were obtained from Sigma-Aldrich

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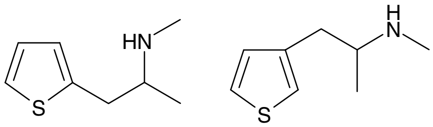


1a **1b**

Figure 1. Stuctures of methiopropamine (**1a**) and its 3-thienyl isomer (**1b**).

Chemical Co. (Arklow, Ireland). Thiophene-3-carboxaldehyde was obtained from Alfa Aesar Ltd. (Heysham, UK) and 2 M ethereal hydrogen chloride from Acros Chemicals (Fisher Scientific, Dublin, Ireland). Reactions were heated and stirred magnetically as required using an IKA RCT basic hotplate/stirrer with an ETS-D5 temperature probe (Dublin, Fisher Scientific, Ireland).

Instrumentation

^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectra were recorded on a Bruker AV600 NMR spectrometer using a 5 mm TCI cryoprobe. High resolution electrospray mass spectra (HR-ESIMS) were recorded on by direct injection on an LTQ Orbitrap Discovery (Thermo Scientific, Bremen, Germany). Melting points are uncorrected. GC/EIMS (electron impact mass spectrometry) under the following conditions: Agilent 6890 gas chromatograph with split-splitless injection (2 µl injected) and a HP-5 MS column (30 m × 0.25 mm, 0.25 µm film thickness). Helium (He) was used as the carrier gas at a flow rate of 1.0 ml/min. The GC was coupled to an Agilent 5973 MSD (EI, 70 eV, TIC mode scanning m/z40–800) and injector port was set at 300 °C, the transfer line at 280 °C, the ionization source at 220 °C and the quadrupole at 150 °C. The following temperature program was used: 50 °C for 1 min, 15 °C/min to 280 °C, 280 °C for 6.33 min, 10 °C/min to 300 °C and 300 °C for 10.34 min

1-(2-Thienyl)-2-nitropropene (3a)

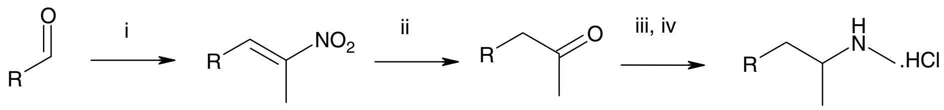
A mixture of thiophene-2-carboxaldehyde (17.7 g, 0.158 mol), nitroethane (32 ml, 0.45 mol), n-butylamine (18 ml), and acetic acid (80 ml) was heated at 80 °C for 1 h with constant stirring (magnetic stirrer). The mixture was allowed to cool and product was collected by filtration to give **(3a)** as yellow needles (12.58 g, 0.074 mol, 47%): ^{1}H NMR ($CDCl_3$) δ 8.31 (1 H, s, $C\underline{H}{=}C$), 7.67 (1 H, d, J = 5.0 Hz, thiophene H-5), 7.45 (1 H, d, J = 3.8 Hz, thiophene H-3), 7.21 (1 H, dd, J = 5.0 Hz, J' = 3.8 Hz, thiophene H-4) and 2.57 (3 H, s, $C\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 144.31, 135.15, 134.7, 131.70, 128.15, 127.16 and 14.17; EIMS m/z (%) 169 (M^+, 46), 121 (88), 112 (81), 84 (81), 77 (62) and 45 (100); m. pt. 66–68 °C (lit.[10] 65–67 °C).

1-(2-Thienyl)propan-2-one (4a)

A mixture of iron powder (25 g, 0.45 mol) and 90% acetic acid (200 ml) was heated to 50–60 °C. 1-(2-Thienyl)-2-nitropropene (**3a**) (6.29 g, 38 mmol) was added in several portions over approximately 5 min (with manual swirling during each addition). Some effervescence was noted. The mixture was then heated (with occasional manual swirling) at 90–100 °C for 1 h, allowed to cool and added to water (500 ml). Extraction (dichloromethane), washing (saturated aqueous sodium bicarbonate), drying (magnesium sulphate) and removal of solvent afforded a brown oil (3.69g, 26 mmol, 68%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.23 (1 H, d, $J = 4.9$ *Hz,* thiophene H-5), 6.98 (1 H, dd, $J = 4.9$ *Hz*, $J' = 3.0$ *Hz*, thiophene H-4), 6.90 (1 H, d, $J = 3.0$ *Hz,* thiophene-H-3), 3.89 (2 H, s $C\underline{H_2}$) and 2.21(3 H, s, $C\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 204.04, 134.7, 127.1, 126.8, 125.0, 44.4, and 28.9; EIMS m/z (%) 140 (M^+, 44), 97 (100) and 43 (54); HR-ESIMS found 163.0193 (theor. for M + Na, C_7H_8OSNa, 163.0188).

1-(2-Thienyl)-2-(methylamino)propane hydrochloride (1a)

Sodium cyanoborohydride (500 mg, 8 mmol) was added to a mixture (adjusted to pH 6) of 1-(thiophen-2-yl)propan-2-one (**4a**) (420 mg, 3 mmol), ethanolic methylamine (8 M, 30 ml, 0.24 mol), acetic acid (14.4 ml), water (10 ml) and methanol (30 ml). The mixture was allowed to stir (magnetic stirrer) overnight at room temperature and then concentrated under vacuum. Water was added to the residue, the solution was then basified (aqueous ammonia hydroxide solution) and extracted into dichloromethane. The dichloromethane extract was washed with aqueous hydrochloric acid (2M). The acid extract was then washed with ether, basified (ammonia) and extracted into dichloromethane. Drying (magnesium sulphate), removal of the solvent and formation of the hydrochloride salt (ethereal 2M HCl) afforded an off white powder. This was recrystallized from ethanol/acetone, the resulting product was suspended in acetone and sonicated. The mixture was centrifuged (2000 rpm, g, 5 min, room temperature) to afford a white powder (185 mg, 0.97 mmol, 32%): ^{1}H NMR (d_6 DMSO) δ 9.18 (2 H, s, $\text{-N}\underline{H_2}$), 7.44 (1 H, dd, J = 5.1 Hz, J' = 1.1 Hz, thiophene H-5), 7.02 (1 H, dd, J = 5.1 Hz, J' = 3.0 Hz, thiophene H-4), 7.00 (1 H, dd, J = 3.0 Hz, J' = 1.1 Hz, thiophene H-3), 3.36 and 3.35 (overlapping; 1 H, dd, J = 14.5 Hz, J' = 4.0 Hz, one H from $C\underline{H_2}$; 1 H, ddq, J = 10.0 Hz, J' = 4.0 Hz, J'' = 6.5 Hz, $C\underline{H}N$), 3.00 (1 H, dd, J = 14.5 Hz, J' = 10.0 Hz, one H from $C\underline{H_2}$), 2.56 (3 H, s, $\text{-NC}\underline{H_3}$) and 1.18 (3 H, d, J = 6.5 Hz, $CC\underline{H_3}$); ^{13}C NMR (d_6 DMSO) δ 138.15 (thiophene C-2), 127.25 (thiophene C-4), 126.84 (thiophene C-3), 125.12 (thiophene C-5), 55.13 ($\underline{C}CH_3$),



2a, **b** **3a**, **b** **4a**, **b** **1a**, **b**

1-4a R = 2-Thienyl

1-4b R = 3-Thienyl

i. n-$BuNH_2$, CH_3COOH, $C_2H_5NO_2$; ii. Fe, CH_3COOH; iii. $MeNH_2$, $NaBH_3(CN)$; iv. ethereal HCl

Figure 2. Synthetic scheme for methiopropamine (**1a**) and its 3-thienyl isomer (**1b**).

32.32 ($\underline{C}H_2$), 29.50 ($N\underline{C}H_3$) and 14.98 ($C\underline{C}H_3$); EIMS *m/z* (%) 154 (M^+-H, 0.5), 140, (1), 97 (11) and 58 (100); HR-ESIMS found 156.0841 (theor. for M + H, C_8H_{14} NS, 156.0841); m. pt. 131–3 °C (lit.[2] 133–5 °C).

The ^1H NMR spectrum was also noted to contain a small amount (3.8% by comparing the integrals of the $NC\underline{H_3}$ peaks) of a second compound believed to be **2-(methylamino)-1-(2-thienyl)propan-1-one**: ^1H NMR (d_6 DMSO) δ 8.22 (1 H, dd, *J* = *4.9 Hz*, *J′* = *1.1 Hz*, thiophene H-3), 8.18 (1.1 Hz, dd, *J* = *3.8 Hz*, *J′* = *1.0 Hz*, thiophene H-5), 7.36 (1 H, dd, *J* = *4.9 Hz*, *J′* = *3.8 Hz*, thiophene-H-4), 5.01 (1 H, q, *J* = *7.0 Hz*, $C\underline{H}$), 2.50 (3 H, s $NC\underline{H_3}$) and 1.53 (3 H, d, *J* = *7.0 Hz*, $CC\underline{H_3}$); HR-ESIMS found 170.0632 (theor. for M + H, $C_8H_{12}NOS$, 170.0640).

1-(3-Thienyl)-2-nitropropene (3b)

This was prepared as for 1-(2-thienyl)-2-nitropropene (**3a**), staring with thiophene-3-carboxaldehyde (8.85 g, 0.079 mol), to give yellow needles (6.61 g, 0.039 mol, 50%): ^1H NMR ($CDCl_3$) δ 8.10 (1 H, s, $C\underline{H}{=}C$), 7.62 (1 H, d, *J* = 2.9 Hz, thiophene H-2), 7.46 (1 H, dd, *J* = 5.0 Hz, *J′* = 2.9 Hz, thiophene H-5), 7.30 (1 H, dd, *J* = 5.0 Hz, *J′* = 1.1 Hz, thiophene H-4) and 2.52 (3 H, s, $C\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 146.19, 133.64, 129.86, 128.14, 127.51, 126.95 and 14.14; EIMS *m/z* (%) 169 (M^+, 66), 121 (36), 111 (62), 77 (71) and 45 (100); m. pt. 68–70 °C (lit.[10] 73–75 °C).

1-(3-Thienyl)propan-2-one (4b)

This was prepared as for 1-(2-thienyl)propan-2-one (**4a**),starting with 1-(3-thienyl)-2-nitropropene (6.29 g, 38 mmol) (**3b**) to give a light brown oil (3.95 g, 28 mmol, 74%) which was used without further purification:^1H NMR ($CDCl_3$) δ 7.29 (1 H, dd, *J* = *5.0, Hz, J′ 3.2 Hz,* thiophene H-5), 7.09 (1 H, d, *J* = *3.2 Hz,* thiophene H-2), 6.90 (1 H, dd, *J* = *5.0 Hz, J′* = *1.2 Hz,* thiophene-H-4), 3.72 (2 H, s $C\underline{H_2}$) and 2.15 (3 H, s, $C\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ 205.70, 133.81, 128.36, 125.86, 122.80, 45.04 and 29.07; HR-ESIMS found 163.0195 (theor. for M + Na, C_7H_8OSNa, 163.0188).

1-(3-Thienyl)-2-(methylamino)propane hydrochloride (1b)

This was prepared as for 1-(2-thienyl)-2-(methylamino)propane hydrochloride (**1a**), starting 1-(3-thienyl)propan-2-one (**4b**) (420 mg, 3 mmol), to give a white powder (325 mg, 1.7 mmol, 57%): ^1H NMR (d_6 DMSO) δ 9.14 (2 H, s, $N\underline{H_2}$), 7.54 (1 H, dd, *J* = 4.9 Hz, *J′* = 2.9 Hz, thiophene H-5), 7.33 (1 H, d, *J′* = 2.9 Hz thiophene H-2), 7.05 (1 H, dd, *J* = 4.9 Hz, *J′* = 1.0 Hz, thiophene H-4), 3.36 (1 H, ddq, *J* = 10.0 Hz, *J′* = 4.0 Hz, *J″* = 6.5 Hz, $C\underline{H}N$), 3.15 (1 H, dd, *J* = 13.5 Hz, *J′* = 4.0 Hz one H from $C\underline{H_2}$), 2.77 (1 H, dd, *J* = 13.5 Hz, *J′* = 10.0 Hz one H from $C\underline{H_2}$), 2.54 (3 H, s, $N(C\underline{H_3})$) and 1.14 (3 H, d, J = 6.5 Hz, $C(C\underline{H_3})$); ^{13}C NMR (d_6 DMSO) δ 136.71 (thiophene C-3), 128.47 (thiophene C-4), 126.47 (thiophene C-5), 122.91 (thiophene C-2), 54.54 ($\underline{C}CH_3$), 32.32 ($\underline{C}H_2$), 29.53 ($N\underline{C}H_3$) and 15.22 ($C\underline{C}H_3$); EIMS *m/z* (%) 154 (M^+-H, 0.5), 140, (1), 97 (9) and 58 (100) HR-ESIMS found 156.0840 (theor. for M + H, C_8H_{14} NS, 156.0841); m. pt. 94–6 °C ((lit.[12] 97–8 °C).

Sample preparation for GC-EIMS separation of (1a) and (1b)

An aqueous solution (500 µl) containing 50 µg/ml each of 1-(2-thienyl)-2-(methylamino)propane hydrochloride (**1b**) and 1-(3-thienyl)-2-(methylamino)propane hydrochloride (**1b**), both synthesized as above, was made basic with aqueous ammonia hydroxide solution (to approx. pH 10) and extracted into dichloromethane. The two compounds were also extracted individually at the same concentration. The dichloromethane extract was analysed by GC-EIMS (Figure 3): relative retention time (RRT, to caffeine) – 1-(2-thienyl)-2-(methylamino)propane (**1a**) 0.575, 1-(3-thienyl)-2-(methylamino)propane (**1b**) 0.584.

Results and discussion

The condensation of thiophene-2-carboxaldehyde (**2a**) with nitroethane at 80 °C afforded the nitropropene derivative (**3a**) in 47% yield.[12] Work-up was straightforward and it involved collection of the yellow crystalline product by filtration. A reductive hydrolysis of the nitroalkene derivative (**3a**) with iron powder in acetic acid proceeded smoothly and safely affording the ketone (**4a**) as a brown oil.[15] The estimated purity, by GC-EIMS, for the ketone (**4a**) was 96% (integration of TIC). There were also small amounts (approximately 2% and 1% of summed peak areas in TIC) of thiophene-2-carboxaldehyde and what was tentatively from its EI mass spectrum as 1-(2-thienyl)propane-1,2-dione present. The EI mass spectrum for the latter displayed the correct molecular ion *m/z*154, along with the thienyl acylium ion *m/z*111, the thienyl ion *m/z*83 and the acetylium ion *m/z*43. The ketone derivative (**4a**) was converted to methiopropamine in a reductive amination with methylamine/sodium cyanoborohydride[15] affording free base methiopropamine which was estimated to be 89% pure by GC-EIMS (integration of TIC). Formation of the hydrochloride salt with ethereal hydrogen chloride afforded a readily crystallisable solid with an estimated purity 96% by ^1H NMR. The overall yield from the starting material, thiophene-2-carboxaldehyde was 10%.

In addition to the expected M + H ion, the HR ESIMS of the final product (**1a**) was observed to contain a small peak (approximately 2% intensity) with mass 170.0632 Da which fits an empirical formula of $C_8H_{12}NOS$ (theoretical value 170.0640 Da, $\Delta = -4.5$ ppm). Removing one hydrogen introduced through ionization gives an empirical formula $C_8H_{11}NOS$, suggesting a possible keto methiopropamine (i.e. M − 2H + O) impurity. GC-EIMS analysis revealed a small impurity peak with a base ion *m/z*56 along with *m/z*111 (10.3%) and 167 (0.5%). The *m/z*111 fragment may be due to the thiophene acylium ion indicating the possible presence of 2-(methylamino)-1-(2-thienyl)propan-1-one ('β-keto methiopropamine'). Mass ions *m/z*56 and 167 were also observed in the EI mass spectrum instead of the expected the immonium ion, *m/z*58, and M^+, *m/z* 169 for this amino ketone. However, this 'M-2' phenomenon has been reported during the GC analysis of cathinones and oxidation (loss of H_2) to form an enamine has been reported to occur during the analysis of methcathinone.[16,17] The 'β-keto methiopropamine' impurity in the final product was also readily identifiable in the ^1H NMR spectrum and it was estimated to be present at a level 3.8% by comparing the integrals of the $NC\underline{H_3}$ peaks. It is possible that it was produced from what was tentatively identified by GC-EIMS as 1-(2-thienyl)propane-1,2-dione as a minor impurity in the ketone precursor (**4a**). A reductive amination of the 2-ketone group would produce 'β-keto methiopropamine'.

An analysis of the synthetic scheme for methiopropamine (Figure 2) reveals that it is flexible and starting material or reagent substitution would readily lead to an array of analogues. Varying the choice of (1) the starting aldehyde will facilitate the preparation of a number of heterocyclic analogues, (2) the nitroalkane chain length allows modification of the alkyl substituent at the alpha position, and (3) the amine will lead to a series of *N*-alkyl

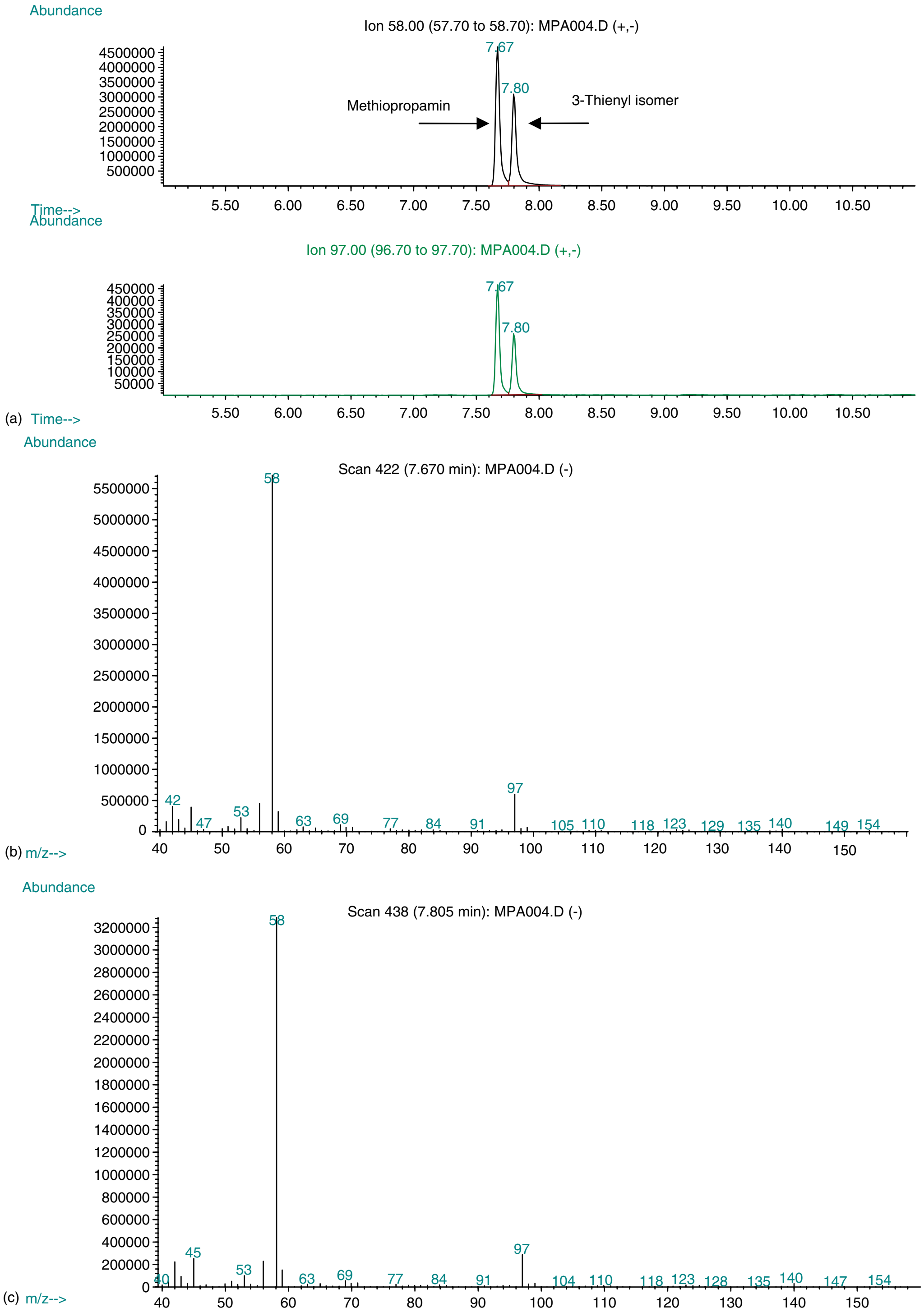


Figure 3. (a). EIC's (m/z 58 and 97) for isomer separation, (b). EI MS for methiopropamine (**1a**) (7.67 min) and (c). EI MS for the 3-thienyl isomer (**1b**) (7.80 min).

derivatives. With this in mind, it was decided to apply the synthetic methodology to a potentially useful analogue, the 3-thienyl isomer of methiopropamine.[14] The occurrence of isomers of recreational drugs in commercially available products is not unusual and this phenomenon has already been observed with naphyrone.[18,19]

As GC/EIMS is probably the most commonly used method in forensic drugs testing laboratories and, considering the fact that an increase in the popularity methiopropamine (**1a**) will likely lead authorities to control it, robust chromatographic methodologies will be required to distinguish it from related compounds. In this respect, it was felt that the 3-thienyl analogue (**1b**) would have a similar GC retention time to methiopropamine (**1a**) and that their EI mass spectra would be similar. Failure to have evidence that analytical protocols could distinguish the two isomers could potentially weaken future forensic cases. The 3-thienyl isomer (**1b**)

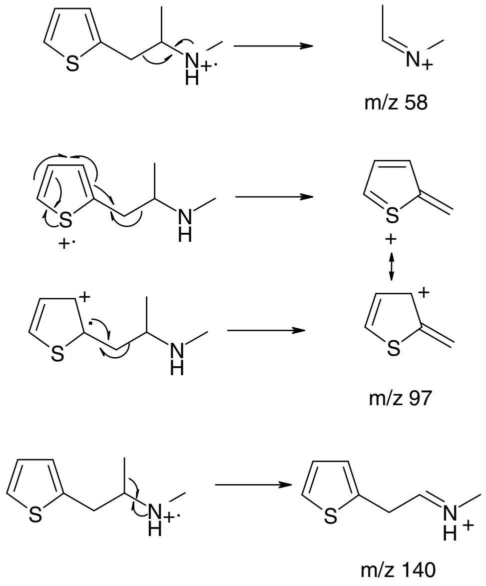


Figure 4. EI MS fragmentation pathways for methiopropamine.

was synthesized using the same protocol as for methiopropamine in an overall yield of 21% from thiophene-3-carboxaldehyde.

GC/EIMS analysis (Figure 3) of methiopropamine (**1a**) and it's 3-thienyl isomer (**1b**), both synthesized by the methodologies presented here, revealed that they are separable with a 0.13 min difference in retention times using one of our routine GC methods for the analysis of 'legal highs'. The EI mass spectra were indeed found to be essentially identical and it would certainly not be possible to distinguish the two isomers from their mass spectra alone, thus necessitating the need for authentic standards. The base peak in the EI mass spectrum of methiopropamine is the *m/z*58 immonium ion. The *m/z*97 methylidene thiophenylium ion is also observed and *m/z*140 arises from loss of the methyl group through α cleavage (Figure 4). The fragmentation for the 3-thienyl isomer may be interpreted in a similar manner.

Conclusion

1-(2-Thienyl)-2-(methylamino)propane (methiopropamine) and 1-(3-thienyl)-2-(methylamino)propane hydrochlorides have been successfully synthesized in three steps, in 10 and 21% overall yields respectively, using straightforward methodologies. We have also demonstrated that the two compounds are separable by gas chromatography but their EI mass spectra are essentially identical.

It would not be possible to distinguish the two isomers from their mass spectra alone, thus necessitating the need for authentic standards. With the rapid evolution and diversification of the recreational drugs industry, analytical chemists may well find themselves taking on the role of organic synthetic chemists as well.

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