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The syntheses and characterization 3β-(4-fluorobenzoyloxy)tropane (fluorotropacocaine) and its 3α isomer

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3β-(4-Fluorobenzoyloxy)tropane (3β-FBT, fluorotropacocaine) was first reported by Finnish authorities to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) *via* the Early Warning System (EWS) in 2008 and our own laboratory tentatively identified it in 2010 in several products purchased from head shops. Very little is known about this cocaine-like drug and, as no reference standards were available, we have synthesized and characterized both 3β-FBT and its 3α isomer for use as reference standards. The two compounds are separable by gas chromatography (GC) but their electron-impact (EI) mass spectra were found to be almost identical. ^{19}F NMR spectroscopy was also found to be a useful technique for distinguishing the two isomers. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: FBT; fluorotropacocaine; forensic; isomer

Introduction

3β-(4-Fluorobenzoyloxy)tropane (3-pseudotropyl 4-fluorobenzoate, 3β-FBT, fluorotropacocaine) (Figure 1) was first reported by Finnish authorities to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) *via* the Early Warning System (EWS) in 2008.[1] It was found in powder form and structural assignment was made based on the mass spectral data coupled with information given in package. Our own laboratory tentatively identified 3β-FBT in 2010 in products purchased from head shops.[2] Again identification was initially based on mass spectral evidence and it was presumed to be the β isomer as that has been popularly identified as fluorotropacocaine.[3] The configuration at the 3 position in 3β-FBT is equivalent to that found in cocaine.

In fact, very little is known about 3β-FBT. It has been reported to be a local anaesthetic and ^{18}F labelled 3β-FBT has been used as a muscarinic acetylcholine ligand for PET imaging.[4,5] Although naturally occurring organofluorine compounds are very rare, fluorine is widely used in drug development for its inductive effects. It confers improved resistance to metabolism and also increases lipophilicity.[6,7] Its introduction into a cocaine-like molecule such as tropacocaine is not surprising as recreational drugs chemists strive to produce more active products.

Tropacocaine (3-pseudotropyl benzoate) is better known and has been used as a local anaesthetic.[8] It is found in minor amounts, along with its α isomer, benzoyltropeine, in the coca leaf and has been identified as an impurity in cocaine.[9–12] Previous authors have identified benzoyltropeine, using gas chromatography-mass spectrometry (GC-MS), thin layer chromatography (TLC), and nuclear magnetic resonance (NMR), in street heroin samples but no explanation as to its presence was noted.[13]

The occurrence of isomers of recreational drugs is not unusual and this may makes unambiguous identification difficult as reference standards may not be available.[14] Such isomers may be produced deliberately to circumvent laws and improve activity or even inadvertently where the wrong staring material is used or manufacturing conditions are changed. For 3β-FBT (*exo* isomer) the most likely isomer that one might expect is its 3α epimer (*endo* isomer), 3α-FBT. (Figure 1). To establish if either or both 3α and 3β-FBT were present in our test purchase products, we have synthesized and characterized the two epimers for use as reference standards. 3α and 3β-FBT are not currently controlled in the European Union but as with all new recreational drugs, the possibility exists that authorities may seek to impose control measures in the future, making isomer identification crucial for forensic cases.

Experimental

Chemicals

4-Fluorobenzoyl chloride, tropine, triethylamine and toluene were obtained from Sigma Aldrich Ltd (Arklow, Wicklow, Ireland). Pseudotropine was prepared by the reduction of tropinone (Sigma Aldrich, Arklow, Wicklow, Ireland) with *iso*-butanol/sodium.[15]

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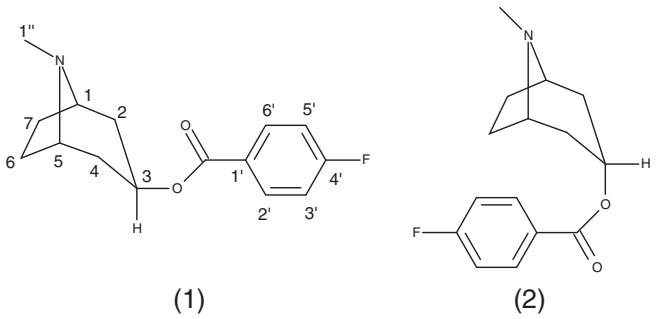

Figure 1. Structures of (1). 3β-FBT (fluorotropacocaine) and (2). 3α-FBT.

Instrumentation

^{1}H (600 MHz), ^{13}C (150 MHz) and ^{19}F NMR (decoupled, 377 MHz) 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 Fisher, Bremen, Germany). Melting points are uncorrected.

GC-EIMS (gas chromatography with electron impact mass spectrometry) under the following conditions: Agilent 6890 gas chromatograph with an HP-ULTRA 1 capillary column (12 m × 0.2 mm 0.33 μm). Helium (He) was used as the carrier gas at a flow rate of 1.0 ml/min. The injector port was set at 250°C and the transfer line at 280°C. The following temperature program was used: 100°C for 1 min, 9°C/min to 180°C, 180°C for 2 min, 25°C/min to 295°C and 295°C for 2 min. The GC was coupled to an Agilent 5975 MSD (EI, 70 eV, TIC mode scanning *m/z* 40–450). Samples for GC-MS analysis were dissolved in methanol.

LC-ESIMS was performed on Agilent 1100 LC system (column – Allure PFP Propyl, 5 μm, 50 × 2.1 mm (Restek, Bellefonte, PA, USA), mobile phase A acetonitrile containing 0.05% formic acid, mobile phase B water containing 0.05% formic acid) coupled to an Agilent LC-MSD (positive electrospray mode, capillary voltage 3000 V, drying gas (N_2) 12 lt/min at 350°C, nebulizer pressure 60 psig, *m/z* 50–500). Samples for LC-MS analysis were dissolved in acetonitrile/water(1/1, containing 0.05% formic acid) at a concentration of 5 μg/ml. Samples were analyzed in duplicate. The following conditions were used.

Table 1. ^{1}H and ^{13}C NMR data for 3β-FBT

Position	^{1}H(ppm)	No. H	Multiplicity	J (Hz)	^{13}C (ppm)	J(C-F) (Hz)
1,5	3.96	2	m	-	62.1	-
2,4	2.24	2	m	-	34.0	-
2,4	2.32	2	m	-		
6,7	2.02	2	m	-	23.9	-
6,7	2.27	2	m		65.3	-
3	5.27	2	m	-		
1′	-	-	-	-	126.3	2
2′,6′	8.01	2	dd	8.8 (H-H), 5.6 (H-F)	132.0	10
3′, 5′	7.38	2	dd	8.8 (H-H), 8.8 (H-F)	116.0	22
4′	-	-	-	-	164.2	252
CH_3	2.66	3	s	-	37.7	-
C=O	-	-	-	-	166.0	-
NH	11.3	-	-	-	-	-

Table 2. ^{1}H and ^{13}C NMR data for 3α-FBT

Position	^{1}H (ppm)	No. H	Multiplicity	J (Hz)	^{13}C (ppm)	J(C-F) (Hz)
1,5	3.89	2	m	-	61.1	-
2,4	2.11	2	m	-	34.0	-
2,4	2.65	2	m			
6,7	2.25	4	m	-	23.7	-
3	5.18	1	m	-	65.4	-
1′	-	-	-	-	126.3	3
2′,6′	8.04	2	dd	8.8 (H-H), 5.6 (H-F)	132.0	10
3′, 5′	7.42	2	dd	8.8 (H-H), 8.8 (H-F)	116.0	22
4′	-	-	-	-	164.1	252
CH_3	2.69	3	s	-	38.1	-
C=O	-	-	-	-	166.0	-
NH	10.80	1	-	-	-	-

The effect of the fragmentor voltage on the ESI mass spectra. 0 min. 50% A up 70% at 10 min using a linear gradient; flow rate 500 μl/min; column temp. 35°C; 10 μl injected. The fragmentor voltage was adjusted as required from 70–130 V.

Separation of the isomers. 0–5 min. 12% A, then up to 35% at 30 min using a linear gradient; flow rate 1000 μl/min; column temp. 30°C; 2 μl injected. The fragmentor voltage was set at 70 V.

3β-(4-Fluorobenzoyloxy)tropane

4-Fluorobenzoyl chloride (1.75 g, 1.3 ml, 11 mmol) was added to a refluxing solution of pseudotropine (1.41 g, 10 mmol) and triethylamine (1.53 ml, 11 mmol) in toluene (15 ml). Refluxing was continued for 3 h. The mixture was allowed to cool to room temperature and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in dichloromethane and ethereal 2 M hydrogen chloride solution was added. The solution was evaporated to dryness yielding an almost colourless solid. This was recrystallized twice from ethanol to give colourless crystals (1.188 g, 45%): ^{1}H and ^{13}C NMR (d_6 DMSO) (Table 1); EIMS *m/z* (%) 263 (M^+, 25.7), 140 (6.9), 124 (100.0), 94 (35.1) and 82 (41.5); HR-ESIMS found 264.1394 (theor. for M+H, $C_{15}H_{19}O_2NF$, 264.1394); m. pt. m. pt. 281-3°C (decomp. to brown tar, partially sublimed before melting).

3α-(4-Fluorobenzoyloxy)tropane

This was prepared as for 3β-(4-fluorobenzoyloxy)tropane using tropine to give colourless crystals (451 mg, 17%): ^{1}H and ^{13}C NMR (d_6 DMSO) (Table 2); EIMS *m/z* (%) 263 (M^+, 14.0), 140 (13.7), 124 (100.0), 94 (26.9) and 82 (34.9); HR-ESIMS found 264.1394 (theor. for M+H, $C_{15}H_{19}O_2NF$, 264.1394); m. pt. 289-91°C (decomp. to brown tar, partially sublimed before melting).

Results and discussion

Pseudotropine, the starting material for 3β-(4-fluorobenzoyloxy) tropane (3β-FBT), was prepared by the reduction of tropinone with sodium/2-butanol.[15] Esterification with 4-fluorobenzoyl chloride in the presence of triethylamine in refluxing toluene,

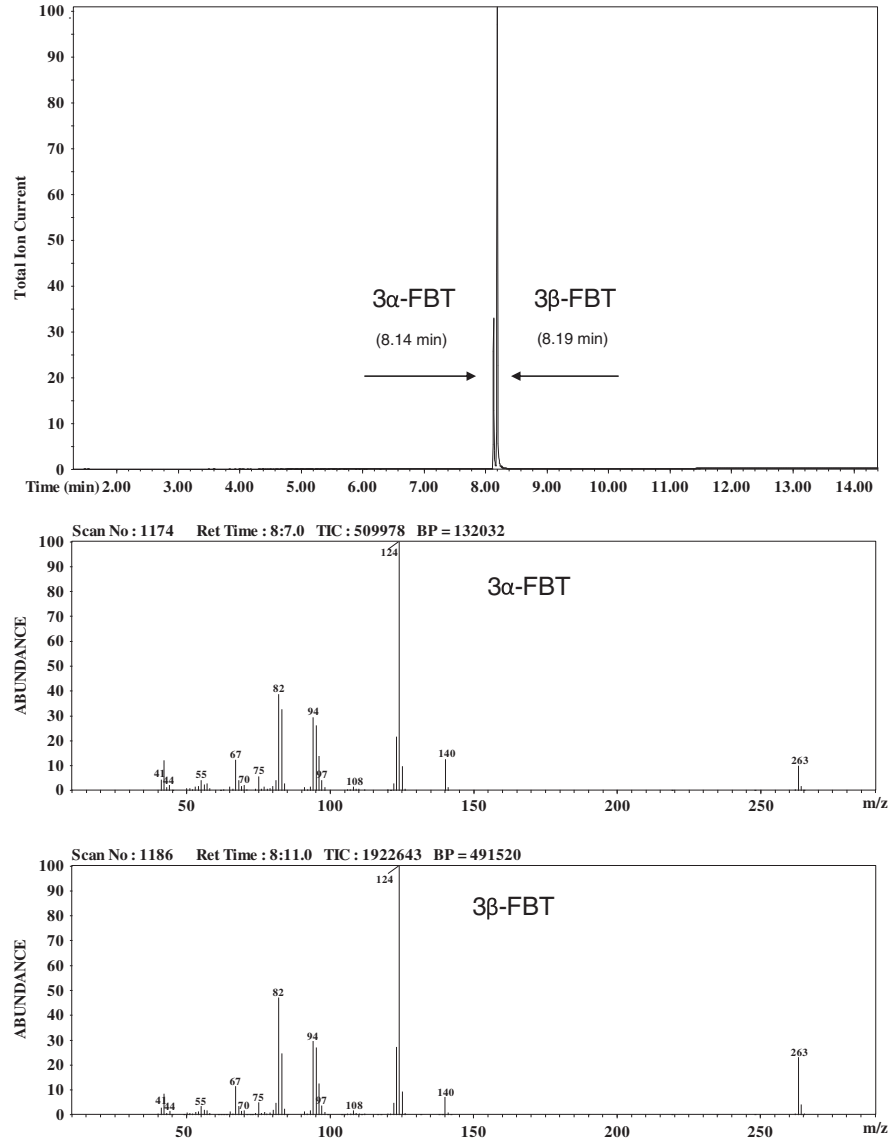

Figure 2. GC separation and EI mass spectra for 3α and 3β-FBT.

formation of the hydrochloride salt and recrystallization afforded 3β-FBT in 45% yield.[16] 3α-(4-Fluorobenzoyloxy)tropane (3α-FBT) was similarly prepared from the commercially available tropine but the yield was found to be much lower yield (17%) which was probably due to steric effects. Both compounds were obtained as colourless crystals which were noted to partially sublime on heating. GC-MS analysis of the residue/sublimate from the determination of the melting point of 3β-FBT revealed the presence of 4-fluorobenzoic acid which is similar to the formation of benzoic acid observed during the pyrolysis of cocaine.[17]

The EI mass spectra of 3α and 3β-FBT were found to be very similar, both displaying a prominent molecular ion (*m/z* 263) (Figure 2). The fragmentation pattern parallels that of cocaine.[18,19] The base peak, *m/z* 124 arises by loss of the benzoate radical and *m/z* 140 from loss of the benzoyl radical (Figure 3). Further loss of propylene from the *m/z* 124 cation produces *m/z* 82, and *m/z* 94 is attributable to the *N*-methylpyridinium ion. The fragment ion, *m/z* 82 may also be produced from the *m/z* 83 and it was noted that the ratio of mass ions 82/83 was greater in the α isomer which was similarly noted by previous authors for tropacocaine/benzoyltropeine.[13] However, based on EI mass spectral alone it would be difficult to distinguish the two isomers.

Apart from the *m/z* 264 M+H ion, the positive ESI mass spectra of both isomers displayed an *m/z* 124 ion which became more prominent as the fragmentor voltage increased. This arises by loss of 4-fluorobenzoic acid from the molecule which may occur in several ways and a similar loss of benzoic acid is observed with cocaine.[20] It was noted that the β (*exo*) isomer produced relatively more of the *m/z* 124 ion at a given fragmentor voltage. This may be due to the closer proximity of the equatorial ester carbonyl to the protonated nitrogen providing another pathway for elimination (Figure 4). Even at high fragmentor voltages there were insufficient differences in the ESI mass spectra to allow the isomers to be distinguished. However, in both the cases of GC and LC-MS, adequate chromatographic separations were achieved thus allowing us to distinguish the isomers (Figures 2 and 5).

The infrared spectra of the two isomers are shown in Figure 6. The spectra are very similar but some differences were observed around the 3000 cm^{-1} region, which correspond to the C-H symmetric and asymmetric stretch of the methyl and methylene groups. A sharp

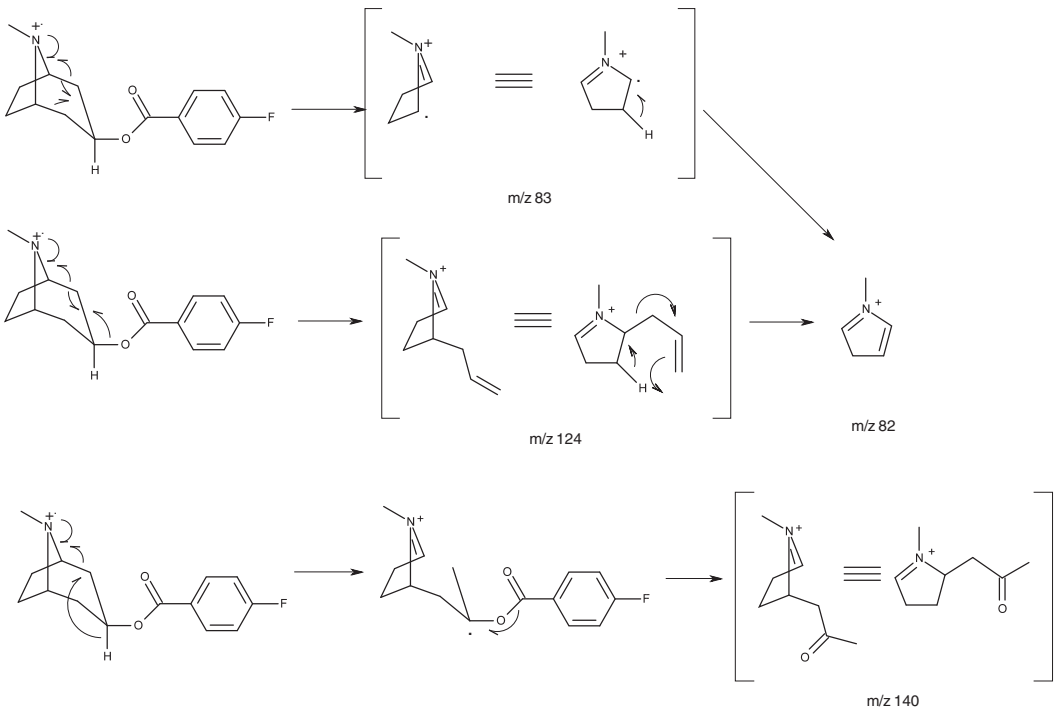

Figure 3. EI fragmentation pathways.

peak at 1078 cm^{-1} in the 3α-FBT spectrum is missing in the 3β-FBT spectrum and a sharp peak at 994 cm^{-1} in the 3β-FBT spectrum is absent in the 3α-FBT spectrum. These differences may be due to different cycloheptane ring vibrations in the isomers. Another feature of note in the spectra are the broad carbonyl C=O stretching bands which may be due to conformational effects.

NMR (^{1}H and ^{13}C) data for both isomers are presented in Tables 1 and 2. The ^{13}C NMR spectra are very similar. However, the ^{1}H NMR spectra display some differences, most notably the epimeric H3 was observed at 5.18 and 5.27ppm in the α and β isomers, respectively. This may be of limited value to differentiate the isomers as other compounds such as diluents likely to be present in street samples may obscure that region of the NMR spectrum. The ^{19}F NMR spectra also show differences between the two isomers (101.4 and 106.0 ppm for α and β, respectively). Considering that the relative sensitivity of ^{19}F NMR spectroscopy is quite high (83% that of ^{1}H), and that a limited number of fluorinated compounds are used as recreational drugs, this technique

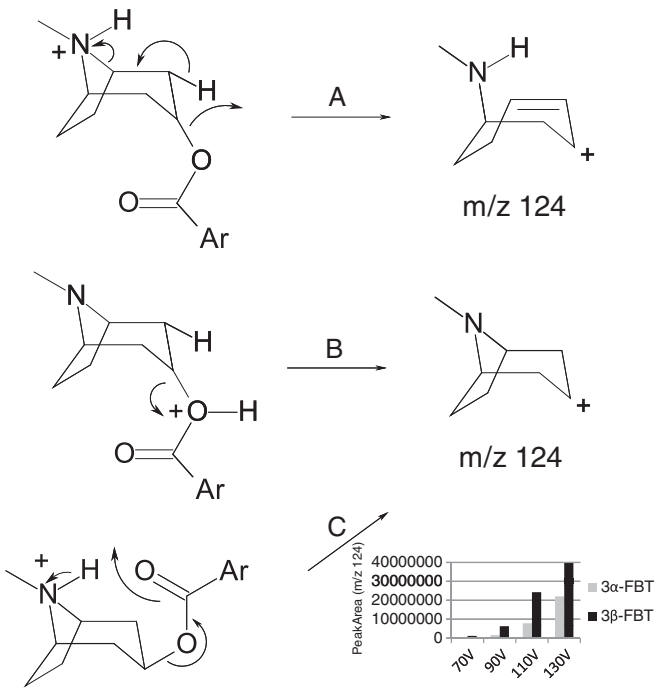

Figure 4. ESI fragmentation pathways showing loss of 4-fluorobenzoic acid (Pathway C is more likely for the 3β (exo or equatorial) isomer.

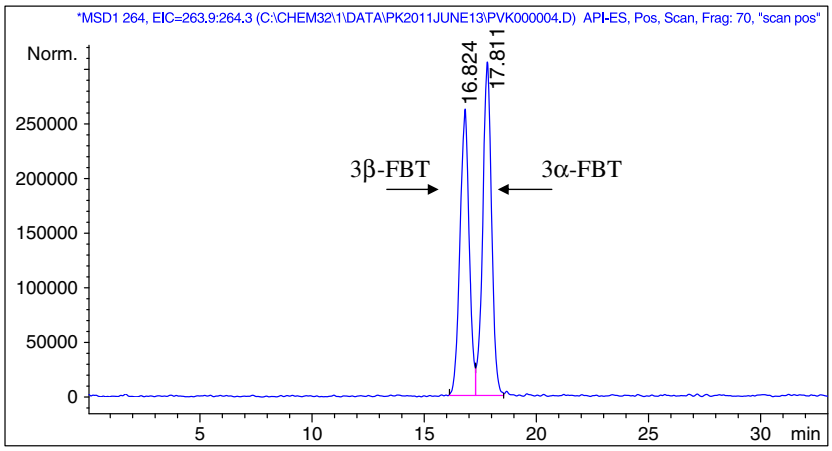

Figure 5. LC separation (m/z 264, M+H) for 3α and 3β-FBT.

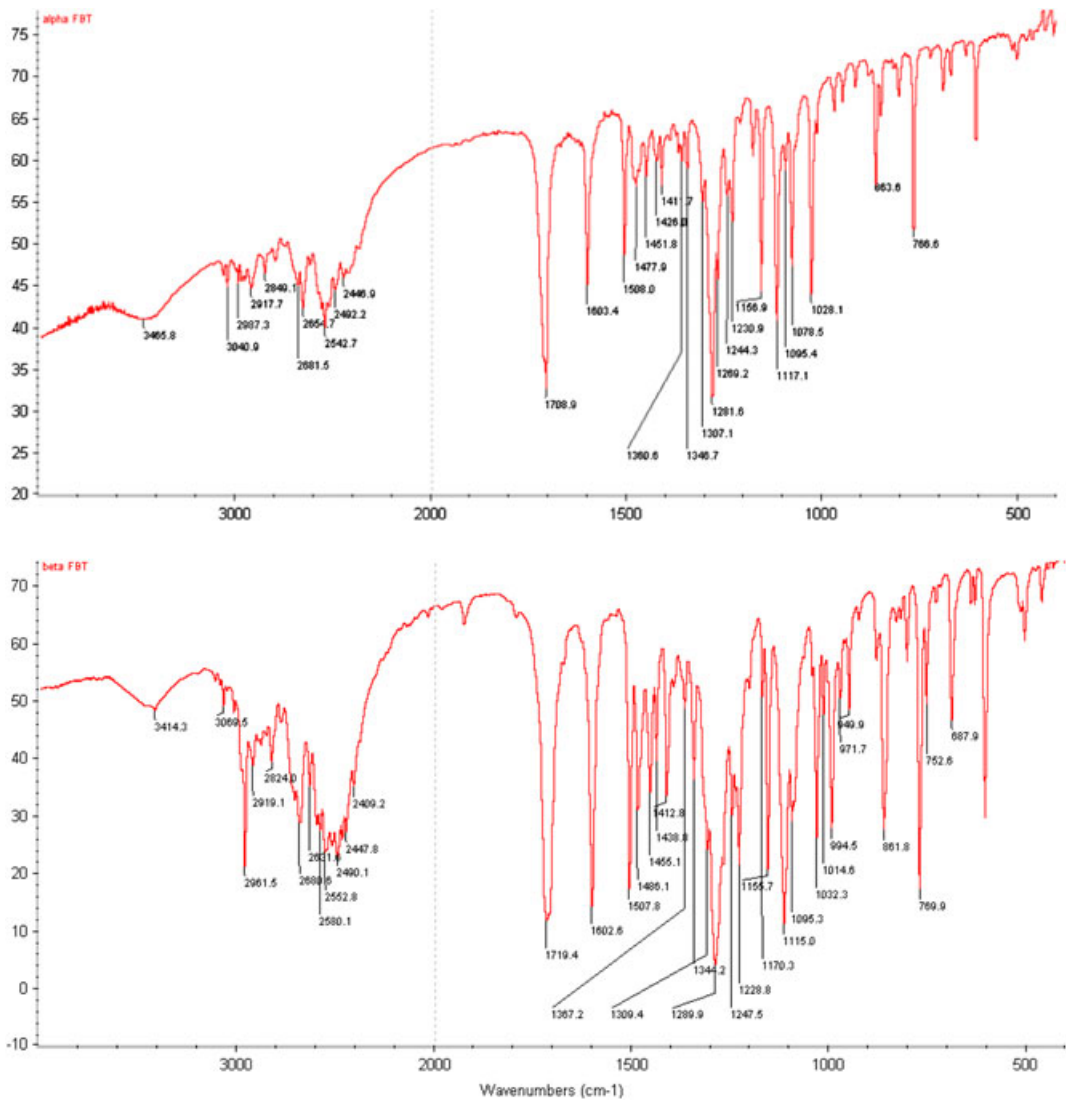

Figure 6. IR spectra for 3α and 3β-FBT.

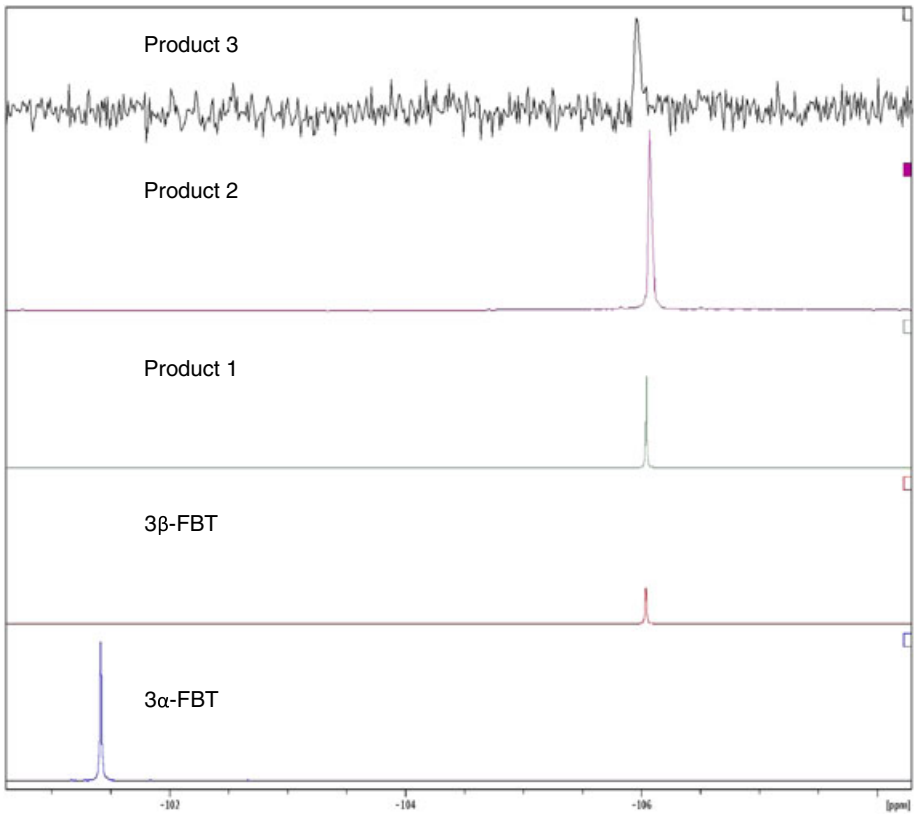

Figure 7. ^{19}F NMR spectra for 3 heads shop test purchase products, 3α and 3β-FBT.

could prove to be the most useful to establish FBT isomer identity in crude samples. It has been used similarly for the identification of fluoromethcathinone isomers.[21]

Three products, purchased from head shops (Dublin, Ireland) during summer 2010 were analyzed by GC-MS, LC-MS and ^{19}F NMR (Figure 7) using the 3α and 3β isomers synthesized here as reference standards. The products were found to contain the more cocaine-like β isomer; the α isomer was not detected. Initially, in the absence of standards we tentatively assigned the β isomer structure primarily on what we expected to be on sale and this been confirmed by the analysis presented here.

Conclusion

3β-(4-Fluorobenzoyloxy)tropane (fluorotropacocaine) and its 3α isomer were synthesized (45 and 17% yields, respectively) and characterized. The EI and ESI mass spectra were found to be quite similar for the two isomers and any differences may prove inadequate for satisfactory identification. However GC and LC separations were readily achieved and coupled with mass spectrometry, both techniques successfully allowed the identification of the β isomer in case samples purchased from head shops. ^{19}F NMR spectroscopy was also found to be a useful technique for distinguishing the isomers.

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