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Synthesis, full chemical characterisation and development of validated methods for the quantification of (±)-4′-methylmethcathinone (mephedrone): A new "legal high"

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ABSTRACT

The recent global increase in the abuse of 4′-methylmethcathinone and related compounds has developed a requirement for full chemical characterisation of these products. In this work we present full synthetic and chemical characterisation data and supplemental information for mephedrone synthesised as both the hydrobromide and hydrochloride salt. Additionally we report the first fully validated chromatographic methods for the detection and quantitative analysis of the substance both in its pure form and in the presence of a number of common adulterants used in illicit drug manufacture.

1. Introduction

In the last few years there has been a striking increase in the sale of "*legal highs*" [1]. These chemicals may be bought through the internet at low cost and are sometimes pure compounds which display highly similar chemical structures to existing and illegal drugs of abuse within the phenethylamine class.

(±)-4′-Methylmethcathinone or (±)-mephedrone (**3**) [2–11] is a synthetic β-ketoamphetamine that is structurally similar to methcathinone (**4**, R=Me), related to cathinone (**4**, R=H), a psychoactive compound found in Khat. (±)-Mephedrone has begun to recently emerge in drug seizures as its use as a "*legal high*" replacement for controlled stimulants including amphetamines such as methamphetamine (**5**) and MDMA (**6**) has increased (Scheme 1). (±)-Mephedrone is now a substance controlled by legislation in the United Kingdom, Germany, Norway, Sweden, The Netherlands, Finland, Romania, Republic of Ireland, Denmark, Canada and Israel. Since the legislative change a number of second-generation "*legal high*" products, which pertain to contain legal mephedrone substitutes, have become available – however many of these have been reported to contain structurally related cathinone derivatives that are themselves controlled substances [12].

The prevalence of these cathinone-derived "*legal high*" drugs has given rise to both legal and analytical challenges in the identification of these substances – thus the robust analytical profiling and the development of validated methods of testing are required. Though a number of groups have independently reported the synthesis [9,10] and selected analytical information (such as the NMR [9–11], MS [9–11] and IR [9,10]) for (±)-mephedrone – there has been no comprehensive analytical profiling or development of validated chromatographic methods for this substance. This paper seeks to address this by presenting the chemical synthesis, determination of key physicochemical parameters (Log *P*, pK_a) and full structural elucidation of two salt forms of (±)-4′-methylmethcathinone by NMR, IR, UV and MS. Additionally we report fully validated chromatographic methods (HPLC and GCMS) for the detection and quantitative analysis of the substance both in its pure form or in the presence of a number of common adulterants used in illicit drug manufacture.

2. Experimental

All reagents were of commercial quality (obtained from Sigma–Aldrich, Gillingham, UK or Alfa-Aesar, Heysham, UK) and used without further purification. Solvents were dried, where necessary, using standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AS-400 (400 MHz) instrument (JEOL, Tokyo, Japan). Infrared spectra were obtained in the range of

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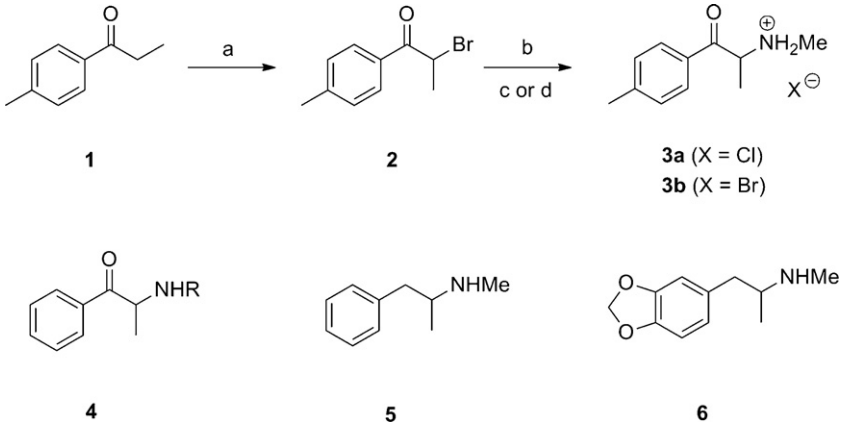

Scheme 1. *Reagents and Conditions*: (a) Br_2/HBr (48% in water)/CH_2Cl_2/rt/1h (99.6%); (b) $MeNH_2$.HCl/NEt_3/CH_2Cl_2/rt/24h; (c) HCl (3M in *n*-butanol)/^{i}PrOH/rt/1h (51.2% from **2**); (d) HBr (33% in AcOH)/AcOH/rt/1h (67.4% from **2**).

4000–400 cm^{-1} using a ThermoScientific Nicolet iS10ATR-FTIR instrument (ThermoScientific, Rochester, USA). Mass spectra were recorded on a ThermoScientific LTQ ORBITRAP mass spectrometer (ThermoScientific, Rochester, USA) using electrospray ionisation. Ultraviolet spectra were obtained using a Unicam 300 UV spectrophotometer (ThermoScientific, Rochester, USA). Thin-Layer Chromatography (TLC) was carried out on aluminium-backed SiO_2 plates (Merck, Darmstadt, Germany) and spots visualised using ultra-violet light (254 nm). Microanalysis was carried out in the Department of Pure and Applied Chemistry using a PerkinElmer 2400 Series II elemental analyser (PerkinElmer, San Jose, USA). Melting points were determined either using a Gallenkamp melting point apparatus (Gallenkamp-Sanyo, UK) (**2**) or by differential scanning calorimetry DSC; Netzsch STA449C, Netzsch-Gerätebau, Wolverhampton, UK (**3a** and **3b**). Optical rotation values $[\alpha]_D^{22}$ (10^{-1} deg cm^2 g^{-1}) were performed on a Bellingham & Stanley ADP-220 polarimeter (Bellingham & Stanley, Tunbridge Wells, UK). Log *P* and pK_a values were determined on a Sirius T3 instrument (Sirius Analytical Instruments, Forest Row, UK). Calculated Log *P* and pK_a values were determined using Pipeline Pilot software, Vers. 7.5 (Accelrys, San Diego, USA).

2.1. Synthesis of (±)-4′-methyl-2-bromopropiophenone (**2**) [13,14]

The title compound was prepared using the method reported by Kalendra et al. [13] with the following modifications: To a solution of 4-methylpropiophenone (**1**, 14.8 g, 100 mmol) in dichloromethane (50 mL) was added one drop of hydrobromic acid (48% aqueous solution) and one drop of bromine. The mixture was stirred at room temperature until the bromine colour was discharged (*circa.* 30 s) and additional bromine (5.1 mL, 100 mmol total including the original drop) was introduced dropwise with stirring. The mixture was stirred for 1 h and then concentrated *in vacuo* to reveal a dark orange oil which solidified on standing. The crude product was recrystallised from diethyl ether to give (±)-4′-methyl-2-bromopropiophenone (22.6 g, 99.6%) as colourless prisms. Mpt. (Et_2O) 76–77 °C (lit. [14] 75–77 °C); R_f [SiO_2, EtOAc:*n*-hexane (1:3)] = 0.79; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ = 7.91 (2H, d, *J* = 8.3 Hz, AA′BB′), 7.27 (2H, d, *J* = 8.3 Hz, AA′BB′), 5.28 (1H, q, *J* = 7.0 Hz, **CH**(Br)CH_3), 2.42 (3H, s, Ar**CH_3**) and 1.86 ppm (3H, d, *J* = 7.0 Hz, CH(Br)**CH_3**); ^{13}C NMR (400 MHz, 23 °C, $CDCl_3$) δ = 193.1 (C=O), 144.8 (ArC), 131.6 (ArC), 129.5 (2× ArCH), 129.1 (2× ArCH), 41.6 (**CH**(Br)CH_3), 21.8 ($ArCH_3$) and 20.3 ppm (CH(Br)**CH_3**); GCMS (EI, 70 eV): t_R = 5.09 min; *m*/*z* = 225.5 (5, $[MBr^{79}]^+$), 227.5 (5, $[MBr^{81}]^+$), 118.3 (100), 108.4 (12), 90.5 (85) and 64.5 (70%). The bromide was used in the subsequent steps without further purification.

2.2. Synthesis of (±)-4′-methylmethcathinone hydrochloride [(±)-mephedrone hydrochloride] (**3a**) [9,10]

The title compound was prepared using the method reported by Camilleri et al. [9] with the following modifications: to a suspension of (±)-4′-methyl-2-bromopropiophenone (4.54 g, 20 mmol) and methylamine hydrochloride (1.35 g, 20 mmol) in dichloromethane (40 mL) was added triethylamine (5.58 mL, 40 mmol). The mixture was stirred at room temperature overnight and then acidified (pH ~ 1) with 6 M hydrochloric acid (50 mL). The aqueous layer was washed with dichloromethane (3 × 50 mL), basified (pH ~ 10) with 5 M sodium hydroxide (*circa.* 100 mL) and then re-extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give a viscous yellow oil. The oil was dissolved in isopropanol (4 mL), treated with hydrochloric acid (3 M solution in butanol, 10 mL) and stirred at room temperature for 1 h. The mixture was diluted with diethyl ether (150 mL) and stirred to reveal a pale yellow solid (*circa.* 30 min). The crude product was filtered, washed with diethyl ether and recrystallised from acetone to give (±)-4′-methylmethcathinone hydrochloride (1.09 g, 51.2% from **2**) as a colourless powder. Mpt. (acetone) 251.18 °C; R_f [SiO_2, EtOAc:*n*-hexane (1:3)] = 0.11; $[\alpha]_D^{22}$ = 0 (*c* = 0.5 g/100 mL in MeOH); found: C, 61.61; H, 7.35; N, 6.17. $C_{11}H_{16}ClNO$ requires C, 61.82; H, 7.55 and N, 6.55%; UV (EtOH): λ_{max} = 259.5 nm (*A* = 0.735, *c* = 9.95 × 10^{-4} g/100 mL); IR (ATR–FTIR): 2717.5 (NH_2^+), 1689.5 (C=O), 1606.3 cm^{-1} (C=C); ^{1}H NMR (400 MHz, 60 °C, d_6-DMSO) δ = 9.35 (2H, br s, CH(**NH_2^+**CH_3)CH_3); 7.96 (2H, d, *J* = 8.3 Hz, AA′BB′), 7.41 (2H, d, *J* = 8.3 Hz, AA′BB′), 5.08 (1H, q, *J* = 7.2 Hz, **CH**($NH_2^+$$CH_3$)$CH_3$), 2.59 (3H, s, CH($NH_2^+$**$CH_3$**)$CH_3$), 2.41 (3H, s, Ar**$CH_3$**) and 1.46 ppm (3H, d, *J* = 7.2 Hz, CH($NH_2^+$$CH_3$)**$CH_3$**); ^{13}C NMR (400 MHz, 60 °C, d_6-DMSO) δ = 195.8 (C=O, C1), 145.5 (ArC, C4′), 130.4 (ArC, C1′), 129.7 (2× ArCH, C3′/C5′), 128.9 (2× ArCH, C2′/C6′), 58.1 (**CH**CH_3, C2), 30.6 (NCH_3,), 21.2 ($ArCH_3$, C7′) and 15.5 ppm (CH**CH_3**, C3); LRMS (ESI+, 70 eV): *m*/*z* = 178 (6%, $[M+H]^+$), 160 (47), 145 (100), 130 (7), 119 (16) and 91 (5); HRMS (ESI+, 70 eV) calculated for [M+H] $C_{11}H_{16}NO$: 178.1226, found: 178.1226.

2.3. Synthesis of (±)-4′-methylmethcathinone hydrobromide [(±)-mephedrone hydrobromide] (**3b**)

The title compound was prepared using an analogous method for (**3a**) with the following modifications: The yellow oil, (±)-4′-methylmethcathinone, was dissolved in glacial acetic acid