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The analysis of substituted cathinones. Part 3. Synthesis and characterisation of 2,3-methylenedioxy substituted cathinones

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ABSTRACT

The first synthesis of the 2,3-isomers of MDPV, butylone and methylone is reported. The isomers were characterised by ^{1}H and ^{13}C NMR spectroscopy and compared to the corresponding 3,4-isomers. A GC method is described which separates the 3,4- and the 2,3-isomers from each other. IR spectra of the 2,3-isomers are also compared with the corresponding 3,4-isomers. Two seized drug samples were analysed by GCMS and the samples were found to contain the 3,4-isomers.

1. Introduction

Analogs of methcathinone that possess the methylenedioxy ring substituent on the phenyl ring are widely available to purchase on the internet [1]. Their popularity is related to their structural similarity to the commonly abused drug 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). Amongst the most common methylenedioxy methcathinones are 3,4-methylenedioxymethcathinone (methylone), bk-MBDB (butylone) and 3,4-methylenedioxypyrovalerone (MDPV).

The chemical characterisation of these compounds has been previously reported [2–4]. The legal status of these compounds can vary from country to country, however they are widely abused and frequently encountered in seized drug samples.

New analogs of controlled drugs are encountered on an ongoing basis in forensic laboratories. Part of the duty of the forensic chemist is to determine if the seized sample is a controlled substance under the legal system in the country in question. This may be a straightforward process if the seized substance is unambiguously stated in the legislation and the chemical analysis gives an unambiguous result. Some difficulties arise when only one isomeric form of a drug is listed in the legislation as being controlled. This opens the possibility of asking forensic scientists to prove that the seized sample contains the controlled substance and not a closely related analog. This process has been explored relative to methylenedioxyamphetamines [5,6] where the authors synthesised the 2,3-isomers of a series of 3,4-substituted amphetamines and compared the pairs of isomers. Differences in the spectroscopic and chromatographic properties allowed for routine differentiation of the isomers.

The same problem exists with 3,4-substituted cathinones. The legislation in Ireland specifically names the 3,4-isomers of methylone, butylone and MDPV as being controlled substances with no mention of the 2,3-isomers. It is therefore necessary to establish that the seized compound is in fact the 3,4-isomer. NMR analysis should easily differentiate the pairs of isomers, however few forensic laboratories have such instruments and, in the presence of adulterants, NMR spectra can be difficult to interpret.

The 2,3-isomers of methylone, butylone and MDPV are not available commercially and no reference to their synthesis or characterisation could be found in the literature. With this as the background we proceeded to synthesise the 2,3-isomers, to

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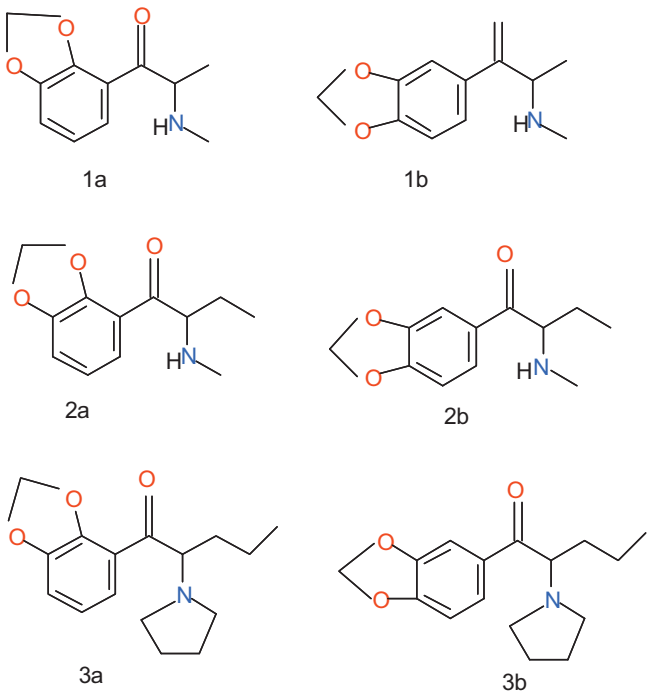

Fig. 1. Structures of 2,3- and 3,4-substituted cathinones.

characterise and compare them with the corresponding 3,4-isomers.

2. Materials and methods

2.1. Reagents and standards

1,3-Benzodioxole-4-carbaldehyde (2,3-methylenedioxybenzaldehyde) (Maybridge Chemicals), hydrogen chloride (2 M) solution in diethyl ether (Acros Organics), ethyl acetate (99.5% HPLC grade), hexane (95% HPLC grade), dichloromethane (99.8+% HPLC grade), acetone (99.8% HPLC grade) and pyridinium chlorochromate (Acros Organics) were purchased from Fisher Scientific (Dublin, Ireland), butyl magnesium chloride (2 M in THF), piperonal, methylamine (2 M in THF), propyl magnesium chloride (2 M in diethyl ether), ethyl magnesium chloride (3 M in diethyl ether) anhydrous THF, bromine, magnesium sulphate and pyrrolidine were purchased from Sigma Aldrich (Arklow, Ireland).

1-(1,3-Benzodioxol-5-yl)-2-(methylamino) butan-1-one hydrochloride (3,4-butylone hydrochloride) (**2b**), 1-(1,3-benzodioxol-5-yl)-2-(methylamino) propan-1-one hydrochloride (3,4-methylone hydrochloride) (**1b**) and 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl) pentan-1-one hydrochloride (3,4-MDPV hydrochloride) (**3b**) were all obtained from LGC, London, UK.

2.2. Synthesis of compounds

2.2.1. 1-(1,3-Benzodioxol-4-yl)-2-(methylamino) butan-1-one hydrochloride (2,3-butylone hydrochloride) (**2a**)

2.2.1.1. 1-(1,3-Benzodioxol-4-yl) butan-1-one. Propyl magnesium chloride (2 M, 25 ml, 50 mmol) was added to solution of 1,3-benzodioxole-4-carbaldehyde (5.00 g, 33 mmol), in THF (30 ml). The mixture was stirred overnight at room temperature. Water was cautiously added (5 ml) and the mixture was extracted with dichloromethane. Drying (magnesium sulphate) and removal of the solvent afforded 1-(1,3-benzodioxol-4-yl) butan-1-ol as a yellow oil (5.75 g, 30 mmol). This was dissolved in dichloromethane (100 ml). Pyridinium chlorochromate (7.66 g, 36 mmol) and silica (15 g) were added and the mixture was stirred for 3 h. This mixture was passed through a short column of flash silica and the solvent was removed. Flash column chromatography (hexane/ethyl acetate, 95/5) afforded colourless crystals (3.12 g, 12 mmol, 62%): ^{1}H NMR ($CDCl_3$) δ 7.42 (1H, d, J = 8.0 Hz, H-6′), 6.99 (1H, d, J = 8.0 Hz, H-4′), 6.91 (1H, tr, J = 8.0 Hz, H-5′), 6.10 (2H, s, H-7′), 2.95, (2H, tr, J = 7.4 Hz, H-2), 1.76 (2H, m, H-3) and 1.02 (3H, tr, J = 7.4 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 197.9, 148.5, 147.6, 121.4, 121.2, 120.3, 112.2, 101.4, 44.3, 17.3 and 13.8; EIMS m/z (%) 192 (30.9), 149 (100.0), 121 (7.1), 91 (7.1) and 65 (29.5); HR-ESIMS found 215.0678 (theor. for M+Na, $C_{11}H_{12}O_3Na$, 215.0679); m.p. 52–54 °C.

2.2.1.2. 1-(1,3-Benzodioxol-4-yl)-2-(methylamino) butan-1-one hydrochloride. Bromine (0.54 ml, 14 mmol) was added to a solution of 1-(1,3-benzodioxol-4-yl) butan-1-one (2.00 g, 14 mmol) in dichloromethane (12 ml) and the mixture was stirred for 2 h. The solvent was removed and methylamine solution in THF (20 ml, 2 M, 40 mmol) added. Flash chromatography (ethyl acetate/methanol, 99/1), formation of the hydrochloride salt with ethereal hydrogen chloride (2 M) and recrystallization from ethanol/acetone afforded a white powder (1.44 g, 7 mmol, 46%); ^{1}H and ^{13}C NMR (see Tables 3 and 4); EIMS m/z (%) 192 (3.5), 149 (6.1), 121 (2.6), 91 (2.2), 72 (100.0), 65 (5.2), 57 (5.3), and 42 (2.6); HR-ESIMS found 222.1128 (theor. for M+H, $C_{12}H_{16}O_3N$, 222.1125); m.p. 208–210 °C.

2.2.2. 1-(1,3-Benzodioxol-4-yl)-2-(methylamino) propan-1-one hydrochloride (2,3-methylone hydrochloride) (**1a**)

This was prepared as for 2,3-butylone using ethyl magnesium chloride (3 m in diethyl ether) in the Grignard reaction.

2.2.2.1. 1-(1,3-Benzodioxol-4-yl) propan-1-one. 1-(1,3-Benzodioxol-4-yl) propan-1-one (2.72 g, 11 mmol, 54%), colourless crystals: ^{1}H NMR ($CDCl_3$) δ 7.44 (1H, d, J = 7.9 Hz, H-6′), 7.00 (1H, d, J = 7.9 Hz, H-4′), 6.91 (1H, tr, J = 7.9 Hz, H-5′), 6.10 (2H, s, H-7′), 3.00 (2H, q, J = 7.1 Hz, H-2) and 1.21 (3H, tr, J = 7.1 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 198.4, 148.5, 147.7, 121.5, 121.2, 120.1, 112.2, 101.4, 35.7 and 7.9; EIMS m/z (%) 178 (41.9), 149 (100.0), 121 (7.6), 91 (9.5) and 65 (35.7); HR-ESIMS found 201.0524 (theor. for M+Na, $C_{10}H_{10}O_3Na$, 201.0522); m.p. 47–49 °C.

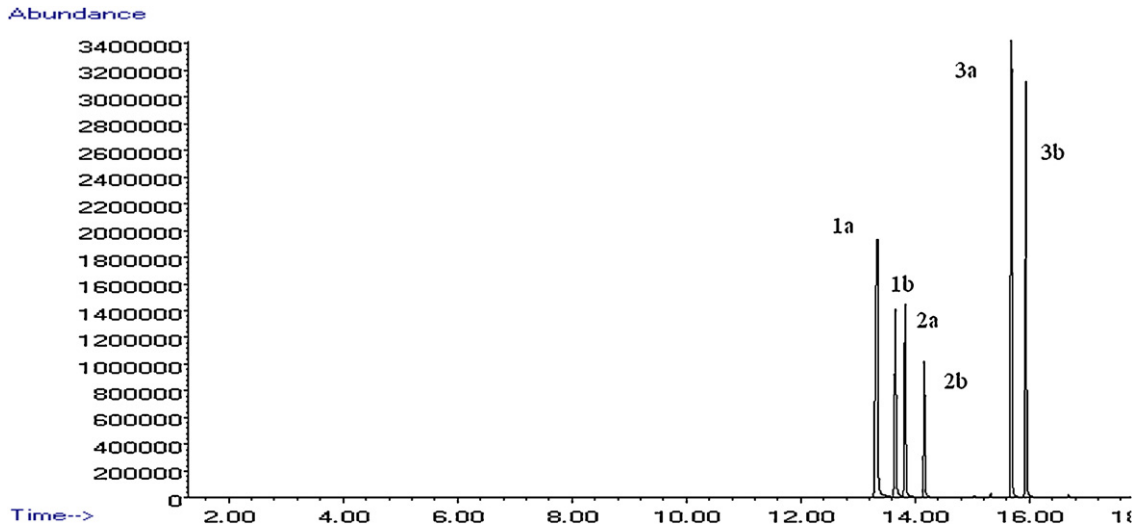

Fig. 2. Gas chromatograph of 2,3- and 3,4-substituted cathinones.