Forensic Science International 223 (2012) 189–197

Contents lists available at SciVerse ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Synthesis and GC–MS analysis of a series of homologs and regioisomers of 3,4-methylenedioxypyrovalerone (MDPV)

Younis F. Hamad Abiedalla [a], Karim Abdel-Hay [a,b], Jack DeRuiter [a], C. Randall Clark [a,*]

[a] Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University, Auburn, AL 36849, USA
[b] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt

ARTICLE INFO

Article history:
Received 3 July 2012
Received in revised form 20 August 2012
Accepted 22 August 2012
Available online 17 September 2012

Keywords:
MDPV
Cathinones
Homologs
Regioisomers
GC–MS

ABSTRACT

A series of ten homologous and regioisomeric aminoketones related to the designer synthetic cathinone derivative MDPV were evaluated in this study. These compounds were prepared from a common precursor chemical, piperonal (3,4-methylenedioxybenzaldehyde). These aminoketones show major peaks in their mass spectra corresponding to the regioisomeric and homologous immonium cation fragments from the loss of the methylenedioxybenzoyl radical species. All ten compounds in this study show equivalent EI MS fragments for the 3,4-methylenedioxybenzoyl fragments (*m*/*z* 149) and the methylenedioxybenzene fragment at *m*/*z* 121. The *m*/*z* 149 results from ionization of the carbonyl oxygen followed by an alpha-cleavage fragmentation. The loss of CO from this ion yields the *m*/*z* 121 fragments common to all spectra. The regioisomeric aminoketones yield equivalent mass spectra including mass equivalent regioisomeric immonium cation base peaks. A subset of these compounds has the same molecular weight and almost identical mass spectra to that of the designer drug MDPV. An evaluation of the effects of homologation on gas chromatographic retention showed that addition of a methylene (CH_2) in the nitrogen-containing ring increases retention more than the equivalent group added to the alkyl side-chain.

1. Introduction

A number of synthetic cathinones (aminoketones, "bath salts") have appeared on the illicit drug market in recent years and these compounds represent a new emphasis in the development of designer drugs [1–5]. Derivatives identified in clandestine samples to date include a number of aromatic aminoketones such as MDPV (3,4-methylenedioxypyrovalerone), mephedrone, N-methylcathinone (also known as methcathinone or cat), 4-fluoromethcathinone (also known as flephedrone or 4-FMC) and 3,4-methylenedioxy-N-methylcathinone (also known as methylone, MDMC, bk-MDMA, or M1) [1]. These drugs are also structurally related to several schedule IV and V prescription drugs including bupropion (Zyban®, Wellbutrin®), diethylpropion (Tenuate®) and pyrovalerone (Centroton®). Synthetic cathinones are typically marketed as "bath salts" as well as plant food/fertilizer, insect repellant, pond cleaner, vacuum fresheners and "plant food" and are sold under various names (Ivory Wave, Blizzard, etc.) in most areas of the United States [2].

MDPV is a so-called "designer drug" with stimulant effects similar to cocaine and amphetamine [5]. It is an analogue of pyrovalerone, a psychostimulant that was considered the first commercially available drug from the alpha-pyrrolidinophenone drug class which was synthesized and introduced to the market in the 1960s [6]. This stimulant was used to treat lethargy and chronic fatigue in the 1970s, but was later withdrawn from the market because of problems with abuse and dependency [7]. MDPV structurally resembles cathinone, found in Khat, and has thus been referred to as a synthetic cathinone derivative [8]. Acute toxicity of MDPV causes neurological, cardiovascular and psychopathological symptoms such as tachycardia, chest pain, dizziness, hypertension, hyperthermia, tremors, psychomotor agitation, hallucinations and depression [9,10]. The amphetamine-like effects of these synthetic cathinones appear to be a result of the release of norepinephrine, serotonin and dopamine as well as the inhibition of their reuptake [3,4].

Recently, a GC–MS method was described for the quantitative determination of MDPV in the urine of opioid-dependent patients [11]. Westphal et al. confirmed the structure of MDPV in a seized sample in Germany in 2007 using product ion mass spectrometry as well as with ^{1}H and ^{13}C NMR [12]. Westphal et al. [13] recently reported the infrared spectroscopic, nuclear magnetic resonance and mass spectrometric data for the designer drug 3,4-methylenedioxypyrrolidinobutyrophenone (MDPBP), a homolog of 3,4-methylenedioxy-pyrovalerone (MDPV). MDPBP was first seized in Germany in the year 2009. The structure elucidation of the aliphatic part of MDPBP was carried out by product ion spectrometry of the immonium ion at *m*/*z* = 112 formed after

* Corresponding author. Tel.: +1 334 844 8326.
E-mail address: clarkcr@auburn.edu (C.R. Clark).

0379-0738/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.forsciint.2012.08.040

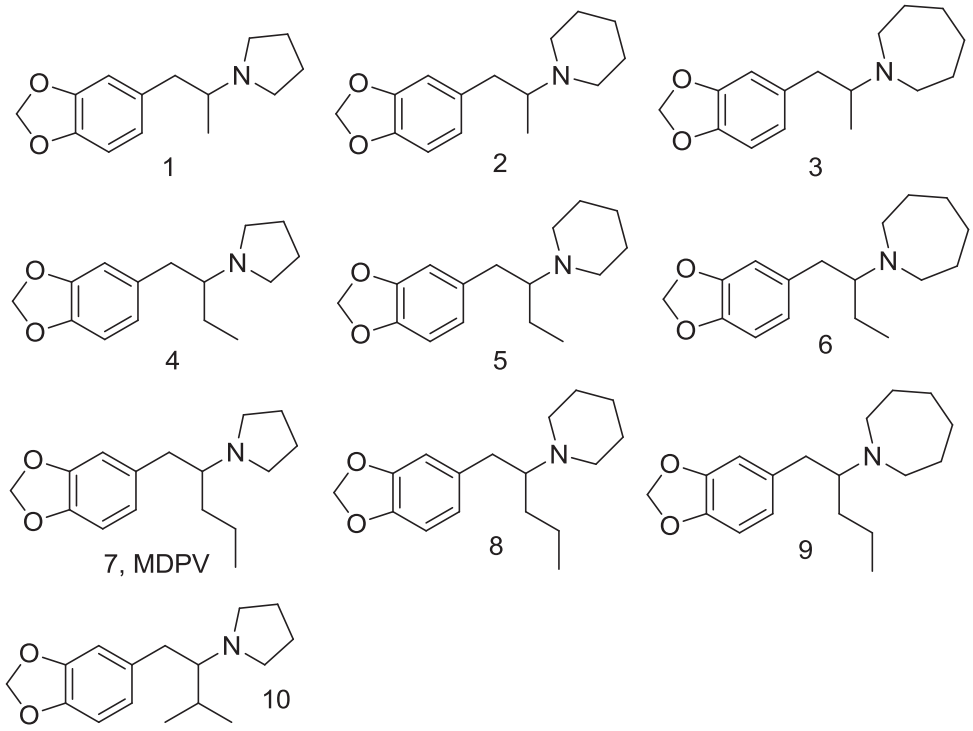

Fig. 1. Structures of the ten synthetic cathinone derivatives in this study.

electron ionization and by one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopy.

Based on the structure of the unsubstituted cathinone molecule, designer modifications are possible in three distinct regions of the molecule: the aromatic ring, the alkyl side chain and the amino group. Based on current trends all three of these areas of the cathinone structure are being explored by designer-type modifications. In addition to those derivatives described above, Russell and Bogun [14] recently reported a series of N-substituted beta-keto-analogues of MDMA, while two new alkyl side chain homologues of methcathinone were reported by Maheux and Copeland [15]. Also, Brandt et al. [16] recently described the three regioisomers of trifluoromethyl ring substituted methcathinone. Thus, these recent reports confirm that the exploration of the aromatic substituents, alkyl side chain and nitrogen substitution is continuing in the substituted cathinones. Legal control of a specific molecule often provides the driving force for clandestine development of additional substituted cathinone designer molecules whose structures place them just outside the chemical boundaries described by the language of the legal control documentation.

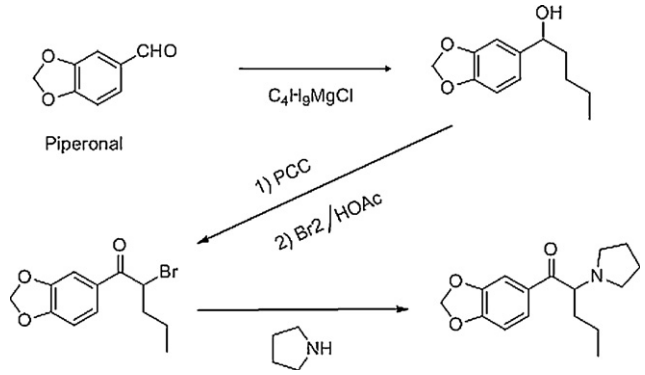

Fig. 2. General synthetic scheme for preparation of the cathinone derivatives.

This study involves the synthesis and analytical evaluation of a series of ten side chain and amino-group homologs and regioisomers related to the synthetic cathinone derivative MDPV, as shown in Fig. 1. All the compounds in this project have the MDPV aromatic ring substituent and substitution pattern, the 3,4-methylenedioxyphenyl-group and were prepared via a common synthetic pathway (Fig. 2) using the precursor aldehyde piperonal, 3,4-methylenedioxybenzaldehyde.

2. Experimental

2.1. Instrumentation

GC–MS analysis was performed using an Agilent Technologies (Santa Clara, CA) 7890A gas chromatograph and an Agilent 7683B auto injector coupled with a 5975C VL Agilent mass selective detector. The mass spectral scan rate was 2.86 scans/s. The GC was operated in splitless mode with a helium (grade 5) flow rate of 0.7 mL/min and the column head pressure was 10 psi. The MS was operated in the electron impact (EI) mode using an ionization voltage of 70 eV and a source temperature of 230 °C. The GC injector was maintained at 250 °C and the transfer line at 280 °C.

GC–MS chromatographic separations were carried out on a column (30 m × 0.25 mm i.d.) coated with 0.50 μm film of 50% phenyl–50% methyl polysiloxane (Rxi-50) purchased from Restek Corporation (Bellefonte, PA). The separations of the ten studied compounds were performed using a temperature program consisting of an initial hold at 70 °C for 1.0 min, ramped up to 250 °C at a rate of 30 °C/min followed by a hold at 250 °C for 15 min.

2.2. Synthetic methods

The synthetic methods needed to complete the preparation of the various isomeric and homologous aminoketones (Fig. 1) in this study are well established in the chemical literature and in our laboratory. The desired compounds can be prepared from the substituted benzaldehydes via a 4-step synthetic procedure