Science and Justice 57 (2017) 6–12

Contents lists available at ScienceDirect

Science and Justice

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

Indirect chiral separation of 8 novel amphetamine derivatives as potential new psychoactive compounds by GC–MS and HPLC

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ARTICLE INFO

Article history:
Received 18 April 2016
Received in revised form 22 August 2016
Accepted 28 August 2016

Keywords:
Phenylethylamine derivatives
Enantioseparation
Indirect chiral separation
Position isomers
"Legal Highs"
Chiral derivatization agents

ABSTRACT

Amphetamine and its derivatives gained high popularity on the illegal drug market. In the last few years, a lot of new psychoactive compounds structurally related to amphetamine, such as 4-fluoroamphetamine and 4-fluoromethamphetamine swamped the drug market. They were designed to circumvent prohibition of amphetamine and *N*-methylamphetamine and are distributed via the Internet. Often, a halogen atom is introduced into the phenyl ring of amphetamine to turn the illegal amphetamine legal. Since amphetamines possess a chiral centre, two enantiomers are available, which might differ in activity. Since most of them are partially not commercially available to date, synthesis and characterisation of amphetamine derivatives might help authorities to identify these substances of abuse.

The aim of this study was to investigate self-synthesized amphetamines concerning their identity and their enantiomeric status either by GC–MS or by HPLC. For GC–MS, derivatization with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or (1*R*)-(−)-menthylchloroformate prior to analysis on a HP-5MS column was done. For chiral separation by HPLC a LiChrospher 100 RP-18e column and sulfated beta-cyclodextrin added to the mobile phase as chiral selector were used. Enantioseparation was accomplished successfully by both methods. Furthermore, simultaneous chiral separation of three positions isomers, namely 2-fluoroamphetamine, 3-fluoroamphetamine and 4-fluoroamphetamine, was shown successfully by HPLC.

1. Introduction

Amphetamine and its derivatives belong to the compound class phenylethylamines [1]. Amphetamine was used to treat overweight people, people who suffer from narcolepsy or the attention deficit hyperactivity disorder [2]. Most of the European countries limited its use or completely banned it from the market because of its high addiction potential. A popular amphetamine derivative represents *N*-methamphetamine, which was administered to soldiers to fight their fatigue and fear during World War II. The trading name of the compound was Pervitin and a lot of people suffered from addiction. Besides *N*-methamphetamine, also other amphetamine derivatives, such as 3,4-methylenedioxymethamphetamine (MDMA) or β-ketoamphetamines, play an important role on today's illegal drug market.

Chemical structure of amphetamine is similar to ephedrine, which can be produced synthetically or is present in the plant *ephedra*. The effects of amphetamine range from increase of alertness, high self-confidence, suppression of tiredness, higher concentration potential to euphoria and relaxation. Apart from these effects, also negative side effects can appear, especially in combination with other medication or drugs or when administered in high doses. Tremor, psychosis, insomnia, repetitive obsessive behaviour, elevated body temperature, neurotoxicity [3] and abnormal heart beat are considered as negative side effects [4]. In worst cases the consumption of amphetamine derivatives can cause severe damage to the body and the brain [5] of the consumer or even lead to death.

Aside from drug addicts, occasionally some athletes and body builders consume amphetamine for doping.

Amphetamine derivatives have appeared along with a lot of other new psychoactive compounds at the world wide drug market. They are sold as so called "Legal Highs" [6] or "bath salts" [7], which are powerful in stimulating the central nervous system of the consumer. The idea behind the flooding of the drug market with new amphetamine type stimulants is to circumvent laws, which regulate the consumption and the disposal of other controlled compounds [4]. E.g. 4-fluoromaphetamine, 3-fluoroamphetamine and 4-fluoromethamphetamine replaced amphetamine and methamphetamine as controlled drugs and changed drug consumption behaviour during past few years [8,9].

All new psychoactive compounds based on amphetamine structure are chiral. As a consequence two different enantiomers are possible. Regarding chiral drugs, enantiomers may exhibit different

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http://dx.doi.org/10.1016/j.scijus.2016.08.007
1355-0306/

pharmacological effects, whereas the eutomer is the effective isomer. In contrast, the distomer represents the enantiomer, which can be effectless, can cause unwanted side effects or even be toxic [10]. A suitable illustration in this context of chirality is amphetamine, where the *S*-isomer has stronger effects on the nervous system than the *R*-isomer [11,12].

Drugs are mostly sold as racemic mixtures, in some cases mixed with other substances such as caffeine, lactose, pain killers or ephedrine. Consumption of pure eutomers can cause overdose or even might lead to lethal cases. Due to this fact, one aim of this work was to check amphetamine derivatives after synthesis concerning their enantiomeric composition.

In this work eight different amphetamine derivatives were synthesized, namely 2-fluoroamphetamine (2-FA), 2-fluoromethamphetamine (2-FMA), 4-bromoamphetamine (4-BA), 4-bromomethamphetamine (4-BMA), 4-nitroamphetamine (4-NA), 4-nitromethamphetamine (4-NMA), 2-chloroamphetamine (2-CA) and 2-chloromethamphetamine (2-CMA). Their chemical structures and mass spectral data are listed in Fig. 1. The compounds were synthesized in our laboratory in small amounts (mg scale), to show a common strategy for their synthesis as well as because they are partially not yet commercially available.

Goal of this work was successful enantioseparation of the abovementioned amphetamine derivatives both by GC–MS and HPLC. For GC–MS, indirect separation on a common HP-5MS column should be tested after derivatization of the compounds either by (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or by (1*R*)-(−)-menthylchloroformate. Chiral separation by HPLC should be accomplished on a common RP-18e column and addition of a chiral selector to the mobile phase.

Synthesis of 2-fluoroamphetamine was carried out, because two of its position isomers, 3-fluoroamphetamine (3-FA) and 4-fluoroamphetamine (4-FA) are commercially available on the drug market since a few years. A further goal of this work was to distinguish between all three position isomers in one single run by chiral separation both on GC–MS and HPLC.

2. Materials and methods

2.1. Chromatographic conditions

A Shimadzu (Kyoto, Japan) GC-2010 Plus gas chromatograph equipped with a Shimadzu (Kyoto, Japan) GCMS-QP2010SE mass selective detector was used for GC experiments. The system was equipped with an AOC-20i auto injector and an AOC-20s auto sampler, both from Shimadzu (Kyoto, Japan). Data collection was done by scan mode, which started 4 min after the injection. Injection volume was 1 μl with a split ratio of 2:1. Helium was used as carrier gas (1 ml/min). Temperature of the GC–MS interface was 250 °C and of the injector was 280 °C. As stationary phase, a HP5-MS capillary column with a length of 30 m, a 0.25 μm film thickness and an inner diameter of 0.25 mm was used (Agilent, Waldbronn, Germany). Void time of 1.16 min was defined experimentally. Amphetamines were injected as free bases (1 mg/ml).

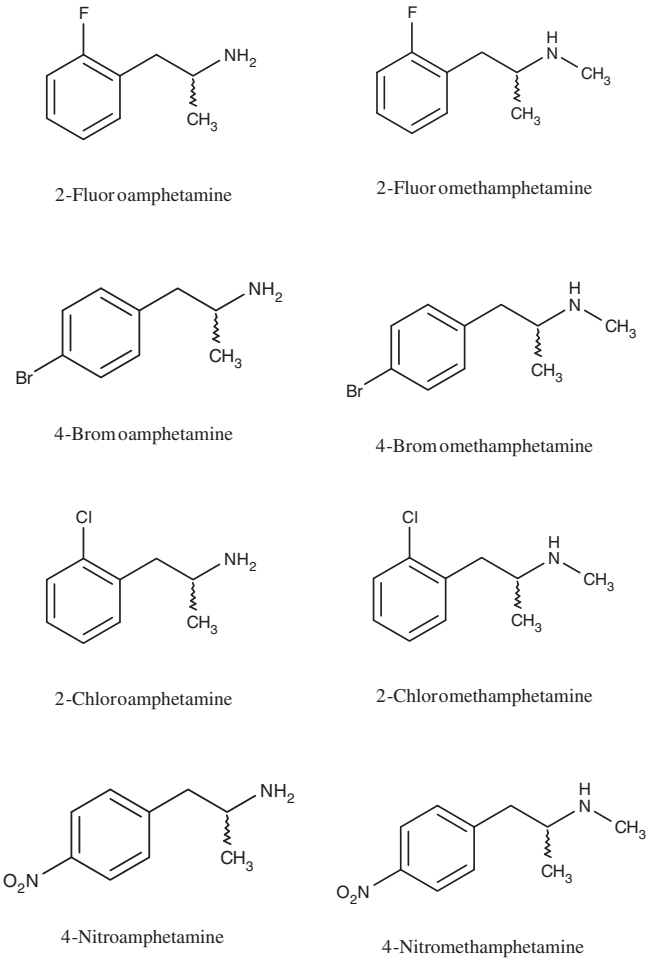

Fig. 1. Chemical structures of the 8 synthesized and investigated amphetamine- and methamphetamine derivatives and their mass spectral data. Conditions: GC–MS, temperature programme 1; 1: 2-FMA, 2: 2-FA, 3: 3-BA, 4: 4-NA, 5: 2-CA, 6: 2-CMA, 7: 4-BMA, 8: 4-NMA.