(*2S*)-1-(4-Methoxyphenyl)-*N*-[(*1R*)-2-(4-methoxyphenyl)-1-methylethyl]-2-propanamine in Crude *p*-Methoxyamphetamine (PMA) Produced by the Leuckart Method

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Amphetamine Analogs, Stereochemistry, Phenylethylamines

The synthesis and separation of both diastereoisomers of 1-(4-methoxyphenyl)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-2-propanamine as markers of clandestine *p*-methoxyamphetamine have been described. The stereochemistry of the *meso* diastereomer was established by crystallographic method.

Introduction

A variety of phenylisopropylamines remain popular drugs of abuse in Poland, as well as in other countries in Europe. Depending on their *N*-alkyl and/or aryl substitution and/or side-chain extension, the so-called "designer drugs" produce hallucinogen or stimulant-like effects. Among these, 3,4-methylenedioxymethylamphetamine (MDMA) and 3,4-methylenedioxethylamphetamine (MDE) have gained considerable popularity probably due to their atypical effects such as positive mood changes enhanced communication and improved interpersonal relationship [1]. Recently, *p*-methoxyamphetamine (PMA) **1** and its *N*-methyl derivative *p*-methoxymethylamphetamine (PMMA) **2** have appeared in a tablet form on the illicit market [2,3] (Fig. 1).

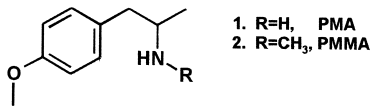


Fig. 1. The chemical structure of *p*-methoxyamphetamine **1** and *p*-methoxymethamphetamine **2**.

Several fatal intoxications following consumption by these agents have recently been reported in Australia [4] and in Poland [5]. The suggested possibility that there might be a narrow margin between the behaviorally active and the lethal dose of PMA and PMMA in humans, clearly indicates that a severe risk is associated with the ingestion of these drugs of abuse [6].

Since the appearance of these, without any doubt, the number of very dangerous amphetamine analogs has increased during the last year, a comprehensive study concerning their illicit preparation has been undertaken in our laboratory [7].

Results and Discussion

The present work is part of a wider project, within which we investigate impurity formation patterns in illegally produced amphetamine analogs.

Many compounds, including the starting materials, by-products and products of the side reactions were observed in clandestine produced drugs, as they were not exactly purified following their synthesis. The confirmation of the presence of specific impurities provides a valuable information base, which serves as an excellent tool for establishing the synthetic route, as well as in comparison of the samples of diverse origin [8,9].

The most common clandestine synthesis route for amphetamine uses the Leuckart reaction with

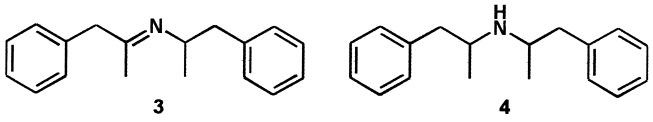
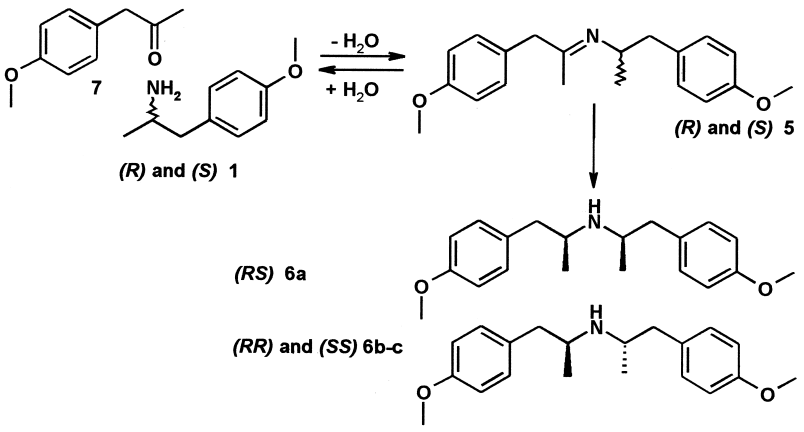


Fig. 2. The chemical structures of some impurities found in amphetamine produced by the Leuckart method.

benzylmethylketone (BMK) as a starting material. The imine **3** and the secondary amine **4** could be detected in illicitly produced amphetamine [10,11] (Fig. 2).

Kirkbridge *et al.* [2] have recently reported that the amine **1** found in illicit tablets had probably also been produced by the Leuckart method. Strong support for this assumption was the identification of the methoxy derivatives of 4-methyl-5-phenylpyrimidyne and 4-benzylpyrimidyne in seized material. GC-MS examination of **1** from our own synthesis additionally indicated the presence of *para*-methoxy derivatives of **3** and **4**. The formation of **4** probably results from the condensation between the amphetamine and benzylmethylketone, followed by the reduction of the intermediate imine **3.** The analogous formation pattern can be proposed for compounds **5** and **6a-c** (Scheme 1). In the case of the preparation of reference compounds **6a-c,** we followed the same reaction scheme using $NaBH_4$ as the reducing agent. It should be noted that in "real" preparations of amphetamines by the Leuckart method, formic acid serves as the reducing agent.

In the course of the reduction of **5**, a second stereogenic center was formed yielding compound **6** as the mixture of the *meso* derivative **6a** and enantiomers **6b-c**. Upon GC analysis compound **6** appeared in the form of two well-resolved peaks with identical electron ionization mass spectra. The signal ratio was approximately 35/65, in favor of the second peak eluted. A similar phenomenon was noted by Lindeke *et al.* [12] who found that borohydride reduction of the appropriate imines formed by reaction of alkyl benzyl ketones with both *R*- and *S*-α-phenylethylamine yielded mainly the *RR* and the *SS* form, whereas the *meso* derivative was produced in a lesser amount. Thus, the first stereogenic center has a strong influence on the configuration of the second center being formed. This example of an asymmetric synthesis seems to follow Cram's rule. Nucleophilic attack occurs from the less hindered side of the prochiral center [13]. The ratio between *RR/SS* and *RS* forms may strongly depend on the reagent used during the reduction of the imine **5**, thus providing a better insight into the methods applied in clandestine synthesis. Therefore, it seemed to be important to establish the stereochemistry of the compounds under consideration. Until now however, there is no firm evidence for the structures of compounds **6a,b-c**. Therefore, we decided to perform the study on a preparative scale. Thus, the imine **5** was obtained by condensation of *p*-methoxyamphetamine **1** with *p*-methoxyphenylacetone in refluxing toluene. Since the imine **5** ap-



Scheme 1.

peared to be relatively unstable, we decided to subject it to the next step without purification. Subsequent borohydride reduction in ethanol afforded **6** as a mixture of stereoisomers in good chemical yield.

This mixture was then subjected to repeated procedures of column chromatography and crystallization of sulfate or hydrochloride salts until pure diastereomers were obtained. The diastereomer that was eluted first during the column chromatography and that was more volatile on GC analysis was transformed into its hydrochloride salt from which a crystal suitable for an X-ray study was obtained [14]. As indicated in the ORTEP diagram, compound **6a** possesses *RS* configuration of the stereogenic centers (Fig. 3):

The results of the gas chromatographic-mass spectrometric analysis of crude compounds **6a-c** after treatment the imine **5** with borohydride in ethanol are presented in Fig. 4A, whereas Fig. 4B shows the GC-MS analysis of the crude product **1** obtained by the Leuckart method.

4-Methoxyphenylacetone was heated to 190 °C in a mixture of formamide and formic acid for 6 hours, cooled, and treated with concentrated hydrochloric acid for 4 hours under reflux conditions. After usual workup, crude **1** was analyzed by GC-MS. The first major component eluting at 7.46 min showed chromatographic properties and a fragmentation pattern matching that of **1** [15]. The second intense compound eluted after 11.16 min and was identified as 4-methyl-5-(4′-methoxyphenyl)pyrimidine [2]. A next peak at 11.33 min eluting just after the pyrimidine was *p*-methoxyformylamphetamine – intermediate in Leuckart synthesis of **1**. The chromatographic and mass spectral properties of compounds eluted at 16.22 and 16.37 min perfectly matched those obtained for the synthesized reference diastereomers **6a** and **6b-c**, respectively. An exact examination of the crude PMA extract revealed the presence of two additional compounds with essentially the same mass spectra but eluted at 19.07 and 19.35 min. The assignment of their structures is currently underway.

Experimental Section

All reagents and solvents employed were of analytical or HPLC grade. Toluene, formamide, chloroform and sodium borohydride were purchased from Merck (Germany). 4-Methoxyphenylacetone was obtained from Lancaster (England).

TLC was performed on the Merck Kieselgel 60 F-254 plate with chloroform-methanol (93:3, v/v) as eluent. Column chromatography was carried out at atmospheric pressure using silica gel 100–200 mesh with chloroform and chloroform-methanol (9:1, v/v) mixture as a solvent system.

Melting points were uncorrected. NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR, respectively. Resonances were measured in parts per million relative to tetramethylsilane (TMS) (δ = 0.0) for hydrogen, and chloroform (δ = 77.0) for carbon. The GC-MS system consisted of HP 6890 Series gas chromatograph coupled with HP 5973 mass-selective detec-

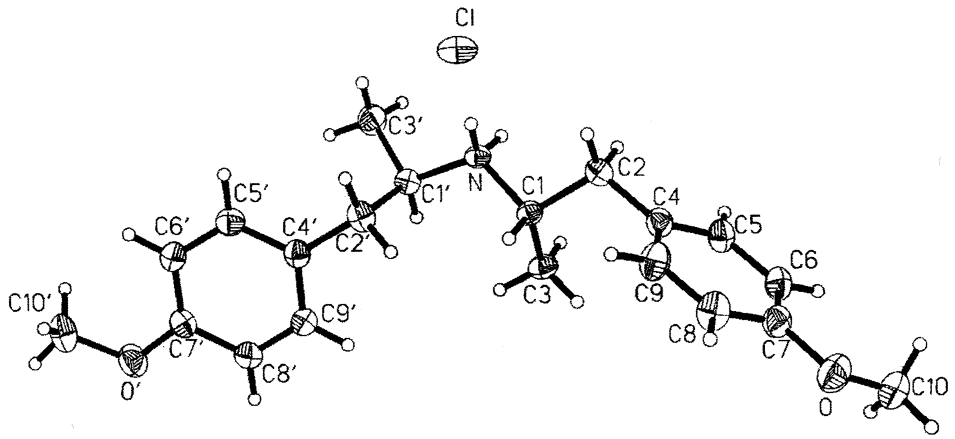


Fig. 3. The ORTEP diagram for hydrochloride of **6a** [14]. The non-hydrogen atoms are shown as 30% probability ellipsoids.

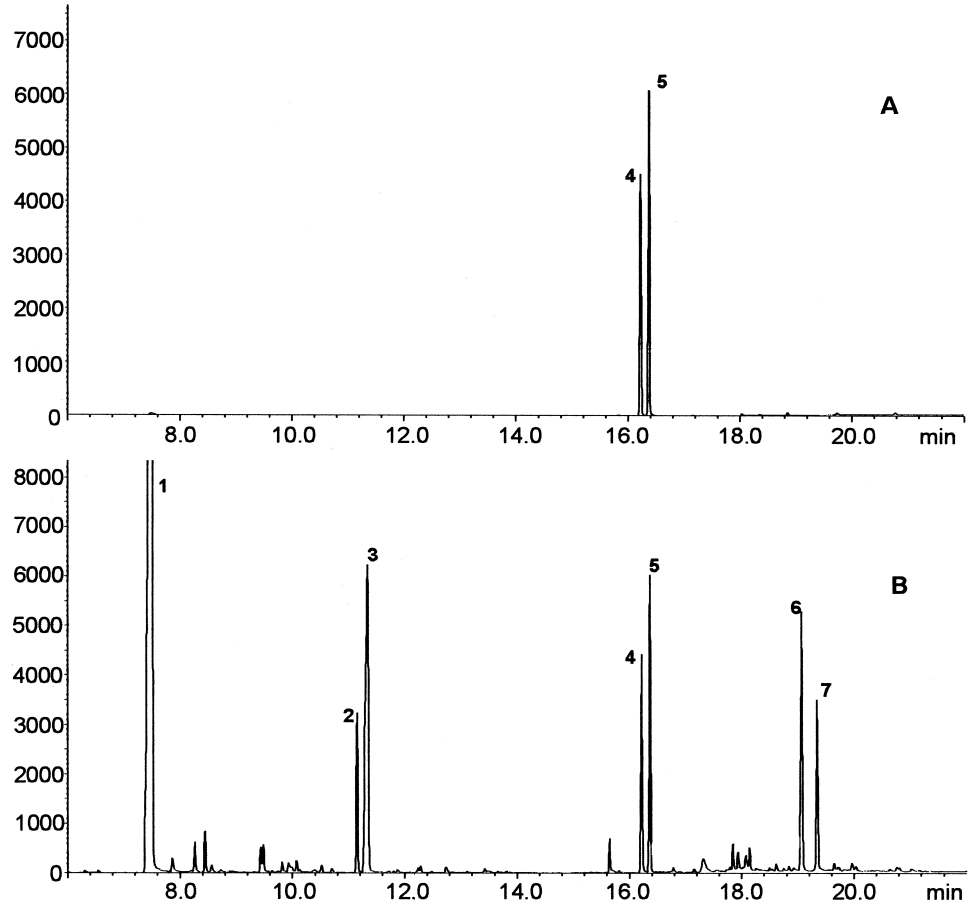


Fig. 4. The gas chromatogram of (A) crude **6a-c,** (B) crude PMA after second step of the Leuckart synthesis; 1 = PMA (t_r = 7.46 min), 2 = 4-methyl-5-(4′-methoxyphenyl)pyrimidine (t_r = 11.16 min), 3 = *p*-methoxyformylamphetamine (t_r = 11.33 min), 4 = amine **6a** (t_r = 16.22 min), 5 = amine **6b-c** (t_r = 16.37 min), 6 and 7 = unknown (t_r = 19.07 and 19.35 min).

tor. A column SPB-5 20 m × 0.22 mm I. D. with 0.25 μm film thickness was used with helium as a carrier gas with constant flow F = 0.6 ml/min. The injector temperature was 250 °C. Samples (1 μl) were introduced in a split mode with a split ratio 50:1. During analysis of impurity extracts splitless mode was used. The oven temperature was programmed as follows: the initial temperature was set at 130 °C, held for 1 min and ramped at 12 °C/min to 300 °C and held for 5 min.

Synthesis of (4-methoxyphenyl)-2-propanamine (**1**)

Compound **1** was prepared according to the literature procedure [15]; precipitated hydrochloride salt after recrystallization from ethanol afforded analytical sample of **1** as a colorless crystals M.p. 205–206 °C, lit. [16] M.p. 206–207 °C.

Synthesis of 1-(4-methoxyphenyl)-N-[-2-(4-methoxyphenyl)-1-methylethyl]-2-propanamines (**6a-c**)

The solution of 4-methoxyphenylacetone (7.9 g, 48 mmol) and 4-methoxyphenyl-2-aminopropane (8.0 g, 48 mmol) **1** in toluene (300 ml) was refluxed for 7 h with continuous removal of water (Dean-Stark apparatus). After evaporation of the solvent *in vacuo*, the resulting imine **5** was dissolved in 200 ml 99.8% ethanol. To this solution a solid sodium borohydride (4.0 g, 90 mmol) was added portionwise and the resulting mixture was stirred for 3 h. After completion of the reduction (monitored by GC) the borohydride complex was destroyed by the addition of 10% H_2SO_4 (5.0 ml). During evaporation of the solvent, white precipitate was obtained, which was filtered and next, recrystal-

lized from EtOH/H_2O (1:2) yielding sulfate salt of **6** (7.3 g). The filtrate was treated with 10% NaOH (150 ml) and extracted with chloroform (3 × 100 ml). Combined extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo* yielding pale brown oil. Column chromatography of resulting oil afforded additional portion of **6** (2.0 g). Overall yield (free base) of **6** was 63%. The crude mixture obtained after the reduction step revealed on GC the relative proportion **6a** (more volatile) to **6b-c** (less volatile) as 36:65.

The analytical samples of the *meso* form **6a** and the mixture of enantiomers **6b-c** were obtained after repeated recrystallization of its, respectively, hydrochloride and sulfate salts. The salts were recrystallized from methanol until a diastereomeric purity of ≥97% (as measured by GC-MS) was obtained.

Analytical data for **6a**: hydrochloride M.p. 257–258 °C – ^{1}H NMR (500.61 MHz, $CDCl_3$): δ = 1.03 (d, 6H, J = 6.5 Hz, CH-CH_3), 2.45 (dd, 2H, ^1J = 13.5 Hz, ^2J = 6.0 Hz, CH-CH_2), 2.58 (dd, 2H, ^1J = 13.5 Hz, ^2J = 6.5 Hz, CH-CH_2), 2.95 (m, 2H, CH-CH_2), 3.79 (s, 6H, O-CH_3), 6.77 (d, 4H, J = 8.5 Hz, O-C-CH_{arom}), 6.96 (d, 4H, J = 8.5 Hz, CH_2-C-CH_{arom}) – ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.29 (CH-CH_3), 42.29 (CH-CH_2), 51.77 (CH-CH_2), 55.16 (O-CH_3), 113.69 (O-C_{arom}-C_{arom}H), 130.17 (CH_2-C_{arom}-C_{arom}H), 131.25 (CH_2-C_{arom}), 157.91 (O-C_{arom}) – MS (EI, 70 eV) m/z (%): 312 (1) [$M^{\bullet+}$ – $H^{\bullet}$], 192 (80) [$M^{\bullet+}$ – $C_8H_9O^{\bullet}$], 149 (100) [192 – C_2H_5N], 121 (60) [$M^{\bullet+}$ – $C_{12}H_{18}NO^{\bullet}$], 91 (14) [121 – CH_2O] – $C_{20}H_{28}NO_2Cl$ (349.9): calcd. C 68.65, H 8.07, N 4.00, Cl 10.13, found C 68.42, H 7.93, N 4.12, Cl 10.97.

Analytical data for **6b-c**: sulfate, M.p. 273–278 °C – ^{1}H NMR (500.61 MHz, $CDCl_3$): δ = 0.94 (d, 6H, J = 6.0 Hz, CH-CH_3), 2.48 (dd, 2H, ^1J = 13.0 Hz, ^2J = 7.5 Hz, CH-CH_2), 2.71 (dd, 2H, ^1J = 13.0 Hz, ^2J = 6.0 Hz, CH-CH_2), 2.97 (m, 2H, CH-CH_2), 3.78 (s, 6H, O-CH_3), 6.81 (d, 4H, J = 8.0 Hz, O-C-CH_{arom}), 7.07 (d, 4H, J = 8.5 Hz, CH_2-C-CH_{arom}) – ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.02 (CH-CH_3), 43.33 (CH-CH_2), 51.33 (CH-CH_2), 55.20 (O-CH_3), 113.70 (O-C_{arom}-C_{arom}H), 130.23 (CH_2-C_{arom}-C_{arom}H), 131.56 (CH_2-C_{arom}), 157.93 (O-C_{arom}) – MS (EI, 70 eV) m/z (%): see compound **6a** - $C_{20}H_{28}NO_2Cl$ (349.9): Elemental analysis for a free base: calcd.for $C_{20}H_{27}NO_2$ (313.43) C 76.64, H 8.68, N 4.47; found C 76.51, H 8.49, N 4.25.

Crystal data for **6a** *hydrochloride:* colorless platy monoclinic crystal, space group $P2_1/n$, a= 7.315(5), b= 30.19(2), c= 8.817(8) Å, β= 95.73(7)°, V= 1937(3) Å^3, Z = 4, M= 349.88, ϱ_x= 1.200 gcm^{-3}, $F(000)$= 752, λ(Mo–K$_\alpha$)= 0.71073 Å, μ(Mo–K$_\alpha$)= 0.209 mm^{-1}. 5805 reflections collected. Final R_1= 0.0387 and wR= 0.1086 for 2558 reflections with $I>2\sigma(I)$.

[1] D. E. Nichols, R. A. Oberlender, Structure – activity relationships of MDMA and related compounds: A new class of psychoactive drugs?, NYAS 600 (1990) 613–625.
[2] J. C. Coumbaros, K. P. Kirkbridge, G. Klass, J. Forensic Sci. **44**, 1237–1242 (1999).
[3] T. A. Dal Cason, Microgram **33**, 207–222 (2000).
[4] R. A. James, A. Dinan, Med. Sci. Law **38**, 83–85 (1998).
[5] A. Siwińska-Ziółkowska, personal communication, Department of Forensic Medicine, Warsaw.
[6] T. D. Steel, J. L. Katz, G. A. Ricaurte, Brain Research **589**, 349–352 (1992).
[7] D. Błachut, Z. Czarnocki, K. Wojtasiewicz, Forensic Sci. Int. **123**, 182–190 (2001).
[8] L. Strömberg, H. Bergkvist, Edirisinghe A. M. K. Edirisinghe, J. Chromatogr. **258**, 65–72 (1983).
[9] D. G. Sanger, I. J. Humphreys, A. C. Patel, M. Japp, R. G. L. Osborne, Forensic Sci. Int. **28**, 7–17 (1985).
[10] J. N. Lomonte, W. T. Lowry, I. C. Stone, J. Forensic Sci. **21**, 575–582 (1976).
[11] A. B. E. Theeuwen, A. M. A. Verweij, Forensic Sci. Int. **15**, 237–241 (1980).
[12] U. B. Paulsen-Sörman, K-H. Jönson, B. G. A. Lindeke, J. Med. Chem. **27**, 342–346 (1984).
[13] E. L. Eliel, S. H. Wilen, "Stereochemistry of Organic Compounds", Wiley, London (1994).
[14] Full crystallographic data were deposited with CCDC under the number CCDC 169114.
[15] F. T. Noggle, C. R. Clark, C. L. McMillian, J. DeRuiter, J. Chrom. Sci. **27**, 607–611 (1989).
[16] K. Bailey, H. D. Beckstead, D. Legault, D. Verner, J. Assoc. Off. Anal. Chem. **57**, 1134–1143 (1974).

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