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Synthesis markers in illegally manufactured 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine

M. Bohn[1], G. Bohn[1], and G. Blaschke[2]

[1]Institut für Rechtsmedizin, Westfälische Wilhelms-Universität, v. Esmarch-Strasse 86, D-48149 Münster, Germany
[2]Institut für Pharmazeutische Chemie, Westfälische Wilhelms-Universität, Hittorfstrasse 58, W-48149 Münster, Germany

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Summary. In this paper the isolation and identification of 12 compounds as impurities in illicit 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) is reported. Isolation of these substances is performed by preparative TLC, while identification is performed by using mass spectrometry and ^{1}H-NMR spectroscopy. A simple and rapid method for detection of these impurities in seized MDA and MDMA samples is described. The identification of the impurities can provide numerous points on which to base comparative analysis of different exhibits.

Key words: MDA – MDMA – Synthesis markers – Leuckart-Wallach synthesis – Reductive amination

Zusammenfassung. Es wird die Isolierung und Identifizierung von 12 Synthesebeiprodukten in illegalem 3,4-Methylendioxyamphetamin (MDA) und 3,4-Methylendioxymethamphetamin (MDMA) beschrieben. Die Isolierung dieser Substanzen wird durch präparative Dünnschichtchromatographie erreicht, während die Identifizierung durch GC/MS und ^{1}H-NMR Spektroskopie erfolgt. Anschließend wird eine einfache und schnelle Methode, diese Substanzen in beschlagnahmten MDA- bzw. MDMA-Proben nachzuweisen, vorgestellt. Der Nachweis dieser Substanzen kann eine wichtige Hilfe dabei sein, eine vergleichende Analytik verschiedener Proben vorzunehmen.

Schlüsselwörter: MDA – MDMA – Synthesemarker – Leuckart-Wallach Synthese – Reduktive Aminierung

Introduction

The amphetamine derivative 3,4-methylenedioxyamphetamine (MDA) (I) was first synthesised in 1910 by Mannich and Jacobsohn [1] and the N-methyl derivative 3,4-methylenedioxymethamphetamine (MDMA) (II) has been known and patented since 1914 [2]. Both substances fell into oblivion for a long time but at the end of the 1970s both amphetamines became significant in the drug scene.

Because there is no therapeutic application the synthesis was carried out exclusively in clandestine laboratories. Therefore the manufactured products do not occur in pharmaceutical purity. They are normally found as white to yellow powder but other forms are also known, especially a preparation in the form of white or pink tablets or coloured capsules.

In connection with criminal proceedings the question was raised whether samples which had been seized in different places originated from the same clandestine laboratory. Because the reaction pathway is very simple, the syntheses of MDA and MDMA from

3,4-(Methylenedioxy)phenyl-2-propanone (III) can be carried out by reductive amination or the Leuckart-Wallach synthesis. This ketone is no longer available in the most countries so that 3,4-(methylenedioxy)phenyl-2-propanone (III) must be obtained from, for example, isosafrole (IV) or 3,4-(methylenedioxy)phenylacetic acid (V).

The following paper reports on whether by-products are formed during the syntheses, which are characteristic impurities for the identity of samples.

Experimental details:

Gas chromatography/mass spectrometry. 70 eV electron impact mass spectra were obtained with a Model 5890A GC (Hewlett-Packard) coupled to a 5970A Mass Selective Detector (MSD). A fused silica capillary column Ultra 2 (25 m × 0.2 mm i.d. × 0.11 µm) was used. The temperature program used with this column consisted of an initial temperature of 100°C held for 2 min, followed by a linear ramp to 280°C at 10°C/min. The final temperature was held for 15 min. The split/splitless injector and detector temperatures were 280°C and the carrier gas was helium.

This study contains results from the dissertation of M. Bohn

Correspondence to: M. Bohn

Gas chromatography. Gas chromatographic analysis was carried out on a Carlo Erba HRGC fractovap series 4160 gas chromatograph equipped with a flame-ionisation detector (FID). The column was a commercially available fused silica capillary column HP1 (25 m × 0.2 mm × 0.33μm). Injector and detector temperatures were both 300°C, splitless mode. Column temperatures were 100–300°C at 10°C. The final temperature was held for 10 min.

Nuclear magnetic resonance. ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 MHz. Samples were measured as the free base dissolved in deuterated chloroform. Tetramethylsilane (TMS) was used as an internal standard.

Thin-layer chromatography. Precoated plates (silica gel 60 GF 254, Merck, 6100 Darmstadt, Germany) were used in all cases. Detection was achieved by examination under ultraviolet light.

Chemicals. Isosafrole, formamide, N-methylformamide, formic acid, methylamine-HCl, ammonium acetate, hydrogen peroxide and acetic anhydride were obtained from Merck, 6100 Darmstadt, Germany. 3,4-(Methylenedioxy)phenylacetic acid was obtained from Aldrich Chemicals, 7924 Steinheim, Germany.

Isolation of the substances VI-XVII. All substances were isolated using preparative thin-layer chromatography (pTLC) with various solvent systems.

Substances VI-X. 3,4-(Methylenedioxy)phenyl-2-propanone (III) was obtained from isosafrole (IV) by the method of Fujisawa et al. [6] and converted using formamide according to Crossley and Moore [3]. The crude MDA product was dissolved in aqueous solution, adjusted to pH-5–6 with 0.5 N HCl and extracted with CH_2Cl_2. The organic phase was concentrated and one half of the extract was spotted onto Merck Silicagel 60 F-254 plates using hexane/ether (50/50) as eluent. The main impurity substance VI (Rf 0.25) was obtained in a second pTLC in hexane/acetone (50/50), (Rf 0.56).

The second half of the CH_2Cl_2 extract was subjected to chromatography in hexane/ether (50/50) and 4 bands (Rf 0.31; Rf 0.36; Rf 0.38; Rf 0.41) were again subjected to chromatography using a second solvent system, hexane/ether (90/10). In this eluent the same plates were developed eleven times. In this way substances X (Rf 0.56), IX (Rf 0.60), VIII (Rf 0.65) and VII (Rf 0.72) were obtained.

Substance XI. III was obtained from IV according to Fujisawa et al. [6] and converted by the method of Braun et al. [12]. The crude MDA product obtained was dissolved in aqueous solution, adjusted to pH 5–6 with 0.5 N HCl and extracted with CH_2Cl_2. The purification of the extract was carried out in the solvent system $CHCl_3$/MeOH/H_3CCOOH (90/10/0.5). Substance XI was obtained at Rf 0.50.

Substances XIII and XIV. III was manufactured according to Magidson and Garkusha [13] and converted by the method of Crossley and Moore [3]. The crude MDA product obtained was dissolved in aqueous solution, adjusted to pH 5–6 with 0.5 N HCl and extracted with CH_2Cl_2. The purification of the extract was carried out after evaporation in the solvent system diethylether/dibutylether/diethylamine (45/45/5). XIII was obtained at Rf 0.35. Purification of substance XIV was carried out using the mixture toluene/acetone/diethylamine (75/20/3): (Rf 0.49).

Substance XV. The crude MDMA product obtained by the synthesis after Fujisawa et al. [6] and Braun et al. [12] was dissolved in aqueous solution, adjusted to pH 5–6 with 0.5 N HCl and extracted with CH_2Cl_2. After evaporation, chromatography was carried out in the solvent system diethylether/dibutylether/diethylamine (45/45/5). XV was obtained at Rf 0.72.

Substances XVI and XVII. III was manufactured after the method of Magidson and Garkusha [13] and converted with N-methyl-formamide according to Crossley and Moore [3]. The crude MDMA product obtained was dissolved in aqueous solution, adjusted to pH 5–6 with 0.5 N HCl and extracted with CH_2Cl_2. The purification of the extract was carried out after evaporation using the solvent system diethylether/dibutylether/diethylamine (45/45/5). XIII was obtained at Rf 0.37. Substance XVII was purified using the mixture toluene/acetone/diethylamine (75/20/3): (Rf 0.43).

Analysis of the substances III-XIX in illegal MDA- and MDMA-samples. 300–500 mg of the sample was dissolved in 3 ml of phosphate buffer solution (pH 6) and applied to an Extrelut-3 column. The column was washed with ca. 3 ml aqua dest. and eluted with ca. 10 ml CH_2Cl_2. The dried organic phase was concentrated to 50 μl and investigated using GC/MS.

Results and discussion

A. Synthesis of MDA from isosafrole by the method of Leuckart-Wallach

The synthesis of amphetamines by the method of Leuckart-Wallach from the appropriate ketones is described in the literature [3–5]. This reaction is based on the principle of the condensation of a ketone with a formamide. A formyl-bond is formed which is hydrolized to amine with dilute acid. This synthesis can also be carried out by the use of propenylbenzenes as the primary products of the ketone synthesis [6].

This variation is also often used for the clandestine manufacture [7]. Under the reaction conditions described [3–5], Leuckart-Wallach specific impurities occur, which were described by v. d. Ark et al. [8] for the synthesis of amphetamine.

In our investigations the following compounds could be isolated and identified as impurities of the MDA synthesis.

VI. *4-methyl-5-(3,4-methylenedioxy)phenylpyrimidine*
VII. *4-(3,4-methylenedioxy)benzylpyrimidine*
VIII. *2,6-dimethyl-3,5-di-[(3,4-methylenedioxy)phenyl]-pyridine*
IX. *2,4-dimethyl-3,5-di-[(3,4-methylenedioxy)phenyl]-pyridine*
X. *4-methyl-5-(3,4-methylenedioxy)phenyl-2-(3,4-methylenedioxy)benzylpyridine*
XI. *N,N di-[1-(3,4-methylenedioxy)phenyl-2-propyl]-amine*

The pyrimidines VI and VII can be considered as condensation products of one molecule 3,4-(methylenedioxy)-phenyl-2-propanone (III) and two molecules formamide. The pyridines VIII–X are formed from two molecules ketone and one molecule of formamide.

In one synthesis variation, using the condensation of the ketone and the formamide in the presence of formic acid, the substances VI–X could not be demonstrated. In this variation the presence of excess formic acid as a reducing agent inhibits the aromatisation to the heterocyclic compounds. The substances XI and XV can be identified here, as previous described by Lukaszewski [9].

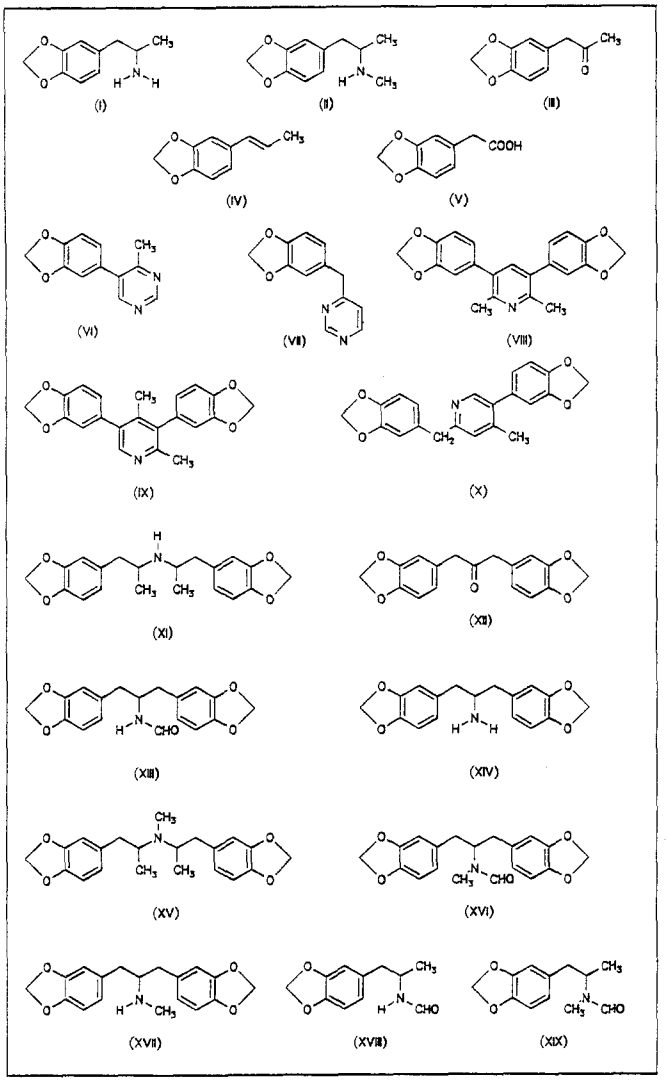

Fig. 1. Structure of the compounds, roman numerals correspond to the listing in the text

The identity of all substances was proved using GC/MS methods and ^{1}H-NMR spectroscopy. The eight peak index of the mass spectra is shown in Table 1 [20] and the ^{1}H-NMR resonances are listed in Table 2.

B. Synthesis of MDA using reductive amination

By reductive amination a ketone reacts with an amine to form an imine as intermediate product which is then subsequently reduced to the corresponding amine.

The syntheses of amphetamines using this reaction pathway has been extensively described in the literature [10, 11, 12].

Amination under normal pressure, as well as amination under increased pressure led to substance XI, as a conspicuous artefact. The substances VI–X are not formed because they are specific for the Leuckart-Wallach synthesis.

C. Synthesis of MDA from 3,4-(methylendioxy)phenylacetic acid by the method of Leuckart-Wallach

Arylmethylketones can be produced from arylacetic acids as primary products of a Leuckart-Wallach reaction using the method of Magidson and Garkusha [13].

There is however a side reaction to produce diarylacetones [14, 15] and 3,4-(methylenedioxy)phenyl-2-propanone (III) produced from 3,4-(methylenedioxy)phenylacetic acid (V) can therefore be contaminated with 1,3-di-[3,4-(methylenedioxy)phenyl]-2-propanone (XII). If 3,4-(methylenedioxy)phenyl-2-propanone (III) manufactured in this way is subjected to the Leuckart-Wallach synthesis [3], the following impurities can be identified in addition to substances VI–XI:

XIII. α-*(3,4-methylenedioxy)benzyl-N-formyl-(3,4-methylenedioxy) phenethylamine*

XIV. α-*(3,4-methylenedioxy)benzyl-(3,4-methylenedioxy)-phenethylamine*

If 3,4-(methylenedioxy)phenyl-2-propanone (III) manufactured in this way is subjected to e.g. reductive amination, the substances XI, XIV and XV can be detected.

In substance XIII the cis- trans-isomeration of formamides can be recognized from the ^{1}H-NMR spectrum [16, 17]. The NMR-spectroscopic data of both isomers are listed in Table 2.

Table 1. Eight-peak index of mass spectra

Compound	M.W.	Peaks								Intensities							
VI	214	214	213	155	62	102	88	63	146	100	48	19	17	13	12	12	11
VII	214	213	212	154	63	77	214	91	127	100	46	31	27	24	20	19	18
VIII	347	347	346	288	173	172	189	143	316	100	28	10	6	5	5	5	4
IX	347	347	346	288	144	102	63	173	76	100	16	11	10	9	8	8	7
X	347	346	347	77	288	73	158	318	135	100	65	12	12	8	8	8	6
XI	341	163	206	135	105	77	133	70	164	100	59	34	26	26	16	14	11
XIII	327	282	135	77	164	106	79	134	192	100	80	63	61	37	25	21	16
XIV	299	164	106	77	135	134	79	136	107	100	23	22	15	14	11	8	7
XV	355	163	220	135	105	77	133	79	164	100	69	35	31	27	18	13	11
XVI	341	282	178	149	206	77	135	120	283	100	77	75	73	56	44	27	18
XVII	313	178	77	192	135	179	120	79	148	100	15	14	13	12	11	5	5

Table 2. ^{1}H-NMR data; solvent $CDCl_3$, reference TMS[a, b]

Compound	Signal δH =	Compound	Signal δH =
VI	2.52 (s, CH_3) 6.05 (s, O−CH_2−O) 6.75 (d, ^{m}J 1.7; phenyl−H) 6.80 (dd, ^{m}J 1.7; ^{0}J 7.7; phenyl−H) 6.92 (d, ^{0}J 7.7; phenyl−H) 8.50 (s, pyrimidine−H) 9.04 (s, pyrimidine−H)	XIII 1. isomer	2.66 (m, CH_2) 3.55 (m, CH) 5.86 (s, O−CH_2−O) 6.62 (m, phenyl−H) 7.42 (d, J 5.9; CHO)
VII	2.60 (s, CH_2) 6.02 (s, O−CH_2−O) 6.92 (d, ^{m}J 1.8; phenyl−H) 7.03 (dd, ^{m}J 1.8; ^{0}J 8.4; phenyl−H) 7.05 (d, ^{0}J 8.4; phenyl−H) 7.20 (d, ^{0}J 8.0; pyrimidine−H) 7.70 (dd, ^{0}J 8.0; ^{m}J 1.8; pyrimidine−H) 8.66 (d, ^{m}J 1.8; pyrimidine−H)	XIII 2. isomer	2.66 (m, CH_2) 4.31 (m, CH) 5.87 (s, O−CH_2−O) 6.62 (m, phenyl−H) 7.98 (d, J 0.6; CHO)
VIII	2.50 (s, CH_3) 6.00 (s, O−CH_2−O) 6.76 (d, ^{m}J 1.6; phenyl−H) 6.81 (dd, ^{m}J 1.6; ^{0}J 7.7; phenyl−H) 6.87 (d, ^{0}J 7.7; phenyl−H) 7.32 (s, pyridine−H)	XIV	1.3 (s, NH_2) 2.6 (2dd, ^{2}J 13.7; ^{3}J 2.3; ^{3}J 4.3; CH_2) 3.15 (m, CH) 5.95 (s, O−CH_2−O) 6.63 (d, ^{m}J 1.7; phenyl−H) 6.68 (dd, ^{m}J 1.7; ^{0}J 7.7; phenyl−H) 6.74 (d, ^{0}J 7.7; phenyl−H)
IX	1.96 (s, CH_3) 2.31 (s, CH_3) 6.01 (s, O−CH_2−O) 6.03 (s, O−CH_2−O) 6.60 (d, ^{m}J 1.6; phenyl−H) 6.65 (dd, ^{m}J 1.6; ^{0}J 7.8; phenyl−H) 6.80 (d, ^{0}J 7.8; phenyl−H) 6.74 (d, ^{m}J 1.7; phenyl−H) 6.79 (dd, ^{m}J 1.7; ^{0}J 8.2; phenyl−H) 6.91 (d, ^{0}J 8.2; phenyl−H) 8.30 (s, pyridine−H)	XVI 1. isomer	2.79 (s, N−CH_3) 2.80 (m, CH_2) 3.67 (m, CH) 5.92 (s, O−CH_2−O) 6.65 (m, phenyl−H) 7.52 (s, CHO)
		XVI 2. isomer	2.67 (s, N−CH_3) 2.80 (m, CH_2) 4.65 (m, CH) 5.91 (s, O−CH_2−O) 6.65 (m, phenyl−H) 7.89 (s, CHO)
X	2.22 (s, CH_3) 4.05 (s, CH_2) 5.95 (s, O−CH_2−O) 6.05 (s, O−CH_2−O) 6.80 (m, phenyl−H) 6.97 (s, pyridine−H) 8.35 (s, pyridine−H)	XVII	1.25 (s, NH) 2.46 (s, NCH_3) 2.80 (2dd, ^{2}J 14.0; ^{3}J 6.7; ^{3}J 6.9; CH_2) 3.15 (m, CH) 5.95 (s, O−CH_2−O) 6.75 (d, ^{m}J 1.6; phenyl-H) 6.80 (dd, ^{m}J 1.6; ^{0}J 7.6; phenyl-H) 6.92 (d, ^{0}J 7.6; phenyl−H)

[a] δ = chemical shift in ppm relative to internal reference; s = singlet; d = doublet; m = multiplet; J = coupling constant in Hz
[b] NMR data of XI and XV see Lukaszewski et al. [9]

D. Synthesis of MDMA from isosafrole by the method of Leuckart-Wallach

The synthesis can be carried out as described in A [3–5]. The nitrogen component for condensation is *N*-methylformamide.

Substance XV could be identified as the most conspicuous by-product.

XV. *N,N di-[1-(3,4-methylenedioxy)phenyl-2-propyl]methylamine*

E. Synthesis of MDMA by reductive amination

This reaction pathway has previously been investigated with respect to synthesis-specific impurities [18].

The substance XV could be isolated as an important and characteristic by-product in addition to the previously described substances [18].

F. Synthesis of MDMA from 3,4-(methylenedioxy)phenylacetic acid

If the synthesis of 3,4-(methylenedioxy)phenyl-2-propanone (III) is carried out as described in C according to Magidson and Garkusha [13], the substances XVI and XVII can be identified in addition to substance XV after using the Leuckart-Wallach synthesis.

XVI. α-*(3,4-methylenedioxy)benzyl-N-formyl-N-methyl-(3,4-methylenedioxy)phenethylamine*

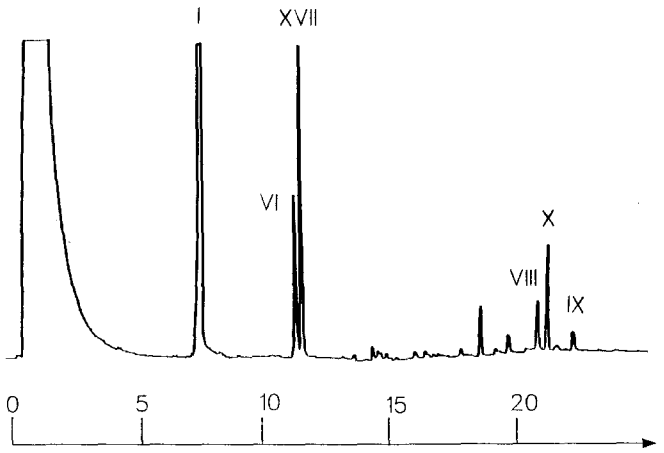

Fig. 2. Gas chromatogram of impurities in a MDA sample; flame ionisation detection

XVII. *α-(3,4-methylenedioxy)benzyl-N-methyl-(3,4-methylenedioxy)phenethylamine*

However if this is subjected to a reductive amination, the substances XV and XVII can be predominantly identified as nitrogen-containing impurities.

Analogous to substance XIII a cis- trans-isomeration could be identified in substance XVI by ^{1}H-NMR-spectroscopy. The data are shown in Table 2.

G. Investigations of MDA and MDMA samples

Independent of the grade of purity, the presence of traces of neutral or weakly basic impurities must be identified in addition to the strongly basic amphetamine. The samples were therefore dissolved in phosphate buffer solution (pH 6.0) and extracted with CH_2Cl_2. Neutral primary or intermediate products can also be extracted in this way.

The organic phase was concentrated to 50 µl and investigated with GC/MS. N-formyl-MDA (XVIII) or *N*-formyl-MDMA (XIX) can often be detected in the samples as specific intermediate products of the Leuckart-Wallach synthesis [19].

Figure 2 shows the gas chromatographic results of an extracted MDA sample. In addition to MDA, the intermediate *N*-formyl-MDA (XVIII) can also be detected as well as the substances VI, VIII, IX and X.

The detection of these synthesis markers in addition to the intermediate product allows a definite identification of the samples investigated.

The authors discovered many other compounds as by-products or precursors with the described syntheses, but most of them are neutral compounds and seem to be not present in MDA- or MDMA preparations.

In conclusion the identity, the reaction pathway as well as the possible inclusion of a ketone synthesis in different MDA and MDMA samples can be determined by the detection of the synthesis markers III-XIX in confiscated samples.

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