Determination of synthesis route of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) based on impurity profiles of MDMA

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Abstract

In our study 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P or PMK) was prepared by two different routes, i.e. by oxidizing isosafrole in an acid medium and by 1-(3,4-methylenedioxyphenyl)-2-nitropropene reduction. The final product-MDP-2-P was subjected to GC/MS analysis. The intermediates and reaction by-products were identified and the ‘route specific’ impurities were established. The following impurities are the markers of the greatest importance: 1-(3,4-methylenedioxyphenyl)-1-propanone (compound 10, Table 2), 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 11, Table 2) and 2,2,4-trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolane (compound 13, Table 2) (the ‘oxidising isosafrole route’) and N-cyclohexylacetamide (compound 3, Table 1), 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15, Table 1) (the ‘MDP-2-nitropropene reduction route’). Subsequently, MDMA was prepared by reductive amination of MDP-2-P using NaBH4 as reducing agent (so-called ‘cool method’). Impurities were extracted with n-heptane under alkaline conditions. The impurity profiles were obtained by means of GC/MS, some reaction by-products were identified by means of the EI mass spectra including low energy EI mass spectra and ‘route specific’ impurities were established. 4-Methyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolan-2-one (compound 22, Table 2), N-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethanamine (compound 18, Table 2), 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15, Table 1) and N-cyclohexyloacetamide (compound 3, Table 1) were found to be the synthesis markers of greatest importance.

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Keywords: MDMA; MDP-2-P; Reductive amination; Route specific impurities

1. Introduction

Impurity profiling of drugs can be used for two purposes-determination of synthesis route and comparative analysis of seizures of drugs. Impurities which are characteristic for particular synthetic route are called synthesis markers. A marker can be called ‘ideal’, if it emerges only in particular synthetic route, but this occurs very rarely. In most cases, the marker of one route emerges in other synthesis methods as well. For instance N-formylnMDMA, which is known marker for Leuckart route, is also found in impurity profiles of MDMA prepared by reductive amination and bromination of safrrole. Therefore, instead of individual compounds, the groups of markers should be considered for determination...
of synthetic route. By increasing number of informative
synthesis markers for each synthesis method, possibility
of a false identification of synthesis method is reduced.

Moreover, there is also an issue of ‘availability of
markers’ in the impurity profiling process. The route specific
markers could not appeared in the impurity profiles for
several reasons, e.g. if drug is thoroughly purified after
synthesis, the extraction of impurities is not efficient and/
or if analytical technique, used to provide profiles, is not
sensitive enough. In order to deal with the above problems
successfully, identification of individual impurities is essen-
tial.

Out of synthetic drugs, amphetamine and methamphet-
tamine have been thoroughly investigated in respect to the
route specific impurities and comparative analysis. Numer-
ous papers have been devoted to the route specific impurities
in these drugs and the procedures of impurity profiling [1–6].
Other synthetic drugs, such as 3,4-methylenedioxyamphetamine
(MDA) or 3,4-methylenedioxymethamphetamine
(MDMA, ecstasy) have not been sufficiently investigated
so far [7–13].

In clandestine manufacture of MDMA the most popular
synthesis route is reductive amination of 1-(3,4-methylen-
dioxyphenyl)-2-propanone (MDP-2-P or PMK) [5,7,14–17].
The present controlled status of MDP-2-P has resulted in
increase in illegal production of this precursor. A variety of
methods have been reported for the synthesis of MDP-2-P
[14] and a few papers were devoted to the impurities in
MDP-2-P [11,13]. Fig. 1 shows a summary of two most
probable synthesis routes of MDP-2-P in clandestine pro-
duction [13–15] which were also chosen by authors to
synthesized MDP-2-P, i.e. synthesis of MDP-2-P from
piperonal via 1-(3,4-methylenedioxyphenyl)-2-nitropropene
(MDP-2-nitropropene) and oxidation of isosafrole in an acid
medium. So far the first method was not yet investigated in
respect to the route specific impurities, but some studies have
been done concerning impurities produce in the second
method [13].

Identification of individual impurities is particularly
useful for both the determination of synthetic route of
MDMA and comparative analysis of seized MDMA tablets.
Knowledge about by-products and intermediates enables
identification of all steps in a synthesis of MDMA as well
as identification of precursors such as piperonal, isosafrole
and MDP-2-P. These compounds are very often produced
during the synthesis as by-products. Therefore their identi-
fication in impurity profiles of MDMA is not equivalent with
their use as precursors. This fact was found during our
research on route specific impurities of MDMA prepared
by different synthesis methods, from which only some
results are presented in this paper. For example MDP-2-P
and isosafrole were undoubtedly identified in impurity pro-
files of MDMA synthesized by safrole bromination followed
by methylamination of bromosafrole.

In this work impurities produced in synthesis of MDP-2-
P by the methods mentioned above, and impurities in
MDMA-HCl prepared by reductive amination (Fig. 1) were
investigated and route specific markers were identified. By
means of these markers, the synthetic route of MDP-2-P and
MDMA could be determined.

2. Materials and methods

2.1. Chemicals and reagents

In synthesis the following reagents were used: formic
acid (98%), hydrochloric acid (36–38%), methylene chlor-
ide, sodium hydroxide, acetic acid (99.5%), acetone, hydro-
gen peroxide (~33%), sulfuric acid (95%), all POCh,
Poland, analytical grade, piperonal (99%, Aldrich), isosa-
frole (97%, Aldrich), nitroethane (96%, Aldrich), cyclohex-
ylamine (99%, Aldrich), methylamine solution (40%
aqueous, Aldrich), diethyl ether (anhydrous, >99%,
A.C.S. Reagent), NaBH4 (Aldrich, for synthesis).

In impurity profiling experiments the following reagents
were used: carbonate buffer pH 10 (10.7 ml, 0.1 M NaOH,
50 ml 0.05 M NaHCO3, 39.3 ml H2O), n-heptane (Aldrich,
HPLC grade), diphenylamine (Supelco, used as internal
standard).

2.2. Synthesis

The following synthesis methods of MDP-2-P and
MDMA have been chosen by the authors according to the
preferences of the clandestine laboratories. The physical and
spectral (IR, NMR) properties of all synthesized compounds
were identical with the data reported formerly [18].

MDP-2-P was synthesized by two different routes, i.e. by
oxidation of isosafrole in an acid medium and by reduction of
1-(3,4-methylenedioxyphenyl)-2-nitropropene, which
was previously prepared by condensation of piperonal and
nitroethane. Those syntheses were performed according to
the procedures described by Shulgin [15].

MDMA was prepared according to the following method.

2.2.1. Reductive amination with NaBH4
(sos-called ‘cool method’)

Aqueous solution (40%) of methylamine (2 ml) was
added to a cold mixture of MDP-2-P (1.51 g) in MeOH
(5 ml). The mixture was cooled to −20 °C and then NaBH4
(30 mg) was slowly added. After dissolving of reductive
agent, reaction mixture was left at −20 °C for 2 h. The
addition of NaBH4 was repeated three times, in portions of
30, 30 and 40 mg, and reaction mixture was left at −20 °C
for 24 h. Methanol was evaporated, 10% HCl (10 ml) was
added to a residue, and the solution was washed with CH2Cl2
(3 × 8 ml). The organic solution was extracted with 10% 
HCl, combined aqueous layers were alkalized with 25%
NaOH (~10 ml) and extracted with CH2Cl2 (3 × 10 ml).
Combined extracts were dried over MgSO4, evaporated, a
residue was dissolved in Et2O (18 ml) and dry HCl was
2.3. Extraction of impurities

Piperonal (0.015 g), isosafrole (0.015 g) and MDP-2-P (0.015 g) were dissolved in 200 μl of Et₂O and analyzed using GC/MS. Extraction of MDMA impurities was performed according to adopted method of amphetamine profiling used in Central Forensic Laboratory of the Police in Warsaw (Poland): a portion of 200 mg of MDMA-HCl was dissolved in 2 ml of carbonate buffer (pH 10), the solution was then vigorous shaken (25 min) following by addition of 200 μl of n-heptane containing diphenylamine as an internal standard, and then again shaken (25 min). The extracts were subjected to GC/MS analysis and impurity profiles were obtained. In the same way the extraction of impurities from MDP-2-nitropropene was performed.

2.4. Apparatus

GC/MS impurity profiles of MDMA were obtained according to adopted method of amphetamine profiling used in Central Forensic Laboratory of the Police in Warsaw (Poland). GC/MS analysis was carried out on Hewlett-Packard 6890 series gas chromatograph coupled to 5984B mass spectrometer. The deactivated, single taper splitless liner which had internal volume equal 900 μl and HP5-MS fused silica capillary column (30 m × 0.25 mm × 0.25 μm) were applied and helium 6.0 was used as a carrier gas (1.0 ml/min). The injection (2 μl) was made splitless by the autosampler. The following temperature program was applied: 50 °C maintained for 1 min, then ramped at 10 °C/min up to 150 °C, maintained 5.5 min, and again increased to 280 °C at 10 °C/min ramp, and maintained for the final 10 min. Mass spectrometer was operated in positive electron ionization mode (EI). The temperature of MS source was 230 °C, MS quadrupol −150 °C and transfer line −280 °C. A full-scan mass spectra 40–500 amu were obtained.

3. Results and discussion

In Tables 1 and 2 all compounds identified in the precursors, intermediates and final products were collected. The identification of all presented compounds was based on the EI mass spectra including low energy EI mass spectra.

3.1. Markers of MDP-2-P synthesis carried out by reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene

The compound 3 (Table 1), a product of the reaction of catalyst (cyclohexylamine) with acetic acid (Fig. 2), emerges in the first step of this synthesis and is present as
an impurity in the precipitate of MDMA-HCl. The identification of this compound in impurity profiles of MDMA simultaneously with compounds 7, 8, 9, 14 and 15 (Table 1) indicates the synthesis of MDP-2-P by reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene and MDMA by reductive amination.

In the above synthesis method cyclohexylamine could be replaced by some other amines as the catalysts, such as ethylamine, butylamine, pentyamine, etc. Hence, instead of compound 3, one could expect other \(N\)-alkylacetamide corresponding to amine used as catalyst. The compounds 7, 8, 9 and 14 were also found in impurity profiles of MDMA prepared by Leuckart method, but the compounds 3 and 15 (Table 1) were found in MDP-2-P and impurity profiles of MDMA only while MDP-2-P was prepared from piperonal, therefore their presence in seizures of MDMA tablets, simultaneously with these mentioned above, makes a strong proof of the use of this synthesis route under consideration.

<table>
<thead>
<tr>
<th>Structure of impurity</th>
<th>Synthesis of MDMA from piperonal</th>
<th>Identified in</th>
<th>Eight-peak index of mass spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>Impurity name</td>
<td>MDP-2-nitropropene, MDP-2-P, MDMA-HCl</td>
<td>MW</td>
</tr>
<tr>
<td>150</td>
<td>Piperonal</td>
<td>MDP-2-nitropropene, MDP-2-P, MDMA-HCl</td>
<td>149, 150, 32, 63, 44, 121, 43, 65</td>
</tr>
<tr>
<td>147</td>
<td>Piperonylonitrile</td>
<td>MDP-2-nitropropene</td>
<td>146, 147, 62, 63, 89, 38, 88, 148</td>
</tr>
<tr>
<td>141</td>
<td>N-Cyclohexyl-acetamide</td>
<td>MDP-2-nitropropene, MDP-2-P, MDMA-HCl</td>
<td>60, 56, 43, 32, 44, 141, 41, 98</td>
</tr>
<tr>
<td>165</td>
<td>Piperonal oxime</td>
<td>MDP-2-nitropropene</td>
<td>165, 122, 121, 146, 63, 149, 148, 65</td>
</tr>
<tr>
<td>192</td>
<td>1-(3,4-Methylenedioxyphenyl)-1,2-propanedione</td>
<td>MDP-2-P</td>
<td>149, 121, 65, 63, 150, 192, 91, 43</td>
</tr>
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<td>194</td>
<td>1-Hydroxy-1-(3,4-methylenedioxyphenyl)-2-propanone</td>
<td>MDP-2-P</td>
<td>151, 194, 121, 91, 43, 77, 152, 137</td>
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<td>179</td>
<td>N,N-Dimethylpiperonylamine</td>
<td>MDMA-HCl</td>
<td>135, 179, 58, 136, 77, 178, 32, 51</td>
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<tr>
<td>179</td>
<td>3,4-Methylenedioxyamphetamine (MDA)</td>
<td>MDMA-HCl</td>
<td>44, 135, 136, 32, 77, 50, 43, 42</td>
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<tr>
<td>165</td>
<td>N-Methylpiperonylamine</td>
<td>MDMA-HCl</td>
<td>135, 164, 165, 136, 77, 42, 44, 51</td>
</tr>
<tr>
<td>207</td>
<td>N-Ethyl-MDA</td>
<td>MDMA-HCl</td>
<td>72, 77, 73, 42, 135, 51, 44, 70</td>
</tr>
<tr>
<td>180</td>
<td>1-(3,4-Methylenedioxyphenyl)-2-propanol</td>
<td>MDMA-HCl</td>
<td>135, 136, 180, 77, 32, 51, 45, 78</td>
</tr>
<tr>
<td>221</td>
<td>N-Formyl-MDMA</td>
<td>MDMA-HCl</td>
<td>86, 162, 58, 135, 77, 51, 30, 56</td>
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<tr>
<td>205</td>
<td>3-Methyl-6,7-methylenedioxy-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>MDMA-HCl</td>
<td>148, 190, 147, 205, 188, 204, 149, 89</td>
</tr>
<tr>
<td>221</td>
<td>2-Methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine</td>
<td>MDMA-HCl</td>
<td>71, 56, 149, 43, 70, 72, 149, 42</td>
</tr>
<tr>
<td>217</td>
<td>3-Methyl-6,7-methylenedioxyisoquinoline-1,4-dione</td>
<td>MDP-2-P, MDMA-HCl</td>
<td>217, 148, 147, 188, 89, 63, 218, 149, 91</td>
</tr>
</tbody>
</table>
Table 2
Impurities identified in isosafrole and subsequently in MDP-2-P and MDMA/HCl prepared from isosafrole

<table>
<thead>
<tr>
<th>Structure of impurity</th>
<th>Synthesis of MDMA from isosafrole</th>
<th>Identified in</th>
<th>Eight-peak index of mass spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>Impurity name</td>
<td>Eight-peak index of mass spectra</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>154</td>
<td>Terpineol (p-menth-1-en-8-ol)</td>
<td>Isosafrole</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>2-Isopropyl-5-methylphenol (thymol)</td>
<td>Isosafrole</td>
</tr>
<tr>
<td>3</td>
<td>204</td>
<td>1,7-Dimethyl-7-(4-methyl-3-pentenyl)-tricyclo[2.2.1.0^2,6]heptane</td>
<td>Isosafrole</td>
</tr>
<tr>
<td>4</td>
<td>204</td>
<td>2,6-Dimethyl-6-(4-methyl-3-pentenyl)-bicyclo[3.1.1]hept-2-ene</td>
<td>Isosafrole</td>
</tr>
<tr>
<td>5</td>
<td>162</td>
<td>Safrole</td>
<td>Isosafrole, MDP-2-P</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>Piperonal</td>
<td>Isosafrole, MDP-2-P</td>
</tr>
<tr>
<td>7</td>
<td>220</td>
<td>1-(2,3-Dimethyltricyclo[2.2.1.0^2,6]hept-3-yl)-4-methylpentan-3-one</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>8</td>
<td>192</td>
<td>1-(3,4-Methylenedioxyphenyl)-1,2-propanedione</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>9</td>
<td>162</td>
<td>Isosafrole</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>10</td>
<td>178</td>
<td>1-(3,4-Methylenedioxyphenyl)-1-propanone</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>11</td>
<td>208</td>
<td>1-Methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>12</td>
<td>210</td>
<td>1-Methoxy-1-(3,4-methylenedioxyphenyl)-2-propanol</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>13</td>
<td>223</td>
<td>2,2,4-Trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolane</td>
<td>MDP-2-P</td>
</tr>
<tr>
<td>14</td>
<td>179</td>
<td>N,N-Dimethylpiperonylamine</td>
<td>MDMA-HCl</td>
</tr>
<tr>
<td>15</td>
<td>165</td>
<td>N-Methylpiperonylamine</td>
<td>MDMA-HCl</td>
</tr>
<tr>
<td>16</td>
<td>193</td>
<td>N-Ethyl-N-methylpiperonylamine</td>
<td>MDMA-HCl</td>
</tr>
<tr>
<td>17</td>
<td>193</td>
<td>N-Methyl-1-(3,4-methylenedioxyphenyl)-1-propaneamine</td>
<td>MDMA-HCl</td>
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</tbody>
</table>
The mass spectra of compounds 5, 6, 13, 14 and 15 are presented in Figs. 11, 12, 8, 9 and 3.

3.2. Synthesis markers of MDP-2-P synthesized by oxidizing isosafrole

The compound 13 and 22 (Table 2) are produce in reaction of oxidation of isosafrole by using acetone as a solvent [13]. Actually, the compound 13 have not been identified in impurity profiles of MDMA-Cl, because it was completely converted to MDP-2-P. However the compound 22 was only present in impurity profiles of MDMA-Cl.

The compound 18 is a product of the reaction of methylaniline with compound 11 (Fig. 4). The compound 11 is produced as a by-product during the synthesis of MDP-2-P. The compound 3 (Table 2) which was identified in the

Table 2 (Continued)

<table>
<thead>
<tr>
<th>Structure of impurity</th>
<th>Synthesis of MDMA from isosafrole</th>
<th>Identified in</th>
<th>Eight-peak index of mass spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>223 N-Methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethaneamine</td>
<td>MDMA-Cl</td>
<td>58, 149, 165, 150, 59, 30, 77, 119</td>
</tr>
<tr>
<td>19</td>
<td>207 N-Ethyl-MDA</td>
<td>MDMA-Cl</td>
<td>72, 77, 73, 42, 135, 51, 44, 70</td>
</tr>
<tr>
<td>20</td>
<td>193 3,4-Methylenedioxybenzylmethyketoxime</td>
<td>MDMA-Cl</td>
<td>135, 193, 146, 77, 136, 51, 160, 105</td>
</tr>
<tr>
<td>21</td>
<td>205 3-Methyl-6,7-methylenedioxy-3, 4-dihydroisoquinolin-1(2H)-one</td>
<td>MDMA-Cl</td>
<td>148, 190, 147, 205, 188, 204, 149, 89</td>
</tr>
<tr>
<td>22</td>
<td>222 4-Methyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolan-2-one</td>
<td>MDMA-Cl</td>
<td>178, 134, 149, 163, 44, 43, 72, 222</td>
</tr>
</tbody>
</table>

Fig. 3. Mass spectrum of 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15 in Table 1).

Fig. 4. One of the side-reactions occurring during the reductive amination of MDP-2-P prepared from isosafrole.
commercially available isosafrole after oxidation gives compound 7 which is a marker of MDP-2-P synthesized from isosafrole. Compound 10 which is a by-product produced during the synthesis of MDP-2-P (Table 2) in the reaction with methyamine gives a corresponding amine, the compound 17 (Table 2). The compounds 14, 15 and 16 are the products of piperonal reaction with methyamine and its impurities (dimethylamine and methylethylamine). Their
Fig. 7. Mass spectrum of 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 11 in Table 2).

Fig. 8. Mass spectrum of 3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolin-1(2H)-one (compound 13 in Table 1).
Fig. 9. Mass spectrum of 2-Methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine (compound 14 in Table 1).

Fig. 10. Mass spectrum of N-methyl-1-(3,4-methylenedioxyphenyl)-1-propaneamine (compound 17 in Table 2).
Fig. 11. Mass spectrum of 1-(3,4-methylenedioxyphenyl)-1,2-propanedione (compound 5 in Table 1).

Fig. 12. Mass spectrum of 1-hydroxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 6 in Table 1).
appearance in the impurity profile, together with compound 18 confirms the above synthesis route. The mass spectra of compounds 7, 10, 11, 17 and 18 are presented in Figs. 13, 6, 7, 10 and 5.

4. Conclusion

In summary, the synthesis markers of MDP-2-P prepared by two different synthesis routes were identified. These markers are present in impurity profiles of MDMA. On the basis of this fact, during the process of profiling of seized MDMA tablets, one can identify MDP-2-P as a precursor in the synthesis of MDMA. Moreover, the synthesis markers presented in this work enables determination of synthesis route of MDP-2-P.

Acknowledgments

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References


