Electron ionization mass spectrometry as a tool for the investigation of the *ortho* effect in fragmentation of some Schiff bases derived from amphetamine analogs†

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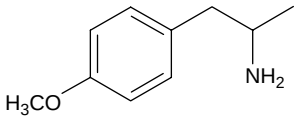
The electron ionization-induced fragmentation patterns of three forensically relevant Schiff bases, originating from the condensation between 2-, 3- and 4-methoxyamphetamine and the corresponding ketones, were studied. The proposed fragmentation routes and ion structures are supported by high-resolution data and *B*/*E* linked-scan and mass-analyzed ion kinetic energy spectra. The rationalization of the *ortho* effect, which is responsible for the formation of the [M − OCH_3] fragment in the case of the imine bearing *ortho*-substituted methoxy group, is given. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: amphetamine derivatives; electron ionization; fragmentation mechanism; *ortho* effect

INTRODUCTION

Phenylisopropylamine forms part of the structure of a great number of ring- and/or nitrogen-substituted amphetamines, the so-called 'designer drugs'. Over the past several years, there has been significant toxicological[1–3] and forensic[4–6] interest in 4-methoxyamphetamine (**1**).



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This compound, also known as a *p*-methoxyamphetamine (PMA), displays amphetamine-like stimulating activity and some hallucinogenic (LSD-like) properties.[7,8] It is important to note that PMA consumption is associated with a much higher rate of lethal complications than with other designer drugs, and that no guarantee can be made that tablets sold as 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) do not contain PMA. In Poland, PMA has been distributed in the tablet form, the appearance and cost of which were comparable to those of MDMA.[9] Simultaneously, several fatal intoxications related to PMA have been reported.[10,11] The considerable risk of an overdose could be linked to the fact that the initial absence of the MDMA-like properties might have led consumers to take more tablets in the belief that the first dose was too low.

The fairly simple structure of phenylisopropylamine derivatives and with the availability of the necessary precursors and reagents make their chemical synthesis relatively easy. However, the final products are always accompanied by different quantities of by-products and remaining starting materials. Unambiguous identification of these impurities in street samples and complex reaction mixtures is essential for the successful recognition of a synthetic route by which seized drug samples might have been produced.[12,13] In addition, the comparison of the so-called 'impurity profile' may serve as a tool for distinguishing samples from different batches and/or laboratories.[14,15]

Although a variety of methods may be used for the synthesis and manufacture of amphetamines, one of the common approaches used by clandestine chemists involves the treatment of the appropriate ring-substituted phenylacetone with nitrogen-containing species (ammonia, ammonium acetate, formamide) under reducing conditions (Scheme 1).

Recently, we described the synthesis and identification of several impurities in PMA synthesized by the Leuckart method.[16,17] The presence of two diastereomers of secondary amine **2** and imine **5** (Fig. 1) was confirmed in the reaction mixtures and also in the final product.

The Schiff base **5** was identified only in trace amounts. As a continuation of our study on the identification of specific impurities present in illegally produced ring-substituted amphetamines, we focused our attention on the mass spectrometric properties of the previously described compound **5**. Although the mass spectra of **5** and its

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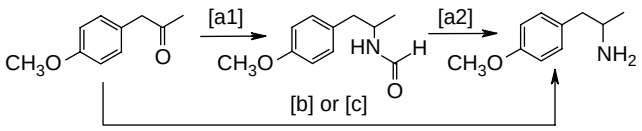
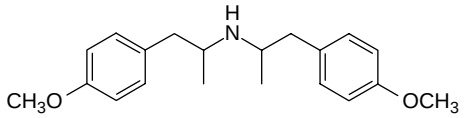


Scheme 1. Common synthetic methods used for the preparation of PMA: [a1], formamide–HCOOH, 160–180 °C, 5–8 h; [a2], 30% HCl, 1 h; [b], NH_3, $HgCl_2$–Al, EtOH; [c], NH_3, H_2–Pd, 25–160 °C, 1–200 atm, EtOH.



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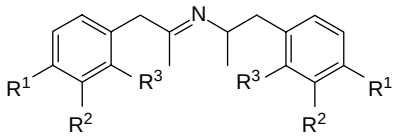
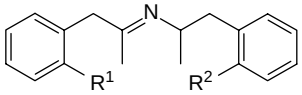


3 $R^1 = R^2 = H$, $R^3 = OCH_3$
4 $R^1 = R^3 = H$, $R^2 = OCH_3$
5 $R^2 = R^3 = H$, $R^1 = OCH_3$



6 $R^1 = H$, $R^2 = OCH_3$
7 $R^1 = OCH_3$, $R^2 = H$

Figure 1. Structures of imino and amino compounds related to the synthesis of methoxyamphetamine isomers.

desmethoxy analog have been reported previously,[17,18] a systematic study of its fragmentation has never been carried out. We decided also to extend our work to the *ortho* and *meta* isomers of **5.** The Schiff bases **3** and **4** were initially identified in 2-methoxyamphetamine (OMA) and 3-methoxyamphetamine (MMA) synthesized by the above method. Since both of the appropriate precursors, *ortho*- and *meta*- substituted ketones, are readily available from commercial sources, and the manufacturing processes can be based on identical transformations, the appearance of the corresponding 2- and 3-methoxyamphetamine on the illicit market in the near future seems highly probable.

Gas chromatography–mass spectrometry (GC/MS) is currently the mandated method for the identification of 'route-specific' impurities in clandestinely produced phenylisopropylamines. This combination has two well-known advantages: high sensitivity and high specificity, that allow the detection of a trace amounts of impurities in complex mixtures, and a high separation power which is necessary for their proper separation. Because only an MS-based detection method is capable of identifying Schiff bases **3**–**5** present at low concentration levels in rich matrices, our attention was focused on the MS behavior of these compounds. In particular, we hope that the recognition of the fragmentation mechanisms of **3**–**5** may provide important information useful in the identification of closely related and route-specific 'markers' in the group of other forensically relevant amphetamines.

EXPERIMENTAL

Synthesis

Amphetamine and 2-, 3- and 4-methoxyamphetamine were prepared from the benzyl methyl ketone and corresponding methoxyphenylacetones according to the procedure described by Noggle *et al*.[19] All imines were prepared from the corresponding amines and ketones, as follows.

General procedure

A solution of the amine (25 mmol) and ketone (30 mmol) in 80 ml of toluene was heated under reflux for 6 h with continuous removal of water. Toluene was evaporated *in vacuo* and resulting imine was separated from unreacted amine and ketone by fractional distillation under vacuum using an apparatus equipped with short Vigreaux column. According to the GC analysis, the distillates contained the following compounds.

N-[2-(2-Methoxyphenyl)-1-methylethyl]-*N*-[(2-(2-methoxyphenyl)-1-methylethylidene]amine (**3**) from 2-methoxyamphetamine and 2-methoxyphenylacetone, yellow oil 2.3 g, b.p. 160–168 °C/0.5 mmHg, purity ~86%, IR (ν_{max}) 1655 cm^{-1} (C=N).

N-[2-(3-Methoxyphenyl)-1-methylethyl]-*N*-[2-(3-methoxyphenyl)-1-methylethylidene]amine (**4**), from 3-methoxyamphetamine and 3-methoxyphenylacetone, orange oil, 2.2 g, b.p. 161–173 °C/0.5 mmHg, purity ~71%, IR (ν_{max}) 1655 cm^{-1} (C=N).

N-[2-(4-Methoxyphenyl)-1-methylethyl]-*N*-[2-(4-methoxyphenyl)-1-methylethylidene]amine (**5**), from 4-methoxyamphetamine and 4-methoxyphenylacetone, yellow oil that solidified after storage in a refrigerator, 2.5 g, b.p. 168–175 °C/0.6 mmHg, purity ~85%, IR (ν_{max}) 1655 cm^{-1} (C=N).

N-[2-(2-Methoxyphenyl)-1-methylethyl]-*N*-[1-Methyl-2-phenylethylidene]amine (**6**), from 2-methoxyamphetamine and phenylacetone, slightly yellow oil, 3.1 g, b.p. 154–161-°C/0.6 mmHg, purity ~87%, IR (ν_{max}) 1656 cm^{-1} (C=N).

N-[2-(2-Methoxyphenyl)-1-methylethylidene]-*N*-(1-methyl-2-phenylethyl)amine (**7**), from amphetamine and 2-methoxyphenylacetone, slightly yellow oil, 3.0 g, b.p. 156–163 °C/0.6 mmHg, purity ~86%, IR (ν_{max}) 1656 cm^{-1} (C=N).

All our attempts to obtain analytical samples of **3**–**7** by means of vacuum distillation and column chromatography failed. Therefore, the NMR data obtained did not allow an unambiguous interpretation.

Measurements of mass spectra

All electron ionization (EI) mass spectra were measured with an AMD-604 double-focusing mass spectrometer (AMD Intectra, Germany) with BE geometry (electron energy 70 eV, accelerating voltage 8 kV, source temperature 200 °C). During analysis of the mass-analyzed ion kinetic energy (MIKE) and fragment ions (B/E linked scan), 4–8 scans were recorded and averaged to improve the mass accuracy

and signal-to-noise ratio. Accurate mass measurements were performed by narrow-range high-voltage scanning at 10 000 resolving power (10% valley definition) using perfluorokerosene (PFK) as the reference standard. Samples were introduced into mass spectrometer using a direct insertion probe heated to 20–120 °C, depending on the sample.

All ion formulae presented were confirmed by accurate mass measurements under high resolving power conditions. Fragmentation pathways were confirmed by at least one metastable ion measurement technique.

GC/MS analysis was performed with an HP 5973 mass-selective detector interfaced with an HP 6890 Plus GC system (Agilent Technologies). The GC system was fitted with a 30 m × 0.25 mm i.d. fused-silica capillary column coated with 0.25 μm HP-5 (J&W Scientific). A pressure-programmed constant linear velocity of 32 cm s^{-1} of helium (99.9999%) was used. The injection port (30 : 1 split) was maintained at 250 °C. The oven temperature was programmed as follows: initial temperature, 120 °C; initial hold 2.2 min; program rate, 12 °C min^{-1}; final temperature, 295 °C; final hold, 6.0 min. Mass spectral data were recorded from m/z 40 to 450. Schiff bases were dissolved in dry toluene to achieve final concentrations between 0.5 and 1 mg ml^{-1}. Volume of 1 μl of solutions were injected into the GC/MS system.

RESULTS AND DISCUSSION

A detailed search revealed that forensically relevant Schiff bases originating from phenylisopropylamines and their synthetic precursors, benzyl methyl ketones, have not been subjected to systematic MS study. The most similar compounds investigated were Schiff bases originating from the condensation of benzaldehyde with various aliphatic amines and phenylisopropylamine.[20] In the first step of fragmentation, the largest alkyl group or benzyl radical is lost preferentially, leading to an immonium-type ion, which after a subsequent isomerization sequence with further rearrangement, eliminates hydrogen cyanide. However, the presence of an additional methylene group between the phenyl group and nitrogen atom, as is the case with imines **3**–**5**, completely suppresses the above phenomenon, making their mass spectrometric behavior similar to those reported previously for *N*,*N*-di(phenylalkyl)amines[21] and their *N*-methyl derivatives.[22]

The low-resolution mass spectra of **3**–**5** are shown in Fig. 2.

For evaluation of the fragmentation pathways of the compounds under investigation, accurate mass measurements, B/E linked scan and MIKE spectra were used. The EI mass spectra of Shiff bases **3**–**5** are similar, with one exception in the case of **3**, which exhibits a moderately intense peak at m/z 280. The high intensity of the peaks at m/z 190, 149, 121 and 91 is a characteristic feature of all compounds investigated. Although weak (1–3%) molecular ions were detected in each case, their B/E linked scan and MIKE spectra turned out to be valuable for the characterization of the fragmentation pattern.

The preliminary screening of the results revealed that their interpretation requires additional measurements of the

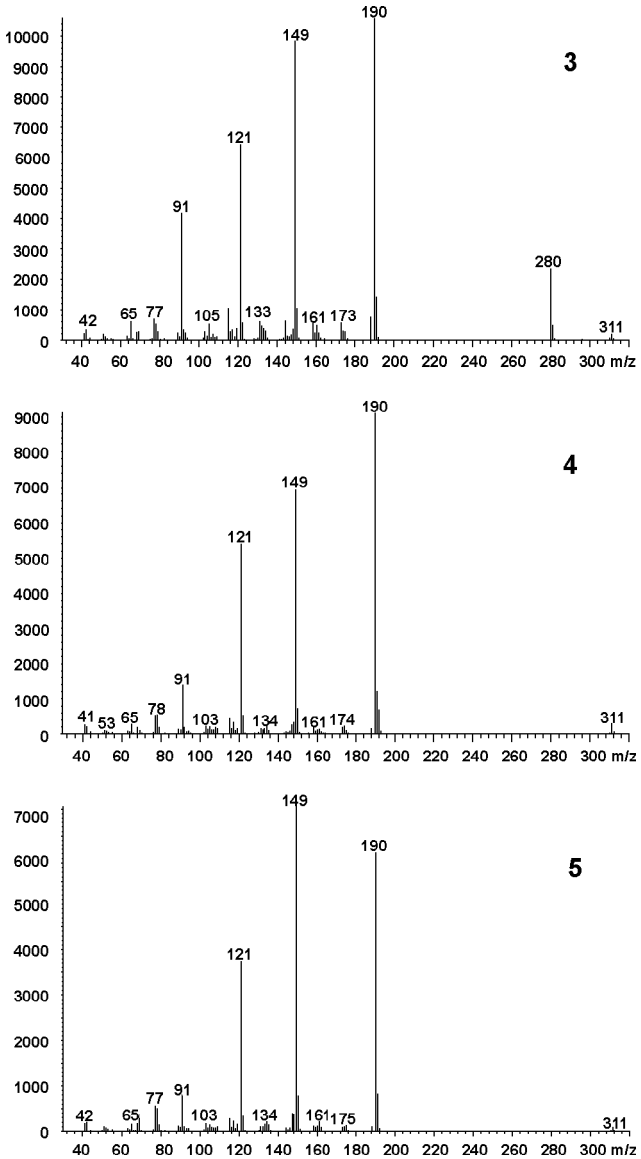


Figure 2. EI mass spectra of imines **3**–**5** ($M = 311$ Da) (recorded with an HP 5973 GC/MS system).

model compounds. Therefore, two isomeric Schiff bases, **6** and **7**, were synthesized. Their EI mass spectra are shown in Fig. 3.

According to the B/E linked scan, MIKE and accurate mass measurement results, fragmentation patterns of the model monomethoxyimines **6** and **7** can be proposed as Shown in Schemes 2 and 3, respectively.

The two main fragmentation paths of the molecular ions of **6** and **7** start with α-cleavages induced by the radical center on the nitrogen atom, usually observed in the fragmentation of alkylamines,[23] providing even-electron ions **b6** and **c6** from **6** and ions **b7** and **c7** from **7.**

Ions **b6** and **c7** (m/z 190) in the mass spectra of **6** and **7** have the same empirical formula, as was shown by high-resolution data. However, comparison of their B/E linked scan and MIKE spectra shows unequivocally that they possess two different structures. Ion **c7** easily loses a molecule of acetonitrile in a process which can be described as the reversal of the well-known Ritter reaction which takes place between

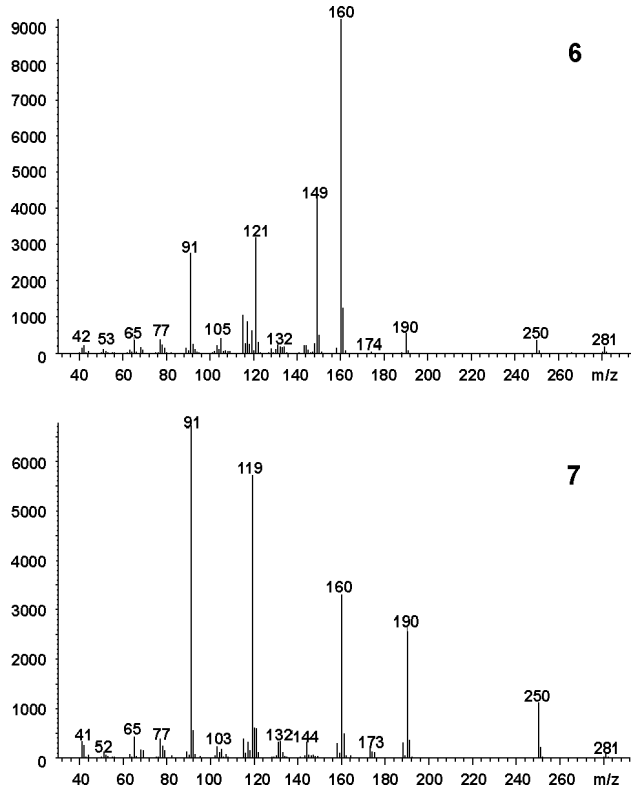


Figure 3. EI mass spectra of imines **6** and **7** ($M = 281$ Da) (recorded with an HP 5973 GC/MS system).

nitriles and carbonium ions.[24] Further fragmentation of the resulting ion **e6** is typical and yields finally the tropylium cation **g**. Ion **b6** undergoes another type of fragmentation resulting in a consecutive loss of H_2 and CH_3 fragments yielding, most likely, the isoquinoline derivative **h7** (Scheme 3).

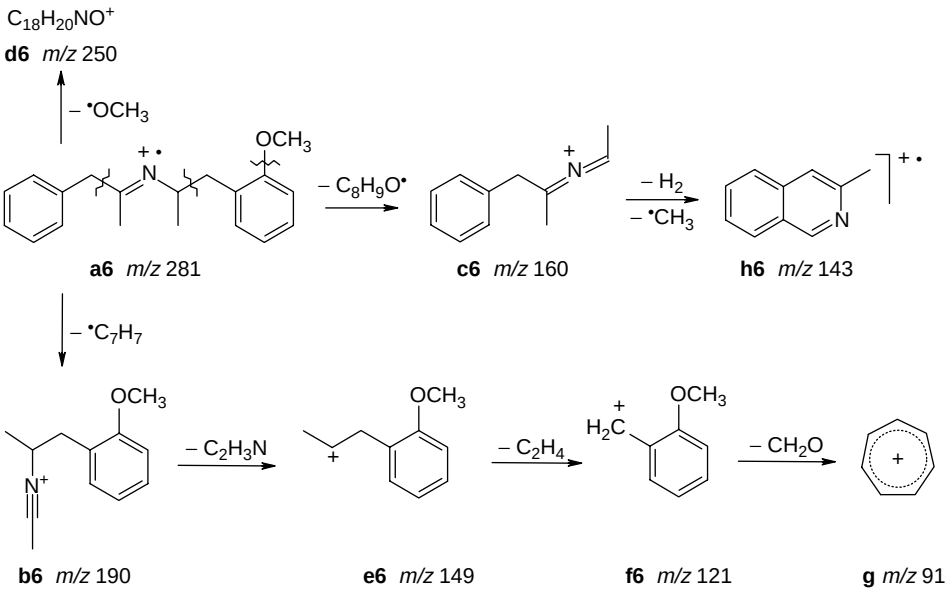
Analogous fragmentation reactions take place for m/z 160 ions **c6** and **b7**. Ion **c6** shows the same fragmentation pattern as the ion **c7** and ion **b6** fragments analogously to the ion **b7** (Schemes 2 and 3). Comparison of the MIKE and B/E linked scan spectra of the molecular ions of **6** and **7** shows that α-cleavage at the saturated carbon atom yielding ions **c6** and **c7**, respectively, predominates for both compounds. The relatively low intensity of the m/z 190 peak corresponding to the ion **c7** in the EI spectrum of **7** is most likely the result of its easier further fragmentation. The methoxy group in benzene ring of the ion **c7** facilitates the electrophilic addition reaction, which is the first step in the formation of ion **h7**.

A very important feature of the mass spectrometric behavior of **6** and **7** is the presence of even-electron ions **d6** and **d7** (m/z 250), which arise from the loss of a methoxy radical from the parent ions. It seems reasonable that the driving force for the expulsion of a methoxy radical from **a6** and **a7** is the participation of the nitrogen atom leading to the cyclized species **i6** and **i7**, respectively, according to Scheme 4.

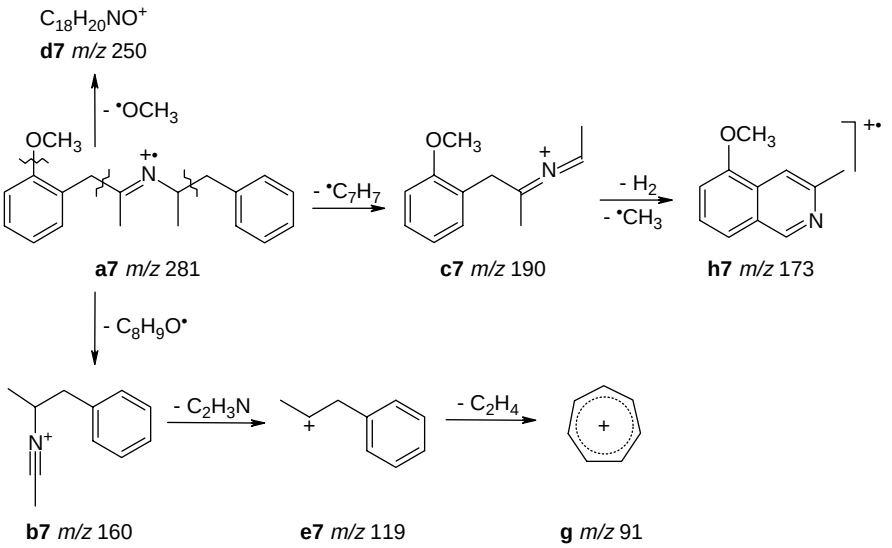
Such structures seem to be relatively stable owing to additional delocalization of the charge in the double-ring system. In the case of **6,** the less stable ion **i6** with an exocyclic double bond can be postulated. The higher stability of endocyclic species **i7** may account for its increased abundance (18%) in the mass spectrum of **7**. Consequently, the lower stability of exocyclic **i6** may rationalize its significantly lower abundance (3.5%). Nevertheless, the stability of both ions is high enough to prevent almost completely further fragmentation, as shown by MIKE and B/E linked scan spectra.

The results obtained for the model compounds **6** and **7** were used to interpret the spectra of **3**–**5**. The proposed fragmentation paths of these compounds are summarized in Scheme 5.

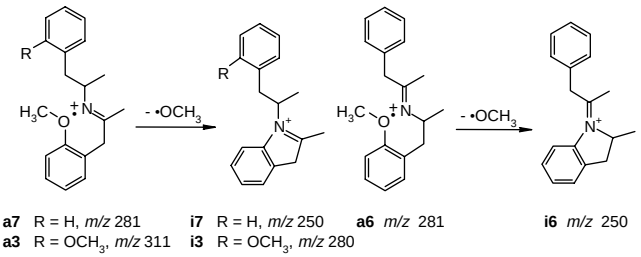
These paths are analogous to those observed for the model compounds **6** and **7**. Decomposition of the molecular ions **a3**–**a5** (m/z 311) proceeds mainly via an α-cleavage, providing even-electron ions with m/z 190. The exact inspection of the mass range between m/z 260 and 270 indicated that the loss of the CH_3 radical in the competitive α-cleavage also takes place producing an ion of m/z 267.



Scheme 2. Fragmentation paths of **6** on electron ionization.



Scheme 3. Fragmentation paths of **7** on electron ionization.



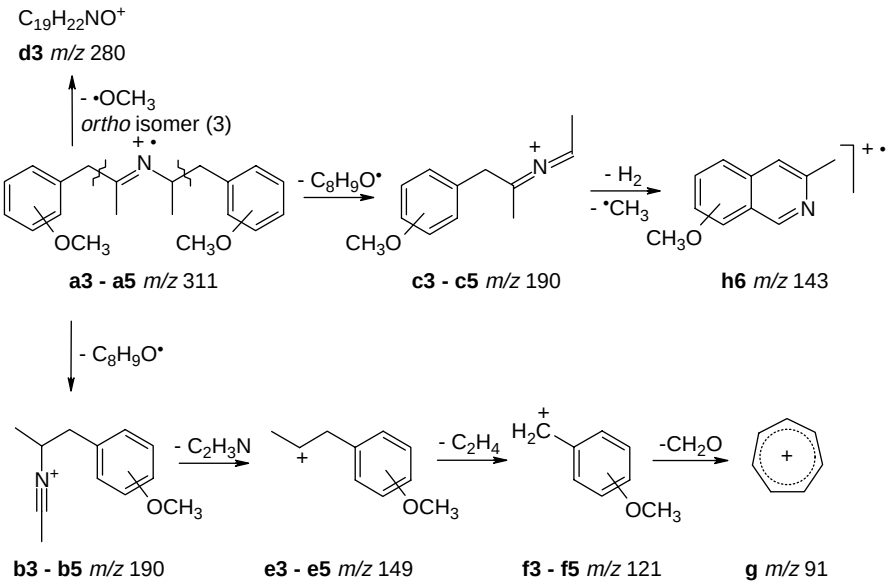
Scheme 4. Proposed mechanism of elimination of the OCH_3 radical from the molecular ions of **3**, **6** and **7** with a methoxy group in an *ortho* position.

However, the process in which benzyl radical is cleaved predominates. The order in aminic α-cleveage, benzyl > alkyl > H, is the same as described for phenylisopropylamine and its regioisomers.[25] Moreover, as it has been proved during experiments with imines **6** and **7**, the elimination of methoxybenzyl radical proceeds in two ways, leading to even-electron ions **b3**–**b5** and **c3**–**c5** for which different structures could be proposed. In the *B*/*E* linked scan and MIKE spectra of the *m*/*z* 190 ions, fragments corresponding to both fragmentation paths were observed.

Fragmentation patterns of **3**–**5** are very similar, with the exception of the methoxy radical elimination from **3**, a process not observed for two other isomers. These results show that the *ortho* position of the methoxy groups in imine **3** is essential for their expulsion from the molecular ion **a3**.

The fragmentation mechanisms proposed above led to the following general conclusions:

1. The *ortho* position of the methoxy group in imine **3** is essential for its expulsion from the parent ion **a3**.
2. The localization of the methoxy substituent close to the C═N bond appears to be of secondary importance for this process, although the loss of OCH_3 occurring in the case of derivative **6** is more profound.



Scheme 5. Main fragmentation paths of **3**–**5** upon electron ionization.

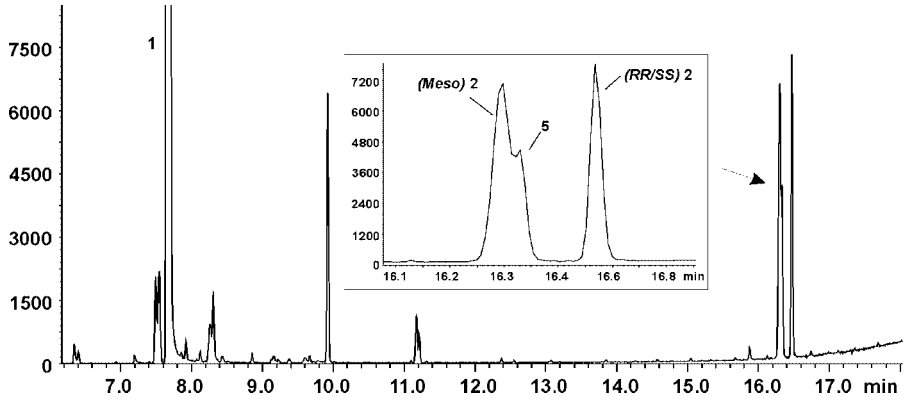


Figure 4. GC/MS analysis of the crude PMA obtained from the reductive amination of 4-methoxyphenylacetone. 1, PMA; 2, diastereomers of **2**; imine **5**.

3. The formation of the *m/z* 280 ion (from imine **3**) is the result of the loss of either of the methoxy groups present in the molecule, although the dominant fragmentation process probably refers to the methoxyphenyl fragment in the neighborhood of the C═N moiety, as it has been proved for compounds **6** and **7**.
4. Two different structures can be ascribed to the *m/z* 190 ion in the mass spectrum of imines **3**–**5**.

As was mentioned previously,[17] only a trace amount of **5** was detected in the crude PMA obtained by the Leuckart method. The major reason responsible for this result is general instability of imines, especially in the acidic water environment. Because the second step of the Leuckart synthesis involves hydrolysis of an intermediate, formylamine, in boiling concentrated hydrochloric acid, any amount of **5** formed during the first step of the reaction is rapidly destroyed. In contrast, a significant amount of the des-methoxy derivative of **3** has been reported in amphetamine synthesized by the low- and high-pressure amination of benzyl methyl ketone.[18]

In our case, as can be seen in Fig. 4, the treatment of 4-methoxyphenylacetone with methanolic ammonia in the presence of reducing agent ($NaCNBH_3$ or Al foil/$HgCl_2$) gave the desired product, PMA, accompanied by considerable amounts of imine **5** and secondary amine **2**. The final content of impurities **5** and **2** will be dependent on the reaction conditions, e.g. hydrogen pressure, catalyst activity and quality of the work-up procedure. Since the reduction of the iminium moiety in **5** creates a second stereogenic center, the resulting compound **2** consists in fact of a mixture of *meso* (*R*/*S*) and two (*SS* and *RR*) enantiomeric forms. As can be seen from the inset in Fig. 4, imine **5** co-elutes with the *meso* form of **2**, giving an unsymmetrical peak eluting at 16.30 min. In spite of the similar GC data, **5** and **2** exhibit sufficiently distinctive mass spectra. Therefore, regardless the similar GC data, **5** and **2** exhibit sufficiently distinctive mass spectra to permit their positive identification even in the case when one of them is present in a large excess.

CONCLUSION

The EI-induced decomposition of the molecular ions of **3**–**5** depends on the position of the methoxy substituents in the aromatic ring. The Shiff base **3** bearing *ortho* methoxy groups shows a facile formation of the *m/z* 280 cation, and this behaviour can be explained by the *ortho* effect involving the methoxy group and the nitrogen atom in the imine moiety. It should be pointed out that a similar process with an *ortho* aromatic proton was not observed. On the basis of the MS experiments with the additionally synthesized monomethoxy imines **6** and **7**, the participation in the *ortho* effect of both methoxy groups of **3** has been proved.

The GC/MS examination of the crude PMA, which was obtained by means of the reductive amination of the *p*-methoxyphenylacetone, revealed a detectable amount of imine **5**. In our opinion, the presence of a considerable quantity of imine **5** is connected specifically with the type of reaction used by illegal producers and should be considered as a 'route specific' by-product.

Acknowledgements

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