Mass spectrometric properties of new representative of designer drugs of NBOMe series and derivatives thereof

Vadim Shevyrin [1, 2], Olga Kupriyanova [3], Albert T. Lebedev [4], Yuri Shafran [1], Yuri Morzherin [1]

1. Institute of Chemistry and Technology, Ural Federal University, Ekaterinburg , Russia
2. Main Agency of the Ministry of the Interior of the Russian Federation, Expert and Criminalistic Center, Ekaterinburg, Russia
3. A.E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, Kazan , Russia
4. Organic Chemistry Department, Lomonosov Moscow State University, Moscow, Russia

1st GC/Q-TOF Forum
Barcelona. 24 & 25 November, 2016

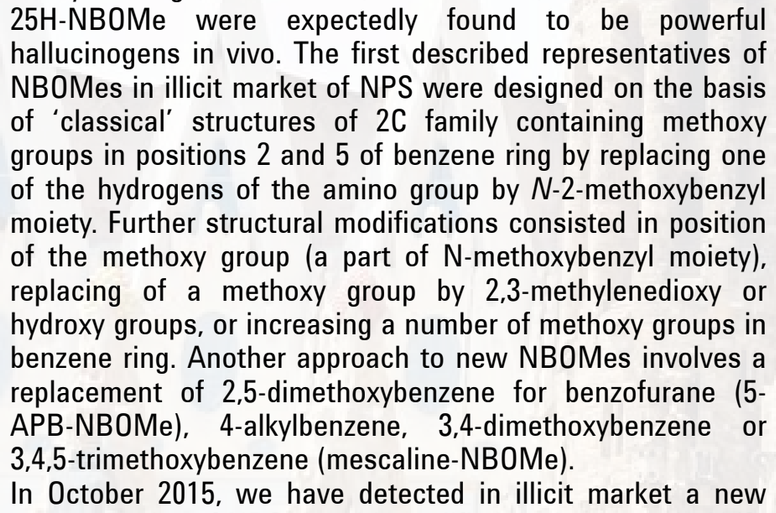
Agilent Technologies

Introduction

Last years, the number of new psychoactive substances (NPS) in illicit drug market is constantly growing. According to United Nations information, more than 500 NPS were detected in 95 countries during 2009–2014. Phenethylamines are the most numerous class of NPS worldwide and are number two after synthetic cannabinoids. NPS are created by chemical similarity with known narcotics (so-called designer drugs) or belong to quite new series of compounds. In any case, their action on the human organism is determined by their ability to bind to certain receptors, responsible for psychoactive potential. Designer phenethylamines, known in the illicit market, are strong psychedelics, hallucinogens and stimulators of CNS similar to hallucinogens of LSD type or tryptamines. All these compounds act as full or partial agonists of serotonin 5-HT_{2A} receptors, causing hallucinogenic activity. Most popular designer phenethylamines contain methoxy groups in positions 2 and 5 and different lipophilic substituents in position 4 in benzene ring (2C family).

The tendency of recent years deals with repeating attempts to obtain round legislative regulation by emerging into the market new compounds with temporarily legal status but possessing pharmacological activity similar to preparations under control. Thus, in 2011, a new series of compounds belonging to phenethylamine class was put into illicit market and gained high popularity among the consumers. This series is presented by *N*-2-methoxybenzyl substituted (NBOMe) analogues of known phenethylamines of 2C family. The introduction of *N*-2-methoxybenzyl substituent leads to a substantial growth of in vitro affinity of NBOMes to serotonin receptors, which was already high for 2C family. Because the affinity to 5-HT_{2A} receptors correlates with hallucinogenic ability of drugs, 25I-NBOMe, 25B-NBOMe, 25C-NBOMe and 25H-NBOMe were expectedly found to be powerful hallucinogens in vivo. The first described representatives of NBOMes in illicit market of NPS were designed on the basis of 'classical' structures of 2C family containing methoxy groups in positions 2 and 5 of benzene ring by replacing one of the hydrogens of the amino group by *N*-2-methoxybenzyl moiety. Further structural modifications consisted in position of the methoxy group (a part of N-methoxybenzyl moiety), replacing of a methoxy group by 2,3-methylenedioxy or hydroxy groups, or increasing a number of methoxy groups in benzene ring. Another approach to new NBOMes involves a replacement of 2,5-dimethoxybenzene for benzofurane (5-APB-NBOMe), 4-alkylbenzene, 3,4-dimethoxybenzene or 3,4,5-trimethoxybenzene (mescaline-NBOMe).

In October 2015, we have detected in illicit market a new representative of NBOMe with modified design, namely *N*-(2-methoxybenzyl)-2-(2,4,6-trimethoxyphenyl)ethanamine (conventionally named as 2,4,6-TMPEA-NBOMe) (**1**). Structural elucidation of 2,4,6-TMPEA-NBOMe was performed in the most reliable manner using the advanced techniques of mass spectrometry (tandem mass spectrometry and accurate mass measurements) and multidimensional NMR. In current investigation, we have prepared methyl (**2**), acetyl (**3**), trifluoroacetyl (**4**), *bis*-trifluoroacetyl (**5**) and dideutero (**6**) derivatives of 2,4,6-TMPEA-NBOMe.



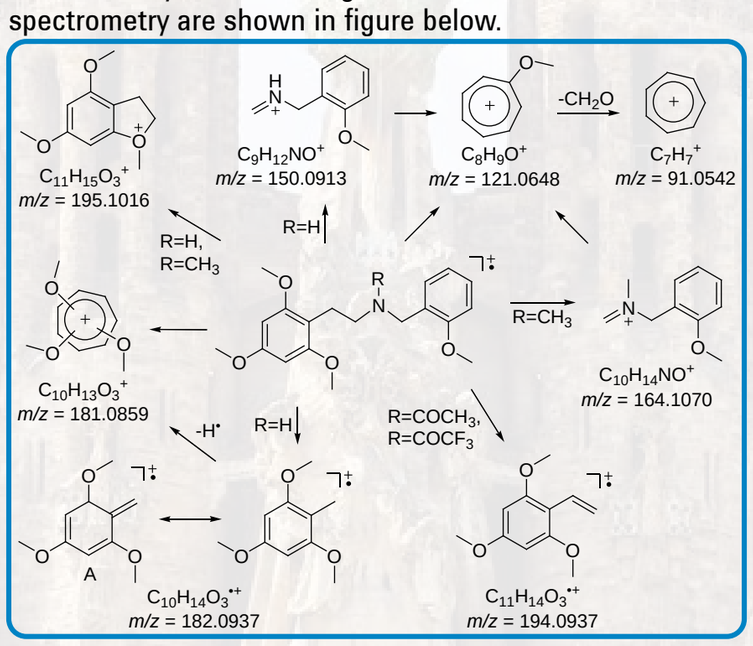
Electrophilic substitution of hydrogen by trifluoroacetyl or deuterium is an interesting feature of 2,4,6-trimethoxybenzene ring in compound **1**. The structure of all derivatives **2**–**6** is proven by mass spectrometry and NMR. The analytical data presented in current work for compound **1** detected in illicit market of NPS and for the derivatives thereof will be helpful for forensic chemists. Moreover, we consider the peculiarities of mass spectrometric fragmentation of the compounds revealed with HRMS and tandem experiments to have a scientific interest themselves.

Experimental

Fragmentation of compounds in EI mode was studied by GC/HRMS with an Agilent 7890A chromatograph connected with a tandem quadrupole time-of-flight accurate-mass detector (Agilent 7200 Accurate-Mass Q-TOF GC–MS). For chromatographic separation, an HP–5ms capillary column (30.0m× 0.25mm× 0.25 μm; 19091S-433) was used. The oven temperature was maintained at 70 °C for 1.0 min then programmed at 15°/min to 295 °C, which was maintained for 15min. The injector temperature was 280 °C, and the interface temperature 290 °C. Helium in constant flow-mode was used as carrier gas; the flow rate was 1.0ml/min. The mass detector was equipped with an EI source (70 eV). The quadrupole detector was adjusted for total ion current in MS mode and for the isolation of the precursor ions with bandwidth $\Delta m/z$ = 1.3 in MS/MS mode. Collision-induced dissociation (CID) spectra were recorded at collision energy in the range of 5–20 eV in a hexapole collision cell filled with nitrogen (99.999%). The accurate mass detector (TOF) was operated in extended dynamic range mode (2GHz) with an acquisition rate of five spectra/s. Tuning and operation of the instrument and data processing were performed by means of MASSHUNTER QUALITATIVE ANALYSIS B.05.00 software.

Results and Discussion

Main directions of fragmentation of compounds **1**–**4** in EI elucidated by means of high resolution and tandem mass spectrometry are shown in figure below.



First we would like to note the formation of tropylium-type ion $C_8H_9O^+$ (*m/z* 121.0648), forming due to C–N bond cleavage in compounds **1**–**6**. Tropylium cation $C_7H_7^+$ appears due to elimination of formaldehyde molecule from the $C_8H_9O^+$ ion. Another typical direction of fragmentation is β-cleavage leading either to iminium cation $C_9H_{12}NO^+$ (*m/z* 150.0913), which is observed as an intense peak in mass spectra of compounds **1** and **6** or to analogous $C_{10}H_{14}NO^+$ (*m/z* 164.1070) cation for compound **2**. It is worthy to note that the charge during this bond cleavage may retain at the complementary fragment. The signals of the corresponding fragment $C_{10}H_{13}O_3^+$ (*m/z* 181.0859) are quite pronounced in the spectra of compounds **1**–**4**.

The formation of the iminium cation becomes unfavorable for *N*-acyl derivatives **3**–**5**. The reason may involve more competitive McLafferty rearrangement when the cleavage is accompanied by the hydrogen transfer and formation of a stable trimethoxystyrene radical cation (McLafferty rearrangement with charged olefinic product). For compounds **3** and **4**, this rearrangement results in the formation of radical cation $C_{11}H_{14}O_3^{\bullet+}$ (*m/z* 194.0937), which further eliminates CH3• and CHO• radicals as the tandem experiments demonstrate. Similar radical cations are registered for compound **5** and other *N*-acyl derivatives in NBOMe series.

A cleavage of C–N-bond at *β*-carbon atom of 2,4,6-trimethoxyphenylethyl fragment in compounds **1** and **2** leads to formation of $C_{11}H_{15}O_3^+$ (*m/z* 195.1016) ion with low intensity. This usually inefficient process becomes competitive due to the possibility of cyclization into benzofuran.

Formation of $C_{10}H_{14}O_3^{\bullet+}$ (*m/z* 182.0937) radical cation in the course of fragmentation of compound **1** may be rationalized by McLafferty rearrangement with migration of the amine hydrogen atom to the benzene ring. This mechanism of formation of $C_{10}H_{14}O_3^{\bullet+}$ is proved by the absence of this ion in mass spectra of compounds **2**–**4** without hydrogen atom in their amino group.

Results and Discussion

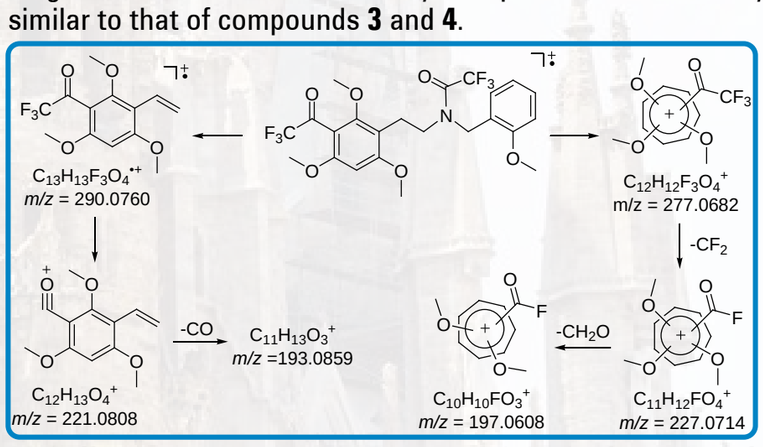
Similar process is observed in fragmentation of *β*-phenethylamines of 2C family, some derivatives of amphetamine and of other NBOMes. Electron-donating moiety in para-position of benzene ring in NBOMes favors the rearrangement, which is evidenced by higher intensity of corresponding peaks of radical cations in mass spectra of such compounds.

In general, formation of methylenecyclohexadiene radical cation (ion A in figure, for compound **1**) is considered in the literature by mass spectrometry as the most probable mechanism of rearrangement of alkyl benzenes. At the same time, it is assumed that when both *ortho*-positions in the benzene ring are substituted, the rearrangement does not take place because of steric hindrance. In fact, most of *β*-phenethylamines, including all NBOMes and compounds of 2C family described in the literature, demonstrate the same rearrangement, containing at least one free *ortho*-position in benzene ring. In this respect, 2,4,6-TMPEA-NBOMe presents a surprising example of the rearrangement with both substituted *ortho*-positions. It is difficult to rationalize, why McLafferty rearrangement is so efficient in the case of compound **1**. Because the steric hindrance due to two methoxy groups in *ortho*-positions is rather pronounced, one may speculate about *ipso*-substitution in this highly activated benzene ring. Alternatively, one may propose that rather electrono-donating properties of the substituted ring than steric effects play the major role in the rearrangement. Anyway, the presence of three highly electrondonating methoxy groups in the *ortho*-positions and *para*-positions favors the rearrangement.

For dideuterated compound **6**, corresponding $C_{10}H_{12}D_2O_3^{\bullet+}$ (*m/z* 184.1063) ion is formed.

Tandem mass spectrometry experiments (MS/MS) in CID mode have shown that the directions of further fragmentation of $C_{10}H_{14}O_3^{\bullet+}$ (*m/z* 182.0937) radical cation are typical for methoxy derivatives of benzene and involve elimination of the hydrogen atom, CH3• and CHO• radicals or formaldehyde molecule.

Fragmentation of *bis*-trifluoroacetyl compound **5** is essentially similar to that of compounds **3** and **4**.



McLafferty rearrangement in **5** may result in the formation of $C_{13}H_{13}F_3O_4^{\bullet+}$ (*m/z* 290.0760) radical cation. The very fact of this rearrangement and the *m/z* value of the radical cation confirm the presence of the second trifluoroacetyl moiety in the benzene core. Formation of $C_{12}H_{12}F_3O_4^+$ (*m/z* 277.0682) cation with the highest intensity in the mass spectrum for compound **5** is a result of benzyl cleavage. The further fragmentation of *m/z* 290 and *m/z* 277 ions was studied by means of tandem mass spectrometry in CID mode. Thus, it was found that $C_{12}H_{13}O_4^+$ (*m/z* 221.0808) ion is formed as a result of elimination of $CF_3^\bullet$ radical from $C_{13}H_{13}F_3O_4^{\bullet+}$ (*m/z* 290.0760) radical cation. Decomposition of $C_{12}H_{12}F_3O_4^+$ (*m/z* 277.0682) ion involves elimination of difluorocarbene. Product ion $C_{11}H_{12}FO_4^+$ (*m/z* 227.0714) thus formed further looses a molecule of formaldehyde to afford $C_{10}H_{10}FO_3^+$ (*m/z* 197.0608) ion.

Conclusions

- Substitution of the both *ortho*-positions in benzene ring of 2,4,6-TMPEA-NBOMe does not block McLafferty rearrangement involving migration of the hydrogen atom from the amino group to the benzene ring. This fact allows revising the previous knowledge on McLafferty rearrangement. Moreover, three methoxy groups in 2, 4 and 6 positions of benzene favor this rearrangement in EI conditions.
- In mass spectra of acyl derivatives of 2,4,6-TMPEA-NBOMe, McLafferty rearrangement with the formation of a charged olefinic product was observed.
- A peculiar feature of 2,4,6-TMPEA-NBOMe is an ease of electrophilic substitution of the hydrogen atoms in its 2,4,6-trimethoxybenzene ring. The fact is evidenced by the readiness of formation of *bis*-trifluoroacetyl and dideutero derivatives from 2,4,6-TMPEA-NBOMe.