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Basic and neutral route specific impurities in MDMA prepared by different synthesis methods Comparison of impurity profiles

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Abstract

In this work, the neutral and basic impurities found in the precipitate of MDMA·HCl are presented. MDMA·HCl was prepared by the most popular synthesis methods used in clandestine manufacture, i.e. safrole bromination, Leuckart method and reductive amination with various reducing agents: Al/Hg, $NaBH_4$, $NaBH_3CN$. 3,4-Methylenedioxyphenyl-2-propanone (MDP-2-P), the starting material in Leuckart reaction and reductive amination, was prepared by two different synthesis methods, i.e. by isosafrole oxidation and MDP-2-nitropropene reduction. The extraction of impurities was performed under alkaline and neutral conditions. Impurity profiles were obtained using GC/MS. Each synthesis method is characterised by its own route specific impurities. The influence of pH on the extraction of synthesis markers from 3,4-methylenedioxymethamphetamine (MDMA) samples is discussed and comparison of the profiles of basic and neutral impurities is presented.

Keywords: MDMA; L–L extraction; Reductive amination; Leuckart method; Safrole bromination synthesis; Route specific impurities

1. Introduction

'Ecstasy' is the common name for 3,4-methylenedioxymethamphetamine (MDMA). It is almost entirely produced in clandestine laboratories. The word 'ecstasy' may cover other drugs besides MDMA.

As 'ecstasy' popularity increased in the 1990s, illegal production of this drug has risen significantly. Illegal manufacturers and distributors have divided into groups which have specialised in acquiring precursors, producing ecstasy powders, pressing powder into pills or smuggling ecstasy into the consumer countries.

A promising methodology which is useful in identifying illegal production, distribution networks and in providing clear and conclusive evidence for the use in criminal investigations is the profiling of drugs, i.e. physical and chemical characterisation of seized drug samples. It embraces a visual inspection of the product, the nature of packaging used, the size, shape, logo and colour of tablets. After this examination, seized samples of drugs are subjected to detailed analysis in order to detect and quantify impurities such as starting materials, intermediates, by-products, diluents and adulterants. Each seized sample of drug has its own, characteristic pattern of impurities which is also called a profile. Profiles can be obtained by the use of an instrumental method and subject to comparative analysis in order to establish whether or not the samples from different seizures correspond to a common origin.

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Profiling of drugs might be also used to identify the synthesis method. However, so far characterization of individual impurities (in case of 'ecstasy'), which would enable identification of the synthesis method, is still not completed [1–10]. Furthermore, the problem of cutting agents and diluents influence on the extraction of impurities has not been yet solved.

This work reveals how large changes in the impurity profiles of MDMA are caused by the modification of conditions during extraction from neutral to basic. The new important route specific impurities are presented and the influence of pH on their extraction is discussed.

2. Materials and methods

2.1. Chemicals and reagents

In the synthesis of MDMA, the following reagents were used: formic acid (98%), hydrochloric acid (36–38%), methylene chloride, sodium hydroxide, acetic acid (99.5%), acetone, diethyl ether, toluene, isopropanol, hydrogen peroxide (∼33%), sulfuric acid (95%) (all POCh, Poland, analytical grade), piperonal (99%, Aldrich, for synthesis), isosafrole (97%, Aldrich, for synthesis), safrole (97%, Aldrich, for synthesis), nitroethane (96%, Aldrich, for synthesis), cyclohexylamine (99%, Aldrich, for synthesis), ethyl formate (97%, Aldrich, for synthesis), hydrobromic acid (62%, Aldrich, analytical grade), methylamine solution (33% in abs. ethyl alcohol, Aldrich, analytical grade), methylamine aqueous solution (40%, Aldrich, analytical grade), diethyl ether (anhydrous, >99%, Aldrich, A.C.S. Reagent), methanol (Merck, HPLC grade), $NaBH_4$ (Aldrich, for synthesis), $NaBH_3(CN)$ (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 $NaHCO_3$; 39.3 ml H_2O), *n*-heptane (Aldrich, HPLC grade), phosphate buffer, pH 7 (Merck), diphenylamine (Supelco, used as internal standard).

2.2. Synthesis

3,4-Methylenedioxyphenyl-2-propanone (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

Table 1
Synthesis of MDMA via reductive amination with Al/Hg as a reducing agent

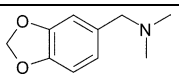
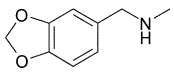
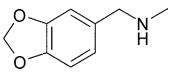
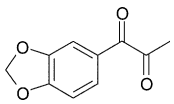
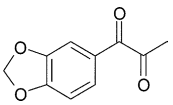
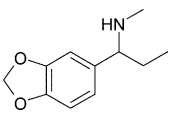
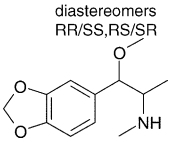
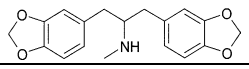
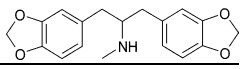
Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
5	–	
8		
16		
13	–	
22, 22′	–	mixtures of diastereomers RR/SS,RS/SR 
30		

Table 2
Synthesis of MDMA via safrole bromination

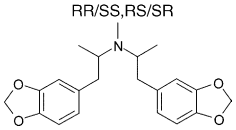
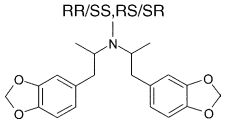
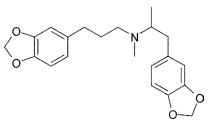
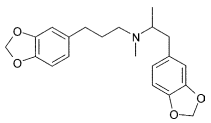
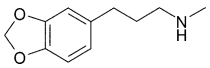
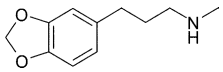
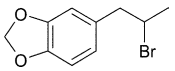
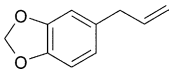
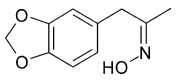
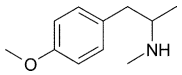
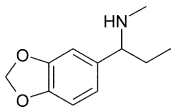
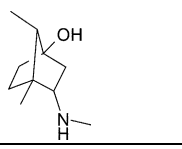
Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
33, 33′	mixtures of diastereoizomers RR/SS,RS/SR 	mixtures of diastereoizomers RR/SS,RS/SR 
32		
17		
20		–
4		–
24	–	
12	–	
13	–	
3	–	

Table 3
Synthesis of MDMA via Leuckart reaction

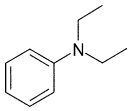
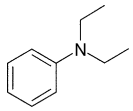
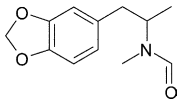
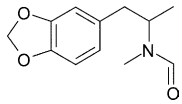
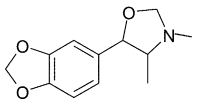
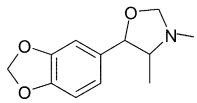
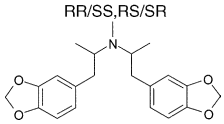
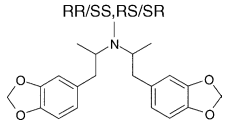
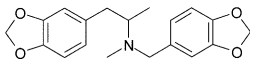
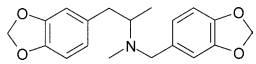
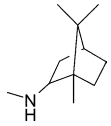
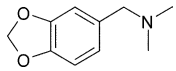
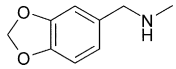
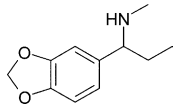
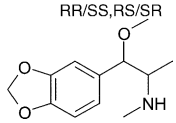
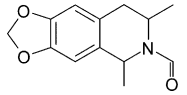
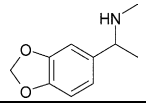
Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
1		
28		
26		
33, 33′	mixtures of diastereoizomers RR/SS,RS/SR 	mixtures of diastereoizomers RR/SS,RS/SR 
31		
2	–	
5	–	
8	–	
13	–	
22, 22′	–	mixtures of diastereomers RR/SS,RS/SR 
25	–	
6	–	

Table 4
Synthesis of MDMA via reductive amination with $NaBH_3CN$ as a reducing agent

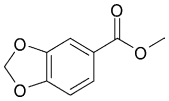
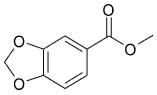
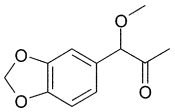
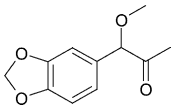
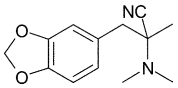
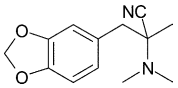
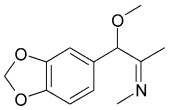
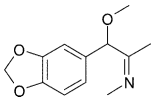
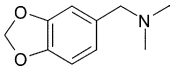
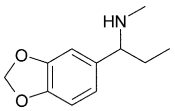
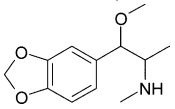
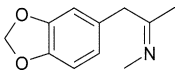
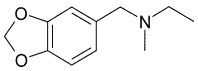
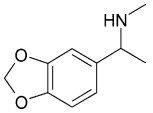
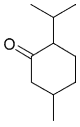
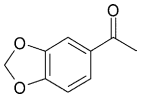
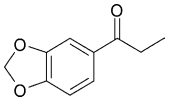
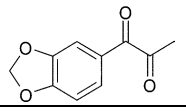
Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
10		
21		
29		
23		
5	–	
13	–	
22, 22′	–	mixtures of diastereomers RR/SS,RS/SR 
19	–	
11	–	
6	–	
4		–
7		–
14		–

Table 4 (*Continued*)

Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
16		–

nitroethane. The syntheses were performed according to the procedures described by Shulgin and Shulgin [11]. Subsequently, MDP-2-P, prepared by the oxidation of isosafrole, was used in Leuckart reaction, cyanoborohydride reduction, dissolving metal reduction and borohydride reduction in low temperature. MDP-2-P prepared by the reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene was only subjected to borohydride reduction in low temperature.

Leuckart method was performed according to the modified MDA synthesis procedure described by Elks and Hey [12]. Safrole bromination was carried out according to the procedure described by Biniecki and Krajewski [13]. Cyanoborohydride reduction ($NaBH_4CN$) was performed according to the modified MDA synthesis procedure described by Shulgin and Shulgin [11]. Dissolving metal reduction (aluminium–mercury amalgam) was performed according to the procedure described by Shulgin and Shulgin [11]. Borohydride reduction ($NaBH_4$) was performed as

Table 5
Synthesis of MDMA via reductive amination with $NaBH_4$ as a reducing agent (preceded by MDP-2-P synthesis from piperonal)

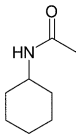
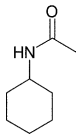
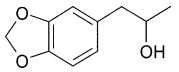
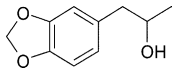
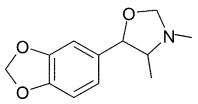
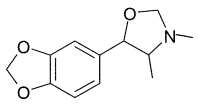
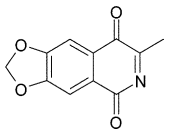
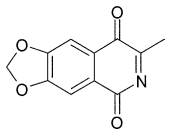
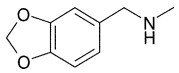
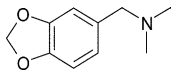
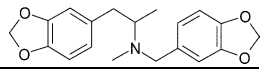
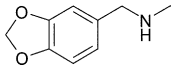
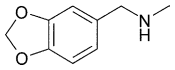
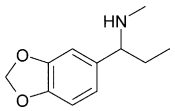
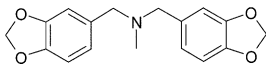
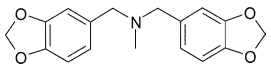
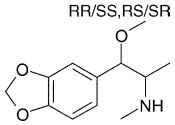
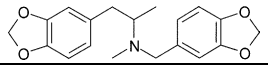
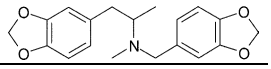
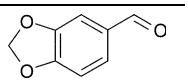
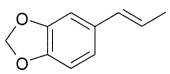
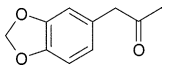
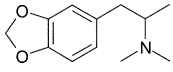
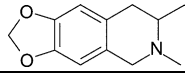
Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
9		
15		
26		
27		
8	–	
5	–	
31	–	

Table 6
Synthesis of MDMA via reductive amination with $NaBH_4$ as a reducing agent (preceded by MDP-2-P synthesis from isosafrole)

Peak number	Phosphate buffer, pH 7	Carbonate buffer, pH 10
8		
13	–	
18		
22, 22′	–	mixtures of diastereomers RR/SS,RS/SR 
31		

follows: 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 $NaBH_4$ (30 mg) was slowly added. After dissolving of reductive agent, reaction mixture was left at −20 °C for 2 h. The addition of $NaBH_4$ 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 CH_2Cl_2 (3 ml × 8 ml). The organic solution was extracted with 10% HCl, combined aqueous layers were alkalized with 25% NaOH (∼10 ml) and extracted with CH_2Cl_2 (3 ml × 10 ml). Combined extracts were dried over $MgSO_4$, evaporated, a residue was dissolved in Et_2O (18 ml) and dry HCl was passed through the solution. Precipitate of MDMA·HCl was filtered off, dried and homogenised prior to analysis.

Table 7
The most often encountered impurities in MDMA

A	
B	
C	
D	
E	

2.3. Extraction of impurities

Two hundred milligrams of MDMA·HCl was dissolved in 2 ml of buffer. Two different buffers, phosphate buffer, pH 7, and carbonate buffer, pH 10, were tested. The suspension was vigorously shaken (25 min) following by the addition of 200 ml 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.

2.4. Apparatus

GC/MS analysis was carried out on Hewlett-Packard 6890 series gas chromatograph coupled to 5984B mass spectrometer. Chromatographic separation was achieved on HP5-MS fused silica capillary column (30 m × 0.25 mm × 0.25 μm) 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 ionisation 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.

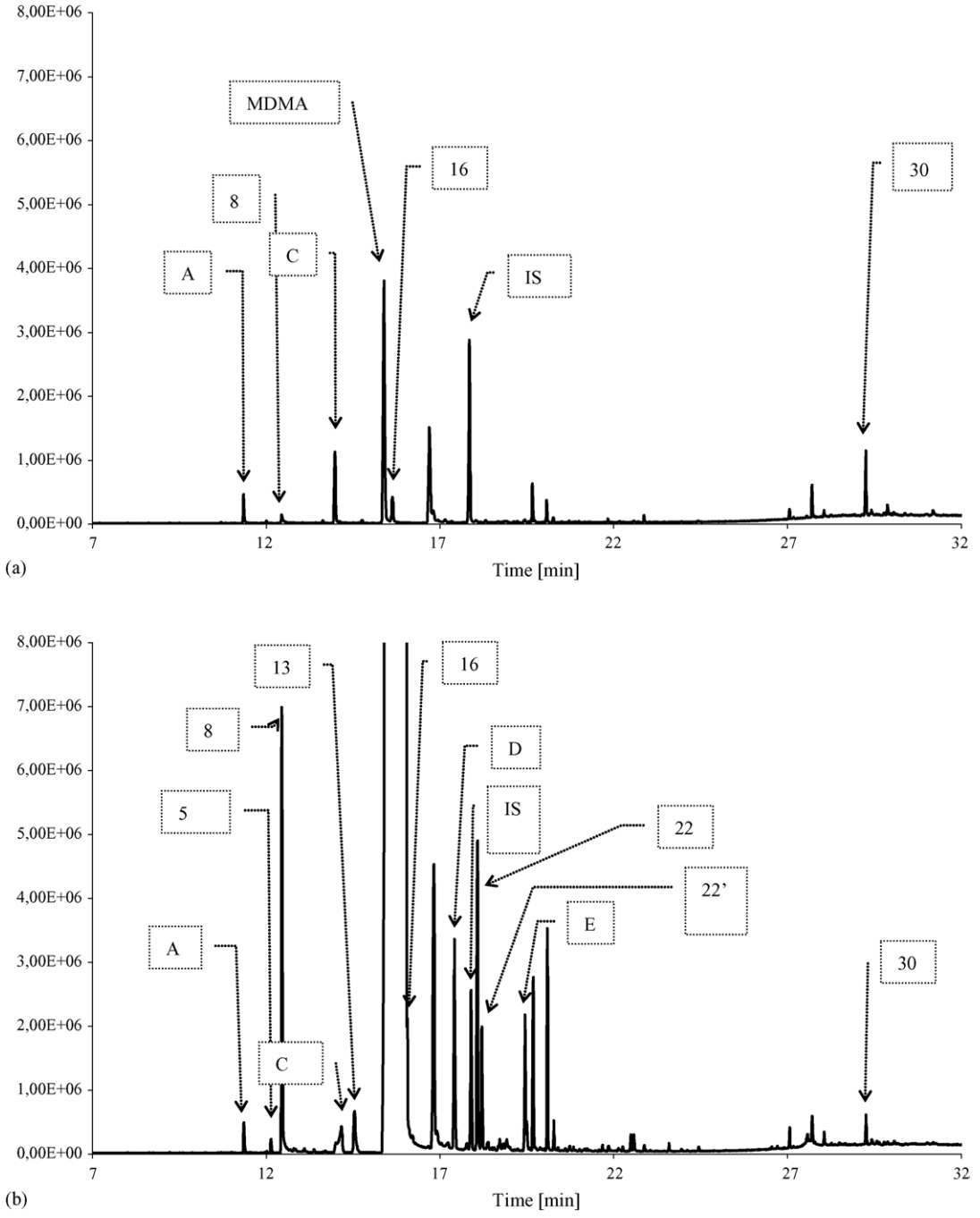


Fig. 1. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by reductive amination with Al/Hg as a reducing agent.

3. Results and discussion

In this work, our attention was focused on the neutral and basic impurities present in the precipitate of MDMA·HCl, synthesized as described above. Most of the studies devoted to the route specific impurities of MDMA reported so far [2–4,8–10,14] were based on the reaction mixtures collected during syntheses. Therefore, there are some differences between the results presented in this paper and those reported formerly.

Impurities identified in basic and neutral impurity extracts are presented in Tables 1–6, according to synthesis method. These are route specific impurities which indicate synthesis method of MDMA. The impurities which occur in all the synthesis methods are separately presented in Table 7.

The impurity profiles obtained after the extraction from neutral and basic buffer solutions are compared in Figs. 1–6. The pick indexes correspond appropriately to the compounds presented in Tables 1–7.

Generally we did not observe overlapping of the peaks in the profiles but there are some exceptions, i.e. MDMA peak overlaps partly with the peak of compound 16 (Fig. 1b) and compound 17 (Fig. 2b).

Results of this study show that amines constitute majority of impurities found in MDMA·HCl. Therefore, extraction

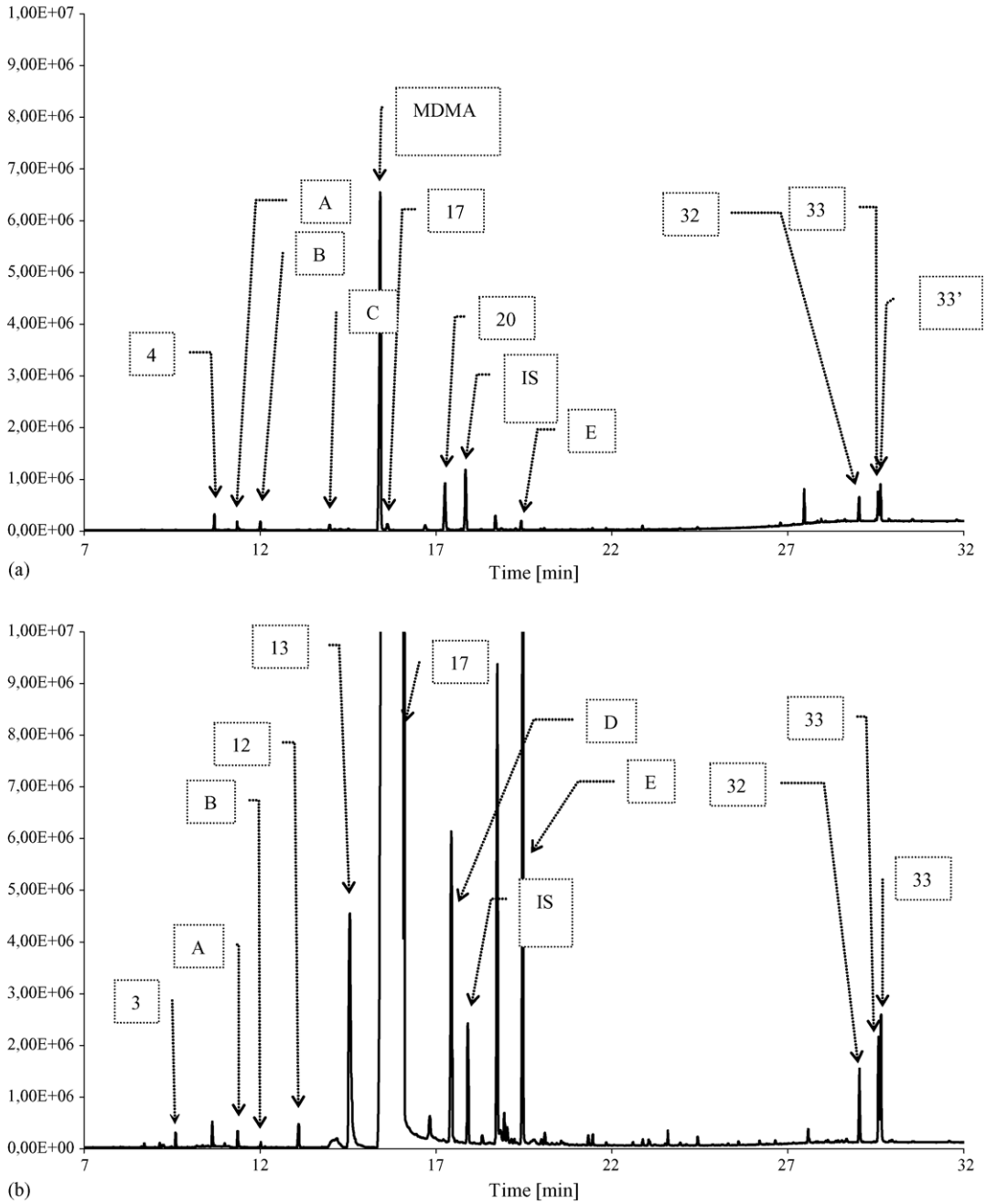


Fig. 2. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by safrole bromination method.

under alkaline conditions seems to be more adequate. However, in the case of some methods of MDMA synthesis, the important markers are extracted only under neutral conditions. Actually, such situation occurs in two synthesis methods, safrole bromination and reductive amination preceded by MDP-2-P synthesis from piperonal (Figs. 2 and 5). In the first method, an important specific synthesis marker, 3,4-methylenedioxyphenyl-2-bromopropane, is absent in the extracts from alkaline buffer because it is completely converted to isosafrole in basic conditions. In the second

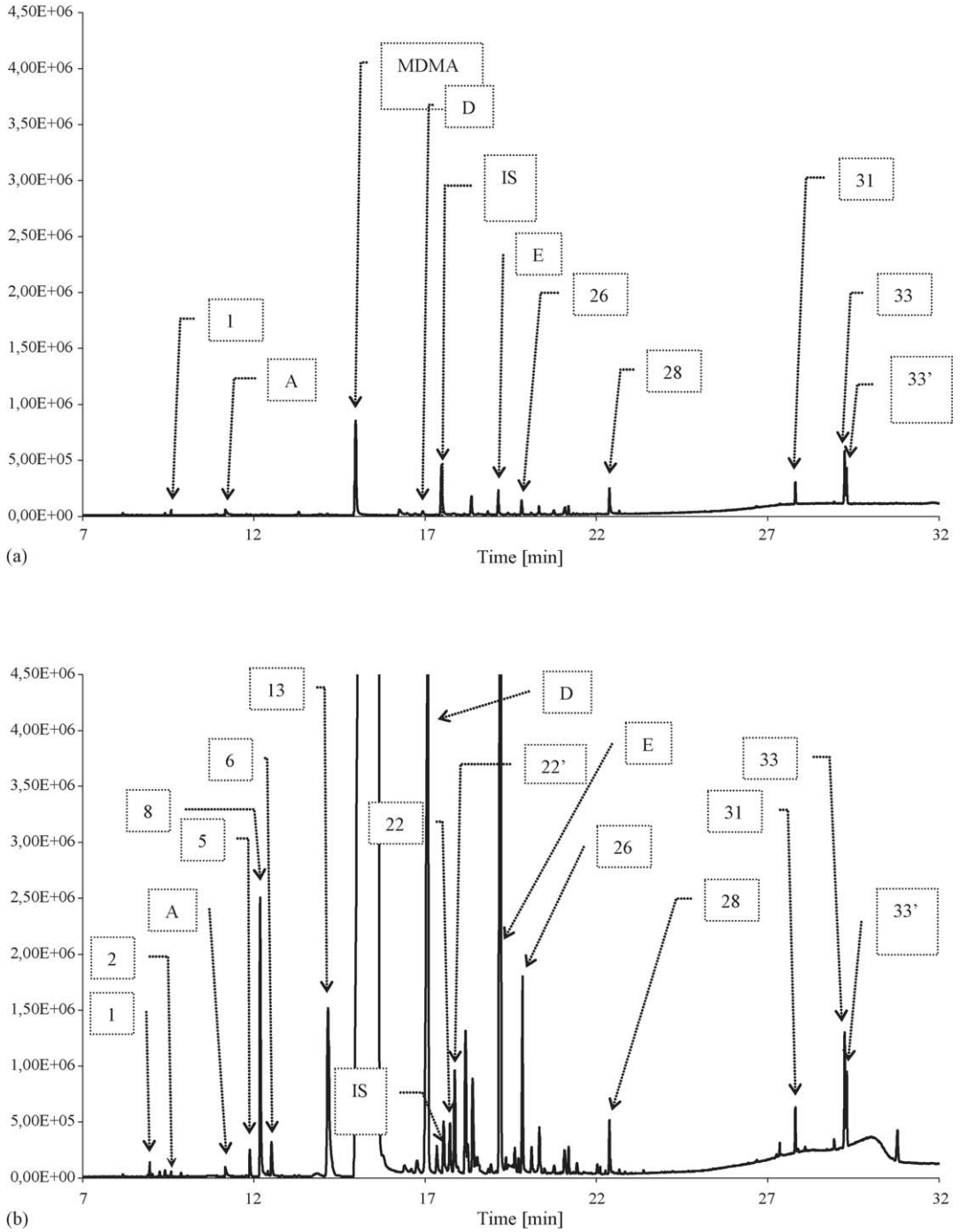


Fig. 3. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by Leuckart method.

method, this problem concerns 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 27 in Table 5)—the marker of the MDP-2-P synthesis from piperonal. As can be seen in Fig. 5, efficiency of extraction of this compound is significantly higher under neutral conditions than basic.

The analysis of impurities in starting materials, i.e. in safrole, isoafrole and piperonal, was done in order to find out if there are any impurities in MDMA·HCl which comes directly from these precursors. The results of this analysis proved that none of the impurities presented in Tables 1–7 derives directly from the starting materials. The route specific impurities presented in this paper are the by-products produced either from the impurities in starting materials, for example compound 12 (Table 2), compound 2 (Table 3), compound 4 (Table 4) or from impurities generated in side-reactions running parallel to main reaction, for instance,

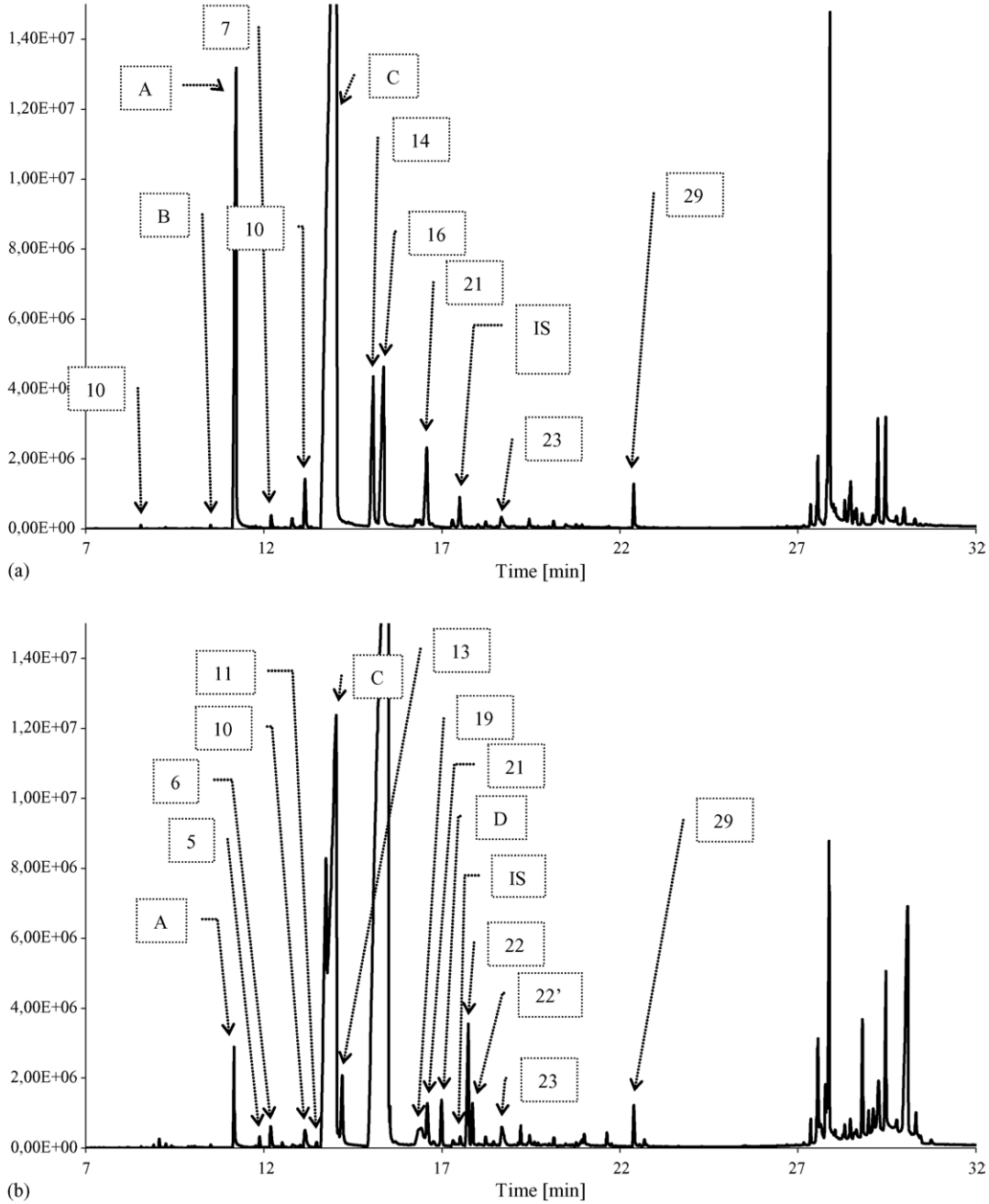


Fig. 4. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by reductive amination with $NaBH_3CN$ as a reducing agent.

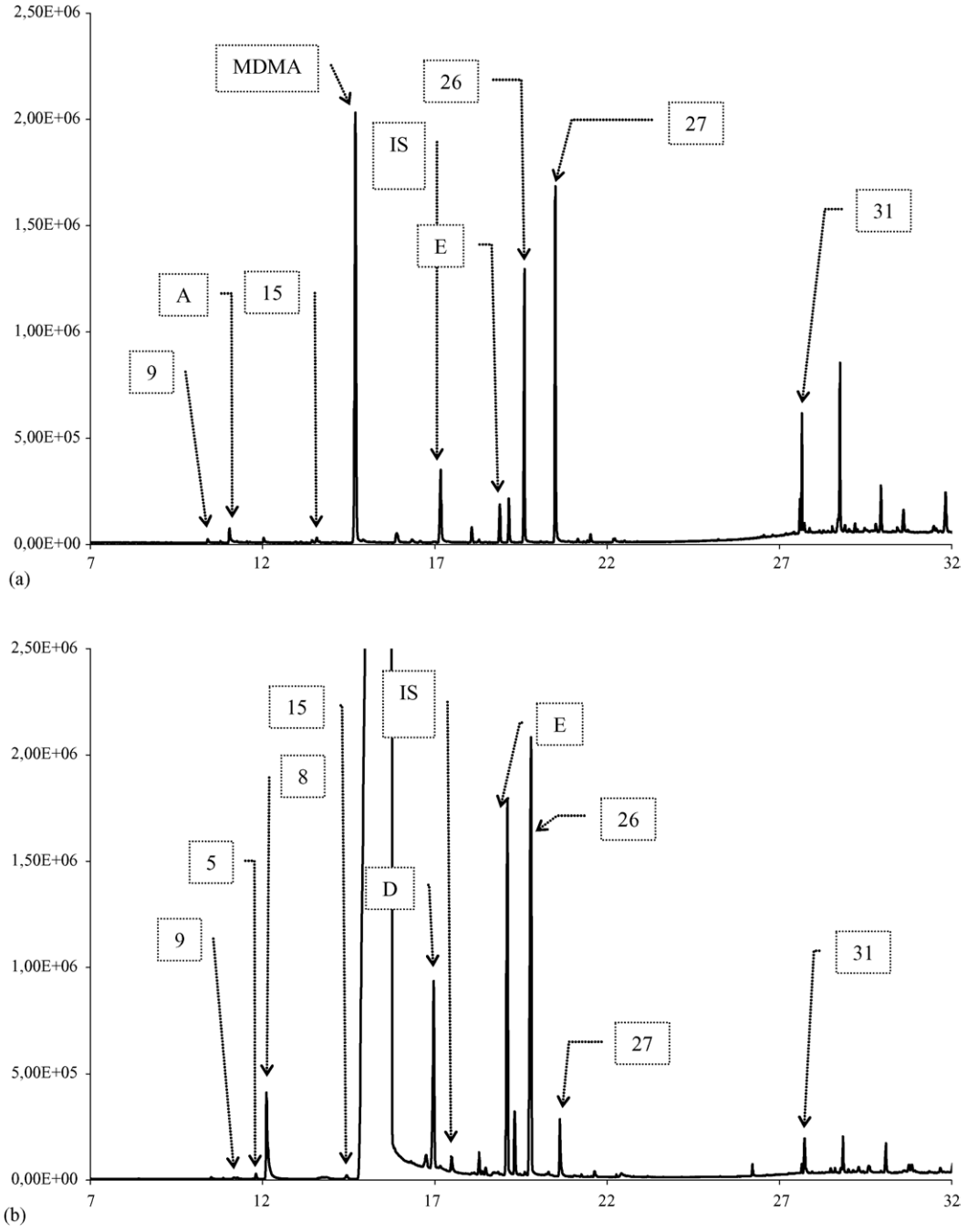


Fig. 5. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by reductive amination with $NaBH_4$ as a reducing agent (preceded by MDP-2-P synthesis from piperonal).

compound 13 (Table 1), compound 22 (Table 1), compound 17 (Table 2), compound 32 (Table 2), compound 26 (Table 3).

The results presented in the paper titled 'Determination of synthesis method of ecstasy based on the basic impurities' which is to be published soon in this journal shows that the discussed by-products are integral part of the synthesis of MDMA and they occur repeatedly if the synthesis is performed in similar conditions and according to the same procedure.

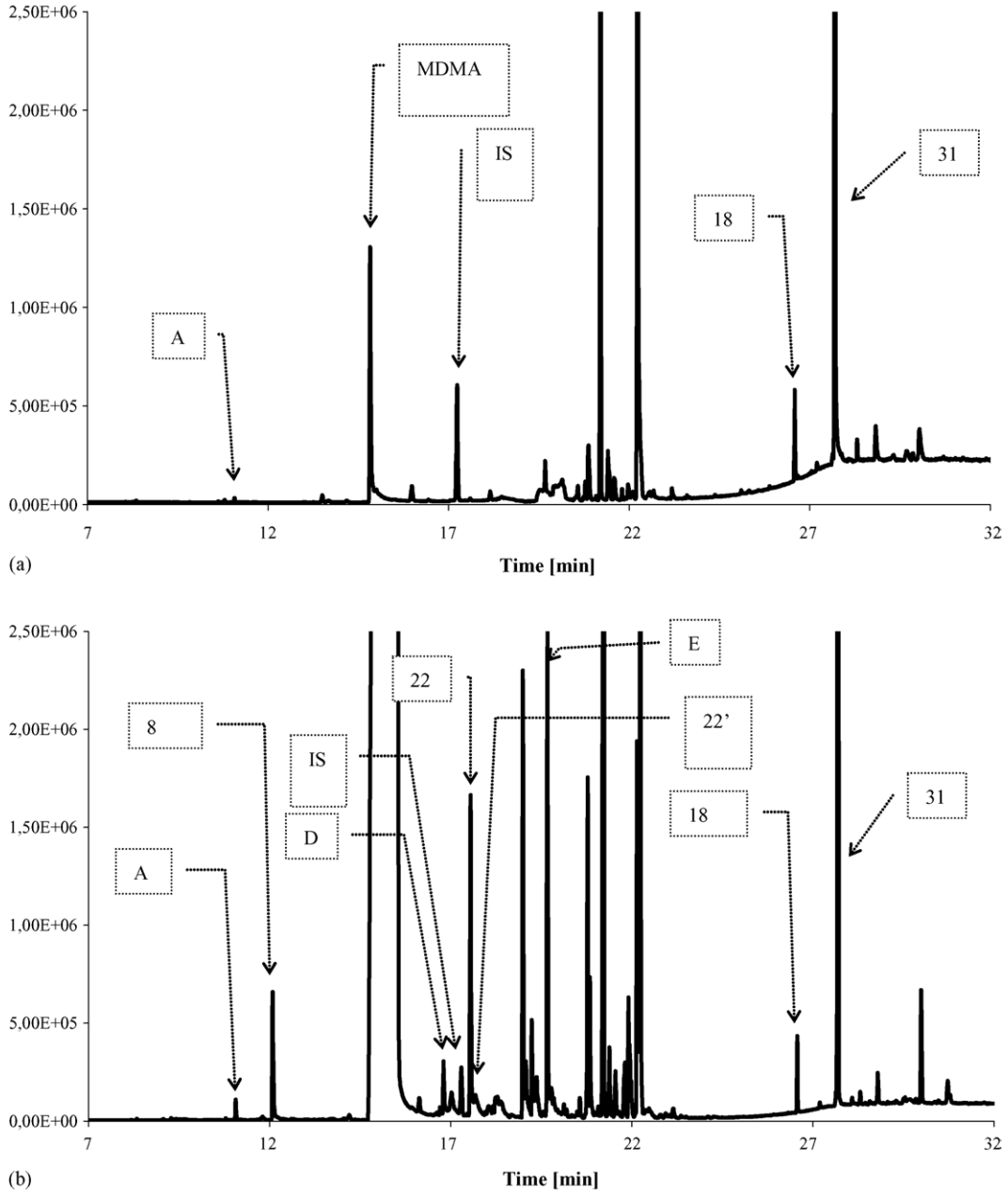


Fig. 6. Comparison of (a) neutral and (b) basic impurity profiles of MDMA prepared by reductive amination with $NaBH_4$ as a reducing agent (preceded by MDP-2-P synthesis from isosafrole).

4. Conclusions

Apart from the exceptions described above, the extraction of specific MDMA impurities carried out under basic conditions is much more efficient than the extraction under neutral conditions in respect to route specific impurities. Therefore, it is recommended that in the identification of synthesis method of seized, ecstasy tablets samples are dissolved in alkaline buffer from which the characteristic impurities are extracted to the organic phase.

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