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Analysis of amphetamines illegally produced in Serbia§

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Abstract: Forensic practice in the Republic of Serbia faced the illegal production of amphetamine for the first time in 2003. This paper presents the results of the chemical characterization of 32 batches of amphetamine samples from three separate cases, for the purpose of identification of the active components and additives. Through the profiling of impurities of all samples, using gas chromatography/mass spectrometry (GC/MS), 30 compounds associated with amphetamine were identified. The results of the analysis of powder tartrate, sulfate and phosphate salts of amphetamine, as well as variously formulated tablets are presented in this study. The analyses showed that the amphetamines were synthesized by the Leuckart method in all cases.

Keywords: amphetamine; impurity profiling; Leuckart synthesis.

INTRODUCTION

Abuse of amphetamine type stimulants (ATS) is on the rise worldwide. According to UNODC data, the number of ATS users is larger than the number of heroin and cocaine users combined. The situation is similar on the illegal market of the Republic of Serbia: ATS abuse is increasing; ecstasy tablets containing the active agent MDMA are the most common, amphetamines are less common, while abuse of methamphetamine is negligible. According to 2003 data, Europe is considered the largest consumer and producer of amphetamine. Reports submitted to Interpol by East European member countries mention the production of amphetamine tablets intended for the illicit market in the Middle Eastern countries. Three illegal amphetamine laboratories in parallel producing tablets were discovered on the territory of the Republic of Serbia in 2003. According to UN

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data, one of them was among the largest discovered to date in Europe, with an estimated production of several tons of amphetamine salts. All the discovered tablets had the characteristic "captagon" logo on them, and were never again found on the illegal market of the Republic of Serbia.

Amphetamine ((±)-2-amino-1-phenylpropane), one of the oldest synthetic stimulants, was first synthesized in 1887. The synthesis of amphetamine by the Leuckart method[1] is most commonly performed illegally and is accompanied by varying levels of impurities in the final product, depending on the quality of the starting materials, route of synthesis, reaction conditions, extent of purification of the final product and, above all, on the skills of the clandestine chemist.[2–8]

"Captagon" is a trademark of a drug containing the active substance fenethylline hydrochloride, a theophylline derivative of amphetamine having effects similar to those of amphetamine. It is used in medicine as a medicament for hyperactivity disorders in children, but is also subject to abuse.[9] The primary market for fenethylline has traditionally been countries located on the Arabian Peninsula, namely Saudi Arabia, Kuwait and Qatar, where fenethylline is one of the most popular drugs among the younger population.[10] Tablets with the "Captagon" logo have also been seized in Turkey, where illegal production was also discovered.[11] In Jordan, a transient country for illicit Captagon tablets, geographically located between the European countries, where they are produced, and the Arabian Peninsula consuming countries, multiple capture of such tablets have been accomplished. Alabdalla in his study determined the chemical composition of those seized tablets.[12] The common point of all the published analyses of "Captagon" tablets is the absence of fenethylline and the presence of amphetamine in combination with caffeine, quinine and several other substances.[10–12]

In this study, the powder substances and tablets seized in police raids on illegal laboratories were analyzed and compared. The results of routine chemical characterization based on the identification of components through FTIR and GC/MS, as well as the results of the determination of organic impurities, in order to determine the route of synthesis, through GC/MS[13,14] are quoted. This is one of the first studies of this type conducted in our laboratory; therefore, identification was made through comparison with bibliographical data[15–20] and NIST database spectra, without any reference standards.

EXPERIMENTAL

Materials and reagents

In this study, 32 types of amphetamine samples from three different criminal cases of illegal production on the territory of the Republic of Serbia were analyzed. From case I, 3 kinds of powder samples (I-10–I-12, from seizures of 6.74, 2.36 and 48 kg, respectively) and 20 types of tablets (total weight of 33.06 kg) of various colors and forms were analyzed (I-1–I-9 and I-13–I-23). From case II, 7 white-colored powder samples (4 kg in 7 separate packets, II-1––II-7), as well as tablets (total weight of 12 kg, II-8) were analyzed. From case III, tablets (III-1)

with the same appearance and content, seized in the tablet production plant, were analyzed. The average weight of a tablet from all three seized batches was 170 mg, while average dimensions were 8 mm in diameter and 3.5 mm in thickness. They were of different colors (brown, cocoa, beige, yellow, pink, pastel pink, ivory, gray and white), and were marked with the "Captagon" logo on one side, and scored on the other, as shown in Fig. 1.

Fig. 1. Photograph of a tablet produced in Serbia.

The D,L-amphetamine reference standard ($C_9H_{13}N\times HCl$) was obtained from the UN (Lipomed, Switzerland). All the reagents used in the study (chloroform, toluene, octadecane, KBr, tris, water) were of analytical grade purity.

Instrumentation

Infrared spectra (450–4000 cm^{-1}) of the compounds were obtained using the KBr disc technique or thin films on KBr plates; Thermo Nicolet 5700 and Spectrum One (Perkin–Elmer) instruments were used for the measurements.

Gas chromatography/mass spectrometry was performed using a ThermoFinnigan TraceGC gas chromatograph interfaced with an ion trap PolarisQ mass spectrometer. One microliter of each extract was injected in the splitless mode using a CombiPal autosampler. The column was an Rtx-5MS capillary column (crossbond 5 % diphenyl–95 % dimethylpolysiloxane); 30 m (*L*)×0.32 mm (i.d.) with a 0.25 μm film thickness. The oven temperature was programmed as follows: initial temperature 90 °C, delay for 1.0 min, ramp to 300 °C at a rate of 8.0 °C min^{-1}, held for a further 10 min). The injection port and transfer line temperatures were set to 250 and 275 °C, respectively. The ion source temperature was set at 230 °C, while the flow rate of He carrier gas was fixed at 1.0 ml min^{-1}. The mass spectrometer was tuned to electron impact ionization (EI); the mass spectra were recorded in intervals from *m*/*z* 30 to 300.

Sample preparation

Standard extraction procedure. Preparation of the sample for conventional chemical characterization was made according to the traditional fractional extraction method, depending on the solubility specific to a particular class of compounds, followed by successive measurement of the extracts or residues by FTIR and/or GC/MS. Traditional wet-chemistry anion tests were used to determine sulfate, phosphate and tartrate.[13]

Extraction of impurities. Amphetamine powder samples (200±5 mg of each sample) and thoroughly crushed whole pills (average mass 170±5 mg) were dissolved in Tris buffer (4.0 ml, 0.10 M, pH 8.10) and the mixture was shaken for 10 min. Toluene (200 μl) containing octadecane as internal standard (10 μg ml^{-1}) was added and the test tube shaken for a further 10 min and then centrifuged at 3000 rpm for 3.0 min. An aliquot of the organic layer was analyzed by GC/MS.

RESULTS AND DISCUSSION

Powder substances from case I were identified by infrared spectrometry as amphetamine tartrate (I-10), amphetamine sulfate (I-11) and mixture of amphetamine sulfate and lactose (I-12), while all 7 powder substances from case II (II-1––II-7) were amphetamine phosphate salts. The infrared spectrum of the amphetamine tartrate salt (detected for the first time in Serbia) is shown in Fig. 2.

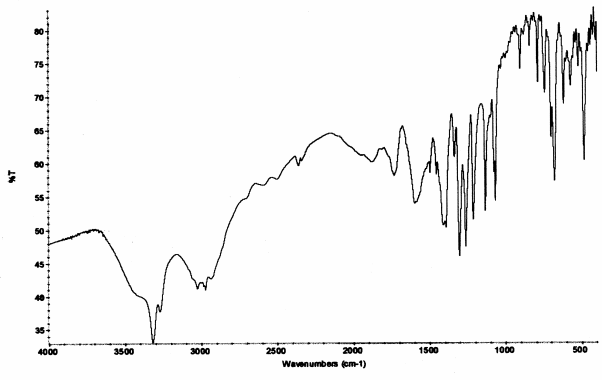

Fig. 2. Infrared spectrum of amphetamine tartrate.

The physical characteristics and logo of the tablets were almost identical in all three cases. Amphetamine (in concentrations ranging from 4.0 to 25 %) was identified in all the analyzed tablets. The chemical characterization of the illegal amphetamine tablets produced in Serbia is shown in Table I; wherein the composition of selected tablets of heterogeneous contents are shown from case I, while II-8 and III-1 refer to cases II and III, where there was no difference in their content and appearance.

TABLE I. Substances detected in nine tablets as representative of the total seized batch

Sample	Color	Amphetamine			Adulterant				Diluents		
		Sulfate	Tartrate	Phosphate	Caffeine	Quinine	Amino-pyrine	Ranitidine	Lactose	Microcr. cellulose	Others[a]
I-4	Pink	√[b]			√		√		√	√	√
I-5	White	√							√	√	√
I-14	Pastel pink	√	√			√			√	√	√
I-20	Gray	√				√	√		√	√	
I-21	Beige	√			√	√		√	√	√	√
I-22	Ivory	√	√		√	√	√		√	√	√
I-23	Yellow	√	√		√	√			√	√	
II-8	Pink			√	√	√			√		√
III-1	Pink			√	√	√			√		√

[a]Povidone and/or starch/stearic acid/glucose; [b]detected

White tablets (5 kinds), which were all from case I but found at different locations in the tablet producing plant, contained solely amphetamine sulfate in higher concentrations, whereas the colored tablets (17 kinds) contained a mixture of amphetamine salts, caffeine and quinine, and, in some cases, aminopyrine and ranitidine. Lactose, microcrystal cellulose, povidone and/or starch/stearic acid/glucose were used as excipients.

It is interesting that within a single clandestine laboratory various salts and huge variations in the diluents, adulterants and excipients were found.

A complete analysis of the impurities present was performed by GC/MS. The compounds were identified based on comparison with reference spectra (Wiley and NIST database) or comparing the ion chromatograms with the spectra from the available literature.

The chromatograms of the accompanying impurities in three types of amphetamine salt samples are shown in Fig. 3.

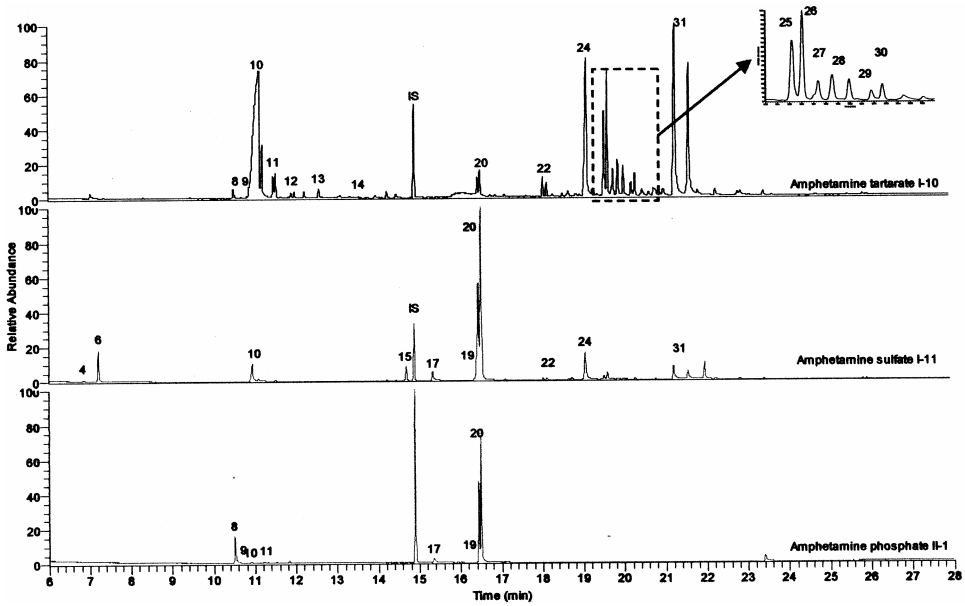

Fig. 3. Chromatograms between 6 and 28 min of impurities in tartrate, sulfate and phosphate amphetamine salts with expansion of the data between 19.30 and 20.70 min, and the identity of the main peaks.

A list of the main impurities and their characteristic mass ions found as a result of GC/MS analysis is given in Table II. The identification numbers associated with the compounds is connected with the annotated peaks in Figs. 3 and 4.

Some of the listed compounds were not visible in the chromatograms (Figs. 3 and 4) because they were either not present or present in only trace amounts in the selected samples. Impurity origins quoted in Table II are not exclusive.

All the samples analyzed in this study contained benzyl methyl ketone (BMK, R_t = 5.3 min), identified using extracted ion chromatograms, although its peak was irresolvable from the much larger amphetamine peak. The main product, amphetamine (R_t = 5.3 min) is not visible within the time range presented in Figs. 3 and 4.

Compounds which eluted at 10.51 and 10.84 min in an abundance ratio of about 5:1 were identified as 4-methyl-5-phenylpyrimidine (8) and 4-benzylpyrimidine (9). These are impurities connected entirely with the Leuckart method of

amphetamine synthesis.[8] The peak eluting at 11.13 min retention time is *N*-formylamphetamine (10), which can, when remaining in large quantities as a consequence of incomplete hydrolysis, mask the presence of pyrimidine derivatives under the given chromatographic conditions.

TABLE II. Compounds detected in samples through gas chromatograph/mass spectrometry

Compound	*m/z*	R_t	Origin
Amphetamine	44, 91, 120	5.35	Major product
Benzyl methyl ketone (P2P)	43, 91, 134	5.35	Precursor
Methamphetamine	58, 91, 92, 65	6.08	By-product
N-Ethylamphetamine	72, 44, 91	6.84	By-product
N,*N*-Dimethylamphetamine	72, 91, 65	7.01	By-product
Isopropylamphetamine	86, 44, 91, 120	7.22	By-product
Ephedrine/pseudoephedrine	58, 77, 105	9.04	Adulterant/ /contaminant
4-Methyl-5-phenylpyrimidine	170, 169, 102, 115	10.51	By-product
4-Benzylpyrimidine	169, 170, 115, 91	10.84	By-product
N-Formylamphetamine	118, 72, 91, 44	11.13	Intermediate
Unidentified-11	198, 197, 115, 116	11.54	Unknown
N-Formylmethamphetamine	86, 58, 118	11.91	Intermediate
Unidentified-13	100, 72, 44	12.58	Unknown
1,3-Diphenyl-2-propanone	91,65, 119, 210	13.53	Impurity BMK (P2P)
N-(*β*-Phenylisopropyl)benzaldimine	132, 105, 91	14.68	By-product
Octadecane	57	14.90	IS
1,3-Diphenylisopylamine	120, 91, 103	15.34	By-product
Caffeine	194	15.84	Adulterant
α-Methyldiphenethylamine	148, 105, 91	16.40	By-product
Bis(*β*-phenylisopropyl)amine[a]	162, 91, 119, 44	16.42, 16.50	By-product
Aminopyrine	231, 97, 56	17.06	Adulterant
N,*N*-Bis(*β*-phenylisopropyl)methylamine[a]	176, 91, 58, 119	18.03, 18.13	By-product
N-benzoylamphetamine	105, 148, 77, 118	18.62	By-product
Unidentified-24	44, 91, 162, 65	19.10	Unknown
Pyridine P1[b]	273	19.51	By-product
Pyridine P2[b]	272, 273	19.60	By-product
Pyridine P3[b]	258, 259	19.73	By-product
Pyridine P4[b]	258	19.85	By-product
Pyridine P5[b]	258	19.99	By-product
Pyridine P6[b]	272	20.27	By-product
N,*N*-Bis(*β*-phenylisopropyl)formamide[a]	190, 91, 119, 162	21.20, 21.56	By-product
Unidentified-32	91, 132, 133, 222	26.24	Unknown
Quinine	136	26.69	Adulterant

[a]Stereoisomers; [b]temporarily identified compound

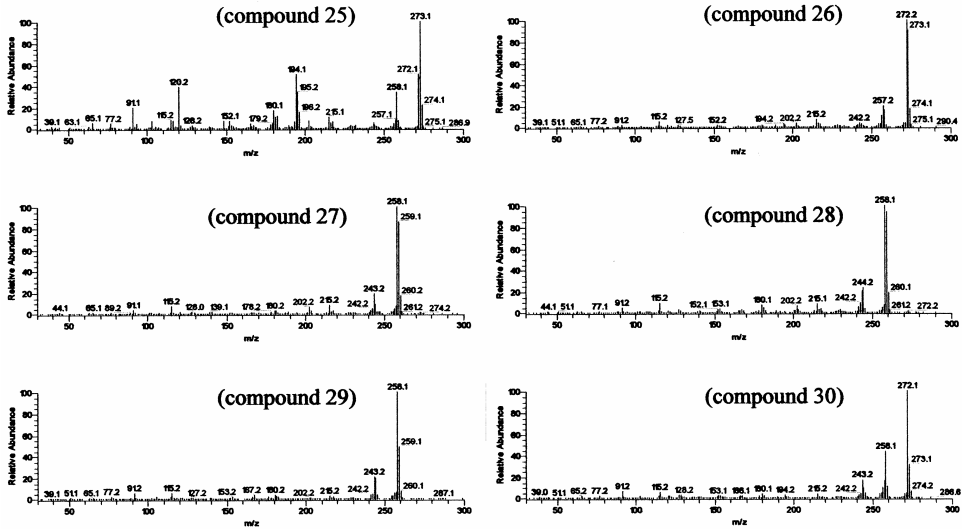

Fig. 4. Profiling of selected tablets with the identity of the major peaks.

Three pairs of peaks eluting at 16.42/16.50, 18.03/18.13, and 21.20/21.56 min show the elution characteristics of non-resolved stereoisomers and the mass spectra of bis(*β*-phenylisopropyl)amine (20), *N,N*-bis(*β*-phenylisopropyl)methylamine (22) and *N,N*-bis(*β*-phenylisopropyl)formamide (31).

As by-products in the analyzed samples, methamphetamine (R_t = 6.13 min), *N*-formyl methamphetamine (R_t = 11.91 min), *N*-ethylamphetamine (R_t = 6.84 min), *N,N*-dimethylamphetamine (R_t = 7.01 min) and isopropylamphetamine (R_t = 7.22 min) were also found.

The origin of 1,3-diphenyl-2-propanone (R_t = 13.53 min) is the impurity of the starting material BMK (P2P) and it is supposed that 1,3-diphenyl-isopropylamine (R_t = 15.34 min) was formed in the course of amphetamine synthesis as the aminated derivative of the above mentioned ketone.

For the following group of compounds, the identification approach had a temporary character: in the time interval between 19 and 21 min (Fig. 3), a group of compounds elute showing poor mass spectra with fragmentation with base peaks at *m*/*z* 258, 259 or 272, 273 (Fig. 5). The high abundance of such ions could indicate the presence of very stable molecules which do not readily undergo the fragmentation process. The most likely structure of these molecules is composed of the so-called pyridines, well known from the literature on the preparation of amphetamine by the Leuckart synthesis as "high-boiling pyridines".[3,16–18]

Through extraction of ion *m*/*z* 105, a chromatogram was obtained with the peaks of *α*-methyldiphenethylamine (R_t = 16.40 min) and *N*-benzoylamphetamine (R_t = 18.62 min).[18,19]

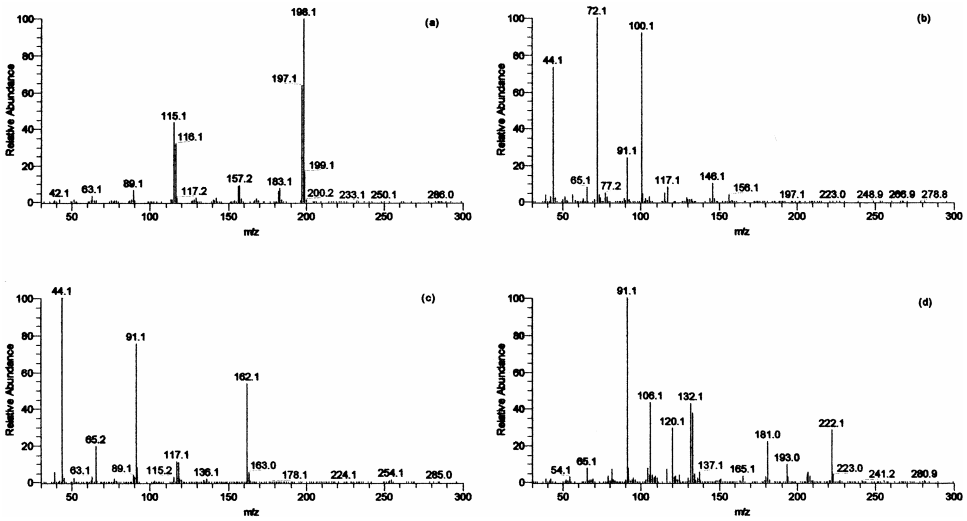

Fig. 5. Mass spectra of the pyridine derivatives with M_r = 259 and 273 g mol^{-1}.

The occurrence of Schiff bases in illicit amphetamine preparations has already been published by Theeuwen and Verweij.[20] These authors stated that imines could be found in every amphetamine synthesis in which P2P was employed as a precursor. Due to their instability in strongly acid environment, after the second step of the Leuckart synthesis, detection of imines in relatively small quantities is to be expected. *N*-(*β*-Phenylisopropyl)benzalimine was also identified in the tablets, although only in traces, at 14.68 min.

Neither a comprehensive bibliographical search, nor spectral analysis, resulted in the final identification of compounds marked with the numbers 11, 13, 24 and 32, the mass spectra of which are shown in Fig. 6. Unidentified compound 11, detected in all the samples, has the fragmentation of 5-benzyl-2,3-dimethylpyrazine or 2-benzyl-5,6-dimethylpyrazine; as for compound 13, it is assumed to be *N,N*-diethylamphetamine. The unidentified compound 24 is also noteworthy; in all the analyzed samples it eluted at 19.09 min, with a fragmentation very similar to that of compound 20, but with different relative ion ratios.

Although the amphetamine sulfate and tartrate originated from the same illegal production, a difference in their impurity levels was evident. It was revealed that although compound 20 was the dominant impurity in amphetamine sulfate, it was only found in traces when compared to compound 10 and its methylized (22) and formylized (31) derivatives in the tartrate salt.

The amphetamine phosphate samples from case II were poorer and only compound 20 was detected as the main impurity, with traces of compound 8. The absence of compound 10 was easily noticeable, which corresponds to earlier findings (internal unpublished results) connected with the establishment of proofs in the production plant itself, which indicated a thorough approach to the synthesis,

where control of the hydrolysis stage of *N*-formylamphetamine to amphetamine by TLC was performed in the plant. The conclusion that the synthetic route was Leuckart reaction was made because of the presence of compound 8.

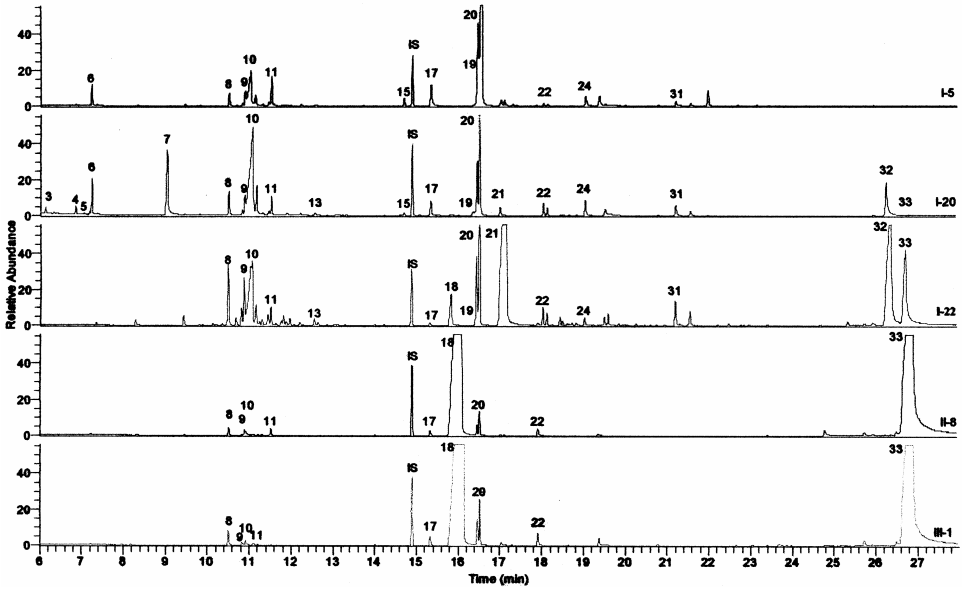

Fig. 6. Mass spectra of unidentified compounds: (a) compound 11; (b) compound 13; (c) compound 24; (d) compound 32.

Among the impurities detected in the analyzed tablets are all the impurities also contained in the powder substances (compounds 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 17, 19, 20, 22, 24 and 31 listed in Table II and shown in Figs. 3 and 4). The impurity profiling chromatograms of selected tablets from case I, II and III, the chemical characterization of which were given in Tables I and II, are shown in Fig. 4.

The analyzed white tablets (5 types) found at different locations in the tablet--making plant (case I) had a relatively similar characteristic impurity profile, as they contained solely amphetamine sulfate. The main impurity was compound 20. The content of impurities, *i.e.*, their relative main impurity concentration ratio, varied more in the colored tablets (15 types), which could be explained by the presence of a mixture of amphetamine salts. However, this evidence is not conclusive, as the origin of the production batches could not be determined. The main impurities in these cases were compounds 10, 20 and 8.

In some tablets, ephedrine/pseudoephedrine was identified (R_t = 9.04 min), for which it is supposed that it was present as a contaminant from the tablet-making process, or a deliberately added adulterant.

In tablets containing aminopyrine (Fig. 4, chromatograms I-20 and I-22) the peak at retention time 26.24 min belongs to the unidentified compound 32, the mass spectrum of which is shown in Fig. 6d.

Impurity profiling of tablets from cases II and III (Fig. 4, chromatograms II-8 and III-1) shows their essential similarity in the presence of compound 20, as the main impurity, and compounds 8, 9 and 10, as well as a significant dissimilarity from the profile of all the tablets from case I.

CONCLUSION

It was established that the amphetamines produced in clandestine labs in Serbia were in the form of sulfates, tartrates and phosphates. The amphetamine tartrate form is reported for the first time in the Republic of Serbia. From the results of the analysis of the tablets, it should be emphasized that they contained a mix of amphetamine salts and a great variety of additives. The complex mixtures of additives used included caffeine, quinine, aminopyrine, ranitidine, lactose, glucose, starch, microcrystal cellulose, povidone and/or stearic acid. Although engraved with the usual logo previously encountered in captagon, the tablets did not contain fenethylline. The presence of the synergically acting amphetamine, caffeine and quinine, as well as the characteristic logo, suggest that all the seized quantities were intended for the illegal market as surrogate for captagon. The impurity profiles of all the analyzed samples show that the synthetic route for amphetamine was the Leuckart reaction.

И З В О Д

АНАЛИЗА АМФЕТАМИНА ИЛЕГАЛНО ПРОИЗВЕДЕНОГ У СРБИЈИ

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Форензичка пракса у Републици Србији се први пут срела са илегалном производњом амфетамина 2003. године. У овом раду представљени су резултати хемијске карактеризације 32 врсте узорака амфетамина који потичу из три одвојена случаја у циљу идентификације активних компоненти и адитива. Профилисањем нечистоћа свих узорака помоћу гасно–масене спектрометрије идентификовано је 30 једињења повезаних са амфетамином. Дати су резултати анализа прашкастих тартаратних, сулфатних и фосфатних соли амфетамина као и различито формулисаних таблета. Анализе нечистоћа су показале да је у свим случајевима синтеза амфетамина вршена Leuckart-овом реакцијом.

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