Impurities in illicit amphetamine: a review

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ABSTRACT

The paper reviews the most common synthesis of amphetamines which may be found in illicit traffic. Emphasis is laid on the detection, isolation and identification of impurities in illicit amphetamines through gas chromatography and thin-layer chromatography. The latter method was also used for isolation purposes. Impurities were identified by mass spectral and NMR spectroscopic methods and relevant data are presented.

Introduction

Illegally produced drugs are frequently contaminated, as is readily shown by chromatographic analysis. Contaminations in drugs can be caused by laboratory diet, impurities in the starting chemicals, side- and subsequent reactions, intermediate products, diluents of the drugs and from handling and packing of the drugs. Hence two different approaches can be used for their identification:

(a) The chromatographic data can be collected for comparison purposes in a class of drugs, the so-called "signature" method.

(b) Contaminants of the main compound may be identified.

In this review, attention will be focused on the latter approach, since chemical compounds present in the final amphetamine, due to inadequate purification of the raw product, will give valuable clues to the method of synthesis. In this way, suspected illicit sources of amphetamine can be confirmed and information provided to the police which may contribute to tracking down the illegal production locations.

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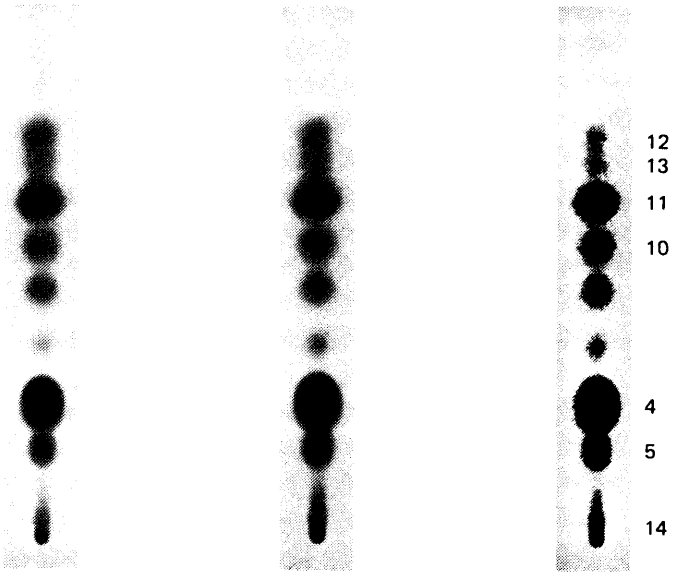
Synthesis of amphetamine

To date, 23 clandestine laboratories have been discovered in the Netherlands [1]. The Leuckart reaction (see figure I) [2] was the most frequently encountered, though in some cases reductive amination of benzyl methyl ketone was found (figure II). No other syntheses such as the oxime or the phenylnitropropene routes were encountered. Only once was a methamphetamine production location found; in this instance the substance was prepared by an almost professional procedure [3]. Our findings therefore contrast with those reported in the United States of America, where the accent seems to be on the production of methamphetamine [4]. Most of the amphetamine was intended for the markets of the Federal Republic of Germany and Scandinavia; only a minor portion of it was sold in the Netherlands.

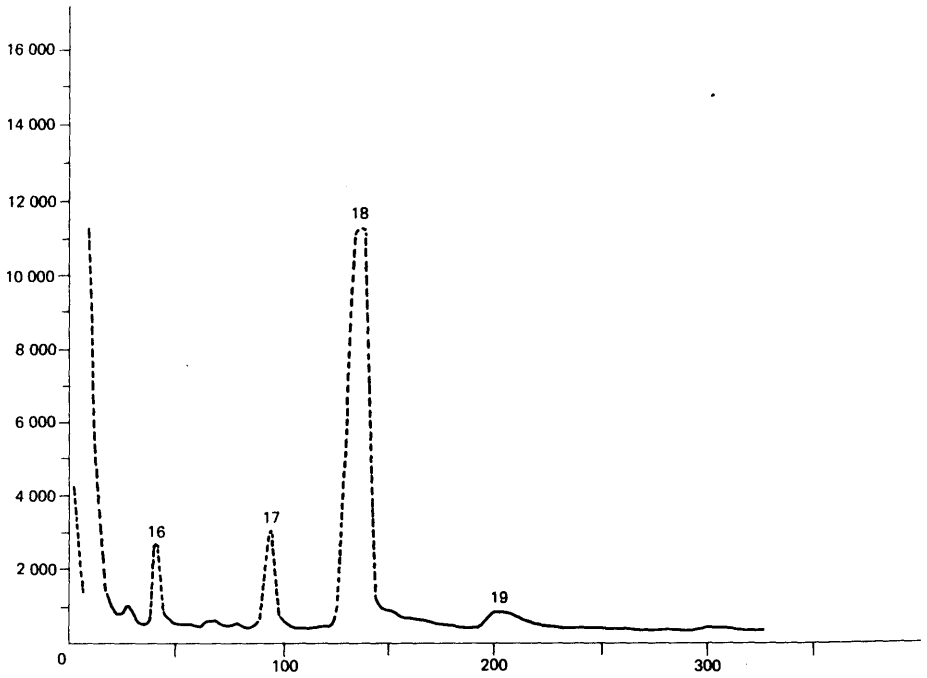


4 4-methyl-5-phenylpyrimidine
5 5-benzylpyrimidine
9 2,4-dimethyl-3,5-diphenylpyridine
10 2,6-dimethyl-3,5-diphenylpyridine
11 4-methyl-5-phenyl-2-(phenylmethyl)pyridine
12 2-methyl-3-phenyl-6-(phenylmethyl)pyridine
13 2,4-dimethyl-3-phenyl-6-(phenylmethyl)pyridine
14 2-benzyl-2-methyl-5-phenyl-2,3-dihydropyrid-4-one

Compounds 4 and 5 were stained yellow by spraying the spots with 1% p-dimethylaminobenzaldehyde in 50% sulphuric acid and heating the plate at 100°C in a drying box. The three pyridine derivatives with no α-hydrogens were stained blue-purple with iodoplatinate reagent, the other two pyridines and pyrimidines became yellow or brown. With the latter reagent the pyridone turns reddish.

Figure I

Thin-layer chromatogram of weakly basic fraction on Merck precoated silica gel 60 F-254 with hexane/ether (50 + 50) as eluent



16 N-acetylamphetamine
17 N-(β-phenylisopropyl)benzaldimine
18 N-(β-phenylisopropyl)benzyl methyl ketimine
19 1-oxo-1-phenyl-2-(β-phenylisopropylimino)propane

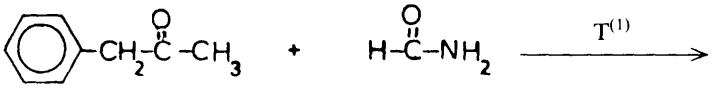
Chromatographic conditions were as follows: 2 metre s.s. (Ø 1/8''), column packed with Apiezon/KOH 10%/10% on Chromosorb G DCMS (80–100 mesh), oven temperature 220°C, carrier gas He, flow rate 10 ml/min.

Figure II

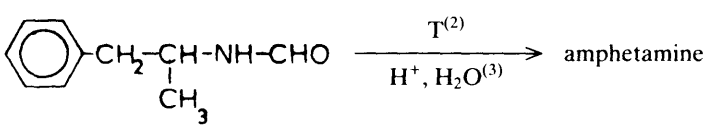
Computer reconstructed chromatogram of the low-pressure, low-temperature reductive amination reaction mixture

The Leuckart reaction

This reaction can be described by the following scheme:



benzyl methyl ketone formamide

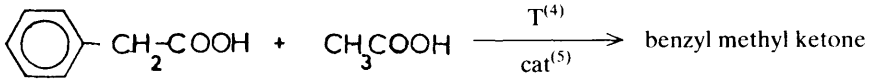


N-formylamphetamine

in which (1): 180–195°C.
(2): 90–125°C.
(3): H_2SO_4, HCl (diluted).

Reaction conditions can vary [5], formamide being sometimes replaced by ammonium formate [6] or a mixture of ammonia and formic acid [7]. It is clear that, due to the many possibilities for condensation of benzyl methyl ketone with formamide, a host of other products can be expected. This gives rise to a large number of impurities in the more or less purified amphetamine. In practice, approximately 50% amphetamine is recovered [8]; with the formic acid variant, recovery of about 30% is feasible [9]. Methamphetamine prepared according to this method contains fewer impurities as the N-methylformamide, used as starting material, has fewer possibilities for condensation with benzyl methyl ketone.

Benzyl methyl ketone may be purchased from wholesale dealers, but can also be easily synthesized [10].

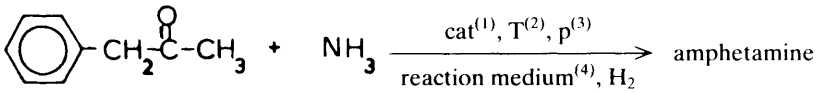


in which (4): 450°C.
(5): ThO_2.

Other methods have also been reported [11–13]. Dibenzyl ketone is a side-product of this reaction and its presence in amphetamine is readily understood if benzyl methyl ketone is produced in this way.

The reductive amination of benzyl methyl ketone

Benzyl methyl ketone can be aminated as follows [14]:

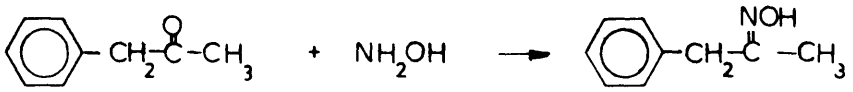


in which (1): Raney-Ni, Pt, Al powder in the presence of $HgCl_2$, nickel plated Zn.
(2): 20–170°C.
(3): 1–130 Atm.
(4): Ethanol or methanol.

Reaction conditions reported in the literature differ widely [15–18]. To date, only low-pressure and low-temperature aminations have been found in this country. Recoveries of approximately 90% can be reached if optimized reaction conditions are carefully maintained and freshly prepared Raney-nickel used [19]. In this case there are fewer impurities than in the Leuckart route.

The oxime route

Upon reaction with hydroxylamine, benzyl methyl ketone gives the oxime, which can subsequently be hydrogenated to yield amphetamine [20].



benzyl methyl ketone oxime

$\xrightarrow[T^{(1)}, p^{(2)}, (H)^{(3)}]{}$ amphetamine

in which (1): 20–170°C.

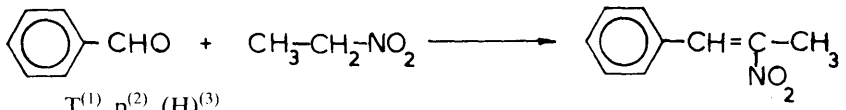
(2): 1–130 Atm.

(3): Na (amalgamated), Na (absolute ethanol), $LiAlH_4$, or H_2 and Raney-Ni or Ni or Fe or nickel plated Zn.

Great differences are reported in the reaction conditions [21–23]. Electrolytical reduction has also been described [24]. However, this route has to our knowledge not been put into practice for the illegal production of amphetamine. Recoveries of up to 90% have been reported.

The phenylnitropropene route

Condensation of benzaldehyde with nitroethane yields 1-phenyl-2-nitropropene. Hydrogenation of the double bond and reduction of the nitro-group give the amphetamine.



$\xrightarrow[\text{reaction medium}^{(4)}]{T^{(1)}, p^{(2)}, (H)^{(3)}}$ amphetamine

in which (1): 20–100°C.

(2): 1–80 Atm.

(3): $LiAlH_4$, H_2 and Raney-Ni or Pd/C.

(4): CH_3OH; C_2H_5OH; $H_2O/HCOOH$; CH_3COOH/C_2H_5OH.

Reaction conditions vary widely [25, 26] and electrolytical reduction has been mentioned [27]. This synthesis has been of importance in Sweden in illegal amphetamine production [28].

We have given a rather extensive description of some methods for the production of illegal amphetamine for which the starting material can be purchased easily and in which the chemical operations are not too complicated. Many other synthetic routes for amphetamine, often with obscure or intricate chemicals, are known,[1] but in this context are of lesser importance.

[1] A literature search is available for the interested reader.

Detection, isolation and identification of impurities in illicit amphetamine

To obtain impurities in sufficient quantities for analysis, the raw material was diluted with water and acidified with tartaric acid. This solution was extracted with ether, and the ether layer was extracted with 4N hydrochloric acid. A portion of the hydrochloric acid solution was made alkaline and extracted with chloroform to give fraction A (weak bases). A quantity of the ether layer was evaporated to give fraction B (neutral substances). Likewise, the tartaric acid solution was made alkaline and extracted with chloroform to give fraction C (strong bases). All three fractions were investigated, but our attention was directed mainly to the weak bases.

For a quick survey of the impurities present, thin-layer chromatography is the method of choice. Several eluents, e.g. cyclohexane-benzene-diethylamine (75:15:10), hexane-acetone (50:50) or (80:20), hexane-ether (50:50) or (90:10) and methanol-ammonia 25% (99:1) were tried, of which hexane-ether (50:50) gave the best results (see figure I).

Gas chromatography on 2% OV-17 or 10%/10% Apiezon/KOH columns in an isothermal (200°C) or better, in a programmed mode (100–250°C, 2°C/min) was performed (see figure II).

Isolation of the compounds with a purity of better than 95% can be achieved by repetitive thin-layer chromatographic runs, using a combination of the above-mentioned eluents. In the literature, a high-performance liquid chromatographic (HPLC) method for these purposes has been reported [28]. The isolated compounds were identified by a combination of low- and high-resolution mass spectrometry, and ^{1}H and ^{13}C NMR spectroscopy [29–34].

None the less, the described isolation procedure does not always give the desired results. The gas chromatograph/mass spectrometer combination can then be used in the low- and the high-resolution mode. Compounds, whose structures were tentatively derived from mass spectral data, were synthesized. In most instances the problem of structure elucidation was then solved by comparison of the chromatographic and the mass spectral data of the synthesized substances with those whose structures are to be elucidated [35, 36].

The use of low-resolution mass spectral data alone in structure determination is not recommended. It can easily lead to erroneous results because the mass spectra of the various compounds can be very similar.

Impurities found in illicit amphetamine prepared via the various synthetic routes

The impurities found so far in the Leuckart synthesis and the reductive amination routes are presented in tables 1 and 2.

Remarkably few impurities are known of the other two routes. Strömberg reported [28] the presence of phenylacetoxime in a seizure of amphetamine prepared by the electrolytic reduction of phenylnitropropene, while Kotera [37] has indicated 2-methyl-3-phenylaziridine and 2-benzylaziridine as by-products in the reduction of phenylacetoxime with lithium aluminium hydride.

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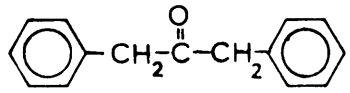
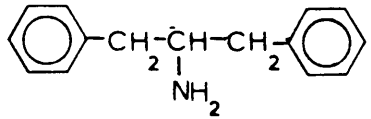
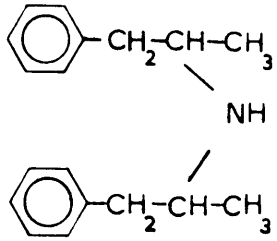
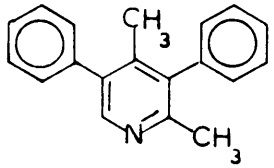
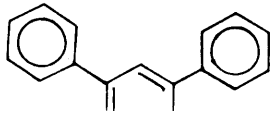
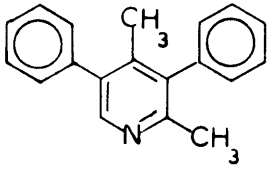
Table 1

Reported impurities in amphetamine synthesized by the Leuckart method

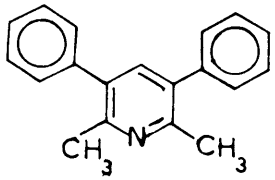
Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*
46.0	CH_2O_2	Formic acid HCOOH	a	4
134.1	$C_9H_{10}O$	Benzyl methyl ketone (phenylacetone, 1-phenylpropanone) 	a	4
163.1	$C_{10}H_{13}NO$	N-formylamphetamine 	b/d	4
170.1	$C_{11}H_{10}N_2$	4-Methyl-5-phenylpyrimidine 	c/d	29
170.1	$C_{11}H_{10}N_2$	4-Benzylpyrimidine 	c/d	29

Table 1 (continued)

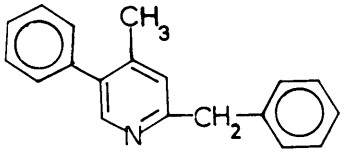
Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*
210.1	$C_{15}H_{14}O$	Dibenzylketone (1,3-diphenylacetone, 1,3-diphenylpropanone) 	c	4
211.1	$C_{15}H_{17}N$	α-Benzylphenethylamine (dibenzylmethylamine) 	c	39
253.2	$C_{18}H_{23}N$	Di-(β-phenylisopropyl)amine 	c	12/40
259.1	$C_{19}H_{17}N$	2,4-Dimethyl-3,5-diphenylpyridine 	c	31
259.1	$C_{19}H_{17}N$	2,6-Dimethyl-3,5-diphenylpyridine 	c	31



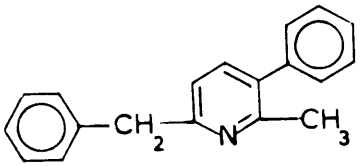
259.1	$C_{19}H_{17}N$	2,6-Dimethyl-3,5-diphenylpyridine	c	31



259.1	$C_{19}H_{17}N$	4-Methyl-5-phenyl-2-(phenylmethyl)pyridine	c	31



259.1	$C_{19}H_{17}N$	2-Methyl-3-phenyl-6-(phenylmethyl)pyridine	c	32



273.2	$C_{20}H_{19}N$	2,4-Dimethyl-3-phenyl-6-(phenylmethyl)pyridine	c	32

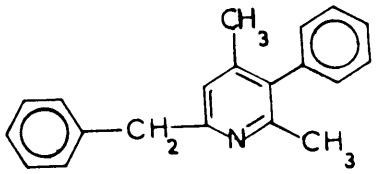
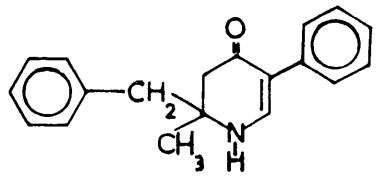
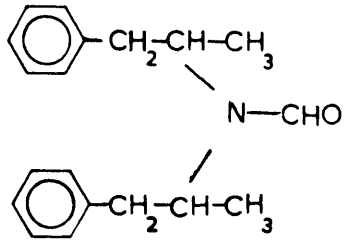


Table 1 (continued)

Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*
277.1	$C_{19}H_{19}NO$	2-Benzyl-2-methyl-5-phenyl-2,3-dihydropyrid-4-one 	c	30
281.2	$C_{19}H_{23}NO$	N,N-di-(β-phenylisopropyl)formamide 	c	41

Note: a = starting material; b = intermediate product; c = product of side reaction; d = "route specific" impurity.

Table 2

Reported impurities in amphetamine synthesized by low-pressure and low-temperature reductive amination

Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*

Table 2

Reported impurities in amphetamine synthesized by low-pressure and low-temperature reductive amination

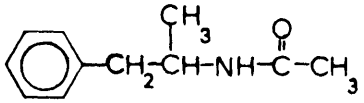
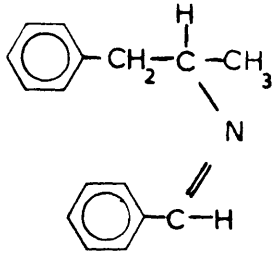
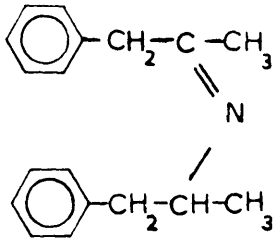
Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*
177.1	$C_{11}H_{15}NO$	N-acetylamphetamine 	b	36
223.1	$C_{16}H_{17}N$	N-(β-phenylisopropyl)benzaldimine 	a	35
251.2	$C_{18}H_{21}N$	N-(β-phenylisopropyl)benzyl methyl ketimine 	a	35

Table 2 (continued)

Molecular weight	*Formula*	*Name and structure*	*Remarks*	*References*
253.2	$C_{18}H_{23}N$	Di-(β-phenylisopropyl)amine	a	14/40
265.2	$C_{18}H_{19}NO$	1-Oxo-1-phenyl-2-(β-phenylisopropylimino)propane	b	36
268.2	$C_{18}H_{20}O_2$	2,4-Dihydroxy-1,5-diphenyl-4-methylpentene-1	b	34

Note: a = intermediate product; b = product of side reaction.

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Molecular w
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Mass spectrometric and ^2H NMR spectroscopic data

In table 3 the mass spectral fragmentations are given for the compounds described in tables 1 and 2 (m/e of the most intense fragments are in decreasing order of intensity).

In table 4, ^1H NMR spectroscopic data are given for most of the impurities in tables 1 and 2.

Table 3

Mass spectral data of impurities (m/e of most intense fragments in decreasing order of intensity)

Molecular weight	*Fragments*	*References*
46.0	B 46 – 29 – 45 – 18 – 28 – 44 – 17 –	42
134.1	B 91 – 134 – 92 – 43 – 65 – 77 – 89 –	4
163.1	B 72 – 44 – 118 – 91 – 65 –	4
170.1	B 170 – 169 – 102 – 115 – 116 – 171 – 51 –	29
170.1	B 169 – 170 – 91 – 115 – 142 – 65 – 116 –	29
210.1	B 91 – 65 – 39 – 119 – 92 – 63 – 89 –	4
211.1	B 120 – 91 – 42 – 77 – 103 – 65 – 51 –	33
253.2	B 91 – 44 – 162 – 119 – 65 – 41 –	34
259.1	B 259 – 260 – 244 – 115 – 215 – 202 – 116 –	31
259.1	B 259 – 260 – 115 – 244 – 101 – 202 – 215 –	31
259.1	B 258 – 259 – 243 – 244 – 260 – 115 – 91 –	31
259.1	B 258 – 259 – 180 – 244 – 260 – 182 – 115 –	31
273.2	B 272 – 273 – 258 – 55 – 57 – 71 – 79 –	32
277.1	B 186 – 91 – 158 – 143 – 187 – 65 – 115 –	30
281.2	B 91 – 190 – 119 – 72 –	41
177.1	B 44 – 86 – 119 – 91 – 65 – 58 – 51 –	36
223.1	B 132 – 105 – 91 – 77 – 65 – 51 – 39 –	35
251.2	B 91 – 119 – 160 – 41 – 65 – 77 – 39 –	35
265.2	B 91 – 119 – 43 – 105 – 77 – 160 – 41 –	36
268.2[a]	B 91 – 159 – 131 – 65 – 115 – 51 – 39 –	34

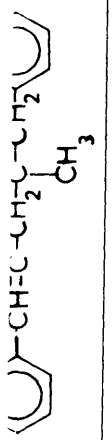
Note: B = base peak. In most cases 70 eV electron impact spectra are given.

[a] The actual mass spectrum is of the dehydrated compound.

Table 4

^1H NMR spectroscopic data and assignments for most of the impurities

Molecular weight	*Solvent*	*NMR data and assignment (δ-values, ppm)*	*References*
46.0	D_2O	8.22 (s): *H*COOH	4
134.1	CCl_4	2.00 (s,3H): CH_3; 3.56 (s,2H): CH_2; ~7.2 (5H): phenyl	4
163.1	CCl_4	1.08 (d,3H, J=7Hz): CH_3; 2.70 (m,2H): CH_2; 4.20 (m,1H): CH; 7.12 (5H): phenyl; 7.57 (ss,1H): NH[a]; 7.85 (s,1H): *H*CONH	
170.1	$CDCl_3$	2.5 (s,3H): CH_3; 7.4 (5H): phenyl; 8.6 (s,1H): 6–H; 9.1 (s,1H): 2–H	29
170.1	$CDCl_3$	4.0 (s,2H): CH_2; 7.0 (d,1H, J=6Hz): 5–H; 7.2 (5H): phenyl; 8.6 (d,1H, J=6Hz): 6–H; 9.2 (s,1H): 2–H	29



Note: a = intermediate product; b = product of side reaction.

Table 4 (continued)

Molecular weight	*Solvent*	*NMR data and assignment (δ-values, ppm)*	*References*
210.1	CCl_4	3.53 (s,4H): $2CH_2$; 7.0–7.5 (10H): 2 phenyl	4
211.1	D_2O	3.00, 3.02 (4H): $2CH_2$; 3.0–4.0 (m,1H): CH; 7.37 (10H): 2 phenyl	39
259.1	$CDCl_3$	1.90 (s,3H): 4–CH_3; 2.27 (s,3H): 2–CH_3; 7.0–7.5 (10H): 2 phenyl; 8.22 (s,1H): 6–H	31
259.1	$CDCl_3$	2.53 (s,6H): $2CH_3$; 7.35 (ψ-s,11H): 4–H+2 phenyl	31
259.1	$CDCl_3$	2.17 (s,3H): CH_3; 4.13 (s,2H): CH_2; 6.97 (s,1H): 3–H; 7.3 (10H): 2 phenyl; 8.35 (s,1H): 6–H	31
259.1	$CDCl_3$	2.50 (s,3H): CH_3; 4.17 (s,2H): CH_2; 6.90 (d,1H, J=8Hz): 5–H; 7.3 (d,1H, J=8Hz): 4–H	32
273.2	$CDCl_3$	1.92 (s,3H): 4–CH_3; 2.25 (s,3H): 2–CH_3; 4.12 (s,2H): CH_2; 6.78 (s,1H): 5–H; 7.0–7.5 (10H): 2 phenyl	32
277.1	$CDCl_3$	1.20 (s,3H): CH_3; 2.50 (s,2H): CH_2; 2.83 (AB,2H, J=12Hz): cycl.–CH_2; 5.63 (d,1H, J=7Hz): NH; 7.2 (11H): 6–H+2 phenyl	30
281.2	$CDCl_3$	1.10 (d,3H): CH_3; 1.21 (d,3H): CH_3; 2.55, 2.83, 2.88 (4H): $2CH_2$; 3.49, 3.93 (2H): 2CH; 6.9–7.5 (10H): 2 phenyl; 8.22 (s,1H): *H*CON=	41
268.2[b]	$CDCl_3$	1.32 (s,3H): CH_3; 2.90 (s,2H): 3–CH_2; 3.05 (s,2H): 5–CH_2; 3.73 (s,2H): 1–CH_2; ~4.9 (bs): OH; 7.0–7.4 (10H): 2 phenyl	34

Note: s = singlet; d = doublet; m = multiplet; ss = double singlet; ψ-s = pseudo-singlet; bs = broad singlet; AB = a proton pair for which the difference in chemical shift is of the same order as the coupling constant; J = coupling constant.

[a] A double singlet, with unequal intensities, is observed from two isomers due to restricted rotation about the C–N bond.

[b] The data are for the keto-form, which dominates in solution.

Conclusions

Among the impurities identified so far in illicit amphetamine produced by the Leuckart synthesis, some compounds such as N-formylamphetamine, 4-methyl-5-phenylpyrimidine and 4-benzylpyrimidine can be designated as "route specific" [38], i.e. by their presence they give direct evidence of the synthesis used. In particular 4-methyl-5-phenylpyrimidine is extremely well suited for this purpose as we found it present in high quantities in nearly all illicit amphetamines analysed. Thin-layer chromatography, preceded by the extraction described above, is the method of choice at this point in the analysis. The use of the Leuckart route can then further be established by looking for some of the other impurities mentioned in tables 1 and 2. This should be done by the gas chromatographic/mass spectrometric method in the low-resolution mode, making use of the mass spectral data in table 3. The variation in mass spectral data between classes of compounds is specific enough to ascertain the class. Within a class the various compounds must first be isolated and then structure elucidation is straightforward by NMR spectroscopic methods.

	References
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H):	39
H):	31
	31
7.3	31
Hz):	32
H_2;	32
Hz): +2	30
H): .22	41
H_2; : 2	34

= broad singlet; upling constant;

d rotation about

The art of low-pressure, low-temperature reductive amination seems somewhat underdeveloped as compared with the Leuckart route. The impurity, 2,4-dihydroxy-1,5-diphenyl-4-methylpentene-1, was incidentally found to originate in our opinion from imperfect chemical handling. Of the other five impurities in table 2, Haskelberg [14] already mentioned di-(β-phenylisopropyl)amine as an impurity in reductive amination (the compound is already known from the Leuckart route). The intermediate product N-(β-phenylisopropyl)benzyl methyl ketimine is, to our knowledge, present in fair quantities in all amphetamines produced by this method. It was pointed out, however, that N-(β-phenylisopropyl)benzyl methyl ketimine together with N-acetylamphetamine, N-(β-phenylisopropyl)benzaldimine and 1-oxo-1-phenyl-2-(β-phenylisopropylimino)propane can also be obtained by refluxing equivalent amounts of amphetamine and benzyl methyl ketone in benzene [34, 35]. The presence of N-(β-phenylisopropyl)benzyl methyl ketimine on its own by no means gives substantial evidence of the reductive amination route to amphetamine. The simultaneous presence of di-(β-phenylisopropyl)amine and N-(β-phenylisopropyl)benzyl methyl ketimine separated by gas chromatography using capillary columns and then identified by mass spectroscopy using the difference between their molecular ions m/e 253 and m/e 251 and the abundant m/e 162 and m/e 160 ions, leads us to conclude that a hydrogenation step at least was involved. This evidence of organic impurities may possibly be supported by a higher level of inorganic impurities from the catalyst used in the production of amphetamine.

Due to scarcity of published data no further remarks about the oxime and phenylnitropropene route are given here.

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