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Weakly Basic Impurities in Illicit Amphetamine

In the last two years several illegal workshops for the production of amphetamine were discovered in the Netherlands. The substance was mainly prepared for the Scandinavian and German drug markets, but a portion was sold in Holland and some of it was seized by the police.

The product did not have the pure white appearance of the pharmaceutical quality; it was off-white, sometimes a bit yellow, and smelled peculiar and unpleasant. As several illicit production locations were raided, it became clear that the Leuckart synthesis had been used. Probably just one man had provided the recipe to a chain of workshops, although minor variations were found in the "cookbooks" recovered. In almost all cases the starting materials were obtained from regular wholesale firms.

The general procedure was as follows: benzyl methyl ketone (2 to 6 litres) was heated with twice its volume of formamide at about 195°C for approximately 6 h. After cooling the reaction mixture was washed with water and hydrolyzed with twice its volume of concentrated hydrochloric acid at boiling temperature during 7 to 8 h. To the cooled solution 50% sodium hydroxide was added until an ammoniacal odor was perceived. The oily layer was steam-distilled and the purified amphetamine dissolved in methanol (1 litre in 5 litres). Then 36 to 50% sulfuric acid was added until neutral reaction precipitated the amphetamine sulfate, which was centrifuged and dried in a drying box. The product, which is white as it precipitates, turns yellowish upon drying.

It is well known that side reactions and incomplete conversions can easily occur in the Leuckart synthesis and a host of impurities can thus be anticipated in illegal amphetamine. The actual presence depends on whether or not the crude amphetamine is adequately purified. Thin-layer chromatography of the illicit amphetamine showed some additional spots strongly absorbing under ultraviolet light. A systematic investigation was initiated to isolate and identify these impurities, for which material originating from illegal workshops was used.

It stands to reason that the mere presence of impurities in amphetamine points to illegal preparation and that by identifying these by-products information is gathered about the method of synthesis. Besides, a further knowledge of the impurities could be helpful in avoiding possible interference by the by-products in the analytical techniques used by the forensic chemist analyzing the amphetamine. Furthermore, the detection of these by-

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products elsewhere, in soil or water, can support the assumption that amphetamine production is going on in the neighborhood.

Several impurities found in amphetamine and methamphetamine of illicit origin are mentioned in the literature. Starting materials and their impurities like benzyl methyl ketone, dibenzyl ketone, formamide, methylformamide, formic acid, and methylamine have been found [*1*]. Intermediate products such as *N*-formylamphetamine and *N*-formylmethamphetamine have been reported [*1*], and products like *N,N*-dimethylamphetamine [*1*], di-(1-fenylisopropyl)amine [*1*], (1,3-diphenylisopropyl)methylamine [*1–4*], and benzylamine[3] have been described. This paper reports the isolation and identification of compounds (Table 1, Fig. 1) newly discovered as impurities in amphetamine obtained by the Leuckart reaction and describes the chromatographic properties, the mass spectra, and the nuclear magnetic resonance (NMR) spectroscopic data of these compounds.

TABLE 1—*Nomenclature used throughout the text.*

1	4-benzylpyrimidine
2	5-methyl-4-phenylpyrimidine
3	4-methyl-5-phenyl-2-benzylpyridine
4	2,4-dimethyl-3,5-diphenylpyridine
5	2,4-dimethyl-3-phenyl-6-benzylpyridine
6	2-methyl-3-phenyl-6-benzylpyridine
7	2,6-dimethyl-3,5-diphenylpyridine
8	2-benzyl-2-methyl-5-phenyl-2,3-dihydropyrid-4-one

Experimental Procedures

Isolation

For the isolation of those compounds we were interested in, we started with an extraction of the crude, not yet steam-distilled, amphetamine. A quantity of this product was diluted with 20 times its volume of water. Enough tartaric acid was added to obtain a weakly acidic solution, which was extracted with twice its volume of ether. The ethereal solution was extracted four times with a tenth of its volume of 4*N* hydrochloric acid; the combined hydrochloric acid fractions were made alkaline with sodium hydroxide and extracted with chloroform. The organic solvent was freed from water by filtering over phase-separating paper and evaporated. The residue was dissolved in ether. In this way the weakly basic components in the reaction mixture could be separated from the neutral and more basic substances. Gas chromatographic and thin-layer runs of this fraction are given in Figs. 2 and 3, respectively.

From the ethereal solution Substances 1 through 7 could be isolated with a purity better than 95% by repeatedly performing thin-layer chromatography. Precoated Merck silica gel 60 F-254 plates were used with the following solvents: hexane/ether (50:50), hexane/ether (90:10), and hexane/acetone (50:50).

In all instances a second chromatographic run with another eluant had to be done to achieve the desired purity of the compounds. For full details refer to Refs *5* to *8*. Compound 8 could be isolated by diluting the ethereal solution with hexane, and after a few days in the refrigerator the compound precipitated.

[3] H. Huizer and A. B. E. Theeuwen, personal communications.

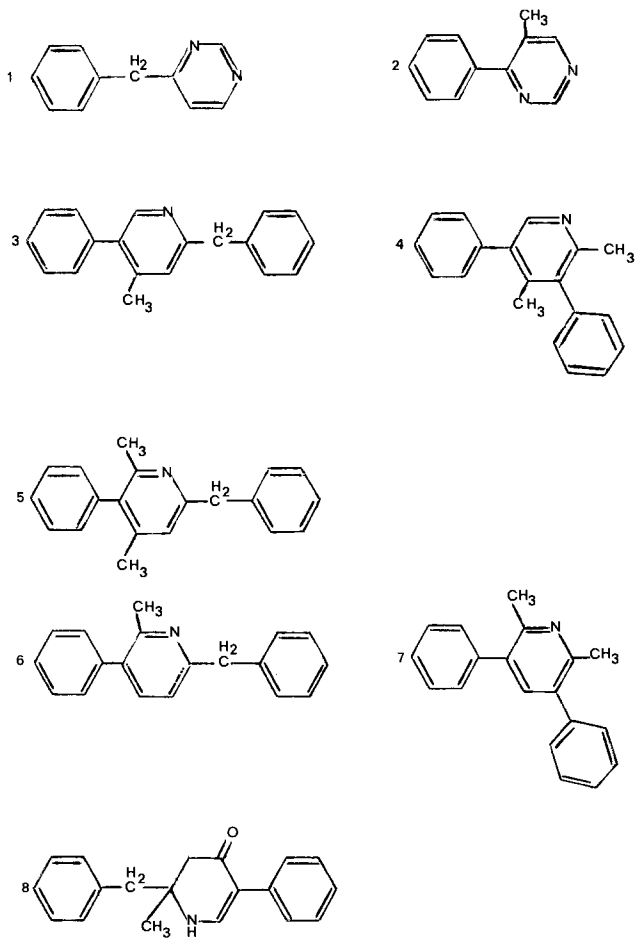

FIG. 1—*Structure of compounds; numerals correspond to the listing in Table 1.*

Identification

Identification of the compounds was done mainly by interpretation of the high and low resolution mass spectra and especially of the ^{1}H and ^{13}C NMR spectroscopic data. In Table 2 the *m/e* values of the most intense fragments are mentioned. In Table 3 ^{1}H NMR spectroscopic data are given, while in Table 4 the ^{13}C NMR data are listed for some compounds. With the help of this evidence and knowledge of the reaction possibilities of benzyl methyl ketone and formamide, a complete structural proof could be given [5-8].

Gas Chromatography

When an OV-17 3% column was used no separation could be reached between Compounds 4 and 7, even when the temperature programming as stated in Table 5 was employed. In order to achieve a quantitative analysis of the various compounds an Apiezon L/KOH column had to be used. A separation between Compounds 4 and 7 was then possible; however, Compounds 3 and 6 were not separated and Compound 8 was not eluted from this column. In Table 5 data are given about the occurrence of the weakly

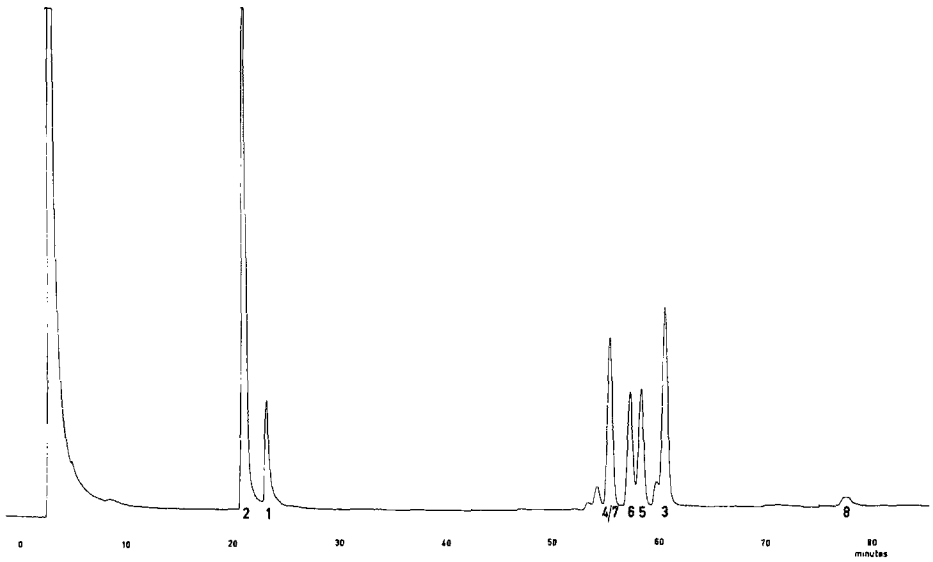

FIG. 2—*Gas chromatogram of weakly basic fraction; column, OV-17 3% on Chromosorb WHP (80-100) mesh; oven, 100–250°C at 2°C/min; and carrier gas, nitrogen at 20 ml/min.*

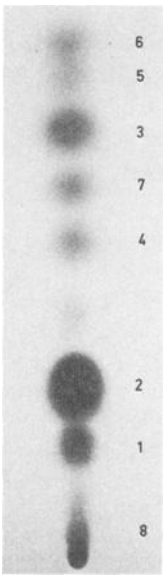

FIG. 3—*Thin-layer chromatogram of weakly basic fraction on Merck precoated silica gel 60 F-254 plates with hexane/ether (50:50) as eluant.*

TABLE 2—*The* m/e *values of the most intense fragments in decreasing order of intensity.*

Compound	Molecular Weight	Fragments[a]						
1	170	B, 169	170	91	115	142	65	116
2	170	B, 170	169	102	115	116	171	51
3	259	B, 258	259	243	244	260	115	91
4	259	B, 259	260	244	115	215	202	116
5	273	B, 272	273	258	55	57	71	79
6	259	B, 258	259	180	244	260	182	115
7	259	B, 259	260	115	244	101	202	215
8	277	B, 186	91	158	143	187	65	115

[a] B = base peak.

TABLE 3—*Hydrogen-1 NMR data; solvent, deuterochloroform and internal reference, tetramethylsilane.*[a]

1	δ_H = 4.0 (s,2H); 7.0 (d,1H); 7.2 (s,5H); 8.6 (d, 1H); 9.2 (s,1H)
2	δ_H = 2.5 (s,3H); 7.4 (s,5H); 8.6 (s,1H); 9.1 (s,1H)
3	δ_H = 2.17 (s,3H); 4.13 (s,2H); 6.97 (s,1H); 7.30 (m,10H); 8.35 (s,1H)
4	δ_H = 1.90 (s,3H); 2.27 (s,3H); 7.0-7.5 (m,10H); 8.22 (s,1H)
5	δ_H = 1.92 (s,3H); 2.25 (s,3H); 4.12 (s,2H); 6.78 (s,1H); 7.0-7.5 (m,10H)
6	δ_H = 2.50 (s,3H); 4.17 (s,2H); 6.90 (d,1H; $\mathcal{J}$ = 8 Hz); 7.3 (m,11H)
7	δ_H = 2.53 (s,6H); 7.35 (ψ-s, 11H)
8	δ_H = 1.20 (s,3H); 2.50 (s,2H); 2.83 (AB, $\mathcal{J}$ = 12Hz, 2H); 5.63 (d, $\mathcal{J}$ = 7Hz, 1H); 7.17 (m,11H)

[a] δ = chemical shift in ppm relative to internal reference.
ψ = pseudo.
s = singlet.
d = doublet.
m = multiplet.
$\mathcal{J}$ = coupling constant in Hz.
AB = two protons for which the chemical shift difference is of the same order as the coupling constant between the protons.

TABLE 4—*Carbon-13 NMR data; solvent, deuterochloroform and internal reference, tetramethylsilane.*[a]

3	δ_C = 19.83; 44.43; 124.44; 126.41; 127.50; 128.41; 128.66; 129.21; 129.39; 135.56; 138.05; 139.77; 145.08; 149.53; 159.61
4	δ_C = 18.06; 23.68; 127.41; 128.41; 128.43; 129.02; 129.57; 148.00
5	δ_C = 20.29; 23.62; 44.50; 121.82; 126.34; 127.19; 127.74; 128.04; 128.65; 129.14; 129.33; 130.43; 139.89; 145.81; 155.50; 158.68
6	δ_C = 23.43; 44.60; 120.23; 126.40; 127.31; 128.40; 128.59; 129.14; 129.33; 134.51; 137.75; 139.70; 140.19; 155.20; 159.29
7	δ_C = 23.07; 127.31; 128.41; 129.21; 134.39; 138.54; 139.94; 153.87
8	δ_C = 24.7; 44.1; 48.0; 56.7; 109.6; 125.5; 126.9; 127.6; 128.1; 128.2; 130.6; 136.1; 136.4; 149.3; 189.5

[a] δ = chemical shift in ppm relative to internal reference.

basic compounds in a reaction mixture and in an illegal amphetamine. The reaction mixture was diluted 100 times with chloroform; a quantity of the illegal amphetamine was extracted with acetone, the solvent evaporated, and the residue taken up in chloroform.

Thin-Layer Chromatography

The R_f values of the compounds after development in hexane/ether (50:50) are recorded in Table 6. Compounds 1 and 2 are stained yellow by spraying the spots with 1% *p*-dimethylaminobenzaldehyde in 50% sulfuric acid and heating the plates at 100°C in a drying box. The three pyridines without alpha hydrogen are stained blue-purple with the well-known iodoplatinate reagent; the other two pyridines and the pyrimidines become yellow or brown. The pyridone derivative turns reddish by iodoplatinate (not sensitive), as does the *N*-formylamphetamine for which it can be mistaken.

Apparatus

Gas Chromatography—A Perkin-Elmer F 30 gas chromatograph was used. Columns were either OV-17 3% on Chromosorb WHP (80-100 mesh) or Apiezon L 10%-KOH 10% on Chromosorb G-DECS (80-100 mesh). The column length was 1.8 m (6 ft) and the diameter, 3.175 mm (⅛ in.).

TABLE 5—*Occurrence of the weakly basic compounds in a reaction mixture* (A) *and in an illegal methamphetamine* (B).

			Chromatographic Conditions		
Compound	A, %	B, ppm	Column	Oven Temperature, °C	Gas Velocity, ml/min
1	2.1	80	Apiezon L/KOH, 10%/10%	150	30
2	4.7	14	Apiezon L/KOH, 10%/10%	150	30
3	1.2	35	Apiezon L/KOH, 10%/10%	220	20
4	0.9	30	Apiezon L/KOH, 10%/10%	220	20
5	1.4	24	OV-17, 3%	150-250 at 2°C/min	20
6	1.9	17	OV-17, 3%	150-250 at 2°C/min	20
7	0.8	22	Apiezon L/KOH, 10%/10%	220	20
8	8.9	60	OV-17, 3%	250	20

TABLE 6—*The* R_f *values of the compounds after development in hexane/ether (50:50).*

Compound	R_f Value × 100
1	19
2	22
3	55
4	40
5	62
6	64
7	46
8	10

Mass Spectrometry—A Varian-MAT 111 mass spectrometer coupled to a Varian-MAT Spectro-System 100 MS was used in low resolution work. The high resolution spectra were run on a Varian-MAT 311 system. The electron energy was 70 eV.

Hydrogen-1 NMR Spectroscopy—Hydrogen-1 NMR spectra were taken on a Varian T-60 spectrometer equipped with a T-6059 spin decoupler or on a Varian XL-100-15 spectrometer.

Carbon-13 NMR Spectroscopy—Carbon-13 NMR spectra were obtained on a Varian CFT-20 spectrometer; the pulse-Fourier-transform technique was employed.

Discussion

It can be supposed that in the Leuckart reaction one molecule of benzyl methyl ketone is condensed with one molecule of formamide. The resulting intermediate product has still further possibilities for condensation. Another formamide molecule can react with the intermediate product, giving rise to Substances 1 and 2 by ring closure. The other six compounds can originate from the condensation of two molecules of benzyl methyl ketone with one molecule of formamide. It is remarkable that in a reaction mixture the amounts of Compounds 1, 2, and 8 are fairly high as compared with the quantities of the other components.

The formation of so many by-products in such a high quantity presents a difficult problem to the producer of illegal amphetamine. The substances should be removed by steam-distilling the reaction mixture and by selective precipitation of the steam-distilled amphetamine from methanol by the addition of sulfuric acid. Perhaps this purification is the most boring production stage, but it is very important, because the whiter the product, the higher the price of amphetamine on the drug market. However, all illegal amphetamines we have seen until now were off-white and sometimes a bit yellow; the described impurities could be found in them, of course at the low levels indicated.

In our opinion the detection of the described impurities presents a perfect means to confirm that the amphetamine was produced by the Leuckart reaction. However, it remains impossible for us to state from which batch a certain amphetamine has come because the amounts of the different impurities in amphetamine greatly depend on the skill of the producer in purifying the amphetamine.

As suggested before, the by-products are present in high quantities and the wastes originating from the purification should be discarded. In most instances this refuse matter is dumped somewhere in the neighborhood of the production place, polluting soil and water. In two cases we succeeded in finding the impurities in dirt that was collected by police sergeants from a drain and a sink near suspected places. In these cases the suspicion could be confirmed.

Acknowledgments

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Summary

In this paper the isolation and identification of two pyrimidines, five pyridines, and one pyridone as impurities in illicit amphetamines prepared by the Leuckart synthesis are reported. Isolation was achieved by repeated thin-layer chromatography with various solvent mixtures, while identification was done by both high and low resolution mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. Some chromatographic data are reported and a quantitative analysis of a reaction mixture and an illicit amphetamine is given.

References

[1] Kram, T. C. and Kreugel, A. V., *Journal of Forensic Sciences,* Vol. 22, No. 1, Jan. 1977, pp. 40-52.
[2] Barron, R. P., Kreugel, A. V., Moore, J. M., and Kram, T. C., *Journal of the Association of Official Analytical Chemists,* Vol. 57, No. 5, 1974, pp. 1147-1158.
[3] Lomonte, J. M., Lowry, W. T., and Stone, I. C., *Journal of Forensic Sciences,* Vol. 76, No. 3, July 1976, pp. 575-582.
[4] Bailey, K., Boulanger, J. G., LeGault, D., and Taillefer, S. L., *Journal of Pharmaceutical Sciences,* Vol. 63, No. 10, Oct. 1974, pp. 1575-1578.
[5] van der Ark, A. M., Theeuwen, A. B. E., and Verweij, A. M. A., *Pharmaceutisch Weekblad,* Vol. 112, 1977, pp. 977-979.
[6] van der Ark, A. M., Sinnema, A., van der Toorn, J. M., and Verweij, A. M. A., *Pharmaceutisch Weekblad,* Vol. 112, 1977, pp. 980-982.
[7] van der Ark, A. M., Sinnema, A., Theeuwen, A. B. E., van der Toorn, J. M., and Verweij, A. M. A., *Pharmaceutisch Weekblad,* Vol. 113, 1978, pp. 41-45.
[8] van der Ark, A. M., Sinnema, A., van der Toorn, J. M., and Verweij, A. M. A., *Pharmaceutisch Weekblad,* Vol. 113, 1978, in press.

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