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Di-(β-Phenylisopropyl)amine in Illicit Amphetamine

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ABSTRACT: Illicit amphetamine samples frequently contain di-(β-phenylisopropyl)amine as a main impurity. Its formation during the Leuckart synthesis is discussed. A method for synthesis is given. Special attention is given to its stereoisomerism. Analytical data are presented; the role of the compound in the comparison of illicit amphetamine samples is discussed.

KEYWORDS: toxicology, amphetamine, di-(β-phenylisopropyl)amine, impurities in illicit amphetamine, narcotics

The presence of di-(β-phenylisopropyl)amine (DPIA) (Fig. 1) as a by-product in amphetamine synthesis has been described by several authors [*1-3*]. Although the substance was first mentioned in relation to catalytic reductive amination of ketones, later work showed DPIA to also be present in amphetamine prepared via the Leuckart reaction [*4*].

Until 1981 the main impurity in amphetamine, illicitly produced in the Netherlands, was 4-methyl-5-phenylpyrimidine [*5,6*]. However, nowadays in most samples the main impurity is DPIA (or its *N*-formyl derivative or both).

It is supposed that this change in the impurity pattern is connected to a modification in the production method that was observed in illegal laboratories, namely, the addition of formic acid in the first step of the synthesis, that is, the condensation of benzyl methyl ketone and formamide.

The aim of this paper is to give additional analytical data on DPIA, to give attention to its diastereoisomerism, and to discuss its role in the comparison of samples.

Experimental Procedures

Synthesis of DPIA

A mixture of 13.5 g of amphetamine base (0.1 mol) and 13.5 g of benzyl methyl ketone (0.1 mol) in 500 mL of toulene was refluxed for 6 h. At regular intervals the water formed during the reaction was removed by azeotropic distillation. Finally the toluene was distilled off completely. The reaction mixture was cooled and a solution of 12 g of sodium borohydride in 500 mL of absolute ethanol was added slowly. After 2-h refluxing the mixture was cooled, diluted with 200 mL of water, and—after evaporation of the ethanol in vacuo—extracted with chloroform. The chlo-

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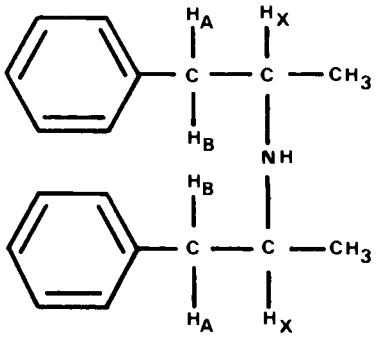

FIG. 1—*Chemical structure of di-(β-phenylisopropyl)amine.*

roform was evaporated; the remaining oil was diluted with 40 mL of methanol and neutralized with 50% sulfuric acid. A precipitate (18.5 g) was obtained, which was removed by filtration. After standing overnight a second crop (1.7 g) was obtained. The precipitates were thrice washed with acetone, combined, and recrystallized from water.

The Leuckart Synthesis: First Step

1. Benzyl methyl ketone, 100 mL, and 300 mL of formamide were heated together in a 1-L three-necked roundbottom flask at 190°C during 4 h. The flask was fitted with a water condenser and a thermometer.
2. Benzyl methyl ketone, 100 mL, 200 mL of formamide, and 100 mL of formic acid were heated together in a 1-L three-necked roundbottom flask at 140°C during 3 h. The flask was fitted with a water condenser and a thermometer.

In both cases 0.5-mL samples were taken at regular intervals. The samples were extracted with 15.0 mL of ethyl ether and analyzed by gas chromatography (GC).

Nuclear Magnetic Resonance (NMR)

The proton NMR spectra were recorded on a Brucker W.M.300 in combination with an Aspect 2000 computer. Samples were measured as the free base dissolved in deuterated chloroform. Trimethylsilane was used as reference.

Thin-Layer Chromatography (TLC)

Two solvent systems were used: System 1—toluene-acetone-ethanol-ammonia 25% (45:45:7:3) and System 2—cyclohexane-toluene-diethylamine (75:15:10). In both cases precoated plates (silica gel 60 GF 254, Merck, Darmstadt, West Germany) were used.

Detection was achieved by examination under 254-nm ultraviolet light, followed by spraying with iodoplatinate reagent [7].

Gas Chromatography (GC)

Gas chromatographic analysis was carried out on a Perkin Elmer Sigma 3 gas chromatograph equipped with a flame-ionization detector (FID). The column was a commercially available fused silica capillary column (25 m long and 0.24-mm inside diameter) with a chemically bonded methyl silicone as stationary phase, film thickness 0.11 μm (CP sil 5 CB,

Chrompack, the Netherlands). The carrier gas was nitrogen; the inlet pressure was 100 kPa; the split 1 : 100; and the injection volume was 0.5 μl. Injector and detector temperatures were both 300°C. Column temperatures were

(1) 220°C during the quantitative determination of "total" DPIA and
(2) 125 to 250°C at 10° /min in all other analysis.

For plotting and integration the gas chromatograph was connected to a Sigma 15 data station.

Quantitative Determination of "Total" DPIA

To about 150 mg of an amphetamine sample 1 mL of 1 *N* sodium hydroxide was added; this mixture was extracted with 3.0 mL of chloroform (containing 0.5 mg/mL of octadecane as an internal standard). The chloroform layer was separated and injected into the gas chromatograph; conditions see above, column temperature 220°C.

Sample Preparation in Comparative Studies

A homogenized sample of amphetamine sulphate (150 mg) was extracted according to one of the following procedures.

(1) with 10 mL of chloroform during 15 min in an ultrasonic bath;
(2) with 20 mL of chloroform during 15 min in an ultrasonic bath;
(3) with 1.0 mL of 1 *N* hydrochloric acid and 10 mL of chloroform during 5 min under vigorous stirring on a Vortex mixer;
(4) the same as under 3 except extraction from 1 *N* sodium hydroxide; and
(5) the same as under 3 except extraction from water.

In all cases the mixtures were filtered through phase separating paper; the chloroform was removed by careful evaporation under nitrogen; the residues were dissolved in 500 μL of chloroform (in recovery experiments the chloroform contained octadecane 0.5 mg/mL as internal standard).

Mass Spectrometry (MS)

Electron impact mass spectra at 70 eV were obtained using a Finnigan MAT 212 GC/MS combination, coupled to a MAT SpectroSystem 100 MS. The low resolution mode was used. Ion source and GC/MS interface were at 250 and 300°C, respectively. The acceleration voltage was 3 kV, and an ionization current of 0.5 mA was used. The chromatographic column was of similar type as described above; oven temperature 60 to 250°C at 10°/min. Carrier gas was helium and flow rate was about 2.5 mL/min.

Microchemical Tests

Spot tests according to Marquis [7] and Ruybal [8] were performed on solid substance and amphetamine samples. Preparation of the Ruybal reagent; add to 45 mL of a 2% cobalt thiocyanate solution 65 mL of 25% phosphoric acid containing 250 mg of platinum chloride; mix well; and let stand at least five days before using. The precipitate that is formed should not be removed or separated from the reagent.

Results and Discussion

Synthesis

DPIA can be synthesized by coupling amphetamine with benzyl methyl ketone to the corresponding imine, and subsequent reduction. This reduction can be performed by the action of triethylammonium formate [9], analogous to the Leuckart reaction. However a simpler reduction step was chosen by using sodium borohydride as described under the Experimental Procedure section.

The recovery of the synthesis represented about 60% of the theoretical yield. Analytical samples were obtained by recrystallization from methanol. The products consisted of a white microcrystalline powder. The molecular formula was determined as $(DPIA)_2 \cdot H_2SO_4$ by conductometric titration; $M = 604$.

Microchemical Tests

Marquis: orange color, changing to brown.

Ruybal: blue precipitate; in low concentration in samples built of blue needles.

In routine amphetamine screening the reaction of DPIA with the Marquis reagent is not relevant; the Ruybal reagent, however, can be very practical in recognizing the presence of DPIA in amphetamine samples at a level of more than 0.5%.

Thin-Layer Chromatography

System 1: R_f amphetamine = 0.63 and R_f DPIA = 0.88.
System 2: R_f amphetamine = 0.33 and R_f DPIA = 0.74.

The visibility of DPIA under ultraviolet (UV) light (254 nm) on the plate is low, but it shows a strong reaction with iodoplatinate reagent (sensitivity 1 to 2 μg).

Gas Chromatography

Using capillary GC the synthesized product appeared to give two peaks, with a distinct although not base-line separation with Kovat's indices of 1872 and 1877, respectively. It was assumed that the peaks represented two diastereomers of DPIA.

Mass Spectrometry

The mass spectrum of the synthesized product was in agreement with the spectrum already given in literature [3]. Mass fragments found were 162, 91, 44, 119, 163, 41, 70, and 65.

The Formation of DPIA in the Leuckart Synthesis

As mentioned in the introduction, the change in the impurity pattern coincided with a modification in the production method that was observed. This modification consisted of the addition of formic acid during the first reaction step, namely, the condensation of benzyl methyl ketone with formamide at boiling temperature.

To study the influence of formic acid on the formation of by-products, two syntheses were carried out: one with and one without formic acid. Temperatures were chosen as 193 and 140°C, respectively, since these temperatures were mentioned in the recipes found at illicit production laboratories, and represent the boiling temperatures of the reaction mixtures; the ratio of the reactants was also taken from such recipes.

Figure 2 shows the gas chromatograms of the resulting reaction mixtures after 1, 2, and 3 h. It shows that under both conditions the by-products 4-methyl-5-phenylpyrimidine, DPIA,

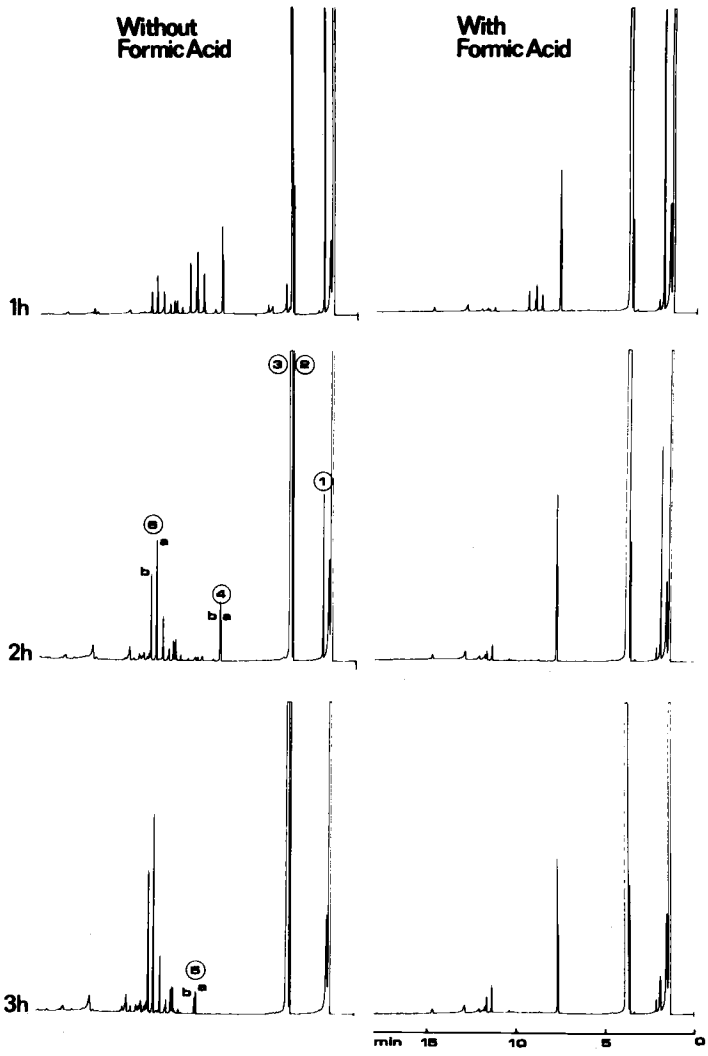

FIG. 2—*Gas chromatograms of reaction mixtures of benzyl methyl ketone and formamide, with and without formic acid added, after 1, 2, and 3 h. Peak 1 = benzyl methyl ketone, 2 = 4-methyl-5-phenylpyrimidine, 3 = formylamphetamine, 4a/4b = DPIA, 5a/5b = N-methylDPIA, 6a/6b = N-formylDPIA: (a/b are diastereomers).*

and *N*-formylDPIA are formed. However, under the conditions chosen some obvious differences can be observed. In the presence of formic acid considerably less by-products are formed. The reaction time in both cases seems to lie between 2 and 3 h. This is about half of the time that is used by illegal producers. The yield on formylamphetamine is higher when formic acid is present. Without formic acid:

- 4-methyl-5-phenylpyrimidine is the main by-product;
- DPIA is formed, but is converted to its *N*-formyl derivatives in the course of the reaction; and
- many other by-products arise.

DPIA seems to be the main by-product when formic acid is used.

Although the results are indicative for a strong influence of formic acid on the formation of by-products it must be emphasized, however, that from these experiments no conclusions can be made concerning the final composition of the illicit amphetamine sulphate, because a great number of factors are involved. So, many producers tend to use longer reaction times, thereby enhancing the amounts of *N*-formylDPIA. Sanger and Humphreys [*4*] found *N*-formylDPIA as the main by-product when higher reaction temperatures were used. Variations in starting volumes of the reactants are also important.

When formylamphetamine is hydrolyzed to amphetamine, *N*-formylDPIA will be partly converted to DPIA, although experiments showed *N*-formylDPIA to be relatively stable to 1-h hydrolysis of the reaction mixture with 30% hydrochloric acid.

The purification stage will have the most influence on the final impurity pattern. Steam distillation, which is the method that is most frequently used in the Netherlands, can purify the amphetamine base from most of its impurities; however, both 4-methyl-5-phenylpyrimidine and DPIA are volatile on steam distillation. As the latter substance is less volatile than the first one the time of distillation becomes an important factor for the final result.

Washing with organic solvents will remove pyrimidines, whereas the less soluble DPIA will remain in the final product.

Stereoisomerism

DPIA has two asymmetric centers and theoretically there are four possible isomers: RR, SS, RS, and SR. However, because of the symmetry of the molecule the SR and RS are identical (meso compound). The RR and SS isomers are enantiomeric, so physico-chemically identical except in rotation. The meso compound RS (or SR) is diastereomeric with respect to the RR and SS compounds. Diastereomers can differ in physical and chemical properties.

In GC analysis the synthesized product showed two peaks. That these peaks represented diastereomers could not be confirmed by direct GC-MS analysis because the separation was not complete. However, by formylating the synthesized product, by boiling it during 20 min in formamide, the product was converted into a mixture which gave upon GC analysis two well-separated peaks (Fig. 3, Peaks 6a and 6b). GC-MS analysis showed that the peaks were the diastereomers of *N*-formylDPIA. These isomers have been extensively described in the literature [*4,10,11*]. Further evidence for the existence of diastereomers was obtained by the isolation of one of them.

The isolation was based on the difference in solubility of the sulphates: the synthesized DPIA sulphate was converted into the base; the base was dissolved in a large amount of methanol (30 g/L). By adding 50% sulfuric acid until a neutral reaction to litmus, a crystallization occurred.

GC analysis revealed that one peak had disappeared almost completely; after repeated crystallization only one peak of DPIA appeared on the chromatogram. Now formylation showed only one peak of *N*-formylDPIA (Fig. 4, Peak 6a). The identity was confirmed by GC-MS.

During the formylation of DPIA another compound was formed (Fig. 3, Peaks 5a and 5b) which showed the same phenomenon. GC-MS and NMR analysis showed this substance to be *N*-methylDPIA. This compound, and its diastereoisomerism, was first described by Barron et al [*12*] in relation to illicit methamphetamine. Its formation by formylation of DPIA can be explained by reduction of *N*-formylDPIA. The compound is frequently encountered in illicit amphetamine samples.

A part of the NMR spectrum of the isolated DPIA diastereomer is given in Fig. 5*c*; Fig. 5*a* shows the spectrum of a mixture of the enantiomeric RR/SS compounds and the meso compound RS (or SR). The two methyl groups of the RR as well as the SS compound are equivalent and give rise to one signal, which is split up into one doublet (about 1 ppm) by their neighboring CH group. The other doublet in Fig. 5*a* can be attributed to the meso compound. The hydrogens of the CH_2 group are not equivalent (H_A, H_B in Fig. 1) because they are situated

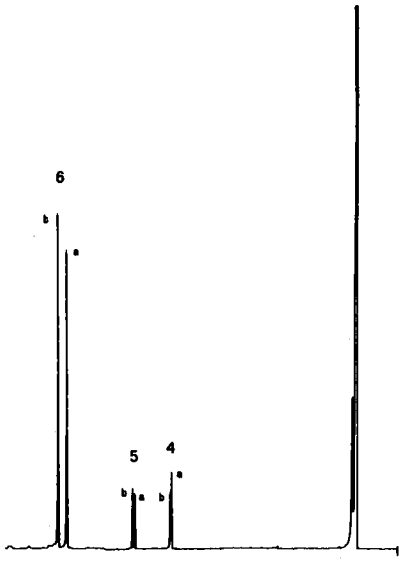

FIG. 3—*Gas chromatogram of the reaction mixture obtained after treatment of DPIA with formamide where 4a/4b = DPIA (diastereomers), 5a/5b =* N-*methylDPIA (diastereomers), and 6a/6b =* N-*formyl DPIA (diastereomers).*

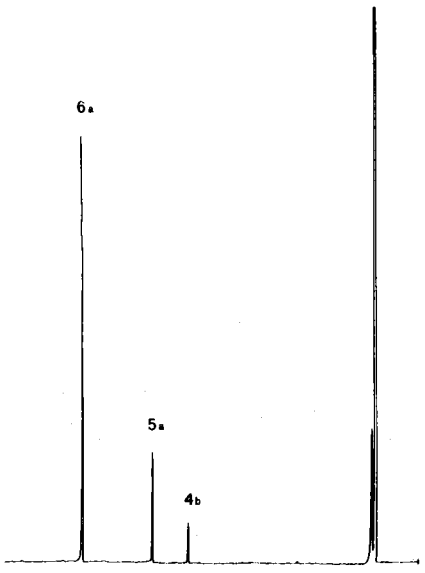

FIG. 4—*Gas chromatogram obtained when one isolated diastereomer of DPIA was treated with formamide; same peak numbers as in Fig. 3.*

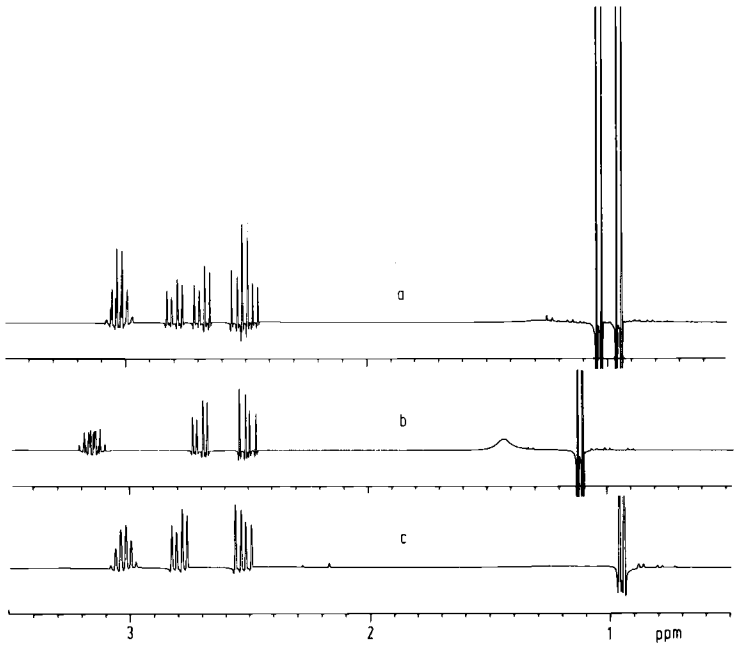

FIG. 5—*NMR spectra of* (a) *DPIA (mixture of diastereomers).* (b) *amphetamine, and* (c) *DPIA (isolated RR/SS diastereomer).*

near a chiral center; coupling with the CH (H_X) gives rise to an ABX spectrum. By comparison Fig. 5*b* shows part of the NMR spectrum of amphetamine. The signals between 2.4 and 3.1 ppm in Fig. 5*a* originate from two ABX spectra.

Figure 5*c* clearly shows one diastereomer that is either the RR/SS compound or the meso compound. The techniques used so far are not capable of indicating which diastereomer was isolated.

However, by using the S(+)amphetamine instead of the racemic amphetamine in the synthesis of DPIA, one chiral center is fixed (S) [*13*]. The second chiral center that is formed during the reduction of the imine gives rise to a mixture of R and S configuration. So there are two stereoisomers (SS and SR) instead of four. The SS compound is optically active while the meso compound SR is not. The two compounds are diastereomeric with respect to each other.

The less soluble compound that was obtained when the synthesis was started with S(+)amphetamine showed optical activity ($[a]_D^{22} = +25.2$; methanol c = 0.3) and it must therefore be the SS compound. An analytical sample was obtained by recrystallization from methanol ($[a]_D^{22} = +35.2$; methanol $c = 0.3$; melting point 264 to 265°C, uncorrected). The NMR spectrum of this compound is identical with the spectrum of the less soluble compound obtained from racemic amphetamine; therefore, this compound must be the enantiomeric mixture RR/SS (melting point 264 to 265°C, uncorrected).

The NMR data are given in Table 1.

The GC data of the diastereomers investigated are summarized in Table 2.

In several syntheses it was noticed that the yield on the meso compound was less than the yield on RR/SS diastereomers. Direct GC analysis of the ethanolic solution obtained after the reduction of the imine intermediate (see Synthesis) showed a ratio of about 1 : 2. A similar ratio was observed during the first step of the Leuckart reaction (Fig. 2). The basis of this phenomenon must be found in the reduction of the imine. Nichols et al [*13*] found that heterogeneous reduction of imines formed by reaction of benzyl methyl ketone with either R- or S-α-methyl-

TABLE 1—*NMR data: chemical shifts (ppm) and coupling constants (Hz).*[a]

Compound	CH_3(d)	J_{CH_3}	H_A(q)	H_B(q)	H_X(m)	J_{AB}	J_{AX}	J_{BX}	Ph(m)
RR/SS DPIA	0.95	2.08	2.53	2.79	3.03	−13.22	7.38	5.88	7.2
Meso DPIA	1.03	2.09	2.48	2.68	3.03	−13.24	6.70	6.29	7.2
Amphetamine	1.11	2.11	2.51	2.71	3.16	−13.23	8.09	5.31	7.2

[a]d: doublet; q: quartet; and m: multiplet.

TABLE 2—*Gas chromatographic data: Kovat's indices.*

Meso DPIA	1872
RR/SS DPIA	1877
RR/SS *N*-methylDPIA	2000
Meso *N*-methylDPIA	2006
RR/SS *N*-formylDPIA	2257
Meso *N*-formylDPIA	2289

benzylamine yielded mainly the RR or the SS compound, respectively, and relatively small amounts of the meso compound. So, the first chiral center in the molecule has a strong influence on the configuration of the second chiral center that is formed.

A similar influence appears to occur during the homogeneous reduction with sodium borohydride.

Samples and Comparison of Samples

At the moment, DPIA can be found in about one third of the illicit amphetamine samples by routine TLC analysis.

One special amphetamine seizure, consisting of 400 g of white powder, is mentioned here as it contained 33% DPIA sulphate and 38% amphetamine sulphate. DPIA was isolated from this sample by dissolving it in excess of boiling water. After cooling the DPIA sulphate crystallized out. The infrared (IR) spectrum is given in Fig. 6. The sample mentioned above must be considered as a curiosity; the idea that it was prepared via reductive catalytic amination was

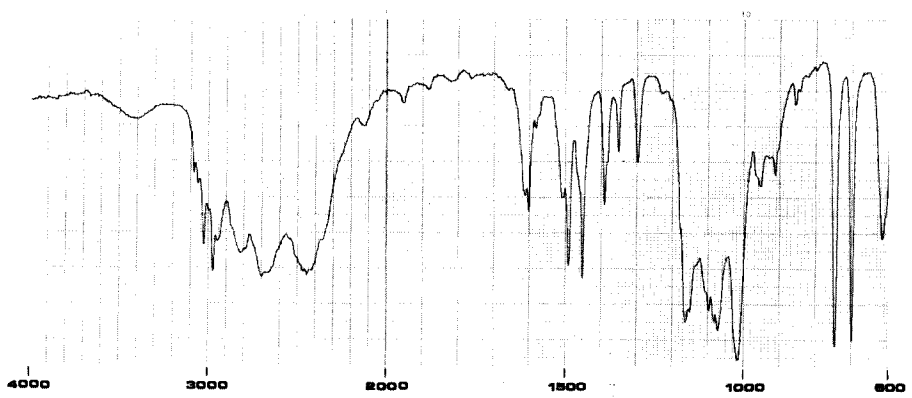

FIG. 6—*Infrared spectrum of DPIA sulphate.*

not supported by Energy Dispersive Analysis of X-rays (EDAX), as no traces of metal catalysts could be found. Furthermore the sample contained *N*-formylDPIA; this could be an indication that the Leuckart synthesis had been used.

Usually illicit amphetamine samples contain only small amounts of DPIA. Table 3 shows the results obtained on seven samples analyzed. The samples had been selected by their positive reaction with the Ruybal test. The percentages are expressed as "total" DPIA, and calculated as sulphate.

Also represented is the ratio of the diastereomers of DPIA, the ratio of the *N*-formylDPIA diastereomers and the ratio of RR/SS *N*-formylDPIA and RR/SS DPIA (see also Fig. 7, Peak 4a/4b, Peak 6a/6b, and Peak 6a/4b).

Remarkable is the rather constant ratio of DPIA diastereomers. Although this ratio is in the first place determined in the reduction during synthesis, we had expected more variation because of the strong influence of the methanol concentration during crystallization proce-

TABLE 3—*Percentages and ratios of some impurities found in seven illicit amphetamine samples ("uncut" samples).*

Sample	"Total" DPIA, %	Meso DPIA[a] RR SS DPIA	RR SS *N*-formylDPIA[a] Meso *N*-formylDPIA	RR/SS *N*-formylDPIA[a] RR/SS DPIA
1	1.5	0.55	1.73	0.35
2	1.3	0.56	1.62	0.47
3	0.2	0.53	1.70	0.42
4	0.7	0.39	neg	...
5	0.5	0.59	1.90	0.38
6	1.3	0.56	1.75	0.52
7	1.7	0.57	1.65	0.31

[a]Peak heights.

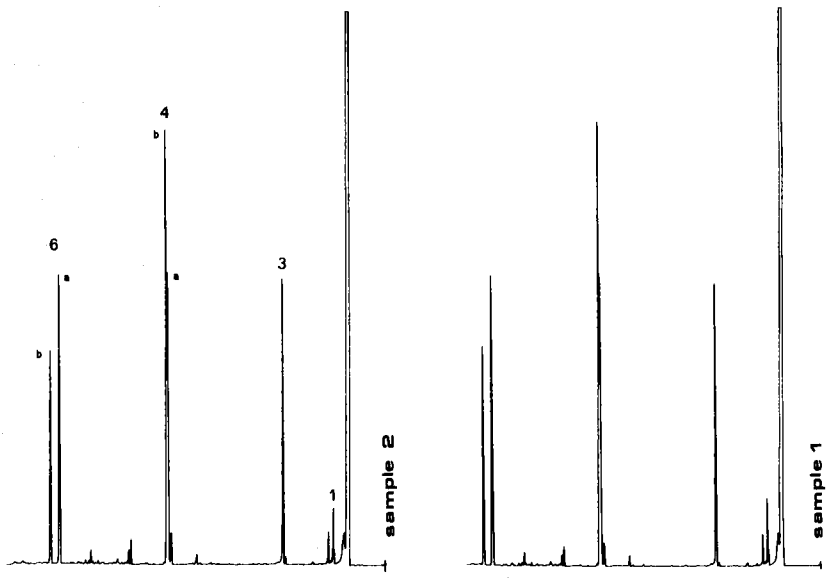

FIG. 7—*Gas chromatograms showing impurity patterns of two illicit samples of amphetamine sulphate. Peak 1 = amphetamine, 3 = formylamphetamine, 4a/4b = DPIA, and 6a/6b = N-formylDPIA.*

TABLE 4—*Effectiveness of extraction[a] of impurities from an illicit amphetamine sample by different extraction procedures.*[b]

	1	2	3	4	5
Amphetamine	6	6	2	309	1
4-methyl-5-phenylprimidine	0.44	0.47	0.53	0.54	0.51
Meso DPIA	0.24	0.26	0.27	1.06	0.80
RR/SS DPIA	0.35	0.41	0.42	1.73	1.26
RR/SS *N*-methylDPIA	0.14	0.14	0.08	0.70	0.53
Meso *N*-methylDPIA	0.10	0.11	0.04	0.47	0.35
RR/SS *N*-formylDPIA	0.56	0.55	0.64	0.78	0.62
Meso *N*-formylDPIA	0.32	0.32	0.37	0.42	0.35

[a]Areas, normalized to internal standard.

[b]1 = chloroform extraction of dry sample; 2 = chloroform extraction of dry sample with the double amount of chloroform; 3 = extraction from acid solution; 4 = extraction from alkaline solution; and 5 = extraction from water. For details see Experimental Procedure, sample preparation in comparative studies.

dures (in The Netherlands the amphetamine base is usually diluted with methanol before it is neutralized with sulfuric acid). Also the *N*-formyl derivatives seem to occur in a rather constant ratio.

These results indicate that for a comparison of samples the ratio of diastereomers may not be significant. However more data must be collected here. The table shows that discrimination of the samples investigated can be made on the basis of their amounts of "total" DPIA and the ratio RR/SS *N*-formylDPIA versus RR/SS DPIA.

A comparison of samples is often based on a gas chromatographic "signature" as described by Sanger and Humphreys [*3*] and Strömberg [*14*]. Usually an attempt is made to take extracts from an illicit drug sample under such conditions that the minor components are extracted from the bulk of the samples. From samples of amphetamine sulphate the weakly basic and neutral impurities can be isolated by extracting them with organic solvents from solid samples or from neutral or weakly acid solutions.

In the case of DPIA sulphate, however, it can be expected that the extraction will be incomplete under nonalkaline conditions. To study the influence of the extraction procedure an amphetamine sample was extracted under five different conditions, mentioned under Experimental Procedures. Table 4 shows the results obtained for the compounds discussed. A strong effect of the pH on the extraction of DPIA and *N*-methylDPIA is demonstrated. The extraction of *N*-formylDPIA undergoes relatively little influence.

So, in the case of "fingerprinting" an amphetamine sample, when it is preferred to separate the impurities from the bulk of the sample the extraction from water—although not complete—is a reasonable choice. For quantitative determination of DPIA the extraction from alkaline solution (Extraction 4) must be chosen.

An example of a comparison of samples is shown in Fig. 7. The exhibits consisted of 30 and 60 g of offwhite powder, containing 48 and 47% amphetamine sulphate, respectively, as determined by capillary GC. Both samples contained mannitol as diluent. The samples were extracted via extraction Procedure 1. In this case an exceptionally high resemblance was obtained, leading to the conclusion that both exhibits probably originated from one batch.

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