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COMPARATIVE GAS CHROMATOGRAPHIC ANALYSIS OF NARCOTICS

IV. METHAMPHETAMINE HYDROCHLORIDE

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SUMMARY

Chemical signatures (or impurity profiles) of methamphetamine hydrochloride were displayed by gas chromatography. The analyses of samples from two series of batches showed that the inter-batch variation of signatures was significantly greater than the corresponding intra-batch variation. In many cases, this permits the establishment of common or different origins of methamphetamine seizures.

INTRODUCTION

Some types of organic impurities in single-component drugs may be analysed by gas chromatography (GC). The resulting chromatograms are called chemical signatures (or impurity profiles). As pointed out in earlier parts of this series[1,2] such chemical signatures may be used for the tracing of drug seizures to common sources, provided that the variation of the signatures between different batches is of a greater order of magnitude than the variation within the batches. The variation between different batches, called inter-variation, depends on how strongly the conditions of the synthesis influence the chemical signature. In the present work, several experimental conditions of the Leuckart synthesis were studied in one series of experiments in order to determine their influence on the signature. The variation within the batches, called intra-variation, may be caused by heterogeneity and chemical instability of the main constituent or of the impurities. Intra-variation was studied in a second series of experiments.

EXPERIMENTAL

Apparatus

The gas chromatograph used was a Perkin-Elmer Sigma 2 with a FID–NPD

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dual-detector system (flame ionisation and nitrogen–phosphorus detectors) and a W + W 1200 double-pen potentiometric recorder. The column used was a fused-silica capillary (11 m × 0.20 mm I.D.). The stationary phase was methylphenylvinylsilicone gum (SE-54) with a film thickness of 0.25 μm. The column temperature was initially 110°C, first programmed to 212°C at 6°C/min, then programmed to 272°C at 10°C/min and finally kept at 272°C for 10 min.

Other analytical conditions were as follows: inlet split ratio, *ca.* 1:40; effluent split ratio, 1:1; carrier gas velocity (helium), 0.4 m/sec; injector temperature, 250°C; detector temperature, 300°C; attenuations, FID × 8, NPD × 16.

Synthesis

The condensation of phenylacetone and N-methylformamide was carried out in a distillation apparatus, as proposed by Ingersoll *et al.*[3]. This arrangement permits the escape of liberated water. Further, formic acid was initially added to the reaction mixture in order to increase the yield, as proposed by Crossley *et al.*[4]. Under these conditions, a molar yield of *ca.* 70% of methamphetamine calculated on the ketone was obtained in all syntheses. Phenylacetone, N-methylformamide and formic acid were taken from the same batches within the two series. All syntheses were carried out by the same operator.

In the first series of syntheses, (batches I–VIII) 75 mmoles (10 ml) of phenylacetone, 450 mmoles (26 ml) of N-methylformamide and 450 mmoles (17 ml) of formic acid were boiled under the conditions shown in Table I. The reaction mixture was then hydrolysed by refluxing with 37 ml of 12 *M* hydrochloric acid (450 mmoles) for 6 h. The hydrolysate was then diluted with 100 ml of water, alkalised with an excess of potassium hydroxide pellets and extracted with 100 ml of diethyl ether. The ether layer from batches I–VII was extracted with 200 ml of 0.6 *M* hydrochloric acid. The aqueous layer was diluted with 100 ml of water and alkalised with an excess of potassium hydroxide pellets. The resulting product was steam distilled. The first ethereal fraction was discarded and the following two-phase steam distillate was collected in a volumetric cylinder. The distillation was interrupted when the (lower) aqueous layer reached 100 ml. The volume of the supernatant layer of methamphetamine was

TABLE I

CONDITIONS OF THE LEUCKART SYNTHESES CARRIED OUT

Batch No.	*Condensation step*		*Clean-up step*		*Yield (g)*
	Boiling time (h)	*Boiling temp. (°C)*	*Steam distillation*	*Number of crystallisations*	
I	10	180	Yes	0	10
II	4	180	Yes	0	10
III	10	160	Yes	0	10
IV–VI	4	160	Yes	0	10
VII	4	160	Yes	0	10
VIII	4	160	No	0	10
IX	4	160	Yes	1	20
X	4	160	Yes	4	20

ca. 10 ml. The methamphetamine layer was finally dissolved in the water layer by the addition of hydrochloric acid to pH 5.2. As far as batch VIII was concerned, the steam distillation step was omitted. Thus, the methamphetamine in the ether layer from the extraction of the alkalised hydrolysate was directly dissolved in 100 ml of water by the addition of hydrochloric acid to pH 5.2. The ether residue in this water solution was gently evaporated on a water-bath.

The second series of syntheses was carried out on double the scale of the first series, under the same conditions as for batches IV–VII (*cf.* Table I). The final water solutions were evaporated to dryness on a water-bath. The resulting batches of solid methamphetamine hydrochloride were crystallised once (batch IX) and four times (batch X), respectively, from acetonitrile.

Analysis

The GC analyses of batches I–VIII were carried out on 9-ml aliquots of the final water solutions. These aliquots contained *ca.* 1 g of methamphetamine hydrochloride. The analyses of the solid batches (IX and X) were carried out on 1-g samples dissolved in 9 ml of tap water. Each 9-ml water solution was extracted by vigorous shaking for 2 min with 1 ml of redistilled *n*-heptane in 10-ml cylinders with ground-glass stoppers. After phase separation, the heptane layer was transferred into a glass tube with a pipette, leaving *ca.* 0.1 ml behind in order to avoid the transfer of any aqueous phase. The glass tube (70 mm × 5 mm I.D.) was conical, with an I.D. of *ca.* 1 mm at the end. The tube was placed in a water-bath (60–70°C), and the evaporation of heptane was accelerated by suction with a pipette attached to a water-pump. The tube was gently shaken three or four times during evaporation in order to avoid deposition of extracted matter on the wall. Then 2 μl of the concentrated extract were injected into the gas chromatograph.

Tap water and redistilled analytical grade *n*-heptane were used in the extraction step. Deionized water is not recommended because impurities from the ion-exchange resin will occasionally produce background peaks. All glassware used was thoroughly rinsed with redistilled *n*-heptane before use. Under these conditions, blank samples gave no GC peaks on the NPD channel, whereas the FID showed 2 or 3 peaks at the 1-ppm level (*cf.* Fig. 1).

RESULTS AND DISCUSSION

The analytical system with a capillary column and the FID–NPD combination offers many advantages over the one previously used with a packed column and the FID–electron-capture detector (ECD) combination[2]. Firstly, the higher sensitivity permits the comparative analysis of smaller samples, roughly by a factor of ten. Secondly, the increased chromatographic resolution together with the detector combination used strongly enhances the characterisation of individual components of the chemical signature, *e.g.* impurities of the type described by Kram *et al.*[5]. This type of impurities may permit the establishment of the synthetic route used. Similarly, the analysis of reaction mixtures seized in a raid of a clandestine laboratory may reveal the identity of the attempted final product in cases where this is not available for direct analysis. Further, it seems obvious that the increased chromatographic resolution will facilitate the interpretation of complex signatures of mixed drugs, although

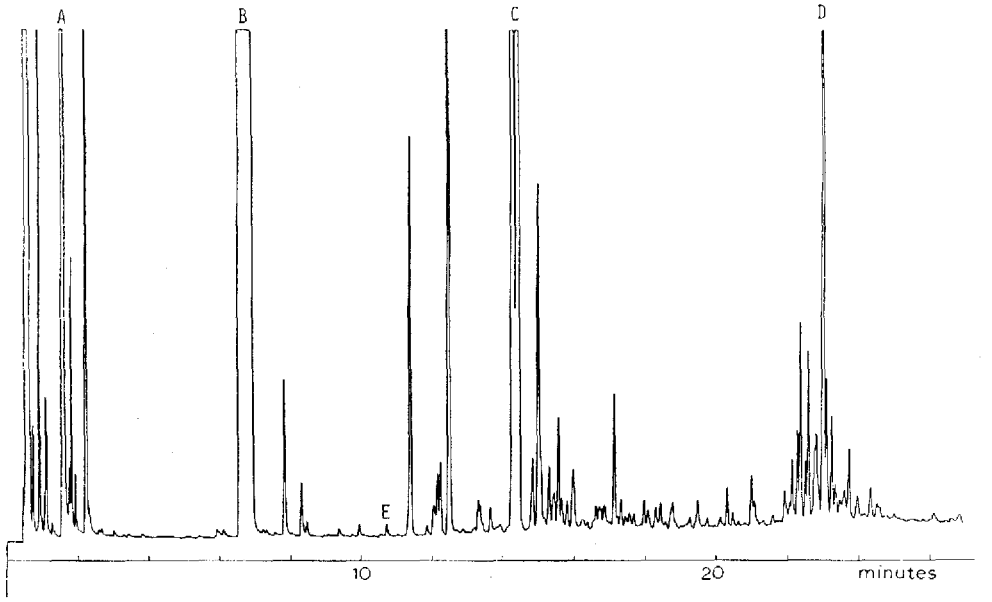

Fig. 1. FID signature of batch VIII. Peak A corresponds to the small amount of methamphetamine extracted from the acidic water solution. The concentrations in the batch of the major impurities B (N-formylmethamphetamine), C and D are in the range 1000–10,000 ppm. Minor impurity peaks may be seen ranging from 10 to 1000 ppm. Peak E has a signal-to-noise ratio of *ca.* 10:1.

the present study only concerns methamphetamine. A typical FID signature of methamphetamine is shown in Fig. 1. Finally, the NPD offers some advantages over the previously used ECD. It has a higher stability, a larger linearity range and is sensitive only to nitrogen (and phosphorus) compounds. This means that many types of external contamination, *e.g.* by plastic bags or by gasoline (from smuggling in car tanks) are not displayed in the NPD signature.

Inter-variation

As indicated in the Introduction, the establishment of common sources of drugs is dependent on the inter-variation of their chemical signatures. The inter-variation can be estimated by analysis of casework samples, analysis of samples of batches synthesised under various controlled conditions or preferably by both types of analysis. However, during the time this study was carried out, methamphetamine turned out to be sparingly encountered on the Swedish market, in contrast to the markets of other countries, such as Japan.

The different types of inter-variation considered in this study are (i) the proportions of the starting materials, (ii) the reaction time and temperature in the first step of the synthesis, *i.e.* the condensation of phenylacetone and N-methylformamide, (iii) the effects of distillation and crystallisation in the final clean-up step and (iv) the coincidental variations seen upon repetition of syntheses under constant conditions. Another obvious source of inter-variation is the conditions of the hydrolysis step, *i.e.* the acid hydrolysis of the intermediate N-formylmethamphetamine; however, the time and resources available for this project did not permit investigation of this.

In a preliminary series of syntheses, it was revealed that the proportions of the starting materials had a strong effect, not only on the chemical signature but also on the yield of methamphetamine. Therefore, this source of variation was not further studied, because it may be assumed that synthetic routes giving low yields are avoided by "underground chemists" and consequently, this type of inter-variation does not necessarily contribute to the one encountered in casework analysis. For this reason the molar proportion 1:6:6, indicated in the Experimental section, was used throughout the study. The preliminary experiments further revealed that virtually all phenylacetone was consumed after 4 h at 160°C and these figures were therefore chosen as the lower limits for these parameters. The upper limit for the reaction temperature was set at 180°C, because the ketone tended to escape through the condensor at higher temperatures.

In general, the inter-variations observed were quantitative, *i.e.* pertaining to peak intensities of the chemical signatures. This result was expected, because all chemicals used in the syntheses were taken from the same batches. Batches IV, V and VI (*cf.* Table I) were synthesized under the same conditions on three consecutive days. Their signatures showed a pronounced similarity, although the variations were significantly greater than the intra-variation of batch IX, which will be discussed later.

The signatures of batches I and IV showed a still greater inter-variation than the one mentioned above, reflecting the combined effects of boiling time and boiling temperature. The single effects of each of these parameters seemed somewhat smaller. It should be pointed out, however, that all inter-variations among these four batches were of the same order of magnitude. This shows that the reaction mixture in the first step was near equilibrium after 4 h at 160°C.

Batches VI and VII were synthesized under the same conditions, the latter *ca.* 2 months later. Their signatures showed an inter-variation of a greater order of magnitude than the one mentioned in the previous paragraph. This indicates the difficulty of reproducing chemical signatures, and the question that immediately arises is what the variation would be if a series of syntheses were carried out by different operators. This seems likely to be an important source of inter-variation in comparative casework analysis.

A comparison of the signatures of batches VII and VIII demonstrated the effect of omitting the steam distillation in the clean-up step. This variation was larger than that observed among batches I–IV. Finally, the signatures of batches IX and X showed that the total intensity of the chemical signatures may be decreased by several orders of magnitude by recrystallisation of the final products. Obviously, this observation is somewhat trivial but it does not seem unlikely that this source of inter-variation plays a great role in comparative casework analysis.

Intra-variation

The following sources of intra-variation are considered in this study: (i) heterogeneity, (ii) instability of the main constituent, (iii) instability of the impurities and (iv) contamination. Comparative analysis of four random samples from batch IX showed a variation of the same order of magnitude as that corresponding to the slight irreproducibility of the GC process. This result is in accordance with earlier findings concerning amphetamine and phenmetrazine[1,2].

The stability of methamphetamine hydrochloride was studied by storing two 1-g samples from batch X in closed glass containers in darkness and in daylight (not direct sunlight), respectively, at room temperature. The original signature of this batch had not shown any peaks beyond the 1-ppm level. After storage for 5 months under the conditions mentioned above, the FID signatures showed *ca* five peaks around the 10-ppm level in both cases. The NPD signatures were unaffected. These results indicate either a slight instability of methamphetamine hydrochloride or a minor contamination by a slow adsorption process. The latter explanation seems more likely, however, because the degradation of methamphetamine would be expected to give rise to NPD peaks from nitrogen-containing degradation products.

Another two samples from batch X were stored in polyethylene bags under conditions corresponding to those mentioned above. In this case, storage in darkness gave an FID signature containing not only peaks corresponding to those mentioned above but also *ca* ten additional peaks. Storage in daylight further added to the FID signature a peak cluster at the 10-ppm level and a single peak at the 100-ppm level. Because the NPD signatures were again unaffected, the FID signatures observed indicate a slight bleeding from the container material. In the latter case, this bleeding was enhanced by daylight. Again, instability of the methamphetamine seems less likely.

The study of the stability of the individual impurities is greatly facilitated by using the capillary system, which permits their chromatographic resolution within a large concentration range. However, the time and resources available for this project dit not permit the study of the stability of individual impurities in more than one case. For this purpose, 1-g samples of batch IX were stored under the same conditions as batch X. The only effect seen after storage in glass containers was a decrease of the peak heights of two components having retention times of *ca.* 8 min. One of these components was known to be N-formylmethamphetamine. After storage in polyethylene bags these peaks vanished almost completely. The most likely explanation for these losses is evaporation. Furthermore, storage in polyethylene bags caused the same additional peaks in the FID signatures as in the case of batch X. With the exceptions mentioned above, the original FID and NPD signatures, each containing some twenty peaks, were virtually unaffected.

Interpretation

In this study, the chemical signatures obtained were compared visually. Computerised comparisons by means of a suitable similarity index may also be carried out using the latest generation of gas chromatographs. Because the computations concerned are based on peak intensities, the quality of these comparisons is enhanced by the high resolution of the capillary column.

The NPD signature has the advantage over the FID counterpart of being less sensitive to external contamination. It should be pointed out, however, that the NPD is inferior to the FID in some respects, such as long-term response stability.

All types of inter-variation observed in this study were significantly greater than the intra-variations. As far as the smallest inter-variation is concerned, *i.e.* among batches IV–VI, it should be pointed out that these syntheses were carried out with the aim of signature reproduction. This is hardly the aim for "underground chemists" in general, so that a much greater inter-variation is to be expected in

comparative casework. The risk of coincidental similarities, giving false positive results, is minimised by the large number of components in the signatures. Therefore, similarities such as those observed from random sampling of batch IX strongly indicate a common batch of synthesis.

As far as conclusions from dissimilarities are concerned, the risk of false negative results cannot be neglected. The main reason for this is the lack of a general study of the stability of methamphetamine signatures. There are, however, many factors that limit this type of intra-variation. Illegal drugs are likely to be stored near room temperature and in darkness. For many reasons, illegal drugs are short-lived on the black market and the time available for signature changes to develop is therefore limited. Changes of signatures due to evaporation are easily recognised in gas chromatograms, the lightest components being affected to the greatest extent. Batch IX was synthesised under conditions normally encountered in clandestine laboratories. The observed stability of the corresponding signature should therefore not be unusual. As far as methamphetamine is concerned, the large majority of the components of the FID signatures have their counterparts in the NPD signature. This means that many of these impurities are amino compounds. A corresponding picture is generally observed in amphetamine signatures. In solid drugs, these amines are in the form of salts and should therefore display a stability comparable with those of methamphetamine hydrochloride and amphetamine sulphate[1]. Although the individual importance of these factors is hard to estimate, it seems likely that they together strongly limit the risk of false negative results in comparative analysis of methamphetamine seizures.

Generalisations of comparative analysis of narcotics

For the forensic drug analyst, the question is whether a comparative method of the type described in this paper can be generalised in various respects. The possibility of establishing common sources of uni-component drugs was discussed in a previous paper of this series[2]. The establishment of different sources of methamphetamine seizures is discussed in the previous paragraph. A further generalisation concerns diluted and adulterated drugs and drug mixtures, *i.e.* the establishment of common or different sources of the individual constituents of drug mixtures. The corresponding mixed signatures will depend on the types of additive encountered as well as on their concentrations. It seems that the comparison of such signatures should be based on a limited number of selected components. These should correspond to the main impurities in the synthesis of the drug in question, ensuring their presence in most preparations containing that drug. Other prerequisites are of a statistical nature and concern inter- and intra-variation (of individual components, not signatures), distributions and correlations. This statistical approach is generally applied in many fields of forensic science[6]. Its applicability to comparative analysis of mixed drugs will be reported in future papers of this series. Generalised methods of comparative analysis may make it possible to develop a kind of drug intelligence work based on chemical signatures.

CONCLUSION

A GC method was developed for the display of chemical signatures of Leuck-

art-synthesised methamphetamine. The method permits the establishment of common sources with a high degree of reliability. As far as the establishment of different sources is concerned, false results may occur owing to possible instability of the impurities analysed.

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