

UNITED NATIONS INTERNATIONAL DRUG CONTROL PROGRAMME

SCIENTIFIC AND TECHNICAL NOTES

**SCITEC/17
AUGUST 2000**

**A practical guide to
METHAMPHETAMINE CHARACTERIZATION / IMPURITY PROFILING:**

**Method procedures, mass spectral data of selected impurities, and
literature references**



prepared by

**Scientific Section
Division for Operations and Analysis**

Table of contents

	<i>page</i>
1. INTRODUCTION	1
1.1. Background	1
1.2. UNDCP activities	1
1.3. Purpose of publication	2
2. EXPERIMENTAL PART	3
2.1. Purpose	3
2.2. Method procedures	3
2.2.1. Compressed Gases	3
2.2.2. Solvents, standard substances	3
2.2.3. Solutions	3
2.2.3.1. Buffer solution (pH 10.5)	3
2.2.3.2. Instrument performance solution (' <i>test mixture</i> ') ...	4
2.2.3.3. Internal standard solution for methamphetamine profiling (' <i>ISTD-prof</i> ')	4
2.2.3.4. Internal standard solution for calibration curve / methamphetamine purity determinations (' <i>ISTD-purity</i> ')	4
2.2.3.5. Methamphetamine calibration standards	5
2.2.4. Apparatus and equipment	5
2.2.5. Instrument parameters	6
2.3. Procedure to check instrument performance	7
2.4. Extraction of methamphetamine samples for impurity profiling	9
2.5. Determinations of drug content ("purity")	9
2.6. Data handling and analysis	10
3. MODEL TABLET IDENTIFICATION SHEET	12
4. MASS SPECTRAL DATA OF SELECTED IMPURITIES FOUND IN SEIZED SAMPLES OF METHAMPHETAMINE	14
5. SELECTED BIBLIOGRAPHY	21

1. INTRODUCTION

1.1. Background

Clandestine manufacture, trafficking and abuse of methamphetamine and the involvement of large-scale organized criminal groups in these activities, are increasing around the world, particularly in East and South East Asia, and North America. With ever larger consignments of clandestinely manufactured methamphetamine being intercepted, law enforcement authorities require enhanced capacity to identify the sources of supply of those drugs and to establish trafficking routes / distribution patterns and conspiracy links. A tool which adds valuable, scientific information in support of law enforcement intelligence gathering and operational work is drug characterization / impurity profiling, i.e., the systematic characterization of seized drug samples by physical and chemical means.

Worldwide, characterization / impurity profiling of seized drugs is increasingly viewed as a valuable complement to routine law enforcement investigative work. Chemical links between samples can be established, material from different seizures can be classified into groups of related samples, and the origin of samples can be identified. This information can be used for evidential purposes, or it can be used as a source of more general intelligence to identify trafficking patterns and distribution networks. Drug characterization / impurity profiling may also assist in the identification of output from new illicit laboratories, and in the monitoring of common methods used for drug manufacture, which, in turn, may provide information helpful to other intelligence gathering tools, for instance in precursor monitoring programmes. Finally, drug characterization studies may provide supportive evidence in cases where a differentiation of illicitly manufactured drugs from those diverted from legitimate sources is required.

1.2. UNDCP activities

In response to a mandate by the Commission on Narcotic Drugs (CND)¹, which recognized the need for a cohesive international strategy in this field, UNDCP's Scientific Section (Laboratory) has in recent years devoted resources to developing standard "methods for the profiling / signature analysis of key narcotic drugs and psychotropic substances". Activities are aimed at developing methods for the characterization / impurity profiling of those substances, at supporting basic research to assist in the interpretation of analytical results, and at assisting in the development of operational capacity, at national and regional levels, in drug and precursor characterization / impurity profiling. Work has concentrated so far on methamphetamine and its main precursor ephedrine, substances which were also specifically addressed in the action plan against illicit manufacture, trafficking and abuse of amphetamine-type stimulants (ATS) and their precursors, as endorsed by the 20th special session of the United Nations General Assembly (UNGASS) in June 1998. The geographic focus has been South East Asia, a region which is particularly affected by clandestine manufacture, trafficking, and abuse of methamphetamine.

Impurity profiling methods for methamphetamine and ephedrine have been developed by UNDCP. Analysis of samples using the methods developed has enabled the identification and/or confirmation of new trends in illicit manufacture, and the development of operational intelligence by law enforcement personnel in the countries concerned. As a result, more and more countries have shown an interest in the potential of drug characterization / impurity profiling work. The need to develop appropriate tools and operational programmes in this field

¹ CND Resolution I (XXXIX), adopted at CND 39th session, 1996.

was recently also agreed by participants at a sub-regional technical meeting² in Bangkok, Thailand, which discussed, in an operational framework, concepts, value and methods of methamphetamine characterization / impurity profiling.

1.3. Purpose of publication

The present note is intended as a practical guide for laboratories interested to embark on profiling activities³. It provides details of the method procedures developed by UNDCP⁴, mass spectral data of selected impurities found in seized samples of methamphetamine and ephedrine, as well as selected literature references. To facilitate their practical application, method procedures are presented with a high level of detail, i.e., in the form of standard operating procedures (SOP). It should be understood, however, that the exact methods and procedures depend on (i) the intended utilization of results, and (ii) the availability and specifications of the analytical equipment and data processing software available.

Finally, it is important to recognize that even in the absence of sophisticated analytical equipment a substantial scientific contribution to law enforcement operational work can be made on the basis of the systematic characterization of seized drug samples, i.e., the systematic comparison of samples based on their physical characteristics. This applies particularly to samples in tablet form. To facilitate the building of appropriate databases in this field, at both national and regional levels, a tablet identification sheet, which was agreed on at the Bangkok meeting, is also included as a model for the collection of standardized data.

² Sub-regional meeting on drug characterization / impurity profiling and its investigational value for law-enforcement authorities; special focus: methamphetamine in South East Asia, Bangkok, 6-8 June 2000.

³ See also UN publication entitled "Drug characterization / impurity profiling: background and concepts" (ST/NAR/32).

⁴ The method described has been tested and used by collaborating laboratories.

2. EXPERIMENTAL PART

2.1. Purpose

The method described below was developed by UNDCP's Scientific Section as a means for the characterization / impurity profiling of seized samples of methamphetamine⁵. It includes:

- (i) liquid/liquid extraction of neutral / basic impurities from methamphetamine, and gas chromatographic analysis of extracted impurities ("impurity profiling"),
- (ii) establishment of calibration curves and determination of the contents ("purity") in illicit samples of methamphetamine hydrochloride, and
- (iii) data handling and analysis.

Criteria for method development included (i) universality, i.e., the applicability of the method to methamphetamine samples synthesized via different synthesis routes, (ii) simplicity in extraction and analytical techniques, (iii) repeatability and reproducibility, and (iv) a focus on methamphetamine synthesis by-products which are mostly basic or neutral substances, as opposed to diluents, cutting agents, and substances carried over from starting materials or preparations thereof.

To facilitate the building of appropriate databases for methamphetamine tablets a model tablet identification sheet is also included (see Part 3 below).

2.2. Method procedures

2.2.1. Compressed Gases

Nitrogen is employed as carrier gas (>99.999% pure). FID gases are synthetic air (20.5 % O₂ in N₂) and hydrogen (>99.999% pure).

2.2.2. Solvents, standard substances

- **ethyl acetate**, spectroscopic grade
- **n-hexane**, for chromatography
- **phosphate buffer** (buffer solution ready for use, pH 7.00, ± 0.02, at 20 °C)
- **diphenylamine**
- **(+)-methamphetamine hydrochloride**
- **n-tridecane**
- **n-tetracosane**

2.2.3. Solutions

2.2.3.1. Buffer solution (pH 10.5)

- a) **10% (w/v) Na₂CO₃**: Weigh 10.0g of Na₂CO₃ in a 100ml volumetric flask. Dissolve in a small amount of distilled water. Fill with distilled water to the mark and shake. Label flask as to date and concentration. Discard solution after six months⁶.
- b) **Buffer solution (pH 10.5)**: Add 4 parts of phosphate buffer (pH 7) to one part of 10% (v/v) Na₂CO₃. Check pH, adjust to pH 10.5 by adding 10% Na₂CO₃, if

⁵ Necessary adjustments to this method for the impurity profiling of ephedrine samples are also included.

⁶ Note: The amount of any of the described solutions to be prepared depends on the sample throughput of individual laboratories. As a general rule, if properly stored, solutions which are not used for quantitation (including aqueous buffer solutions and retention time reference standards) can be used for a maximum of six months, all other solutions should be discarded after three months.

necessary. Solution can be stored at room temperature in a glass stoppered flask. Label flask as to date and concentration. Discard solution after six months.

2.2.3.2. Instrument performance solution ('test mixture')

Weigh out 7.0 mg ($\pm 5\%$) of (+)-methamphetamine hydrochloride into a 5 ml screw-capped glass tube, and add 1 ml of buffer (pH 10.5). Screw up tube and place it on the platform of a circular shaker. Shake for 5 minutes. Add 2 ml of n-hexane using a volumetric glass pipette. Shake for another 5 minutes. Centrifuge for 5 minutes at 3000 rpm and room temperature (approx. 21 °C).

Transfer 1.0 ml of the n-hexane phase into a 100ml glass stoppered volumetric flask using a volumetric glass pipette. Add 3.50 mg ($\pm 5\%$) of diphenylamine and 2.50 mg ($\pm 5\%$) of n-tetracosane. Record actual weight to the tenth of a milligram. Dilute to the mark with hexane. Shake final solution. Concentrations obtained: approx. 35mg/l of (+)-methamphetamine hydrochloride, 35mg/l of diphenylamine and 25mg/l of n-tetracosane.

Label the flasks as to date and concentrations. Seal with Parafilm™, and store in the refrigerator. Discard solution after three months. When removed from the cold, fill an autosampler vial, and let the solution equilibrate to ambient temperature.

2.2.3.3. Internal standard solution for methamphetamine profiling ('ISTD-prof')

- a) **Stock internal standard solutions:** Weigh out 25.0 mg ($\pm 5\%$) of n-tridecane (C₁₃), 35.0 mg ($\pm 5\%$) of diphenylamine and 20.0 mg ($\pm 5\%$) of n-tetracosane (C₂₄)⁷ into separate 10 ml volumetric flasks using an analytical balance. Record the actual weight to the tenth of a milligram. Dissolve each substance in a small amount of ethyl acetate. Dilute with ethyl acetate to the mark of each volumetric flask. Shake final solutions. Label each stock solution as to date and concentration. Discard solutions after three months. When not in use, stopper, seal the top of the flasks with Parafilm™, and store in refrigerator.
- b) **Internal standard solution ('ISTD-prof')**: Remove the *stock internal standard solutions* prepared above from the cold and allow them to equilibrate to ambient temperature. Transfer as much of each *stock internal standard solution* into a 100ml glass stoppered volumetric flask as to get the following concentrations: n-C₁₃ at 25 mg/l, diphenylamine at 35 mg/l and n-C₂₄ at 20 mg/l. Dilute with ethyl acetate to the mark. Shake final solution. Label the flask as to date and concentration. Discard solution after three months. When not in use, stopper, seal the top of the flask with Parafilm™, and store in refrigerator. Before use, when removed from the cold, allow the solution to equilibrate to ambient temperature.

2.2.3.4. Internal standard solution for calibration curve / methamphetamine purity determinations ('ISTD-purity')

Weigh out 50.00 mg ($\pm 5\%$) of diphenylamine into a glass stoppered 100ml flask using an analytical balance. Record the actual weight to the hundredth of a milligram. Dissolve in a small amount of ethyl acetate. Dilute with ethyl acetate to the mark and shake. Label solution as to date and concentration. Discard solution after three months. When not in use, stopper, seal the top of the flask with Parafilm™, and store in refrigerator. Before use, when removed from the cold, allow the solution to equilibrate to ambient temperature.

⁷ The two hydrocarbon ISTDs are used to bracket the impurity peaks of interest, to enable synchronization of the time axis of different chromatograms.

2.2.3.5. Methamphetamine calibration standards

- a) **Methamphetamine stock solution:** Weigh out 30.00 mg ($\pm 5\%$) of (+)-methamphetamine hydrochloride into a 15 ml screw-capped glass vial using an analytical balance. Record the actual weight to the hundredth of a milligram. Add 1 ml of buffer solution (pH 10.5). Screw up tube and place it on the platform of a circular shaker. Shake for 5 min. Add 12 ml of '*ISTD-purity*' solution. Shake for another 5 min. Centrifuge sample for 5 min at 3000 rpm and room temperature (approx. 21 °C). Transfer 10 ml of organic layer into a screw-capped glass vial using a 10ml volumetric pipette. Label flask as to date and concentration of methamphetamine hydrochloride (approx. 2.5 mg/ml). Discard solution after preparation of the different calibration standards.
- b) **Methamphetamine calibration standards:** Transfer the required amount of stock solution into a 1 ml volumetric flask using a 100 μ l-syringe. Add '*ISTD-purity*' solution using the same syringe (i.e., wash it into flask), then dilute with '*ISTD-purity*' solution to the mark and shake. Each concentration is prepared directly from the stock solution. Keep calibration standards for the period of use of the corresponding calibration curve (see 2.5.1, below).

2.2.4. Apparatus and equipment

2.2.4.1. Gas chromatograph

The gas chromatograph (GC) is equipped with a GC autosampler controller, an autosampler tray, an automatic injector, and a flame ionization detector (FID).

A fused silica capillary column, 25 m x 0.2 mm x 0.33 μ m, crosslinked, 5% phenylmethylsilicone, is used for analysis.

Split/splitless injection port liners are used. To avoid any loss of chromatographic performance, liners should be continuously checked for contamination and replaced at least once a month. Used liners can be cleaned with chromic sulphuric acid (by immersion overnight). They are then rinsed with distilled water and dried. Silanization is achieved by immersion overnight in a solution of 5% DMDCS (dimethyldichlorosilane) in toluene. Liners are then rinsed twice with toluene, and immediately afterwards with absolute methanol. They are dried under clean nitrogen.

The septum should be replaced after approx. 100 injections.

2.2.4.2. Vials

5ml screw-capped glass vials with 1.2 cm outer diameter⁸ are used for the extraction procedures (methamphetamine and ephedrine samples for impurity profiling).

Clear 2 ml autosampler vials with microvolume glass inserts (100 μ l, with polymer support feet) and plastic open-top screw-caps with silicone / teflon septa are used for GC analysis.

15 ml screw-capped glass vials are used for the preparation of the methamphetamine stock solution for calibration standards.

⁸ A small diameter of the tube is desirable as it determines the height (and thus, the ease of recovery) of the organic phase.

2.2.4.3. Analytical balance

The balance used has a readability of 0.1 mg and 0.01 mg, respectively. The balance is calibrated daily using the manufacturer's internal calibration procedure.

2.2.4.4. Shaker

The shaker is a circular shaker with a foam-top platform.

2.2.4.5. Other

Automatic pipette with 5 ml and 2.5 ml tips.

Disposable Pasteur pipettes, 20 cm.

pH Indicator stripes (pH 7.5-14 and pH 5.0-10.0, respectively).

2.2.5. Instrument parameters

2.2.5.1. Gas flows

The FID gases air and hydrogen are set to 2.5 bar ($\pm 5\%$) and 1.4 bar ($\pm 10\%$), respectively. The corresponding flow rates are approx. 300 ml/min and 30 ml/min, respectively (measured with a bubble flow meter).

The carrier gas nitrogen is set to 150 kPa (approx. 22 psi), corresponding to a column flow of 1.4 ml/min at 50°C oven temperature (measured with a bubble flow meter). The total nitrogen flow (carrier gas plus make-up gas) is 30 ml/min.

2.2.5.2. Injection mode

Splitless injection is used, the valve is closed for 1 min. Split vent is set to 30 ml/min.

2.2.5.3. Parameters for automatic injector

Sample washes	1
Sample pumps	5
Injection volume	1.0 μ l
Syringe size	10.0 μ l
Post injection washes	6
Viscosity delay	2 seconds
Plunger speed	fast

2.2.5.4. Temperature programming

Injector temperature	250°C
Detector temperature	300°C
Initial temperature	50°C (for 1 min)
Final temperature	300°C (for 4 min)
Temperature rate	10°C/min
Oven equilibrium time	2 min

The total run time is 30 min.

2.2.5.5. Signal parameters

Peak width	0.013
Sampling rate	10 Hz
Signal plot	10% offset

2.2.5.6. Sequence of injection

- ▶ solvent (instrument blank)
- ▶ reference (check) sample in duplicate⁹ (i.e., replicate extractions)
- ▶ 2 method blanks (i.e., replicate blank extractions)¹⁰
- ▶ 1 sample in duplicate¹¹ (i.e., replicate extractions of the same sample)
- ▶ solvent (instrument blank)
- ▶ 1 sample in duplicate
- ▶ solvent (instrument blank)
- ▶ 1 sample in duplicate
- ▶ solvent (instrument blank)
- ▶ reference (check) sample
- ▶ solvent (instrument blank)
- ▶ 1 sample in duplicate
- ▶ solvent (instrument blank)
- ▶ 1 sample in duplicate
- ▶ solvent (instrument blank)
- ▶ 1 sample in duplicate
- ▶ solvent (instrument blank)
- ▶ reference (check) sample

This sequence is recommended provided that proper instrument performance (i.e., checking by injection of 'test mixture') is ensured before starting the sequence (see 2.3. below).

The maximum number of samples (including blanks, check samples, etc.) should ideally not exceed 26¹².

2.3. Procedure to check instrument performance

2.3.1. To check basic column performance, perform analysis of the 'test mixture' daily, for example, each time after turning on the GC.

Shewhart charts (see [Figure 1](#)) are created based on date and peak area ratios of methamphetamine / diphenylamine and n-C₂₄ / diphenylamine, respectively. The standard deviation (STDEV) is determined based on the mean of 10 consecutive injections of the instrument performance solution ('test mixture') on the same day. The warning limit of instrument performance is within two STDEVs, the action limit within 3 STDEVs of the area ratios of

⁹ A reference (check) sample is prepared from a stock of methamphetamine sample available in sufficient quantity to allow for repeated analyses over a prolonged period of time to ensure comparability of results.

¹⁰ As part of every sequence, two method blanks should be prepared and analyzed. To this end, steps 2.4.2 to 2.4.8 (see below) should be carried out, without methamphetamine being present.

¹¹ Two injections of the same sample without a solvent run in between require that it has been previously determined that none of the impurities of interest causes a memory effect. Memory of methamphetamine itself does not pose a problem since this peak is of no interest in the comparison of impurity profiles.

¹² Sequences longer than 18 hours should be avoided as samples late in the sequence, kept at room temperature, may degrade.

methamphetamine / diphenylamine, and n-tetracosane / diphenylamine, respectively. The acceptance criteria are drawn as follows (see [Figure 1](#)):

- warning limit: $mean \pm 2 STDEV$
- action limit: $mean \pm 3 STDEV$.

If acceptance criteria are not met, the column must be conditioned (see 2.3.3. below) or a new column used.

2.3.2. To check specific instrument performance (i.e., suitability of instrument status for methamphetamine profiling), perform analysis of a methamphetamine check sample as part of every sequence, as described in 2.2.5.6. Repeated GC impurity profiles of the check sample have to show similarities, based on the same criteria as overall sample comparison, which are acceptable within the chosen comparison criteria (i.e., they should show the closest similarities).

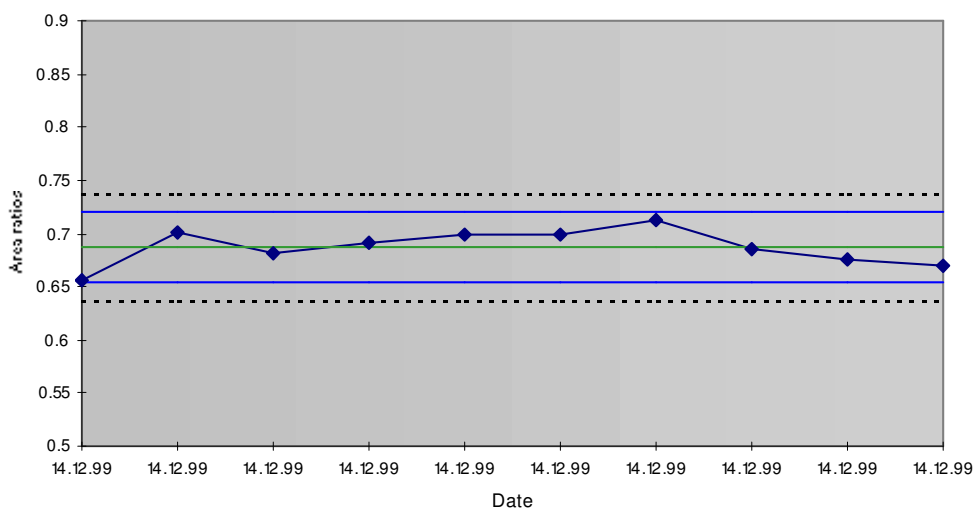


Figure 1. 'Test mixture' analyzed 10 times on the same day. The upper and lower lines bracket the range of acceptance (warning limit and action limit, respectively) of the area ratio of methamphetamine / diphenylamine.

2.3.3. If the instrument performance solution ('test mixture') does not meet the acceptance criteria (action limit), especially after a change of the column, the new column can be conditioned using injections of pyridine, until criteria are met. The ultimate acceptance criterion is the repeatability of the check sample (see 2.3.2 above).

2.4. Extraction of methamphetamine samples for impurity profiling¹³

- 2.4.1. Homogenize illicit sample material in a mortar and weigh 30.0 mg ($\pm 5\%$) of illicit sample material into a 5 ml screw-capped glass tube using an analytical balance. Record the actual weight to the tenth of a milligram.
- 2.4.2. Add 1 ml of buffer solution (pH 10.5) using an automatic pipette with a 5 ml tip.
- 2.4.3. Screw up tube, and place it on the platform of a circular shaker. Shake the sample for 5 min. Check and record pH with pH indicator stripes (pH 7.5-14), record colour of water phase, and the appearance of a precipitate or insoluble material, if any.
- 2.4.4. Add 200 μ l of '*ISTD-prof*' solution using an automatic pipette with a 2.5 ml tip. Screw up.
- 2.4.5. Place tube on the shaker platform, and shake it for another 5 min. Record colour of organic phase.
- 2.4.6. Centrifuge for 5 min at 3000 rpm and room temperature (approx. 21 °C).
- 2.4.7. Transfer the organic layer with a disposable Pasteur pipette into a 2 ml autosampler vial with glass insert, and close it with silicone/teflon caps.
- 2.4.8. Analyze the sample on the same day of extraction.

2.5. Determinations of drug content ("purity")¹⁴

Calibration standards should be prepared so that they cover the range of concentrations expected in the unknown samples. It is useful to prepare at least 6 calibration standards (six-point calibration) across a range of 50% to 150% of the expected sample concentration.¹⁵ Each calibration point is calculated based on two injections of each standard. The calibration should be linear across the range of likely use, i.e., correlation coefficient > 0.999.

The calibration points are constructed by calculating the amount ratio (*concentration of component* divided by *concentration of internal standard*) and response ratio (*area of component* divided by *area of internal standard*).

The equation for the curve through the calibration points is calculated using the following type of curve fit: Curve type: *linear*

Origin: *included*

Weight: *equal*

2.5.1. Extraction of methamphetamine samples for drug content determinations

Weigh out approx. 2.50 mg ($\pm 5\%$) of seized methamphetamine into a 5 ml screw-capped glass tube using an analytical balance. Record the actual weight to the hundredth of a milligram. Add 2 ml of buffer solution (pH 10.5) using an automatic pipette with a 5 ml tip. Screw up tube, and place it on the platform of a circular shaker.

¹³ A suitable extraction procedure for **ephedrine samples** is as follows:
100 mg homogenized sample material
+ 1 ml buffer (pH 7.0), shake, centrifuge
+ 0.2 ml ethyl acetate containing three ISTDs ('*ISTD-Prof*', see 2.2.3.3 above) shake, centrifuge

Analytical conditions are the same as for methamphetamine (see 2.2.4.1 and 2.2.5 above).

¹⁴ As an easy means for the quick comparison of illicit methamphetamine samples based on the ratios of their methamphetamine, ephedrine, and caffeine 'contents', manual integration of the three peaks, and calculation of the respective peak area percentages, can be used.

¹⁵ To cover the range of concentrations of methamphetamine in illicit tablets from Thailand, calibration standards starting at a concentration of approx. 30 ng/ μ l, and additional standards in 150 ng/ μ l-steps, have proven to be suitable. For methamphetamine samples of very high purity ("ice"), a separate calibration curve should be prepared, covering a concentration range from approx. 0.6 μ g/ μ l to 2 μ g/ μ l.

Shake for 5 min. Add 2 ml of 'ISTD-purity' solution using a 2 ml volumetric glass pipette, and screw up. Place tube on the shaker platform, and shake it for another 5 min. Centrifuge for 5 min at 3000 rpm and room temperature (approx. 21 °C). Transfer organic layer with a disposable Pasteur pipette into a 2ml autosampler vial, and close it with a silicone/teflon cap. Analyze the sample on the same day of extraction. Every fourth sample in the GC sequence should be a 'purity check sample', i.e., an aliquot of an original methamphetamine calibration standard. The quantitative results (in ng/μl) of these samples should be within ± 5% of the true value.

2.5.2. Calculation of drug content of unknown samples

The amount of methamphetamine hydrochloride (in ng/μl) is calculated based on an internal standard report. Conversion into percent (%) purity is based on the amount of methamphetamine weighed out initially. In addition, for tablets, the total amount (in mg) of methamphetamine hydrochloride is calculated.

2.6. Data handling and analysis

The sophistication of impurity data analysis can range from comparison and evaluation of a limited number of peak area ratios to multivariate data analysis, or a combination thereof. Visual comparison of chromatograms for final conclusions is recommended.

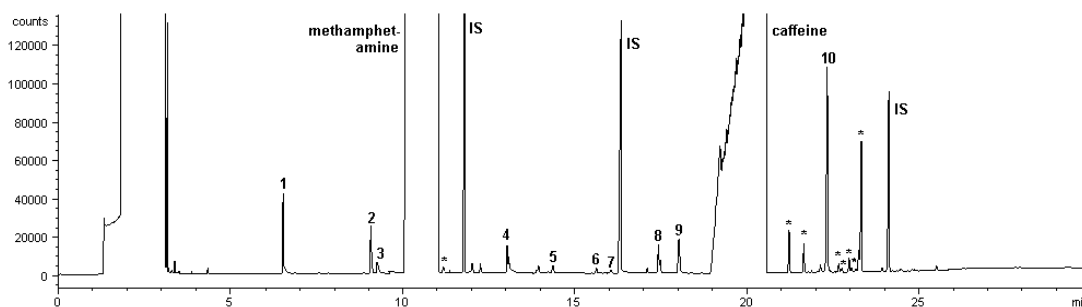


Figure 2: Impurity profile of a typical methamphetamine tablet (IS = internal standard).

Selected impurities include: (1) benzaldehyde, (2) cis-1,2-dimethyl-3-phenylaziridine, (3) amphetamine, (4) 3,4-dimethyl-5-phenyl-oxazolidine¹⁶, (5) ethyl vanillin (known to be frequently added as flavouring agent), (6) N-methyl-ephedrine, (7) N-formylmethamphetamine, (8) N-acetylmethamphetamine, (9) N-acetylephehrine, and (10) methamphetamine dimer.

For MS spectra of these and other impurities found in seized samples of methamphetamine, see Part 4 below.

Note: Asterisks (*) indicate peaks which appear to be useful for the screening of impurity profiles. These peaks were characterized in terms of retention time and MS spectra, but could not yet be identified.

Figure 2 shows the impurity profile of a typical methamphetamine tablet. The selection of peaks for comparison depends on the intended utilization of results and the availability of software for data analysis. If, for example, links are to be made at the level of the source of the methamphetamine powder material (i.e., differentiating at the level of the clandestine methamphetamine laboratories), only peaks of synthesis by-products and not of cutting agents should be used. In general, the following selection criteria should be applied:

¹⁶

Ephedrine has the same retention time. However, the distinction between ephedrine and the oxazolidine, based on GC data only, does not pose a problem since the ephedrine peak, if present, is usually quite large. In none of the methamphetamine tablet samples examined, ephedrine was present in concentrations approaching the impurity level.

- high frequency of occurrence in multiple samples (i.e., relevance of peak);
- no artifacts;
- no co-eluting peaks, i.e., peaks should be single compounds;
- good repeatability (ideally: CV < 5-10%); therefore, highly volatile compounds at the beginning of the chromatogram should be avoided;
- if possible, selected peaks should be linked to synthesis routes.

In general, for GC data comparison, both relative retention times and relative peak areas (ratios) should be used. Normalization of peak heights is another suitable option. The selection of integration events should involve the use of a representative, seized methamphetamine sample containing relevant impurities in usually encountered concentrations (e.g., the reference (check) sample). It should follow common integration practice and the GC instrument manufacturer's procedure.

The establishment of a database on physical (and relevant chemical) data as well as background information is recommended.

3. MODEL TABLET IDENTIFICATION SHEET

TABLET IDENTIFICATION SHEET

Name of Laboratory:

Case Agency / Case Officer:
Tel./Fax:

















Laboratory Code No.

Case No.

Name of drug:		Date received:
Place of seizure:	Date of seizure:	Size of seizure:

No. of tablets, etc. received:

Comments:

PLAN	1  4  7  2  5  8  3  6  9 Other:	COATING	39. Uncoated 40. Film coated 41. Sugar coated 42. Undecided 43. Other (please specify):	
ELEVATION	10  13  15  11  14  16  12  17  17 Other:	MARKING	44. Unmarked 45. Logo only 46. Alphanumeric only 47. Logo & Alphanumeric 48. Undecided 49. Other (eg Greek, Arabic; please specify):	
COLOUR TYPE	18. Solid 19. Mottled 20. Undecided 21. Other (please specify):		50. Embossed 51. Relief 52. Imprinted	
COLOUR	22. White 23. Red 24. Orange 25. Yellow 26. Green 27. Blue 28. Violet/Purple 29. Grey 30. Brown	31. Pink 32. Black 33. Colourless 34. Silver 35. Gold 36. Bicoloured 37. Multicoloured 38. Undecided	SCORING	53. Unscored 54. ½ scored, no mark 55. ½ scored, mark same side 56. ½ scored, mark other side 57. ½ scored, mark both sides 58. ¼ scored, no mark 59. ¼ scored, mark same side 60. ¼ scored, mark other side 61. ¼ scored, mark both sides 62. Undecided

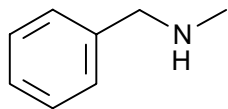
Detailed description:	Reproduce markings; use upper and lower case as appropriate:
SIZE <input style="width: 60px;" type="text"/> mm <input style="width: 60px;" type="text"/> mm (Diameter) (Thickness)	WEIGHT <input style="width: 60px;" type="text"/> mg
MARKING <input style="width: 60px;" type="text"/> <input style="width: 60px;" type="text"/>	

DRUG CONTENT	%	mg
--------------	---	----

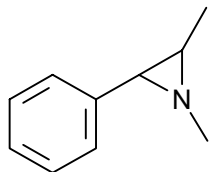
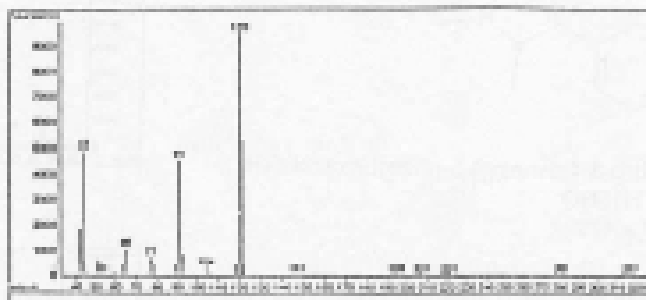
Other observations (e.g., smell):

**4. MASS SPECTRAL DATA OF SELECTED IMPURITIES
FOUND IN SEIZED SAMPLES OF METHAMPHETAMINE**

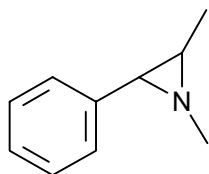
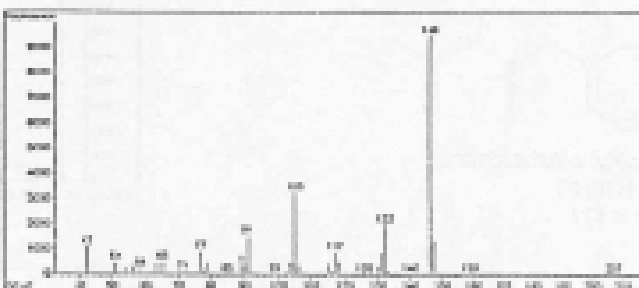
(Mass spectral data sorted by molecular weight)



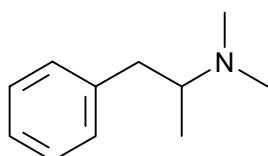
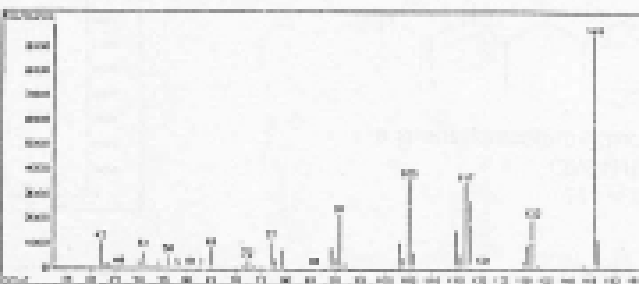
N-methylbenzylamine
C₈H₁₁N
MW = 121



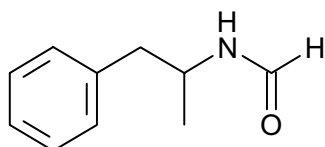
trans-1,2-dimethyl-3-phenylaziridine
C₁₀H₁₃N
MW = 147



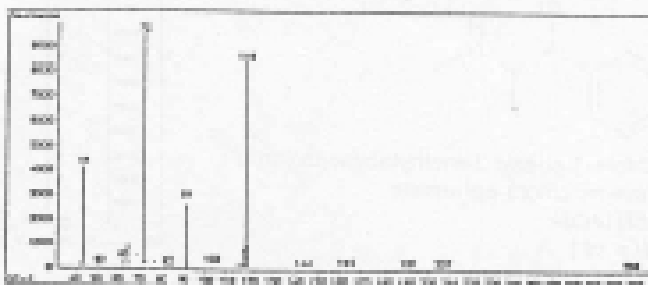
cis-1,2-dimethyl-3-phenylaziridine
C₁₀H₁₃N
MW = 147

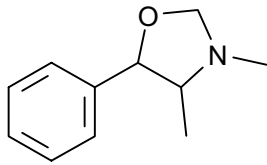


N,N-dimethyl-amphetamine
C₁₁H₁₇N
MW = 163

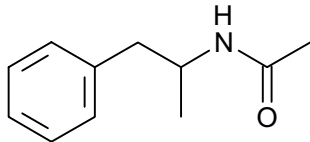
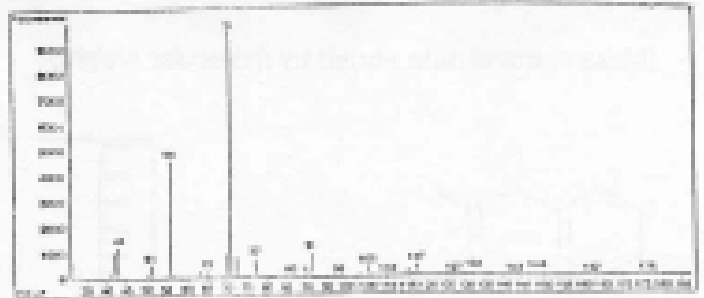


N-formyl-amphetamine
C₁₀H₁₃NO
MW = 163

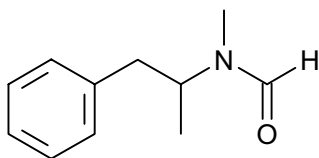
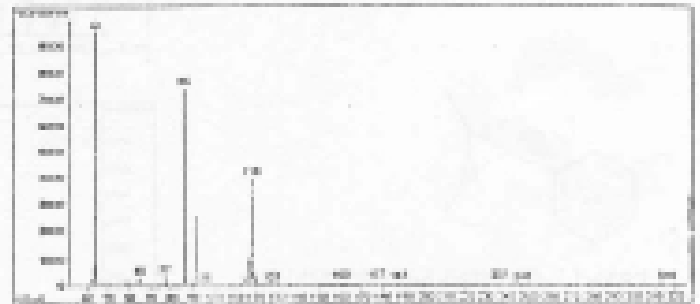




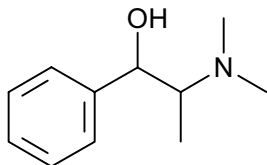
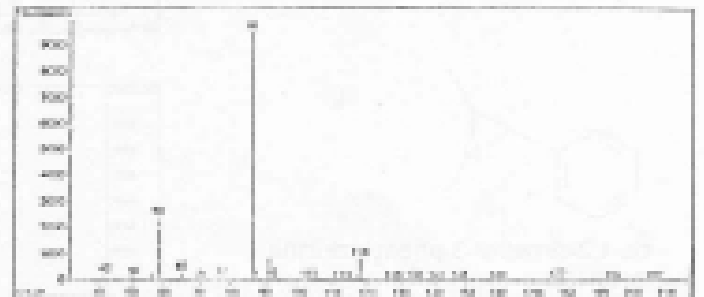
erythro-3,4-dimethyl-5-phenyl-oxazolidine
 C₁₁H₁₅NO
 MW = 177



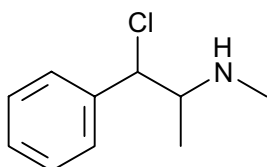
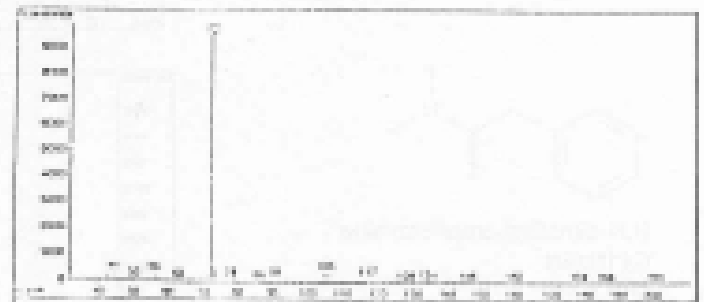
N-acetyl-amphetamine
 C₁₁H₁₅NO
 MW = 177



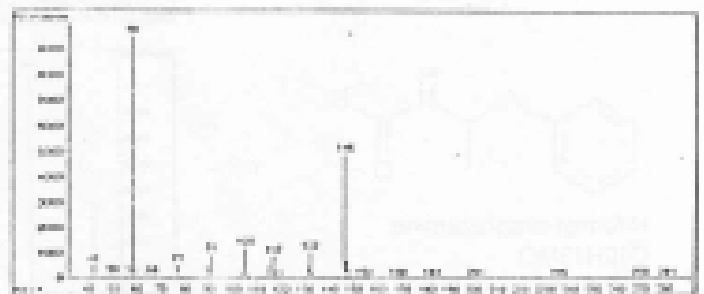
N-formyl-methamphetamine
 C₁₁H₁₅NO
 MW = 177

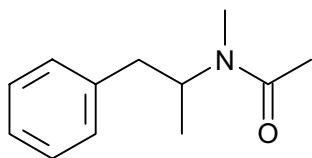


(1R,2S)-(-)-N-methylephedrine
 C₁₁H₁₇NO
 MW = 179

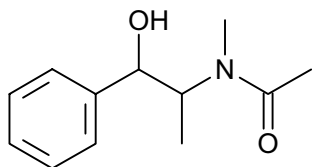
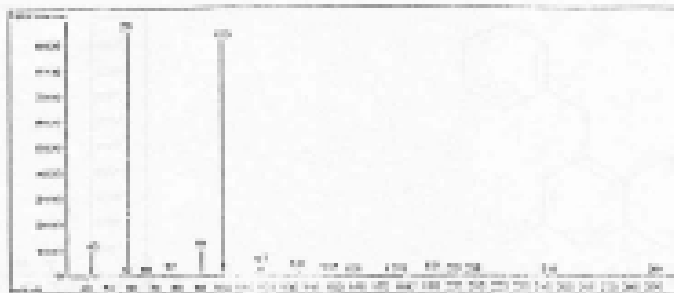


1-chloro-1-phenyl-2-methylaminopropane
 synonym: chloro-ephedrine
 C₁₀H₁₄ClN
 MW = 183

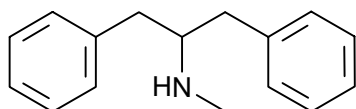
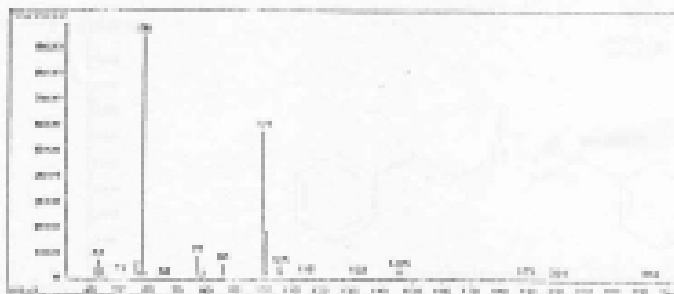




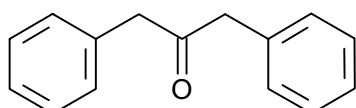
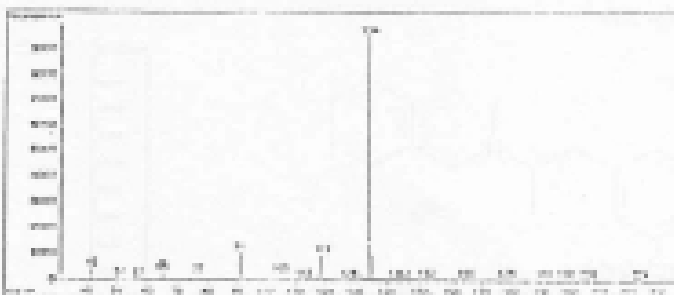
N-acetyl-methamphetamine
C₁₂H₁₇NO
MW = 191



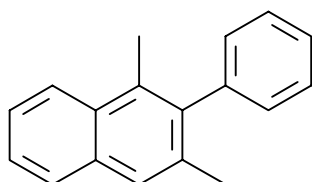
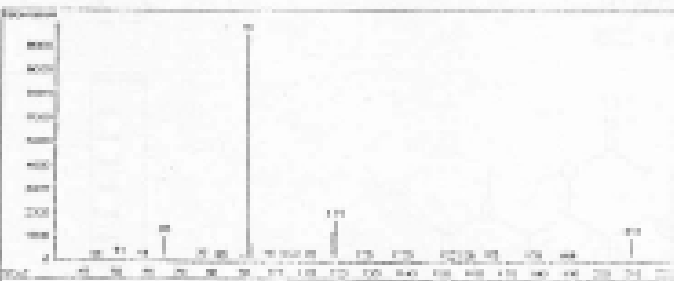
N-acetyl-ephedrine
C₁₂H₁₇NO₂
MW = 207



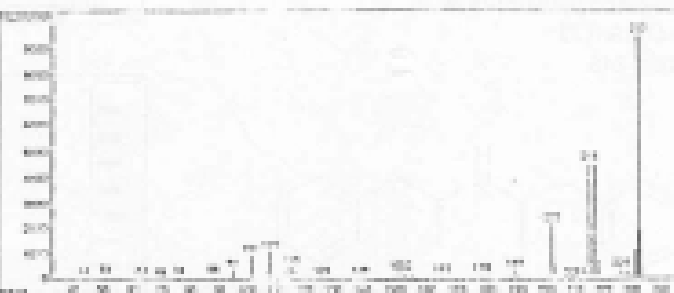
N-methyl-2-(1,3-diphenyl)propylamine
synonym: α -benzyl-N-methylphenethylamine
C₁₆H₁₉N
MW = 225

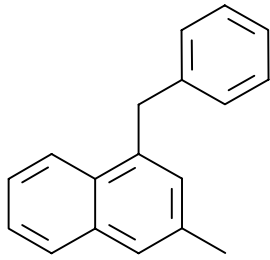


dibenzylketone
C₁₆H₁₉O
MW = 227

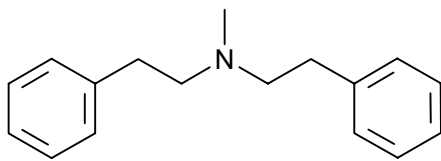
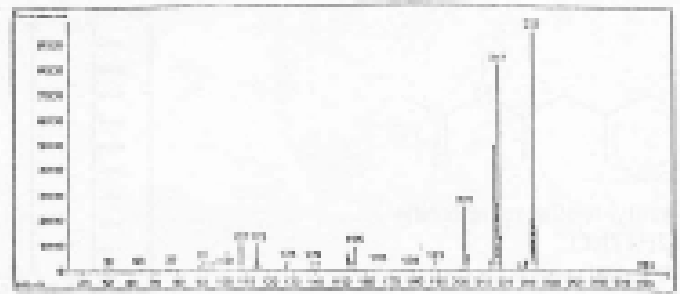


1,3-dimethyl-2-phenylnaphthalene
synonym: naphthalene A
C₁₈H₁₆
MW = 232

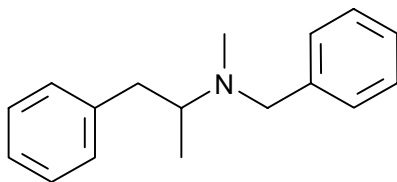
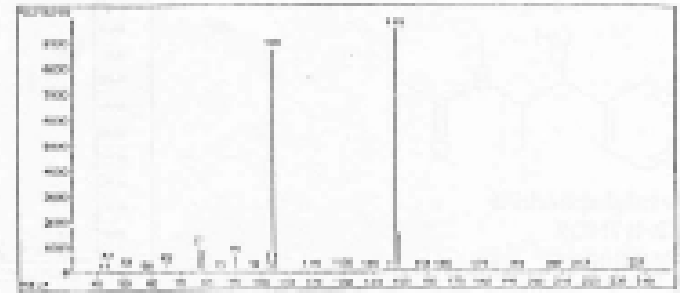




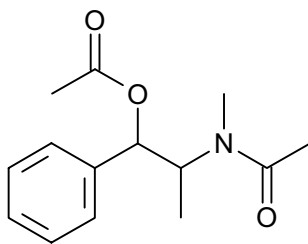
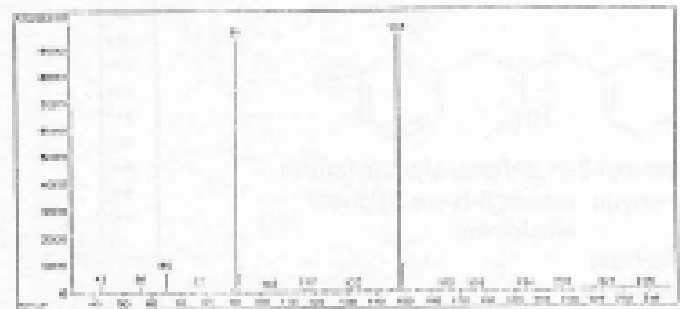
1-benzyl-3-methylnaphthalene
 synonym: naphthalene B
 C₁₈H₁₆
 MW = 232



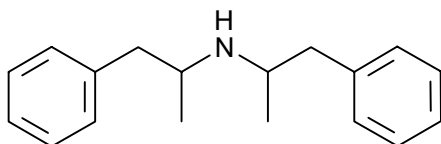
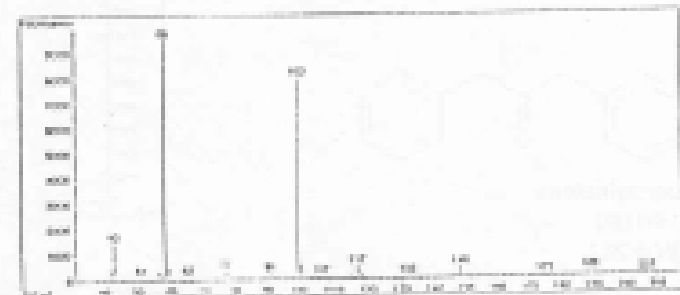
N-methyl-di-β-phenethylamine
 C₁₇H₂₁N
 MW = 239



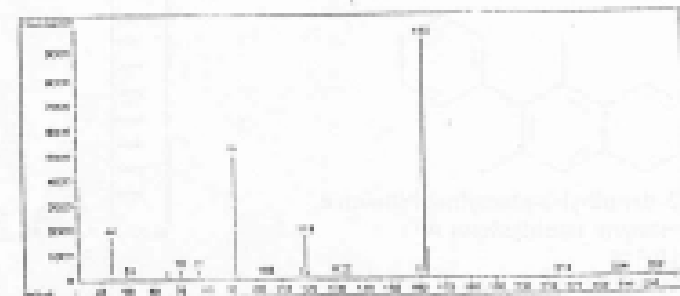
benzfetamine
 synonym: N-benzyl-methamphetamine
 C₁₇H₂₁N
 MW = 239

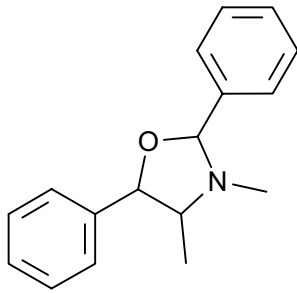


N,O-diacetyl-ephedrine
 C₁₄H₁₉NO₃
 MW = 249

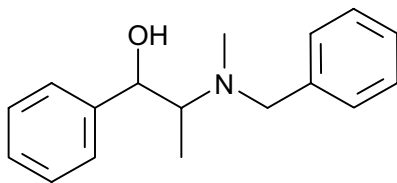
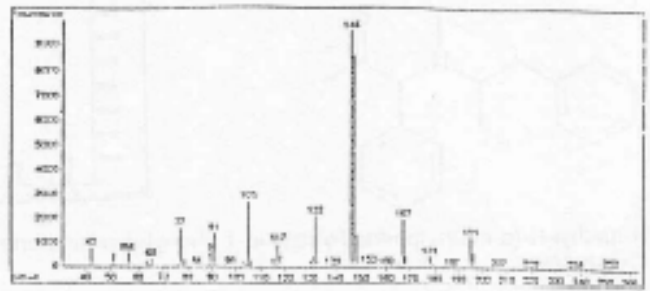


N,N-di(β-phenylisopropyl)-amine, diastereomer
 synonym: diphenylisopropylamine (DPIA)
 C₁₈H₂₃N
 MW = 253

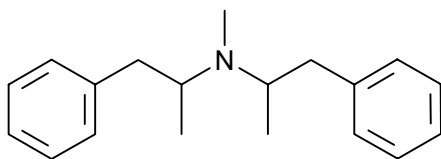
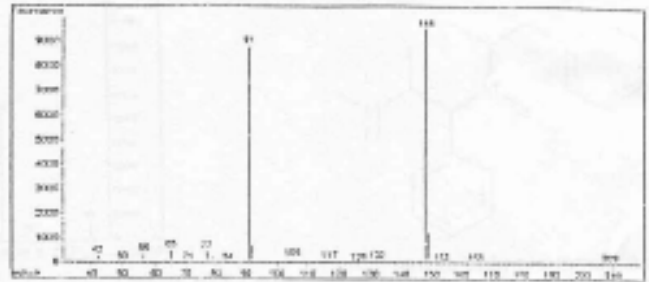




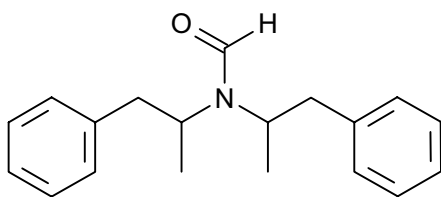
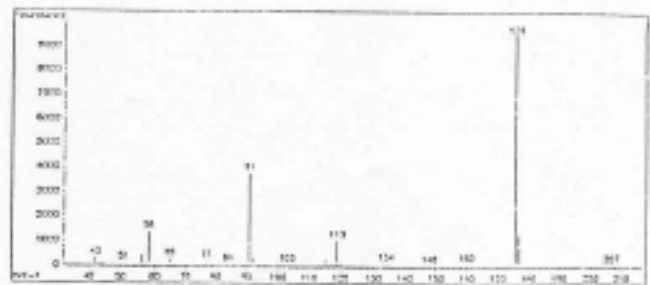
erythro-3,4-dimethyl-2,5-diphenyl-oxazolidine
 C₁₇H₁₉NO
 MW = 253



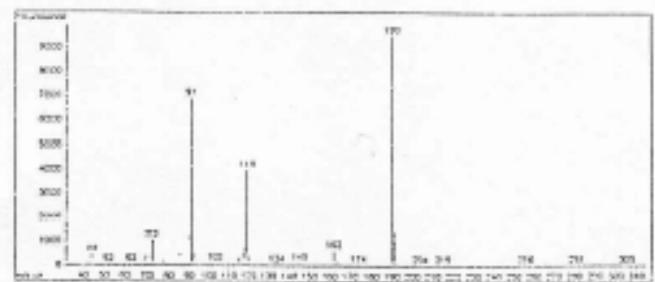
N-benzyl-ephedrine
 C₁₇H₂₁NO
 MW = 255

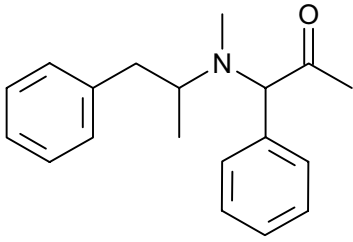


N,N-di(β -phenylisopropyl)-methylamine,
 diastereomer
 synonym: diphenylisopropylmethylamine (DPIMA)
 C₁₉H₂₅N
 MW = 267

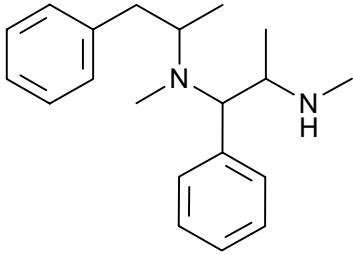
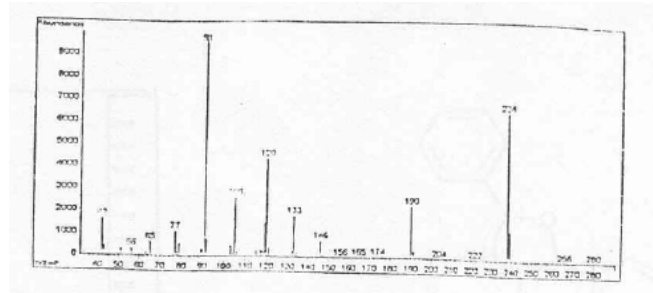


N,N-di(β -phenylisopropyl)-formamide,
 diastereomer
 synonym: N-formyl-diphenylisopropylamine
 C₁₉H₂₁NO
 MW = 279

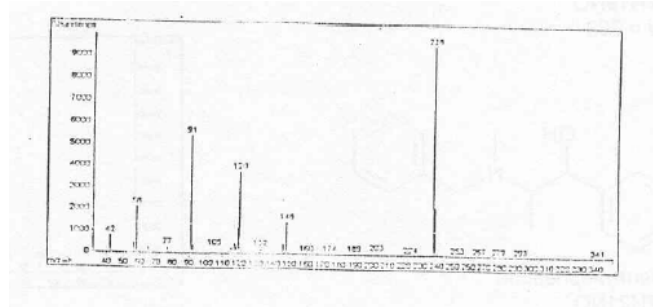




N-methyl-N-(α -methylphenethyl)amino-1-phenyl-2-propanone
 $C_{19}H_{23}NO$
 MW = 281



methamphetamine dimer
 $C_{20}H_{28}N_2$
 MW = 296



5. SELECTED BIBLIOGRAPHY

- 5.1. Tablet characterization, dyes
- 5.2. Methamphetamine (general)
 - 5.2.1. Methamphetamine from ephedrine
 - 5.2.2. Methamphetamine from P2P
- 5.3. Amphetamine
- 5.4. Ephedrine / pseudoephedrine
- 5.5. 1-Phenyl-2-propanone (P2P)
- 5.6. Miscellaneous chemistry
- 5.7. Data analysis
- 5.8. Other (including profiling and clandestine laboratories)

5.1. Tablet characterization, dyes

Gomm, P.J., Identification of the Major Excipients in Illicit Tablets Using Infra-red Spectroscopy, CRE Report No. 160.

Gomm, P.J., et al., Physical Methods for the Comparison of Illicitly Produced Tablets, CRE Report No.187, 1976.

Gomm, P.J., An Investigation of the Properties of Illicitly Produced Tablets, HOCRE Report No.252, 1977.

Joyce, J.R., The Identification of Dyes in Illicit Tablets, J. Forensic Sci., 20, 1980, pp.247-252.

Joyce, J.R., et al., The Use of HPLC for the Discrimination of a Range of Dylon Home-dyeing Products and Its Potential Use in the Comparison of Illicit Tablets, J. Forensic Sci. Soc., 22, 1982, pp.337-341.

Joyce, J.R., et al., Comparison of Extraction Procedures for Insoluble Food Dyes in Illicit Drug Preparations, HOCRE Report No. 341.

Joyce, J.R., et al., A procedure for the Identification of Soluble Food Dyes in Illicit Drug Preparations, J. Forensic Sci., 19, 1979, pp.203-209.

Joyce, J.R., et al., The Detection of Trace Impurities in Soluble Food Dyes, J. Forensic Sci. Soc., 22, 1982, pp.253-256.

5.2. Methamphetamine (general)

Anonymous, Clandestine Synthesis of Methamphetamine - The Whole Drug Manufacturer's Guide, Microgram, 13(8), 1980, pp.137-141.

Anonymous, A Novel Synthesis of Methylamphetamine, Microgram, 19(12), 1986, pp.164-165. (Reprint from Analog, 8(3), October 1986)

Anonymous, Methamphetamine Blotter Papers and Steroid Pellets Reported in Michigan, Microgram, 29(8), 1996, p.198.

Burton, B.T, Heavy Metal and Organic Contaminants Associated with Illicit Methamphetamine Production, in: NIDA Research Monograph Series 115, Methamphetamine Abuse: Epidemiologic Issues and Implications, 1991, pp.47-59.

Cutler, R., White Phosphorous Replacing Red Phosphorous in Idaho, JCLICA, 8(1), 1988, pp.3-5.

Ely, R.A., Serial Dry Extraction of Illicit Methamphetamine Powders for the Identification of Adulterants and Diluents by Infrared Spectroscopy, JCLICA, 3(1), 1993, pp.21-23. (Summary, Microgram, 26(4), 1993, p.59)

Fonseca, A., Separation and Identification of Trimethyldiphenethylamine in Illicit Methamphetamine, Microgram, 11(2), 1978, pp.18-23.

Henderson, B.A., et al., Clandestine Manufacture of Hydriodic Acid via Iodine, Red Phosphorous, and Hydrochloric Acid, Microgram, 27(11), 1994, pp.382-385.

Kazankov, S.P., et al., The Methods of Methamphetamine Syntheses Most Commonly Used in Russia, JCLICA, 5(2), 1995, pp.12-13.

Kishi, T., Analysis of Trace Elements in Methamphetamine Hydrochloride by Inductively Coupled Plasma-Mass Spectrometry, Journal of Research of the National Bureau of Standards, 93(3), 1988, pp.469-471.

Marumo, Y., et al., Analysis of Inorganic Impurities in Seized Methamphetamine Samples, Forensic Sci. Int., 69, 1994, pp.89-95.

Martin, W.G., Clandestine Manufacture of Methamphetamine from Ephedrine, Part I. Microgram, 16(8), 1983, pp.122-315.

Masseti, J., Amphetamine in Suspected Methamphetamine Samples, JCLICA, 5(4), 1995, pp.9-11.

Moore, K.A., The Analytical and Pharmacological Characterization of Alpha-Benzyl-N-Methylphenethylamine, and Impurity in Illicit Methamphetamine Synthesis, U.M.I. Dissertation Information Service (UMI no.9619739), 1996

Moriwaki, W., et al., Dimethyl Sulfone in Methamphetamine Exhibits, Microgram, 29(3), 1996, pp.58-60.

Noggle, F.T., et al., Characterization of Methamphetamine and Synthetic By-Products in Clandestine Samples: A Case Report, Microgram, 27(8), 1994, pp.253-267.

Noggle, F.T., et al., Evaluation of Allylbenzene as Precursor for the Synthesis of Methamphetamine, Microgram, 27(9), 1994, pp.302-315.

Noggle, F.T., et al., Gas Chromatographic and Mass Spectral Analysis of Methamphetamine Synthesized from Allylbenzene, J. Chromatogr. Sci., 33, 1995, pp.153-161.

Oulton, S., Dichlorofluoroethane in the Clandestine Manufacture of Methamphetamine, Microgram, 29(10), 1996, pp.261-263.

Oulton, S.R., et al., Reaction Byproducts of Common Cold Tablet Ingredients Via Hydriodic Acid / Red Phosphorous, Microgram, 32(10), pp.257-285.

Perkal, M. et al., Impurity Profiling of Methylamphetamine in Australia and the Development of a National Drugs Database, Forensic Sci. Int., 69, 1994, pp.77-87.

Perkal, M., Methamphetamine via Friedel-Crafts Alkylation, JCLICA, 8(2), 1998, pp.15-16.

Repke, D.B., et al., Synthesis of Dextroamphetamine Sulfate and Methamphetamine Hydrochloride from *D*-Phenylalanine, J. Pharm. Sci., 67, 1978, pp.1167-1168.

Strömberg, L., et al., Comparative Gas Chromatographic Analysis of Narcotics, IV. Methamphetamine Hydrochloride, J. Chromatogr., 258, 1983, pp.65-72.

Suzuki, S.-I., et al., Analyses of Impurities in Methamphetamine by Inductively Coupled Plasma Mass Spectrometry and Ion Chromatography, J. Chromatogr., 437, 1988, pp.322-327.

Willers-Russo, L.J., Three Fatalities Involving Phosphine Gas, Produced as a Result of Methamphetamine Manufacturing, J. Forensic Sci, 44(3), 1999, pp.647-652.

Wilson, W.L. (Ed), Authentication of N-Formylmethamphetamine, Bureau of Drug Research (Canada), Drug Identification Division, Analytical Report 85-2, April 1985

Yoo, Y., et al., Identification and Determination of Impurities in Illicit Drugs, Annual Report of N.I.S.I., 17, 1985.

5.2.1. Methamphetamine from ephedrine

Allen, A.C., et al., Methamphetamine from Ephedrine: I. Chloroephedrines and Aziridines, J. Forensic Sci., 32(4), 1987, pp.953-962.

Andrews, K.M., Ephedra's Role as a Precursor in the Clandestine Manufacture of Methamphetamine, J. Forensic Sci., 40, 1995, pp.551-560.

Anonymous, New "Cold Method" Methamphetamine Labs! Microgram, 25(12), 1992, pp.306-307.

Anonymous, "Ice Methamphetamine Analog", Microgram, 28(1), 1995, p.1.

Anonymous, Ephedra-Based Methamphetamine Found in New Mexico, Microgram, 29(4), 1996, p.86

Cantrell, T.S., et al., A Study of Impurities Found in Methamphetamine Synthesized from Ephedrine, Forensic Sci. Int., 39, 1988, pp.39-53.

Christian, D., Desert Methamphetamine: An Empirical Study of the Effects of Outside Temperature on the Ephedrine/HI reaction Mixture, Microgram, 27(10), 1994, p.342. (Abstract)

Dal Cason, T.A., Perspectives on "NAZI Dope" and the *Mythical* "NAZI Patent", Microgram, 30(1), 1997, pp.22-23.

Dawson, N., The Sodium-Ammonia "Nazi" Method of Methamphetamine Synthesis: An Historical Overview, Methodology and Case Reviews, JCLICA, 5(3), (1995), pp.12-14.

Ely, R.A., et al., Lithium-Ammonia Reduction of Ephedrine to Methamphetamine: An Unusual Clandestine Synthesis, J. Forensic Sci., 35(3), 1990, pp.720-723.

Inoue, T. et al., Impurity Profiling Analysis of Methamphetamine Seized in Japan, Forensic Sci. Int., 69 (1994) 97-102.

Kikura, R., et al., Studies on the Origin of Illicit Methamphetamine and Its Raw Material (Ephedrine), Eisei, Shikensho Hokoku, 110, 1992, pp.1-6.

Kishi, T. et al., Analysis of Impurities in Methamphetamine, Eisei Kagaku, 29, 1983, pp. 400-406. (Article in Japanese, abstract in English)

Lurie, I.S., et al., Effects of various anionic chiral selectors on the capillary electrophoresis separation of chiral phenethylamines and achiral neutral impurities in illicit methamphetamine, Electrophoresis, 19, 1998, pp.2918-2925.

Lurie, I.S., et al., Profiling of Impurities in Illicit Methamphetamine By High-Performance Liquid Chromatography and Capillary Electrochromatography, J. Chromatogr. A, 870, 2000, 53-68.

Noggle, F.T., et al., Liquid Chromatographic Determination of the Enantiomeric Composition of Methamphetamine Prepared from Ephedrine and Pseudoephedrine, *Anal. Chem.*, 58, 1986, pp.1643-1648.

Pederson, L., Methamphetamine Synthesized from *Ephedra* Extract Encounter, *Microgram*, 27(10), 1994, p.241 (Abstract)

Skinner, H.F., Methamphetamine Synthesis via Hydroiodic Acid / Red Phosphorous Reduction of Ephedrine, *Forensic Sci. Int.*, 48, 1990, pp.123-134.

Tanaka, K., et al., Analysis of Impurities in Illicit Methamphetamine, *Forensic Sci. Int.*, 56, 1992, pp.157-165.

Tanaka, K., et al., Impurity Profiling Analysis of Illicit Methamphetamine by Capillary Gas Chromatography, *J. Forensic Sci.*, 39 (2), 1994, pp.500-511.

Windahl, K.L., et al., Investigation of the Impurities Found in Methamphetamine Synthesized from Pseudoephedrine by Reduction with Hydroiodic Acid and Red Phosphorous, *Forensic Sci. Int.*, 76, 1995, pp.97-114.

5.2.2. Methamphetamine from P2P

Bailey, K., et al., Identification and Synthesis of Di-(1-phenylisopropyl)methylamine, an Impurity in Illicit Methamphetamine, *J. Pharm. Sci.*, 63(10), 1974, pp.1575-1578.

Barron, R.P. et al., Identification of Impurities in Illicit Methamphetamine Samples, *J.A.O.A.C.*, 57 (1974) 1147-1158.

Conn, C., et al., Identification of N-Acetylmethamphetamine in a Sample of Illicitly Synthesized Methamphetamine, *J. Forensic Sci.*, 41(4), 1996, pp.645-647.

Kram, T.C., The Identification of Methylamine Hydrochloride in Methamphetamine Exhibits, *Microgram*, 7(10), 1974, pp.117-120.

Kram, T.C., Applications of GC/MS in a Forensic Chemistry Laboratory: I. Detection of Impurities in Illicit Methamphetamine Exhibits, *Microgram*, 9(1), 1976, pp.3-6.

Kram, T.C., et al., The Identification of Impurities in Illicit Methamphetamine Exhibits by Gas Chromatography/Mass Spectrometry and Nuclear Magnetic Resonance Spectroscopy, *J. Forensic Sci.*, 22(1), 1977, pp.40-52.

Kram, T.C., Analysis of Impurities in Illicit Methamphetamine Exhibits. III: Determination of Methamphetamine and Methylamine Adulterant by Nuclear Magnetic Resonance Spectroscopy, *J. Forensic Sci.*, 22(3), 1977, pp.508-514.

LeBelle, M. et al., Identification of a Major Impurity in Methamphetamine, *J. Pharm. Sci.*, 62, 1973, p.862.

Liu, J.H., et al., Approaches to Drug Sample Differentiation. III: A Comparative Study of the Use of Chiral and Achiral Capillary Column Gas Chromatography/Mass Spectrometry for the Determination of Methamphetamine Enantiomers and Possible Impurities, *J. Forensic Sci.*, 27(1), 1982, pp.39-48.

Skinner, H.F., Methamphetamine Synthesis via Reductive Alkylation Hydrogenolysis of Phenyl-2-propanone with *N*-Benzylmethylamine, *Forensic Sci. Int.*, 60, 1993, pp.155-162.

Teer, C., et al., Identification of alpha-benzyl-*N*-methyl-phenethylamine, *Microgram*, 14(8), 1981, pp.99-104.

van der Ark, A.M., et al., Verunreinigungen in illegalem Amphetamin, 6. Identifizierung von Phenylpropanol-2, Amphetamine und *N,N*-Dimethylamphetamin in Methamphetamine, *Arch. Krim.*, 162, 1978, pp.171-175.

5.3. Amphetamine

Alm. S., et al., Classification of Illegal Leuckart Amphetamine by Gas Chromatographic Profiling, Report 25, 20/01/1992, The National Laboratory of Forensic Sciences, Linköping, Sweden.

Anonymous, Novel Amphetamine Laboratory, *Microgram*, 27(4), 1994, p.98.

Cooper, D., 1-Chloro-1-phenyl-2-aminopropane: An Amphetamine Precursor, *Microgram*, 12(5), 1979, pp.108-117.

Hider, C.L., Preparation of Evidence in Illicit Amphetamine Manufacturing Prosecutions, *J. Forensic Sci. Soc.*, 9, 1969, pp.75-79.

Huizer, H., et al., A New Method in Illegal Amphetamine Production, *Microgram*, 13(7), 1980, pp.118-123.

Huizer, H., et al., Di-(β -Phenylisopropyl)amoinen in Illicit Amphetamine, *J. Forensic Sci.*, 30(2), 1985, pp.427-438.

Huizer, H. et al., Impurities in Illicit Amphetamine, *J. Forensic Sci. Soc.*, 21 (1981) 225-232.

Jonson, C.S.L., et al., Computer Aided retrieval of Common-Batch Members in Leuckart Amphetamine Profiling, *J. Forensic Sci.*, 38(6), 1993, pp.1472-1477.

Jonson, C.S.L., et al., Two-Level Classification of Leuckart Amphetamine, *Forensic Sci. Int.*, 69, 1994, pp.31-44.

Jonson, C.S.L., Amphetamine Profiling - Improvements of Data Processing, *Forensic Sci. Int.*, 69, 1994, pp.45-54.

Jonson, S., et al., Factors Influencing the Extraction of Impurities from Leuckart Amphetamine, *Forensic Sci. Int.*, 93, 1998, pp.99-116.

Kärkkäinen, M. et al., Automated Gas Chromatographic Amphetamine Profiling, *Forensic Sci. Int.*, 69, 1994, pp.55-64.

King, L.A. et al., Amphetamine Profiling in the UK, *Forensic Sci. Int.*, 69, 1994, pp.65-75.

Kram, T.C., Identification of an Impurity in Illicit Amphetamine Tablets, *J. Pharm. Sci.*, 66(3), 1977, pp.443-444.

Kram, T.C., Reidentification of a Major Impurity in Illicit Amphetamine, *J. Forensic Sci.*, 24, 1979, pp.596-599.

Lambrechts, M., et al., Analysis of Impurities in Illicit Amphetamine by High Performance Liquid Chromatography, *J. Chromatogr.*, 295, 1984, pp.264-268.

Lambrechts, M., et al., Use of Bonded-Phase Silica Sorbents for Rapid Sampling of Impurities in Illicit Amphetamine for High-Performance Liquid Chromatographic Analyses, *J. Chromatogr.*, 331, 1985, pp.339-348.

Lambrechts, M., et al., Profiling of Impurities in Illicit Amphetamine Samples by High-Performance Liquid Chromatography Using Column Switching, *J. Chromatogr.*, 369, 1986, pp.365-377.

Lomonte, J.N., et al., Contaminants in Illicit Amphetamine Preparations, *J. Forensic Sci.*, 21(3), 1976, pp.575-582.

Noggle, F.T., et al., GC-MS Analysis of Products, By-Products and Impurities in the Synthesis of Amphetamine from 1-Phenyl-2-Nitropropene, *Microgram*, 27(5), 1994, pp.153-167.

Pikkarainen, A.L., Systematic Approach to the Profiling Analysis of Illicit Amphetamine, *Forensic Sci. Int.*, 82, 1996, pp.141-152.

Poortman-van der Meer, A.J., Artifacts in the GC Analysis of Amphetamine and MDA, *Microgram*, 29, 1996, pp.91-93.

Sanger, D.G., et al., Classification of Illicit Amphetamine Samples According to Their Route of Manufacture and Source-related Impurity Patterns; Part I: The Leuckart Reaction, HOCRE Report No.258, Home Office Central Research Establishment, Aldermaston, Reading, Berkshire, January 1978.

Sanger, D.G., et al., Classification of Illicit Amphetamine Samples According to Their Route of Manufacture and Source-related Impurity Patterns, Part II: The "Oxime" and "Nitrostyrene" Routes, HOCRE Report No.301, January 1979

Sanger, D.G., et al., The Significance of Gas Chromatographic Impurity Patterns Obtained from Illicitly Produced Amphetamine, *Forensic Sci. Int.*, 28, 1985, pp.7-17.

Sinnema, A., et al., Impurities in Illicit Amphetamine: A Review, *Bull.Narc.*, 33(3), 1981, pp.37-54.

Sippola, E, et al., Automated Gas Chromatographic Amphetamine Profiling. Part I: Optimization of the Gas Chromatographic Analysis, Proceedings of International Symposium of Forensic Science, Tokyo 1993, pp.147-150.

Strömberg, L., et al., Two-Level Classification of Leuckart Amphetamine, Proceedings of the International Symposium of Forensic Science, Tokyo, 1993.

Strömberg, L., et al., Classification of Illicit Amphetamine, I. Selection of Class Descriptors, Proceedings of the International Symposium of Forensic Science, Tokyo, 1993.

Theeuwen, A.B., et al., Impurities in Illicit Amphetamine. 7. Identification of Benzyl Methyl Ketone Phenylisopropylimine and Benzyl Methyl Ketone Benzylimine in Amphetamine, *Forensic Sci. Int.*, 15, 1980, pp.237-241.

Theeuwes, A.B., et al., Verunreinigungen in illegalem Amphetamin, 9. Identifizierung von N-Acetylamphetamin und 1-Oxo-1-Phenyl-2-(β -phenylisopropylimino)propan, Arch. Kriminol., 168(1-2), 1981, pp.23-28.

van der Ark, A.M., et al., Weakly Basic Impurities in Illicit Amphetamine, J. Forensic Sci., 23, 1978, pp.693-700.

Varesio, E., et al., Chiral Separation of Amphetamines by High-Performance Capillary Electrophoresis, J. Chromatogr. A, 717, 1995, pp.219-228.

5.4. Ephedrine / Pseudoephedrine

Beckett, A.H., et al., Degradation of (-)-Ephedrine in Solution and During Extraction with Diethyl ether, J. Pharm. Pharmac., 30, 1978, pp.15-19.

Duddu, S.P., et al., Liquid Chromatographic Analysis of the Enantiomeric Impurities in Various (+)-Pseudoephedrine Samples, Pharm. Res., 8(11), 1991, pp.1430-1433.

Gilbert, M.T., et al., Characterization of Diastereomeric and Enantiomeric Ephedrines by Gas Chromatography Combined with Electron Impact Mass Spectrometry and Isobutane Chemical Ionization Mass Spectrometry, Biomedical Mass Spectrometry, 4(4), 1977, pp.226-231.

Hutchinson, K. et al., The Use and Availability of *Ephedra* Products in the United States, Microgram, 28 (1995) 256-263.

Larizza, A. et al., L-, D-, and DL-Ephedrine Phosphates, J. Med. Chem., 9, 1966, p.966 (Abstract)

Popovich, G.L., A New Reducing Agent for Ephedrine, Microgram, 28, 1995, pp.79-84.

van der Merwe, P.J., et al., Identification of Ephedrines as Their Carbon Disulfide Derivatives, J. Chrom. B, 663, 1995, pp.160-166.

5.5. 1-Phenyl-2-propanone (P2P)

Allen, A.C. et al., Differentiation of Illicit Phenyl-2-propanone Synthesized from Phenylacetic Acid with Acetic Anhydride versus Lead (II) Acetate, J. Forensic Sci., 37, 1992, pp.301-322.

Anonymous, "New" Synthetic Routes to Phenyl-2-propanone (P-2-P, BMK), Drug Abuse Trends, 107, 1995, p.21.

Barbato, J.J, Identification of 1-Phenyl-2-Nitropopene, Microgram, 23(2), 1990, pp.35-36.

Dal Cason, T.A., et al., A Clandestine Approach to the Synthesis of Phenyl-2-Propanone from Phenylpropenes, J. Forensic Sci., 29(4), 1984, pp.1187-1208.

Dal Cason, T.A., Some Information Regarding Phenyl-2-Propanone, Microgram, 27(4), 1994, p.99 (Abstract)

Forbes, I.J., et al., The Origin of Alkenes in Illicit Amphetamine: An Examination of the Illicit Synthesis of Phenyl-2-Propanone, J. Forensic Sci., 37(5), 1992, pp.1311-1318.

Hanel, H.F., Substitute Bases for Sodium Acetate in the Clandestine Synthesis of Phenyl-2-propanone (P2P), *Microgram*, 25 (1992) 236-237.

Mason, J.P., et al., Preparation of Phenylacetone, *J. Amer. Chem. Soc.*, 62, 1940, p.1622.

Nguyen, M., et al., Separation of Methamphetamine and Phenylacetone from Clandestine Laboratory Samples by HPLC, *Microgram*, 18(10), 1985, pp.139-143.

Norris, R., Clandestine Laboratory Making P2P, Analog, 19(1), p.1.

Sottolano, S.M., The Quantitation of Phenyl-2-Propanone Using High-Performance Liquid Chromatography, *J. Forensic Sci.*, 33(6), 1988, pp.1415-1420.

5.6. Miscellaneous chemistry

Allen, A.C., et al., Synthetic Reductions in Clandestine Amphetamine and Methamphetamine Laboratories: A Review, *Forensic Sci. Int.*, 42, 1989, pp.183-199.

ervinka, O., et al, Asymmetric Reactions. XXIX. Absolute Configuration of ω -Phenyl-2-alkylamines and Their *N*-Methyl Derivatives, *Coll. Czech. Chem. Commun.*, 33 (1968) 3551. (Abstract)

Clark, C.R., et al., GC-MS Identification of Amine-Solvent Condensation Products Formed During Analysis of Drugs of Abuse, *J. Chromatogr. Sci.*, 30, 1992, pp.399-404.

CND Analytical, Inc., Analytical Profiles of Amphetamines and Related Phenethylamines, CND Analytical, Inc., P.O.Box 1527, Auburn, Alabama 36831-1527, USA, 1989.

CND Analytical, Inc., Forensic and Analytical Chemistry of Clandestine Phenethylamines, CND Analytical, Inc., P.O.Box 1527, Auburn, Alabama 36831-1527, USA, 1994.

Crossley, F.S., et al., Studies on the Leuckart Reaction, *J. Org. Chem.*, 9, 1944, pp.529-536.

DEA (Drug Enforcement Administration), Office of Science and Technology, Clandestine Laboratory Guide for Agents & Chemists, 1994, Monographs on Ephedrine (p.68a-68b), Hydriodic Acid (p.72a), Hydrogen Chloride Gas (p.72b), Methamphetamine (p.110-116e), Phenylacetic Acid (p.136a-136h), Phenyl-2-Propanone (138-143g).

Emde, H., Concerning Diastereoisomers, I. Configuration of Ephedrines; III. Chloro- and Bromoephedrine; IV. Steric Rearrangement of Ephedrines with Sulphuric Acid, *Helv. Chim. Acta*, 12 (1929) p.365. (Abstracts, translation)

Erlenmeyer, H., et al., Structural Chemistry Studies IV. Concerning a Reductive Cleavage of 5-Phenyl-4-methylthiazole, *Helv. Chim. Acta*, 25 (1942) p.528. (Abstract, translation)

Friedrichsen, W., Method for the Preparation of 1-Phenyl-2-aminopropane or Its *N*-Substituted Derivatives, German Patent No. 819,400. (Abstract, translation)

Fujisawa, S., Methyl-(2-phenylisopropyl)-amine, *Chemical Abstracts*, 46 2432a (1952).

Gerö, A., Some Reactions of 1-Phenyl-1-chloro-2-methylaminopropane. I. Reaction with Metals and with Hydrogen, *J. Org. Chem.*, 16, 1951, pp.1731-1735.

Hess, U., et al., Untersuchungen zur elektrochemischen Oxidation von Amphetamin und Methamphetamin, *Pharmazie*, 31(7), 1976, pp.452-453.

Kindler, K., et al., Study of Mechanism of Chemical Reactions. X. Phenyl and Cyclohexyl-alkylamines by Hydrogenation, *Annalen*, 560, 1948, pp.215-221 (Abstract, translation)

Laboratoires Amido, Aralkyl amines, *Chemical Abstracts*, 62, 1964, 5228b.

Opfermann, A.C.J., Improvement in the Manufacture of Organic Compounds Containing Nitrogen, Arsenic, Sulphur or Selenium, U.K. Patent Specification 782,887 (1953).

Rosenmund, K.W., et al., Concerning the Preparation of β -Aryl-alkylamines, *Berichte*, 758, 1942, pp.1850-1859 (Abstract, translation)

Sy, W.-W., et al., Nitration of substituted styrenes with nitryl iodide, *Tetrahedron Letters*, 26(9), 1985, pp.1193-1196.

Temmler, T.H., Process for the Production of Amines from Esters of Amino-Alcohols, U.K. Patent Specification 509,661 (1938).

Temmler, T.H., Amines, *Chemical Abstracts*, 49, 1955, 15958c.

Temmler-Werke, Amines, *Chemical Abstracts*, 34, 1940, 7544⁶.

Tindall, J.B., et al., Process for the Production of Secondary Amines, United States Patent Office, 2,828,343 (1958).

Weibel, P.A., et al., Substituenteneinfluss bei der massenspektrometrischen Fragmentierung: Untersuchungen an N-Methyl- β,β' -diphenyl-diethylaminen, *Helvetica Chimica Acta*, 56(7), 1973, pp.2460-2479.

5.7. Data analysis

Derde, M.P., et al., Extraction of Information from Large Data Sets by Pattern Recognition, *Fresenius Z. Anal. Chem.*, 312, 1982, pp.484-495.

Welsh, W.J., et al., Pharmaceutical Fingerprinting: Evaluation of Neural Networks and Chemometric Techniques for Distinguishing Among Same-Product Manufacturers, *Anal. Chem.*, 68, 1996, pp.3473-3482.

Wold, S., et al., Principal Component Analysis, *Chemometrics and Intelligent Laboratory Systems*, 2, 1987, pp.37-52.

5.8. Other (including profiling and clandestine laboratories)

Alvarez, J.J., et al., N,N-Dimethylamphetamine and Phenyl-2-Propanol, *Microgram*, 12(6), 1979, pp.125-134.

Christian, D., Courtroom Presentation of Clandestine Drug Laboratory Cases, *JCLICA*, 2(4), 1992, pp.20-24.

Frank, R.S., The Clandestine Drug Laboratory Situation in the United States, *J. Forensic Sci.*, 28(1), (1983) 18-31.

Glennon, R.A., Synthesis and Evaluation of Amphetamine Analogues, in: *Clandestinely Produced Drugs, Analogues, and Precursors - Problems and Solutions*, Proceedings of an International Conference on Assessment of Drug Control Issues of Controlled Substance Analogues, Co-sponsored by the WHO and the DEA (USA) in Rabat, Morocco, 8-11 September 1987, pp.39-65.

Görög, S., et al., Estimation of impurity profiles in drugs and related materials, *Journal of Pharmaceutical & Biomedical Analysis*, 6(6-8), 1988, pp.697-705.

Gunn, J.W., et al., Clandestine Drug Laboratories, *J. Forensic Sci.*, 15(1), 1970, pp.51-64.

Huizer, H., et al., Contribution to Comparison, *Forensic Sci. Int.*, 69, 1994, pp.17-22.

Inoue, T., Discrimination of Abused Drug Samples by Impurity Profiling Analysis (Chemical Fingerprint), *Hochudoku*, 10, 1992, pp.204-217. (Article in Japanese, abstract in English)

Klein, M., Public Health Risks Resulting from Processing Impurities in Clandestine Drugs, *Clandestinely Produced Drugs, Analogues and Precursors, Problems and Solutions*; Proceedings of an International Conference on Assessment of Drug Control Issues of Controlled Substance Analogues, co-sponsored by the WHO and the DEA (USA), in Rabat, Morocco, 8-11 September 1987, p.175-193.

Knox, M.E. et al., Identification of Diethylaminoethylaniline in a Clandestine Laboratory Reaction Mixture, *Microgram*, 26, 1993, pp.28-35.

Lambrechts, M., et al., Leuckart-Specific Impurities in Amphetamine and Methamphetamine Seized in Norway, *Bull. Narc.*, 36(1), 1984, pp.47-57.

Lambrechts, M. et al., Analysis of Leuckart-Specific Impurities in Amphetamine and Methamphetamine, *J. Chromatogr.*, 284, 1984, pp.499-502.

Noggle, F.T., et al., GC-MS and Liquid Chromatographic Analysis of Amphetamine and Amphetamine-type Products Formed in the Reaction of Arylpropenes with Acetonitrile and Sulfuric Acid, *Microgram*, 28(1), 1995, pp.12-26.

Perillo, B.A., et al., Recent Advances by the U.S. Drug Enforcement Administration in Drug Signature and Comparative Analysis, *Forensic Sci. Int.*, 69, 1994, pp.1-6.

Reagan, D.M., Clandestine Laboratory Update, Texas Narcotic Officers Association, 1988.

Sanger, D.G., et al., A Review of Analytical Techniques for the Comparison and Characterization of Illicit Drugs, *J. Forensic Sci. Soc.*, 19, 1979, pp.65-71.

Tillson, A.H., et al., Identification of Drug Tablet and Capsule Evidence as to Source, *J. Forensic Sci.*, 19, 1974, pp.873-883.

Verweij, A.M.A., Impurities in Illicit Drug Preparations: Amphetamine and Methamphetamine, *Forensic Sci. Rev.*, 1(1), 1989, pp.2-11.