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Note

Analysis of Leuckart-specific impurities in amphetamine and methamphetamine

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Among several different methods for synthesis of amphetamine and methamphetamine, the Leuckart method[1] is frequently employed in illicit production[2,3]. As incomplete reactions and side reactions are common, the final Leuckart product is usually contaminated. The degree of contamination largely depends on the purification method. Some of these impurities are specific for the Leuckart route and the identification of such contaminants will enable the analyst to state if the method of Leuckart has been used.

N-Formylmethamphetamine, being an intermediate in the Leuckart synthesis, is a Leuckart-specific impurity in methamphetamine products[4]. The intermediate N-formylamphetamine and the byproducts 4-methyl-5-phenylpyrimidine and 4-benzylpyrimidine from the Leuckart synthesis of amphetamine, are all associated specifically with this route[3].

In this work some analytical methods have been evaluated for the study of Leuckart-specific contaminants. The occurrence of these compounds as a function of various experimental conditions during synthesis has been examined. The amphetamine and methamphetamine products were purified in different ways and the possibilities of finding the specific contaminants were investigated.

EXPERIMENTAL

Chemicals

Benzyl methyl ketone and N-methylformamide were obtained from Fluka (Buchs, Switzerland). Formamide was purchased from Koch-Light (Colnbrook, U.K.). They were all of pure grade. Standard amphetamine and methamphetamine were supplied by Norsk Medisinaldepot (Oslo, Norway). Other chemicals used were of analytical grade and were purchased from E. Merck (Darmstadt, F.R.G.).

Synthesis

Six Leuckart syntheses of both methamphetamine and amphetamine were carried out according to Moore[5] and Van der Ark *et al.*[6], respectively. The batches were treated differently with regard to isolation and purification methods, such as ether

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extraction, steam distillation and recrystallization. Methamphetamine was precipitated as the hydrochloride salt and amphetamine as amphetamine sulphate.

N-Formylmethamphetamine and N-formylamphetamine were prepared by formylation of methamphetamine and amphetamine, respectively[7].

Quantitative determination of amphetamine and methamphetamine. The purity of the synthesized methamphetamines and amphetamines was determined by high-performance liquid chromatography (HPLC) according to the method of Jane[8]. Peak height measurements were used to quantify the components.

Analysis of impurities

Sample preparation. Amphetamine or methamphetamine salt (300–500 mg) was dissolved in 5 ml of distilled water, and 2 ml of redistilled benzene were added. The aqueous phase was made weakly acidic and trace components were extracted into benzene by vigorous shaking for 4 min. After separation, most of the benzene layer was transferred to a glass tube and concentrated to 2–5 μl.

Gas–liquid chromatography (GLC). A Fractovap 2900 gas chromatograph (Carlo Erba, Milan, Italy) equipped with a flame ionization detector and a fused-silica capillary column (25 m × 0.33 mm I.D.) wall-coated with SE-30 was used. The injector and detector temperatures were 275°C. The oven temperature was programmed from 130°C to 250°C at 10°C/min. Helium was used as carrier gas and the flow-rate was adjusted to 30 ml/min through the capillary column, 20 ml/min at the outlet of the splitter and 5 ml/min as septum flush. Samples of 1 μl were injected.

GLC–mass spectrometry (MS). A Micromass 7070 F mass spectrometer (VG-Micromass, Altrincham, U.K.) combined with a Fractovap 4200 gas chromatograph (Carlo Erba, Milan, Italy) was used. The electron energy was 70 eV.

RESULTS AND DISCUSSION

Methamphetamine contaminants

All the methamphetamine products had a white appearance, sometimes with a touch of violet, and they contained more than 97% methamphetamine. The steam-distilled samples showed a purity greater than 99%. Discoloration was not observed after several months of storage.

The amounts of impurities varied and their relative proportions were different in all products. Different impurity patterns were also observed in samples prepared according to the same experimental procedure, in agreement with earlier findings[9].

The Leuckart-specific impurity, N-formylmethamphetamine (N-f-MA), was identified in all samples by GLC–MS and was found to be one of the main impurities in products purified by ether extraction. Steam-distilled samples and recrystallized samples contained just detectable amounts of N-f-MA by GLC. The presence of N-f-MA, however, was readily verified by GLC–MS analysis.

These results demonstrate that by using GLC–MS, N-f-MA can be detected in illicit seizures regardless of the purification method employed (*i.e.* ether extraction, steam distillation or recrystallization).

Amphetamine contaminants

Except for the recrystallized samples that remained white, the products exhib-

ited a slight yellow colour that darkened during storage. All samples contained more than 90% amphetamine.

GLC and GLC–MS analysis of the benzene-extracted impurities showed that the Leuckart-specific compound 4-methyl-5-phenylpyrimidine (4-me) was a major contaminant in the ether-extracted as well as in the steam-distilled products. The recrystallized samples gave, in general, low intensity chromatograms which required GLC–MS for detection of the Leuckart-specific impurities; 4-me was detected in recrystallized samples by this method. It was detected in all samples as a major impurity, and can therefore be described as the most important of the Leuckart-specific contaminants.

As was the case with N-formylmethamphetamine, most of the intermediate N-formylamphetamine was removed by steam distillation. 4-Benzylpyrimidine did occur only in three samples and is thus less reliable as a proof of the Leuckart synthesis.

All the tested products showed different impurity patterns, though an expected similarity existed between batches produced by the same procedure. Fig. 1 shows a typical impurity pattern of a steam-distilled product with 4-me as the predominant

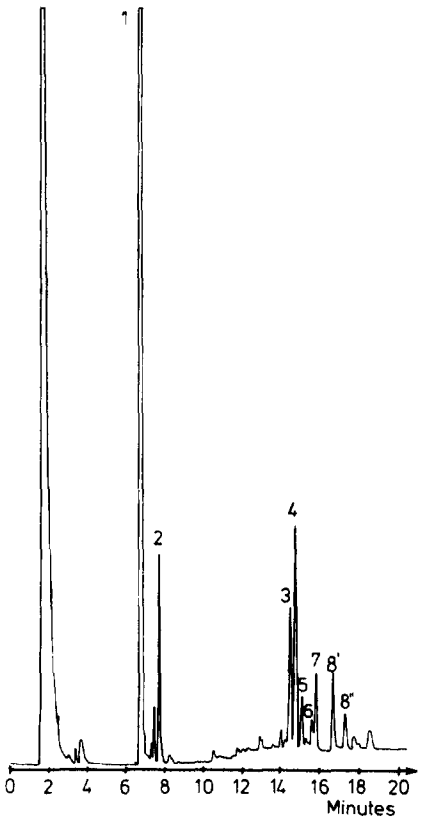

Fig. 1. Gas chromatogram of impurities in amphetamine purified by steam distillation; flame ionization detection. Peaks: 1 = 4-methyl-5-phenylpyrimidine; 2 = unknown; 3–7 = high-boiling pyridines; 8′ and 8″ = N,N-di(β-phenylisopropyl)formamide.

peak (peak 1). The doublet of N,N-di(β-phenylisopropyl)formamide (peak 8′ and 8″) is due to stereoisomerism[10]. Peaks 3–7 are high boiling pyridines indicated by their mass spectra[6]. As the high-boiling pyridines have very limited steam volatility they will only appear as minor impurities in steam-distilled samples. These byproducts contribute, however, to a significant extent to the impurity pattern of the ether-extracted products.

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