BRIEF COMMUNICATION

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Identification of *N*-Acetylmethamphetamine in a Sample of Illicitly Synthesized Methamphetamine

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ABSTRACT: Analysis of illicit methamphetamine samples revealed the presence of a hitherto unreported impurity. This was identified as *N*-acetylmethamphetamine by synthesis and GC-MS. This impurity is believed to arise by transesterification of methamphetamine during reflux with propyl acetate. Other circumstantial evidence and intelligence data indicate that propyl acetate was used to increase yields of methamphetamine hydrochloride by azeotropic removal of water remaining after salt formation with aqueous hydrochloric acid.

KEYWORDS: forensic science, methamphetamine, *N*-acetylmethamphetamine, drug identification, controlled substance, illicit drug manufacture, street drug, chemistry

The incidence of illicit manufacture of amphetamine and methamphetamine in Australia has been steadily increasing over the last decade (1). Clandestine amphetamine and methamphetamine laboratories pose a number of hazards to the operators of the laboratory, to police and to the community in general. The operators of the laboratory are often inexperienced and face risks from corrosive chemicals, toxic chemicals, fires and explosions (2). However, illicit amphetamine manufacture poses the greatest risk to the end users, because of the high level of contamination typically present in the final products (3, 4). To date, the toxicology of many of the by-products produced during amphetamine and methamphetamine manufacture has not been reported. Therefore, the identification of these by-products is of interest from a toxicological point of view. It is also important for law-enforcement purposes, as impurity profiling may help link two samples as arising from a common source, thus assisting in establishing distribution networks (5).

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Experimental Procedures

Samples (2 solid samples and 14 liquid samples) from an illicit methamphetamine laboratory were supplied by the New South Wales Department of Public Prosecutions. *d,l*-Methamphetamine hydrochloride reference material was supplied by the Department of Pharmacology, University of Sydney. All solvents used were of analytical grade.

GC-MS analysis (6) was performed on a Hewlett-Packard 5890 GC (Series I) coupled to a 5970 MSD. All GC-MS analyses were performed using a 0.25 mm ID × 30 m fused silica capillary column coated with 0.25 μm of 5% phenyl-95% methyl-silicone. Both the injector and the detector (FID) temperatures were set at 250°C. The GC oven program consisted of 70°C, 1 min; 70–220°C at 16°C/min; 220°C, 1 min; 220–290°C at 8°C/min; 290°C, 4 min. Helium was used as the carrier gas, with an inlet pressure of 275 kPa. Mass spectra were obtained at 70 eV. ^{1}H-NMR spectroscopy was performed in deuterochloroform on a Bruker AC200 operating at 200 MHz. Infrared spectroscopy was performed on a Bio-Rad SPC FTIR using thin films between sodium chloride plates. *d,l-N*-Acetylmethamphetamine was prepared as follows: *d,l*-methamphetamine (0.055 g) was stirred for 16 h in dry pyridine (5 mL) containing acetic anhydride (1 mL). The solution was then poured into saturated aqueous sodium hydrogen carbonate (20 mL) and stirred for 30 min. This solution was then extracted with diethyl ether (3 × 10 mL) and the combined ether extracts washed successively with hydrochloric acid (5%, 2 × 10 mL), then water (2 × 10 mL) and finally dried over anhydrous sodium sulfate. After concentration of the sample at reduced pressure, the concentrated ether solution was passed through a small column (5 × 30 mm) of silica gel (230–400 mesh) to afford pure (by ^{1}H-NMR) *N*-acetylmethamphetamine (0.051 g, 73%) as a colorless oil after removal of the remaining ether at reduced pressure. ^{1}H-NMR δ 1.01, 1.25, each d (J = 8 Hz), *cis* and *trans* CHC**H**$_3$; 1.76, 1.98, each s, *cis* and *trans* COC**H**$_3$; 2.74, d (J = 8 Hz), PhC**H**$_2$; 2.78, 2.85, each s, *cis* and *trans* NC**H**$_3$; 4.02, 5.03, each m (J = 8 Hz), C**H**N; 7.09–7.30, m, Ar**H** (7). IR (ν_{max}) 2960, 2920, 1630, 1450, 1400, 1360, 1340, 1125, 1020, 700 cm^{-1}. This material was used as an authentic sample of *d,l-N*-acetylmethamphetamine.

Discussion

Analysis of the 16 solid and liquid samples from the clandestine laboratory by GC-MS showed impurity profiles consistent with manufacture using the Leuckart reaction (7,8). Compounds identified by their mass spectra included methamphetamine (Retention time, RT 5.49 min), *N*-formylmethamphetamine (RT 8.91), *N,N*-dimethylamphetamine (RT 6.12), β-benzyl-*N*-β-phenylethylamine (RT 10.93) phenyl-2-propanone (4.07) and *N*,α,α'-trimethyldiphenylethylamine (RT 12.79). Phenylacetic acid was also identified in one of the samples, indicating that phenyl-2-propanone was also being manufactured at the site or had been purchased from another clandestine source (4). Two of the liquid samples containing methamphetamine also contained an unknown compound with a retention time of 9.17 minutes. One of these samples originated from a 2.5 L bottle, containing 120 mL of liquid, while the other sample originated from a large open plastic container. The latter vessel contained 5 L of liquid (later shown to consist of propyl acetate, propanol, acetone, acetic acid and toluene) and small quantities of a light brown precipitate (subsequently identified as impure methamphetamine hydrochloride). The supernatant from this liquid sample was concentrated at reduced pressure, leaving a small amount of oily residue, which was dissolved in dichloromethane and subjected to GC-MS analysis. The total ion chromatogram of this residue is shown in Fig. 1.

The mass spectrum of the unknown is shown in Fig. 2. The base peak at m/z 58 is consistent with the fragment $C_3H_3N^+$, typical of *N*-methyl-β-phenylethylamines. The peak at m/z 100 was attributed to $C_5H_{10}NO^+$; thus, the peak at m/z 58 arises from the loss of ketene from the former ion, as shown in Fig. 3. When the fragmentation pattern was considered along with the peak assigned as the parent ion (m/z 191) the impurity was tentatively identified as *N*-acetylmethamphetamine. This was confirmed by comparison with authentic *d,l-N*-acetylmethamphetamine, which displayed identical RT and mass spectral data.

To our knowledge, this is the first report of the presence of *N*-acetylmethamphetamine in illicit methamphetamine (9). In attempting to identify the source of this unusual impurity, we examined the 5 L liquid sample referred above, using head space/GC-MS analysis. A number of compounds were identified, including, propyl acetate, propanol, acetone, acetic acid and toluene. It is likely that the acetic acid and propanol found in this sample arose by acid-catalyzed hydrolysis of propyl acetate. The presence of acid is possible, given that in some illicit laboratories in Australia, methamphetamine hydrochloride is formed from the free base and hydrochloric acid. This is accomplished by addition of a stoichiometric amount of concentrated hydrochloric acid to a solution of the free base in acetone and/or another organic solvent. The resulting solution is then set aside in a freezer to allow the precipitation of the hydrochloride salt.

Our inference for the presence of *N*-acetylmethamphetamine found in some of the samples is that this impurity arose via acid-catalyzed transesterification of methamphetamine with propyl acetate. In order to test this hypothesis, *d,l*-methamphetamine hydrochloride was refluxed in propyl acetate with and without hydrochloric acid as a catalyst. While both reactions produced *d,l-N*-acetylmethamphetamine in trace amounts, in the acid-catalyzed experiment, it was found after only 8 h reflux. In contrast, the uncatalyzed experiment took seven days to form detectable quantities of *d,l-N*-acetylmethamphetamine.

We believe that efforts were made by the operators of the clandestine laboratory to maximize yields of methamphetamine hydrochloride by azeotropic removal of water from the mother liquor obtained following precipitation of the hydrochloride salt. Thus, it appears that during this attempt at azeotropic removal of water, transesterification took place, resulting in the formation of *N*-acetylmethamphetamine.

In conclusion, the use of impurity profiling of illicit drugs can provide drug-enforcement agencies with valuable information on the common origins of different samples of drugs. It can also enable intelligence information to be gathered concerning the method of synthesis and thereby help identify individual illicit laboratories. In depth analysis of impurities present in samples can also reveal

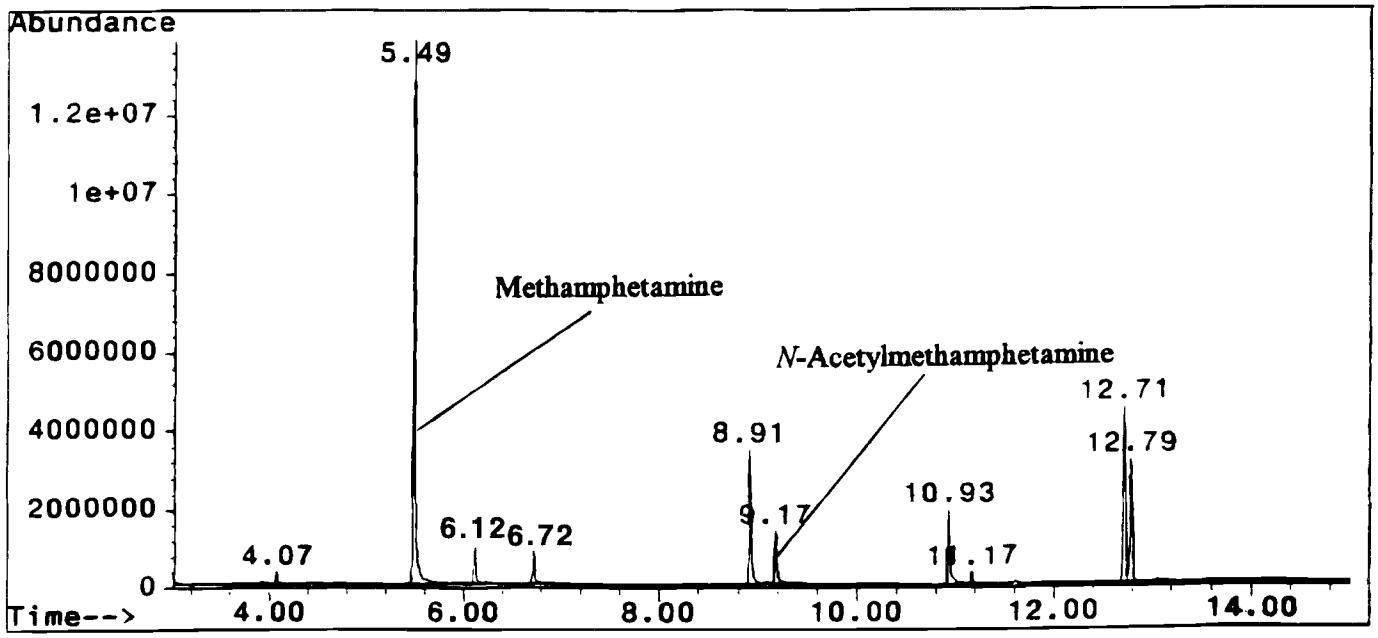

FIG. 1—*Chromatogram of sample containing N-acetylmethamphetamine.*

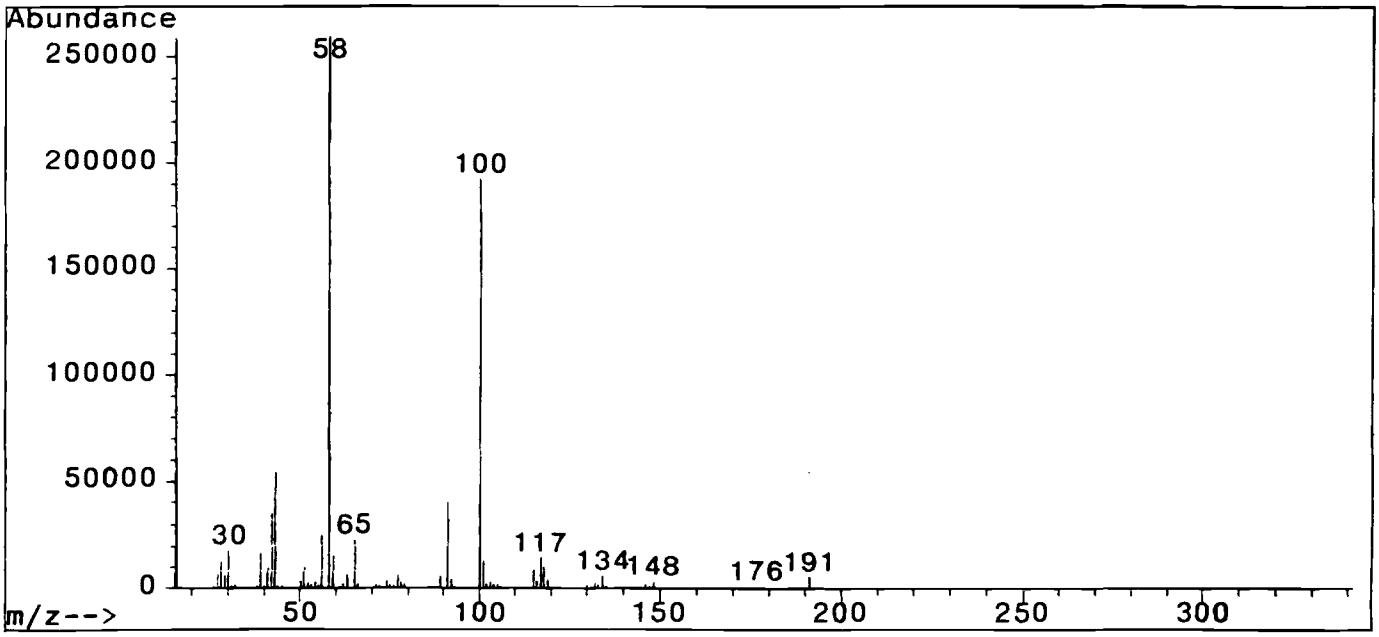

FIG. 2—*Mass spectrum of peak at 9.17 minutes.*

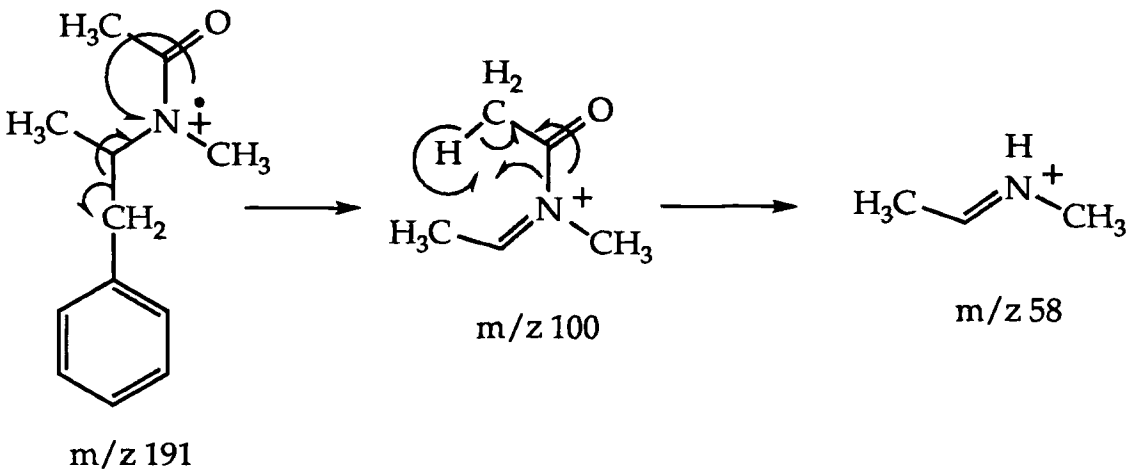

FIG. 3—*Fragmentation of N-acetylmethamphetamine.*

the presence of hitherto unidentified compounds, as was found to be the case in this study. These compounds may or may not be of toxicological importance.

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