J Forensic Sci, Jul. 1979, Vol. 24, No. 3

TECHNICAL NOTE

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Reidentification of a Major Impurity in Illicit Amphetamine

Di-(1-phenylisopropyl) formamide (I) has been identified as a by-product in the Leuckart synthesis of *N*-formylamphetamine [*1,2*], a reaction precursor to *dl*-amphetamine. Significantly, it has been detected as an impurity in exhibits of illicitly manufactured *dl*-amphetamine [*3,4*] but identified incorrectly as tri-(1-isopropylphenyl) amine (II) [*3*].

Discussion

Compound I is detected as a doublet in the gas chromatographic analysis[2] of impure *N*-formylamphetamine and *dl*-amphetamine, both peaks presenting identical mass spectra.[3] The ions of greatest abundance appear at *m/e* 91 (base peak), 190, and 119. No ions are detected beyond *m/e* 190. The overall fragmentation pattern suggests a structure of the type shown as III in Fig. 1. Several representative compounds, some of which have been identified as impurities in illicit methamphetamine [*5–8*], have been compared previously [*5*]. Mass spectral-structural correlations via the fragmentation processes outlined below are shown in Table 1:

(a) cleavage beta to *N* [*9,10*];
(b) fragmentation of ion produced by (a) alpha to *N* with charge transfer to the phenylalkyl moiety [*5,8*];
(c) alpha, beta cleavage to *N* with hydrogen rearrangement [*9,10*]; and
(d) benzyl is indicated by the presence of an intense *m/e* 91 fragment with additional fragmentation at *m/e* 77, 65, 51, and 39 [*11*].

Since Mechanism (a) is expected to produce ions of great intensity in phenethylamines [*9,12,13*], the lack of a *m/e* 280 fragment eliminates Structure II from serious consideration, particularly since its structure provides three sites for such cleavage to occur.

The great abundance of ions at *m/e* 119 and corresponding lack of *m/e* 105 fragments support the phenylisopropyl configuration for both major attachments to *N*. R_2 must then consist of a group with a mass of 29. This may be attributed to either CH_2CH_3 or CHO. However, the amine function is all but denied by failure of the compound to extract with acid (dilute tartaric, hydrochloric, and sulfuric) to any detectable extent from ether.

Received for publication 18 Jan. 1979; accepted for publication 31 Jan. 1979.
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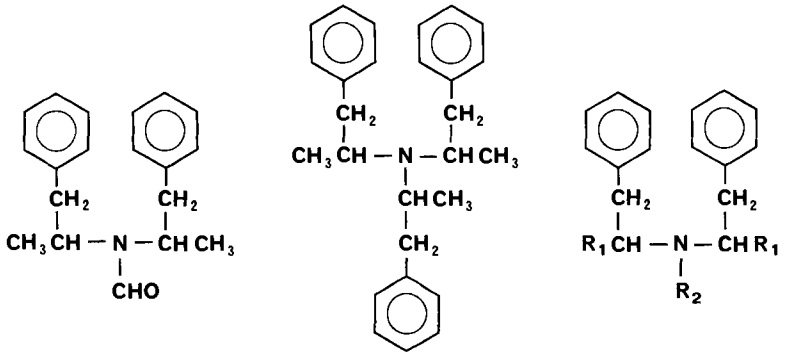
[2] By procedures discussed in Refs *3* and *5*, using OV-1 and alkaline Apiezon as liquid phases.
[3] Finnigan Model 3000, 3100D [*3*], and 4000 quadrupole electron impact mass spectrometers.

A doublet obtained by reverse phase high pressure liquid chromatography[4] of an impure *N*-formylamphetamine synthesis product was found to correspond to the gas-liquid chromatography (GLC) doublet, both components eluting in the same order, as determined by gas chromatographic/mass spectral analysis of collected fractions. This result supported a hypothesis that the GLC doublet arises from stereoisomerism inherent in the injected material [*4*] and not from some form of chromatographic degradation. Rotational isomerism is also excluded as a factor.

Chloroform extracts of fractions representing pure cuts of each peak were evaporated and then subjected to infrared[5] and proton magnetic resonance[6] analysis. The infrared spectra of both extracts showed no significant differences. The strongest band, at 1668 cm^{-1}, confirmed the presence of carbonyl, suggesting, particularly, a tertiary amide. Lack of "Amide II" bands denied the presence of primary and secondary amido functions [*14*]. The second and third most intense bands, at 696 and 741 cm^{-1}, indicated mono-substituted phenyl. Other bands, all of medium intensity, appeared at 1494, 1453, 1431, 1375, 1310, 1270, 1150 (doublet), 1120, and 1028 cm^{-1}.

Proton magnetic resonance spectroscopy (deuterated chloroform solution) clearly supported Structure I while emphasizing the stereoisomeric differences of the material. Assignments for the substance producing the earlier eluting chromatographic peak, obtained from chemical shifts, splitting patterns, and peak areas, are as follows: singlet at 8.22 ppm[7] (one formyl hydrogen), broad peak at 6.9 to 7.5 ppm (ten phenyl hydrogens), multiplet at 3.93 ppm (one methine hydrogen), multiplet at 3.49 ppm (one methine hydrogen), doublets for the methylene hydrogens at 2.88 (one hydrogen), 2.83 (one hydrogen), and 2.55 ppm (two hydrogens), and doublets of three hydrogen intensity each at 1.21 and 1.10 ppm (methyl). Significant differences in the proton magnetic resonance spectrum of the other substances were evident for methine (multiplets of one hydrogen intensity each at 4.04 and 3.60 ppm) and methylene (doublets of one hydrogen intensity each at 3.03, 2.98, 2.78, and 2.75 ppm). The methyl protons (doublets of three hydrogen intensity, each) absorbed at 1.21 and 1.00 ppm. A more detailed report concerning the stereochemistry of Structure I is in process.



I II III

FIG. 1—*Structures discussed in the text.*

[4]Micro-Bondapak C-18 column (Waters Associates, Milford, Mass.) with 65% methanol/water mobile phase.

[5]Beckman IR 4240.

[6]JEOL C-60HL (60 MHz).

[7]From tetramethylsilane.

TABLE 1—*Comparative data for major ions, for compounds of structural Type III.*

Compound	Molecular Weight	R_1	R_2	*m/e* of the Ion Produced (a)	(b)	(c)	(d)
N-Methyldiphenethylamine	239	H	CH_3	148	105	44	91
Di-(1-phenylisopropyl)-amine	253	CH_3	H	162	119	44	91
Di-(1-phenylisopropyl)-methylamine	267	CH_3	CH_3	176	119	58	91
Di-(1-phenylisopropyl)-formamide (proposed)	281	CH_3	CHO	190	119	72	91

Conclusion

The synthesis of amphetamine by the Leuckart synthesis requires the reaction of methyl benzyl ketone with either formamide or ammonium formate, producing *N*-formylamphetamine as an intermediate [*1,2*]. It is believed that Structure I is produced by reaction between *N*-formylamphetamine and excess ketone. Its presence in *dl*-amphetamine, therefore, should provide strong evidence for the implication of the Leuckart synthesis in the manufacturing process.

Summary

An impurity previously reported in illicit amphetamine has been found as a by-product in the synthesis of *N*-formylamphetamine, a reaction precursor to amphetamine by the Leuckart synthesis. Its reidentification as di-(1-phenylisopropyl) formamide has been supported by combined spectroscopic analysis of isolated fractions.

Acknowledgment

The author thanks Miss Susan Ash for her assistance with the high pressure liquid chromatographic fraction collections.

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