

1-Phenylethylamines: a new series of illicit drugs?

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Abstract

Since 1993 many seizures of 1-phenylethylamine have been made in several European countries. It was originally thought that 1-phenylethylamine had been made in error, but later information suggested that it had been prepared deliberately. The related compounds, 1-amino-1-(4-methylphenyl)ethane and 1-methylamino-1-phenylethane and the 1-propanamine isomer of 3,4-methylenedioxyamphetamine, have also occurred in isolated cases. Analytical data are presented on these amines as well as a number of Leuckart impurities in 1-phenylethylamine. The pharmacological effects of these substances are largely unknown.

Keywords: Drug abuse; Phenylethylamines; Leuckart impurities; Illicit synthesis; Monoamine oxidase inhibitors; Mass spectra; Designer drugs

1. Introduction

Starting in 1993, forensic science laboratories in several European countries received numerous submissions of powders and occasional tablets containing 1-phenylethylamine (1-PEA, α -phenylethylamine, α -methylbenzylamine, Fig. 1). Many of these seizures comprised multi-kilogram quantities. The 1-PEA was often found mixed with amphetamine and/or caffeine, but other drugs/cutting agents were also seen. The 1-PEA was most commonly encountered as the sulphate salt.

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There are many psychotropic drugs and natural products based on the 2-phenylethylamine (2-PEA) skeleton (Fig. 1). The Leuckart synthesis [1], involving the reaction of a ketone with formamide or ammonium formate, has often been used for the preparation of these amines. Shulgin and Shulgin [2] have described the preparation of 178 stimulants and hallucinogens based on 2-PEA. This parent compound is also a natural substance; it is a metabolite of the amino acid phenylalanine, and is found in normal urine and as a putrefactive product in decomposing tissues. As far as is known, neither 1-PEA nor any of its simple derivatives occur naturally. The synthesis of 1-PEA from acetophenone was described by Leuckart and Janssen in 1889 [3].

The major use for 1-PEA is a resolving agent and chiral intermediate in synthesis [4]; it is available from several chemical suppliers as the (*R*)-(+) isomer, the (*S*)-(–) isomer or the racemate.

There are only a few synthetic drugs based on the 1-phenylethylamine skeleton. They fall into various therapeutic categories; none is in widespread use and none appears to have obvious potential for abuse.

One of the earliest investigations into the pharmacology of substituted phenylethylamines and related amines was carried out by Barger and Dale [5] in 1910. They studied the sympathomimetic effects in animals on blood pressure and isolated muscle tissues, and found that optimal activity was shown by '... a benzene ring with a side chain of two carbon atoms, the terminal one bearing the amino-group'. This is an exact definition of the 2-PEA nucleus. It was reported that 1-PEA was only weakly active. The same relationship (i.e. 2-amine > 1-amine) also occurred when the ring was *para*-substituted with an hydroxy group. In a study of the toxicology of amines in small rodents it was reported that 1-PEA had a low toxicity similar to that of 2-PEA [6,7]. Depending on the species and sex, the LD₅₀ of 1-PEA varied from 240 mg/kg (intraperitoneal) to 1550 mg/kg (oral). Grana and Lilla [8] showed that (+)-1-PEA and (+)-amphetamine were equally active in inhibiting rat liver amine oxidase, but the latter was found to be 5–6 times more active as a central stimulant.

Whereas, many drugs based on the 2-PEA skeleton have been synthesised, the 1-series has been largely ignored. Schütz [9] reported on the structure-activity relationships in rats and mice of a wide range of 1-amino-1-phenylalkanes, using parameters such as blood pressure and relief of barbiturate narcosis. It was concluded that, depending on the nature of the substituents, these substances were not unlike the sympathomimetic amines (i.e. 2-phenylethylamines) and in addition might also possess interesting psychotropic effects. There appear to have been no published studies on the pharmacology of 1-PEA in humans.

2. Materials and methods

2.1. Reference compounds

Racemic 1-phenylethylamine was obtained from the Sigma Chemical Company Ltd., Poole, Dorset, BH17 7BR, UK. The compounds, *N,N*-di-(1-phenylethyl)amine and *N,N*-di-(1-phenylethyl)formamide were synthesised by Dr. J.

Brussee, Department of Organic Chemistry, Leiden University, The Netherlands. The identity of these compounds was confirmed by NMR. The α -regioisomer of 3,4-methylenedioxyamphetamine, i.e. 1-amino-1-(3,4-methylenedioxyphenyl)propane, was synthesised from 3,4-methylenedioxypropiophenone (Lancaster Synthesis, Morecambe, Lancashire, LA3 3DY, UK) by reductive amination with sodium cyanoborohydride and ammonium acetate.

2.2. Thin-layer chromatography

Thin-layer chromatography was carried out using precoated Silicagel 60 GF 254 plates (Merck, Darmstadt, Germany). The solvent consisted of cyclohexane:toluene/diethylamine (75:15:10 v/v); detection was achieved with Fluram reagent [10] and iodoplatinate spray.

2.3. Gas-chromatography/mass spectroscopy

The GC/MS spectra were recorded using a Hewlett-Packard 5890 gas chromatograph coupled to a 5971 Mass Selective Detector. An HP Ultra-1 column 12 m \times 0.22 mm I.D. \times 0.25 μ m film thickness was used. The carrier gas was helium; flow rate 0.8 ml/min; split 50:1. The injector temperature was 275°C; detector temperature was 280°C. The column oven temperature was programmed from 100°C to 280°C with a rate of 10°C/min; final hold 10 min. Scan range was 35–400 amu.

2.4. Sample preparation

Solid samples were dissolved in methanol (1 mg/ml). Solid or liquid case samples were diluted or extracted with methanol to give an appropriate concentration of the target compounds.

3. Results

3.1. Analysis of 1-phenylethylamine

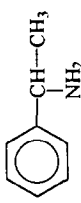
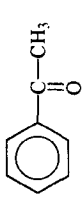
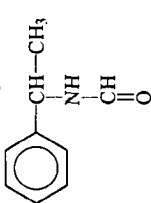

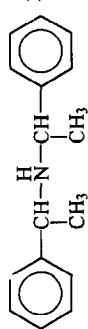
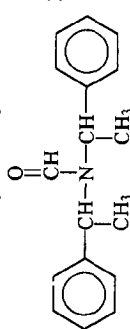
With the Marquis reagent [11], 1-PEA showed an orange colouration that was different from, but could easily be confused with amphetamine. Using thin-layer chromatography, 1-PEA separated from amphetamine; R_f values were 0.44 and 0.38 respectively. These compounds were also easily distinguished by gas-chromatography and mass-spectrometry.

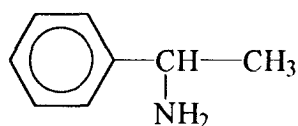
3.2. Leuckart impurities in 1-PEA

As far as is known, no active laboratories preparing 1-PEA have been found, but on several occasions 1-PEA, its precursor acetophenone and the intermediate 1-formylamino-1-phenylethane were detected in the residues recovered from laboratories. In some cases, notes on the synthesis were found. Fig. 2 shows the total ion chromatogram of a sample from a reaction mixture; the compounds identified and their analytical details are listed in Table 1.

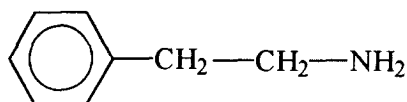
As seen in Fig. 2, the major component is 1-formylamino-1-phenylethane, clearly resulting from the Leuckart reaction of acetophenone. This compound is analogous

Table 1
1-PEA and impurities derived from Leuckart synthesis (see Fig. 2 for key)

Peak	MW	Molecular formula	Name and structure	Retention index	Most intense EI ions (m/z) and relative intensities
1	121	$C_8H_{11}N$	1-Phenylethylamine 	1029	106, 79, 77, 51, 107, 42, 44, 78 100, 25, 16, 8, 7, 6, 5 Ref. [20]
2	120	C_8H_8O	Acetophenone 	1042	105, 77, 120, 51, 50, 106, 43, 78 100, 80, 25, 21, 9, 9, 7, 6 Ref. [20]
3	149	$C_9H_{11}NO$	1-Formylamino-1-phenylethane 	1371	149, 106, 148, 134, 104, 105, 103, 107 100, 75, 68, 65, 53, 30, 23, 16 Ref. [20]
4	156	$C_{10}H_8N_2$	4-Phenylpyrimidine 	1432	156, 129, 102, 103, 52, 76; 77, 155 100, 57, 47, 22, 17, 15, 15, 13 Ref. [20]
5a, 5b	225	$C_{16}H_{19}N$	<i>N,N</i> -di-(1-phenylethyl)amine isomers 	(a) 1638 (b) 1670	105, 106, 210, 77, 79, 103, 104, 120 100, 73, 48, 28, 19, 13, 10, 8
6a, 6b	253	$C_{17}H_{19}NO$	<i>N,N</i> -di-(1-phenylethyl)-formamide isomers 	(a) 2041 (b) 2069	148, 105, 120, 77, 79, 103, 104, 42 100, 56, 27, 26, 18, 13, 12, 10



(1-PEA)



(2-PEA)

Fig. 1. The structures of 1-phenylethylamine (1-PEA) and 2-phenylethylamine (2-PEA).

to *N*-formylamphetamine found in the Leuckart reaction of phenyl-2-propanone [12]. Similarly, 4-phenylpyrimidine is analogous to the 4-benzylpyrimidine found in illicit amphetamine [13].

One of the major impurities found in illicit amphetamine is *N,N*-di-(2-phenylisopropyl)amine [12,14]. In the sample under investigation, the corresponding isomeric *N,N*-di-(1-phenylethyl)amines as well as the *N,N*-di-(1-phenylethyl)formamide isomers were identified by GC/MS using reference compounds. The mass spectra of *N,N*-di-(1-phenylethyl)amine and *N,N*-di-(1-phenylethyl)formamide are presented in Figs. 3 and 4.

The characteristics and processing methods used to manufacture 1-PEA were strikingly similar to those commonly found in the illegal manufacture of amphetamine by the Leuckart method. In several laboratories, amphetamine and its typical Leuckart impurities were also found mixed with 1-PEA and its impurities, suggesting that the two substances had been synthesised in the same place.

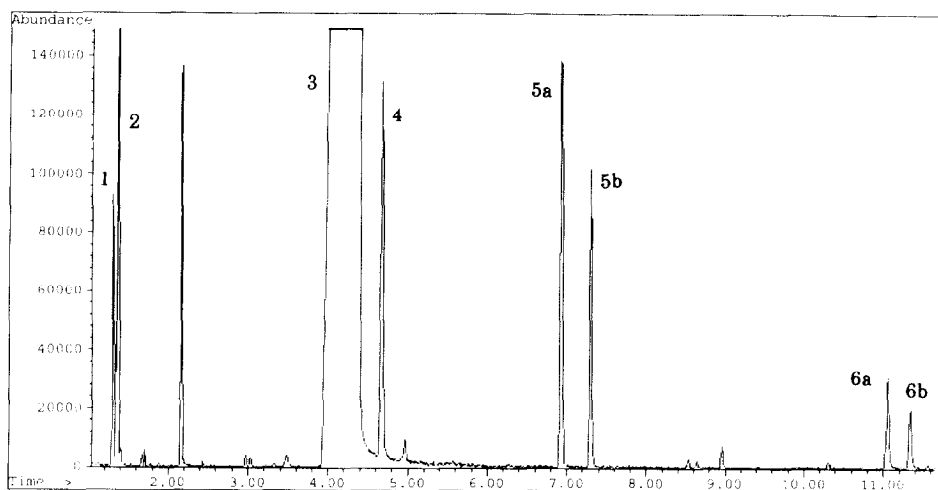


Fig. 2. The total ion chromatogram from a reaction mixture derived from a Leuckart synthesis of acetophenone.

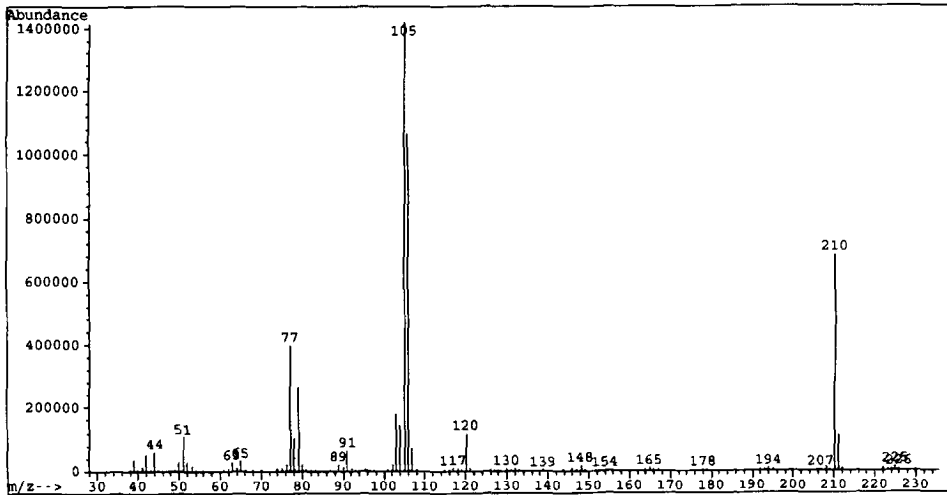


Fig. 3. The mass spectrum of *N,N*-di(1-phenylethyl)amine.

3.3. Analogues of 1-PEA

Whereas 1-PEA has been regularly found on the illicit market, several other 1-amino compounds have occurred in isolated seizures.

(1) 1-Amino-1-(4-methylphenyl)ethane. November 1993; London; 1.5 kg of a sticky orange-brown powder [15]. Sulphate salt; diluted with lactose to a concentration of less than 5%.

(2) 1-Methylamino-1-phenylethane. Reported in 1993; Miami, Florida; 1.5 kg of a tan sweet-smelling powder [16].

(3) 1-Amino-1-(3,4-methylenedioxyphenyl)propane, the α -regioisomer of 3,4-methylenedioxyamphetamine (MDA), known as ALPHA [2]. March and December

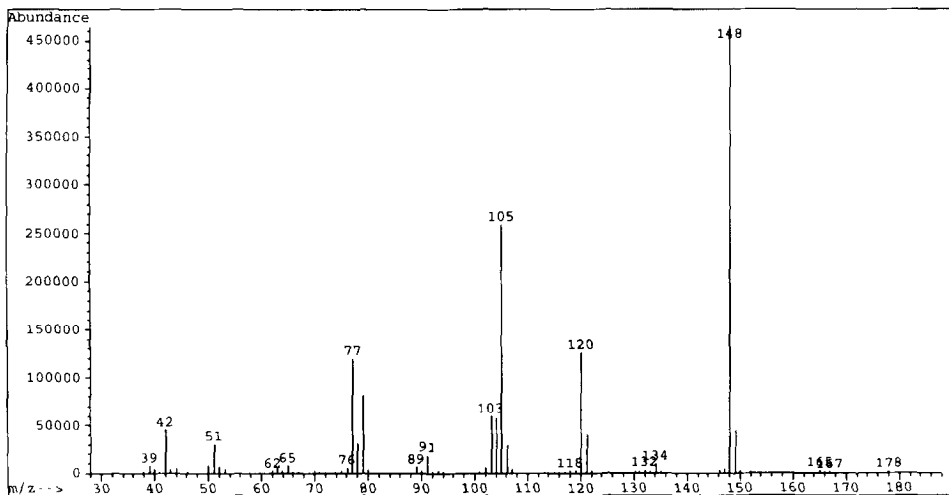
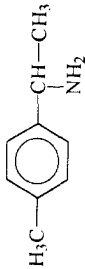
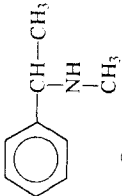
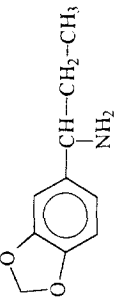


Fig. 4. The mass spectrum of *N,N*-di(1-phenylethyl)formamide.

Table 2
The analogues of 1-PEA

Analogue	MW	Molecular formula	Name and structure	Most intense EI ions (m/z) and relative intensities
	135	$C_9H_{13}N$	1-amino-1-(4-methylphenyl)ethane	120, 93, 91, 121, 77, 60, 134, 44 100, 18, 15, 9, 7, 6, 6, 6 Ref. [15]
	135	$C_9H_{13}N$	1-methylamino-1-phenylethane	120, 42, 58, 77, 105, 121, 51, 56 100, 30, 18, 13, 11, 9, 8, 5 Ref. [16]
	179	$C_{10}H_{13}NO_2$	1-amino-1-(3,4-methylenedioxyphenyl)propane	150, 93, 65, 151, 123, 95, 75, 179 100, 20, 13, 9, 7, 7, 5, 5 Ref. [18]

1994; Rijswijk, Netherlands. It was found in tablets, in a mixture with MDA (estimated ratio 1:2), from which it could only just be resolved by GC. The retention time of ALPHA was 1.017 relative to MDA; Retention Index (RI) of ALPHA = 1456, RI of MDA = 1449. The mass spectrum of ALPHA was clearly distinguishable from that of MDA [17,18].

Further information on these analogues is given in Table 2.

4. Discussion

The appearance of 1-PEA on the drugs market raised a number of questions. Had it been produced simply by salt formation of the commercially available base or had it been synthesised, and if so, whether it had been synthesised by accident or deliberately? Analysis of the *N*-formyl intermediate and impurities has shown that in a number of cases, synthesis by the Leuckart reaction had taken place. This was further supported by indirect information, including statements of dealers, notes and purchases of acetophenone. Producers had stated that they were not making amphetamine. Intelligence information showed that, in addition, purchases of the (racemic) amine had taken place. The (+) isomer was found in a recent seizure.

For 1-amino-1-(4-methylphenyl)ethane, the obvious precursor would have been 4-methylacetophenone, which is commercially available. In the case of 1-methylamino-1-phenylethane, the likely synthesis would have involved a Leuckart reaction between acetophenone and *N*-methylformamide. The most likely synthetic route to ALPHA would involve reductive amination of 3,4-methylenedioxypropiofenone. The latter is commercially available, but is also reported as an impurity in piperonylmethylketone [19].

As noted earlier on the basis of animal studies, 1-PEA is a weak stimulant compared to amphetamine. There were conflicting reports from users on whether 1-PEA had any stimulant properties in humans. This is not surprising since the powders may contain 1-PEA and varying amounts of amphetamine and caffeine. The activity of 1-PEA in mixtures could arise by potentiation of amphetamine. Since 1-PEA is a known monoamine oxidase inhibitor, it may also reduce the rate of metabolism of amphetamine, and thereby cause a prolongation of the stimulant effect.

As far as is known, neither 1-PEA nor its simple derivatives is currently treated as a controlled drug by legislation. If abuse of 1-phenylethylamines continues to increase, then there is an urgent requirement for studies on their synthesis, analysis, biochemistry, pharmacology and epidemiology.

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