

Potential Misrepresentation of 3,4-Methylenedioxyamphetamine (MDA). A Toxicological Warning

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Abstract

The illicit synthesis of the popular drug 3,4-methylenedioxyamphetamine (MDA) has frequently called upon the precursor piperonylacetone, which is reductively aminated with ammonium hydroxide. The term "piperonylacetone" has been used for two distinct chemical entities in the chemical literature, *vis.*, 3,4-methylenedioxyphenylacetone or 3,4-methylenedioxybenzylacetone. It is only the first of these two chemicals which will give rise to MDA. The second chemical has been made commercially available as piperonylacetone and, employing the usual recipes, produces 1-(3,4-methylenedioxyphenyl)-3-aminobutane. This amine could be mistaken for MDA if only simple presumptive tests are employed. This latter base is largely unexplored pharmacologically and toxicologically and, as it may reasonably appear in illicit drug traffic misrepresented as MDA, it may well represent a clinical problem of unforeseeable consequences.

potentially ambiguous, as the prefix "piperonyl" has been used to indicate either the chemical moiety 3,4-methylenedioxyphenyl (as in the term piperonylaldehyde for piperonal), or the homologous 3,4-methylenedioxybenzyl (as in the term piperonyl alcohol for the corresponding benzyl alcohol). This latter terminology would equate piperonylacetone with the ketone HPA-4. The reductive amination of HPA-4 with either ammonia or methyl amine would give rise to the amines HMDA-5 and HMDMA-6, superficially similar to MDA-2 and MDMA-3 by most presumptive tests, but pharmacologically and toxicologically distinct entities. A recent receipt of compound HPA-4 from a major chemical distributor in response to a specific purchase order for compound PA-1 indicates that the potential for confusion and misidentification is real; that material distributed as MDA may in fact be 1-(3,4-methylenedioxyphenyl)-3-aminobutane, HMDA-5. Consequently, a method for distinguishing between these two product amines, and between their precursor ketones, may be needed by the toxicological community.

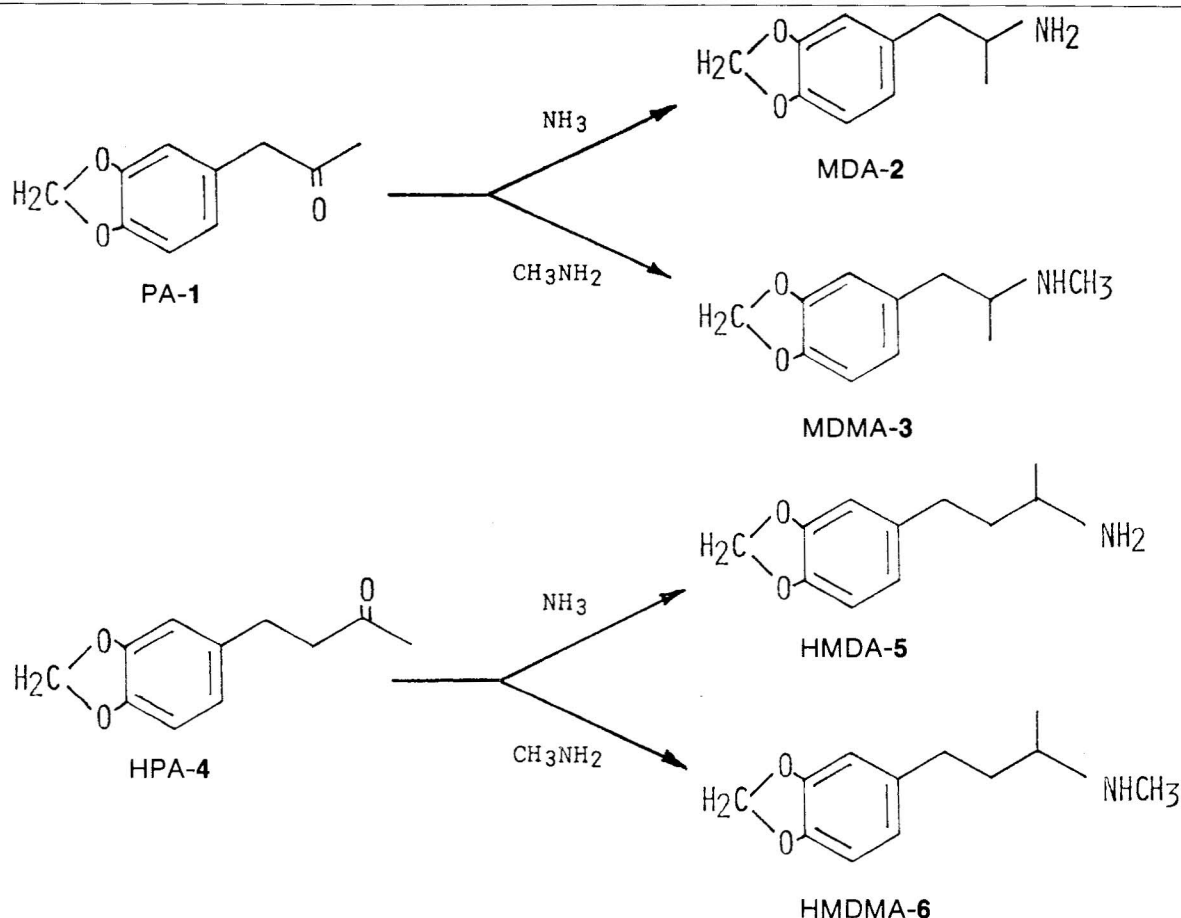
Introduction

A large percentage of the illicit syntheses of amphetamine has employed phenylacetone (phenyl-2-propanone, P-2-P) as a starting material, with reductive amination being achieved with amalgamated aluminum metal and ammonium hydroxide (1). Parallel procedures employing methylamine hydrochloride are frequently used to prepare methamphetamine (2). A similar procedure has been used to synthesize 3,4-methylenedioxyamphetamine (MDA-2), a drug with continuing popular demand in the illicit market. This process utilizes the P-2-P analog, 3,4-methylenedioxyphenylacetone (PA-1). This latter ketone is commercially available, generally under the trivial name of piperonylacetone. The structure that corresponds to this name is

Materials and Methods

Instrumentation

Infra-red spectra were obtained on either a Beckman (Fullerton, California) Acculab 2 or a Perkin-Elmer (Norwalk, Connecticut) Model 283 grating spectrophotometer. Mass spectral data were obtained from a Finnigan (Sunnyvale, California) Model 3600 spectrograph employing electron impact (EI) and a solid probe. Gas chromatographic data were obtained from a Hewlett-Packard (Avondale, Pennsylvania) 5880 chromatograph with nitrogen-phosphorus detectors (NPD), employing an SE-54 substrate on a 25 m x 0.2 mm i.d. WCOT fused silica capillary column or a 6 ft x 2 mm glass column packed with 3% SP-2250 on 100/120 mesh Supelcoport. Nuclear magnetic resonance (NMR) data were from a Varian (Walnut Creek, California) FT-80. Melting points (m.p.) are uncorrected.



Preparation of Authentic PA-1 and HPA-4

3,4-Methylenedioxyphenylacetone (PA-1): A solution of piperonal (15.0 g, 100 mmol) in 80 mL acetic acid was treated with 15 mL nitroethane and 7 g anhydrous ammonium acetate, and heated at 100°C for 4 hours. The addition of a few milliliters water followed by cooling yielded 8.0 g 1-(3,4-methylenedioxyphenyl)-2-nitropropene, melting point 97-98°C (unimproved by recrystallization from acetic acid). This product was dissolved in boiling acetic acid, and added to a suspension of elemental iron (18.0 g, electrolytic grade) in 100 mL warm acetic acid. The mixture was heated gently, with frequent swirling, until an exothermic reaction ensued. After the reaction had subsided, 1 liter of water was added, and the mixture clarified by filtration. The filtrate was extracted with 75 mL methylene chloride three times, the extracts pooled, washed once with 5% NaOH, and the solvent removed *in vacuo*. Distillation of the residue yielded 4.6 g PA-1 as a colorless oil, boiling point (b.p.) 100-110°C at 0.2 mm/Hg.

3,4-Methylenedioxybenzylacetone (HPA-4): A solution of piperonal (15 g, 100 mmol) in 200 mL acetone was treated with 0.75 g KOH and held at reflux for 20 minutes. The solvent was removed *in vacuo*. The residue was triturated under 150 mL 95% ethanol (decanted) and then extracted with 150 mL boiling hexane. Cooling provided 3,4-methylenedioxybenzylideneacetone as yellow crystals (1.1 g, m.p. 106-108°C). This product was hydrogenated in ethanol employing Pd/C (10%) as a catalyst. The product was contaminated with a small amount of the corresponding carbinol, prepared separately by the reduction of the benzylideneacetone with NaBH₄ in methanol. Pure HPA-4,

upon recrystallization from ethanol, had a melting point of 50-51°C.

Preparation of Oximes

A solution of the ketone (1 or 4) in 5 volumes absolute ethanol and 5 volumes pyridine was treated with an equal weight of hydroxylamine hydrochloride and heated for two hours at reflux. The solvent was removed *in vacuo*, and the residue triturated under water until crystallization occurred. The resulting white solids were recrystallized from ethanol.

Preparation of 2,4-dinitrophenylhydrazones

A solution of PA-1 or HPA-4 in 50 volumes absolute ethanol was treated with 75% its weight dinitrophenylhydrazine, and heated to a gentle reflux. The addition of an equal volume concentrated HCl (equal to the initial ketone) effected complete solution with a lightening of color. After 5 minutes continuing reflux, the solution was cooled, allowing spontaneous crystallization. Recrystallization from acetonitrile (7 mL/g) yielded orange crystals of the hydrazone.

Reductive Amination

The PA-1 and HPA-4 were reductively aminated separately with either ammonia or methylamine in aqueous isopropanol employing amalgamated aluminum, as described for the preparation of amphetamine from phenylacetone (1). The product amines were purified by distillation (Kugelrohr, at reduced pressure) and converted to their hydrochloride salts by solution in

isopropanol, titration with concentrated HCl employing external, damp universal pH paper, and the addition of anhydrous ether.

Preparation of *p*-Methoxyphenyl Ureas

A suspension of 1 g of each free base (MDA-2, MDMA-3, HMDA-5, and HMDMA-6) in 10 mL boiling hexane was clarified by the addition of about 1 mL toluene, and the resulting solution treated with 0.75 g *p*-methoxyphenylisocyanate. The resulting solids were removed by filtration, washed with hexane, and recrystallized from acetonitrile.

Results and Discussion

The instigation of this present study was the receipt of a sample of commercially offered piperonylacetone (Research Chemical Company, Belleville, New Jersey #M-378 and structurally described as PA-1) which was a white crystalline solid, although the chemical literature holds that PA-1 is a high boiling oil. The infra-red spectra of PA-1 and HPA-4 (PA-1 as a smear on NaCl, HPA-4 as a melt on warm NaCl) were virtually indistinguishable. Both had similar aliphatic hydrocarbon absorption (at 2800-3000 cm^{-1}), both had ketonic carbonyl function at 1710 cm^{-1} , and the fingerprint presentation (from 600 to 1200 cm^{-1}) were comparable except for minor disturbances between 700 and 800 cm^{-1} , which might well be ascribed to congeneric impurities in PA-1 (presumably prepared from natural sources). NMR spectra were clearly different and characteristic in the methylene proton area. PA-1 and HPA-4 showed the terminal methyl group at 2.14 and 2.12 δ , respectively; the methylenedioxy group at 5.94 and 5.91 δ , respectively; and aromatic protons in the 6.6 to 6.8 δ area. However, with PA-1, there was a singlet methylene at 3.59 δ ; whereas with HPA-4, there was a complex pattern centered at 2.75 δ . All values were obtained in CDCl_3 and measured from internal TMS. The conventional

ketone derivatives, (*i.e.*, oxime and dinitrophenylhydrazone derivatives) were easily distinguishable from one another, as determined by melting point (m.p.) and mixed melting point (m.m.p.) (see Table I).

Of immediate concern to the toxicological community is the fact that either of these two ketones react readily, by reductive amination, to form bases that can only be distinguished from one another with some chemical sophistication.

With the pure chemicals in hand, the reduction products with ammonia or methylamine can be clearly identified by the properties of the hydrochloride salts or the urea derivatives obtained by interaction with *p*-methoxyphenylisocyanate. The infra-red spectra of the salts are given in Figure 1 as KBr pellets. The spec-

Table I. Comparison of the Physical Properties of Ketones 1 and 4 and Their Derivatives

	PA-1	HPA-4	Solvent
Physical Properties (a)	(100° C/0.3 mm)	51 (b)	E
Oxime	89 (c)	100 (d)	E
DNP	141	150 (e)	A
Reductive Amination			
Product with NH_3 ($\cdot\text{HCl}$)	188 (2)(f)	131 (3)(g)	IE
<i>p</i> -Anisylurea	167	154 (h)	A
Reductive Amination			
Product with CH_3NH_2 ($\cdot\text{HCl}$)	153 (5)(i)	130 (6)	IE
<i>p</i> -Anisylurea	112 (j)	161 (k)	A

(a) All solid derivatives have been recrystallized from the solvents indicated (E, ethanol; A, acetonitrile; IE, isopropanol/ether) to a 1° C m.p. range. The higher value of this range is listed.

(b) Ref. 12 gives mp 50-51° C.

(c) Ref 13 gives mp 87-88° C.

(d) Ref. 14 gives mp 98° C. Mmp with 1 oxime, 65-73° C.

(e) Mmp with 1 DNP, 120-136° C. Mmp with synthetic 4 DNPH (see text), undepressed.

(f) Ref. 15 gives 187-188° C.

(g) Product obtained as a broadly melting hydrate (<100). Value obtained either by drying at 100° C to constant weight, or by very slow temperature rise on mp determination.

(h) Mmp with 2-urea (167), 133-140° C. Mmp with 6-urea (161), 135-138° C.

(i) Ref 15 gives 152-153° C.

(j) Two degree mp range (110-112° C).

(k) Mmp with 2-urea (167), 138-146° C.

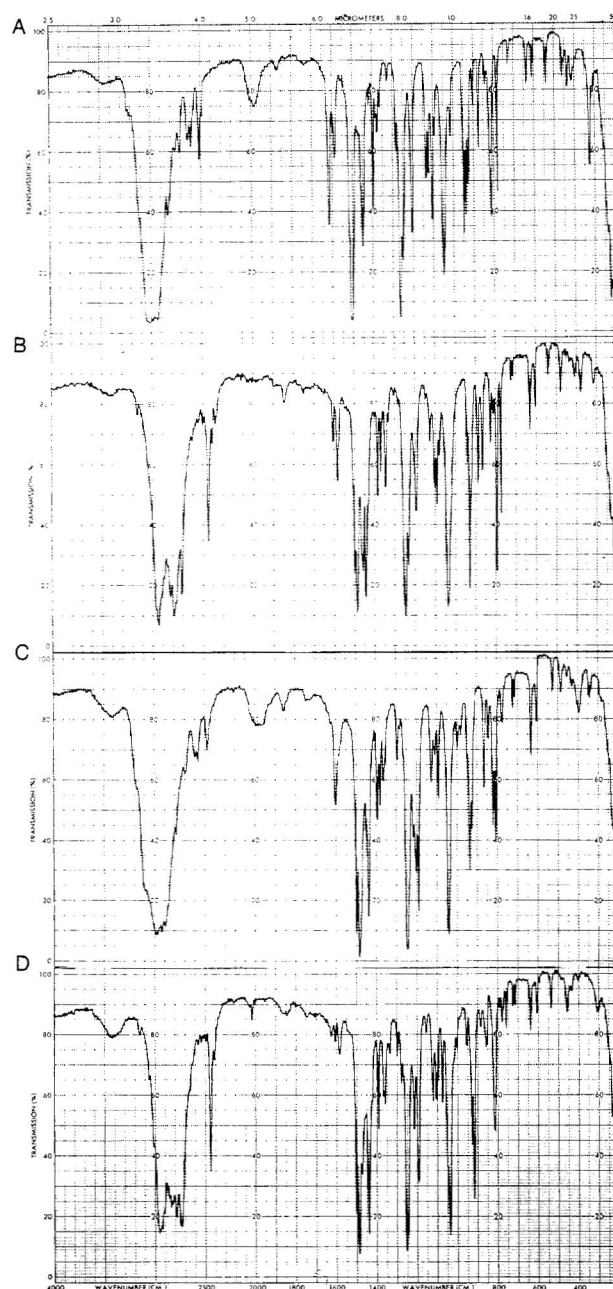


Figure 1. Infrared Spectra of A) MDA-2, B) MDMA-3, C) HMDA-5, D) HMDMA-6. All as KBr pellets.

tra of both MDA-2 and MDMA-3 have appeared in the literature (3,4), and they are presented here for comparison purposes. The mass spectral cracking patterns on EI analysis have also been compared, see Figure 2. All four bases display small but real peaks corresponding to their intact parent structures, but in all four cases, a principal fragment is found at m/e of 135, representing the methylenedioxybenzyl fragment common to all. The spectra are shown with normalization to the maximum fragment.

Of more practical value in toxicological analysis is the fact that all four bases can be completely separated by GLC techniques. A mixture of approximately equal weights of the bases MDA-2, MDMA-3, HMDA-5, and HMDMA-6 was separated isothermally and without prior derivatization, as shown in Figure 3. Detection can be easily accomplished down to the picogram level, employing a NPD and a capillary column. Employ-

ing a normal packed column, even with derivatization with heptafluorobutyric anhydride, MDMA-3 and HMDA-5 could not be resolved.

Pharmacologically, these four bases represent a diverse spectrum of activity. MDA-2 is a popular illicit drug, is frequently encountered, and has been implicated in a number of toxicological crises (5-7). The N-methyl homolog, MDMA-3 (or MDM) has been broadly studied in clinical application as a psychotherapeutic tool, having found little abuse potential. The two remaining amines, HMDA-5 and HMDMA-6, are largely unexplored pharmacologically. The primary amine, HMDA-5, has been studied as a monoamine oxidase inhibitor (8), but has been found to be ineffective in open-field tests that would suggest hallucinogenic activity (9). The secondary amine HMDMA-6 has been studied only as an anticholinergic, wherein it has a feeble atropine action (10). Neither HMDA-5 nor HMDMA-6 has been reported as being evaluated in human subjects.

It is this latter fact that is of the gravest concern. Since HPA-4 can be, and has been, supplied in place of PA-1 in response to commercial purchases, and since the ubiquitous conversion of such ketones to illicitly saleable products such as MDA-2 might proceed in innocence to produce the largely unexplored HMDA-5 as an inadvertent product, caution must be exercised in the analysis of tissue specimens in any suspected MDA exposure (7).

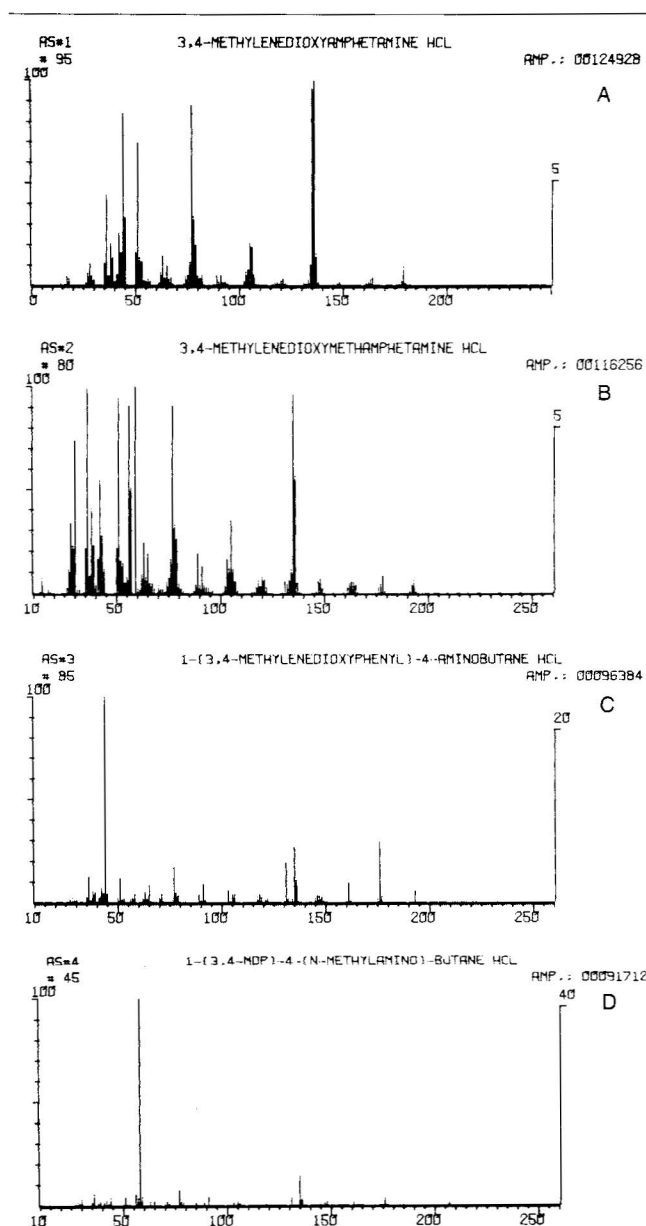


Figure 2. Mass spectral data (EI) for: A) MDA-2, B) MDMA-3, C) HMDA-5, D) HMDMA-6. All are solid probes.

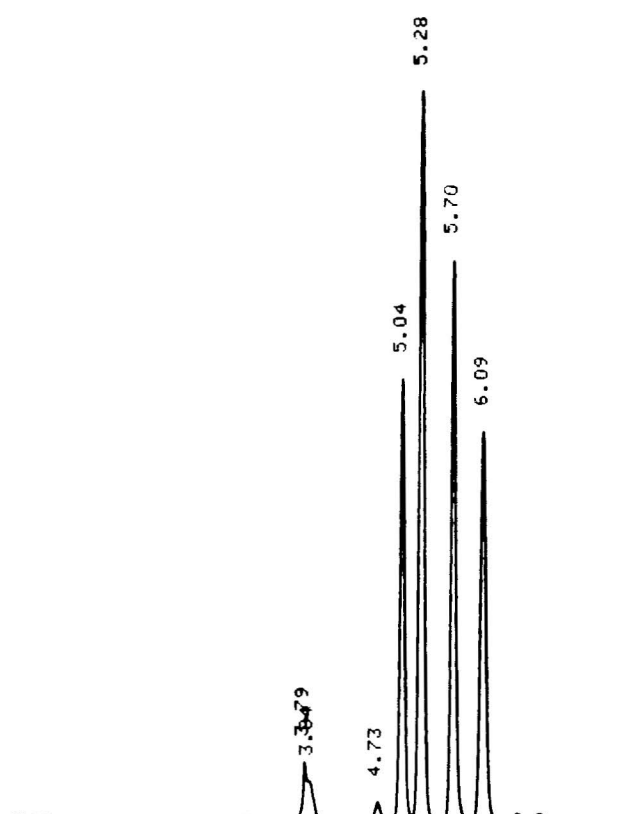


Figure 3. GC analysis of MDA-2, MDMA-3, HMDA-5, and HMDMA-6. The peaks are identified as follows: Toluene solvent peaked at 3.79 min, an impurity in MDMA-3 peaked at 4.73 min, MDA-2 at 5.04 min, MDMA-3 at 5.28 min, HMDA-5 at 5.70 min, and HMDMA-6 at 6.09 min. Conditions: 205°C, isothermal, NPD, 25 m x 0.2 mm SE-54 WCOT fused silica column, 10:1 split ratio.

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