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THE STIMULANTS AND HALLUCINOGENS UNDER CONSIDERATION: A BRIEF OVERVIEW OF THEIR CHEMISTRY AND PHARMACOLOGY

LOUIS S. HARRIS

Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298 (U.S.A.)

SUMMARY

The substances under review are a heterogenous set of compounds from a pharmacological point of view, though many have a common phenylethylamine structure. Variations in structure lead to marked changes in potency and characteristic action.

The introductory material presented here is meant to provide a set of chemical and pharmacological highlights of the 28 substances under consideration. The most commonly used names or INN names, Chemical Abstract (CA) names and numbers, and elemental formulae are provided in the accompanying figures. This provides both some basic information on the substances and a starting point for the more detailed information that follows in the individual papers by contributors to the symposium.

Key words: Stimulants, their chemistry and pharmacology — Hallucinogens, their chemistry and pharmacology

INTRODUCTION

Cathine (Fig. 1) is one of the active principles of khat (*Catha edulis*). The structure has two asymmetric centers and exists as two geometric isomers, each of which has been resolved into its optical isomers. In the plant it exists as *d*-nor-pseudoephedrine. It is a typical sympathomimetic amine with a strong component of amphetamine-like activity. The racemic mixture is known generically in this country and others as phenylpropanolamine (*dl*-norephedrine). It is widely available as an over-the-counter (OTC) anti-appetite agent and nasal decongestant.

Phenylpropanolamine is not readily self-administered and has little amphetamine-like activity. In some countries *d*-nor-pseudoephedrine (cathine) is sold as phenylpropanolamine. There is some evidence for the abuse of the pure chemical compound as well as the plant material containing it.

Cathinone (Fig. 2) is an oxidative product of cathine and is found in the

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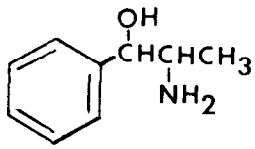

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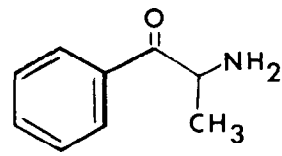

$C_9H_{13}NO$

$C_9H_{11}NO$

Fig. 1. Cathine (Norpseudoephedrine). CA name: α-(1-aminoethyl)-benzenemethanol. CA No. 48115-38-4.

Fig. 2. Cathinone. CA name: 2-amino-1-phenyl-1-propanone. CA No. 5265-18-9.

plant as the (−)-isomer. It has typical amphetamine-like properties and is 7 times more potent than cathine. It is now generally accepted as being responsible for most of the psychoactive properties of khat. The compound is self-administered by the rhesus monkey.

Clobenzorex (Fig. 3) is the racemic *N*-orthochlorobenzyl derivative of amphetamine. Most of its activity resides in the *d*-isomer. It is an amphetamine-like anorexiant. It is not marketed in the U.S.A.

2,5-Dimethoxyamphetamine (Fig. 4) is one of a series of compounds synthesized by Shulgin [1] to study the structure-activity profile the hallucinatory activity of mescaline. The compound is a hallucinogen in man with evidence for street abuse in the U.S.A. It has been placed in Schedule I under the U.S. Controlled Substance Act (CSA). In the spinal dog, Vaupel et al. [2] reported that low doses produced hallucinatory-like activity while higher doses appeared more like amphetamine.

4-Bromo-2,5-dimethoxyamphetamine (Fig. 5) is another of the Shulgin [3] series. It is a hallucinogen in man with evidence for street abuse in the U.S.A. and other countries. It is controlled in Schedule I of the U.S. CSA. It is LSD-like in the spinal dog and has a high affinity for serotonergic (5-HT) binding sites.

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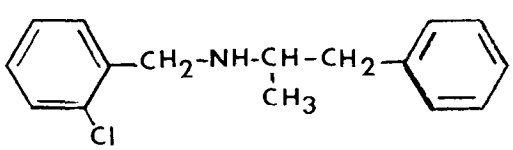

$C_{16}H_{18}ClN$

Fig. 3. Clobenzorex. CA name: *N*-[2-chlorophenyl)methyl]-α-methyl-benezeneethanamine. CA No. (±) 76553-22-5, (+) 13364-32-4.

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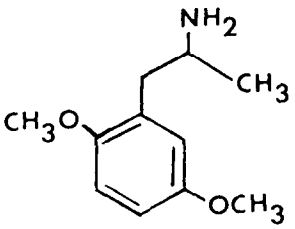

$C_{11}H_{17}NO_2$

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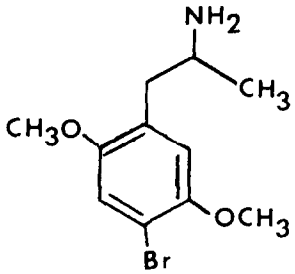

$C_{11}H_{16}BrNO_2$

Fig. 4. 2,5-Dimethoxyamphetamine. CA name: 2,5-dimethoxy-α-methyl-benzeneethanamime. CA No. 2801-68-5.

Fig. 5. 4-Bromo-2,5-dimethoxyamphetamine. CA name: 4-bromo-2,5-dimethoxy-α-methyl-benzeneethanamine. CA No. 32156-26-6.

N-Ethylamphetamine (Fig. 6), is a typical amphetamine-like agent and has been marketed as an anorectic but not in the U.S.A. It is controlled in Schedule I of the U.S. CSA as a stimulant. Woods [4] has found the drug to be self-administered in the rhesus monkey.

Fenbutrazate (Fig. 7) is a derivative of phenmetrazine. Little is known about this compound other than that it has anorectic properties. There is no evidence of abuse and the substance is not controlled under the U.S. CSA.

Fencamfamine (Fig. 8) is a potent CNS stimulant not commercially available in the U.S., but widely sold in Europe as a tonic. Some street abuse has been reported in the U.S. but it is not controlled under the CSA. The drug has been studied by both Schuster and National Institute on Drug Abuse, Addiction Research Center (ARC). It is self-administered by both the dog and monkey.

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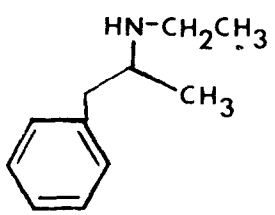

$C_{11}H_{17}N$

Fig. 6. *N*-Ethylamphetamine. CA name: *N*-ethyl-α-methyl-benzeneethanamine. Other names: Adiparthrol, Apetinil. CA No. 457-87-4.

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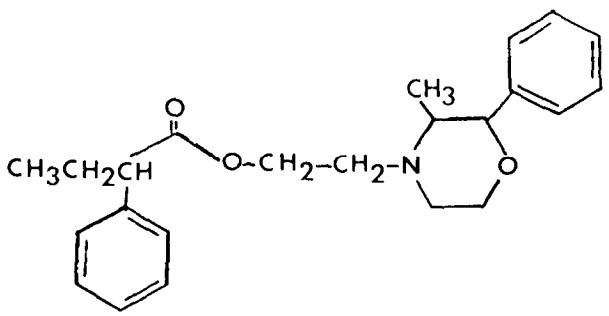

$C_{23}H_{29}NO_3$

Fig. 7. Fenbutrazate. CA name: α-ethyl-2-(3-methyl-2-phenyl-4-morpholinyl)ethyl ester benzeneacetic acid. Other name: Phenbutrazate. CA No. 4378-36-3.

Fenetylline (Fig. 9) is a CNS stimulant widely marketed in Europe, but not available in the U.S. Structurally, it is a combination of a xanthine moiety with amphetamine. Dr. Kristen and co-workers [5], and Dr. Nickel and co-workers [6] discuss the compound more fully in their presentations. The drug is self-administered and some street abuse has been reported in Europe. It is controlled in Schedule I under the U.S. CSA.

Fenproporex (Fig. 10) is the *N*-cyanoethyl derivative of amphetamine. It has been reported to have anorectic properties but little has been published.

Furfenorex (Fig. 11) is the *N*-furfuryl derivative of methamphetamine. It is reported to be an anorectic agent but little has been published on this compound.

Levamphetamine (Fig. 12) is the *l*-isomer of amphetamine. It is a CNS stimulant and anorectic with about 1/3 the potency of the *d*-isomer. It is not presently marketed in the U.S. but is marketed elsewhere. The drug is self-administered by the rat, dog and rhesus monkey. It is controlled in Schedule II of the U.S. CSA.

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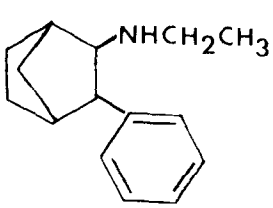

$C_{15}H_{21}N$

Fig. 8. Fencamfamine. CA name: *N*-ethyl-3-phenyl-bicyclo[2.2.1]-heptan-2-amine. Other name: Euvitol. CA No. 1209-98-9.

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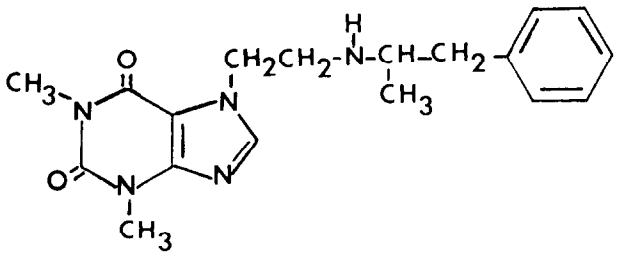

$C_{18}H_{23}N_5O_2$

Fig. 9. Fenetylline. CA name: 3,7-dihydro-1,3-dimethyl-7-[2-[1-methyl-2-phenylethyl) amino]ethyl]-1H-purine-2,6-dione. CA No. 3736-08-1. Other name: Captagon®.

Levomethamphetamine (Fig. 13) is the *l*-isomer of methamphetamine. It is a CNS stimulant with about 1/3 the potency of the *d*-isomer. It is not available commercially in the U.S. I have no knowledge of its availability elsewhere.

Mefenorex (Fig. 14) is an anorectic which is discussed more fully by Dr. Engel and co-workers [7]. It is the *N*-choro-*n*-propyl derivative of amphetamine. It is not commercially available in the U.S. and is not controlled. Little data concerning its abuse liability has been published.

3,4-Methylenedioxyamphetamine (Fig. 15) is another of the Shulgin compounds. It is a hallucinogen with a strong stimulatory component in humans and the spinal dog. It is self-administered by the baboon. It has no known medical use but appears to be associated with a low level of street abuse. It is popularly known as 'MDA' or 'love drug' and is controlled in Schedule I of the U.S. CSA. There have been some deaths reported associated with ingestion of the drug. These deaths resembled acute amphetamine intoxication. The compound has been resolved and its isomers studied.

Morazone (Fig. 16) is a phenmetrazine derivative whose pharmacological properties are those of a non-steroidal anti-inflammatory agent. Thus, it has

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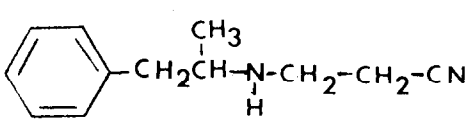

$C_{12}H_{16}N$

Fig. 10. Fenproporex. CA name: 3-[(1-methyl-2-phenylethyl)amino]-propanenitrile. CA No. 15686-61-0.

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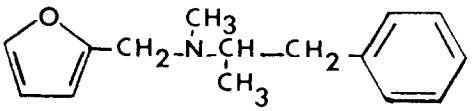

$C_{15}H_{19}NO$

Fig. 11. Furfenorex. CA name: *N*-methyl-*N*-(1-methyl-2-phenylethyl)-2-furanmethanamine. CA No. (±) 13445-60-8, (+) 3776-93-0.

analgesic anti-inflammatory and antipyretic activity. The literature on this compound is sparse. It is not available commercially in the U.S. and is not controlled under the CSA.

Paramethoxyamphetamine (Fig. 17) has some amphetamine-like activity with a component of hallucinogenic activity. Like fenfluramine, it has a strong serotonergic component. It is metabolized to the phenol (hydroxyamphetamine, Fig. 18), which is a more typical amphetamine-like drug. The compound is not self-administered by the baboon. In drug discrimination studies paramethoxyamphetamine produces incomplete discrimination to either amphetamine or mescaline. Paramethoxyamphetamine is not available commercially in the U.S. and is not controlled under the CSA.

Hydroxyamphetamine (Fig. 18) is an indirectly acting sympathomimetic with little CNS stimulatory activity. It is marketed in the U.S. (Paredrine®) and worldwide as an ophthalmic preparation to produce mydriasis. It is not controlled under the U.S. CSA.

Pemoline (Fig. 19) was first described as a memory enhancer. It has strong central stimulatory properties but is not self-administered. Pemoline inhibits catecholamine reuptake and is discussed more fully by Dr. Langer of Abbott

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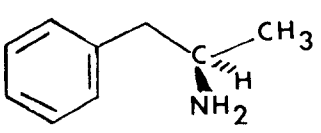

$C_9H_{13}N$

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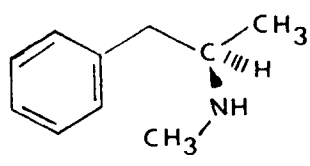
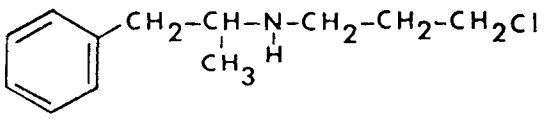


$C_{10}H_{15}N$

Fig. 12. Levamphetamine, λ-form of amphetamine R(—). CA name: (—)-α-methylbenzeneethanamine. Other name: Cydril. CA No. 156-34-3.

Fig. 13. Levomethamphetamine. CA name: (—)-*N*,α-dimethyl-benzeneethanamine. CA No. 33817-09-3 (R—).

14 

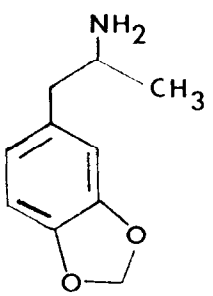
$C_{12}H_{18}ClN$

Fig. 14. Mefenorex. CA name: *N*-(3-chloropropyl)-α-methyl-benzeneethanamine CA No. 17243-57-1. Other names: Anexate, Doracil, Pondinil, etc.

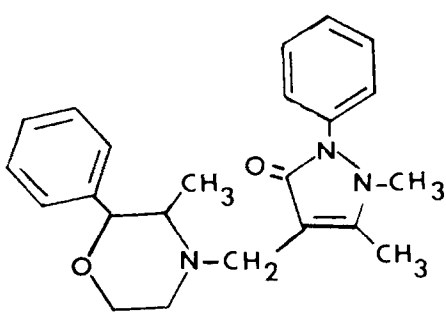
[8]. The drug is available in the U.S. and is used medically as an adjunct in the management of children with hyperkinetic syndrome. It is controlled in Schedule IV of the U.S. CSA, but there is little evidence of abuse.

Propylhexedrine (Fig. 20) is the cyclohexane analog of methamphetamine. It is a nasal vasoconstrictor and anorectic. It is widely available in the U.S. and elsewhere as an OTC nasal decongestant (Benzedrex) sold as inhalers. It is described more fully by Dr. Wesson of Menley and James [9]. While the drug is not controlled under the U.S. CSA, some minor street abuse has been reported. Some deaths have occurred after intravenous use of the material extracted from the inhaler.

Pyrovalerone (Fig. 21) is an indirectly acting sympathomimetic amine. It both releases and inhibits reuptake of norepinephrine. Neurochemically, it is somewhere between amphetamine and imipramine. Little pharmacological data are available. To the best of my knowledge, the drug is not commercially available, is not abused and is not controlled.

15 

$C_{10}H_{13}NO_2$

16 

$C_{23}H_{27}N_3O_2$

Fig. 15. 3,4-Methylenedioxyamphetamine. CA name: α-methyl-1,3-benzodioxole-5-ethanamine. CA No. 4764-17-4. Other name: MDA.

Fig. 16. Morazone. CA name: 1,2-dihydro-1,5-dimethyl-4-[(3-methyl-2-phenyl-4-morpholinyl)methyl]-2-phenyl-3H-prazol-3-one. Other names: Novartrina, Tarugan. CA No. 6536-18-1.

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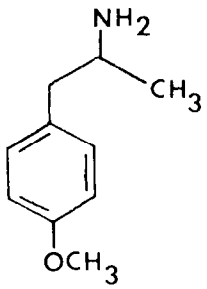

$C_{10}H_{15}NO$

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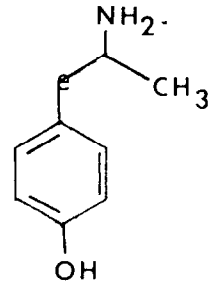

$C_9H_{13}NO$

Fig. 17. Paramethoxyamphetamine. CA name: 4-methoxy-α-methyl-benzeneethanamine. CA No. 64-13-1.

Fig. 18. Paraoxyamphetamine. CA name: 4-(2-aminopropyl)-phenol. CA No. 103-86-6. Other names: Hydroxyamphetamine, Paredrine, Paredrinex, Pulsoton.

3,4,5-Trimethoxyamphetamine (Fig. 22) is the amphetamine analog of mescaline. It is a weak hallucinogen in man approximately equipotent to mescaline. In the spinal dog, the compound has LSD-like activity with some amphetamine-like properties. There is no known medical use and the drug is controlled in Schedule I of the U.S. CSA.

4-Bromo-2,5-dimethoxyphenylethylamine (Fig. 23) may be a hallucinogen in man similar to its amphetamine analog (Fig. 5). There is little literature data available. The drug has no known medical use and is not controlled under the CSA.

2,5-Dimethoxy-4-ethylamphetamine (Fig. 24), popularly known as 'DOET', is a hallucinogen in man. It is more active than the 4-methyl homolog

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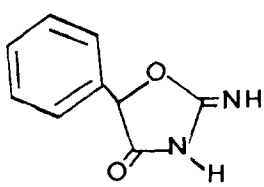

$C_9H_8N_2O_2$

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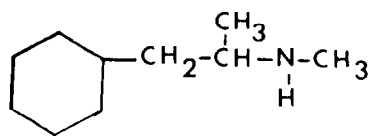

$C_{10}H_{21}N$

Fig. 19. Pemoline. CA name: 2-amino-5-phenyl-4(5H)-oxazolone. Other names: Azoksodon, Cylert, Dantromin, Deltamine, Endolin, Hyton, Kethamed, Nitan, Notair, Pioxol, Pondex, Ronyl, Sigmadyn, Sistral, Sofro, Tradon, Volital, Phenylisohydantoin. CA No. 2152-34-3.

Fig. 20. Propylhexedrine. CA name: *N*,α-dimethylcyclohexaneethylamine. Other names: Benzedrex. CA No. 101-40-6.

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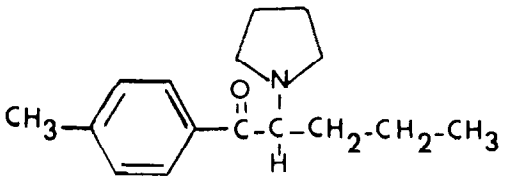

$C_{16}H_{23}NO$

Fig. 21. Pyrovalerone. CA name: 1-(4-methylphenyl)-2-(1-pyrrolidinyl)-1-pentanone. CA No. 3563-49-3. Other names: Centroton, Thymergix.

'DOM'. The drug is not self-administered by the baboon and is discriminated as LSD or mescaline. There is no known medical use or evidence of abuse and it is not scheduled under the CSA as is DOM.

Dimetylamphetamine (Fig. 25) is an amphetamine-like stimulant, but there is little published data. To my knowledge, the compound is not commercially available, has not been reported to be abused and is not controlled under the U.S. CSA.

N-ethyl-3,4-methylenedioxyamphetamine (Fig. 26) is mainly a CNS stimulant with some hallucinatory properties. The drug has no known medical use. I know of no reports of abuse and the compound is not controlled under the U.S. CSA.

5-Methoxy-3,4-methylenedioxyamphetamine (Fig. 27) is another of the Shulgin series [1,3]. It has mixed stimulant hallucinatory activity in man. In the spinal dog, it demonstrates both amphetamine- and LSD-like activity as well as other effects not common to these agents. The drug has been tried as a psychotherapeutic agent in man with no clearcut success. Thus, it has no accepted medical use and is controlled in Schedule I of the U.S. CSA.

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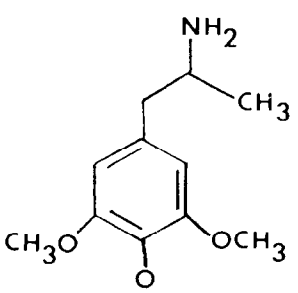

$C_{12}H_{19}NO_3$

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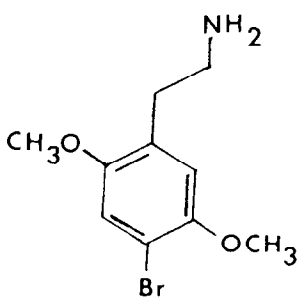

$C_{10}H_{14}BrNO_2$

Fig. 22. 3,4,5-Trimethoxyamphetamine. CA name: 3,4,5-trimethoxy-α-methyl-benzeneethanamine. CA No. 1082-88-8.

Fig. 23. 4-Bromo-2,5-dimethoxyphenylethylamine. CA name: 4-bromo-2,5-dimethoxybenzeneethanamine.

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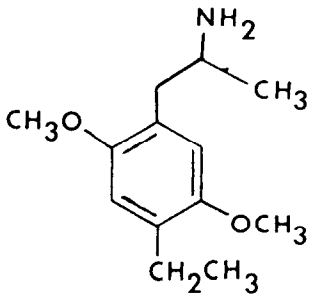

$C_{13}H_{21}NO_2$

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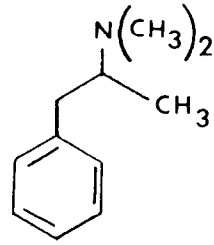

$C_{11}H_{17}N$

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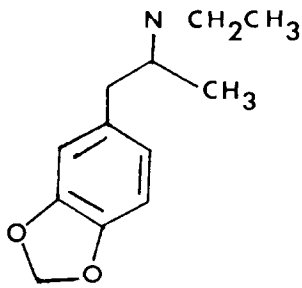

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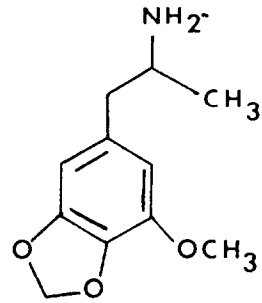

$C_{11}H_{15}NO_3$

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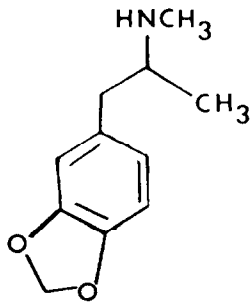

$C_{11}H_{15}NO_2$

Fig. 24. 2,5-Dimethoxy-4-ethylamphetamine. CA name: 2,5-dimethoxy-4-ethyl-α-methyl-benzeethanamine. CA No. 22004-32-6.

Fig. 25. Dimethylamphetamine. CA name: *N,N,* α-trimethyl-benzeneethanamine. CA No. 4075-96-1.

Fig. 26. *N*-Ethyl-3,4-methylenedioxyamphetamine. CA name: *N*-ethyl-α-methyl-1,3-benzodioxole-5-ethanamine. CA No. 14089-52-2.

Fig. 27. 5-Methoxy-3,4-methylenedioxyamphetamine. CA name: 4-methoxy-α-methyl-1,3-benzodioxole-5-ethanamine. CA No. 23693-19-8.

Fig. 28. 3,4-Methylenedioxymethamphetamine. CA name: *N*, α-dimethyl-1,3-benzodioxole 5-ethanamine. CA No. 42542-10-9.

3,4-Methylenedioxymethamphetamine (Fig. 28) is the *N*-methyl derivative of MDA (Fig. 15). In man this compound is more of a stimulant than a hallucinogen. It has been reported to be a 5-HT releaser in rats but the literature is sparse. The compound has no known medical use and is not controlled under the U.S. CSA.

DISCUSSION OF TALK BY DR. HARRIS

Howard McClain (Drug Enforcement Administration, Washington, D.C., U.S.A.): I would like to make a couple of comments. Dr. Harris mentioned that 2,5-dimethoxyamphetamine is not commercially available in this country. It is; it is used in photographic material. It is manufactured by one company in relatively large amounts. It's in Schedule I because a barrel of it was stolen one time. Since that time, it has been controlled. It has been several years, and we haven't really had much of a problem with it since. The hydroxyamphetamine I believe is, or was, marketed by Smith Kline and French as an ophthalmic solution, Paredrine®. But is it still marketed?

Donald Fletcher (Smith Kline & French Laboratories, Philadelphia, PA, U.S.A.): Yes. In a 1% solution.

McClain: You mentioned MDMA. We have had several seizures of that, and as a matter of fact we have a recommendation to the FDA to control it. It is also good for us to see this information. I hope it gets into the record, because it is not available to me. One other remark: Fencamfamine, I believe, is listed in one chemical company's catalogue in the U.S.; we have had some seizures of it, and we think that it came from that source.

Charles R. Schuster (School of Medicine, University of Chicago, Chicago, IL, U.S.A.): I wanted to make one statement regarding toxicity. As those of you who heard the CPDD presentation by Dr. Johanson know, we have been studying the neurotoxicity of many of the anorectic drugs, and we have looked specifically at MDA, cathine and cathinone. I can tell you that, at very low doses, MDA produces relatively long-term depletions of serotonin and that cathine and cathinone produce, I believe, irreversible depletions of brain dopamine. Unfortunately, many of these other drugs have not been tested: but my suspicion on the basis of our study is that any of these drugs which are amphetamine-like will undoubtedly produce long-term, if not irreversible, depletion of dopamine when given in high doses, and some of them will, in addition, produce depletions of serotonin.

Harris: I couldn't agree with you more. One reason I didn't want to talk about LD_{50}s is that, with these compounds, acute toxicities add little real value to what we are discussing; they might have had relevance in the old days, when we had widespread intravenous 'speed' abuse on the street, but that is not a problem now. The big problem is chronic high-dose use, which is producing neurochemical changes that in many cases are irreversible.

Yanagita: Can we state a general rule for the hallucinogenic effects of these substances, such as that they are related to the sympathomimetic effects, or on the other hand, to stimulant effects?

Harris: I would rather wait until Richard Glennon talks, because I believe he has something to say about the ways in which these effects differ based on the molecules that you start from. In discrimination studies, if you've got animals trained to either amphetamine or a hallucinogen, some of these compounds will go purely one way or the other way, but there are a whole group of them that will go either way.

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