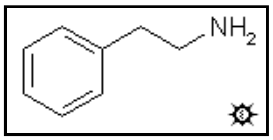
#142 PEA

PHENETHYLAMINE



[3D .mol structure]

SYNTHESIS: This compound has been made industrially by a number of routes, the motant being the reduction of benzyl cyanide and the decarboxylation of phenylanaline. It is offered in the catalogs of all the major chemical supply houses for a few pennies per gram. It is a very strong base with a fishy smell, and rapidly forms a solid carbonate salt upon exposure to the air. It is a natural biochemical in both plants and animals.

DOSAGE: greater than 1600 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 200, 400, 800 and 1600 mg) No effects.

(with 500 mg) No effects.

(with 800 and 1600 mg) No effects.

(with 25 and 50 mg i.v.) RNo effects.

EXTENSIONS AND COMMENTARY: Here is the chemical that is central to this entire book. This is the structural point of departure for every compound that is discussed here. It is the RPS in PIHKAL. It is without activity in man! Certainly not for the lack of trying, as some of the dosage trials that are tucked away in the literature (as abstracted in the "Qualitative Comments" given above) are pretty heavy duty. Actually, I truly doubt that all of the experimenters used exactly that phrase, "No effects," but it is patently obvious that no effects were found. It happened to be the phrase I had used in my own notes.

This, the simplest of all phenethylamines, has always been the darling of the psychopharmacologists in that it is structurally clean, it is naturally present in various human fluids and tissues, and because of its close chemical relationship to amphetamine and to the neurotransmitters. These facts continuously encourage theories that involve PEA in mental illness. Its levels in urine may be decreased in people diagnosed as being depressed. Its levels may be increased in people diagnosed as being paranoid schizophrenics. Maybe it is also increased in people under extreme stress. The human trials were initially an attempt to provoke some psychological change, and indeed some clinicians have reported intense headaches generated in depressives following PEA administration. But then, others have seen nothing. The studies evolved into searches for metabolic difference that might be of some diagnostic value. And even here, the jury is still out.

Phenethylamine is found throughout nature, in both plants and animals. It is the end product of phenylalanine in

the putrefaction of tissue. One of its most popularized occurrences has been as a major component of chocolate, and it has hit the Sunday Supplements as the love-sickness chemical. Those falling out of love are compulsive chocolate eaters, trying to replenish and repair the body's loss of this compound--or so the myth goes. But this amine is voraciously metabolized to the apparently inactive compound phenylacetic acid, and to some tyramine as well. Both of these products are also normal components in the body. And, as a wry side-comment, phenylacetic acid is a major precursor in the illicit synthesis of amphetamine and methamphetamine.

Phenethylamine is intrinsically a stimulant, although it doesn't last long enough to express this property. In other words, it is rapidly and completely destroyed in the human body. It is only when a number of substituent groups are placed here or there on the molecule that this metabolic fate is avoided and pharmacological activity becomes apparent.

To a large measure, this book has emphasized the "phenyl" end of the phenethylamine molecule, and the "what," the "where," and the "how many" of the substituent groups involved. There is a broad variety of chemical groups that can be attached to the benzene ring, at one or more of the five available positions, and in an unending number of combinations. And, in any given molecule, the greater the number of substituents on the benzene ring, the greater the likelihood that there will be psychedelic action rather that stimulant action.

But what can be said about the "ethylamine" end of the phenethylamine molecule? This is the veritable backbone that holds everything together, and simple changes here can produce new prototypes that can serve as starting points for the substituent game on the benzene ring. Thus, just as there is a "family" of compounds based on the foundation of phenethylamine itself, there is an equally varied and rich "families" of other compounds that might be based on some phenethylamine with a small modification to its backbone.

So, for the moment, leave the aromatic ring alone, and let us explore simple changes in the ethylamine chain itself. And the simplest structural unit of change is a single carbon atom, called the methyl group. Where can it be placed?

The adding of a methyl group adjacent to the amine produces phenylisopropylamine, or amphetamine. This has been exploited already as one of the richest families of psychedelic drugs; and over half of the recipes in Book II are specifically for amphetamine analogues with various substituents on the aromatic ring. The further methylation of amphetamine with yet another methyl group, this time on the nitrogen atom, yields methamphetamine. Here the track record with various substituents on the aromatic ring is not nearly as good. Many have been explored and, with one exception, the quality and potency of human activity is down. But the one exception, the N-methyl analogue of MDA, proved to be the most remarkable MDMA.

The placement of the methyl group between the two carbons (so to speak) produces a cyclopropyl system. The simplest example is 2-phenylcyclopropylamine, a drug with the generic name of tranylcypromine and the trade name Parnate. It is a mono-amine oxidase inhibitor and has been marketed as an antidepressant, but the compound is also a mild stimulant causing insomnia, restlessness and photophobia. Substitutions on the benzene ring of this system have not been too promising. The DOM analogue, 2,5-dimethoxy-4-methyltranylcypromine is active in man, and is discussed in its own recipe under DMCPA. The inactive mescaline analogue TMT is also mentioned there.

The dropping of one carbon from the phenethylamine chain gives a benzyl amine, basically an inactive nucleus. Two families deserve mention, however. The phencylidine area, phenylcyclohexylpiperidine or PCP, is represented by a number of benzyl amines. Ketamine is also a benzyl amine. These are all analgesics and anesthetics with central properties far removed from the stimulant area, and are not really part of this book. There is a benzyl amine that is a pure stimulant, which has been closely compared to amphetamine in its action This is benzylpiperazine, a base that is active in the 20 to 100 milligram range, but which has an acceptability similar to amphetamine. If this is a valid stimulant, I think that much magic might be found in and around compounds such as (1) the MDMA analogue, N-(3,4-methylenedioxybenzyl)piperazine (or its N-methyl-counterpart N-(3,4-methylenedioxybenzyl)-N'-methylpiperazine) or (2) the DOM analogue, 2,5-dimethoxy-4-methylbenzylpiperazine. The benzyl amine that results by the relocation of the amine group of MDA from the beta-carbon atom to the alpha-carbon atom is known, and is active. It, and its N-methyl homologue, are described and discussed in the

commentary under MDA. Dropping another carbon atom gives a yet shorter chain (no carbons at all!) and this is to be found in the phenylpiperazine analogue 3-trifluoromethylphenylpiperazine. I have been told that this base is an active hallucinogen as the dihydrobromide salt at 50 milligrams sublingually, or at 15 milligrams intravenously in man. The corresponding 3-chloro analogue at 20 to 40 milligrams orally in man or at 8 milligrams intravenously, led to panic attacks in some 10% of the experimental subjects, but not to any observed psychedelic or stimulant responses.

What happens if you extend the chain to a third carbon? The parent system is called the phenyl-(n)-propylamine, and the parent chain structure, either as the primary amine or as its alpha-methyl counterpart, represents compounds that are inactive as stimulants. The DOM-analogues have been made and are, at least in the rabbit rectal hyperthermia assay, uninteresting. A commercially available fine chemical known as piperonylacetone has been offered as either of two materials. One, correctly called 3,4-methylenedioxyphenylacetone or 3,4-methylenedioxybenzyl methyl ketone, gives rise upon reductive amination to MDA (using ammonia) or MDMA (using methylamine). This is an aromatic compound with a three-carbon side-chain and the amine-nitrogen on the beta-carbon. The other so-called piperonylacetone is really 3,4-methylenedioxybenzylacetone, an aromatic compound with a four-carbon side-chain. It produces, on reductive amination with ammonia or methylamine, the corresponding alpha-methyl-(n)-propylamines, with a four-carbon side-chain and the amine-nitrogen on the gamma-carbon. They are completely unexplored in man and so it is not known whether they are or are not psychedelic. As possible mis-synthesized products, they may appear quite unintentionally and must be evaluated as totally new materials. The gamma-amine analogue of MDA, a methylenedioxy substituted three carbon side-chain with the amine-nitrogen on the gamma carbon, has indeed been made and evaluated, and is discussed under MDA. The extension of the chain of mescaline to three atoms, by the inclusion of an oxygen atom, has produced two compounds that have also been assayed. They are mentioned in the recipe for mescaline.

The chain that reaches out to the amine group can be tied back in again to the ring, with a second chain. There are 2-aminobenzoindanes which are phenethylamines with a one-carbon link tying the alpha-position of the chain back to the aromatic ring. And there are 2-aminotetralines which are phenethylamines which have a two-carbon link tying the alpha-position of the chain back to the aromatic ring. Both unsubstituted ring systems are known and both are fair stimulants. Both systems have been modified with the DOM substituent patterns (called DOM-AI and DOM-AT respectively), but neither of these has been tried in man. And the analogues with the MDA substitution pattern are discussed elsewhere in this book.

And there is one more obvious remaining methylation pattern. What about phenethylamine or amphetamine compounds with two methyl groups on the nitrogen? The parent amphetamine example, N,N-dimethylamphetamine, has received much notoriety lately in that it has become a scheduled drug in the United States. Ephedrine is a major precursor in the illicit synthesis of methamphetamine, and with the increased law-enforcement attention being paid to this process, there has been increasing promotion of the unrestricted homologue, N-methylephedrine, to the methamphetamine chemist. This starting material gives rise to N,N-dimethylamphetamine which is a material of dubious stimulant properties. A number of N,N-dimethylamphetamine derivatives, with "psychedelic" ring substituents, have been explored as iodinated brain-flow indicators, and they are explicitly named within the appropriate recipes. But none of them have shown any psychedelic action.

About this Document

This is as good a place as any to discuss two or three simple compounds, phenethylamines, with only one substituent on the benzene ring. The 2-carbon analog of 4-MA, is 4-methoxyphenethylamine, or MPEA. This is a kissing cousin to DMPEA, of such fame in the search for a urine factor that could be related to schizophrenia. And the end results of the search for this compound in the urine of mentally ill patients are as controversial as they were for DMPEA. There has been no confirmed relationship to the diagnosis. And efforts to see if it is centrally active were failures--at dosages of up to 400 milligrams in man, there was no activity. The 4-chloro-analogue is 4-chlorophenethylamine (4-Cl-PEA) and it has actually been pushed up to even higher levels (to 500 milligrams dosage, orally) and it is also without activity. A passing bit of charming trivia. A positional isomer of MPEA is 3-methoxyphenethylamine (3-MPEA) and, although there are no reported human trials with this, it has been graced with an Edgewood Arsenal code number, vis., EA-1302.

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