Speculations On 1-Substituted Tryptamines

By PSR Research Group Ltd.

A major drawback to many tryptamine-based hallucinogens is that they are not orally active. Such might include psilocin, 5-MeO-DMT, DMT, ayahuasca and others. This is due to the body's MAO (Mono-Amine Oxidase), a chemical formed in the gut, the heart, and other points. MAO dissolves these (and many other) tryptamine-based substances during digestion, making them nonhallucinogenic. The current work of PSR Research focuses on suspending gut MAO with various compounds, and creating new, eatable versions of these legendary substances. PSR's research with its orally active 5-MeO-DMT is outlined as a possible therapeutic tool, and as an experimental reagent for studying schizophrenic states. We are proud to present this very original research to our readers.

1-benzyl psilocin and 1-methyl psilocin: two active 1-substituted psilocin derivatives

Previous to this only three substitutions on the one position of the tryptamine nucleus were reported in the literature. Benzyl and methyl substitution on the one position of the psilocin molecule are said to yield active compounds. (Psilocin cultivation -- F.C. Gould and Richard Meredeth, p. 36.) Sandoz produced 1-methyl psilocin and SKF synthesized 1-methyl alpha-methyltryptamine SKF-7024.

Early in 1983 we at PSR Research undertook to explore the pharmacology of the psychoactive tryptamines. Our first effort was alpha methanol tryptamine, produced by reacting tryptamine with lithium aluminum hydride. Next, because we were unable to obtain DPT, we speculated that because 1-methyl, 1-acetyl LSD and 1-benzyl psilocin are active, 1-substitution was "not critical." So we reacted 1-bromo propane with tryptamine in alcohol in a ratio of greater than 3:1 ratio to give 1-propyl dipropyl tryptamine. At first we believed that PDPT's 1-ethyl and 1-allyl analogs were nearly identical to DPT, DET, DAT and DIsoPT. However, after the synthesis of our first inactive compound lisopropyl DiIsoPropyltryptamine, we were forced to reconsider the idea that 1-substitution had little or no effect. Fur-

ther experiments proved that branch chain substitution in the 1-position, as in 1NN tri-Isopropyl, isobutyl, 1-methylpropyl tryptamines, and 1-Isopropyl N propyl, N Isopropyl tryptamine, all yield inactive compounds.

We explored the idea that the NN alkyl groups and the 1-group interacts in some mysterious way with the compound N-t-butyl 1N diethyl tryptamine is active as are the 1-unbranched derivatives of DIsoPT.

The ability of branched chain 1-substitution to block the psychedelic and psychodysleptic activity of the psychoactive tryptamines could easily be economically useful in pharmacology. Alpha methyltryptamine is limited in usefulness because it induces a psychodysleptic state in subjects not trained in the use of TJMs. By adding a 1-isopropyl group you should prevent the psychodysleptic effect. We produced an effective antidepressant compound, 1NN tri-Isopropyl alpha ethyltryptamine that seems to be free from both psychodysleptic and psychedelic effects. (The tripropyl analog was an active TJM – **TaJen Miru**: a psychedelic – Chinese for Greater Mind or Overmind Medicine.)

Any number of tryptamines would be more useful medically if psychodysleptic effects were blocked. 1-isopropyl lysergic acid isobutylamide should be screened for activity in migraine.

The 1-ethyl, propyl and allyl dialkyl tryptamines have a blocked psychodysleptic (PD) effect, but they retain a psychedelic (TJM) effect. We believe that the PD effect may be explained by a *forced shift in dominance from left to right hemispheres.* Is the cause of the PD effect and the *relative stimulation of the right brain* the cause of the TJM effect?

The 1-ethyl group reduces the PD effect and prolongs the effect of 1-ethyl substituted DET from one to two hours to eight hours.

The 5MeO-DMT Model of Schizophrenia

Previous speculation concerning dialkyl tryptamines has focused mainly on their neurotoxic potential and ignored the possibility that they may function as transmitters in their own right.

It has been established that DMT, MET, DET, and DPT function as neurotransmitters in the CNS, with DMT being the most prominent. Any chemical that the CNS can make seems to function as a transmitter.

Previously we were aware of a TJM (psychedelic) receptor but were not sure of its function in the CNS. The receptor is capable of responding to a wide variety of substances, ranging from mescaline to

Lysergide.

One naturally occurring agonist of the TJM receptor is 5MeO-DMT, something that can be generated by the O-methylation and N-methylation of serotonin (5-HT). Furthermore, it has been detected that in the blood and CSF of schizophrenic subjects. Given that the theory of dialkyltryptaninergic transmission is correct, any number of defects in 5MeO-DMT transmission could produce a schizophrenic-like condition without producing large or easily detectable levels of 5MeO-DMT in blood or urine. In short, the lack of positive findings in blood is not significant.

When administered IP, 5MeO-DMT has a marked toxic effect with nausea, vomiting, delirium, pseudohallucinations and a state resembling a massive overdose of an LSD-like psychedelic, differing in the clouded nature of consciousness. DMT and related compounds are orally inactive because they are metabolized by monamine oxidase-A in the gut. In order to make DMT-like agents orally active, you must first selectively inactivate MAO-A in the gut without impairing enzymatic activity in other target sites by a carefully titrated dose of a nonhydrazine MAOI, (MAO inhibitors).

Our product, 5MeO-DMT/PO, is an orally active preparation incorporating between 100 and 250 mg. tranylcypromine HC1. per gram of 5MeO-DMT expressed as base. a one-gram unit is dissolved in one liter of water. The standard dose for studies of models of borderline schizophrenia is 5-10 mg. PO q4h. 10 mg. is approximately equal to 100 mcg. Lysergide. The threshold dose for effects is approximately 1 mg. with 2 mg. being equal to 25 mcg. LSD. There is no significant tolerance developed to this dosage form and it does not produce the nausea, vomiting, headache or delirium founded with the IP or smoked form. The state produced by the oral preparation resembles psilocin and lasts approximately five hours.

Because the preparation of 5MeO-DMT can mimic the aspects of schizophrenia on a long-term basis and because theory predicts such activity, it is reasonable to set forth the claim that the metabolism of 5MeO-DMT is impaired in many schizophrenics. Negative evidence such as low serum levels does not constitute disproof in that a small synaptic defect in the 5MeO-DMTaminergic system would not be detectable in the peripheral blood because of the tiny amounts of 5MeO-DMT involved.

The Use of 5MeO-DMT/PO, an Orally Active Preparation in Therapy

The use of psychedelics in therapy is not general in the U.S., but continues in other parts of the world. Part of the problem in the U.S.

is the unavailability of orally active, legal psychedelics. The dialkyltryptamines would be more useful in therapy and research if they were orally active; the IP route by nature of the sudden rise in blood level would seem to cause a sudden discharge of monamines into the synaptic cleft, resulting in a delirium-like state that more resembles a high fever than a psychedelic state.

Our research has determined that the tryptamines taken orally are inactivated by monamine oxidase-A in the gut. If you titrate a dose of a *nonhydrazine* MAOI so that it inhibits only gut MAO and leaves heart and brain MAO intact, you can render tryptamines orally active.

1-2 mg. **tranylcypromine** PO one hour before an oral dose of DPT or 5MeO-DMT will render these substances orally active at doses approximating their IP dose.