## EXCERPT FROM **PIKHAL** [*Phenethylamines I Have Known And Loved*] by Alexander Shulgin

## 96 M; MESCALINE; 3,4,5-TRIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 20 g 3,4,5-trimethoxybenzaldehyde, 40 mL nitromethane, and 20 mL cyclohexylamine in 200 mL of acetic acid was heated on the steam bath for 1 h. The reaction mixture was then diluted slowly and with good stirring, with 400 mL H2O, which allowed the formation of a heavy yellow crystalline mass. This was removed by filtration, washed with H2O, and sucked as dry as possible. Recrystallization from boiling MeOH (15 mL/g) yielded, after filtration and air drying, beta-nitro-3,4,5-trimethoxystyrene as bright yellow crystals weighing 18.5 g. An alternate synthesis was effective, using an excess of nitromethane as solvent as well as reagent, if the amount of ammonium acetate catalysis was kept small. A solution of 20 g 3,4,5-trimethoxybenzaldehyde in 40 mL nitromethane containing 1 g anhydrous ammonium acetate was heated on the steam bath for 4 h. The solvent was stripped under vacuum and the residual yellow oil was dissolved in two volumes of hot MeOH, decanted from some insolubles, and allowed to cool. The crystals formed are removed by filtration, washed with MeOH and air dried yielding 14.2 g. of bright yellow crystals of beta-nitro-3,4,5-trimethoxystyrene. The use of these proportions but with 3.5 g ammonium acetate gave extensive side-reaction products even when worked up after only 1.5 h heating. The yield of nitrostyrene was, in this latter case, unsatisfactory.

To a gently refluxing suspension of 2 g LAH in 200 mL Et2O, there was added 2.4 g beta-nitro-3,4,5-trimethoxystyrene as a saturated Et2O solution by use of a Soxhlet extraction condenser modified to allow the continuous return of condensed solvent through the thimble. After the addition was complete, the refluxing conditions were maintained for another 48 h. After cooling the reaction mixture, a total of 150 mL of 1.5 N H2SO4 was cautiously added, destroying the excess hydride and ultimately providing two clear phases. These were separated, and the aqueous phase was washed once with 50 mL Et20. There was then added 50 g potassium sodium tartrate, followed by sufficient NaOH to bring the pH > 9. This was then extracted with 3x75 mL CH2Cl2, and the solvent from the pooled extracts was removed under vacuum. The residue was distilled at 120-130 °C at 0.3 mm/Hg giving a white oil that was dissolved in 10 mL IPA and neutralized with concentrated HCI. The white crystals that formed were diluted with 25 mL Et2O, removed by filtration, and air dried to provide 2.1 g 3,4,5trimethoxyphenethylamine hydrochloride (M) as glistening white crystals. The sulfate salt formed spectacular crystals from water, but had a broad and uncharacteristic mp. An alternate synthesis can employ 3,4,5-trimethoxyphenylacetonitrile, as described under

beta-D.

**DOSAGE:** 200-400 mg (as the sulfate salt), 178-256 mg (as the hydrochloride salt).

DURATION: 10-12 h

QUALITATIVE COMMENTS: (with 300 mg) "I would have liked to, and was expecting to, have an exciting visual day, but I seemed to be unable to escape self-analysis. At the peak of the experience I was quite intoxicated and hyper with energy, so that it was not hard to move around. I was guite restless. But I spent most of the day in considerable agony, attempting to break through without success. I learned a great deal about myself and my inner workings. Everything almost was, but in the final analysis, wasn't. I began to become aware of a point, a brilliant white light, that seemed to be where God was entering, and it was inconceivably wonderful to perceive it and to be close to it. One wished for it to approach with all one's heart. I could see that people would sit and meditate for hours on end just in the hope that this little bit of light would contact them. I begged for it to continue and come closer but it did not. It faded away not to return in that particular guise the rest of the day. Listening to Mozart's Requiem, there were magnificent heights of beauty and glory. The world was so far away from God, and nothing was more important than getting back in touch with Him. But I saw how we created the nuclear fiasco to threaten the existence of the planet, as if it would be only through the threat of complete annihilation that people might wake up and begin to become concerned about each other. And so also with the famines in Africa. Many similar scenes of joy and despair kept me in balance. I ended up the experience in a very peaceful space, feeling that though I had been through a lot, I had accomplished a great deal. I felt wonderful, free, and clear. "

(with 350 mg) "Once I got through the nausea stage, I ventured out-of-doors and I was aware of an intensification of color and a considerable change in the texture of the cloth of my skirt and in the concrete of the sidewalk, and in the flowers and leaves that were handed me by an observer. I experienced the desire to laugh hysterically at what I could only describe as the completely ridiculous state of the entire world. Although I was afraid of motion, I was persuaded to take a ride in a car. The driver turned on the radio and suddenly the music 'The March of the Siamese Children' from 'The King and I' became the most perfect background music for the parody of real life which was indeed the normal activity of Telegraph Avenue on any Saturday morning. The perfectly ordinary people on their perfectly ordinary errands were clearly the most cleverly contrived set of characters all performing all manners of eccentric activities for our particular hilarity and enjoyment. I felt that I was at the same time both observing and performing in an outrageous moving picture. I experienced one moment of transcendent happiness when, while passing Epworth Hall, I looked out of the window of the car and up at the building and I was suddenly in Italy looking up at a gay apartment building with its shutters flung open in sunshine, and with its window boxes with flowers. We stopped at a spot overlooking the bay, but I found the view uninteresting and the sun uncomfortable. I sat there on the

seat of the car looking down at the ground, and the earth became a mosaic of beautiful stones which had been placed in an intricate design which soon all began to move in a serpentine manner. Then I became aware that I was looking at the skin of a beautiful snake--all the ground around me was this same huge creature and we were all standing on the back of this gigantic and beautiful reptile. The experience was very pleasing and I felt no revulsion. Just then, another automobile stopped to look at the view and I experienced my first real feeling of persecution and I wanted very much to leave. "

(with 400 mg) "During the initial phase of the intoxication (between 2 and 3 hours) everything seemed to have a humorous interpretation. People's faces are in caricature, small cars seem to be chasing big cars, and all cars coming towards me seem to have faces. This one is a duchess moving in regal pomp, that one is a wizened old man running away from someone. A remarkable effect of this drug is the extreme empathy felt for all small things; a stone, a flower, an insect. I believe that it would be impossible to harm anything--to commit an overt harmful or painful act on anyone or anything is beyond one's capabilities. One cannot pluck a flower--and even to walk upon a gravel path requires one to pick his footing carefully, to avoid hurting or disturbing the stones. I found the color perception to be the most striking aspect of the experience. The slightest difference of shade could be amplified to extreme contrast. Many subtle hues became phosphorescent in intensity. Saturated colors were often unchanged, but they were surrounded by cascades of new colors tumbling over the edges. "

(with 400 mg) "It took a long time to come on and I was afraid that I had done it wrong but my concerns were soon ended. The world soon became transformed where objects glowed as if from an inner illumination and my body sprang to life. The sense of my body, being alive in my muscles and sinews, filled me with enormous joy. I watched Ermina fill to brimming with animal spirit, her features tranformed, her body cat-like in her graceful natural movement. I was stopped in my tracks. The world seemed to hold its breath as the cat changed again into the Goddess. As she shed her clothes, she shed her ego and when the dance began, Ermina was no more. There was only the dance without the slightest self-consciousness. How can anything so beautiful be chained and changed by other's expectations? I became aware of myself in her and as we looked deeply into one another my boundaries disappeared and I became her looking at me. "

**EXTENSIONS AND COMMENTARY:** Mescaline is one of the oldest psychedelics known to man. It is the major active component of the small dumpling cactus known as Peyote. It grows wild in the Southwestern United States and in Northern Mexico, and has been used as an intimate component of a number of religious traditions amongst the native Indians of these areas. The cactus has the botanical name of Lophophora williamsii or Anhalonium lewinii and is immediately recognizable by its small round shape and the appearance of tufts of soft fuzz in place of the more conventional spines. The dried plant material has been classically used with anywhere from a few to a couple of dozen of the hard tops, called buttons, being consumed in the course of a ceremony.

Throughout the more recently published record of clinical human studies with mescaline, it has been used in the form of the synthetic material, and has usually been administered as the sulfate salt. Although this form has a miserable melting point (it contains water of crystallization, and the exact melting point depends on the rate of heating of the sample) it nonetheless forms magnificent crystals from water. Long, glistening needles that are, in a sense, its signature and its mark of purity. The dosages associated with the above "qualitative comments" are given as if measured as the sulfate, although the actual form used was usually the hydrochloride salt. The conversion factor is given under "dosage" above.

Mescaline has always been the central standard against which all other compounds are viewed. Even the United States Chemical Warfare group, in their human studies of a number of substituted phenethylamines, used mescaline as the reference material for both quantitative and qualitative comparisons. The Edgewood Arsenal code number for it was EA-1306. All psychedelics are given properties that are something like "twice the potency of mescaline" or "twice as long-lived as mescaline." This simple drug is truly the central prototype against which everything else is measured. The earliest studies with the "psychotomimetic amphetamines" had quantitative psychological numbers attached that read as "mescaline units." Mescaline was cast in concrete as being active at the 3.75 mg/kg level. That means for a 80 kilogram person (a 170 pound person) a dose of 300 milligrams. If a new compound proved to be active at 30 milligrams, there was a M.U. level of 10 put into the published literature. The behavioral biologists were happy, because now they had numbers to represent psychological properties. But in truth, none of this represented the magic of this material, the nature of the experience itself. That is why, in this Book II, there is only one line given to "dosage," but a full page given to "gualitative comments".

Four simple N-modified mescaline analogues are of interest in that they are natural and have been explored in man.

The N-acetyl analogue has been found in the peyote plant, and it is also a major metabolite of mescaline in man. It is made by the gentle reaction of mescaline with acetic anhydride (a bit too much heat, and the product N-acetyl mescaline will cyclize to a dihydroisoquinoline, itself a fine white crystalline solid, mp 160-161 °C) and can be recrystallized from boiling toluene. A number of human trials with this amide at levels in the 300 to 750 milligrams range have shown it to be with very little activity. At the highest levels there have been suggestions of drowsiness. Certainly there were none of the classic mescaline psychedelic effects.

If free base mescaline is brought into reaction with ethyl formate (to produce the amide, N-formylmescaline) and subsequently reduced (with lithium aluminum hydride) it is converted to the N-methyl homologue. This base has also been found as a trace component in the Peyote cactus. And the effects of N-methylation of other psychedelic drugs have been commented upon elsewhere in these recipes, all with consistently negative results (with the noteworthy exception of the conversion of MDA to MDMA). Here, too, there is no obvious activity in man, although the levels assayed were only up to

25 milligrams.

N,N-Dimethylmescaline has been given the trivial name of Trichocerine as it has been found as a natural product in several cacti of the Trichocereus Genus but, interestingly, never in any Peyote variant. It also has proven inactive in man in dosages in excess of 500 milligrams, administered parenterally. This observation, the absence of activity of a simple tertiary amine, has been exploited in the development of several iodinated radiopharmaceuticals that are mentioned elsewhere in this book.

The fourth modification is the compound with the nitrogen atom oxidatively removed from the scene. This is the mescaline metabolite, 3,4,5-trimethoxyphenylacetic acid, or TMPEA. Human dosages up to 750 milligrams orally failed to produce either physiological or psychological changes.

One additional manipulation with some of these structures has been made and should be mentioned. These are the analogues with an oxygen atom inserted between the aromatic ring and the aliphatic chain. They are, in essence, aminoethyl phenyl ethers. The first is related to mescaline itself, 2-(3,4,5-trimethoxyphenoxy)ethylamine. Human trials were conducted over the dose range of 10 to 300 milligrams and there were no effects observed. The second is related to trichocerine, N,N-dimethyl-2-(3,4,5trimethoxyphenoxy)ethylamine. It was inactive in man over the range of 10 to 400 milligrams. Mescaline, at a dose of 420 milligrams, served as the control in these studies.



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