

Some Possible Pathways for the Synthesis of *trans*-3-Methyl-2 Hexenoic Acid

Michael A. Roberts 1-

Abstract

The literature concerning the so called "back ward odor" is reviewed, including the identification of the malodorous compound as U3ms-3-methyl-2-hexenoic acid and the later evidence to suggest that the above compound is not responsible for the odor. It is suggested that the evidence against the compound as a candidate for the culprit metabolite is faulty, and that a host of compounds may serve as logical precursors to the acid. Phenylalanine, 2-hydroxydopa-mine, and some unusual catechols are among the possibilities described. One possible precursor, dopamine, can go to the compound via a pathway that is supported by a number of papers in the biochemical and psychopharmacological literature. Hopefully, the ideas presented here will stimulate new avenues of research into the possible biochemical etiology of the schizophrenic syndrome.

For many years, it has been known that a peculiar smell, often called "back ward odor" is present among some mental hospital patients (Clark, 1917; Hotchkiss et al., 1955). This odor is characteristic of schizophrenia

alone and is apparently unrelated to the patients' hygienic regimen. Smith and Sines (1960) demonstrated the existence of this odor, believed to emanate specifically from patients with schizophrenia of catatonic type. In their study, rats were conditioned to discriminate between sweat specimens of schizophrenics and controls ($p=.0001$). In addition, a group of human expert odor testers could also achieve this discrimination, although the results obtained from humans were not as significant ($p=.005$). Posner, Culpan, and Stewart (1962) suggested that the odor may be due to the presence of **Pseudomonas Aeruginosa** in the axillae, but a later study by Skinner, Smith, and Rich (1964) concluded that this organism could not be found in 14 patients described as having the schizophrenic odor, nor in 14 other patients with other psychiatric illnesses living on the same hospital ward.

In 1969, using the methods of gas chromatography, infrared spectroscopy, mass spectroscopy, and nuclear magnetic resonance spectroscopy, Smith, Thompson, and Koster (1969) identified the malodorous component as *trans*-3-methyl-2-hexenoic acid. To further validate this finding, the double bond between carbons two and three was cleaved by alkaline permanganate and gave 2-pentanone and oxalic acid as products. In addition, crystals of the synthetic

'148-01 33rd Avenue Rushing, New York 11354

acid (hereafter referred to as TMHA) were added to normal sweat to produce a sample with an odor that a panel of experts agreed was indeed identical to that of schizophrenic sweat.

Since then, later research has failed to confirm this result. Melancon (1970) and Perry, Melancon, Lesk, and Hansen (1970) reported that an assay of the sweat of eleven schizophrenics by gas chromatography failed to show the presence of TMHA, although it was estimated that the methods used could have detected the acid in concentrations as low as 0.02 micrograms per milliliter of sweat, or one-fifth the concentration of TMHA estimated by Smith, Thompson, and Koster (1969). Perry and his co-workers claim that peaks that occur on gas chromatograms of schizophrenic sweat that were previously explained as being due to the presence of TMHA could also be due to compounds derived from the polyethylene bags used to collect the sweat samples. It is interesting to point out that gas chromatograms of the distillate of the saline solution used to wash the polyethylene bags showed no detected response at the site where TMHA normally appears (Perry et al., 1970). In addition, expert odor testers could not detect TMHA in the steam distillates of Perry et

contained comparable amounts of TMHA. They also found that when both groups were given 10 micro-curies of (1,2-¹⁴Q TMHA, administered intravenously, there was no significant difference in the decay of radioactivity in the serum, in the quantity of expired ¹⁴CO₂, and the rate of ¹⁴C₂ output. The authors concluded that there was no relationship between TMHA and schizophrenia. With regard to this second finding, it should be clear that the fact that the rate of excretion of TMHA is the same in both schizophrenics and normal humans once introduced into the body does not immediately say anything about the possible differential synthesis of this compound across the two groups.

It is the opinion of the author that TMHA exists in schizophrenics and not in normal humans. Inaccuracies in determining the presence of a compound present in such small quantities by only one analytical method might have also obscured the evidence. The author believes that the scientific literature is now overdue for a review of the possible pathways for the *in vivo* synthesis of TMHA.

Possible origins of TMHA

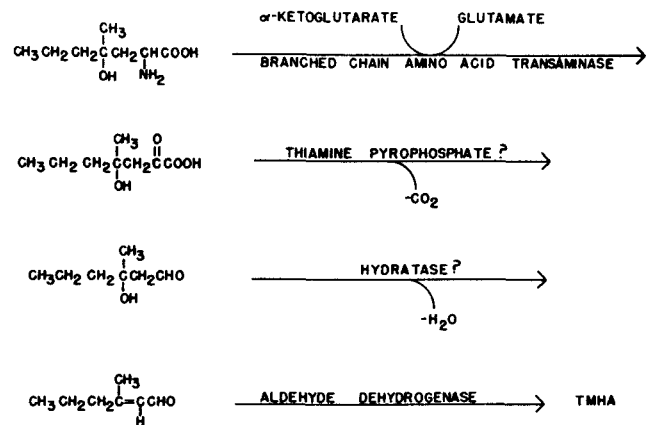


FIGURE 1

al.s' schizophrenic sweat specimens. It may be true that the protocol for obtaining steam distillates and ether extracts of sweat, which was not the same method employed by Smith, Thompson, and Koster (1969) might have caused some chemical change that could have resulted in the loss of the odor and TMHA.

Later studies by Smith (1972) and Cordon, Smith, Rabinowitz, and Vagelos (1973) showed that sweat samples of schizophrenics and controls

At the outset it must be stressed that one of the following pathways may be correct, or perhaps more than one, or maybe none of the hypotheses presented here may be valid.

One possible synthetic pathway begins with an alpha-amino acid, possibly derived from plants, shown in figure one. The first

reaction is one common to all amino acids (Lehninger, 1970). The resulting alpha-keto acid

may be decarboxylated via a mechanism directly analogous to the oxidative decarboxylation of pyruvate to acetaldehyde by thiamin pyrophosphate. The product of this reaction could then lose water to create the more stable allylic

system and then go to the beta-hydroxy acid by aldehyde dehydrogenase to create TMHA.

The remaining pathways concern themselves with phenylalanine metabolism. All pathways will either begin with or have contained in them a phenylethylamine derivative of some sort. In all instances, the pathway will involve a breaking of the six-membered ring and subsequent modification of the product to give TMHA.

The first such pathway I wish to present begins with 3-methyl-4-hydroxyphenylethyl-amine (figure two). This compound could

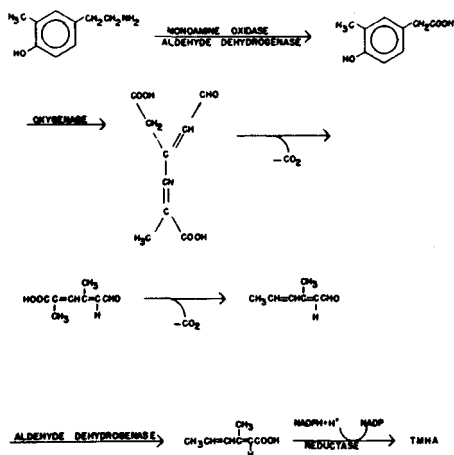


FIGURE 2

arise from the decarboxylation of p-tyrosine and subsequent methylation, perhaps via S-A denosylmethionine or some other methyl donor. The reaction of this species with monoamine oxidase and aldehyde dehydrogenase presents no deviation from normal metabolism. Oxidative cleavage on the product of this reaction between positions four and five on the ring will give rise to a molecule with two carboxylic acid groups that has a low polarity, which is increased by not one, but two decarboxylations. Following this, the conversion of the aldehyde to the carboxylic acid may take place, leaving a reductase-mediated reaction to give TMHA. This last reaction may proceed via a mechanism similar to the reduction of crotonyl-S-ACP to butyryl-S-ACP by enoyl-ACP reductase.

An almost identical pathway could lead to TMHA from 2,3-dihydroxy-5-

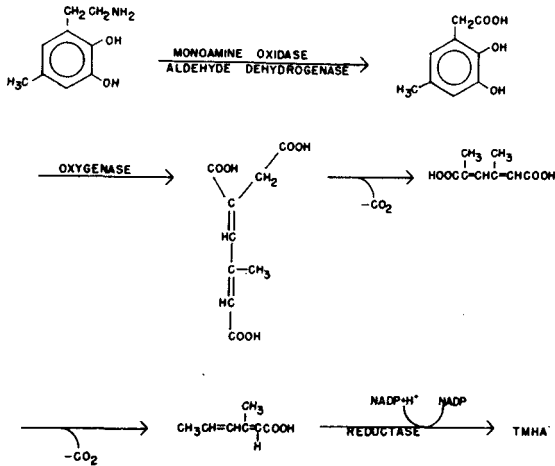


FIGURE 3

Another pathway could give rise to TMHA starting with 3,4-dihydroxy-5-methylphenylethylamine (figure four). The reactions here

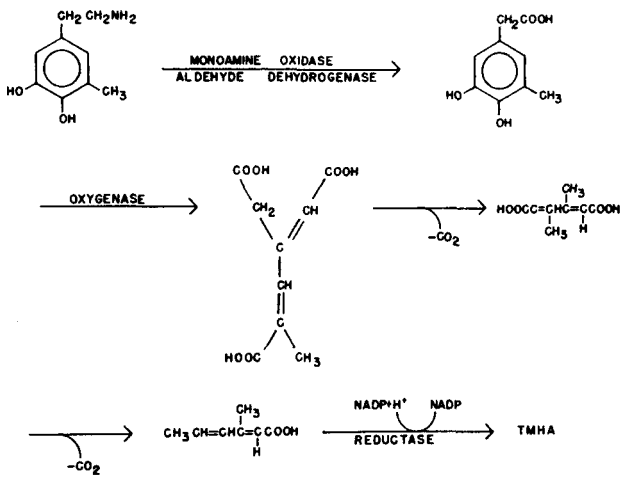


FIGURE 4

are identical to those in figure three, with a different cleavage site for the benzene ring. This pathway is particularly interesting because it starts with a molecule so similar in structure to other compounds with known psychotropic activity, such as mescaline and trimethoxyamphetamine, or TMA (Weil-Malherbe and Szara, 1971). Again, the steps leading to TMHA are almost the same.

The next pathway I would like to present methylphenyl-

ethylamine by the route outline in figure three.

begins with m-tyrosine, a known minor product of the hydroxylation of phenylalanine. This compound could proceed to TMHA (figure five) by decarboxylating to

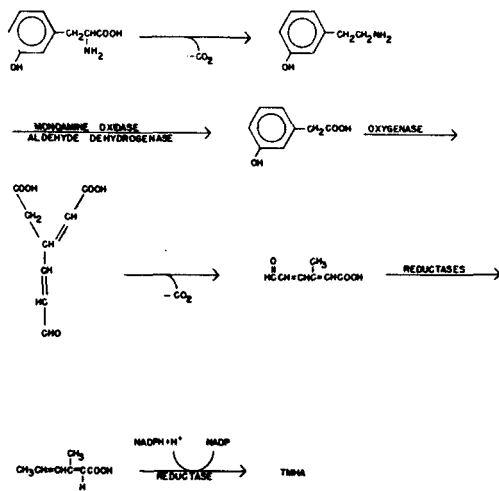


FIGURE 5

form m-tyramine, which is a known reaction (Closs, 1955). Next, it can be postulated that a deficiency, absence, or inhibition of tyramine-4-hydroxylase causes the compound to fail to form dopamine, and instead of being hydroxylated, the m-tyramine species simply moves along to the next step in normal metabolism, which is the reaction with monoamine oxidase and aldehyde dehydrogenase to give 3-hydroxyphenylacetic acid. Next, the ring is broken between positions three and four and modified in much the same ways described before to produce TMHA.

In 1971, Stein (1971) and Stein and Wise (1971) proposed a rather convincing model for the etiology of schizophrenia, naming 6-hydroxydopamine as the abnormal metabolite responsible for the disease, although it was stated that closely related compounds, such as 2-hydroxydopamine could not be ruled out with certainty. One of the lines of evidence given for this theory was a possible connection between both compounds and TMHA. I have thought out another synthetic route from 2-hydroxydopamine, described in figure six. Note that the oxygenase reaction-

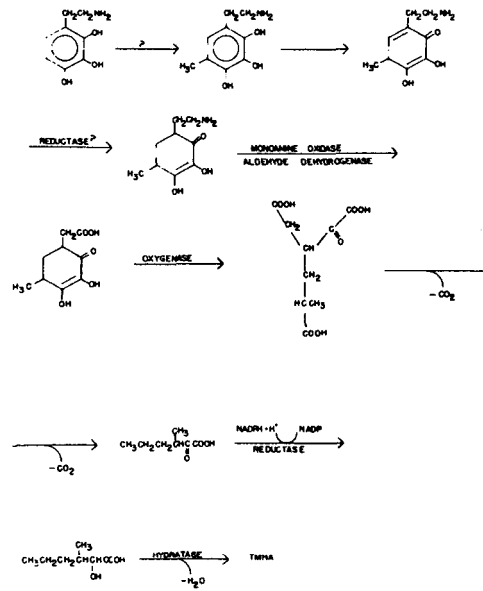


FIGURE 6

tion does not open a benzene ring. I grant that it is an unusual synthetic route, but some of the critical reactions may be mediated by bacteria under the skin.

The last pathway I would like to present seems the most plausible to me (figure seven). It begins with dopamine, which is

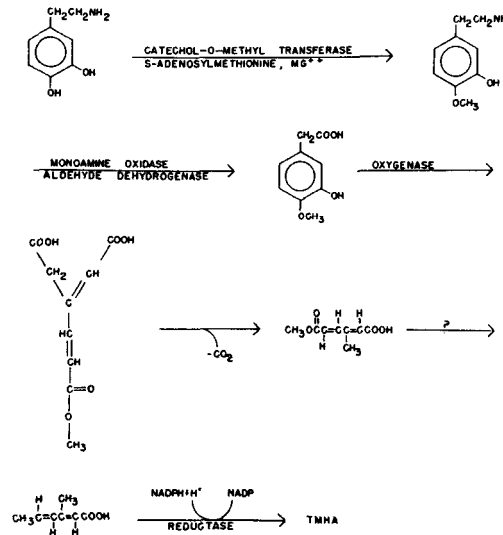


FIGURE 7

then O-methylated at the para position. The resulting product may then react with monoamine oxidase and aldehyde dehydrogenase, exactly as in normal

metabolism to form 3-hydroxy-4-methoxyphenylacetic acid. This species may then interact with an oxygenase to produce a molecule with a low polarity that has a system of double bonds that are all allylic to one another—all except one. This justifies the specificity of the first decarboxylation. The next reaction involves another loss of CO₂. However, I do not know of a case of a decarboxylation of an ester. Perhaps this transformation occurs by another reaction or series of reactions. Once the transformation is made, a reductase-mediated reaction may occur to give TMHA.

Discussion

The evidence for the last pathway mentioned is well documented in the scientific literature. The idea that schizophrenia may be linked to the 4-methylation of catecholamines has already been proposed by Fujimori and Alpers (1971). The notion that schizophrenia may be connected to abnormal O-methylation of dopamine metabolites has been mentioned before (Osmond and Smythies, 1952) and the evidence for the O-methylation of dopamine in para position is well established (Senoh et al., 1959). What makes this information even more interesting is that the para-O-methylation of phenylethylamine derivatives seems to be correlated with hypokinetic rigid syndrome (H.R.S.) described by Ernst (1962a; 1962b; 1965a). In 1964, Kuehl, Hitchens, and Ormond et al. claimed that they could not find evidence for the *in vivo* formation of 3-hydroxy-4-methoxy analogues of catecholamines, but only one year later, Ernst (1965b) found that 3-hydroxy-4-methoxyphenylethylamine, given to cats in dosages of 500 micromoles per kilogram produced mydriasis, salivation, piloerection, and an increase in respiration for one hour, but when pre-treated with Iproniazid (100 micromoles per kilogram), the same cats exhibited hypokinesia within 40 minutes, followed by catatonia, and a H.R.S. that was maintained for about three hours. Later, Kuehl (1967) found that the monomethylation of dopamine *in vitro* took place at the meta and para positions, the ratio of meta to para being about four to one. In 1972, Matthysee and Baldessarini found increased levels of catechol-O-methyl

transferase in schizophrenic venous blood versus that of non-schizophrenics. While the difference was not significant ($.05 < q < 10$), the study also found a significant correlation between catechol-O-methyl transferase activity and S-Adenosyl-methionine (SAM) concentrations ($r = .36$, $p < .05$), suggesting that some schizophrenics may be better methylators than others. I postulate that these higher SAM concentrations and COMT values could be correlated with an increased percentage of para-methylation. It just may be that if Matthysee and Baldessarini used schizophrenics who exhibited the schizophrenic odor, they might have found a significantly higher mean value for COMT activity.

Again, it must be stressed that I have done nothing more than try to apply human biochemistry to fit TMHA. Hopefully, one of the preceding possibilities is correct, thereby establishing a firmer basis for a biochemical etiology of schizophrenia.

Of interest is the note in Gordon, Smith, Rabinowitz, and Vagelos (1973) that a major stimulus for their investigation was that TMHA is so similar in structure to phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) which accumulates in patients with Refsum's disease (Steinberg, 1972). However, the clinical features of this disease, such as retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia, and elevated CSF protein without pleocytosis described by Herndon, Steinberg, Uhlendorf and Fales (1969) do not occur in schizophrenics. Rather, there are other compounds that look even more like TMHA that are more likely to be related to schizophrenia, such as vitamin A acid, which is "presumably further oxidised to unknown products" (Moore 1957), or geranic acid (Deuel, 1957).

Part of the problems encountered in trying to find an etiology of schizophrenia may be in part due to the possibility that schizophrenia may be a great "dumping ground" for a variety of maladies, each with a unique origin, but with some common clinical manifestations. Perhaps we should group

patients into diagnostic categories such as "schizophrenia, back ward odor" or "schizophrenia, DMPEA excreting" and study their biochemistry separately. Maybe then we will begin to find some answers to the questions facing mental health scientists.

REFERENCES

- CLARK, L.P.: The Odor of the Peculiars, *Med. & Surg.* 1:1091-1094,1917.
- CLOSS, K.: Phenylalanine - An Essential Amino Acid. Universitet i Bergen, Medininsk rekke nr 2:1-53, Arbok 1955.
- DEUEL, H.J.: The Lipids: Their Chemistry and Biochemistry, p.93. Inter-science Publishers, Inc., New York, 1957.
- ERNST, A.M.: Phenomena of the Hypokinetic Rigid Type Caused by O-Methylation of Dopamine in the Para Position. *Nature* 193: 178-179, 1962a.
- ERNST, A.M.: Experiments with an O-Methylated Product of Dopamine on Cats. *Acta Physiologica et Pharmacologica Neerlandica* 11:48-53, 1962b.
- ERNST, A.M.: Relation Between the Action of Dopamine and Apo-morphine and their O-Methylated Derivatives Upon the CNS. *Psycho-pharmacologia* 7:391-399,1965a.
- ERNST, A.M.: Relation Between the Structure of Certain Methoxy-phenylethylamine Derivatives and the Occurrence of a Hypokinetic Rigid Syndrome. *Psychopharmacologia* 7:383-390,1965b.
- FUJIMORI, M. and ALPERS, H.: Psychotomimetic Compounds in Man and Animals. In: *Biochemistry, Schizophrenia, and Affective Illnesses*, Himwich, H.E. (Ed.), p.361-413. Williams and Wilkins Co., Baltimore, 1971.
- GORDON, S.G., SMITH, K., RABINOWITZ, J.L., and VAGELOS, P.R.: Studies of trans-3-methyl-2-nexenoic Acid in Normal and Schizophrenic Humans. *J. of Lipid Res.* 14:495-503,1973.
- HERNDON, J.H., STEINBERG, D., UHLENDORF, B.W., and FALES, H.M.: Refsum's Disease: Characterization of the Enzyme Defect in Cell Culture. *The J. of Clin. Invest.* 48:1017-1032,1969.
- HOTCHKISS, G., CARMEN, L., OGILBY, A., and WIESENFELD, S.: Mothers of Young Male Single Schizophrenic Patients as Visitors in a Mental Hospital. *J. Nerv. & Ment. Dis.* 121:452-462,1955.
- KUEHL, F.A., KITCHENS, M., ORMOND, R.E., MEISINGER, M.A.P., GALE, P.H., CIRILLO, V.J., and BRINK, N.G.: Awa-O-Methylation of Dopamine in Schizophrenia and Normal Individuals. *Nature* 203:154-155,1964.
- KUEHL, F.A.: Awa-O-Methylation of Dopamine in Schizophrenic and Normal Individuals. In: *Amines and Schizophrenia*, Himwich, H.E.; Kety, S.S., and Smythies, J.R. (Eds.), p. 23-30, Pergamon Press, Oxford, 1967.
- LEHNINGER, A.L.: *Biochemistry*, p 562-565, Worth Publishers, Inc., New York, 1970.
- MATTHYSEE, S. and BALDESSARINI, R.J.: S-Adenosylmethionine and Catechol-O-Methyl Transferase in Schizophrenia. *Amer. J. Psychiat.* 128:1310-1312,1972.
- MELANCON, S.B.: L'Odeur Particuliere Des Schizophrenes. *L'Union Medicate Du Canada* 99:1445-1446,1970.
- MOORE, T.: *Vitamin A*, p. 282-283. Elsevier Publishing Co., Amsterdam, 1957.
- 134
- OSMOND, H. and SMYTHIES, J.: Schizophrenia: A New Appraoch. *J. Ment. Sci.* 98:309-315,1952.
- PERRY, T.L., MELANCON, S.B., LESK, D. and HANSEN, S.: Failure to Detect trans-3-methyl-2-hexenoic Acid in the Sweat of Schizophrenics. *Clin. Chim. Acta* 30:721-725,1970.
- POSNER, H.S., CULPAN, R. and STEWART, A.: Cause of the Odor of a Schizophrenic Patient. *A.M.A. Arch. Gen. Psychiat.* 7:108-113,1962.
- SENOH, S., DALY, J., AXELROD, J. and WITKOP, B.: Enzymatic *para*O Methylation by Catechol-O-Methyl Tranferase. *J. Amer. Chem. Soc.* 81: 6240-6245,1959.
- SKINNER, K., SMITH, K. and RICH, E.: Bacteria and the Schizophrenic Odor. *Amer. J. Psychiat.* 121:64-65,1964.
- SMITH, K., THOMPSON, G.F. and KOSTER, H.D.: Sweat in Schizophrenic Patients: Identification of the Odorous Substance, *Science* 166: 398-399,1969.
- SMITH, K. and SINES, J.O.: Demonstration of a Peculiar Odor in the Sweat of Schizophrenic Patients. *A.M.A. Arch. Gen. Psychiat.* 2: 184-188,1960.
- SMITH, K.S.: Preliminary Report on Injection of ¹⁴C-Labeled rrans-3-methyl-2-hexenoic Acid Into Schizophrenic Patients and Controls. *J. of Orthomolecular Psychiat.* 1:118-120,1972.
- STEIN, L.: Neurochemistry of Reward and Punishment: Some Implications for the Etiology of Schizophrenia. *J. Psychiat. Res.* 8: 345-361, 1971.
- STEIN, L. and WISE, CD.: Possible Etiology of Schizophrenia: Progressive Damage to the Noradrenergic Reward System by 6-Hydroxydop-amine. *Science* 171:1032-1036,1971.
- STEINBERG, D.: Phytanic Acid Storage Disease. In: *Metabolic Basis of Inherited Disease*, 3rd. ed., Stanbury, J.B.; Wyngaarden, J.B., and Fredrickson, D.S. (Eds.), pp. 833-853, McGraw-Hill, New York, 1972.
- WEIL-MALHERBE, H. and SZARA, S.I.: The Biochemistry of Functional and Experimental Psychoses, p. 270, Charles C. Thomas, Springfield, 1971.