Complete text

+ VI LSD No. 258 (§ 102a)
tryptophan (§ 231 t)

M 500 biosynthesis of lysergic acid
Z 301 ergotchemistry

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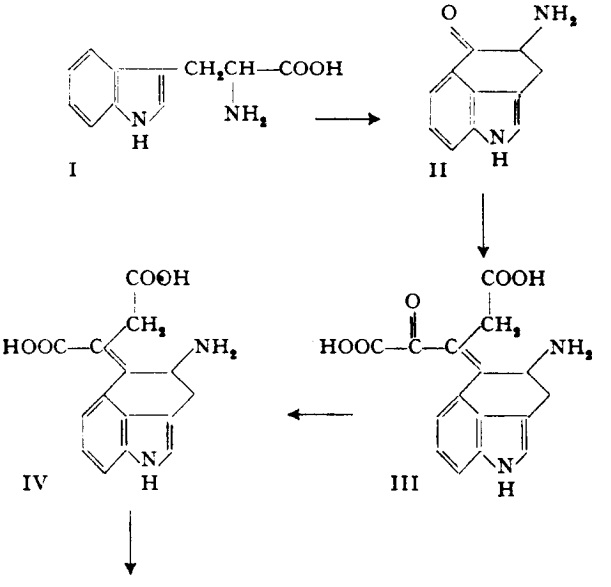
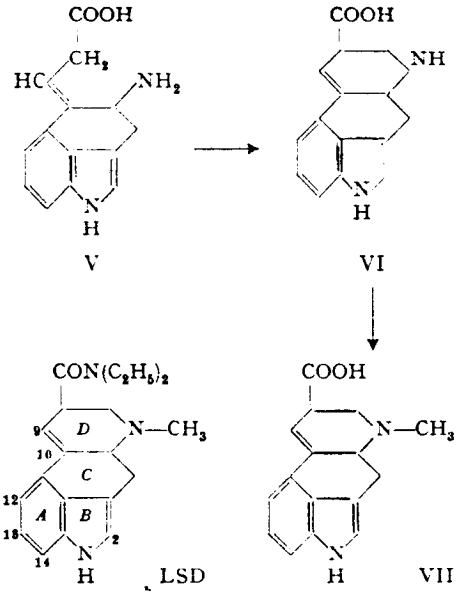
Hypothesis concerning the biosynthesis of lysergic acid.

Experientia 12, 475 (1956).

The remarkable ability of small amounts of LSD to produce in normal human beings mental symptoms which resemble schizophrenia[1] is well known. The possibility suggested itself to us that mental illness might be associated with the formation of an LSD-like metabolite from normally occurring precursors. If such an hypothesis were to be considered, the question of the precursors and their possible metabolic transformations would arise. We wish to outline a pathway by which tryptophan might give rise to lysergic acid (see figure).





Tryptophan (I) when cyclized and condensed with α-ketoglutaric acid may form structure III. Oxidative decarboxylation and the subsequent loss of carbon dioxide would yield structure V. The introduction of a one-carbon fragment to form ring *D* followed by methylation may result then in the formation of lysergic acid (VII). Some of the steps in the sequence may proceed through a number of intermediary enzymatic reactions.

A similar metabolic scheme (see figure) might account for the origin of the lysergic acid nucleus in the ergot alkaloids. VAN TAMELEN[2] suggested a biosynthesis starting with 5-hydroxytryptophan which employed dihydronicotinic acid as an intermediate. HARLEY-MASON[3] also proposed 5-hydroxytryptophan as the precursor, but with β-ketoglutaric acid as the key intermediate. WENDLER[4] evolved a pathway which depends upon tryptophan and citric acid, whereas ROBINSON's scheme[5] employed succinic acid. Our scheme, on the other hand, utilizes tryptophan and α-ketoglutaric acid.

Substituted lysergic acid may be obtained by starting with the appropriately substituted tryptophan. Thus, 2-hydroxytryptophan would yield 2-hydroxylysergic acid. It is interesting to note that LSD is detoxicated by hydroxylation in the 2-position. UDENFRIEND and coworkers[6] have demonstrated that 5-hydroxytryptophan is the precursor of serotonin, and therefore, it may be available for the synthesis of 12-hydroxylysergic acid. The LSD-like metabolite referred to earlier may be lysergic acid or a derivative with a side chain of unknown structure. Many variants of lysergic acid have been prepared and tested for psychotomimetic activity, and it appears that the diethylamide is the most active[7]. This does not exclude, however, the possibility of a more active side chain which has not as yet been tested.

KORNFELD *et al.*[8] have synthesized lysergic acid starting with 1-benzoyl-dihydro-3-indolepropionic acid. The synthesis which we have suggested (see figure) may provide a laboratory method of preparation of lysergic acid and its derivatives. The reaction types are known, i.e., ring closure, aldol condensation, loss of carbon monoxide from α-ketoacids, loss of carbon dioxide from α, β-unsaturated carboxylic acids, the Mannich reaction, and methylation, but have not been applied specifically to the proposed intermediates. The 2-, 12-, 13-, and 14-hydroxy, methoxy and other substituted lysergic acids, which might become available if the synthesis is successfully completed, may find use as tranquilizing agents and central nervous system depressants, as antihallucinatory agents, and may have other valuable pharmacological properties.

Zusammenfassung

Ein LSD-ähnliches Stoffwechselprodukt ist möglicherweise mit Geisteskrankheit gekoppelt. Eine Biosynthese der Lysergsäure und ihrer Derivate, die Tryptophan und α-Ketoglutarsäure als wichtige Intermediärprodukte enthält, wird vorgeschlagen.

[1] W. A. STOLL, Schweiz. Arch. Neurol. Psych. *58*, 279 (1947).

[2] E. E. VAN TAMELEN, Exper. *9*, 457 (1953).

[3] J. HARLEY-MASON, Chem. and Ind. *1954*, 251.

[4] N. L. WENDLER, Exper. *10*, 338 (1954).

[5] R. ROBINSON, *The Structural Relations of Natural Products* (Oxford University Press, London 1955).

[6] S. UDENFRIEND and E. TITUS, in *Amino Acid Metabolism* (ed. by W. D. MCELEOY and H. B. GLASS, 1955) p. 945.

[7] L. H. GERONIMUS, H. A. ABRAMSON *et al.*, Ann. Rep. Biol. Lab. (Cold Spring Harbor, N. Y. 1954-1955), p. 36. – A. CERLETTI, in *Neuropharmacology* (ed. by H. A. ABRAMSON, 1956), p. 9.

[8] E. C. KORNFELD, E. J. FORNEFELD, G. B. KLINE, M. J. MANN, W. E. MORRISON, R. G. JONES, and R. B. WOODWARD, J. Amer. chem. Soc. *78*, 3087 (1956).

(Hypothèse concernant la biosynthèse de l'acide lysergique)

On a pensé que les psychoses peuvent être associées à la formation - à partir de substances normalement présentes - d'un métabolite similaire au LSD. L'auteur décrit les processus par lesquels le tryptophane pourrait donner lieu à la formation d'acide lysergique. Le métabolite similaire au LSD pourrait être l'acide lysergique ou un de ses dérivés avec une chaîne latérale de structure inconnue.

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