Chemical Aspects of Psilocybin, the Psychotropic Principle From the Mexican Fungus, Psilocybe Mexicana Heim. *

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Since the pre-Columbian era, the Indians of Mexico have made the eating of certain fungi a part of their religious rites; tribal soothsayers ate such fungi to acquire clairvoyance. An American ethnologist, R. Gordon Wasson, and his wife made several expeditions into remote regions of Mexico between 1953 and 1955. They studied the way in which these fungi are used today and described their experience of the hallucinatory states occurring in the rituals 1). Roger Heim, Director of the Museum Nationale de l'Histoire Naturelle in Paris, accompanied R.G. Wasson on another expedition into the territories of the Mazatecs, Chatinos and Aztecs in the summer of 1956. He was able to classify and describe these fungi 2); the species were all pileate fungi (Basidiomycetes) belonging to the family of Strophariaceae. R. Heim succeeded together with R. Cailleux in growing cultures of several of these mushrooms in his Paris laboratory 3). Material from a particularly active fungus, Psilocybe mexicana Heim, was sent to the SANDOZ research laboratories in Basle for chemical investigation.

In the Spring of 1958, the psychotropic principle was isolated in crystalline fo 4). It has been called psilocybin. It occurs in the sporophores, mycelium and sclerotia of the fungus. A. Brack and H. Kobel developed in our laboratories an improved method of cultivating the mycelium and sclerotia on a larger scale 5). From this material several gr of psilocybin have now been isolated - sufficient for chemical, pharmacological and preliminary clinical investigations.

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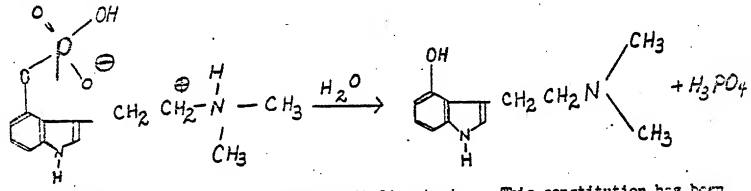
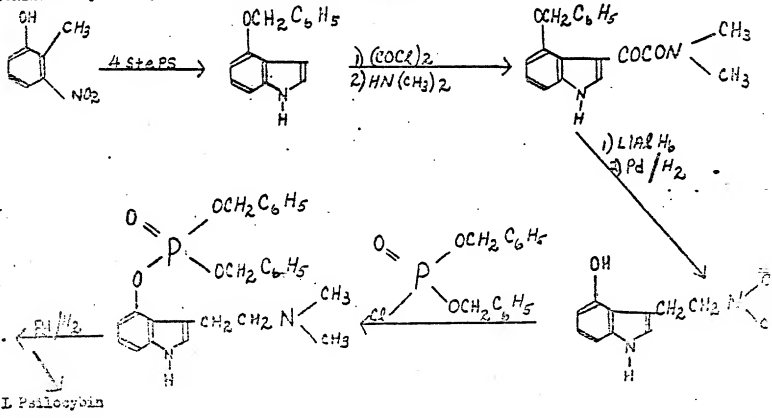
[illegible] synthesis. The following is a brief review of the chemistry of psilocybin:

Psilocybin forms white crystals which are fairly soluble in water, but practically insoluble in the usual organic solvents. It is amphoteric, i.e. it forms salts with both acids and alkalis. Analysis of psilocybin and a study of its spectra and color reactions, have revealed that it is an indole derivative, substituted in the benzene nucleus. It was provisionally assigned the formula: $C_{13}H_{18(20)}O_3N_2P_2$, but later degradation studies have shown it to be $C_{12}H_{17}O_4N_2P$. On hydrolysis the psilocybin molecule is cleaved in two, giving: 4-hydroxy-dimethyltryptamine and phosphoric acid. Thus psilocybin possesses the structural formula I.

I. 

It is the phosphoric ester of 4-hydroxy-dimethyltryptamine. This constitution has been confirmed by the synthesis of psilocybin as demonstrated by the following scheme:

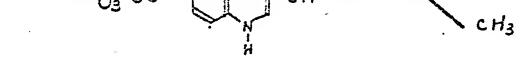


I. Psilocybin

The synthetic compound was identical in every respect with natural psilocybin.

Psilocybin is yet another example of the importance of the indole structure in psychotropic compounds. It is closely related to biochemically important naturally-occurring hydroxytryptamine derivatives such as: serotonin (5-Hydroxytryptamine), bufotenin (5-hydroxydimethyltryptamine), bufotenidine(quarternary base of bufotenin) dihydro-bufotenin and bufothionine. The structure analogy with bufothionine(formula II) which has been isolated from amphibian skin[7] is striking.

II.



Both compounds are acidic esters of a hydroxy-dimethyltryptamine derivative, the one being an ester of phosphoric acid, the other of sulfuric acid.

As it is an indole derivative, psilocybin is furthermore related to the psychotropic indole alkaloids, such as tabernanthine, harmine and reserpine.

A special relationship exists between psilocybin and lysergic acid diethylamide (LSD), hitherto the most potent psychotomimetic known. Both these compounds are indole derivatives substituted in position 4. Psilocybin and the ergot alkaloids, which include LSD, are unique in possessing this special structural feature.

The discovery of a naturally occurring indole derivative with a phosphorylated hydroxyl group in position 4 may lead to a new concept of the biogenesis of the lysergic acid moiety of the ergot alkaloids. The proposals put forward already are not altogether satisfactory in that no explanation has been offered for ring closure in position 4 of the tryptamine moiety. As the phosphorylated hydroxyl group in the psilocybin molecule implies activation of position 4, it does not seem unreasonable to consider hydroxylation and phosphorylation at position 4 as an important step in the biogenesis of the ergot alkaloids.

Literature

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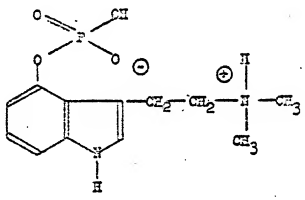
o-phosphoryl-4-hydroxy-N-dimethyl-tryptamine



Physical and Chemical Data:

Empirical formula: $C_{12}H_{17}O_4N_2P \cdot CH_3CH$

Molecular Weight: 284.3 · 32

Melting Point: 200 - 210° with decomposition

Solubility: In 120 parts of water at 20°C.

pH: 5.3

Keller Color Reaction:

0.1 mg. of Psilocybin dissolve in 1 cc. 0.01% ferric chloride - containing acetic acid and stratify with 1 cc. concentrated sulfuric acid. After mixing a permanent violet color is obtained.

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