Isolation, Structure and Syntheses of Central-Active Compounds from Amanita Muscaria (L. ex Fr.) Hooker

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It has been desecribed that the carpophores of Amanita muscaria belong to the class of plant drugs affecting the central nervous system and possibly producing hallucinatory effects (*1*).

Since the classical work of Schmiedeberg and Koppe in 1869, the chemical investigation of these active substances has, until the present day, been almost exclusively concerned with muscarine, whose chemistry is now fully understood (*2*). The pharmacological investigations have shown in fact, that muscarine itself is not the prime cause of the previously mentioned central-activity of A. muscaria. The low plant content (2–3 mg per kg undried fungus), in conjunction with its relatively weak activity on oral consumption, leads to the conclusion that muscarine can only be considered as a minor active component of A. muscaria.

During the last few years it has been proposed that one or another of the bases *bufotenine*, *atropine*, *hyoscyamine* and *scopolamine* could be responsible for the main central-activity of A. muscaria (*3*). With regard to these suggestions the following comments can be made. The amounts of these compounds reported to have been isolated (0.1–0.2 mg atropine; 0.4–0.7 mg scopolamine per kg undried carpophores), although not rigorously confirmed, in relation to their known activity, exclude them as possible causes of A. muscaria poisoning. Moreover, other authors have demonstrated that Belladonna alkaloids (atropine, hyoscyamine, scopolamine) do not occur in A. muscaria (*4*). In addition in our hands, investigation of both Swiss and South German varieties of A. muscaria has led to the isolation of several indolic substances, the structures of which have not yet been elucidated. Bufotenine, however, was found not to be present.

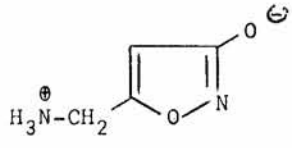
Recently the, in contrast to the above-mentioned products, highly active muscimole and ibotenic acid have been isolated from A. muscaria (*5*).

The pharmacological tests (narcosis-potentiation), which were used as an aid in the isolation of these substances, lead us to the conclusion that they are in fact active on the central nervous system. Their structures have been elucidated and several syntheses published (*6*).

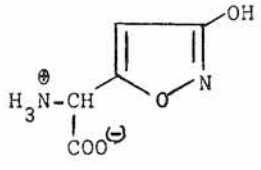
Muscimole, $C_4H_6N_2O_2$, mp. 155–156° (from water), 174–175° (from methanol-water), is a very polar and extremely water soluble substance. It is the enol-betaine of 5-aminomethyl-3-hydroxy-isoxazole (formula I), i.e., it is an unsaturated cyclic hydroxamic acid. Muscimol is easily formed by decarboxylation and loss of water from ibotenic acid, $C_5H_8N_2O_5$ mp. 145°

(dec.). The latter is the zwitterion of α-amino-α-[3-hydroxy-isoxazoylyl-(5)]-acetic acid monohydrate (formula II). It is to be considered a principal active constituent of A. muscaria, being present to the extent of 0.3–1 g per kg of undried carpophores.

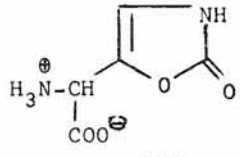
The pharmacologically less active muscazone (*7*), $C_5H_6N_2O_4$, mp. 190° (dec.), co-occurs in varying proportions with muscimole and ibotenic acid in A. muscaria. It is also an amino-acid, namely α-amino-α [2(3H)-oxazolonyl-(5)]-acetic acid (formula III), and can be produced in the laboratory by UV-irradiation of ibotenic acid. It is probable that, in the plant also, ibotenic acid acts as a precursor for muscazone. We therefore assume that the widely known variation in toxicity of A. muscaria results from fluctuations in the ibotenic acid-muscazone ratio.



I



II



III

Our latest investigations have shown that A. muscaria produces still further physiologically active substances, the structures of which are not yet known.

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