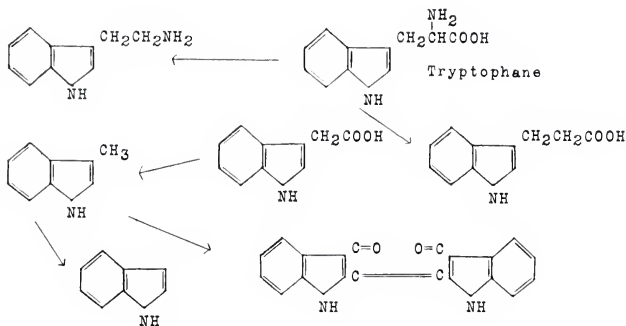


INCREASING RECOGNITION OF THE IMPORTANCE OF TRYPTOPHANE AS A PROTOTYPE IN PHYTO-CHEMICAL PROCESSES

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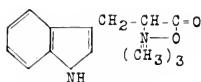
As is well known, tryptophane is an amino acid derived from certain proteins and one of the few amino acids indispensable in the nutrition of higher animals. It was first isolated by Hopkins and Cole (1) in 1901 and afterwards synthesized by Ellinger and Flammand (2) in 1907. Under bacterial action it yields tryptamine, and in the body it undergoes changes which give rise to many substances, some of the most important being illustrated in the following scheme:



The point of particular interest to us just now is the relation of tryptophane to several vegetable alkaloids, and the recent discovery that the powerful alkaloid-like substances found in frogs and commonly known as toad poisons are also tryptophane derivatives. Indeed, it appears that our generally accepted classification of vegetable alkaloids might well be slightly modified to provide for a division to be designated as Tryptophane Alkaloids.

Since two of the members of our teaching staff, assisted by some of our seniors majoring in chemistry, are carrying on investigations in this field, and since their efforts have already met with some success, it seemed to me that it might not be out of order to present to the Academy a brief survey of the advance that has been made in our knowledge of these tryptophane derivatives during the past ten or fifteen years. The topics are not given in strictly chronological order.

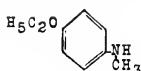
1. *Hypaphorine*. This alkaloid was discovered by Dr. M. Greshoff in 1890, being obtained as a crystalline base from the seeds of *Erythina hypaphorus*, a shade tree grown on the coffee plantations of Eastern Java. In 1911 Pieter Van Romburg and George Barger (3) prepared the betaine of tryptophane by treatment with methyl iodide and sodium hydroxide and proved it to be identical with hypaphorine. Since tryptophane itself can be synthesized, we have here a synthesis of this alkaloid. The drug has only slight physiological action.



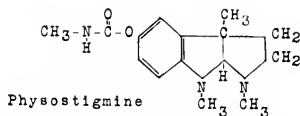
Hypaphorine

2. *Physostigmine* (Eserine). It is interesting to note that Java is also the habitat of the Calabar bean which yields this alkaloid. Physostigmine was first obtained from the seeds of *Physostigma venenosum* by J. Jobst and O. Hesse (4) in 1864. It is a valuable drug, a myotic, contracting the pupil of the eye, for example, when it has been dilated by atropine. It is antagonistic to curare in action on the muscles. It stimulates the respiratory center, increases the secretion of the glands and quickens the peristaltic action of the intestines.

Attempts to synthesize physostigmine had been going on in several universities in Europe for more than twenty years but without success until the present year (1935) when a brilliant synthesis was effected in our laboratory by Percy L. Julian and Josef Piki (5).



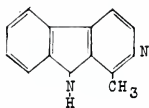
N-Methylphenetidine



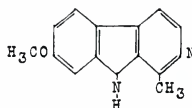
Physostigmine

They start with N-Methylphenetidine and, through a long series of ingenious reactions arrive at their goal, demonstrating the correctness of the formula provisionally assigned to it ten years earlier by Edgar Stedman and George Barger (6). The authors state, "We believe that the route we have taken presents in its essential stages the phytochemical mechanism for the production of this substance."

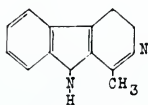
3. *The Harmala Alkaloids*. In 1841 Fr. Goebal described a new dye-stuff which he stated (7) he discovered on December 22nd, 1837, in



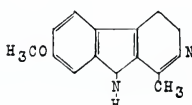
Harman



Harmine



Harmalan



Harmaline

the seeds of *Perganum harmala* and which he named harmaline. It occurs in the seed in combination with phosphoric acid and is both a

dye and an alkaloid. The plant grows in the South Russian Steppes and in Northern India; it is a very objectionable weed with roots running two or three feet in the ground.

In 1847 J. Fritzsche published a larger work on the constituents of these seeds (8) in which he finds a second alkaloid, also a dye, and which he named *harmine*. Both of these substances occur in the tegument of the seed, the kernel having only traces.

In 1885 Otto Fischer and Ernst Trauber (9) undertook a more thorough study of these substances, believing them to be quinoline derivatives since they resemble rather closely the synthetic dye-stuffs *flavaniline* and *chrysaniline*, which were known to be derivatives of quinoline. But they were unable to verify their supposition. Fischer continued these investigations down to 1914 but without succeeding in determining their structure or effecting their synthesis.

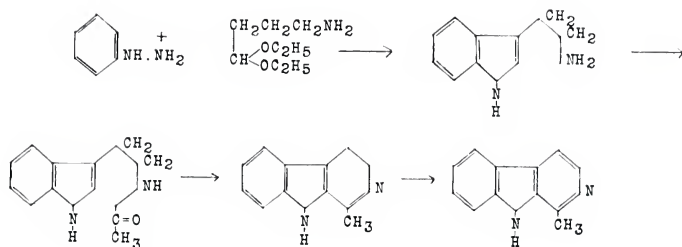
In 1908 William H. Perkin, Jr., and Robert Robinson began a series of studies of these alkaloids, their first paper appearing in 1912 (10), the investigations continuing on down to 1927. In 1919 they proposed for these substances (11) the formulas which were later confirmed on synthetic grounds. Just before this, Otto Fischer (12) prepared what he named *harman* by eliminating the methoxy group from *harmine*. This substance, *harman*, he considered the basis of the other two. A little later E. Spaeth showed (13) that *harman* was also a natural product and identical with the plant bases which had been isolated by O. Hesse and named *aribin* and *loturin*.

Now another interesting fact turns up. In 1928 L. Lewin found (14) that the substance known as *banisterin*, also called *yagein* or *telepathin*, and found in the South American *Liame Banisteria Caapai*, served a valuable purpose in the treatment of influenza. At the same time F. Elger (15) and O. Wolfes and K. Rumpf (16) proved *harmine* to be identical with *banisterin*.

In 1927 Richard H. F. Manske, William H. Perkin, Jr., and Robert Robinson (17) described a synthesis of *harmaline* and *harmine* which confirmed the formulas already proposed. The steps are long and complicated and will not be given here.

In 1930 Ernst Spaeth and Edgar Lederer (18) presented a new synthesis of these alkaloids which is much simpler, much more likely to be of practical application, and has this additional point of interest, that in the last few steps the reactions seem to be identical with those occurring in the plant photosynthetically. They start with *tryptamine* which is easily prepared from *phenylhydrazine* and *amino-n-butyraldehyde* diethylacetate by the method of Arthur Janes Ewins (19). This is converted into *N-acetyltryptamine* by means of *acetic anhydride*. On heating this product in *xylol* with *phosphorus pentoxide*, water is eliminated, the ring closes and *harmalan* is formed. *Harmalan* is readily converted into *harman* by heating with *potassium permanganate* in *sulphuric acid*, or more easily, by heating with *palladium black* for one-half hour at 200°.

Now they start with *3-methoxyphenylhydrazine* and by similar reactions synthesize *harmaline* and *harmine*.



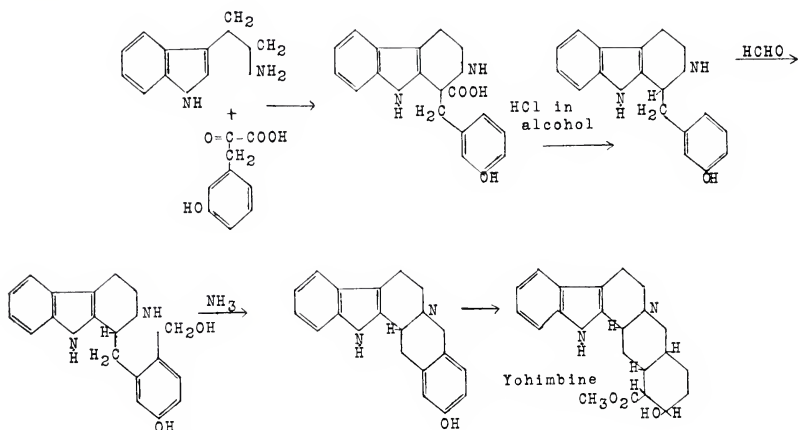
In the same year, 1930, and independently, another synthesis of these substances was carried out by Shiro Akaboni and Kajito Saito (20). They start with tryptamine and 6-methoxytryptamine and synthesize respectively harman and harmine. The ring closure is effected by condensation with acetaldehyde and the reduction is accomplished by heating for several hours in aqueous solution with maleic acid and palladium.

4. *Yohimbine*. In 1896 L. Spiegel obtained from the bark of *Corynanthe yohimba* an alkaloid which he named *yohimbine* and on which he published several papers (21). Many investigations have been carried on in the effort to effect the synthesis and establish the structure of this alkaloid. The synthesis of the frame-work of yohimbine has been accomplished recently, 1934, by Georg Hahn and Henrich Werner (22). Preceding this, in the same year, Georg Hahn, Ernst Kappes, and Hermann Ludewig (23) heated yohimbine with lead tetraacetate (three mols) and obtained tetrahydrogenated yohimbine. When the hydrochloride of this substance was heated one and one-half hours with potassium hydroxide in amyl alcohol, they obtained harman and m-toluic acid. This definitely associates yohimbine with the harmala alkaloids, and hence with tryptophane, and at the same time gives a clue to a possible synthesis of yohimbine.

Now Hahn and Werner (loc. cit) condense tryptaminehydrochloride with m-oxyphenylpyrrolic acid in acetate buffer solution of pH 4.2 in a thermostat at 25° . The p-acid behaves in the same way. The solution was 0.05 molar, the thermostat was of glass, and it stood in the light of a June sun for ten days. A yield of 74 percent of the theoretical amount was obtained. When this product is dried, dissolved in methyl alcohol, and heated for four hours in a stream of dry hydrogen chloride, carbon dioxide is expelled. The hydrochloride of this product is dissolved in a buffer solution of pH 4.4 and treated, on cooling, with 40 percent formaldehyde; there is thereby introduced a CH_2OH group. When this compound is treated in cold solution with ammonia or even with a buffer solution of pH 8, the ring closes, and there is obtained in crystalline form either hexahydroxyhimbol or an isomer. Since the relation of yohimbol to yohimbine had already been determined by Hahn and Stenner (24), this gives us the frame-structure of the alkaloid with only one uncertainty, the position of the hydroxyl group. This is being further investigated.

It is to be noted that in this synthesis, as in that of tetrahydroharm derivatives, at least three of the steps, possibly four, are carried out under physiological conditions. This is most significant.

May I add that we have in progress in our laboratory an investigation which we hope will lead to the synthesis of yohimbine by another method, one that will leave no doubt as to the position of the hydroxyl group.



5. *Bufotenine*. In 1902 Edwin S. Faust (25) obtained the substance known as bufotalin from the alcoholic extract of toad skins. The substance was first obtained in crystalline form by Heinrich Wieland and Fried. Jos. Weil (26). It was found to be a lactone and with no nitrogen hence not an alkaloid. According to Faust it is the active compound of the secretion of the skin of the toad and has physiological properties resembling digitalis. Bufotenine seems to have been obtained for the first time by Hans Handovsky (27) in 1920 from *Bufo vulgaris*. It was obtained from the aqueous extract of the toxin after removal of the bufotalin.

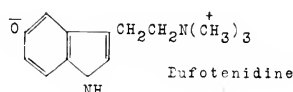
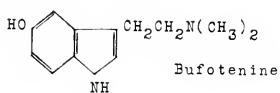
In 1912 John J. Abel and David I. Macht (28) obtained from the parotid glands of the tropical toad (*Bufo agna*) two distinct active principles, one adrenaline, the other, a new substance, which they name *bufargin*, an efficient member of the digitalis series. But it contains no nitrogen.

In 1916 Shigematsu Shimizu (29) isolated from the Chinese drug "Senso" another compound which he called *bufotoxin* and which seems to belong to the picrotoxin group of poisons.

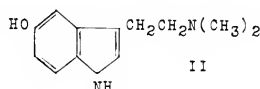
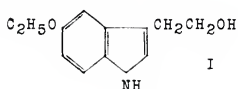
Our chief interest lies in bufotenine. Several papers on it have been published by H. Jensen and K. K. Chen (30) and by Heinrich Wieland and co-workers. On biological and pharmacological grounds Jensen and Chen soon came to the opinion that bufotenine is a tryptophane derivative.

In 1931 Wieland, Hesse, and Mittasch (31) obtained from the skins of toads a base which they call *bufotenidine* and which they prove to be identical with a base which had already been isolated from Chinese "Senso." From this they obtain bufotenine in pure condition by means of the oxalate. From a careful study of this pure product they give evidence that this alkaloid contains (1) the indole skeleton, (2) a hydroxyl

group attached to the indole skeleton, and (3) a dimethyl amine group attached to one of two carbon atoms not forming a part of the indole structure. They show that position (2) in the benzene nucleus is free and hence this hydroxyl group must be in position 4, 5, 6, or 7. Since no natural indole derivatives are known to be hydroxylated in positions 4 or 7 they conclude that the hydroxyl of bufotenine must be in positions 5 or 6. They then synthesize derivatives of both the 5 and 6 type. The methoxyindoles were prepared by the method of Kenneth Guy Blaikie and William H. Perkin, Jr. (32). From these the methoxytryptamines were prepared by the method of Akabori and Suzuki (33). Methylation of the 6-methoxytryptamine with methyl iodide and thallium ethoxide gave a compound which seemed to be identical with that obtained from bufotenine, but the mixed melting point proved otherwise. On methylating the 5-methoxytryptamine they obtained a compound which was shown to be identical with that obtained from natural bufotenine. The conclusion is obvious.



Another synthesis of bufotenine has been effected recently by Toshio Hoshino and Kenya Shimodaira (34). They start with 5-ethoxytryptophol (I). This was converted into the corresponding bromide by means of phosphorus tribromide and this into the dimethylamine derivative. On heating this compound with aluminium chloride in benzol they obtained bufotenine (II).



Again may I state that we have in progress in our laboratory an investigation which we believe will lead to another synthesis of bufotenine, and will give us certain derivatives which we believe will be of pharmacological importance.

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