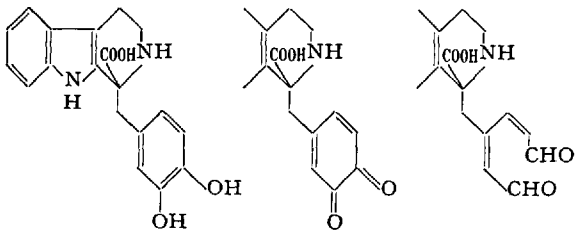
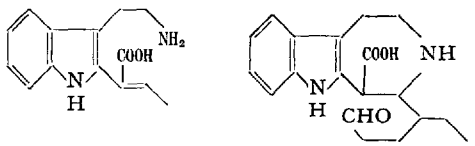
The Biogenesis of the *Tabernanthe Iboga* Alkaloids*

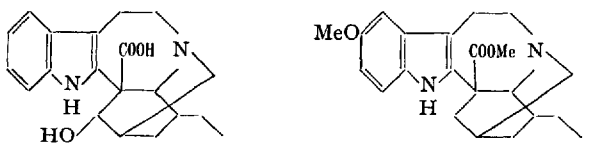
In recent years much progress has been made on the part of chemists to develop a set of working hypothesis by which the biosynthesis of indole alkaloids might be explained in broad outline[1]. In this way the structures of such apparently unrelated compounds as strychnine, yohimbine, ajmaline and cinchonine have been rationalized. Since the ring system of the major *Tabernanthe iboga* alkaloids, ibogaine, ibogamine and tabernanthine, has now been shown to be that in (VIII)[2], it seemed appropriate to consider how it might be possible to account for its formation based on the existing theories.



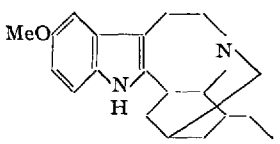
(I) (II) (III)



(IV) (V)



(VI) (VII)



(VIII)

A plausible route starts from the α-type condensation product (I) derived from tryptophan and 3:4-dihydroxyphenylalanine. Ring C can become seven membered as a consequence of an elimination followed by readdition of the basic nitrogen, activation for the first step being provided by a carbonyl group either in an *o*-quinone [such as (II)] or in the Woodward fission product (III). The Michael type ring closure of (IV) in the second step to finally yield (V) requires little comment. Mannich condensation with formaldehyde and ring closure completes the elaboration of the skeleton (VI), whose conversion into voacangine[2] (VII) or ibogaine (VIII) offers no difficulty[3]. One is lead to speculate on the possible occurrence of alkaloids similar to (VI) which would contain a hydroxyl in the position shown. The high molecular weight Voacanga alkaloids, e.g., voacamine[4] and voacorine[5] may well arise from intermediates in such a biogenetic scheme as suggested above.

W. I. TAYLOR

CIBA Pharmaceutical Products Inc., Summit, N. J., USA., July 23, 1957.

Zusammenfassung

Die vorliegende Arbeit schlägt eine Biogenese der Tabernanthe-Alkaloide vor, die von einem α-Kondensationsprodukt von Tryptophan mit 3,4-Dioxyphenylalanin ausgeht. Der siebengliedrige Ring C dieser Alkaloide entsteht durch Ringöffnung und erneute Ringschliessung eines Oxydationsproduktes. Weitere Stufen umfassen eine Mannich-Kondensation, eine Reduktion und einen Ringschluss zu einer Hydroxycarboxyverbindung, aus der durch einfache Reaktionen Voacangin und Ibogain abgeleitet werden können.

* The Alkaloids of *Tabernanthe Iboga*, Part V.

[1] For a recent summary see R. ROBINSON, *The Structural Relations of Natural Products* (Oxford at the Clarendon Press, 1955), p. 100.

[2] W. I. TAYLOR, J. Amer. chem. Soc. *79*, 3298 (1957).

[3] It is already known that voacangic acid suffers decarboxylation in acidic media to furnish ibogaine [M.-M. JANOT and R. GOUTAREL, C. R. Acad. Sci. Paris *241*, 986 (1955)]. Compare the analogous decarboxylation of 2-substituted 2-carboxy-β-carbolines [G. HAHN, L. BÄRWALD, O. SCHALES, and M. WERNER, Ann. *520*, 107 (1935)].

[4] R. GOUTAREL, F. PERCHERON, and M.-M. JANOT, C. R. Acad. Sci. Paris *243*, 1670 (1956).

[5] R. GOUTAREL and M.-M. JANOT, C. R. Acad. Sci. Paris *242*, 2981 (1956).

Hydroxyproline Production in Chick Fibroblast Cultures

Introduction.—While it is well known that argyrophil fibres develop in fibroblast cultures, histological methods provide at best an inadequate quantitative assessment of their production. Hydroxyproline is an imino acid found in collagen, reticulin and in certain soluble substances which are probably their precursors (HARKNESS *et al.*[1], OREKHOVITCH *et al.*[2]). We thought it of interest to measure quantitatively the production of hydroxyproline in chick aorta cultures as an index of their formation of extracellular fibre material. 18-day embryos were used with culture periods of 10, 21 and 28 days.

It has been suggested (STETTEN[3]) that proline is a precursor of hydroxyproline, and we have further assessed the effect of proline enrichment on hydroxyproline formation.

Materials and Methods

Cultures.—White Leghorn eggs were used and incubated at 38°C for 18 days. Embryos were removed under aseptic conditions, the thorax opened, and the heart and proximal parts of the great vessels removed. The latter were cut into small pieces of about 1 mm³ for culture. Cultures were continued to 10, 21 and 28 days.

[1] R. D. HARKNESS, A. M. MARKO, H. M. MUIR, and A. NEUBERGER, Biochem. J. *56*, 558 (1954).

[2] N. N. OREKHOVITCH, K. D. TUSTANOVSKY, K. D. OREKHOVITCH, and N. E. PLOTNIKOVA, Biochimia *13*, 55 (1948).

[3] M. R. STETTEN, J. biol. Chem. *181*, 31 (1949).