LETTERS TO THE EDITORS

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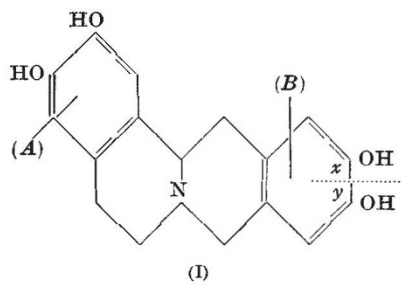
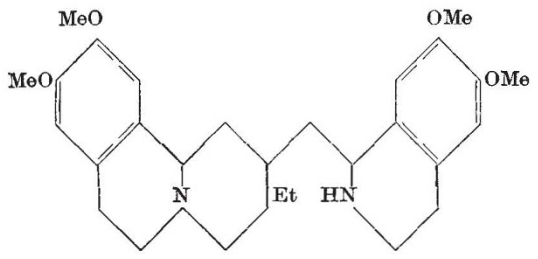
Structure and Biogenesis of Emetine

In making favourable comment on Woodward's ingenious suggestion respecting the biogenesis of strychnine[1], the hope was expressed that further speculation of a similar kind would be based on a comparable "degree of coincidence". The remarkable development mentioned below certainly meets this requirement. It provides an outstanding example of interaction of results in two fields, strengthening theoretical conclusions in both of them.

I noticed that (excluding consideration of the methylation of phenolic hydroxyls) emetine could be constructed from three molecules of dihydroxyphenylalanine and one of the formaldehyde equivalent, assuming a fission of one aromatic nucleus on Woodward's lines. Following these quite closely, it will be noted that the hydroxyl in the meta position to the side-chain of the amino-acid becomes an aldehyde group; that in the para position is found in the alkaloid in a state of oxidation equivalent to that of an alcohol. Postulating exactly the same circumstances in the case of the stages leading, on this hypothesis, to emetine, we arrive without ambiguity at a single formula (II). Thus the *nor*-pseudotetrahydroberberine (I) represents the familiar *nor*-laudanosine of the Winterstein – Trier hypothesis condensed with formaldehyde or its equivalent. What has long been known[2] about emetine proves that our next stage cannot be the degradation of the *A*-nucleus. If we assume the oxidative degradation of the *B*-nucleus, as indicated by the dotted line, and so that *x* becomes a formyl group, and the chain beginning with *y* is fully reduced, and later that the new aldehyde condenses in the usual manner with dihydroxyphenylalanine (decarboxylated at some stage) to an *iso*quinoline derivative, then, after O-methylation, emetine would be (II).



(I)



(II)

No special importance was attached to this speculation until, in the course of a discussion with Dr. M. J. S. Dewar, he wrote down formula (II) as the most likely interpretation of results described in three recent communications[3] on the subject of the chemistry of emetine. Of these, the work of Späth, and of Pailer, solves the problem of the arrangement of carbon atoms in the chain connecting the *iso*quinoline nuclei; that of Karrer and his co-workers supplies a detail which indicates the relation of this carbon skeleton to the tertiary nitrogen.

Thus the constitution (II) appears to be firmly established by these recently disclosed experiments, and by the earlier investigations. It is surely significant that, without knowledge of the recent publications, the same constitution was deduced by applying Woodward's theory of biogenesis of strychnine to a complex member of the *iso*quinoline group.

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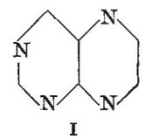
Sept. 5.

[1] Woodward, R. B., *Nature*, **162**, 155 (1948).
[2] Carr, F. H., and Pyman, F. L., *J. Chem. Soc.*, **105**, 1591 (1914); Späth, E., and Leithe, W., *Ber.*, **60**, 688 (1927).
[3] Späth, E., *Monatsh.*, **78**, 348 (1948). Pailer, M., *ibid.*, **79**, 127 (1948). Karrer, P., Eugster, C. H., and Rüttner, O., *Helv. Chim. Acta*, **31**, 1219 (1948).

A Synthesis of Pteridine

Although many derivatives of pteridine, both natural and synthetic, are known, the parent substance pteridine (I) does not appear to have been described. This substance has now been prepared by the condensation of 4 : 5-diaminopyrimidine with glyoxal bisulphite.



I

4 : 5-Diaminopyrimidine has been described by Isay[1], but it is more readily available by a slightly modified procedure. 2-Chloro-4-amino-5-nitropyrimidine, m.p. 232° (Isay, *loc. cit.*, gives m.p. 217°), is hydrogenated in methanol over a nickel catalyst to give 2-chloro-4 : 5-diaminopyrimidine. m.p. 232° (found: C, 33·3; H, 3·7; N, 38·7; Cl, 24·6. $C_4H_5N_4Cl$ requires C, 33·2; H, 3·5; N, 38·8; Cl, 24·5 per cent). Catalytic dehalogenation over palladium on charcoal in the presence of barium oxide gives 4 : 5-diaminopyrimidine, m.p. 204°, which forms a crystalline nitrate decomposing without melting above 260° (found: C, 27·8; H, 4·0; N, 40·0. $C_4H_7O_3N_5$ requires C, 27·7; H, 4·1; N, 40·5 per cent). Reaction of the diaminopyrimidine in aqueous solution with glyoxal bisulphite gives pteridine which crystallizes from alcohol in pale yellow plates, m.p. 140° (found: C, 54·3; H, 2·9; N, 42·9. $C_6H_4N_4$ requires C, 54·5; H, 3·05; N, 42·4 per cent).

Pteridine is soluble in water and alcohol and readily sublimes *in vacuo*. Its ultra-violet absorption spectrum in aqueous solution at *p*H 5·8 shows a sharp maximum at 299 mμ with $\varepsilon = 7{,}890$ (Beckmann spectrophotometer), and in neutral or alkaline solution it shows a violet-blue fluorescence in the ultra-

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