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THE BIOGENESIS OF ASPIDOSPERMINE

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INSPECTION of the molecular structure of aspidospermine recently disclosed[1] allows of the recognition of an interesting biogenesis sequence which raises important side-issues.

Strychnine and vomicine (which contains a methoxyl group in the same position as in aspidospermine) are almost certainly derived from a tryptamine (or substituted tryptamine) residue (or equivalent) condensed with a tyrosine or dihydroxyphenylalanine moiety, modified by the Woodward fission[2] together with a so-called berberine-bridge carbon atom and a molecule of acetic acid (or equivalent). The side chain of the phenylalanine derivative is degraded to $R.CH_2CO.CO_2H$ or $R.CH_2.CHO$ and this carbonyl becomes attached to the 3- (or β-) position of the indole ring. The (B) carbon atom connects the tryptamine nitrogen to a position (originally - CH =) of the benzene ring of the phenylalanine. The aspidospermine skeleton may be

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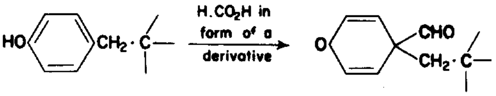
[1] Mills and Nyburg, Tetrahedron Letters, No. 11, 1 (1959); Conroy, Brook and Amiel, Ibid. No. 11, 4 (1959).

[2] Woodward, Nature, Lond. **162**, 155 (1948).

derived from the same starting points but the positions of condensation are different.

The CHO (or $CO.CO_2H$) of the degraded phenylalanine derivative side-chain becomes connected with the 2- (or α-) position of the tryptamine nucleus and the (B) carbon becomes attached to the 3- (or β-) position of the indole nucleus, also to the tryptamine basic N atom and, probably most significantly, to that carbon of the substituted phenylalanine progenitor which is p to the hydroxyl of tyrosine. Reduction, closure of the piperidine ring, and acetylation complete the necessary processes.

The bifurcation which leads to aspidospermine may well be conceived as connected with the mode of introduction of the (B) carbon. This is plausibly derived from formic acid (in suitable combination) and with formation of a hydro-aromatic type represented below as if from tyrosine, merely for purposes of illustration.



If this almost necessary hypothesis is approved it would strongly indicate the origin of aspidospermine from a true aromatic phenylalanine derivative.

By analogy it can be inferred that the original hypothesis of Woodward in regard to the amino-acid progenitors of strychnine (and other indole alkaloids) is strengthened. It seems very probable that these are both benzenoid and that alicyclic intermediates (Wenkert) are not concerned in the process apart from modifications of the aromatic nuclei (as above for example) and naturally in the synthesis of the aromatic nuclei of the amino-acids themselves.

On the other hand it is an obvious possibility that the 1-carboxyl of prephenic acid (Davis, Sprinson) provides the (B) carbon atom in question. Nevertheless this attractive suggestion raises other difficulties, which require more detailed discussion than is possible in this place.

A private communication from Dr. W. I. Taylor, discloses that alkaloids of Hunteria Eburnea Pichon possess the same skeleton as aspidospermine and the suggested biogenesis obviously also applies to these substances.