THE BIOGENESIS OF CISSAMPAREINE AND OF MICRANTHINE-TYPE ALKALOIDS

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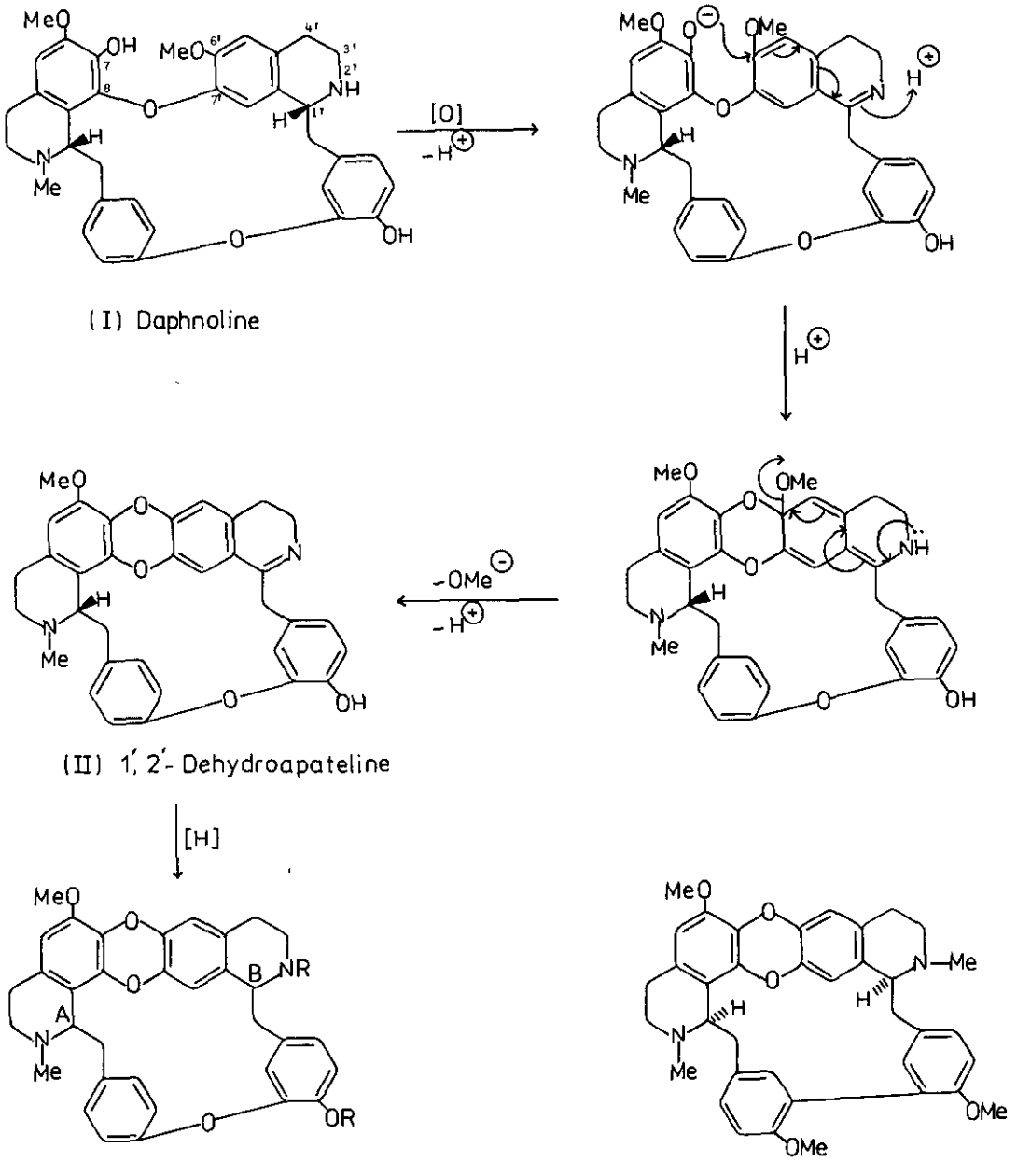
Abstract — A possible mode of biosynthesis is proposed for cissampareine and for the micranthine type of bisbenzylisoquinoline alkaloids.

The bisbenzylisoquinoline alkaloids form the largest single group of naturally-occurring bases with an isoquinoline nucleus[1]. Their biogenesis is considered to take place by phenol oxidative coupling between two units of coclaurine or some simple analogue[2,6], and labelling experiments have confirmed the general outlines of this hypothesis[3,4]. However, it is difficult to account satisfactorily for the biogenesis of certain types of bisbenzylisoquinoline structure purely in terms of phenol oxidative coupling. An intriguing group that has attracted considerable attention[1,2,5,6] has only five oxygens, two of which are involved in a dibenzodioxin nucleus. Examples include micranthine[7,8] (IV), the first base of this type to be isolated, and its diastereomer apateline[9] (III). These alkaloids, together with a number of simple analogues, occur in various Australian monimiaceous plants:[7-12] thus 1',2'-dehydroapateline (II) has recently been found in the bark of the north Queensland tree Doryphora aromatica[12], the principal alkaloid of which is daphnoline (I)[12]. It may be noted that the latter base has the same structure and pattern of substitution as apateline (III), except for a phenolic group at C-7 and a methoxyl at C-6' instead of a diphenyl ether link between these positions; moreover, the two alkaloids have the same stereochemistry. These observations suggest that apateline may be biosynthesised from daphnoline through their 1',2'-dehydro derivatives by nucleophilic displacement of a methoxyl group (Scheme 1). The biosynthesis of micranthine (IV) and of other bisbenzylisoquinolines containing 7,6' and 8,7' diphenyl ether links could be accounted for along similar lines: thus isotrilobine (V) and tiliacorine (VI) could be formed through the corresponding 3',4'-dihydroisoquinolinium intermediates.

Scheme 1



(I) Daphnoline

(II) 1′, 2′- Dehydroapateline

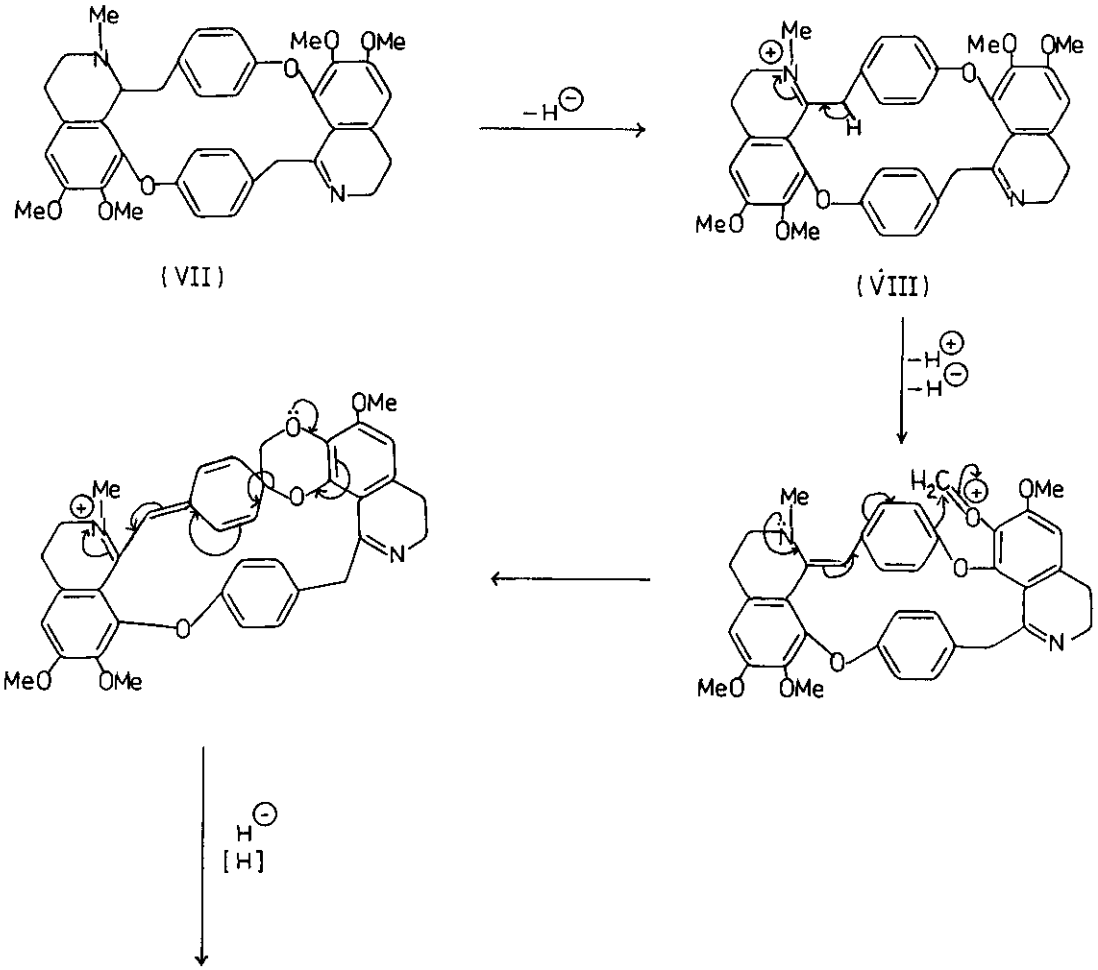
(III) Apateline (R = H; A = S, B = R)

(IV) Micranthine (R = H; A = B = R)

(V) Isotrilobine (R = Me; A = B = S)

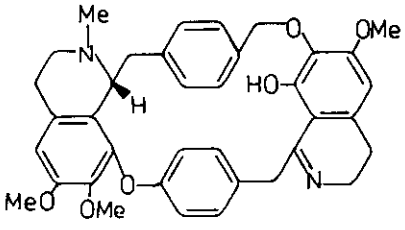
(VI) Tiliacorine

Scheme 2

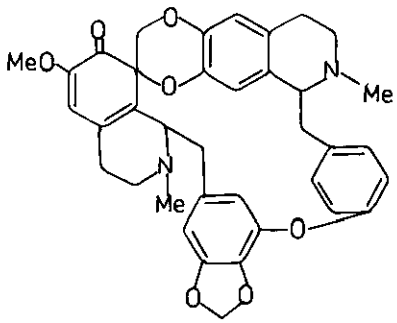


(VII)

(VIII)



(IX) Cissampareine



(X) Repanduline

A 3',4'-dihydroisoquinolinium intermediate (VIII), formed by oxidation of an analogue (VII) of the alkaloid cycleanine, may also be involved in the biogenesis of cissampareine (IX), another bisbenzylisoquinoline base with an unusual structure and substitution pattern, whose biosynthesis plainly does not follow the standard course[13,14]. On deprotonation, the dihydroisoquinolinium derivative VIII could generate an enamine conjugated with an aromatic nucleus (Scheme 2). The latter might then undergo electrophilic substitution with an oxonium ion, formed by oxidation of a methoxyl group[14], to give an intermediate with a 1,4-dioxene ring; a similar ring with a spiro carbon occurs in the structure of the alkaloid repanduline (X). Subsequent opening of this ring and reduction would lead to cissampareine (IX).

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