Asymmetric Synthesis and Absolute Stereochemistry of the Alkaloids Araliopsine, Isoplatydesmine, and Ribalinine. Dual Mechanism for a Dihydrofuroquinolone–Dihydropyranoquinolone Rearrangement

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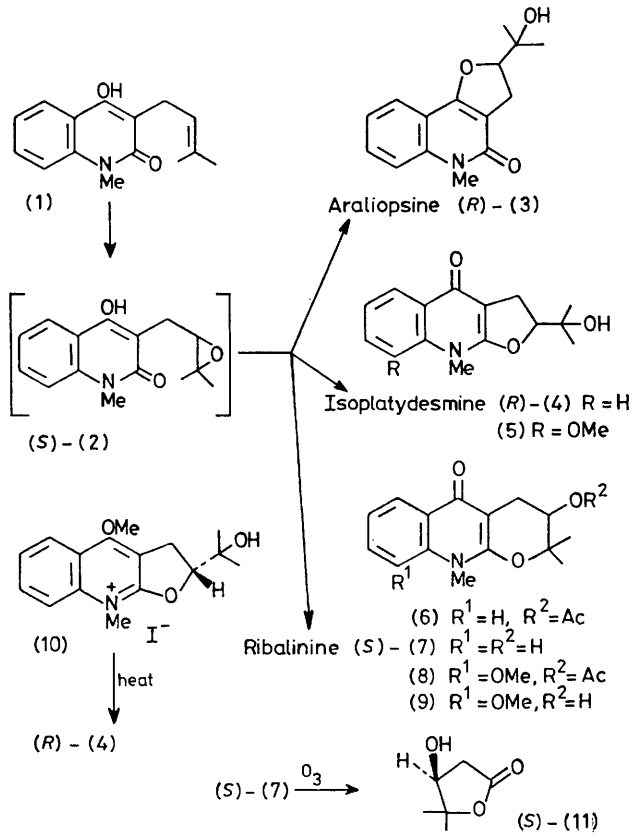
Summary (+)-Isoplatydesmine (**4**), (+)-araliopsine (**3**), and (−)-ribalinine (**7**) were obtained by asymmetric synthesis, and the absolute stereochemistry of each alkaloid was studied; reduction in optical purity in a rearrangement of dihydrofuro- into dihydropyranoquinolones is attributed to competing reactions.

THREE isomeric quinoline alkaloids, (+)-isoplatydesmine (**4**), (−)-ribalinine (**7**), and (+)-araliopsine (**3**) were isolated recently from *Araliopsis soyauxii* Engl.[1] Araliopsine is the first hydroxyisopropyldihydrofuroquinoline with angular annelation to be obtained from natural sources. A plausible biosynthetic route to the alkaloids (Scheme 1) involves oxidative cyclisation of a 3-prenylquinolone (**1**), the furoquinolones (**3**) and (**4**) being formed by inversion of configuration at the chiral centre of an intermediate epoxide (**2**) and the pyranoquinolone (**7**) arising from reaction at the tertiary carbon atom of the side-chain; the

predicted relative stereochemistry is indicated in Scheme 1. Our objective was to confirm the structure of araliopsine by synthesis and to study the asymmetric synthesis of the *Araliopsis* alkaloids as a model for the biosynthetic process and as a means of establishing the absolute stereochemistry of the alkaloids.



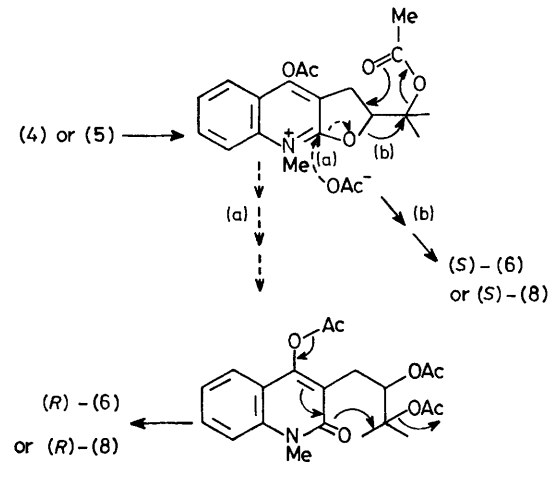
SCHEME 1

The major product from reaction of the 3-prenylquinolone (**1**) with (+)-(*S*)-peroxycamphoric acid was isoplatydesmine (**4**) containing an excess of the (+)-enantiomer. (+)-Isoplatydesmine is the (*R*)-enantiomer since it was obtained from (*R*)-*N*-methylplatydesminium iodide (**10**) in a reaction not affecting the chiral centre;[2] its formation from (*S*)-peroxycamphoric acid is also in accord with an (*R*)-configuration.[3]

(+)-Araliopsine (**3**), with the same spectroscopic properties recorded for the alkaloids, was synthesised by treatment of (+)-isoplatydesmine with sodium methoxide in dimethylformamide at ambient temperature. Base-catalysed rearrangement of balfourodine (**5**) was shown to involve two inversions of configuration[4] and if the rearrangement of (+)-isoplatydesmine occurs by the same mechanism, (+)-araliopsine has the (*R*)-configuration. (±)-Ribalinine (**7**) was isolated from *Balfourodendron riedelianum* Engl. and was synthesised by two methods,[5,6] one involving rearrangement of (±)-isoplatydesmine (**4**) with acetic anhydride and pyridine to give ribalinine acetate (**6**), which was then hydrolysed to the secondary alcohol.[6] Application of this procedure to (+)-isoplatydesmine, $[\alpha]_D$ + 35° ($CHCl_3$) (43% optical purity) gave (+)-ribalinine acetate (**6**), converted by mild basic hydrolysis into (−)-ribalinine (**7**). The latter compound was shown to have an (*S*)-configuration by ozonolysis to the (−)-(*S*)-hydroxylactone (**11**) of established stereochemistry.

Thus the proposed configurations of the alkaloids (**3**), (**4**), and (**7**) are consistent with a biosynthetic route involving an (*S*)-epoxide (Scheme 1). The stereochemical relationship of (+)-(*R*)-isoplatydesmine and (−)-(*S*)-ribalinine in *A. soyauxii* is analogous to the pairs of furo- and pyranocoumarins found in Umbelliferae species,[7,8] but not to that of the quinoline alkaloids (+)-(*R*)-balfourodine (**5**) and (+)-(*R*)-isobalfourodine (**9**) of *B. riedelianum*.[3] It is apparent from the present work that the configurations of (+)-isoplatydesmine and (+)-ribalinine from another species of *Araliopsis*, *A. tabouensis*,[9] is also anomalous in terms of the general stereochemical correlation of aromatic hemiterpenoids.[8]

An interesting feature of our asymmetric synthesis of ribalinine concerns the mechanism of the dihydrofuroquinolone–dihydropyranoquinolone acetate rearrangement. Before the configurations of the alkaloids were established, Rapoport and Holden[10] proposed a mechanism for conversion of balfourodine (**5**) into isobalfourodine acetate (**8**) involving inversion at the chiral centre; when the two compounds were found to have (*R*)-configurations a new mechanism [Scheme 2, route (a)] was suggested in which



SCHEME 2

the chiral centre was not affected.[3] It now appears that the rearrangement of isoplatydesmine, differing from balfourodine only in the absence of an aromatic methoxy group, involves inversion; a mechanism [Scheme 2, route (b)] similar to the Rapoport proposal is suggested. The rearrangement of balfourodine obtained from *B. riedelianum* or from asymmetric synthesis was described as being accompanied by considerable racemisation,[3,10] and we find that reaction of isoplatydesmine with acetic anhydride also results in substantial reduction in optical purity. We attribute the 'racemisation' observed in the rearrangement

to competing reactions with different stereochemical consequences [Scheme 2, routes (a) and (b)]; one predominates with isoplatydesmine and the other is favoured in the 8-methoxy series.

We thank the Department of Education for Northern Ireland for the award of a research studentship (to S. A. S.).

(*Received, 2nd May* 1978; *Com.* 466.)

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