Biomimetic Synthesis of Borreverine and Isoborreverine

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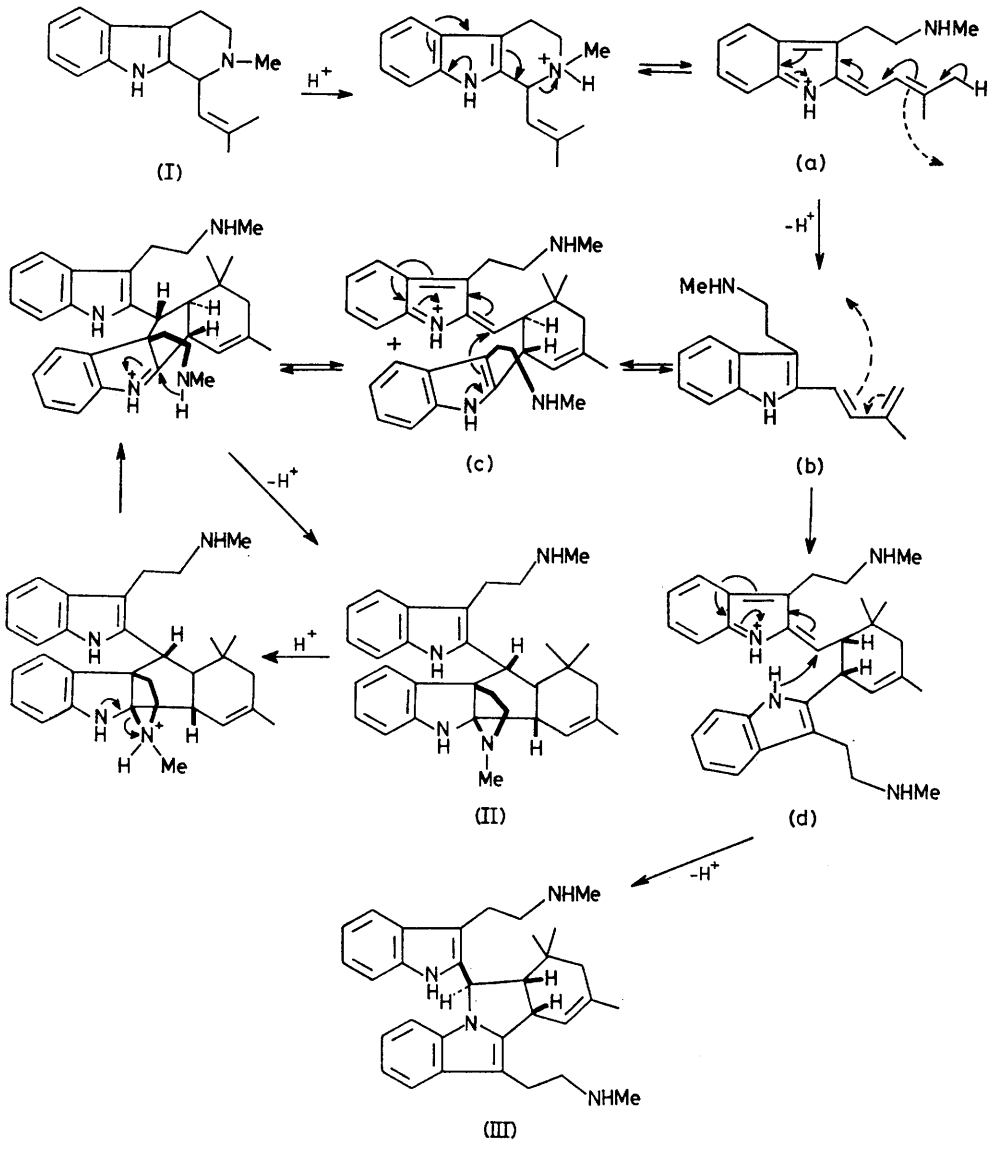
Summary Acidic dimerisation of the isoprene–indole alkaloid borrerine (I) gives borreverine (II) and isoborreverine (III).

The co-occurrence of the indole alkaloid borrerine (I)[1] and of its dimer borreverine (II) in *Borreria verticillata* suggested a simple chemical relationship between these two compounds and the mechanism shown in the Scheme can be

envisaged for the dimerisation of (I): protonation of borrerine (I) gives two open forms (a) and (b), which, after intermolecular cycloaddition, lead to borreverine (II) and isoborreverine (III) *via* two *cis–trans* isomeric intermediates (c) and (d).

C_6H_6, 65 °C, 30 min) borreverine (II)† and isoborreverine (III)‡ were isolated in approximately equal amounts and in *ca.* 80% total yield.

Longer reaction time leads to a change in the ratio of borreverine (II) to isoborreverine (III) in favour of the latter.



SCHEME

In order to verify the above mechanism borrerine (I) was heated with several acids (HCl, $MeCO_2H$, CF_3CO_2H) under various conditions. Both dimers were obtained in each case although the rate of the reaction and the yield depended on the acid used. Under optimum conditions (CF_3CO_2H,

Furthermore, borreverine (II) can be quantitatively transformed into isoborreverine (III) after 12 h under the above conditions. Protonation of the tertiary nitrogen of borreverine (II) may, in fact, lead to a reversal of the reaction sequence depicted in the Scheme whereas isoborreve-

† Identical (u.v., i.r., ^{1}H n.m.r., and mass spectroscopy, and t.l.c.). with an authentic sample (ref. 2).

‡ The structure of isoborreverine (III) has been demonstrated by physical and spectral data and by chemical correlation: $C_{32}H_{40}N$ (M^+ 480·3244, calc. 480·3253); $[\alpha]_{578}^{20}$ 0°; λ_{max} (EtOH) (log ϵ) 226 (4·72), 288 (4·15), and 294 (4·15) nm; 3400, 2960, 2925, 2870, 2800, 1460, 1300, 1135, and 745 cm^{-1}; *m/e* 480 (M^+) (68%), 438 (21), 437 (61), 436 (15), 405 (37), 394 (100), 393 (52), 264 (16), 262 (38), 197 (56), 195 (81), 185 (40), 182 (55), 144 (46), and 130 (18); ^{1}H n.m.r. δ (Me_4Si) 0·76 (3H, s), 1·06 (3H, s), 1·69 (3H, s), 2·42 (3H, s), 2·44 (3H, s), 5·40 (2H, m), 6·40—7·80 (8ArH), and 2·35—2·65 and 4·05 (2H+1H, D_2O exchangable). Acetylation of (III) in cold pyridine leads to a product identical (u.v., i.r., ^{1}H n.m.r. and mass spectroscopy, and t.l.c.) with transposed diacetylborreverine, the structure of which has been shown by *X*-ray diffraction (ref. 2).

rine (III) should not react under these conditions. A similar rearrangement was observed when borreverine (II) was treated with hot acetic anhydride.[2]

Since the dimerisation of borrerine (I) invariably furnishes borreverine (II) as well as isoborreverine (III), their co-occurence within the same plant might be expected. In fact, these two dimeric alkaloids were recently isolated from *B. verticillata*[3] and *Flindersia fournieri*.[4]

Our experimental data and the lack of optical acitivity in both natural and synthetic dimers suggest a non-enzymatic dimerisation of borrerine (I). The isolation of isoborreverine (III) as the major constituent of *Flindersia fournieri*[4] is in full agreement with this hypothesis. Nevertheless, it is interesting to note that borreverine (II) is the main alkaloid in *B. verticillata*.[3]

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