Biomimetic Synthesis of the Bis-indole Alkaloid Villalstonine

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Summary Pleiocarpamine (**2**) and macroline (**3**) react smoothly at room temperature in aqueous hydrochloric acid to give villalstonine (**1**); this reaction may closely parallel the biogenetic pathway to *Alstonia* bis-indole alkaloids.

VILLALSTONINE (**1**),[1-3] the most abundant of the *Alstonia* bis-indole alkaloids[4] obtained so far, can be regarded as an adduct of the known alkaloid pleiocarpamine (**2**) and the base macroline (**3**), which has not yet been identified in nature. Our work[5] on the alkaloids of *A. muelleriana*[6] has interested us in the problem of biomimetic synthesis in this unusual group of bis-indole alkaloids.

Acid-catalysed Michael and vinylogous Michael reactions offer a mechanistically general mode of addition of macroline to the 'non-macroline' portions of the *Alstonia* bis-indole alkaloids. We now report that stirring of pleiocarpamine (**2**) and macroline (**3**)[1,3] together in 0·2N-aqueous HCl for 18 h at 20° gives only villalstonine, apparently the first synthesis of an alkaloid in this series.

The synthetic villalstonine (38% yield of pure base; not yet maximised) was amorphous, but was indistinguishable in t.l.c. (2 systems), i.r. spectrum, and 100 MHz n.m.r. spectrum from authentic villalstonine, and the optical rotations were compatible.†

The reaction probably involves attack by the $\alpha\beta$-double bond of the pleiocarpamine indole function on the enone function of macroline, followed by ring closure.[1] From molecular models the α-face of pleiocarpamine is clearly the more accessible to electrophilic attack, leading to intermediate (**4**). The geometry of this intermediate could allow an almost simultaneous generation of the two new rings, as shown or *via* a hemiacetal.[1] Macroline is stable alone under the reaction conditions. The fact that villalstonine (*four* new asymmetric centres) is the sole reaction product suggests that this reaction, or a closely similar one involving a 'macroline equivalent', may be the biogenetic pathway.

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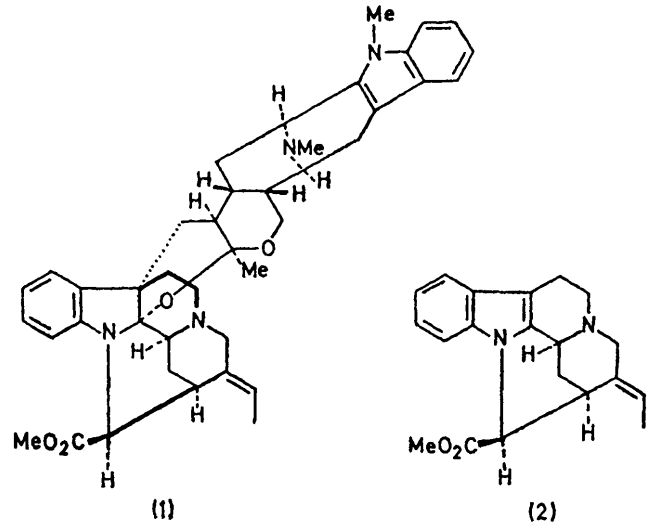
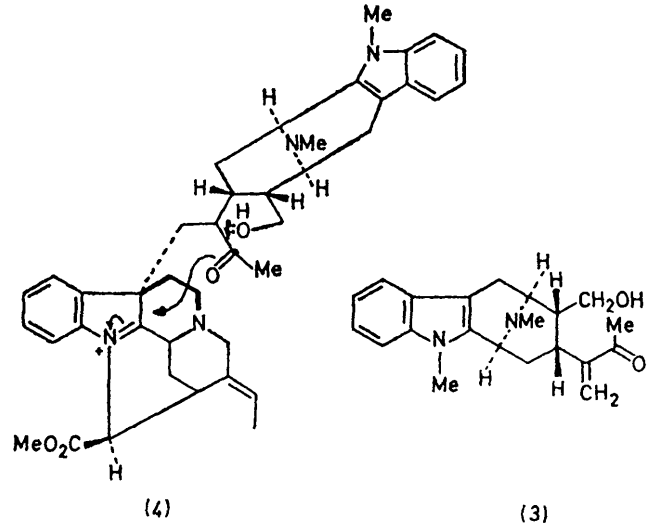


(1)

(2)



(4) (3)

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† Villalstonine free base is difficult to crystallize in small amounts; our synthetic sample was amorphous, and incorporated tenaciously held solvent. The best literature value for the rotation of authentic crystalline villastonine is +79°. Rapid evaporation of chloroform from a solution of authentic crystalline material gave amorphous base which after 3 h at 20° *in vacuo* was identical except for the characteristically different i.r. spectrum and rotation, $[\alpha]_D$ +67° ($CHCl_3$). The synthetic base treated similarly had $[\alpha]_D$ +58° ($CHCl_3$).

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