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TOTAL SYNTHESIS OF (±)-ORIENTALIDINE

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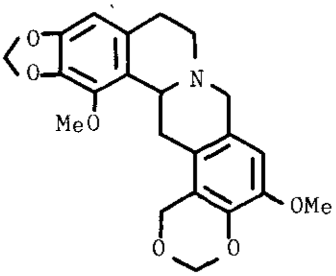
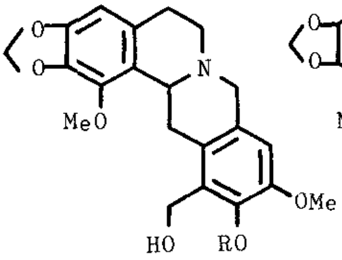
The total synthesis of (±)-orientalidine (1) was accomplished by treatment of (±)-demethylmecambridine (2) with methylene chloride and sodium hydride in dimethylformamide. A synthesis of the tetrahydroprotoberberine (7) containing the 1,3-dioxane system is also described.

Orientalidine, isolated from Papaver orientale, was initially cosidered as (3) on the basis of spectral analyses combined with some chemical degradations.[1,2] However, a comparison of the uv spectra of a series of tetrahydroprotoberberine bismethine derivatives showed that the structural assignment had to be modified to 1.[3,4] We now with to report the verification of the structure (1) by a total synthesis of (±)-orientalidine via (±)-demethylmecambridine (2), an intermediate in the synthesis of mecambridine (4).[5]

To study the formation of the 1,3-dioxane system, the easily available phenolic tetrahydroprotoberberine (5)[6] was stirred with 37 % formalin and 1N sodium hydroxide at room temperature for 3 days to give 9-hydroxymethylprotoberberine (6), mp 186 - 188°; m/e 371 (M^+) and 192. Its ir spectrum ($CHCl_3$) exhibited one hydroxyl group at 3540 cm^{-1} and its nmr spectrum (δ in $CDCl_3$ and DMSO-d_6) showed three O-methyl groups at 3.82 and a hydroxymethyl group at 4.67 together with three aromatic protons at 6.71 (1H) and 6.61 (2H). Heating

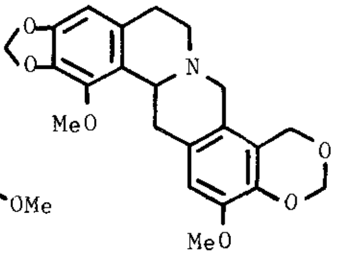


(1)



(2) R=H

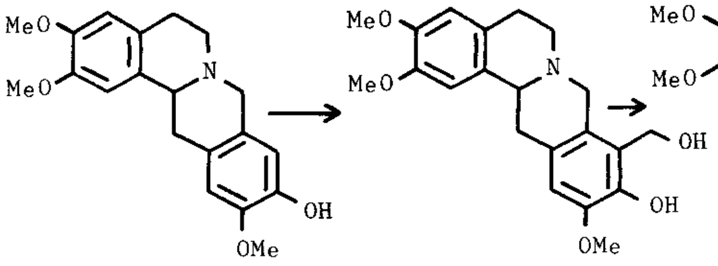
(4) R=Me



(3)

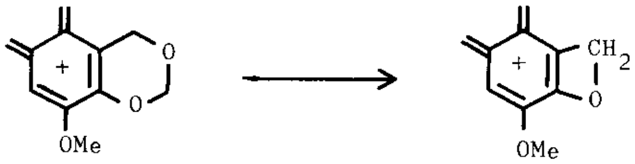
compound (6) with a mixture of either methylene iodide and sodium hydride in dimethylformamide or methylal and *p*-toluenesulphonic acid in dimethylformamide, furnished the desired compound (7) in poor yield as indicated by the nmr analysis of the reaction product. However, by carrying out the reaction with an excess of dry methylene chloride and sodium hydride in dry dimethylformamide at 80° C for 15 min under nitrogen, compound (7) was quantitatively obtained, mp 171 - 172° and characterized by physical-chemical methods. Its ir spectrum showed no hydroxyl group and its nmr spectrum [δ in $CDCl_3$; 3.88 (9H, s, 3 x OMe), 6.74 and 6.63 (1H and 2H, each s, 3 x ArH)] revealed the $ArOC\underline{H}_2OC\underline{H}_2Ar$ group as each singlet at 5.26 and 4.79. Further, its mass spectrum showed the molecular peak at *m/e* 383 and fragment peaks at *m/e* 192 (8 and 9), 190 (10) and 162 (11).[1]

Demethylmecambridine (2) was then reacted as above with dry methylene chloride



(5) (6) (7)

(8) (10)



(9) (11)

and sodium hydride in dry dimethylformamide to afford (±)-orientalidine (1), mp 190 - 192°. The ir (CHCl$_3$), nmr [(δ, CDCl$_3$) 3.87 and 4.01 (each 3H, each s, 2 x OMe), 4.60 and 4.92 (each 1H, each d, each J = 15Hz, $ArC\underline{H}_2O$), 5.26 (2H, s, $ArOC\underline{H}_2$-OCH_2), 5.90 (2H, s, $OC\underline{H}_2O$), 6.36 and 6.52 (each 1H, each s, 2 x ArH)] and mass spectrum [*m/e* 397 (M$^+$), 204, 192 and 162] were superimposable with those of the natural product.

Thus, the total synthesis of (±)-orientalidine has been accomplished and the proposed structure (1) confirmed.

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