Tetrahedron Letters No. 37, pp 3249 - 3252, 1976. Pergamon Press. Printed in Great Britain.

BIOMIMETIC SYNTHESIS OF ALSTONERINE

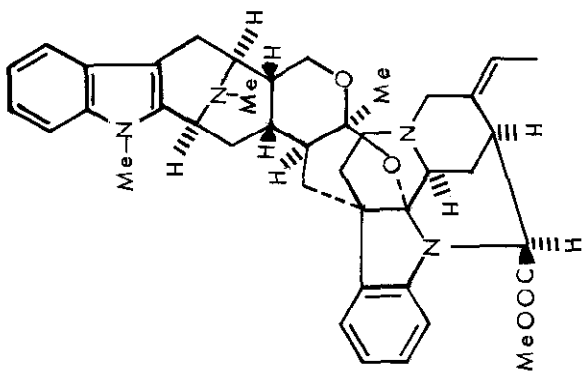
Robert L. Garnick and Philip W. Le Quesne*

Department of Chemistry, Northeastern University, Boston, MA 02115, U.S.A.

(Received in USA 10 May 1976; received in UK for publication 26 July 1976)

Although macroline 1, a chemical degradation product of villalstonine 2, is not known as a natural product, it has been converted by simple and stereospecific reactions into the Alstonia bisindole alkaloids villalstonine 2,[1] alstonisidine 3,[1] and macralstonine 4.[2] Macroline, or some closely related natural derivative, has therefore been implicated as the likely biosynthetic precursor of these alkaloids. We now report a conversion of macroline into the monomeric Alstonia base alstonerine 5[3] by an oxidative sequence which would not only be biomimetic, but which also further establishes the central importance of macroline itself as the likely direct precursor of the monomeric, as well as the dimeric, Alstonia bases.

Methanolic sodium methoxide converted macroline 1 into an approximately 1:1 dynamic equilibrium mixture of 1 and dihydroalstonerine 6. (With $KOBu^t$-Bu^tOH the equilibrium position was shifted markedly towards 6). In view of the importance of Michael and vinylogous Michael-type reactions in the conversions 1→2→4[1,2] we considered 6 to be a likely direct natural precursor of alstonerine 5. However, we found that 6, in contrast to model compounds, could not be converted into either tertiary α-bromo or α-hydroxy-derivatives suitable for further transformation of alstonerine; further, although the model compound 7 was dehydrogenated with 1 equiv. of dichlorodicyano benzoquinone/(DDQ) in freshly distilled dioxan (0°, 1 minute) to 8 in almost quantitative yield, dihydroalstonerine 6 was unaffected by this reagent. The failure of 6 to undergo these attempted conversions arises from its stereochemistry; Dreiding models show that when the two cis-fused terminal heterocyclic rings of 6 have chair conformations, the acetyl group in its preferred equatorial conformation lies directly above the indole nucleus. That 6 possesses this stereochemistry is established by the marked upfield position of the acetyl 3H signal, at δ1.82. This stereochemistry in our view disfavors 6 as



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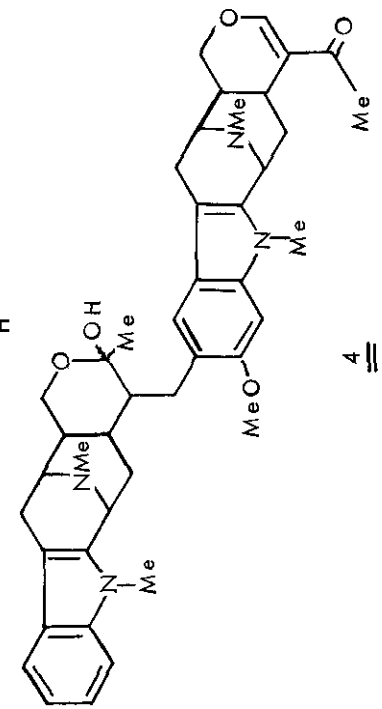

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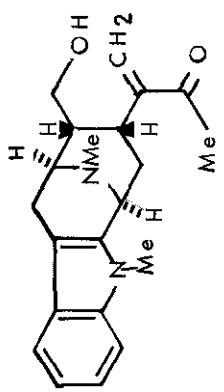

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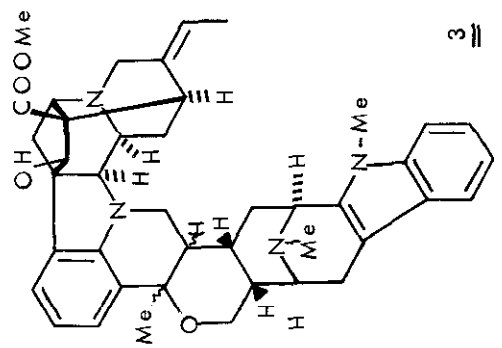

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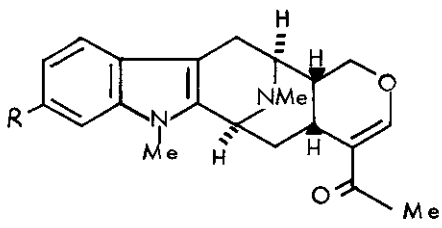
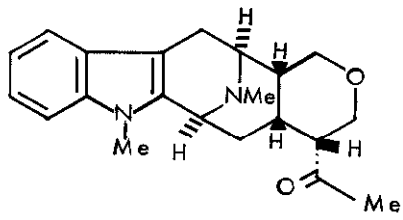


5 R = -H

11 R = -OMe



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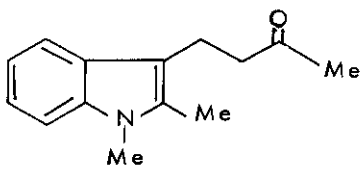

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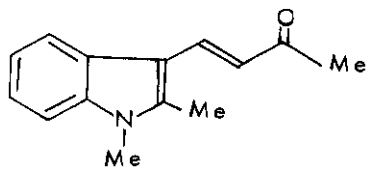

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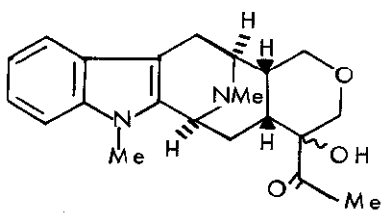

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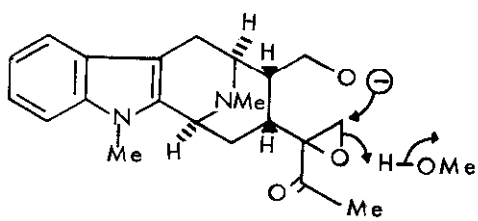

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a direct precursor to the monomeric Alstonia bases and, indirectly, to the macralstonine bisindoles.

Macroline was unaffected by aqueous acids under conditions mild enough to preserve the indole (refluxing 2N HCl, 3 hr, in air), but acidic reagents intended to oxidize the enone unfailingly led to degradation of the indole. However, macroline on treatment with t-butyl hydroperoxide (1 equiv) in benzene containing Triton B (25°, 12 hr.) gave, as well as 6, a mixture (2:1, nmr) of the diastereomeric α-ketols 9 (ν^{film} 3400, 1705, 1610, 1100, 750 cm^{-1}; δ^{CDCl_3} 2.38, 2.35 (N_a-Me); 2.20, 2.17 (COMe); ms M^+ 354, m/e 353, 337, 323, 310). We believe that in this reaction the enone of macroline is converted into an epoxide, which is attacked intramolecularly by alkoxide anion, as in 10, to give 9. The mixed ketols 9 underwent smooth dehydration by excess freshly prepared polyphosphoric acid at 20° (12 hr) to give alstonerine 5, identified by chromatographic and spectral comparison with the natural alkaloid.

The peroxide-induced epoxidation, and the polyphosphate-mediated dehydration of the resulting alcohols both have sound precedent among biological reactions, and the sequence may be regarded, therefore, as biomimetic. This conversion therefore relates macroline 1 directly to alstonerine 5, alstophylline 11,[5] and macralstonine 4, and gives further support to the concept of a central role for macroline in the biogenesis of both monomeric and bisindole Alstonia bases. Additionally, the epoxidation method and the DDQ dehydrogenation should prove useful for oxidative synthetic conversions among indole derivatives in general.

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