

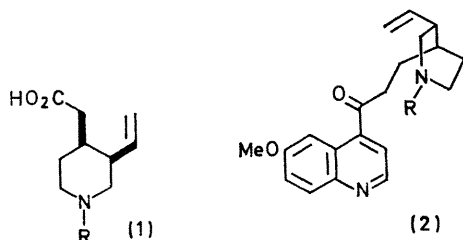
# Stereospecific Approach to the Synthesis of Quinine and Related Alkaloids<sup>1</sup>

By D. L. COFFEN\* and T. E. McENTEE, JUN.

(Department of Chemistry, University of Colorado, Boulder, Colorado 80302)

**Summary** A stereospecific synthesis of *syn*-5-hydroxy-alkyl-3-quinuclidinones is described and their feasibility as intermediates in a new approach to the synthesis of cinchona alkaloids illustrated.

THREE complete syntheses of quinine and/or related alkaloids have been described.<sup>2</sup> In each case an ingenious stereospecific synthesis of a meroquinene (1) or homomeroquinene derivative was developed followed by convergence on quinotoxine (2) related precursors to the complete quinine skeleton. We report an approach, illustrated with a synthesis of 11-hydroxy-7-oxodihydroquinene (13), which utilizes the simple assembly of the quinine ring system *via* aldol condensation of 3-quinuclidinones with quinoline-4-carboxaldehydes.<sup>3</sup> A key feature of this approach is the stereospecific synthesis of the *syn*-5-substituted 3-quinuclidinones (3)—(10).



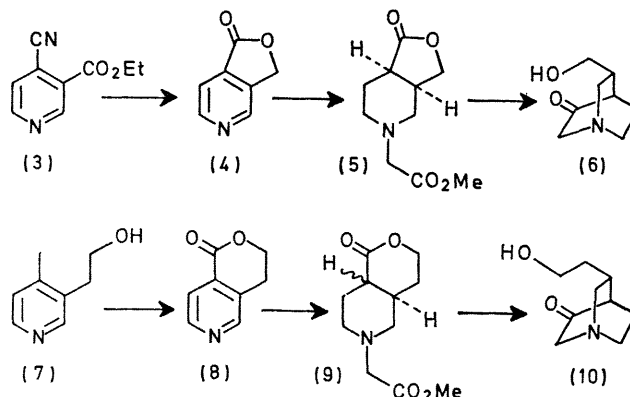
Ethyl 4-cyanonicotinate<sup>4</sup> was converted into the lactone (4) (m.p. 103—104°)<sup>†</sup> by sequential treatment with sodium borohydride and methanolic sulphuric acid. Lactone (8) (m.p. 74—75°)<sup>†</sup> was obtained directly from compound (7)<sup>5</sup> by oxidation with selenium dioxide in pyridine.<sup>6</sup> Alkylation of these pyridine lactones with methyl bromoacetate followed by catalytic reduction of the resulting pyridinium salts<sup>7</sup> afforded the piperidine lactones (5)<sup>†</sup> and (9)<sup>†</sup> respectively. The former is crystalline, *cis*-fused, with m.p. 120—122° but the latter is an oily mixture of *cis*- and *trans*-fused isomers. Dieckmann cyclizations<sup>8</sup> of lactones (5) and (9) yielded the *syn*-5-substituted 3-quinuclidinones (6) and (10). The stereospecificity of this synthesis is an inherent consequence of the conformational requirements for Dieckmann cyclization. Formation of the new carbon-carbon bond is only possible with the piperidine ring in a boat conformation and *cis*-fused to the lactone ring as shown in structure (11). Fortunately in the case of (9), the *cis*- and *trans*-fused isomers are interconvertible under Dieckmann conditions.

Sodium ethoxide-induced condensations<sup>3b</sup> of (6) and (10)

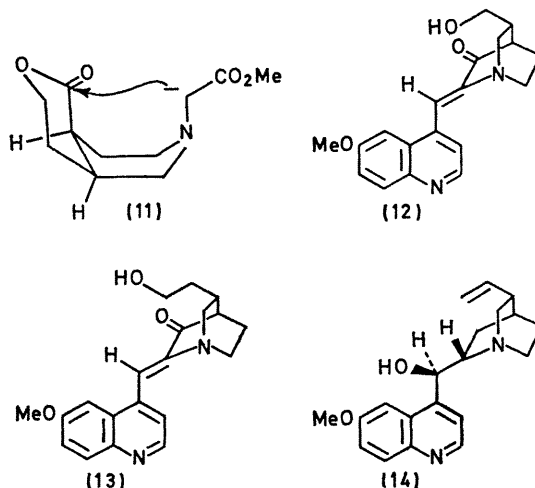
<sup>†</sup> This compound gave spectral data (i.r., n.m.r., m.s.) consistent with the assigned structure.

- <sup>1</sup> For previous paper in the series see: D. L. Coffen and D. G. Korzan, *J. Org. Chem.*, 1971, **36**, 390.  
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<sup>6</sup> D. Jerchel, J. Heider, and H. Wagner, *Annalen*, 1958, **613**, 153.  
<sup>7</sup> D. R. Howton and D. R. V. Golding, *J. Org. Chem.*, 1950, **15**, 1.  
<sup>8</sup> Cf. H. U. Daeniker and C. A. Grob, *Org. Synth.*, 1964, **44**, 86.  
<sup>9</sup> C. E. Kwartler and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1937, **59**, 524; M. Levitz and M. T. Bogert, *J. Org. Chem.*, 1945, **10**, 341.

with 6-methoxyquinoline-4-carboxaldehyde<sup>9</sup> afforded compounds (12) (m.p. 127—129°)<sup>†</sup> and (13) (m.p. 143—146°)<sup>†</sup>,



the latter having the complete quinine (14) skeleton. Appropriate functional group transformations necessary for the realization of total syntheses of quinine and related cinchona alkaloids from compound (12) or (13) are being investigated.



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