Modified Polonovski Reaction: Application to the Total Synthesis of Some Indole Alkaloids

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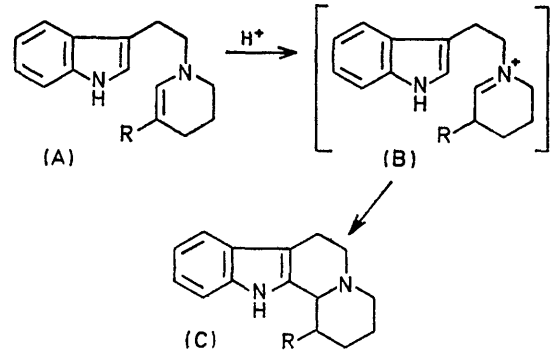
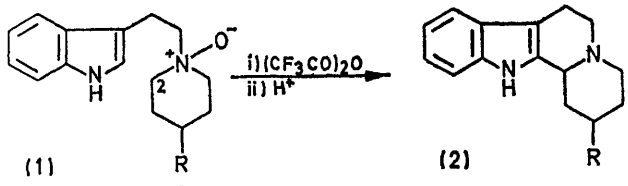
Summary Extension of a modified Polonovski reaction to the preparation of 5,6-dihydropyridinium ions provides a useful process for the preparation of new indole alkaloids of the antirhine and eburnane series, *inter alia*, and may also be of value for the preparation of other alkaloid systems.

MOST of the available methods for the total synthesis of indole alkaloids consist of an electrophilic attack upon the indole nucleus by a suitable immonium ion *i.e.* (A) → (B) → (C).[1] One of the aspects of all these syntheses therefore involves the preparation of the piperideines *e.g.* (A), pre-



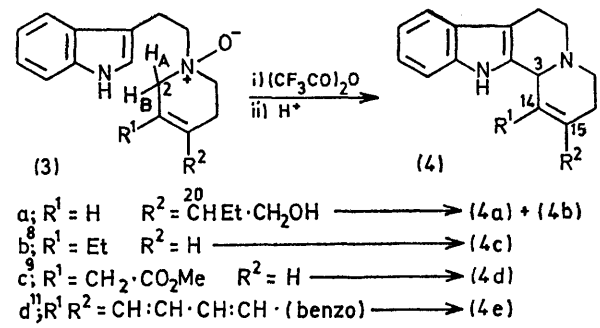
cursors of the necessary immonium ions (B). Wenkert has published a general method for the preparation of Δ^2-piperideines based upon the reduction of 3-acyl- or 3-alkyloxycarbonyl-pyridinium ions. Piperideines are also accessible using our modification of the Polonovski reaction:[3,4] treatment of a methylene chloride solution of an *N*-alkyl-piperidine *N*-oxide with trifluoroacetic anhydride leads to the alkyl-1-piperideiniums which cyclize in acidic medium giving rise to the corresponding ring-closed compounds; *e.g.*: (1a) → (2a); (1b) → (2b).



a; R = H b; R = ^{20}CHEt·CH_2OH

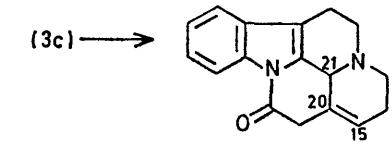
One of the two possible 20-epi-dihydroantirhines[6] (2b) has been prepared in this way, and recently Sakai *et al.* have used our method for the partial synthesis of akuammigine.[7]

The modified Polonovski reaction is particularly useful for the preparation of 5,6-dihydropyridinium ions, which are difficult to obtain using other reagents such as $Hg(OAc)_2$ (over-oxidation and oxymercuration reactions may interfere).



Δ^3-Piperideines are easily formed upon borohydride reduction of 1-alkylpyridinium salts—the greater mobility of the protons (H_A or H_B) on C-2 of the starting *N*-oxide, *e.g.* (3), explains the preponderant formation of the conjugated immonium ions.

The modified Polonovski reaction can be usefully applied to the synthesis of certain pentacyclic indole alkaloids:[5] the base-promoted isomerisation of (4c) [m.p. 115—116° *M*+252, δ ($CDCl_3$): 4·61 (broad s.; 3-*H*); 5·63 (m., 15-*H*)] leads to the isomeric $\Delta^{3(14)}$ compound, a known intermediate in the total synthesis of (±)-eburnamonine,[2] thus making the latter easily accessible.



Ester (3c) leads, *via* (4d), to the pentacyclic amide (5): [oil, *M*+264; ν($CHCl_3$): 1705 cm^{-1}; δ ($CDCl_3$): 4·05 (broad s.; 21-*H*); 5·65 (m. 15-*H*) 8·3 (m. 12-*H*)]. It is also possible to synthetise (±)-vincamine.[10] The alcohol (3a), [m.p. 95°, *M*+298], leads to 20-epimeric compounds (4a) [amorphous, *M*+296, δ ($CDCl_3$): 4·30 (m., 3-*H*); 5·87 (m., 14-*H*)] and (4b) [amorphous, *M*+296, δ ($CDCl_3$): 4·41 (m., 3-H); 5·81 (m., 14-H)] Hexahydrobenz[*a*]indolo[3,2-*h*]quinolizidine (4e) can also be prepared from (3d).[11]

The modified Polonovski reaction thus allows the preparation, in fair yields, of dihydro-5,6-pyridinium ions otherwise impossible or difficult to prepare and opens the way for the synthesis of some complex indole molecules.[12]

(*Received, 8th June* 1972; *Com.* 980.)

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[12] Since our preliminary communication,[4] the work of P. W. Le Quesne *et al.*, has been published; *J. Org. Chem.*, 1972, **37**, 1083.