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NOVEL PROPERTIES OF A SPIROCYCLIC DIENONE RELATED TO THE ALKALOID, CULARINE.

A. H. Jackson and G. W. Stewart.

Department of Chemistry, University College,

Cardiff.

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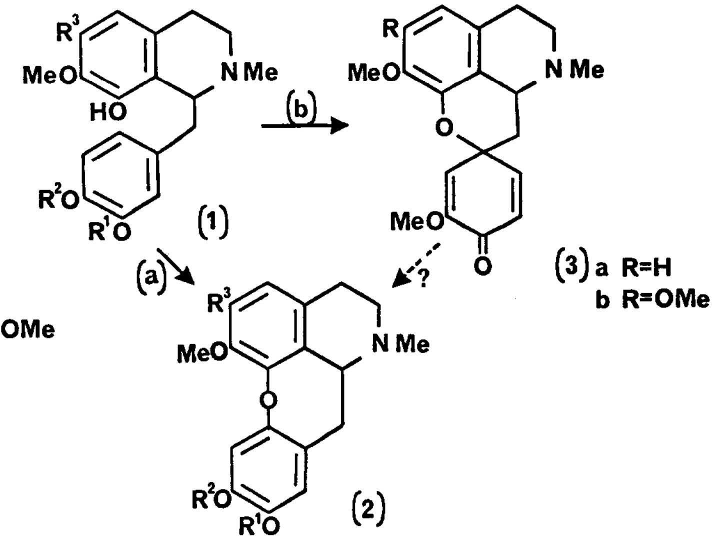
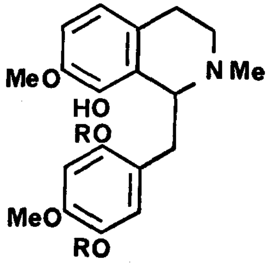
Cularine (2c) and related alkaloids may arise in nature via phenolic coupling of the tetrahydroisoquinoline derivatives (1a) or (1b), as shown below, although alternative pathways involving open-chain bis-(phenylethyl) amines cannot be excluded[1]. In a recent communication[2] we described the synthesis of cularine (2c) by ferricyanide oxidation of (1a) followed by O-methylation (path (a)) and we now wish to report our results on the feasibility



a $R^1=R^3=H$ $R^2=Me$
b $R^2=R^3=H$ $R^1=Me$
c $R^1=R^2=Me$ $R^3=H$
d $R^1=Me$ $R^2=H$ $R^3=OMe$

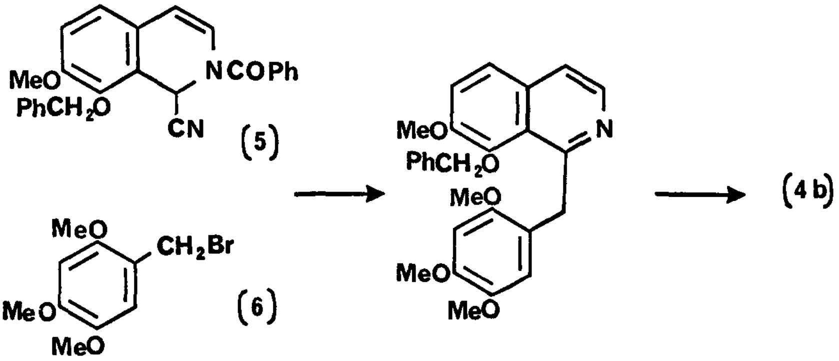
of the indirect route to cularine (2c) through the dienone (3a) (i.e. path (b)).

The tetrahydroisoquinoline (1b) was prepared by a similar route to that which was used earlier[2] for the preparation of (1a), i.e. by the Reissert method from 8-benzyloxy-7-methoxyisoquinoline. Ferricyanide oxidation of (1b) in a two phase system (chloroform: 8% ammonium acetate) then afforded a mixture of diastereoisomeric dienones (3a), m.p. 119-112° isolated in 10% yield by chromatography on alumina in chloroform/benzene. However, all attempts to effect the rearrangement of this dienone to cularine analogues under a variety of acidic conditions were unsuccessful. Kametani, Fukumoto and Fujihara have also described[3] the synthesis of cularine from (1a) and of the dienones (3a) by oxidation of (1b), although (1a) and (1b) were prepared by an entirely different route. The Japanese workers also reported[3] that the dienones could not be rearranged to cularine-type compounds, although in an earlier paper[4] they described the hydrogen chloride in acetic acid catalysed rearrangement of the methoxy-analogue (3b) to the phenolic ether (2d). Under these conditions our dienone gave a glassy product, (88% yield, pure by t.l.c.)tentatively assigned structure (4a) - on the basis of its n.m.r. and mass spectra although it was somewhat unstable and could not be obtained in an analytically pure form.

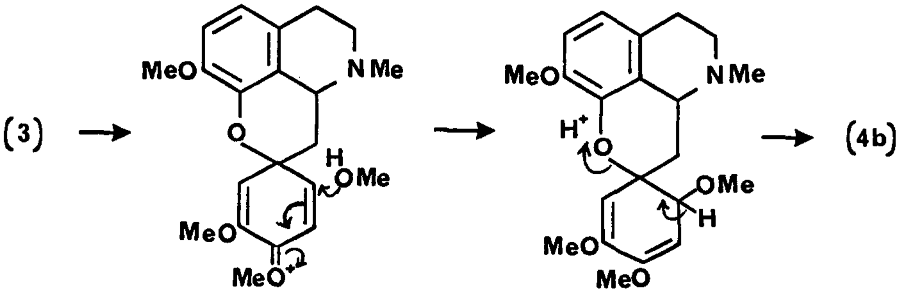


(4) a R=H
b R=Me

However, with hydrogen chloride, or sulphuric acid, in methanol the dienones (3a) afforded the analogous tetramethoxymonophenolic benzylisoquinoline (4b) (70%) which was fully characterised by i.r., n.m.r. and mass spectra; the structure was confirmed by an unambiguous synthesis from the Reissert compound (5) and the trimethoxybenzylbromide (6).



The novel ring opening of the dienone is envisaged as proceeding by the following mechanism, although alternative possibilities involving migration of carbon prior to ring opening cannot be completely excluded from consideration.



Ring opening may be preferred to ring expansion because migration to form the seven membered ring system of cularine (2c) is much less favourable sterically than the analogous and well documented[5] dienone rearrangements to form six membered rings. It will be interesting to discover whether this finding is significant in relation to cularine biosynthesis.

Another unusual feature of the chemistry of this dienone lies in its mass spectral fragmentation; below 150° it gives a molecular ion at m/e 327 and behaves quite normally, but then the fragmentation pattern changes gradually and above 220° the original molecular ion disappears and is replaced by a new 'molecular ion' at m/e 329. The fragmentation pattern of the latter is very similar to those of simple benzyl isoquinolines of type (1) or (4) and it is tempting to suggest that at the higher temperatures in the mass spectrometer reductive ring opening of the dienone has occurred (perhaps by ion - molecule interactions) to give the precursor (1b). The formation of M + 1 ions in the mass spectrometer is a fairly common process, but M + 2 ions are very rare[6], and in the spectra of some naphthaquinones, for example, it has been suggested that the M + 2 ions are due to the formation of the corresponding phenols[6b].

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