Stereoconservative Transformation of Secologanin into Meroquinene and its Derivatives

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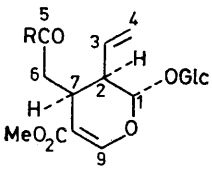
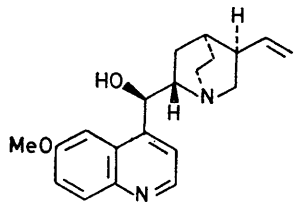
Summary Short reaction sequences convert secologanin (**1**) into meroquinene and its derivatives (**4**) and (**8**), key intermediates in the synthesis of quinine (**2**) and related *Cinchona* alkaloids.

A DEGRADATION product of quinine (**2**), meroquinene (**4a**) has been extensively used in synthetic routes to quinine and related *Cinchona* alkaloids.[1] It has been synthesised from β-collidine in a lengthy sequence which involves

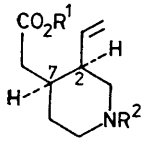
problems in conversion of an ethyl into a vinyl group, control of relative stereochemistry at C-2 and C-7, and resolution of the racemic product. These are avoided by using the natural precursor for the quinuclidine species, secologanin (**1**). Since it already possesses the correct chiralities and the vinyl group, the problems reduce to conservation of (i) the configurations at C-2 and C-7, and (ii) the 3,4-vinyl group. With 3,4-dihydro-derivatives the retention of chirality was readily achieved in a reductive amination reaction,[2] but with the parent series ready rearrangement of the vinyl group into conjugation with the C-1 aldehyde defeated both objectives. We now report that this obstacle can be overcome by appropriate choice of reducing agent and reaction conditions.



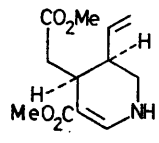
(1), R = H
(3), R = OMe



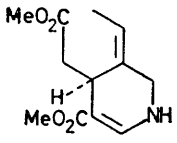
(2)



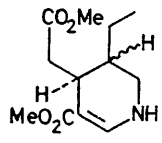
(4)
R¹ R²
a; H H
b; Me H
c; Me COPh



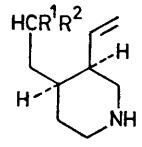
(5)



(6)



(7)



(8)
R¹ R²
a; H OH
b; [SCH₂]₂

Secologanin tetra-acetate was converted into methyl secoxyloganin (**3**) by Jones' oxidation, methylation with diazomethane, and Zemplen deacetylation.[3] After removal of the sugar with β-glucosidase came the crucial step of reductive amination for which several reducing agents were investigated over a range of pH. The most efficient was $NaCNBH_3$ in pH 6·5 NH_4OAc buffer in a 'one-pot' system with β-glucosidase overnight which afforded the vinyl compound (**5**), m.p. 83—85 °C, $[\alpha]^{25}$ — 116° (MeOH), as the major product in *ca.* 60% yield. At pH 6—7 with Me_3NBH_3 as reducing agent, the rearranged ethylidene isomer (**6**), $[\alpha]^{25}$ — 164° (MeOH), was the predominant product, whereas at pH 5 with $NaCNBH_3$ the 3,4-dihydro-derivative (**7**) was a significant component. The pH and reduction potential are obviously critical factors and the essential requirement is seemingly rapid reductive amination of the C-1 aldehyde before rearrangement of the vinyl group to the conjugated aldehyde or imine. Our previous work on the synthesis of heteroyohimbine alkaloids indicated the ease of such a rearrangement and the specific formation of a single ethylidene isomer again pointed to the likelihood of an intramolecular process.[4]

The structure (**5**) was supported by the full range of spectral data. In particular the n.m.r. spectrum showed retention of the vinyl protons, a coupling of *ca.* 3 Hz between 2-H and 7-H indicating no inversion, and a characteristic one-proton doublet at τ 2·55 due to H-9 coupled with NH. Hydrolysis and decarboxylation by heating with 1% HCl in aqueous methanol and subsequent reduction of the imine with sodium borohydride afforded methyl meroquinenate (**4b**) in almost quantitative yield. The product was characterised as the benzamide (**4c**) identical with an authentic sample obtained from quinine.[5]

Several analogous reaction sequences have been carried out with C-5 at the aldehyde and alcohol oxidation levels to afford a range of meroquinene derivatives, *e.g.* (**8a**,**b**) which may be used in synthesis of *Cinchona* alkaloids.

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[1] M. R. Uskokovic and G. Grethe in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1973, vol. XIV, Ch. 5, and refs. therein.
[2] R. T. Brown and J. Leonard, *Tetrahedron Letters*, 1978, 1605.
[3] R. T. Brown, C. L. Chapple, D. M. Duckworth, and R. Platt, *J.C.S. Perkin I*, 1976, 160.
[4] R. T. Brown, J. Leonard, and S. K. Sleigh, *J.C.S. Chem. Comm.*, 1977, 636.
[5] P. Rabe, *Ber.*, 1908, **41**, 62.