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STEREOCONSERVATIVE SYNTHESIS OF DIHYDROMEROQUINENE (CINCHOLOIPON) FROM SECOLOGANIN.

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In a series of publications we have described the transformation of secologanin (1) into Corynanthé-type indole alkaloids[1-5], and recently we exploited the selectivity of sodium cyanoborohydride as a reducing agent for imines to achieve a biomimetic conversion of vincoside and strictosidine into akuammigine and tetrahydroalstonine respectively.[4] We now wish to report a further use of this reagent in a stereoconservative transformation of secologanin into dihydromeroquinene (5) (cincholoipon) - a widely used intermediate in the synthesis of Cinchona alkaloids,[6,7] such as quinine (11). Problems in previous total syntheses have involved the generation of the correct relative stereochemistry at C-15 and C-20 and the resolution of racemic products, both of which are avoided by using secologanin, the natural precursor for the quinuclidine moiety. Since it already possesses the correct absolute configuration at the corresponding C-2 and C-7, the essential requirement then becomes the conservation of chirality at these centres.

Secologanin was converted into the 3,4-dihydrosecoxyloganinonitrile tetra-acetate** (2) in a sequence of mild reactions: catalytic hydrogenation followed by treatment with hydroxylamine in pyridine overnight afforded 3,4-dihydrosecologanin oxime; dehydration and acetylation with acetic anhydride and recrystallisation from methanol gave the nitrile (2), m.p. 160° $[\alpha]_D^{25}$ -121° in ca. 60% yield. The aglycone obtained by Zemplen deacetylation and removal of the sugar with β-glucosidase in pH5 buffer could be reacted with benzylamine to give the carbinolamine (8a). Attempts to reduce 8a to the tetrahydropyridine (8b) with sodium borohydride were unsuccessful, but it could be dehydrated with acetic acid to the 1,4-dihydropyridine (9) which was reduced to a tetrahydropyridine by catalytic hydrogenation. However, it was found that the product comprised a mixture of C-2 epimers in a ratio of ca. 3 : 2, and little stereoselectivity had been obtained.

** Satisfactory analytical and spectroscopic data were obtained for all new compounds.

In other experiments we had observed that sodium cyanoborohydride achieved reductive amination without undue disturbance of a chiral centre by a potential imine-enamine tautomerism.[8] Since it could also be used in weakly acidic media,[4] a 'one-pot' conversion of the glycoside to the tetrahydropyridine was feasible. In the event the nitrile glycoside was dissolved in aqueous ammonium acetate at pH6 together with β-glucosidase and sodium cyanoborohydride. After standing overnight at 37°, extraction with chloroform afforded in ca.70% yield mainly one compound $[\alpha]_D^{25}$ -130°, M^+208.1216; λ_{max} 280nm; ν_{max} 3465, 2245, 1680, 1630 cm^{-1}. The NMR spectrum displayed a characteristic one-proton doublet at τ2.39, attributed to H-9 coupled to NH, since it became a singlet on treatment with D_2O. From these and other data the major product corresponded to a tetrahydropyridine which the subsequent conversion to a dihydromeroquinene derivative confirmed as (3), i.e. the configuration at C-2 had been retained.

Removal of the carbomethoxy group from (3) by acid-catalysed hydrolysis and decarboxylation to an imine and subsequent reduction with sodium borohydride gave a compound corresponding to dihydromeroquinenonitrile (4a) in almost quantitative yield. For purposes of characterisation, part was benzoylated to give the amide (4b) $[\alpha]_D^{25}$ +21° (MeOH) and the remainder was converted by vigorous acid hydrolysis into dihydromeroquinene (cincholoipon) hydrochloride (5).[9] The latter was benzoylated and methylated to give methyl N-benzoyldihydromeroquinenate (6) $[\alpha]_D^{25}$ 0° (MeOH), identified from its spectral data.

An alternative starting material for dihydromeroquinene was methyl dihydrosecoxyloganin tetra-acetate (7), m.p. 134-6°, obtained from 3,4-dihydrosecologanin tetra-acetate by oxidation and methylation,[3] which avoided the necessity for hydrolysis of the nitrile. An analogous reaction sequence afforded the diester (10), $[\alpha]_D^{25}$ -41° ($CHCl_3$) and subsequently the methyl ester of dihydromeroquinene. Since quinine has been synthesised from the latter this also constitutes a formal transformation of secologanin into quinine. Having established the stereospecificity and ease of this reductive amination method we are now investigating its use with other secologanin derivatives for the preparation of useful meroquinene, homomeroquinene, and quinuclidine analogues.

Acknowledgement.

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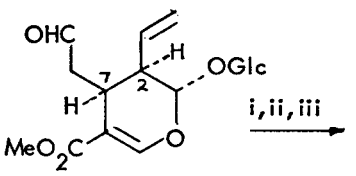

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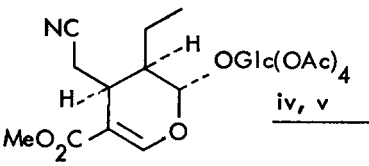

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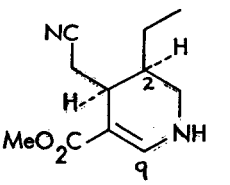

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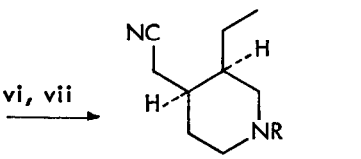
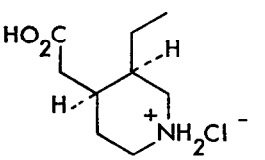


4 R
a: H
b: COPh



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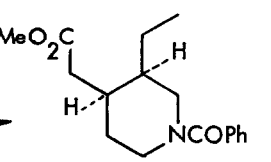

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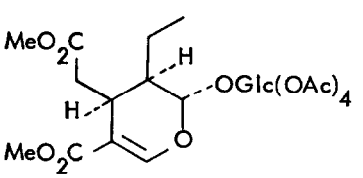
Reagents:- i, H_2/Pd-C; ii, H_2NOH; iii, Ac_2O/py; iv, NaOMe;
v, β-gluc'ase/NH_3/$NaBH_3CN$/pH6; vi, 2% HCl/Δ ;
vii, $NaBH_4$; viii, 6M HCl/Δ ; ix, PhCOCl/py ; x, CH_2N_2



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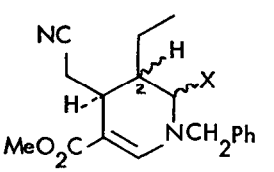
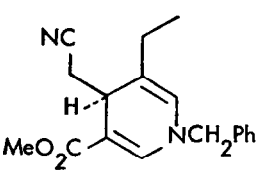


8 X
a: OH
b: H



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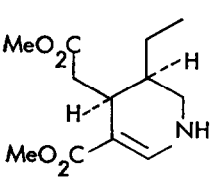

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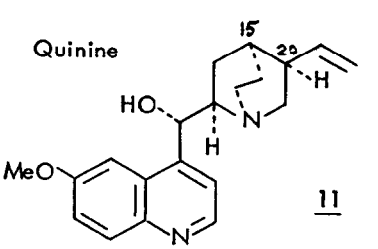

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