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Conversion of Secologanin into *Cinchona* Alkaloids—Part 1.

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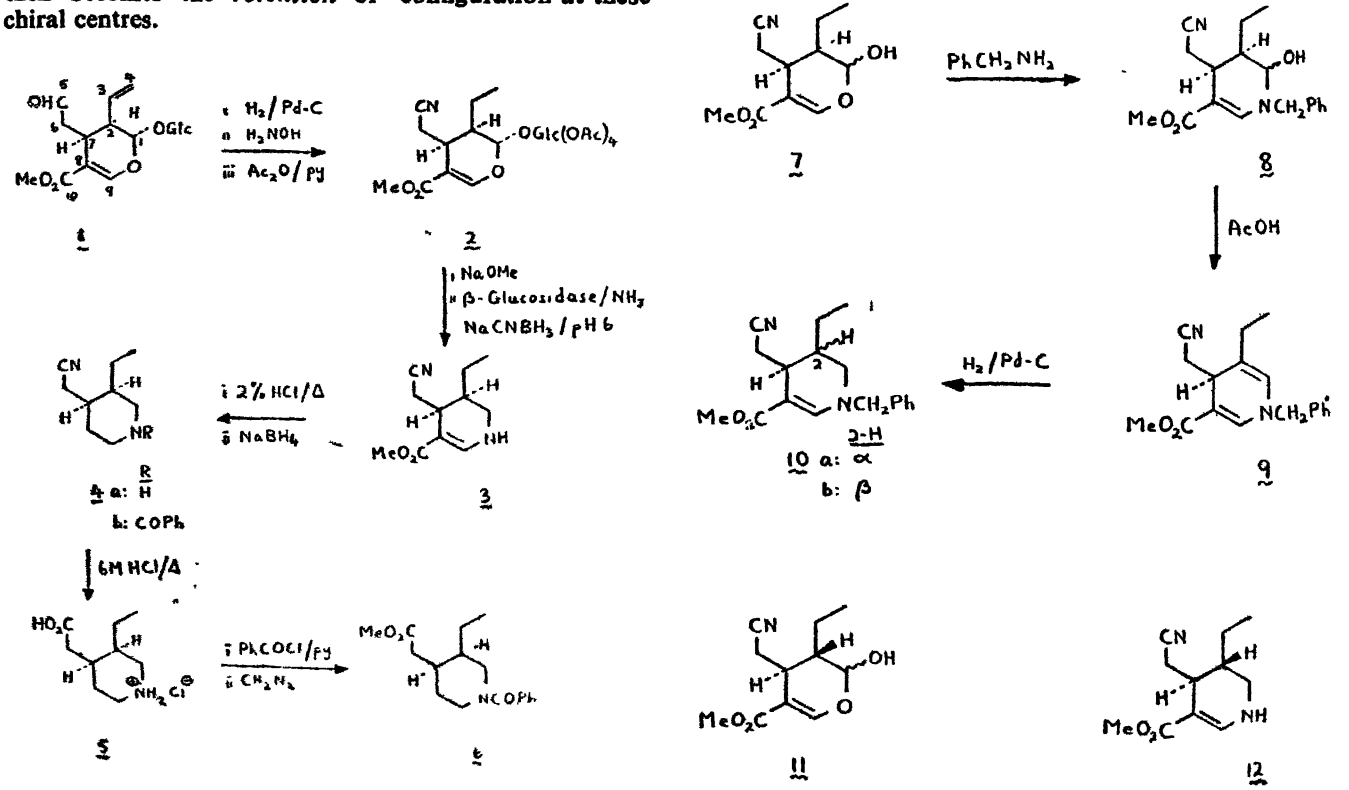
Secologanin (1) has been stereoselectively transformed into dihydromeroquinene (cincholoipon) (5), an important intermediate in the synthesis of quinine (18) and related *Cinchona* alkaloids.

IN a series of publications we have described the transformation of secologanin (1) into *Corynanthe* type indole alkaloids[1-5]. 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 stereo-controlled conversion of secologanin into methyl N-benzoyldihydromeroquinenate (6) a widely used intermediate in the synthesis of *Cinchona* alkaloids[6,7].

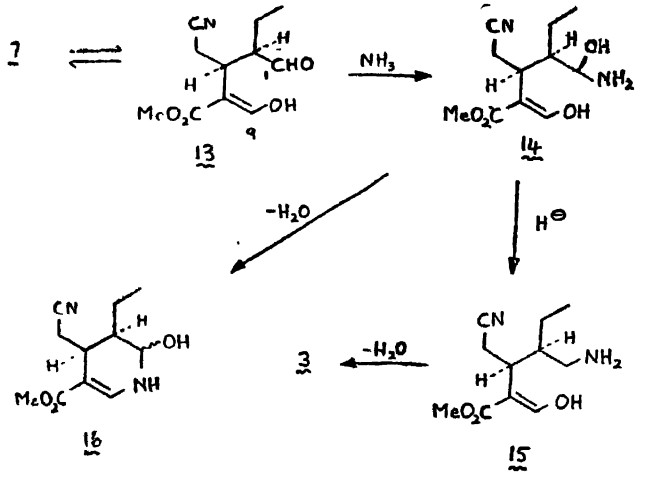
Major problems in previous total syntheses of *Cinchona* alkaloids such as quinine (18) have involved the generation of the correct relative stereochemistry at C-15 and C-20 and the resolution of racemic products. Both of these are avoided by using secologanin, the natural precursor for the quinuclidine moiety. Since it already possesses the correct absolute configuration at the corresponding C-2 and C-7, the essential requirement then becomes the *retention* of configuration at these chiral centres.

Secologanin was converted into the highly crystalline 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 (7) obtained by Zemplén deacetylation and removal of the sugar with β-glucosidase in *p*H5 buffer was then reacted with $C_6H_5CH_2NH_2$ to give the carbinolamine (8). Initial attempts to reduce (8) to the tetrahydropyridine (10) with $NaBH_4$ were unsuccessful, but it could be dehydrated with CH_3COOH to the dihydropyridine (9) which was reduced to a tetrahydropyridine by catalytic hydrogenation. However, when it was found that the product comprised a mixture of two epimers (10a,b) in a ratio of *ca.* 3 : 2, and little stereoselectivity had been obtained, this route was not considered viable, and an alternative was sought.

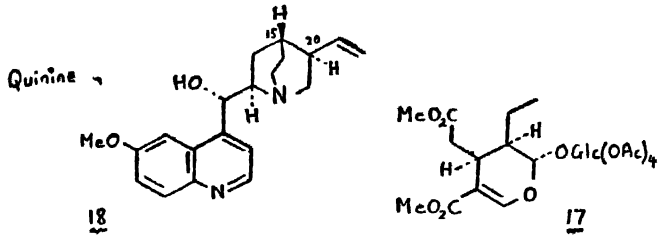


In other experiments we had observed that sodium cyanoborohydride achieved reductive amination without undue disturbance of a chiral centre by a potential imine-enamine tautomerism[8]. Furthermore, it could also be used in weakly acidic media[1] and hence a 'one-pot' conversion of the glycoside to the tetrahydropyridine was a feasible proposition. In the event the nitrile glycoside was dissolved in aqueous ammonium acetate at *p*H6 together with β-glucosidase and sodium cyanoborohydride. After standing overnight at 37°, extraction with $CHCl_3$ afforded in ca. 70% yield mainly one compound $[\alpha]_D^{25}$-130°, M^+ 208.1216, together with a trace of a 1,4-dihydropyridine. From spectral 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.

In order to explain the almost exclusive formation of (3) the mechanism outlined in the Scheme is proposed.



Scheme



Initial nucleophilic attack by ammonia presumably occurs at the more reactive C-1 aldehyde rather than C-9 in the ring-opened aglucone (13), and at *p*H6 dehydration of (14) followed by rapid reduction of the imine to (15) competes effectively with cyclisation to the carbinolamine (16). Previous experiments had shown that neither cyclised carbinolamines like (16) nor the derived 1,4-dihydropyridines were readily reduced by borohydride reagents. Subsequent cyclisation of (15) to the β-aminoacrylate (3) can then occur.

By a variation of the above procedure the epimer (12) with the unnatural 2,7 *trans* stereochemistry could also be obtained as the predominant product. Treatment of the aglucone (7) with base overnight results in almost complete inversion of H-2 to the more stable aglucone (11) which could give (12) by reductive amination as before.

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. Part was characterised as the benzamide (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 in this sequence is methyl dihydrosecoxyloganin tetraacetate (17) m.p. 134-6° obtained from 3,4-dihydrosecologanin tetraacetate by oxidation and methylation[8], which avoids the necessity for hydrolysis of the nitrile. At present the overall yield from secologanin is lower than *via* the nitrile due to a mediocre yield (*ca.* 50%) in the oxidation of dihydrosecologanin, but recent experiments suggest that this step may be improved.

Since quinine has been synthesised from the methyl ester of dihydromeroquinene[9], the conversion of secologanin into the latter also constituted a formal transformation 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. In particular, retention of the 3,4-vinyl group of secologanin throughout is highly desirable and would establish it as an even more useful precursor for *Cinchona* alkaloids.

Experimental

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on an ETL-NPL automatic polarimeter. UV spectra were recorded in methanol on a Perkin-Elmer 402 spectrometer. IR spectra were recorded in chloroform on a Perkin-Elmer 257 spectrometer. NMR spectra were recorded on Perkin-Elmer R32B (90 MHz) or R12B (60 MHz) spectrometers in $CDCl_3$. Mass spectra were run on AEI MS30 (high resolution) or MS12 (low resolution) spectrometers. Merck silica F254 plates were used for TLC.

3,4-Dihydrosecologanin.

A solution of secologanin (1) (15 g) in water (200 ml) was shaken in a hydrogen atmosphere over 10% Pd/C (1.5g) at room temperature and pressure until uptake of hydrogen ceased (6 hr), filtered through Celite and evaporated under reduced pressure to leave

dihydrosecologanin as a crisp cream froth (14.9g): $[\alpha]_D^{25}$ −120° (MeOH); R_f 0.33 ($CHCl_3$/MeOH 4:1); λ_{max} (MeOH): 238 nm; τ(d_6 – Me_2CO): 0.35 (t, J= 2Hz, H-5), 2.51 (s, H-9), 6.37 (s, MeO_2C); 9.0 (t, J= 7=Hz, H_3-4); m/e 391 (M + 1), 390 (M^+).

3,4-Dihydrosecoxyloganinonitrile tetraacetate (2).

Dihydrosecologanin (14.5 g) and hydroxylamine HCl (3.5 g) were dissolved in pyridine (50 ml) and left at room temperature overnight to form the oxime. A small sample of the product (0.2 g) (R_f 0.27, $CHCl_3$/MeOH 4 : 1) was isolated and treated with β-glucosidase (10 mg) in *p*H5 buffer at 37° overnight to give the aglucone (R_f 0.51, EtOAc): λ_{max}: 238 nm: λ_{max} ($OH^{\ominus}$): 275 nm: ν_{max} : 3610, 3450, 1740 cm^{-1}. M^+243.1105. calc. for $C_{11}H_{17}NO_5$ 243.1107.

To the bulk of the solution acetic anhydride (75 ml) was added and it was again left overnight. After removal of the solvents *in vacuo* and azeotroping with toluene, the residue was taken up in chloroform and percolated through a short column of alumina (Woelm activity III, 30 g.). Evaporation and recrystallisation from methanol afforded the nitrile (2) (13g., 60% yield) m.p. 159 – 160° $[\alpha]_D^{25}$ −121° ($CHCl_3$); R_f 0.30 (cyclohexane/EtOAe 1:1); λ_{max} : 234 nm; ν_{max} : 2240 (CN), 1750 (OAc), 1700, 1640 (OC=C – C=O) cm^{-1}; τ : 2.46 (s, H-9), 4.47 (d, J=6Hz, H-1), 4.9 (m, H-1′, 2′, 3′, 4′), 5.67 (dd, J=12, 6Hz, H-6′a), 5.90 (dd, J=12, 6Hz, H-6′ b), 6.27 (s, CO_2Me), 7.0 (t+fc, J=3Hz, H-7), 7.26 (m, H_2-6), 7.9 – 8.0 (4s, 4AcO, 8.96 (t, J 6Hz, H_3-4). m/e : 555 (M^+) 523, 496, 487, 482, 415, 413, 388, 347, 345, 331, 317, 289, 271, 259, 242, 229, 169, 109; Found: C, 54.0; H, 6.0; N, 2.5. Calc. for $C_{25}H_{33}NO_{13}$: C, 54.1; H, 6.0; N, 2.5.

3,4-Dihydrosecoxyloganinonitrile aglycone (7).

The foregoing product (2) (100 mg) was treated with methanol (5 ml) in which sodium (*ca.* 10 mg) had been dissolved. After 4 hrs a lump of dry ice was added, the solution evaporated, the residue taken up in water [15 ml] and the *p*H adjusted to 5 with acetic acid. β-Glucosidase (10 mg) was then added, the solution incubated at 37° for 18 hrs, and the product (40 mg) isolated by chloroform extraction. R_f 0.17 (hexane/ Et_2O 1:1); λ_{max} : 234 nm; λ_{max} (OH^-) : 270 nm; m/e 225 (M^+).

N-Benzyl-5-ethyl-1,4-dihydro-3-methoxycarbonyl-pyridyl-4(S)-acetonitrile (9).

The aglucone (7) (35) mg was taken up in absolute ethanol (5 ml) and a few drops of benzylamine added. Conversion to a β-aminoacrylate chromophore was monitored from the change in UV absorbance from 234 to 285 nm and was virtually complete after 48 hrs, when the solution was evaporated. TLC examination (cyclohexane/EtOAc 1:1) showed one product (R_f 0.44) together with a trace of starting meterial (R_f 0.39). The residue was taken up in glacial acetic acid (2 ml), left to stand for 3 hrs at room temperature, and the solvent removed in vacuo to give essentially one fluorescent compound which was purified by preparative TLC (R_f 0.50). Spectral data established that the product was the 1,4-dihydropyridine (9) $[\alpha]_D^{25}$ +214° (MeOH); λ_{max} : 225, 345 nm. ν_{max} : 2240, 1687, 1605, 1100 cm^{-1}; τ : 2.65 (d, J=1 Hz, H-9), 2.7 (m, Ph), 4.18 (d, J=2Hz, H-1) 5.10 (s, CH_2-Ph), 6.23 (t, J=5Hz, H-7), 6.32 (s, CO_2Me), 7.30 (dd, J=17, 5Hz, H-6a), 7.57 (dd, J=17, 5Hz, H-6b), 7.93 (dq, J=8, 2Hz, H_2-3), 8.97 (t, J=8Hz, H_3-4); m/e : 296, 270, 2 5, 256 base peak), 240, 226, 197, 180, 165, 150, 134, 106, 91; M^+ 296.1521. Calc. for $C_{18}H_{20}N_2O_2$ 296.1525.

N-Benzyl-5-ethyl-1, 4, 5, 6-tetrahydro-3-methoxycarbonyl-pyridyl-4(S)-acetonitrile (10).

The 1,4-dihydropyridine (9) (6 mg) in methanol (3 ml) was hydrogenated over Adams' catalyst (5 mg) for 72 hrs, when the UV maximum at 345 nm had disappeared. After filtration and evaporation, two isomeric major products (10a, b) R_f 0.21 and 0.25 in the ratio of *ca.* 3:2 were separated by preparative TLC in hexane/ Et_2O 1:1. λ_{max} : 288 nm; m/e : 298 (M^+), 267, 258, 169, 167, 149, 120, 109, 91.

5(R)-Ethyl-1,4,5,6-tetrahydro-3-methylcarbonyl-pyridyl-4(S)-acetonitrile (3).

Dihydrosecoxyloganinonitrile tetraaeetate (2) (11 g) was deacetylated by treatment with 1% methanolic sodium methoxide (50 ml) for 2 hrs, a small lump of solid CO_2 was added and the solution evaporated to dryness. The residue was taken up in *p*H6 aqueous ammonium acetate (500 ml), β-glucosidase (1.1 g) and sodium cyanoborohydride (1.1 g) added, and the solution incubated overnight at 37°. Extraction with chloroform (4×50 ml), drying (Na_2SO_4) and evaporation afforded a straw coloured oil (3.1 g, 75% yield TLC in cyclohexane/EtOAc (1:1) showed to be almost entirely one product R_f 0.28. The compound was identified as the tetrahydropyridine (3) from its spectral data and subsequent reactions: $[\alpha]_D^{25}$ – 130° (MeOH), λ_{max} 280nm ν_{max} : 3465(NH), 2245(CN), 1680, 1630(N-C=C-C=O) cm^{-1}; τ 2.39 (d, J=6Hz, H-9), 5.13 (bs, NH), 6.32 (s, CO_2Me), 6.75 (M, H_2-1), 7.00 (M. H-7), 7.25 (dd, J=17, 5Hz, H-6a), 7.62 (dd, J=17, 4Hz, H-6b), 8.20 (M, H-2), 8.50 (M, H_2-3) 9.00 (t, J=8Hz, H_3-4); m/e 208, 177, 168, 138, 136, 108. M^+ 208.1216. Calc. for $C_{11}H_{16}O_2N_2$ 208.1212

3(R)-Ethylpiperidyl-4(S)-acetonitrile (4a).

A solution of the above tetrahydropyridine (1.9 g) in 3% HCl in aqueous methanol (1:1, 50 ml) was heated under reflux for 2 hrs when the β-aminoacrylate UV absorption at 280 nm had disappeared. Addition of excess $NaBH_4$ and extraction with chloroform afforded dihydromeroquinenonitrile (4a) (1.2g, 85%) ν_{max} : 3450, 3320, 2240 cm^{-1}; m/e 152 (M^+), 151, 125, 123, 112, 97, 95, 83, 81.

Treatment of a portion (0.1 g) with benzoyl chloride/ pyridine gave the benzamide (4b) $[\alpha]_D^{25}$ +21° (MeOH); R_f 0.22 (cyclohexane/EtOAc 1:1); λ_{max} : 243 nm; ν_{max} : 2230 (CN), 1625 (N-CO), 1440 cm^{-1}; τ : 2.65 (s, Ph), 7.68 (bs, H_2-6) 9.1 (H_3-4); m/e 256, 255, 227, 216, 151, 122, 105, 91. M^+ 256.1571. Calc. for $C_{16}H_{20}ON_2$ 256.1576.

3(R)-Ethylpiperidyl-4(S)-acetic acid (dihydromeroquinene) HCl (5).

The above nitrile (4a) (1 g) was heated under reflux in 6MHCl (50 ml) for 4 hrs, when the solution was evaporated to dryness *in vacuo*. Recrystallisation from methanol-ether gave dihydromeroquinene (cincholoipon) HCl (5)[9] m.p. 190-5° (dec.) m/e 171 (M^+–HCl), 170, 112, 110, 83.

Methyl N-benzoyl-3(R)-ethylpiperidyl-4(S)-acetate (6).

Dihydromeroquinene HCl (0.9 g) was treated with a slight excess of benzoyl chloride in pyridine in the usual way, and the crude benzamide in methanol was methylated with excess ethereal diazomethane. After purification by column chromatography on silica (20 g) in hexane/EtOAc methyl N-benzoyldihydromeroquinene (6) was obtained (1.0 g) : $[\alpha]_D^{25}$ 0°(MeOH) ; R_f 0.13 (cyclohexane/EtOAc) ; λ_{max} : 229 nm ; ν_{max} : 1735, 1620 ; τ : 2 65 (s, Ph), 6.35 (s, OCH_3), 7.68 (bs, H_2-6), 9.1 (H_3-4) ; m/e 289, 288, 260, 216, 184, 122, 105, 91. M^+ 289. 1671. Calc. for $C_{16}H_{23}O_3N$ 289.1678.

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