Conversion of Secologanin into Elenolic Acid and 18-Oxayohimban Alkaloids

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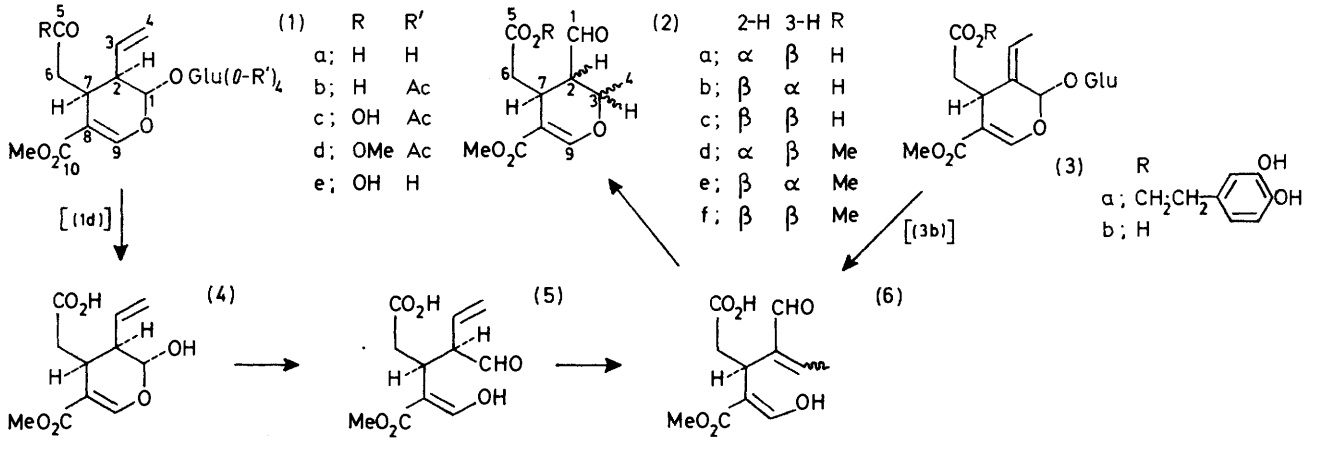
Elenolic acid (2c) has been obtained from secologanin (1a) in accord with its proposed derivation by rearrangement of an aglycone, and converted into ajmalicine (8c), 19-*epi*-ajmalicine (8a), and tetrahydroalstonine (8b).

THE aglycones of some vincoside derivatives undergo a spontaneous rearrangement to a dihydropyran system identical with ring E of the 18-oxayohimbans (8); this reaction has been exploited in syntheses of these alkaloids.[1,2] Partly on the basis of a conversion into ajmalicine (8c), the structure of elenolic acid was recently revised[3] to (2c), which could arise by an analogous rearrangement of an acid aglycone derived from either oleuropein[4] (3a) or secologanin (1a) as indicated in the Scheme. We have examined the feasibility of the latter proposal.

Secologanin tetra-acetate (1b) was oxidised with Jones reagent to secoxyloganin tetra-acetate (1c), $[\alpha]_D^{25}$ −80°, further characterised as the crystalline methyl ester[5] (1d), $[\alpha]_D^{25}$ −107°. Deacetylation of the acid afforded the



SCHEME Glu = β-D-glucosyl

glucoside (1e), $[\alpha]_D^{25}$ −47°, which was cleaved with β-glucosidase in pH 5 buffer during 4 days to yield a mixture of similar rearranged aglycones containing predominantly one compound (*ca.* 80%). N.m.r. data[3]

[1] R. T. Brown and C. L. Chapple, *J.C.S. Chem. Comm.*, 1973, 886; 1974, 740.

[2] R. T. Brown, C. L. Chapple, R. Platt, and H. Spenser, *J.C.S. Chem. Comm.*, 1974, 929.

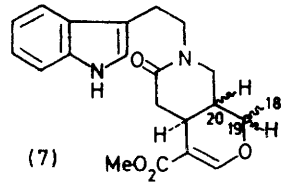
[3] F. A. MacKellar, R. C. Kelly, E. E. van Tamelen, and C. Dorschel, *J. Amer. Chem. Soc.*, 1973, **95**, 7155.

[4] H. Inouye, T. Yoshida, S. Tobita, K. Tanaka, and T. Nishioka, *Tetrahedron*, 1974, **30**, 201.

[5] R. Guarnaccia, L. Botta, and T. J. Coscia, *J. Amer. Chem. Soc.*, 1974, **96**, 7079.

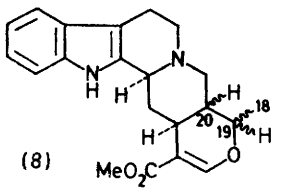
indicated that the major product was elenolic acid (2c): τ 0.38 (CHO), 8.43 (d, Me), and 5.70 [3-H; decoupling showed a *cis* interaction (2.5 Hz) with 2-H *]. Similar treatment of the ester (1d) or methylation with diazomethane afforded a corresponding mixture of methyl esters; again the major component had $J_{2,3}$ 2.5 Hz. Direct comparison (n.m.r., i.r., and mass spectra; t.l.c.) showed that these were identical with authentic samples of 'natural' elenolic acid and methyl elenolate, which also contained similar proportions of the same minor isomers.

The subsequent reaction sequence was similar to that employed previously.[3,7] Condensation of methyl elenolate with tryptamine and reduction gave a mixture of lactams (7), which were cyclised and reduced to afford ajmalicine (8c), 19-*epi*-ajmalicine (8a), and tetrahydroalstonine (8b), identified by comparison with authentic samples. Proportions of the various products depended



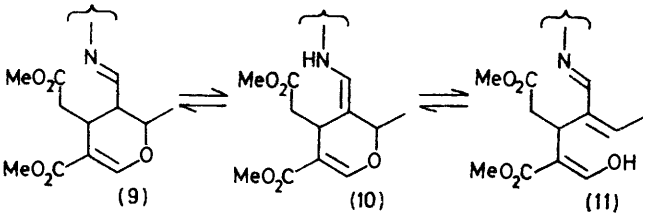
(7)

	19-H	20-H
a;	α	β
b;	β	α
c;	β	β



(8)

	19-H	20-H
a;	α	β
b;	β	α
c;	β	β



(9) (10) (11)

upon the length of time allowed for Schiff base formation: a 3 min reaction gave ajmalicine as the major product [25% from (7)] with 20% of (8a) and 14% of (8b), whereas after 7 h 19-*epi*-ajmalicine (34%) predominated with 10% (8b) and 15% of (8c). The relative amounts of stereoisomeric products do not at any time reflect the ratio of methyl elenolate isomers, and it is apparent that epimerisation takes place during the subsequent reactions. Since one of the lactams, m.p. 186°, $[\alpha]_D^{25}$ +225°, was isolated and converted into 19-*epi*-ajmalicine alone, stereochemical integrity is maintained at this stage. Hence the interconversion can be rationalised as proceeding *via* tautomerisation of the imine (9) to give the enamine (10), retro-Michael ring-opening to give (11), and the reverse sequence.

Since the one isomer of methyl elenolate produces three stereoisomeric products, the reaction is more complex than previously thought. Nevertheless the original[3] stereochemical correlation remains valid since deuterium from C-2 labelled ester is retained in the ajmalicine, which must therefore be derived from molecules reacting before they have an opportunity to equilibrate. As anticipated, the formation of elenolic acid itself occurs by spontaneous rearrangement of an aglycone to an equilibrium mixture in which the most stable isomer predominates.

* We have used the biogenetic numbering system.[6]

[6] *E.g.* A. R. Battersby, S. H. Brown, and T. G. Payne, *Chem. Comm.*, 1970, 827.

EXPERIMENTAL

C.d. and u.v. spectra were recorded for solutions in methanol. N.m.r. spectra were measured with Varian HA- and XL-100 instruments, and mass spectra with A.E.I. MS12 and MS30 instruments. Merck silica (F254) plates were used for t.l.c.

Secoxyloganin Tetra-acetate (1c).—To secologanin [1] tetra-acetate (7.0 g) in ice-cold acetone (40 ml) an excess of Jones reagent was added. After 90 min the excess of oxidant was destroyed with methanol, the solution was evaporated, and the residue was partitioned between chloroform and water. The dried chloroform layer was evaporated to give essentially two compounds, as shown by t.l.c. [$CHCl_3$–MeOH (9 : 1), R_F 0.45 (major) and 0.77 (minor)]. The minor impurity was removed by passing a solution in toluene down a column (30 × 4 cm) of a weakly basic macroreticular ion-exchange resin (Amberlyst A21) followed by elution with methanol to afford the pure secoxyloganin tetra-acetate as a white froth (5.0 g), $[\alpha]_D^{25}$ −80° (MeOH); $\lambda_{max.}$ 234 nm; $\nu_{max.}$ ($CHCl_3$) 3 500, 3 100—2 600, 1 750, 1 710, and 1 630 cm^{-1}; τ ($CDCl_3$) 2.58 (s, 9-H), 4.02—5.02 (8 H, m), 5.70 (m, 6′-H_2), 6.26 (s, OMe), and 7.80—8.00 (4s, 4 OAc). Treatment of a sample in methanol with ethereal diazomethane gave the methyl ester (1d), which crystallised from ethanol as needles, m.p. 145°, $[\alpha]_D^{25}$ −107° ($CHCl_3$) (Found: C, 53.2; H, 6.0. Calc. for $C_{26}H_{34}O_{15}$: C, 43.2; H, 5.9%); $\lambda_{max.}$ 232 nm (log ε 4.22); c.d. $[\theta]_{248}$ −13 500°, $[\theta]_{224}$ −50 000° cm^{-2} $dmol^{-1}$; $\nu_{max.}$ (Nujol) 1 750, 1 710, and 1 630 cm^{-1}; τ ($CDCl_3$) 2.64 (d, $J_{9,7}$ 2 Hz, 9-H), 4.2—5.2 (7 H, m), 6.24 (m, 5′-H), 6.31 and 6.35 (2s, 2 OMe), 6.7—7.0 (m, 7-H), 7.13br (d, 6-H_2), and 7.90—8.09 (4s, 4 OAc).

Elenolic Acid.—Secoxyloganin tetra-acetate (4.3 g) in dry methanol (50 ml) was deacetylated by treatment with an excess of sodium methoxide for 3 h. A small lump of solid carbon dioxide was then added and the solution was evaporated to dryness. Part of the residue (0.2 g) was passed in aqueous solution down a short column of Amberlyte IR 120 acid resin and freeze-dried to give secoxyloganin as an amorphous powder, $[\alpha]_D^{25}$ −47° (MeOH); R_F 0.35 [PhMe–EtOAc–MeOH (1 : 1 : 1) + 1% AcOH]; τ [$(CD_3)_2CO$–D_2O] 2.53 (s, H-9), 4.4—5.1 (8 H, m), 5.26 (d, 6′-H_2), and 6.32 (s, OMe). The remainder was taken up in the minimum of water and the pH was adjusted to 5 by addition of acetic acid before addition of pH 5 citrate–phosphate buffer (40 ml) and β-glucosidase (0.3 g). After purging with nitrogen the solution was incubated at 37 °C for 4 days. The product (1.1 g, 65%) was isolated by extraction with ethyl acetate (5 × 20 ml) and shown to correspond to the same mixture of a major component (2c) (*ca.* 80%) and two minor components (*ca.* 20%) as authentic elenolic acid: R_F 0.37 [$CHCl_3$–MeOH (9 : 1)]; $\lambda_{max.}$ 237 nm (log ε 3.94); c.d. $[\theta]_{223}$ −530 000° cm^{-2} $dmol^{-1}$; $\nu_{max.}$

[7] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1.

($CHCl_3$) 3 630, 3 550—2 500, 1 705, and 1 630 cm^{-1}; τ ($CDCl_3$) 0.38br (s, 1-H), 2.38br (s, 9-H), 5.80 (dq, *J* 2.5 and 6.5 Hz, 3-H), 6.28 (s, OMe), 6.62br (d, *J* 11 Hz, 7-H), 7.04 (dd, *J* 16 and 3 Hz, 6-H_a), 7.33 (m, 2-H), 7.71 (dd, *J* 16 and 11 Hz, 6-H_b), 8.43 (d, *J* 6.5 Hz, 4-Me of major isomer), and 8.52 and 8.58 (d, 4-Me of minor isomers); *m/e* 242, 225, 224, 197, 196, 182, 167, and 153 (Found: M^+, 242.0807. Calc. for $C_{11}H_{14}O_6$: *M*, 242.0790).

Methyl Elenolate.—To a solution of elenolic acid (250 mg) in methanol (5 ml) was added an excess of ethereal diazomethane, destroyed after 35 s by glacial acetic acid. Removal of the solvent, partition between chloroform and water, and evaporation of the organic extract gave methyl elenolate, identical with an authentic sample and consisting of a similar ratio of major (2f) to minor (2d and e) isomers (8 : 1 : 1), $\lambda_{max.}$ 234 nm; $\nu_{max.}$ ($CHCl_3$) 1 760, 1 710, and 1 630 cm^{-1}; τ ($CDCl_3$) 0.37 (d, *J* 1.5 Hz, 1-H), 2.39 (s, 9-H), 5.79 (qd, *J* 6.5 and 2.5 Hz, 3-H), 6.28 and 6.32 (2s, 2 OMe), 6.62br (d, *J* 11, 3, and ? Hz, 7-H), 7.08 (dd, *J* 16 and 3 Hz, 6-H_a), 7.37 (m, 2-H), 7.75 (dd, *J* 16 and 11 Hz, 6-H_b), 8.44 (d, *J* 6.5 Hz, 4-Me of major isomer), and 8.59 and 8.63 (4-Me of minor isomers); *m/e* 256, 242, 225, 224, 196, 182, 167, 163, and 153 (Found: M^+, 256.0920. Calc. for $C_{12}H_{16}O_6$: *M*, 256.0946).

Formation of the Lactams (7).—This reaction was repeated on several occasions with condensation times varying from 3 min to 7 h; the following is typical of the general procedure. A mixture of tryptamine (195 mg) and methyl elenolate (280 mg) in dry benzene (3 ml) was left for 30 min after initial warming on a steam-bath. The solution was evaporated *in vacuo*, and the residue taken up in methanol and treated with sodium borohydride (0.3 g) for 20 min. The excess of hydride was destroyed with acid, the methanol was largely removed, ethyl acetate (20 ml) was added, and the solution was washed with 10% hydrochloric acid (4 × 20 ml) followed by aqueous sodium carbonate (20 ml). Evaporation and t.l.c. in ethyl acetate gave a mixture of isomeric lactams (75 mg). Five recrystallisations from methanol afforded the pure lactam (7a), m.p. 186°, $[\alpha]_D^{25}$ +225° ($CHCl_3$); $\lambda_{max.}$ 226, 283, and 291 nm; $\nu_{max.}$ ($CHCl_3$) 3 480, 1 700, and 1 630 cm^{-1}; τ [$(CD_3)_2$-CO] −0.02br (s, NH), 2.3—3.1 (6 H, m), 6.25 (dq, *J* 10 and 6.5 Hz, 19-H), 6.36 (s, OMe), and 8.84 (d, *J* 6.5 Hz, 18-Me) *m/e* 368, 337, 238, 226, 143 (base), and 130 (Found: M^+, 368.1737. Calc. for $C_{21}H_{24}N_2O_4$: *M*, 368.1735). The lactam (7c) had τ 5.56 (dq, *J* 6.5 and 4 Hz, 19-H) and 8.97 (d, *J* 6.5, 18-Me).

Conversion of Lactams into Alkaloids.—Phosphoryl chloride (640 μl) was added to a solution of the lactams (36 mg) in dry benzene; the mixture was refluxed for 1.5 h and then evaporated to dryness *in vacuo*. The residue was taken up in methanol and reduced with sodium borohydride, and the product was isolated in the usual way. Preparative t.l.c. in cyclohexane–ethyl acetate (1 : 1) afforded ajmalicine (8c) (5 mg, 14%), m.p. 252—253°, $[\alpha]_D^{25}$ −63° ($CHCl_3$); tetrahydroalstonine (8b) (6 mg, 17%), $[\alpha]_D^{25}$ −116° ($CHCl_3$); and 19-*epi*-ajmalicine (8a) (11 mg, 32%), m.p. 125—133 and 218° (polymorphic), $[\alpha]_D^{25}$ +61° (MeOH), identified by direct comparison with authentic samples (mixed m.p., $[\alpha]_D$, t.l.c., i.r., and n.m.r.).[1,2]

A similar reaction with the lactam (7a) gave only 19-*epi*-ajmalicine.

We thank the S.R.C. and I.C.I. Pharmaceuticals Division for financial support, and Professor E. E. van Tamelen for gifts of elenolic acid and methyl elenolate.

[5/1398 *Received*, 16*th July*, 1975]