A Synthesis of Rosenonolactone and Deoxyrosenonolactone

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Summary Rosenonolactone (I) and deoxyrosenonolactone (V) have been synthesised from isocupressic acid (VI).

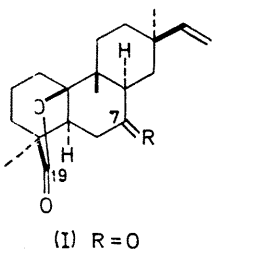
ROSENONOLACTONE (I) was correctly formulated more than ten years ago.[1,2] It was one of the first terpenoids to be subjected to detailed biosynthetic studies,[3,4] whose outcome, supplemented by more recent work,[5–7] establishes a pathway in which the key step is rearrangement of the labdane to the rosane skeleton [possibly as in (II) → (III)[8,9]]. The stages in the biosynthesis at which C-19 and C-7 become oxidised are not defined.

The only synthetic success in this series is Ireland and Mander's recently reported[10] construction of the intermediate (IV). We now describe syntheses, modelled on the biosynthetic pathway, of rosenonolactone (I) and deoxyrosenonolactone (V) from isocupressic acid (VI).

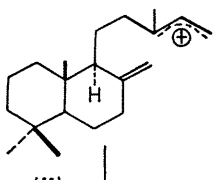
In extension of our earlier syntheses[9] of pimara- and rosa-dienes from labdane precursors, methyl isocupressate[11] (VII) obtained in 30% overall yield from methyl agathate (VIII) *via* reduction of the mixed anhydride (IX)† with sodium borohydride] was converted [AcHO–H_2O–H_2SO_4 (83 : 10 : 7); 3 hr./50°] into a mixture (50% yield) of the C-13 epimeric esters (X) and (XI) (1·3 : 1), assignable by n.m.r. and g.l.c., which were separated by preparative t.l.c. ($AgNO_3$–SiO_2). Further acid treatment [HCO_2H–$CHCl_3$ (1 : 1) 90 hr. at reflux] then transformed (XI) into a mixture of products from which (XII) [25% yield from (XI)] was separated by preparative t.l.c. ($AgNO_3$–SiO_2). Hydrolysis [2% KOH/EtOH–H_2O (9 : 1), reflux] afforded (XIII), m.p. 138—140°, also conveniently obtainable as a relay from deoxyrosenonolactone. Acid-catalysed lactonisation (toluene-*p*-sulphonic acid–benzene/reflux) of the olefinic acid (XIII), afforded not deoxyrosenonolactone (V), but the isomer (XIV), m.p. 174—176°, $[\alpha]_D$ — 22°, ν_{max}(CCl_4) 1783 cm.$^{-1}$; τ 4·63 (1H, *m*), 8·87 and 9·05 (each 3H, *s*), 9·02 (6H, *d J* 7Hz). The dihydro-acid (XV) similarly lactonised not to dihydrodeoxyrosenonolactone [dihydro-(V)], but to its C-5 epimer,[1,12] m.p. 124—125°, $[\alpha]_D$ — 21°, ν_{max}(CCl_4) 1778 cm.$^{-1}$.

Lactonisation in the desired sense was effected indirectly in the following manner, which also made it possible to introduce oxygen at C-7.

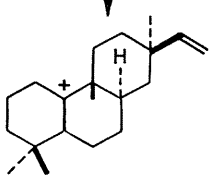
The unsaturated acid (XIII) was converted [*m*-$ClC_6H_4CO_3H$–$CHCl_3$/20°] into the epoxide (XVI; not isolated) and then [BF_3–C_6H_6/0°] into the hydroxy-lactone (XVII), m.p. 182—184° [40%‡ from (XIII)]. Protection of the double bond as the bromohydrin-acetate§ [N.B.S.–H_2O–Me_2CO; Ac_2O–py.; 65%†‡] and dehydration [$SOCl_2$–py. 0°; >90%‡] afforded the Δ^5-lactone (XVIII)§ ν_{max} ($CHCl_3$)



(I) R = O
(V) R = H_2



(II)



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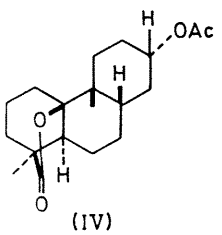
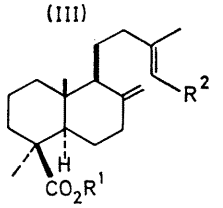
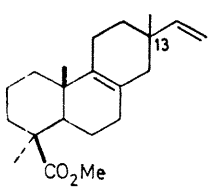


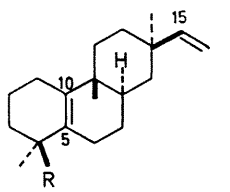
(IV)



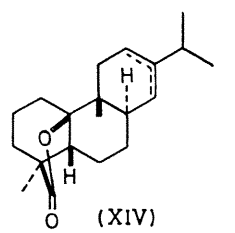
(VI) R^1 = H ; R^2 = CH_2OH
(VII) R^1 = Me; R^2 = CH_2OH
(VIII) R^1 = Me; R^2 = CO_2H
(IX) R^1 = Me; R^2 = CO·O·CO_2Et



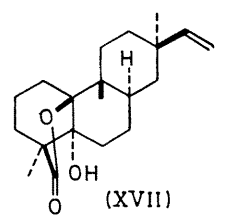
(X) 13β-Me
(XI) 13α-Me



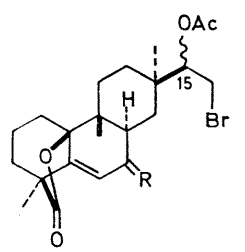
(XII) R = CO_2Me
(XIII) R = CO_2H
(XV) R = CO_2H; 15,16-dihydro
(XVI) R = CO_2H; 5,10-α-oxido



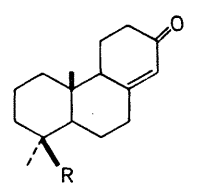
(XIV)



(XVII)



(XVIII) R = H_2
(XIX) R = O



(XX)

† Satisfactory analyses have been obtained for all new compounds and all intermediates have been fully characterised.
‡ Isolated by preparative t.l.c.
§ Mixture of C-15 epimers.

1760, 1740 cm.$^{-1}$; τ 4·74 (1H, *m*). Reduction [Rh–Pt/H_2–AcOH; 20%†‡] and removal of the protecting group [Zn–Cu–EtOH; 78°; 85%‡] afforded deoxyrosenonolactone (V), m.p. 114—116°, $[\alpha]_D$ + 54°, indistinguishable from natural material.

Alternatively (XVIII) was oxidised [$NaCrO_4$–AcOH–Ac_2O; 85%] to the ketone (XIX)‡ ν_{max}($CHCl_3$) 1785, 1745, 1680 cm.$^{-1}$, λ_{max} (EtOH) 234 nm; τ 4·23 (1H, *s*) (also obtainable from rosenonolactone with SeO_2), which was reduced [30% Pd–C/H_2; EtOAc] to 5α,6-dihydro-(XIX)‡ and after removal of the protecting group, afforded rosenonolactone (I), m.p. 210—212°, $[\alpha]_D$ — 121°, indistinguishable from natural material.

A synthesis of cupressic (or isocupressic) acid required to complete the formal total synthesis of rosenono- and deoxyrosenono-lactones could be effected by procedures for which there is close precedent in the literature. For example the readily available tricyclic intermediate (XX; R = CO_2H)[13] should lead to cupressic acid by the route already explored[14] with the enone (XX; R = CH_3).

We are indebted to the Carnegie Trust (T. McC.) and the Salters' Institute of Industrial Chemistry (A.J.A.) for financial support.

(*Received, July 4th*, 1969; *Com.* 982.)

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