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ACETOXYLATION OF STEROIDAL LACTONES BY MEANS OF LEAD TETRAACETATE

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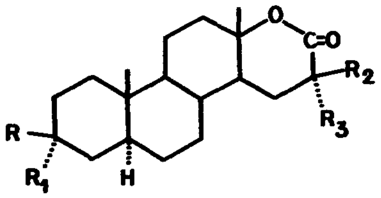
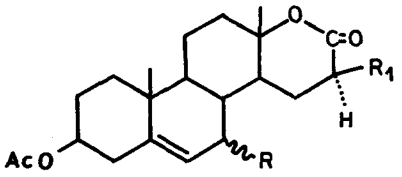
One of the structural features of many bitter principles is the presence of a δ-lactone ring. Some of these compounds differ from one another by the state of oxidation of the molecule as a whole and also by the state of oxidation of the lactone ring (i.e. chaparrin-glaucarubol) (1). However, the correlation of these compounds by direct introduction of an oxygen function into the lactone ring by chemical means represents a great difficulty. Taking into account the versatile reactivity of lead tetraacetate (2), we have investigated the action of this reagent on some steroidal lactones as model substrates. Thus, when 3β-acetoxy-13,17-seco-5α-androstan-13ξ-hydroxy-17-oic acid lactone (Ia) (isoandrololactone acetate) (3) in boiling benzene was treated with 4 moles of lead tetraacetate, a very slow reaction occurs; however, the only product formed after a 150 hours reaction time was the α-acetoxylated lactone (Ib) in a nearly 70% yield. The characteristics of Ib are as follows: m.p. 203-206°, $[\alpha]_D$ -47°± 5 (c=1.07 in $CHCl_3$). IR_{KBr} 1775, 1758, 1740, 1250, 1235, 1215 cm^{-1} (4). NMR ($CDCl_3$) δ 0.80 3 H s (C-19), 1.40 3 H s (C-18), 2.01 3 H s (C-3β-OAc), 2.15 3 H s (C-16β-OAc), 4.65 1 H broad (C-3α-H), 5.25 1 H q (C-16α-H)[*] ppm. The following derivatives were prepared in the usual way. Diol Ic: m.p. 225-228°; $[\alpha]_D$ -44° ± 5. IR_{KBr} 3540, 3360, 1755, 1220, 1210 cm^{-1}. Dione Id: m.p. 169-170°; $[\alpha]_D$ -58 ± 5. IR_{KBr} 1758, 1750, 1720, 1230 cm^{-1}. NMR ($CDCl_3$) δ 1.05 3 H s (C-19), 1.48 3 H s (C-18) ppm.





I a $R = OAc$; $R_1 = R_2 = R_3 = H$
b $R = R_2 = OAc$; $R_1 = R_3 = H$
c $R = R_2 = OH$; $R_1 = R_3 = H$
d $R,R_1 = O$; $R_2,R_3 = O$

II a $R = R_1 = H$
b $R = H$; $R_1 = OAc$
c $R = OAc$; $R_1 = H$
d $R = R_1 = OAc$

Similar results were also obtained in the unsaturated Δ^5-series; the acetoxy-lactone IIb has following characteristics: m.p. 183-186°; $[\alpha]_D$ -105 ± 5°. IR_{KBr} 1785, 1760, 1740, 1245, 1235, 1215 cm^{-1}. NMR ($CDCl_3$) 1.01 3 H s (C-19), 1.41 3 H s (C-18), 2.04 3 H s (C-3β-OAc), 2.17 3 H s (C-16β-OAc), 4.55 1 H broad (C-3α-H), 5.40 1 H broad (C-6 H), 5.55 1 H q (C-16α-H)[**] ppm. Upon catalytic hydrogenation, the acetoxy-lactone IIb affords the saturated analogue Ib.

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[*] X portion of the ABX system with $J_{H_{15}H_{16}} \sim 10$ cps (a,a), $J_{H_{15}H_{16}} \sim 6$ cps (a,e).

[**] $J_{H_{15}H_{16}} \sim 10$ cps (a,a), $J_{H_{15}H_{16}} \sim 6$ cps (a,e).

Rigorous proof of configuration at C-16 in both Ib and IIb was not obtained; the relatively high value of the coupling constant of the C-16 methine proton and the vicinal C-15 methylene protons ($J_{\underline{a},\underline{a}} \sim 10$ cps) indicates a trans-diaxial relationship giving rise to the β-equatorial orientation of the acetoxy-group at C-16 (5). The somewhat higher values of the carbonyl IR absorptions are probably due to additional strain introduced by α-substitution which causes some distortion from the ideal geometry of the lactone ring (6).

In the unsaturated Δ^5-series, competitive allylic oxidation also takes place so that two additional products IIc and IId are formed. This reaction pathway, however, offers wider applicability; it can easily be visualized that the cleaved ring D can be reattached at C-7 yielding products closely related to many Simarubacea constituents. The general scope of this stereospecific lactone acetoxylation by means of lead tetraacetate in different solvents and in presence of catalysts is under current investigation.

References and Notes

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4. Where solubility allowed, the IR spectra were taken in $CHCl_3$ giving rise to lower carbonyl frequencies (15-30 cm^{-1}); however, spectra of solutions gave poor resolution of carbonyl absorptions.
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7. All compounds are new and gave satisfactory elemental analyses.