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Removal of One or Both of the Methyl Groups from 4,4-Dimethyl-steroids

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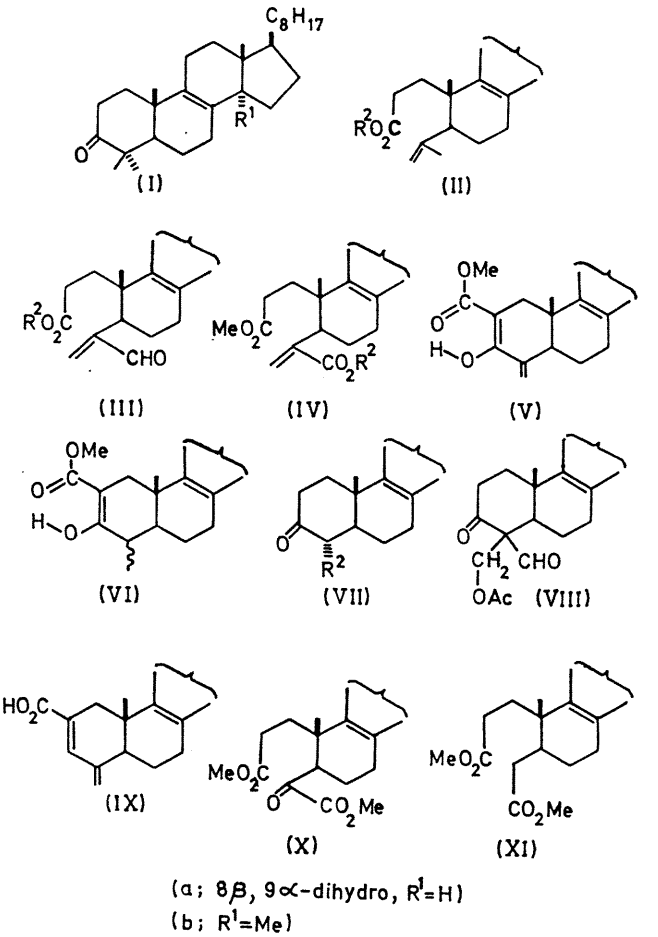
Summary Reaction sequences are described which allow removal of one or both of the C-4 methyl groups from 4,4-dimethyl-steroids without affecting an 8,9-double bond.

FOR some time we have been exploring the possibility of converting the readily available 4-methyl-4-methylene-3,4-seco-triterpene acids (IIb; $R^2 = H$)[1-4] into 4α,14α-dimethyl-steroids and 14α-methyl-steroids. In the former case we were seeking a series of reactions for the modification of ring A of the fungal acids (*e.g.* tumulosic acid[5]) to that present in the triterpenoid antibiotic, fusidic acid,[6] which did not necessitate removal of the 8,9-double bond. This aim has been achieved, except for reduction of a 3-oxo-group to a 3α-hydroxy-group, with a sequence of high yielding steps, proceeding in up to 35% overall yield from the 3-oxo-4,4-dimethyl-compound (I).

For our initial study we chose 4,4-dimethylcholestan-3-one (Ia), which was converted into the methyl ester (IIa; $R^2 = Me$) 90% overall, by the Baeyer–Villiger method of Rosenthal, Niedermeyer, and Fried.[3,7] Selenium dioxide oxidation of (IIa; $R^2 = Me$) in refluxing dioxan resulted in a relatively smooth conversion (70%) into the αβ-unsaturated aldehyde† (IIIa; $R^2 = Me$), m.p. 113—114°, n.m.r. ($CDCl_3$), δ 9·44 (s, C*H*O) 6·26 and 6·12 (narrow multiplets, $>C=CH_2$), which afforded the corresponding carboxylic acid (IVa; $R^2 = H$), m.p. 137—138°, when treated in t-butyl alcohol with selenium dioxide and 90% hydrogen peroxide.[8] Reaction of the acid with phosphorus pentachloride followed by methanol produced the diester (IVa; $R^2 = Me$), m.p. 86—87°, 75% from the aldehyde, which cyclised readily to the β-keto-ester (Va) m.p. 106—107°, 89% on treatment with sodium hydride in tetrahydrofuran. This compound exists entirely in the enol form (Va) as shown by its spectral properties [ν_{max} ($CHCl_3$) 3100—2800, 1657, 1625, and 1588 cm.$^{-1}$; n.m.r. δ 11·98 (s, 1H, exchanged with D_2O), 5·96 and 5·22 (narrow multiplets, $>C=CH_2$)]. Hydrogenation of (Va) in ethyl acetate over Pd–C led to formation of the β-keto-ester (VIa), m.p. 126—127°, which also exists in the enol form as shown [ν_{max} ($CHCl_3$) 3100—2800, 1658,



(a; 8β, 9α-dihydro, R^1=H)
(b; R^1=Me)

† All new compounds analysed correctly, and had i.r., u.v., n.m.r., and mass spectra consistent with the suggested structures.

and 1613 cm.$^{-1}$]. The configuration at C-4 in this compound is as yet unknown. Hydrolysis of (VIa) in methanolic potassium hydroxide at reflux proceeds with decarboxylation (and possibly epimerisation at C-4) to yield 4α-methylcholestan-3-one[9] (VIIa; R^2 = Me), m.p. 118—120°, $[\alpha]_D$ + 25°, 80% from (Va).

No serious difficulties were experienced in carrying out this series of reactions on the lanost-8-en-3-one derivative (IIb; R^2 = H) which was available in 60% yield from (Ib) by the method of Quinkert and Heine.[1] Of particular interest, selenium dioxide oxidation of (IIb; R^2 = Me) afforded the αβ-unsaturated aldehyde [(IIIb; R^2 = Me), m.p. 124—125, 63%, ν_{max} 1728, 1685, and 1617 cm.$^{-1}$, n.m.r., δ 9·51 (s, 1H, C*H*O), 6·15 and 6·30 (multiplets, $\rangle C{=}CH_2$)]. The ester (IVb; R^2 = H), m.p. 80° and the diester (IVb; R^2 = Me), m.p. 97—99°, 44% from (IIIb, R^2 = Me), were readily prepared as above, except that diazomethane was used for methylation. The Dieckmann condensation on (IVb; R^2 = Me) with sodium hydride in benzene yielded the β-keto-ester (Vb), m.p. 120—121°, 80%, ν_{max} 3100—2800, 1664, 1633, and 1590 cm.$^{-1}$ which had spectral properties of the enol form only. Its hydrogenation product (VIb), m.p. 95—97°, ν_{max} 3100—2800, 1659, and 1616 cm.$^{-1}$, also gave no indication from spectra that the keto-form was present at room temperature. Hydrolysis of (VIb) in refluxing methanolic potassium hydroxide produced 4α,14α-dimethylcholest-8-en-3-one (VIIb; R^2 = Me), m.p. 109—111°, 90% from (Vb), the C-4 configuration being assigned by analogy with the formation of (VIIa; R^2 = Me) from (VIa).

It seemed to us that a pathway in the biological demethylation at C-4 could perhaps proceed through the 3,4-seco-compounds *e.g.* (IIb; R^2 = H). A possible sequence was (I) ⟶ (IIb; R^2 = H) ⟶ (IIIb; R^2 = H) ⟶ dihydro-(IIIb; R^2 = H) ⟶ (VIIb; R^2 = Me), the last step occurring by a Claisen-type C-3,C-4 ring closure followed by decarbonylation. In fact a closure of this type has recently been reported by Holker, Jones, and Ramm.[4] Although it is presently thought that biological removal of the C-4 methyl groups takes place in a stepwise manner,[10] it need not necessarily be the only route. A particularly attractive possibility for the removal of both groups appeared to be a sequence of the type (III; R^2 = H) ⟶ (VIII) ⟶ (VII; R^2 = H). An attempt to induce such a ring closure of (IIIa; R^2 = H) m.p. 164—165° formed on alkaline hydrolysis of (IIIa; R^2 = Me), involving initial Michael addition of acetate to the αβ-unsaturated aldehyde moiety, proved to be unsuccessful. Treatment of (IIIa; R^2 = H) with hot acetic anhydride containing sodium acetate gave instead the carboxylic acid (IXa), m.p. 220—222°, λ_{max} 261 nm.

The removal of both C-4 methyl groups was finally achieved in quite a different manner. Oxidation of (IVa; R^2 = Me) by the method of Lemieux and Johnson[11] proceeded smoothly to the α-keto-ester (Xa) m.p. 103—105°. Reduction of this compound to (XIa)[12] was readily achieved by Raney nickel desulphurisation of the ethylene thioacetal derivative (m.p. 132°). The final steps (XIa) ⟶ (VIIa; R^2 = H) have already been reported by Nelson and Schut.[12]

The chemical conversion of a tetracyclic triterpenoid with a *gem*-dimethyl group at C-4 into the corresponding monomethyl compound has not been previously reported;[4] however, a number of publications[13] have been devoted to the removal of both C-4 methyl groups to yield the Δ^4-3-oxo-system.

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