Microbiological Hydroxylation as a Route to 5β-Androstan-1-one

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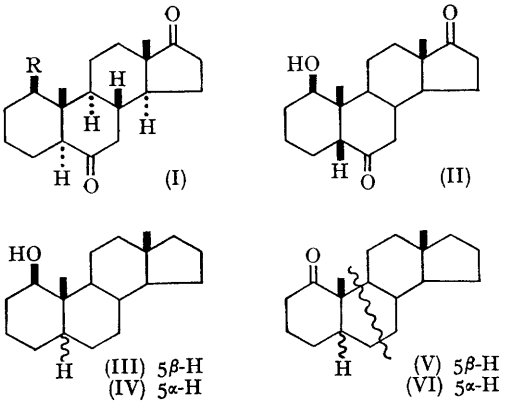
THE methods for obtaining 1-oxo-5α-steroids from *trans*-A/B-3-ketones[1] depend on the latters' propensity for enolisation towards position 2, and are therefore not suitable for the preparation of 1-oxo-5β-compounds. As far as we know, the only 1-oxygenated 5β-steroids previously described are those from the naturally occurring acovenosigenin A, which has been degraded to derivatives of 1-hydroxy- and 1-oxo-5β-etianic acid.[2] During our survey of the microbiological hydroxylation of 3-deoxyandrostanes[3] there emerged a direct route to 5β-androstan-1-one (V) from a readily accessible 5α-steroid.

Incubation of 5α-androstane-6,17-dione[4] (I; R=H) with *Calonectria decora* for two days gave, in 56% yield, the 1β-hydroxy-derivative (I; R=OH). Equilibration in refluxing methanolic potassium hydroxide afforded a mixture of the 1β-hydroxy-5α-diketone (I; R=OH) and the 5β-compound (II) in a ratio of 3:2. [The somewhat greater stability of the 5α-isomer contrasts with the relationship of the 1,6,17-trioxoandrostanes, where the *cis*-A/B-compound is much the more stable.[5]] Huang-Minlon reduction of the 5β-compound (II) was accompanied by some reversion to the *trans*-system, but the mixture of 5β- and 5α-androstan-1β-ols (III and IV) so produced was readily separated by preparative layer chromatography. Oxidation of these alcohols with 8N-chromic acid gave 1-oxo-5β-androstane [(V), m.p. 93–94°, $[\alpha]_D$ − 122°] and 1-oxo-5α-androstane[1] (VI).



N.m.r. examination (see Table) shows that the influence of the 1-oxo-group on the position and

TABLE

τ-Values, C-19 and C-18 protons, of 1-oxoandrostanes

	5α-Compound (VI)		5β-Compound (V)	
	19	18	19	18
CCl_4	8·90	9·32	8·93	9·32
$CDCl_3$	8·83[a]	9·29[b]	8·86[e]	9·32[f]
C_6H_6	9·13[c]	9·31[d]	8·77	9·41
$\Delta\tau$ ($CDCl_3$) ..	−0·38	−0·02	−0·22	+0·01
Δ_1^3	+0·23	−0·01	−0·16	+0·09

$\Delta\tau$ = increase in τ-value when the 1-oxo-group is introduced into the corresponding androstane. $\Delta_1^3 = \tau(C_6H_6) - \tau(CCl_4)$ for a particular signal.

[a–d] Values recorded by D. H. Williams and N. S. Bhacca, *Tetrahedron*, 1965, **21**, 2021, are 8·83[a], 9·31[b], 9·13[c], and 9·31[d].

[e,f] Values calculated from Tables of R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054, are 8·86[e] and 9·31[f].

solvent-dependance of the C-19 protons' signal is characteristic of the 5β- or 5α-configuration. In the mass spectrum of the 5α-ketone (VI) the molecular-ion is the base peak,[6] and among the major fragments is one of *m/e* 124 with an abundance of 79% (relative to $M^+ = 100\%$), which arises by fission at positions 9—10 and then 6—7. With the 5β-ketone (V) the base peak arises from the 124 fragment, and relative to this the molecular-ion has an abundance of 9%.

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