Site-specific Dehydrogenation of Ring D in Steroids

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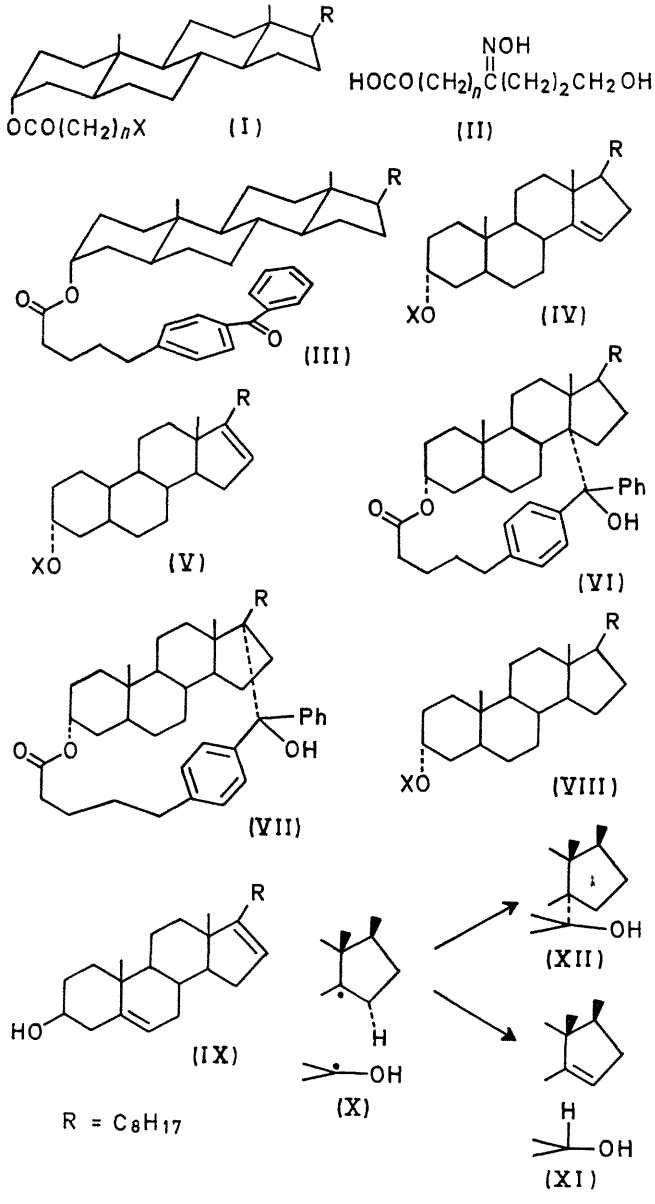
Summary The 3α-cholestanyl ester of 5-(4-benzoylphenyl)-valeric acid underwent direct photochemical hydrogen transfer upon irradiation, thereby providing a simple route to Δ^{14} and Δ^{16} steroids, in 53% yield: a minor proportion of this reaction led to steroidal macrolides.

THE introduction of functional groups at specific, non-activated, positions in steroids and other molecules has been generally limited to those Barton type reactions,[1] which usually involve a six-membered transition state. In contrast to these *in vitro* methods there are many enzymatic systems which can readily carry out such reactions,[2] and in view of the recent report[3] of a successful remote oxidation of a steroid we describe the results of our independent investigation in this area. Taking as a target for initial studies the development of specific means for α-functionalisation, since the absence of *C*-methyl groups confers greater uniformity on this face of the molecule, our approach

has been to attach a reagent at C-3α through an ester linkage, and then to activate this reagent by photochemical, or other means, and thereby produce functionalisation of



the steroid. Thus the alkoxy-radicals (I; X = $-CH_2O\cdot$, n = 6,7) were generated by photolysis of the corresponding nitrite esters (I; X = $-CH_2ONO$, n = 6,7) in benzene solution, the parent alcohols having been prepared by ozonolysis and reduction of the corresponding unsaturated 3α-esters (I; X = $-CH{=}CH_2$, n = 6,7).† Saponification of the ester function showed that 99% of the steroid was recovered unchanged, and examination of the acid structures (II; n = 3,4) so formed proved the operation of a classical Barton reaction with production of a δ-oximino-function.‡ The flexibility of the n-alkane chain rendered that process with a six-membered transition state the overwhelming reaction and we therefore sought more rigid systems to avoid this difficulty. One such system was described by Breslow and his co-workers,[4] namely the use of the benzophenone triplet, and we independently applied this to the cholestanol case. In our system we have used the 5-(4-benzoylphenyl)valeric acid ester of 3α-cholestanol (III). Irradiation of this ester (Pyrex filter, 450 w Hanovia lamp) in benzene solution over 2 h (spectrophotometric disappearance of benzophenone chromophore) led to a mixture of compounds [IV; X = $CO(CH_2)_4C_6H_4CH(OH)Ph$] 44%, [V; X = $CO(CH_2)_4C_6H_4CH(OH)Ph$] 9%, (VI) and (VII) combined yield 25%, as well as some 22% of the corresponding simple reduction product [VIII; X = $CO(CH_2)_4C_6H_4CH(OH)Ph$], separated by chromatography over silica gel. The structures of the esters (IV) and (V) were proved by saponification and inversion at C-3 (chromium trioxide followed by lithium tri-t-butoxyaluminum hydride). The derived 3β-alcohols were shown to contain a trisubstituted, endocyclic, double bond (τ 4·74, 1H, m) and were compared (as methyl ethers) by g.l.c.[5] with authentic samples of all ring B, C, and D trisubstituted 3β-cholestenols. They were identical to Δ^{14}-cholestenol§ and to Δ^{16}-cholestenol in g.l.c. retention time, on t.l.c.,[6] and in their complete m.s. fragmentation patterns.¶ The authentic sample of Δ^{16}-3β-cholestenol was obtained from 3β-hydroxycholesta-5,16-diene (IX)[7] by removal of the Δ^5 double bond through the ring A enone (sequential Oppenauer oxidation, lithium in ammonia reduction, and lithium tri-t-butoxyaluminum hydride).

The macrolides (VI) and (VII) were identified by spectral properties, conversion (lead tetra-acetate in benzene,[8] saponification, and inversion at C-3 as before into $\Delta^{8(14)}$, Δ^{14}-, and Δ^{16}-3β-cholestenols, and comparison with authentic specimens (combined g.l.c.–m.s.)¶. The precursor of the $\Delta^{8(14)}$ and Δ^{14} products is the 14α-bonded macrolide (VI) 16%, and that of the Δ^{16} compound probably the 17α-bonded substance (VII) 8%, since the 17α-hydrogen is tertiary and therefore more labile to hydrogen abstraction than the alternative 16α-atom. A blank experiment which involved irradiation of a mixture of benzophenone and 3α-cholestanyl acetate gave no specific dehydrogenation of the steroidal system thereby proving these effects are truly intramolecular in character.

Our results differ from those earlier reported[3] in the preponderance of dehydrogenation, not previously noted, over macrolide formation. We attribute this to the incorporation of two extra carbon atoms in the linking carbon chain. Thus after initial hydrogen transfer to the ketyl,[9] as (X), the extra length of the valeric chain enables the second hydrogen transfer step (XI), to proceed more rapidly than macrolide formation (XII). The predominance of 14-α attack is both the result of more favoured steric relationships in the abstraction transition state and the known[10] sensitivity of this site for radical abstraction.

† All new compounds have satisfactory analytical and spectral data.

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§ We thank Dr. R. B. Clayton for an authentic sample of Δ^{14}-3β-cholestenol.

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This reaction thereby provides a reasonably practical route to unsaturated ring D steroids.

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