A Novel Route to D-Homoandrostane Derivatives, Including New Methods for the Preparation and Reduction of Hydroxy-azides

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Summary The sequence: oxiran (VI) → hydroxy-azide (VII) → hydroxy-amine (III) → ketone, using novel reaction conditions, provides a convenient general route for the preparation of D-homo-steroids.

D-HOMOANDROSTAN-17a-ONES (IV) have been prepared from androstan-17-ones (I) *via* the cyanohydrin (II).[1] Reduction of the latter to the hydroxy-amine (III), followed by reaction with nitrous acid, gives a mixture of D-homo-17a-one (IV) and -17-one (V) (ratio *ca.* 6 : 1), separable by chromatography. Disadvantages of this route, especially as a large-scale process, include the hazardous nature of hydrogen cyanide, the frequently unfavourable equilibrium constant for cyanohydrin formation,[2] poor reproducibility if the cyanohydrin is reduced catalytically,[1] and the formation of insoluble hydroxy-amine–aluminium complexes if

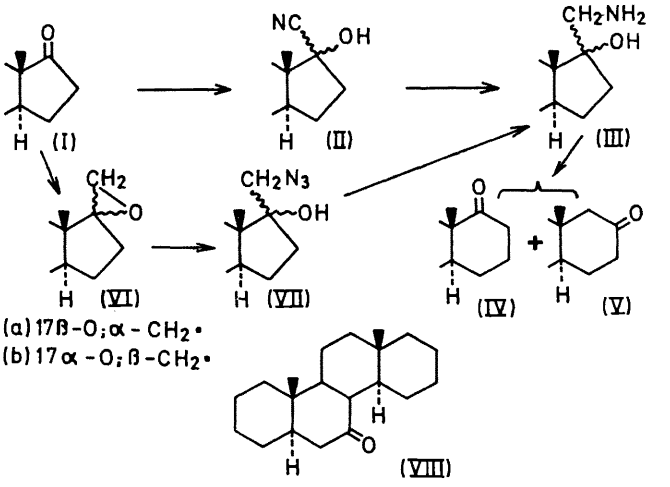
lithium aluminium hydride is used as the reducing agent.[3]

We report a simple reaction sequence which circumvents all these disadvantages. The 17-ketone (I) is converted in virtually quantitative yield into the oxiran (VIa) by means of dimethylsulphonium methylide,[4] or more conveniently into a mixture of the epimeric oxirans (VIa) and (VIb) by dimethyloxysulphonium methylide.[5] The oxirans (VI) are transformed in very high yield into the hydroxy-azides (ν_{max} 2100 cm^{-1}) (VII), by treatment with sodium azide in boiling dimethylformamide containing boric acid as catalyst (*ca.* 3 hr. under reflux). Other reaction conditions, especially stronger acid catalysis, gave large amounts of by-products without incorporating azide.

Attempts to reduce the azido-group with lithium aluminium hydride gave the insoluble aluminium complexes noted above, although sodium or lithium borohydride[6] in refluxing propan-2-ol gave slow formation of the hydroxy-amine (40% after 18 hr.) without problems in isolation. We find, however, that treatment of the crude hydroxy-azides with zinc and hydrochloric acid in acetone, or better with an acidic solution of chromous chloride in aqueous acetone, causes rapid evolution of nitrogen and gives the hydroxy-amine (III) in high yield. These reducing agents for azides do not appear to have been described previously. The reaction seems to be a general one, for conversion of azides into amines.

Traces of non-basic by-products are conveniently extracted from the resulting aqueous-acidic solution of the amine by addition of water and ether, and the amine salt solution can then be treated directly with aqueous sodium nitrite to afford the usual 6 : 1 mixture of D-homo-ketones (IV) and (V), in over-all yields from 17-ketone as high as 70%.

The process described here should have wide applicability for ring-enlargement whenever the oxiran can be prepared, for the azidolysis and reduction steps are mild and specific. Reaction conditions are not critical, excess of reagents being used at each stage. 3β-Acetoxy-D-homo-androst-5-en-17a-one ("D-homo-dehydroepiandrosterone acetate")[3] is directly available without the serious complications of the older route. We were able to prepare D-homo-5α-androstan-7-one (VIII) (m.p. 107—110°, ν_{max} 1704 cm^{-1}) by expanding ring D in 7β-hydroxy-5α-androstan-17-one, followed by Huang-Minlon reduction of the mixed ring-D ketones, and oxidation of the 7β-hydroxy-group. The cyanohydrin route failed completely here because of a very unfavourable ketone ⇌ cyanohydrin equilibrium. A full report of this work and related studies involving the oxirans (VI) will be published shortly.



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