Backbone Rearrangements of Androst-5-ene and D-Homoandrost-5-ene: A Novel Racemisation

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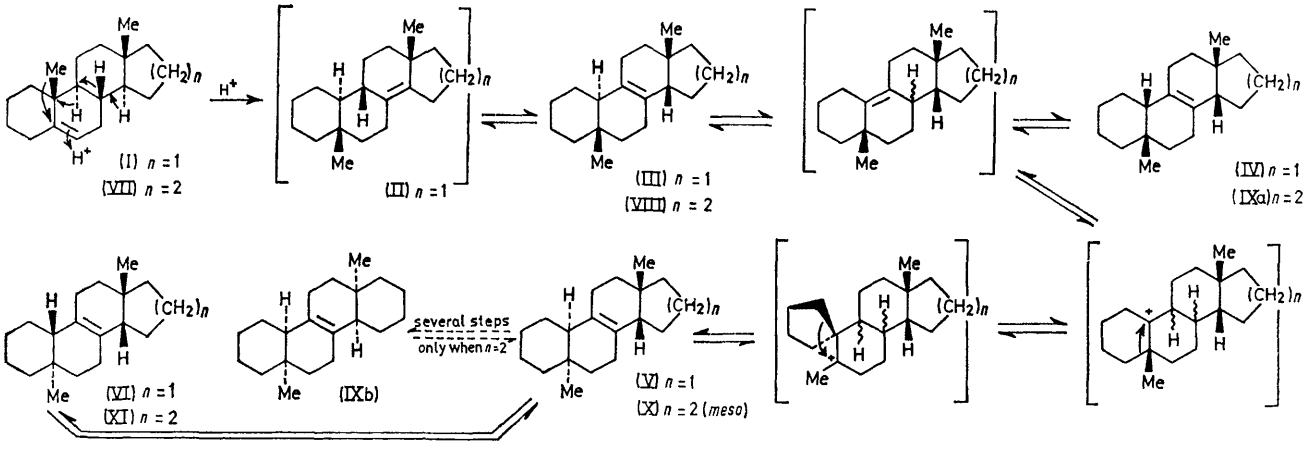
Summary The title compounds rearrange under acidic conditions to give mixtures of 8(9)-enes; equilibration of configurations at C-5, C-10, C-13, and C-14 in the D-homo-compound leads to complete loss of optical activity.

BACKBONE rearrangements have become well-known in the cholestane series,[1,2] and also in androstane[3,4] and pregnane[5] derivatives having suitable functional groups at C-17 or C-20, respectively. Androst-5-ene (I) is reported, without substantiating evidence, to give the partially-rearranged 8(14)-ene (II).[3] Recognition[2] that suitable acidic media permit thermodynamic equilibration of such olefinic steroids prompted us to examine the rearrangements of androst-5-ene and its D-homo-analogue, to determine the preferred location of the unsaturated bond in the absence (a) of a C-17 substituent,[3] and (b) of initial strain at the junction of rings C and D.[1,3]

In acetic acid with *toluene-p*-sulphonic acid, at 80°, both olefins rapidly afforded equilibrium mixtures of Δ^4- and Δ^5-isomers, but reflux temperature enforced further sequential rearrangements which were followed by g.l.c. Androst-5-ene (I) afforded in turn the products (III), (IV) and (V), which came to a final equilibrium ratio of *ca.* 10:43:47 [Ethanolic HCl under the conditions used previously[3] gave (III) and (IV), with unreacted Δ^4- and Δ^5-olefins]. Isomer (VI) should also be formed as a minor component, according to the mechanisms outlined, but was not separated from the other isomers.



The 8(9)-olefinic structures follow from n.m.r. and u.v. spectra, showing tetra-substituted olefinic bonds so placed as to exert no large deshielding on either of the angular methyl groups (contrast the effects of $\Delta^{8(14)}$- or $\Delta^{9(10)}$-unsaturation[6]). Oxidative cleavage of olefins (III) and (IV) [either OsO_4 followed by $Pb(OAc)_4$ or RuO_4 in a single step] gave the corresponding 8,9-seco-8,9-diketones, ν_{max} 1710 cm^{-1} ($\Delta^{8(14)}$-unsaturation would have given two i.r. bands, at *ca.* 1710 and 1740 cm^{-1}). Allylic oxidation of the olefin (IV) with chromic acid gave the 8-ene-7,11-dione (λ_{max} 270 nm; ϵ 5200) and a lesser fraction containing the 8-en-7-one and 8-en-11-one (λ_{max} 252 nm; ϵ 7600). Configurations

at C-5, C-10, and C-14 in the olefins follow from n.m.r. data, supported by analogy with similar olefins in the D-homo-series (see below).

D-Homoandrost-5-ene (VII) rearranged through a series of isomers with g.l.c., n.m.r., and u.v. characteristics very similar to those from androst-5-ene, but with ultimate loss of all optical activity in the product mixture. The skeletal symmetry of the partially-rearranged D-homo structures permits racemization of the isomers (VIII), (IX), and (XI) under the experimental conditions [(IXa) and (IXb), for example are enantiomeric]. The *meso*-isomer (X), the third to appear (g.l.c.), could readily be crystallised from mixtures containing it (all other products were gums), and was optically inactive ($[\alpha]_D$, and c.d. down to 190 nm), whether isolated after partial or complete equilibration. Isomer (IX), however, was optically active when isolated (preparative g.l.c.) after only brief reaction (3/4 h), but was devoid of optical activity when isolated from an equilibrated mixture (1 week). The existence of (IX) as an enantiomeric pair in equilibrium with the *meso*-compound (X) can reasonably be explained only on the basis of the structures shown.

Dreiding models of the various 8(9)-enes show the *cis*-fusion of two six-membered rings to be the more stable, in lacking one "skew-butane" interaction (*e.g.* between 1α and 11α-H), relative to the *trans*-fused isomers in this series. A likely mechanism inverting *both* centres at a ring junction is illustrated. Clearly equilibration takes between all those isomeric structures accessible through a sequence of relatively unstrained tertiary carbonium ions. Racemisation is apparently prevented in the ordinary androstane series by the strain implicit in a C-14 spiro-cyclobutane intermediate, which would be required to invert the configuration at C-13.

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