Methyl Migration in the Rearrangement of a 13-Isosteroid

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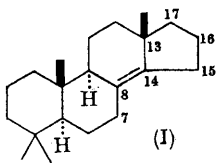
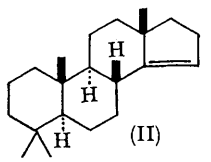
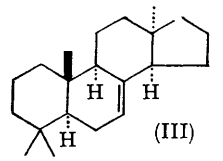
THE acid-catalysed rearrangement of steroidal olefins and dienes, unsaturated in rings B and C, to products unsaturated in ring D, is well known, and has found application in the synthesis of both di-[1,2] and tri-terpenes.[3] For example, 4,4-dimethyl-androst-8(14)-ene (I) is smoothly converted by hydrogen chloride in the presence of palladium–charcoal catalyst to the Δ^{14}-isomer (II).[1] We report that this simple double-bond migration does not take place in the 13α-steroid system, but that instead the 13α-methyl group undergoes a 1,2-shift to C-14. Thus 4,4-dimethyl-13α-androst-7-ene


(I)


(II)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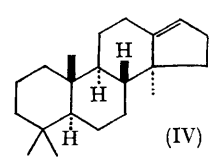

(IV)

(III) is converted under conditions similar to the above but more slowly to a mixture from which the 14α-methyl-18-nor-derivative (IV) can be isolated in 51% yield. A second acid treatment of the residue after separation of (IV) yields further quantities of the rearranged olefin. Since (III) is itself readily available by photoepimerisation[4] and Wolff–Kishner reduction of 4,4-dimethylandrost-7-en-17-one, the reaction provides a convenient and stereospecific route to the novel 14α-methyl-18-norsteroid system.

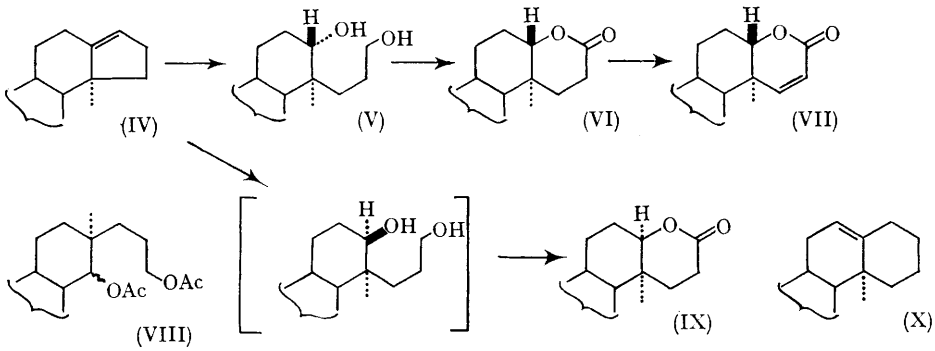
Structure (IV) is assigned to the rearrangement product on the following evidence. The double bond is trisubstituted (τ, 4·96 p.p.m.). Ozonolysis of (IV) and reduction of the ozonide with lithium aluminium hydride yielded a mixture of two epimeric diols, (*cf.* ref. 1), of which the major and more polar component (V) could be separated in 41% yield. The diacetate showed the C-13 proton as a quartet (τ 5·34 p.p.m., splittings 4 and 11 c./sec.), unchanged at 60 and 100 Mc./sec., in deuterochloroform and in benzene, and over a temperature range of 20—100°. These observations are not consistent with structures such as (VIII), which would arise from cleavage of an unrearranged Δ^{14}-olefin.

Lactone (IX) showed the C-13 proton as a poorly resolved triplet (τ 5·96 p.p.m., band width 6 c./sec.), thus confirming on the grounds of coupling constants[5] and chemical shifts[6] the stereochemical assignments at C-13 both in the lactones and their precursors. Furthermore, both lactones gave o.r.d. curves in agreement with prediction.[7]

Dehydrogenation[8] of the lactone (VI) with dichlorodicyanobenzoquinone gave the dehydrolactone (VII) (τ 4·14 and 3·01 p.p.m., one proton doublets, *J* 10 c./sec., C-15 and C-16 protons). The formation of a disubstituted olefin in this reaction eliminates the alternative structure (X) for the initial rearrangement product.

When the Δ^{7}-olefin (III), tetradeuteriated at C-16 and C-17 (58% deuteriation by mass spectrometry), was isomerised, nearly half the deuterium was lost in the product (IV). Thus both deuterium atoms at C-17 are largely eliminated during the isomerisation reaction, and the remaining deuterium is adjacent to the olefinic proton (τ 4·96 p.p.m., width at half height 3·0 c./sec., *cf.* undeuteriated (IV), width at half height 5·0 c./sec.).

Analogy for the rearrangement of (III) to (IV) is found in the conversion of euphenyl acetate to isoeuphenyl acetate,[9] which may be a concerted

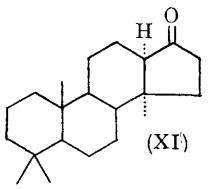

(IV) (V) (VI) (VII) (VIII) (IX) (X)

Manganese dioxide oxidation[1] of the diol (V) yielded the lactone (VI) (84%, τ 6·15 p.p.m., splittings 4 and 11 c./sec.). Similar oxidation of the mixed diols remaining after separation of (V) gave a mixture of lactones from which both (VI) and its C-13 epimer (IX) could be isolated.

process; it is probable that in our case the $\Delta^{8(14)}$-isomer of (III) is an intermediate in the reaction. In the $\Delta^{8(14)}$-isomer of (III), ring c occupies a boat or a half-boat conformation in which the C-13 methyl group takes on a quasi-axial orientation favourable for migration. Protonation at C-8 on

the β-face of the molecule then allows concerted rearrangement with formation of the stable all-*trans* steroid backbone in the product (IV).

The reaction may be contrasted with two examples in which Δ^7-tetracyclic triterpenes are converted into Δ^{14}-olefins *without* migration of the adjacent 13α-methyl group. However, these reactions were effected by chromic acid oxidation[10] or by the action of boron trifluoride on the 7,8-epoxide,[11] and have apparently not been observed in simple proton-catalysed reactions. The present rearrangement has potential for the preparation of 18-nor-analogues of the known 14α-methyl-steroid hormones,[12] and also in the synthesis of triterpenes related to lanosterol. Thus in preliminary experiments, the olefin (IV) has been converted *via* the intermediate epoxide to the 17-ketone (XI). Ketone (XI) possesses the necessary function for the re-introduction of the 13β-methyl group and for the elaboration of a variety of side chains at C-17. The problem of retaining unsaturation in rings B and C and other aspects are under investigation.



(XI)

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