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A TRANSANNULAR HOMOLYTIC HYDROGEN SHIFT [1]

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Recently we have shown that oxy radicals generated by thermal decomposition of lead esters produced from steroidal alcohols and lead tetraacetate are in certain cases epimerized at one or both of the α and β carbon atoms by a fragmentation-recombination process. [2]

We now report a further example of this reaction in which the carbon radical produced by fragmentation of an oxy radical is isomerized by a transannular hydrogen shift before recyclisation occurs: Treatment of 3β,20β-diacetoxy-6α-methyl-6β-hydroxy-5α-pregnane [3] (I) with lead tetraacetate in boiling cyclohexane gave a mixture of products from which two isomeric diacetoxy-ethers A (m.p. 165-172°) and B (m.p. 112-114°) could be isolated in yields of approximately 15 and 20 per cent. respectively. Compound A proved to be identical with the previously described 3β,20β-diacetoxy-6α-

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[1] 197th Communication on Steroids; 196th Comm. cf. J. Kalvoda, K. Heusler, G. Anner & A. Wettstein, Helv.Chim.Acta 46, (1963).

[2] J. Kalvoda, K. Heusler, G. Anner & A. Wettstein, (a) Chimia 17, 23 (1963); (b) Helv.Chim.Acta 46, 352 (1963).

[3] K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner & A. Wettstein, Helv.Chim.Acta 45, 2161 (1962).

-methyl-6β,19-oxido-5α-pregnane [3] (VI). Ether B which does not show any hydroxyl or ketonic carbonyl absorption in the I.R. contains, according to its NMR. spectrum, one secondary and three tertiary methyl groups, a ditertiary oxide and only one secondary acetoxy group (at C-20). Because of the tertiary nature of the 3-acetoxy group, the oxide bridge must extend from C-6 to C-3, i.e. be part of a hemiketal-acetate grouping. In agreement with this formulation alkaline hydrolysis produced a 3-keto-6,20-diol (m.p. 181-186°; λ_{CO} = 5.84 μ) which could be reacetylated in 20-position (acetate, m.p. 221-222°; λ_{OH} = 2.70 μ; λ_{CO} = 5.78 and 5.88 μ). On treatment with p-toluene sulphonic acid in hot acetic acid an α,β-unsaturated ketone (m.p. 138-140°; $\varepsilon_{245\ m\mu}$ = 15900) was formed. After hydrolysis (keto-diol, m.p. 216-221°) and mild chromic acid/sulfuric acid oxidation it gave a diketone (m.p. 156-158°) which was stable to further acid treatment and different from but isomeric with both 6α- and 6β-methyl-progesterone as well as 6α-methyl-17α-progesterone.[4] The UV., IR. and NMR. data ($\varepsilon_{245\ m\mu}$ = 14500; λ_{CO} = 5.88 and 6.01 μ; methyl ketone, 2 tertiary, 1 secondary methyl group) were inconsistent with a structurally rearranged carbon skeleton, but suggested a stereoisomer of the known 6-methyl-progesterones, the isomerized center being most probably C-10. The formulation of the final product as 6α-methyl-10α-progesterone is consistent with the physical data and further supported by

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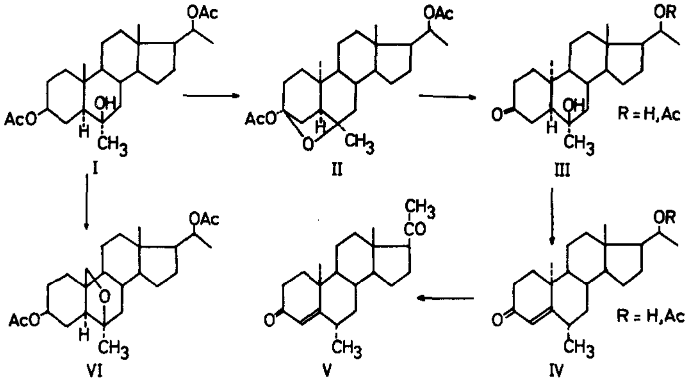
[4] D. Burn, B. Ellis, V. Petrov, I.A. Stuart-Webb & D.M. Williamson, J.chem.Soc. **1957**, 4092.

the typical shift in optical rotation (M_D 6α-methyl-progesterone - M_D 6α-methyl-10α-progesterone = + 950; corresponding value in the testosterone-O-acetate series [5]: + 1035).

The reactions described are thus formulated as follows:



It is assumed that the reaction I ⟶ II involves formation of the 6-oxy radical, cleavage of the 5,6-bond with formation of a methyl ketone grouping and a C-5 carbon radical, *a transannular homolytic hydrogen shift* from C-1 to C-5 and rotation of ring A around the C-9, C-10 axis. This leads to inversion of the configurations at C-3 and C-10.

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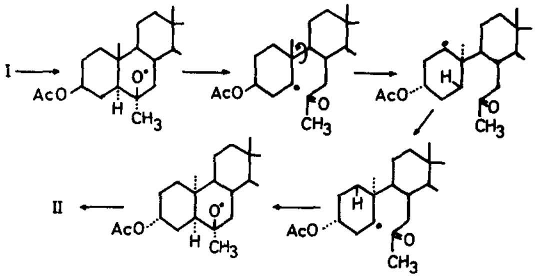
[5] R. Wenger, H. Dutler, H. Wehrli, K. Schaffner & O. Jeger, *Helv.Chim.Acta* **45**, 2420 (1962).



In view of the close structural similarity of the two carbon radicals involved in the above isomerisation a substantial difference in free energy does not seem to be a prerequisite for the hydrogen transfer reaction. It is clear that similar homolytic hydrogen shifts might be expected in other cases, more especially in bridged systems where the stereochemistry for such reactions seems even more favorable.

Finally recyclisation by reaction of the rearranged carbon radical with the 6-carbonyl group gives a 3α-acetoxy-6α-methyl-6β-oxy-5α,10α-pregnane radical in which the electron deficient oxygen atom is suitably oriented for abstraction of the 3-hydrogen atom and for ether formation. The above reaction mechanism is further substantiated by the results of the same reaction sequence using a specifically deuterated starting material. Full details will be published in Helvetica Chimica Acta.