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STEROIDS LXXVII. A NOVEL REARRANGEMENT IN AN ALCOHOL-LEAD TETRAACETATE REACTION[1a,b]

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We wish to report the first observation of a 1,2 migration of an alkyl group from carbon to oxygen during the course of a lead tetraacetate-alcohol oxidation. Previous oxidations of this type have yielded either cyclic ethers[2] which are formed by the attack of the activated hydroxyl group on proximate carbon atoms or by cleavage of the bond adjacent to the C-OH bond resulting in the formation of carbonyl compounds.[3]

When 6β-methyl-B-nor-androstane-3β,5β,17β-triol,3,17-diacetate[*4] (I, m.p. 90-92°; $[\alpha]_D^{25}$ +45°; n.m.r.: 54 c.p.s. (C-19); 6.0 g.) was heated under reflux in benzene with excess lead tetraacetate in the presence of calcium carbonate for 43 hours, there were isolated, after chromatography on alumina, two crystalline esters, IIa (R = Ac, 40% yield, $C_{23}H_{34}O_5$, m.p. 130-131°; $[\alpha]_D^{25}$ -255°; $\epsilon_{213m\mu}$ 3360; ν_{CS_2} 1730, 1675, 1240 cm.$^{-1}$) and IIIa ($R_1 = R_2 = R_3$ = Ac; 25% yield; $C_{25}H_{38}O_7$; m.p. 161-171°d.; $[\alpha]_D^{25}$ -38.5°). These new substances were given the 5,10 ether structural assignments shown based on the following evidence.

Compound IIa, a diacetate (n.m.r., 6 H- at 123 c.p.s.), was converted

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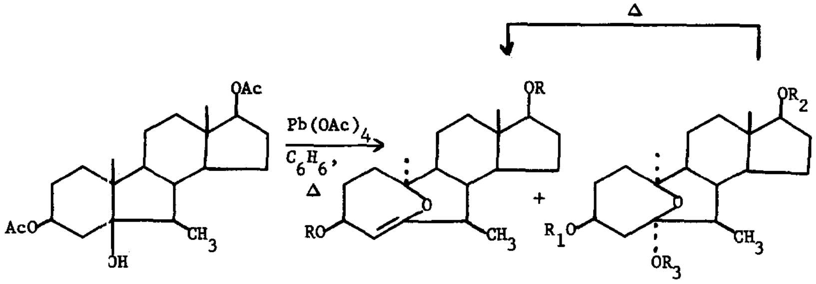
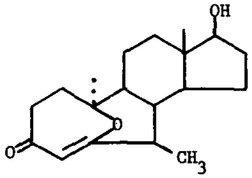
[*] Satisfactory carbon and hydrogen analyses were obtained for this and all other new compounds reported. N.m.r. samples were run on a Varian A-60 spectrometer in deuteriochloroform solution. Absorption bands are stated in c.p.s. downfield from tetramethylsilane internal standard.



I II III

to the diol IIb (R = H; $C_{19}H_{30}O_3$; m.p. 169-171°; $[\alpha]_D^{25}$ -274°) with either potassium carbonate in methanol-water or with lithium aluminum hydride. Compounds IIa and IIb each showed a characteristic enol ether band at 1675 and 1670 cm.$^{-1}$, respectively.

Compound IIb was also shown to be an allylic alcohol by its selective oxidation to the α,β-unsaturated ketone IV ($C_{19}H_{28}O_3$; m.p. 154-154.5°; ϵ = 11,800; ν_{KBr} 1635 cm.$^{-1}$) with activated manganese dioxide.



IV

Compound IIIa was a triacetate, (n.m.r., $3C\underline{H}_3CO$- singlets at 122,123 and 126 c.p.s.) showing no hydroxyl absorption in the infrared but a strong ester carbonyl at 1734 cm.$^{-1}$. Mild hydrolysis with potassium carbonate in aqueous methanol yielded the carbonyl free triol IIIb (R_1 = R_2 = R_3 = H, $C_{19}H_{32}O_4$; m.p. 156.5-158°; $[\alpha]_D^{25}$ -25°; ν_{CS_2} 3612, 3570, 3554 cm.$^{-1}$) whose n.m.r. spectrum indicated the presence of two secondary and one tertiary hydroxyl groups (only two $-\overset{|}{C}\underline{H}-OH$ protons centered at 221 and 248 c.p.s.).

This assignment was confirmed by reacetylation of IIIb with acetic anhydride and pyridine which afforded only the 3,17 diacetate IIIc ($R_1 = R_2 =$ Ac, R_3 = H; $C_{23}H_{36}O_6$; m.p. 172-172.5°; $[\alpha]_D^{25}$ -5°; ν_{CS_2} 3580, 1733 $cm.^{-1}$).

In IIIa, the singlet C-19 methyl signal (76 c.p.s.) is deshielded by 22 c.p.s. compared with the corresponding signal in its precursor I; in a similar comparison, the C-6 methyl resonance (doublet, 53 c.p.s., J = 6) is essentially unshifted. These data clearly indicate that the new O-C bond present in IIIa is attached to C-10 rather than to C-6.

The presence of the ketol acetate grouping in IIIa was further confirmed by the mild acid hydrolysis of IIIa to IIIc. Pyrolysis of IIIa at 180° afforded the enol ether IIa in low yield, thus interrelating the two compounds.

We have not investigated the mechanism of this novel reaction in detail. It is generally assumed that the lead tetraacetate-alcohol reaction proceeds via an initial lead alkoxide intermediate, with subsequent homolysis to an alkoxy radical.*[5]

In our case the alkoxy radical intermediate V could cleave to the tertiary radical VI, which after attack on the carbonyl oxygen would form VII, and then proceed either by the loss of hydrogen from C-4 or by combination with an acetoxy radical to form the products IIa and IIIa, respectively. An alternative explanation would involve the direct 1,2 rearrangement of V to VII, etc.

Although a definite conclusion distinguishing between these explanations cannot yet be made, we presently favor the latter, since intermediate

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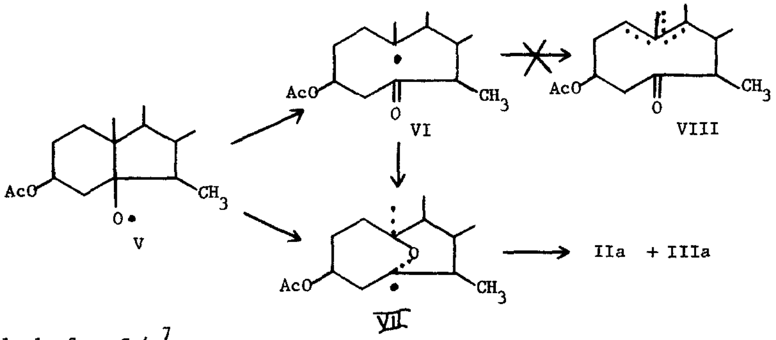
*The detailed nature of the intermediates present in this heterogenious reaction are not known. They may well be complexes involving the lead cation.

VI would be expected either to lose a hydrogen atom from an adjacent carbon (yielding VIII)[*,6] or to abstract a hydrogen atom intramolecularly from C-4.[7]



We failed to observe any products derivable from these processes. Experiments to distinguish between the two possibilities are currently in progress.

The stereochemistry of product IIIa is probably as indicated, involving net retention at C_{10} and inversion at C_5 to form the most stable isomer.[**] A detailed discussion of this point and other aspects of this reaction will be published in our full paper.

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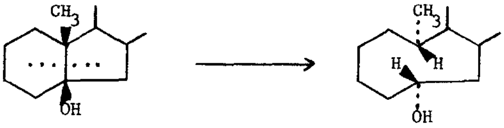
[*] Models of all five of the olefinic ketones VIII could be readily constructed. These compounds would be expected to be stable to the reaction conditions.[6]

[**] The stereochemical assignments of the 5,10 seco compounds have been made with respect to the new nine-membered carbocyclic ring rather than to their precursor. Thus the simple 5,10 cleavage of a compound of structure i with no stereochemical inversions would result in compound ii.



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REFERENCES

1. (a) Paper LXXVI, C. E. Cook, R. C. Corley and M. E. Wall, *Tetrahedron Letters*, 891 (1965); (b) this work was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health under Contract No. SA-43-ph-4351.
2. O. Jeger and collaborators, *Helv. Chim. Acta*, **42**, 1124 (1959), and subsequent papers.
3. M. Amorosa *et al*., *Helv. Chim. Acta* **45**, 2674 (1962).
4. This compound was prepared in 58% overall yield from 5-androstene-3β,17β-diol,3-acetate by an improved method. [M. E. Wall and F. T. Ross, in preparation] See also K. Tanabe and R. Takasaki, Japanese patent No. 10,928 (1964): *C. A.*, **61**, 12063 (1964).
5. K. Heusler and J. Kalvoda, *Ang. Chemie*, Inter. Ed., **3**, 525 (1964).
6. M. L. Mihailovic′, M. Stefanovic′, L. Lorenc, and M. Gašic′, *Tetrahedron Letters*, 1867 (1964).
7. E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publishing Corp., New York, 1954, Chpts. IV and V.