Tetrahedron, 1964, Vol. 20, pp. 2289 to 2294. Pergamon Press Ltd. Printed in Northern Ireland

OPENING OF STEROID RING A BY MEANS OF LEAD TETRAACETATE[1]

M. STEFANOVIĆ, M. GAŠIĆ, LJ. LORENC and M. LJ. MIHAILOVIĆ[2]
Department of Chemistry, Faculty of Sciences
and
Institute of Chemistry, Technology and Metallurgy,
Belgrade, Yugoslavia

(*Received* 22 *June* 1964)

Abstract—The lead tetraacetate oxidation of cholestan-1β-ol and cholestan-1α-ol in benzene solution did not afford cyclic ethers but resulted, in major part, in the opening of ring A with formation of 1,10-seco-aldehydes. In addition, cholestane, cholest-1-ene and cholestan-1-one were also obtained.

Two major reaction courses have been observed[3] in the oxidation of monohydroxylic steroid alcohols with lead tetraacetate in non-polar solvents, with respect to structural and steric factors in the substrate: (a) intramolecular cyclization leading usually to the formation of five-membered cyclic ethers,[4,5] and (b) cleavage of the bond between the carbinol carbon atom and the adjacent carbon atom, affording fragmentation, seco or nor products.[3,5,6]

It was, therefore, of interest to study both these possibilities, i.e. ring closure and fragmentation, as competing reactions on the same compound, in order to determine their ratio and dependence upon structural and steric factors in the substrate. As model molecules for such a study the stereoisomeric cholestan-1β-ol (I) and cholestan-1α-ol (II) were selected. In the case of I, because of the favourable position of and distance between the equatorial 1β-hydroxyl group and the equatorial 11α-hydrogen atom, and in view of the reported[7] facile cyclization of 11α-hydroxy steroids, 1β,11α-ether ring formation might be expected. On the other hand, however, the presence of the quaternary carbon atom C-10, bearing the angular C-19 methyl group, in the β-position to the hydroxyl group, would offer considerable steric hindrance to the suitable approach of the lead reagent for the formation of a six-membered cyclic transition state leading to tetrahydrofuran ring closure, so that the alternate reaction course, i.e. C_1—C_{10} bond fission, would probably outweigh intramolecular cyclization. In the case of II, the position of the axial 1α-hydroxyl group is not favourable to cyclization, and therefore the only possible reaction, unless prior steric rearrangement

[1] Paper III in the series "Reactions with lead tetraacetate." For paper II see M. Lj. Mihailović, M. Stefanović, Lj. Lorenc and M. Gašić, *Tetrahedron Letters* **28**, 1867 (1964),

[2] Full adress: Department of Chemistry, Faculty of Sciences, Studentski trg 16, Post Box 550, Belgrade, Yugoslavia.

[3] For a general survey on homolytic lead tetraacetate reactions see K. Heusler and J. Kalvoda, *Angew. Chem.*, **76** (1964).

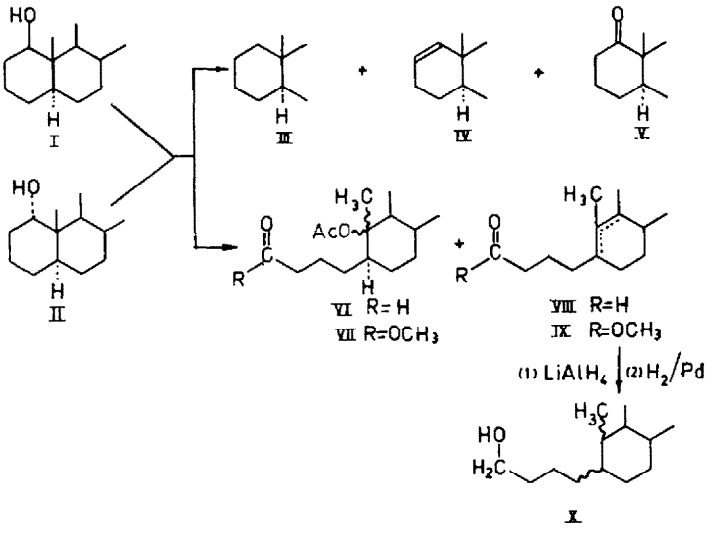
[4] G. Cainelli, M. Lj. Mihailović, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **42**, 1124 (1959).

[5] G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailović, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **44**, 518 (1961), references therein and subsequent papers.

[6] M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailović, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2674 (1962).

[7] J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailović, K. Schaffner and A. Wettstein, *Helv. Chim. Acta* **44**, 186 (1961).

of the C_1—O bond or carbon skeleton occurred,[8,9] would again consist in splitting of the C_1—C_{10} bond to give the same seco products as those expected from the 1β-alcohol (I).



The oxidation of both I and II, which were prepared from 1α,2α-epoxycholestan-3-one[10] according to Djerassi *et al.*,[11] was carried out under the same experimental conditions, i.e. with 1·1 mole of lead tetraacetate per mole of substrate, in boiling benzene and in the presence of anhydrous calcium carbonate. Both alcohols gave oily products, the IR spectra of which were practically identical. The bands at 2680, 1725 and 1250 cm^{-1}, and the positive Tollens test, indicated the presence of aldehyde and acetoxy groups. In order to facilitate chromatographic separation, the reaction mixtures of both alcohols were subjected to further oxidation with silver oxide, followed by esterification of the acid products with diazomethane. Upon separation by chromatography on neutral alumina, in both cases the same two compounds (VII and IX) were isolated in comparable yields, i.e. 20–23% and 14–15%, respectively. These products were obviously derived from the primarily formed 1,10-seco-aldehydes (VI and VIII).

The structure of the acetoxy methyl ester (VII) was established by its IR spectrum (ν_{max} = 1748 (shoulder), 1733, 1253 cm^{-1}) and NMR spectrum (Fig. 1). Besides a singlet at 0·66 ppm (C-18 methyl group) and doublets centered at 0·89 ppm ($J \approx 6$ c/s, C-21 methyl group) and 0·87 ppm ($J \approx 6$ c/s, C-26 and C-27 methyl groups), the signals at 1·13, 1·97 and 3·67 ppm (all singlets) were assigned to the protons of the C-19

[8] If the intermediate oxoalkyl C-radical (XV), leading to the fragmentation products, would recyclize with partial epimerization to the more stable 1β-alkoxy radical (XII), cholestano-1α-ol (II) might also afford the 1β, 11α-oxido compound.[9]

[9] K. Heusler, J. Kalvoda, G. Anner and A. Wettstein, *Helv. Chim. Acta* **46**, 352 (1963); G. B. Spero, J. L. Thompson, W. L. Schneider and F. Kagan, *J. Org. Chem.* **28**, 2225 (1963). See also K. Heusler and J. Kalvoda, *Tetrahedron Letters* No. 16, 1001 (1963); *Helv. Chim. Acta* **46**, 2732 (1963).

[10] P. Striebel and C. Tamm, *Helv. Chim. Acta* **37**, 1094 (1954).

[11] C. Djerassi, D. H. Williams and B. Berkoz, *J. Org. Chem.* **27**, 2205 (1962).

methyl group (δ shifted downfield due to the adjacent acetoxy group), acetoxy methyl group and methoxy methyl group, respectively. The unsaturated methyl ester (IX) (IR, $\nu_{max} = 1750, 1645, 890\ cm^{-1}$) was converted by lithium aluminium hydride reduction followed by catalytic hydrogenation to the saturated 1,10-seco-alcohol (X; IR,

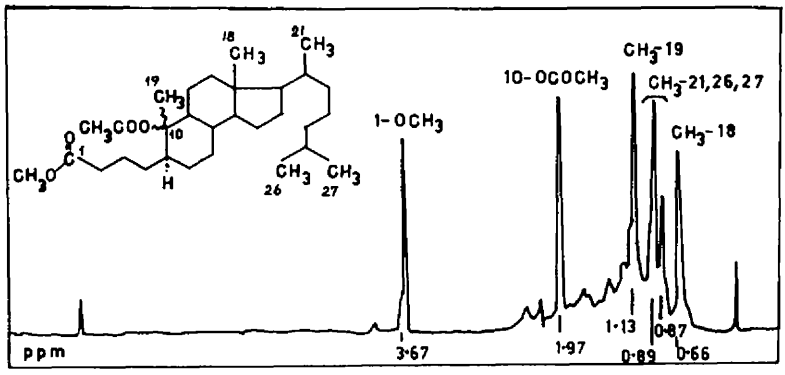


FIG. 1. NMR spectrum of 10ξ-acetoxy-1,10-secocholestan-1-oic acid methyl ester (VII)

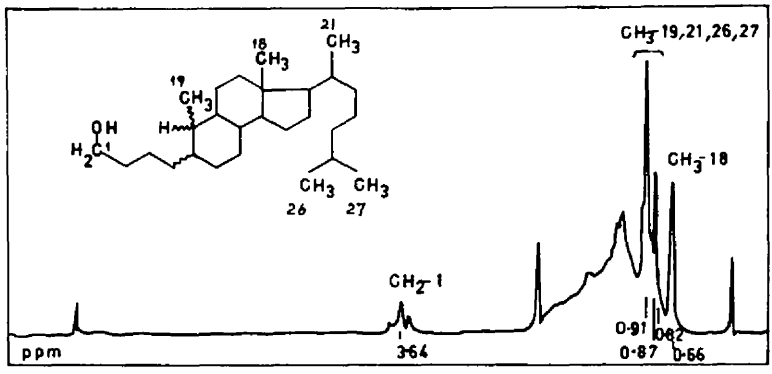


FIG. 2. NMR spectrum of 1,10-secocholestan-1-ol (X)

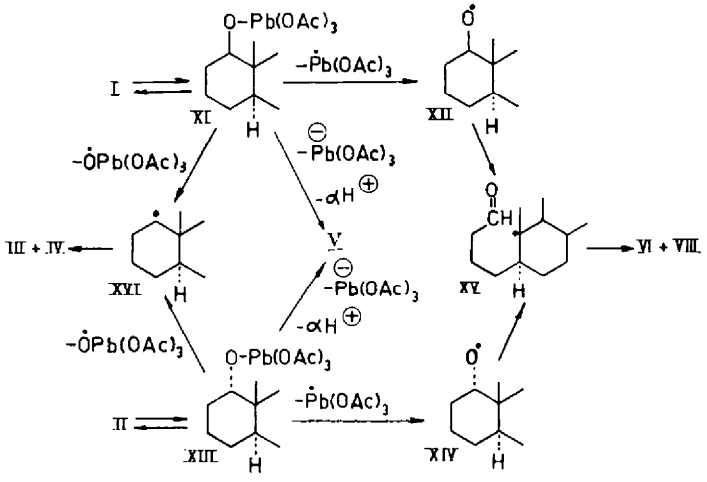
$\nu_{max} = 3330\ cm^{-1}$), the NMR spectrum of which (Fig. 2), besides the usual signals for the C-18 methyl group and methyl groups in the side chain, shows a doublet centered at 0·82 ppm ($J \approx 6$ c/s) ascribed to the protons of the C-19 methyl group, and a complex signal at 3·64 ppm which is due to the methylene protons on the C-1 carbinol carbon atom; because of coupling with protons on C-2, this signal appears as a triplet.

In addition to the 1,10-seco-aldehydes (VI and VIII), both I and II afforded upon lead tetraacetate oxidation cholestane (III; 3–6% yield), cholest-1-ene (IV; small amount) and cholestan-1-one (V; 7–10% yield).

Assuming that the first step of the lead tetraacetate oxidation of alcohols consists in the reversible alcoholysis of the tetravalent lead reagent,[3] the alkoxy lead triacetates[12,13] (XI and XII) can subsequently undergo either O—Pb or C—O homolytic bond

[12] R. Criegee, L. Kraft and B. Rank, *Liebig's Ann.* 507, 159 (1933).
[13] Cf. R. Criegee, *Angew. Chem.* **70**, 173 (1958).

cleavage to give the intermediate alkoxy (XII and XIV) or alkyl (XVI) radicals. When 1,5 (or 1,6) hydrogen transfer from carbon to oxygen in the alkoxy radical (XII, XIV) followed by cyclization is hindered or completely prevented for structural or/and steric reasons, the alkoxy radicals (XII and XIV) may undergo fragmentation[3,14] of the carbinol carbon–β-carbon bond to afford a carbonyl group and carbon radical, particularly when the carbon radical is heavily substituted or stabilized by other factors.[3,5,6] In the case of I and II both the carbonyl group and carbon radical are on the same molecule (XV) and further reaction of this species would lead to the final 1,10-seco-aldehydes (VI and VIII). Compounds III and IV are probably produced from the alkyl C-radical (XVI),[15] the formation of which may be envisaged as resulting from homolytic cleavage of the C—O bond in the alkoxides XI and XIII.[1,16] Heterolytic fission of the O—Pb bond in the complex alkoxy intermediates XI and XIII, with concerted or subsequent elimination of the α-proton, is the most probable pathway leading to V,[13,17,18] although another possible route would be via the alkoxy radicals XII and XIV, followed by oxidation to the corresponding oxonium ions and stabilization by loss of an α-proton.[19]



Although the difference in yields of ketone V obtained from I and II is small (about 3%), the higher yield of V in the case of II may be rationalized in terms of larger energy gain associated with release of steric compression[17] when passing from

[14] Cf. P. Gray and A. Williams, *Chem. Rev.* **59**, 239 (1959).

[15] Neither cholestane (III) nor cholest-l-ene (IV) were formed by heating I or II in benzene solution with acetic acid, calcium carbonate or lead diacetate, i.e. compounds which are present in the lead tetraacetate oxidation.

[16] Similar disproportionation products derived from alkyl C-radicals of type (XVI) were also obtained in the lead tetraacetate oxidation of other steroid alcohols[1] and aliphatic alcohols (to be published).

[17] A. Bowers and E. Denot, *J. Amer. Chem. Soc.* **82**, 4956 (1960).

[18] W. A. Mosher, C. L. Kehr and L. W. Wright, *J. Org. Chem.* **26**, 1044 (1961).

[19] That carbonyl compounds are formed by a heterolytic process rather than by homolytic elimination is substantiated by the fact that lead tetraacetate oxidations of alcohols in polar solvents gave much higher yields of aldehydes or ketones, as compared to reactions which were performed in non-polar solvents (to be published).

the tetrahedral carbinol carbon with a hindered α-hydroxy group to the trigonal carbonyl carbon at C-1, as compared to the same conversion in the less hindered β-hydroxy steroid (I).[20]

The nonformation of cyclic ether from I thus confirms that steric factors associated with the β-carbon atom in the system —C—C—OH are of major importance for the course of the lead tetraacetate oxidation of monohydroxylic alcohols.

EXPERIMENTAL

All m.ps were determined in open capillary tubes and are uncorrected. Optical rotations were measured at 25° in $CHCl_3$, at concentrations of 0·6–1·2%. IR spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer spectrophotometer model 21. NMR spectra were run on a Varian A-60 spectrometer, in $CDCl_3$ solution, using tetramethylsilane as internal standard. For chromatographic separations neutral Merck alumina of activity II[21] was used. The obtained oxidation products, which were previously described in the literature, were identified by comparison of their physical properties (m.p., rotation, IR and NMR spectra) with those of authentic compds, and showed satisfactory analytical data.[22]

Treatment of cholestan-1β-ol (I) *with lead tetraacetate.* Lead tetraacetate (6·0 g), dried *in vacuo* (P_2O_5 and KOH), and 1·5 g anhydrous $CaCO_3$ (dried *in vacuo* over P_2O_5) in 200 ml anhydrous, thiophene-free benzene (dried over Na) were shortly heated under reflux. Upon cooling, 4·8 g I was added and the suspension was heated under reflux with stirring. After 5 hr the starch-iodide test for tetravalent lead was negative, indicating the end of the reaction. The cooled mixture was diluted with ether, filtered through a Celite mat and the insoluble precipitate thoroughly washed with benzene. The combined filtrates were washed with water, $NaHCO_3$ aq and water, and dried ($MgSO_4$). The solvents were evaporated under red. press., leaving 5·0 g pale yellow oil (positive Tollens test; IR, ν_{max} = 2680, 1725 and 1250 cm^{-1}).

This crude reaction product (5 g), dissolved in 80 ml C_2H_5OH, was mixed with a solution containing 3·1 g $AgNO_3$ in 31 ml water, and then treated dropwise and with stirring with a solution of 3·1 g NaOH in 120 ml water. The resulting mixture was stirred for 14 hr at room temp, filtered through a Celite mat and the solid residue washed with water and C_2H_5OH. After removal of C_2H_5OH under red. press., the aqueous filtrate was extracted with ether, and the ethereal solution evaporated to dryness, yielding 1·5 g neutral oily products (neutral fraction). The aqueous alkaline solution was carefully acidified (cooling in ice) with 5% H_2SO_4 aq and extracted with ether. Evaporation of the solvent afforded 2·8 g oily products which were esterified in ether solution by means of diazomethane, in the usual way, to give an oily mixture of esters (ester fraction).

Chromatography of the neutral fraction was carried out on 50 g alumina. Elution with pet. ether (b.p. 40–60°) gave 0·28 g (6%) III, m.p. 78–80°, $[\alpha]_D$ +22°, traces of IV and 0·35 g (7%) V, m.p. 87°, $[\alpha]_D$ +110°. Upon further elution with pet. ether–benzene (4:1 and 1:1) and benzene, 0·43 g (9%) of unchanged I was obtained.

Chromatography of the ester fraction on 70 g alumina, upon elution with pet. ether, furnished 0·72 g (14%) 1,10-*seco*-$\Delta^{5,10(or\ 9,10)}$-*cholesten*-1-*oic acid methyl ester* (IX) as a colourless oil, which was subjected to further purification by molecular distillation. TNM test: intensive yellow; IR, ν_{max} = 1750, 1645, 890 cm^{-1}; $[\alpha]_D$ −8·6°. (Found: C, 80·9; H, 11·8. $C_{28}H_{48}O_2$ requires: C, 80·7; H, 11·6%).

This unsaturated methyl ester (IX) was converted by usual $LiAlH_4$ reduction in ether and subsequent hydrogenation in cyclohexane, in the presence of palladized charcoal (30% Pd), to the saturated alcohol, 1,10-*seco-cholestan*-1-*ol* (X). TNM test: negative; IR, ν_{max} = 3330 cm^{-1}; NMR spectrum: see Fig. 2; $[\alpha]_D$ +17·1°. (Found: C, 83·0; H, 12·7. $C_{27}H_{50}O$ requires: C, 83·0; H, 12·9%).

Further elution of the ester fraction with pet. ether, pet. ether—benzene (in various ratios) and benzene afforded 1·33 g (23%) 10ξ-*acetoxy*-1,10-*secocholestan*-1-*oic acid methyl ester* (VII) as colourless oil, which was purified by molecular distillation. TNM test: negative; IR, ν_{max} = 1748

[20] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955).

[21] H. Brockmann and H. Schodder, *Ber. Dtsch. Chem. Ges.* **74**, 73 (1941).

[22] The microanalyses were performed by Mrs. R. Tasovac and Miss R. Dimitrijević.

(shoulder), 1733, 1253 cm^{-1}; NMR spectrum: see Fig. 1; $[\alpha]_D$ +12·3°. (Found: C, 75·8; H, 10·8. $C_{30}H_{52}O_4$ requires: C, 75·6; H, 11·0%).

Treatment of cholestan-1α-ol (II) *with lead tetraacetate.* Alcohol (II 4·0 g) was oxidized with lead tetraacetate in the same way as I, the reaction being completed after 4 hr. The crude reaction mixture was further oxidized with Ag_2O and then treated as described above. Chromatography of the neutral fraction (1·2 g) gave 120 mg (3%) III, a small amount of IV, 400 mg (10%) of V and 100 mg (2·5%) of unreacted alcohol (II). Chromatography of the ester fraction (2·5 g) afforded 600 mg (15%) of the unsaturated methyl ester (IX) and 970 mg (20%) of the acetoxy methyl ester (VII).