Steroids. CCLXXI.[1] Conversion of a Steroidal 6β-Methyl Ether to a 6α-Formate Ester with Lead Tetraacetate

W. H. W. Lunn[2]

Research Laboratories, Syntex, S. A.,
Apartado 2679, Mexico, D. F., Mexico

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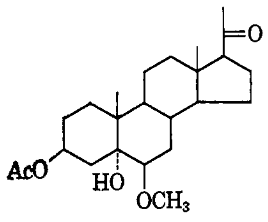
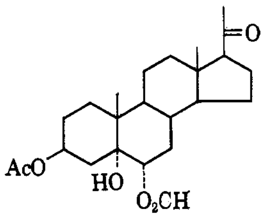
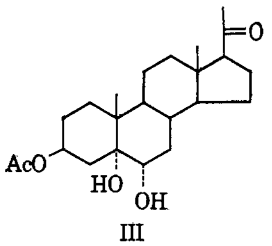
Steroidal 6β,19-oxides have been prepared by treatment of 6β-alcohols with lead tetraacetate.[3] As part of a program designed to define the oxygen-containing functions which will serve as progenitors of such bridges, 3β,5α,6β-trihydroxypregnan-20-one 3β-acetate 6β-methyl ether (I)[4] was refluxed with lead tetraacetate and iodine in benzene. There was obtained a compound judged to contain hydroxy, acetate, and formate groups on the basis of infrared absorption bands at 3450, 1742, and 1253, 1721, and 1190 cm.$^{-1}$, respectively. In the n.m.r. spectrum of this product there appeared singlet resonances at 121 (three protons) and 489 c.p.s. (one proton, signal unaffected on addition of deuterium oxide) assignable to acetate methyl and formate protons, respectively.[5] A three-proton singlet at 197 c.p.s. for methoxyl in the n.m.r. spectrum of the methyl ether I was conspicuously absent from the spectrum of the product, and the analytical data for the latter were in accord with over-all replacement of methoxyl by formate. The absence of proton resonance in the range 200–260 c.p.s. for *C*H(OH) established the hydroxyl as tertiary. This fact, together with the nonidentity of the product with the known 3β,5α,6β-trihydroxypregnan-20-one 3β-acetate 6β-formate[4] led to consideration of the 6α-formate ester II as the most probable structure. Cogent support for this supposition was obtained by alkaline hydrolysis of the formate II to the triol III which proved to be identical with the triol obtained by treatment of 3β-hydroxypregn-5-en-20-one with osmium tetroxide in pyridine, a reaction expected to proceed by α-face attack.



I



II



III

Epimerization of C–O bonds has been shown to occur during the lead tetraacetate oxidation of both androstane-4β,17β-diol 17β-acetate[6] and 11β-hydroxy compounds,[7] these giving rise to 4α,9α- and 1β,11α-oxide bridges, respectively. However, the lead tetraacetate oxidation reported here appears to be the first instance in which an ether reacts with epimerization.

No completely satisfactory mechanistic explanation of the observed result has been arrived at so far.

Experimental[5,8]

Lead Tetraacetate Oxidation of 3β,5α,6β-Trihydroxypregnan-20-one 3β-Acetate 6β-Methyl Ether (I).—A solution of the 6β-methyl ether (I, 0.915 g.), lead tetraacetate (2.0 g.), and iodine (0.29 g.) in dry benzene (53 ml.) was refluxed under anhydrous conditions for 2.75 hr. The mixture was then cooled and water (0.5 ml.) was added with rapid stirring, followed 15 min. later by addition of sodium bisulfite solution (30 ml. of 10%). Benzene extracts were washed with water, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield a crystalline solid which, when crystallized once from acetone–hexane, afforded colorless rhombs (0.28 g.), m.p. 238–243°. Two further crystallizations provided an analytical sample of II: m.p. 247–250°; $[\alpha]_D$ +58°; ν_{max} 3450, 1742, 1721, 1253, and 1190 cm.$^{-1}$; n.m.r. 37 (18-H), 63 (19-H), 126.5 (21-H), 121 (OAc), 290–325 (3α-H and 6β-H), and 487 c.p.s. (O_2CH).

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63; O, 22.82. Found: C, 68.52; H, 8.65; O, 22.92.

No other crystalline homogeneous product could be isolated.

3β,5α,6α-Trihydroxypregnan-20-one (III). A. By Hydrolysis of the Formate Ester II.—The diester II (95 mg.) dissolved in a solution of 0.5 *N* methanolic potassium hydroxide (44 ml.) was allowed to stand overnight at room temperature. Slow addition of water with stirring then produced crystals which, by crystallization from acetone, gave colorless needles (69 mg.), m.p. 233–235°. Further crystallization furnished a sample, $[\alpha]_D$ +80°, identical by melting point, mixture melting point, and infrared spectrum with authentic triol III (*vide infra*).

B. From 3β-Hydroxypregn-5-en-20-one.—Pregnenolone (1.24 g.) and osmium tetroxide (1 g.) were dissolved in anhydrous pyridine (15 ml.) and the solution was kept at room temperature in the dark overnight. A solution of sodium bisulfite (1.8 g.) in water (30 ml.) and pyridine (20 ml.) was then added and the whole was stirred for 45 min. Addition of chloroform and separation of the organic phase from the water afforded a solution from which the chloroform was removed by distillation at reduced pressure. Slow dilution of the resultant pyridine solution with water deposited crystals (1.22 g.), m.p. 231–235°. Recrystallization from acetone afforded pure triol III: m.p. 235–236°, $[\alpha]_D$ +79°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.82; H, 10.07.

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[1] Paper CCLXX: A. D. Cross, I. T. Harrison, F. A. Kincl, E. Farkas, R. Kraay, and R. I. Dorfman, *Steroids*, **4**, 423 (1964).

[2] Syntex Postdoctoral Fellow, 1963–1964; Lilly Research Laboratories Ltd., Bromborough Port, Cheshire, England.

[3] *Inter alia*, A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960); C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

[4] A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, **8**, 116 (1960).

[5] N.m.r. spectra were recorded at 60 Mc.p.s. with 5–8% deuteriochloroform solutions containing a little tetramethylsilane (TMS) as an internal reference. Resonance frequencies are quoted as c.p.s. downfield from the TMS reference (0 c.p.s.) and are accurate to ±1 c.p.s. Thanks are due to Mr. E. Diaz who recorded the spectra on a Varian A-60 spectrometer kindly made available by the Universidad Nacional Autónoma de México.

[6] K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

[7] G. B. Spero, J. L. Thompson, W. P. Schneider, and F. Kagan, *J. Org. Chem.*, **28**, 2225 (1963); K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

[8] Melting points were determined on a Fisher-Johns block and are corrected. Rotations are for chloroform solutions and infrared spectra were recorded using potassium bromide disks.