Tetrahedron Letters No.58, pp. 5057-5059, 1970. Pergamon Press. Printed in Great Britain.

OXIDATION OF SPIROETHERS WITH t-BUTYL CHROMATE

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(Received in USA 6 November 1970; received in UK for publication 13 November 1970)

As both the 17-spiroether[1] and 17-spirolactone[2] moieties are of importance in biologically active steroids, a simple one-step conversion of one group to the other would facilitate the preparation of both and permit a comparison of their biological properties. The conversion of the spirolactone group to a spiroether has been accomplished[3] by reduction of the lactone to the corresponding open chain diol which is then ring-closed to the ether. Other carbonyl groups in the molecule must be protected in this sequence or be regenerated from a reduced state by a subsequent oxidative step. This mode of transformation also has limitations when hydride labile substituents, such as halides, are present in the molecule. We were thus led to explore the reverse process, namely, conversion of the 17-spiroether moiety to the corresponding lactone, as a method to obtain members of both types of compounds, preferably by a one-step reaction.

In the course of studies on the introduction of a 7-oxo function into 3β-acetoxy-2', 3'α-tetrahydrofuran-2'-spiro-17 (5-androstene)[4], I, the traditional t-butyl chromate oxidant was employed. Under standard conditions[5] for this type of reaction the anticipated 3β-acetoxy-2',3'α-tetrahydrofuran-2'-spiro-17 (5-androsten-7-one)[6], II, was obtained in only 4% yield and an appreciable amount of 3-(3β-acetoxy-17β-hydroxy-7-oxo-5-androsten-17α-yl)propionic acid lactone,[6] III, (23%), was isolated as well.

We were thus led to investigate this reaction of t-butyl chromate with other spiroethers to determine the scope of this reaction. With the keto-spiroethers IVa[7], Va[1] and VIa[1] oxidation occurred selectively at the position α- to the ether oxygen affording the lactones IVb[6], Vb[2] and VIb[2] as easily isolable products in yields of 40%, 48%, and 30% respectively. The fact that the 19-norsteroid VIa was not noticeably aromatized under the reaction conditions indicates that the method is reasonably specific. Although we have made

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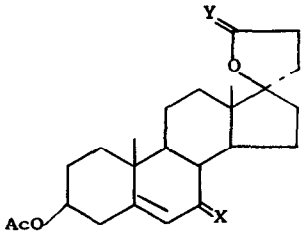
no attempt to find optimum conditions for this oxidation the selectivity of its action, as indicated by thin layer chromatography of the reaction mixture, shows that it can be of value in transformations of this type.[8)]

Typically, a solution of 200 mg of the steroid Va in 4 ml of carbon tetrachloride was treated with 2.8 ml of t-butyl chromate,[5)] 0.8 ml of glacial acetic acid and 0.4 ml of acetic anhydride. The mixture was refluxed for 2-4 hrs, the course of the reaction being followed by thin layer chromatography. The cooled reaction mixture was treated with saturated aqueous oxalic acid solution until gas evolution was complete. The organic solution was worked up and the crude product separated by chromatography on silica gel, elution of the desired lactone occurring with increasing quantities of ethylacetate in benzene. The desired lactone Vb was obtained in 48% yield after recrystallization from MeOH/H_2O.

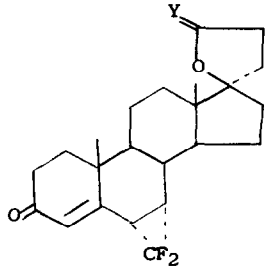
An attempt was made at the selective oxidation of IVa to IVb utilizing ruthenium tetroxide.[10)] The lactone IVb was formed to some extent but attempts to drive the reaction to completion resulted in extensive side-reactions.



I X = H_2, Y = H_2

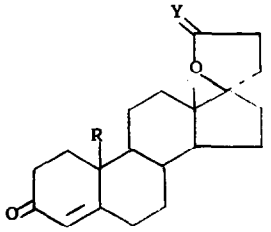
II X = O, Y = H_2

III X = O, Y = O



IVa Y = H_2

IVb Y = O



Va R = CH_3, Y = H_2

Vb R = CH_3, Y = O

VIa R = H, Y = H_2

VIb R = H, Y = O

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4. Melting point 139-140°.[6] Prepared by acetylation of the corresponding 3β-hydroxy compound described by R. A. Firestone and M. Sletzinger, U.S. Patent 3,365,475 (Jan. 23, 1968).
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6. All new compounds described in this paper gave satisfactory analyses. The physical constants for new materials described herein: II, m.p. 178-180°, $[\alpha]_D^{CHCl_3}$ -148.3, λ_{max}^{MeOH} 236mμ (ε12,500); III, m.p. 273-275°, $[\alpha]_D^{CHCl_3}$ -143.5, λ_{max}^{MeOH} 236mμ (ε13,000), τ_{CDCl_3} 4.26 (s,1H), 7.95 (s,3H), 8.76 (s,3H), 9.03 (s,3H), M^+ 400; IVb, m.p. 158-160°, $[\alpha]_D^{CHCl_3}$ +50.6, λ_{max}^{MeOH} 247mμ (ε16,500).
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8. Other reagents which have been used to convert steroidal ethers to lactones are chromium trioxide-acetic acid[9] and ruthenium tetroxide.[10b] Chromic acid in acetone[11] buffered bromine solutions[12] and trichloroisocyanuric acid[13] have also been found to convert ethers into esters.
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