Tetrahedron Letters No. 17, pp 1501 - 1504, 1973. Pergamon Press. Printed in Great Britain.

PREPARATION AND STRUCTURE DETERMINATION OF 14-FUNCTIONALIZED 19-HYDROXY STEROIDS

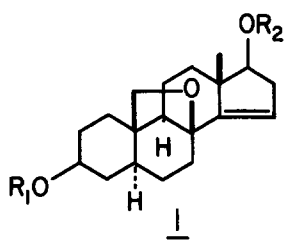
G. Kruger
Bio-Research Laboratories Ltd., Pointe Claire, Quebec, Canada
G.I. Birnbaum
Division of Biological Sciences, National Research Council
Ottawa, Ontario, Canada

(Received in USA 8 November 1972; received in UK for publication 19 March 1973)

The selective conversion of 8,19-oxido-14-dehydro steroids[1] of the androstane series to 19-hydroxy-14-dehydro-8β-androstanes and the conversion of the latter to the corresponding 14α,15α-epoxides is reported.

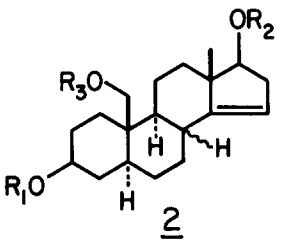
Thus 3β-acetoxy-17β-pivaloxy-8,19-oxido-5α-androst-14-ene 1a was treated with 30 parts of zinc in 125 parts of acetic acid-water (4:1) at 65° for 2 hrs, whereupon the steroidal material was recovered by filtration, dilution of the filtrate with water and extraction. Thin layer chromatography indicated that the resinous product obtained consisted mainly of 19-hydroxy-14-ene 2a besides small amounts of the corresponding 19-acetate 2b and of starting material 1a. Subsequent purification by thin layer chromatography afforded 19-hydroxy-14-ene 2a in 69% yield; dissolution in ether, followed by precipitation with pentane and concentration gave the pure product 2a in more than 45% yield, mp 133-133.5°. Subsequent acetylation with acetic anhydride and pyridine followed by epoxidation of the crude product 2b with *m*-chloroperbenzoic acid in carbon tetrachloride gave 3β,19-diacetoxy-14α,15α-oxide 3b, mp 149-151°.

The 17β-acetoxy analog 1b of 8,19-oxido-14-ene 1a, when similarly reduced with zinc, gave a product consisting mainly of 19-hydroxy-14-ene 2c besides small amounts of 19-acetate 2e. In contrast to its 17β-pivaloxy analog 2a, 17β-acetate 2c could not be induced to crystallize even after chromatographic purification. Dissolution of the product in ether followed by precipitation with pentane led to a separation of the 19-alcohol 2c and its 19-acetate 2e. The resinous 19-hydroxy-14-ene 2c, which was obtained in 56% yield, was then epoxidized as described above for the preparation of 3a, yielding a product consisting mainly of α-epoxide 3c and a more polar by-product, which was not further investigated. Recrystallization from methanol-methylene chloride and methanol-water yielded 19-hydroxy-14α,15α-oxide 3c in approximately 50% yield, mp 175-178°. In order to establish the configuration of C(8) a sample of 3c, recrystallized from methylene chloride-benzene, was subjected to X-ray analysis.



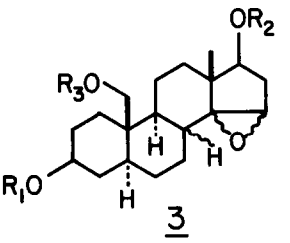
1

a. R_1 = Ac, R_2 = Piv
b. R_1 = R_2 = Ac



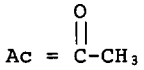
2

a. R_1 = Ac, R_2 = Piv, R_3 = H
b. R_1 = R_3 = Ac, R_2 = Piv
c. R_1 = R_2 = Ac, R_3 = H
d. R_1 = R_2 = R_3 = H
e. R_1 = R_2 = R_3 = Ac

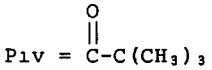


3

a. R_1 = Ac, R_2 = Piv, R_3 = H
b. R_1 = R_3 = Ac, R_2 = Piv
c. R_1 = R_2 = Ac, R_3 = H
d. R_1 = R_2 = R_3 = H
e. R_1 = R_2 = R_3 = Ac



Ac = $C-CH_3$



Piv = $C-C(CH_3)_3$

Precession photographs indicated that the substance crystallized in the orthorhombic space group $P2_12_12_1$. One of the colorless crystals was cut and mounted along the prism (c) axis on a four-circle diffractometer fitted with a copper target tube (λ = 1.5418Å). The following cell dimensions were measured: a = 27.241, b = 12.171, c = 6.585Å The data were collected at room temperature, using the moving-crystal, moving-counter ($\theta/2\theta$) scan technique. A total of 1805 reflections with $2\theta \leq 130°$ had intensities above the threshold value.

In the absence of heavy atoms the structure had to be solved by direct methods[2]. Fixed phases were assigned to four two-dimensional reflections with high E-values in order to define the origin and the enantiomorph. Two additional reflections were chosen and the phases $\pm\frac{\pi}{4}$ and $\pm\frac{3\pi}{4}$ were permutated for them. Each set of six reflections was used as input for tangent refinement and the run with the lowest R_E value (0.24) was extended to include all reflections with $E \geq 1.4$ (316 reflections). An E map calculated with the phases thus obtained revealed all carbon and oxygen atoms except the acetyl group attached to O(3). Those three atoms were found on a subsequent difference Fourier map. The atomic positions have been refined by the least-squares procedure, first with isotropic and then with anisotropic temperature parameters. All but three hydrogen atoms have been located The final value of the conventional agreement factor R = 5.6%.

The structure analysis revealed a normal androstane skeleton with *trans* junctions between each pair of rings (Figure 1). The hydrogen atom at C(8) is thus in β-configuration. The three six-membered rings are in chair conformations

while the conformation of ring *D*, imposed by the presence of the epoxide ring, is an unusual α-envelope with C(17) below the mean plane through the other four atoms. The participation of C(14) and C(15) in a three-membered ring necessitates a rehybridization of these atoms. This is made evident by the fact that all C-C bonds adjacent to the epoxide ring are 0.03-0.04Å shorter than normal. Their lengths correspond to what one would expect if C(14) and C(15) were sp^2 hybridized. The presence of these rehybridized atoms causes a flattening of ring *D* and of the adjacent part of ring *C*. The dihedral angle between the epoxide ring and ring *D* is 77°.

The conformations of both acetoxy groups differ substantially from what has been suggested as the preferred conformation[3], in which the hydrogen atom attached to the ring eclipses the carbonyl carbon atom. The torsional angle H(3)-C(3)-O(3)-C deviates by 33° from that conformation while in the case of the other acetoxy group the rotation amounts to 61°.

In the crystal structure the molecules are linked via hydrogen bonds. The 19-hydroxy group donates a proton to the oxygen atom in the epoxide ring in a symmetry related molecule. Full details of the X-ray analysis will be published elsewhere (by G.I.B.).

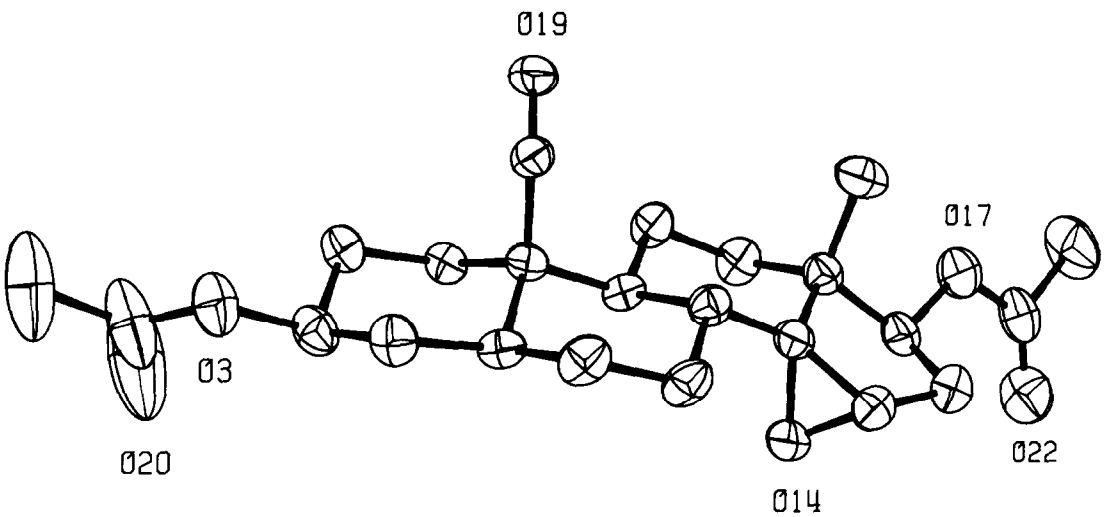


Figure 1. Perspective view of 3c

Alkaline hydrolysis of the ester groups of 14-enes 2b and 2c, and of 14α, 15α-oxides 3b and 3c, gave trihydroxy-14-ene 2d, mp 206-212°, and trihydroxy-14α,15α-oxide 3d, mp 252-255° (evac. sealed tube), respectively. Subsequent acetylation of 3d gave triacetate 3e as a resinous product, which could not be induced to crystallize despite extensive chromatographic purification; triacetate 3e was also obtained from 2d by acetylation to 2e and subsequent epoxidation with *m*-chloroperbenzoic acid in carbon tetrachloride; ir ($CHCl_3$) 3025 (14,

15-epoxide), 1730, 1450, 1380, 1365, 1235, 1040, 1025, 960 and 865 cm^{-1}.

The above reactions constitute an all-chemical route from bulk steroids, such as androstenolone acetate, to 14-functionalized 19-hydroxy steroids. This is of interest since so far only routes from the former to 14-functionalized steroids of the 19-methyl series have been reported[4]. It is of special synthetic interest that in the hydrogenolysis of the β-situated 8,19-oxide bridge only 8β-hydrogen and no 8α-hydrogen isomers could be obtained[5], i.e. that the hydrogenolysis proceeds with retention of the configuration at C(8). It is of further synthetic interest that the hydrogenolysis proceeds without migration of the allylic double bond to the 8(14)-position and that a mild reducing agent, such as zinc, is capable of effecting the hydrogenolysis of allyl ethers in which the double bond is not conjugated to a carbonyl group[6].

Acknowledgements:

G.K. is indebted to Mrs. G. Teodosiu for her diligent and competent assistance and to Dr. C. Chappel, Director of Bio-Research Laboratories Ltd., for encouragement and support.

REFERENCES

[1] Practical methods for the preparation of steroidal 8,19-oxido-14-enes have recently been developed by one of us (G.K.) and will be the subject of a publication in the Canadian Journal of Chemistry.

[2] J. Karle and H. Hauptman, *Acta Cryst* 9, 635(1956).

[3] A. McL. Mathieson, *Tetrahedron Letters*, 4137(1965).

[4] See for example P J. May in "Specialist Periodical Reports, Terpenoids and Steroids", Vol. 1, The Chemical Society, London, 1971, pp 404-421, J. Bos and H.J.C. Jacobs, *Tetrahedron Letters*, 1157(1969) and F. Sondheimer, *Chemistry in Britain*, 1, 454(1965).

[5] A. Serini and W. Logeman, *Ber.*, 71, 186(1938), C. Rufer, E. Schroeder and H. Gibian, *Ann. Chem.*, 705, 211(1967) and D.J. Marshall and R. Deghenghi, *Can. J Chem.*, 47, 3127(1969) have prepared 8α-hydrogen steroids of the estrane series by reduction of the corresponding 7-dehydro steroid analogs; W.G. Dauben and D.S. Fullerton, *J Org. Chem* , 36, 3277(1971), recently reported the synthesis of 8α-methyl steroids having an 18β- as well as a 19β-methyl group.

[6] A survey of several standard treatises on synthetic organic methods and steroid chemistry failed to reveal references to the zinc-reduction of simple allylic ethers. Well known is the reduction of steroidal 6,19-oxide-4-en-3-ones by zinc in acetic acid to the corresponding 19-hydroxy-4-en-3-ones (see, for example, J. Fried and J.A. Edwards (Editors), "Organic Reactions in Steroid Chemistry", Vol. II, Van Nostrand Reinhold Co., New York, 1971, p. 265)