Tetrahedron Letters No. 26, pp. 1281-1285, 1962. Pergamon Press Ltd.
Printed in Great Britain.

THE 17α-HYDROXYLATION OF CARDIAC AGLYCONES. CONVERSION OF THE CARDENOLIDE TO THE CORTISONE SIDE-CHAIN[1]

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(Received 27 September 1962)

WE have found that treatment of digitoxigenin 3-acetate (I) with selenium dioxide in boiling dioxane for 16 hr. leads to 60% of 17α-hydroxydigitoxigenin 3-acetate (II) [m.p. 241-244°; $[\alpha]_D + 155°$ (EtOH); $\lambda_{max.}^{EtOH}$ 216 mμ (ε 12,300)].[3] The same substance II was formed under these conditions from the αβ-unsaturated ester III, the precursor of digitoxigenin 3-acetate (I) in our recently reported[2] synthesis of the latter substance.[4]

The fact that a hydroxyl group had been introduced at C-17 was indicated by the facts that II was recovered unchanged after treatment with acetic anhydride-pyridine at 100°,

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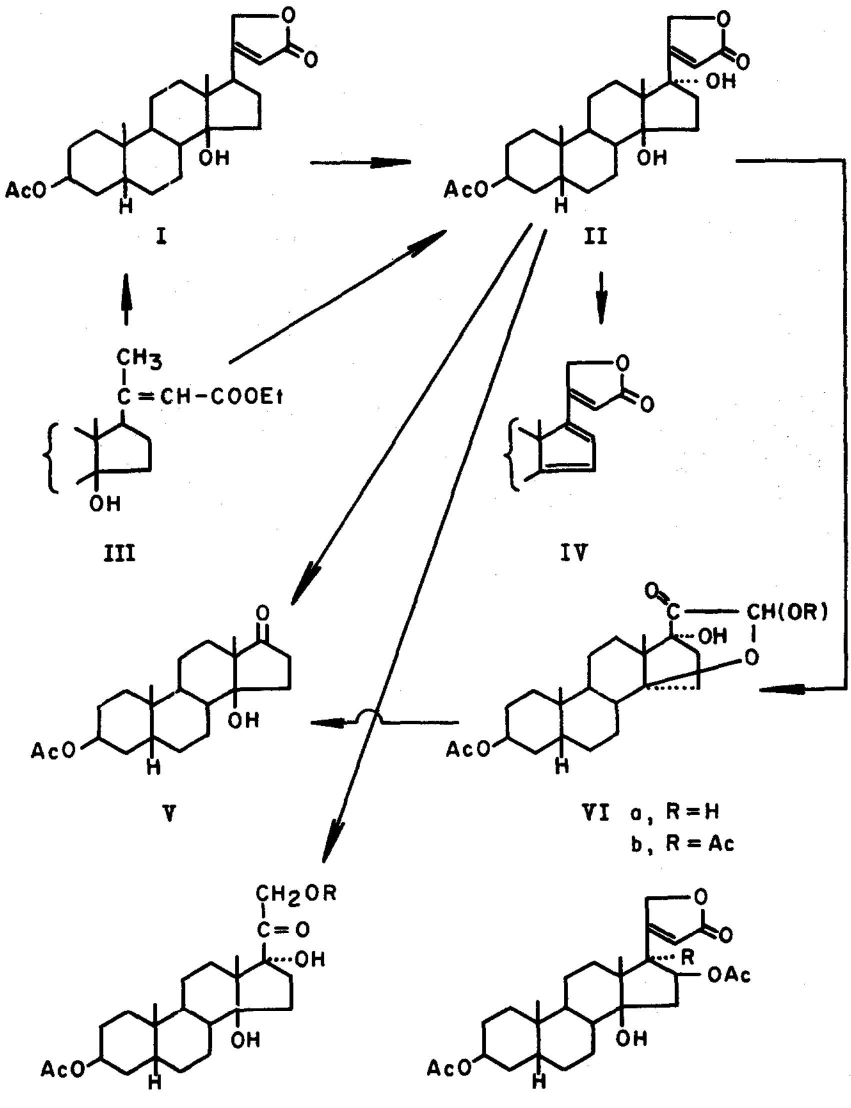
[1] This is part V in the series "Syntheses in the Cardiac Aglycone Field." For part IV, see footnote 2.

[2] N. Danieli, Y. Mazur and F. Sondheimer, J. Amer. Chem. Soc. 84, 875 (1962).

[3] All new substances gave analytical results in accord with the assigned structures.

[4] On the other hand, digitoxigenin 3-acetate (I) was unaffected on treatment with selenium dioxide in boiling benzene, the conditions of its formation from the ester III.[2]


AcO
OH
H
I
II
OH
CH3
C=CH-COOEt
III
IV
O
V
CH(OR)
VI a, R = H
b, R = Ac
CH2OR
C=O
OAc
R
VII a, R = H
b, R = Ac
VIII a, R = H
b, R = OH

and that dehydration with phosphorus oxychloride-pyridine at 100° for 10 minutes yielded 70% of the known dianhydrogitoxigenin acetate (IV) [m.p. 203-204°; $\lambda_{\text{max.}}^{\text{EtOH}}$ 223 and 337 mμ (ε 13,500 and 20,600)].[5]

17α-Hydroxydigitoxigenin 3-acetate (II) was treated with excess of ozone in acetic acid-ethyl acetate (1:1) at 0°, the product was reduced with zinc and then saponified at C-21 by means of potassium bicarbonate in aqueous methanol at room temperature for 48 hr.[6] Chromatography on silica gel then afforded three substances, which, in order of elution, proved to be V, VIa and VIIa, the yields being 30%, 15%, and 25%, respectively.

The 17-ketone V [m.p. 226-228°; $[\alpha]_D$ +20° ($CHCl_3$)] in the infrared (KBr) showed a single carbonyl band at 1727 cm.$^{-1}$ (3-acetate and 17-ketone). The same substance was also obtained, in 55% yield, by oxidation of II with potassium permanganate in acetone.

The cyclic hemiacetal VIa[7] [m.p. 173-175°; $[\alpha]_D$ +18° ($CHCl_3$)] showed infrared bands (KBr) at 1745 cm.$^{-1}$ (3-acetate) and 1715 cm.$^{-1}$ (20-ketone). The nuclear magnetic resonance (n.m.r.) spectrum ($CDCl_3$) exhibited a singlet at 5.68 τ (relative intensity, one proton) ascribed to the hydrogen at C-21. Acetylation of VIa with acetic anhydride-pyridine at

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[5] See O. Schindler and T. Reichstein, Helv. Chim. Acta **35**, 442 (1952), and references to earlier work quoted there.

[6] See M. Zingg and K. Meyer, Helv. Chim. Acta **43**, 145 (1960), and references cited there.

[7] See M.S. Ragab, H. Linde and K. Meyer, Helv. Chim. Acta **45**, 152 (1962).

room temperature gave the 3,21-diacetate VIb [m.p. 202-203°; $[\alpha]_D$ +30° ($CHCl_3$)], which exhibited $\nu_{Max.}^{KBr}$ 1762 cm.$^{-1}$ (21-acetate), 1745 and 1721 cm.$^{-1}$ (3-acetate and 20-ketone). The n.m.r. signal assigned to the proton at C-21 appeared as a singlet at 5.40 τ. Oxidation of VIa with chromic acid in acetic acid at 0° led to the 17-ketone V.

The third ozonolysis product VIIa, which contains the cortisone side-chain, was characterized as the 3,21-diacetate VIIb [m.p. 190-192°; $[\alpha]_D$ +25° ($CHCl_3$)]. In agreement with the assigned structure, the diacetate VIIb showed infrared bands ($CHCl_3$) at 1751 cm.$^{-1}$ (21-acetate) and 1730 cm.$^{-1}$ (3-acetate and 20-ketone), n.m.r. signals due to the two protons at C-21 as a quartet centered at 4.65 τ (J=17c/s), as well as a positive reaction with triphenyltetrazolium chloride reagent.

The α-configuration of the 17-hydroxyl group in II follows from the formation of the cyclic hemiacetal VIa. This assignment was supported by the rotatory dispersion curves of VIa and VIIb, both of which show positive Cotton effects (peak at $[\alpha]_{297}$ +763° for VIa, peak at $[\alpha]_{292}$ +259° for VIIb, both in dioxane). It is known that pregnan-20-ones show a positive Cotton effect, while 17α-pregnan-20-ones show a negative effect,[8] and this behavior is also observed in the presence of a 14β-hydroxyl group.[9]

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[8] See C. Djerassi, "Optical Rotatory Dispersion", Mc Graw-Hill Book Co., Inc., New York, N.Y., 1960, Chapter 4.

[9] Unpublished observations from these Laboratories.

The 17α-hydroxylation of cardenolides with selenium dioxide appears to be general; e.g. gitoxigenin 3,16-diacetate (VIIIa) under the conditions used with I yielded 65% of the corresponding 17α-hydroxy derivative VIIIb [m.p. 242-243°; $[\alpha]_D$-8° (pyridine); $\lambda_{max.}^{EtOH}$ 216 mμ (ε 13,500)].

We wish to thank Dr. G. Friedlander, Teva Ltd., Jerusalem, for a gift of oleandrin, and Miss Rivka Shapira for technical assistance.