Tetrahedron Letters No.17, pp. 2107-2111, 1968. Pergamon Press. Printed in Great Britain.

STEROIDS AND RELATED PRODUCTS. XXVII. THE SYNTHESIS OF 11-OXA STEROIDS. I. 11-OXAPROGESTERONE.

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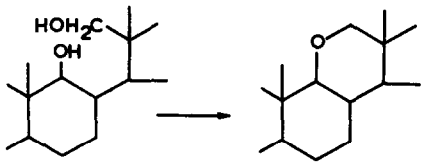
(Received in USA 2 November 1967)

We reported earlier the first synthesis of 11-aza steroids (2) and indicated succintly the interest in such nucleo-hetero steroids. In particular we stressed the special interest of the study of hetero steroids in which the hetero atom takes the place of a carbon atom in a position of high biological importance. In the present series, we are relating syntheses of 11-oxasteroids, the significance of which is apparent if one considers the biological importance of 11-oxygenated steroid hormones. In this paper we report the synthesis of the first 11-oxa analogue of a hormone of the progesterone-corticoid group, 11-oxaprogesterone (IV).

The key reaction of our syntheses of 11-oxa steroids consists in the transformation of an 11-nor 9,12-seco 9,12-diol of type i to an oxa steroid of type ii by acylating agents; we used in particular p-toluenesulfonyl chloride in pyridine at elevated temperatures.



i ii

1) For paper XXVI see reference 1.

In one series of reactions, 3β-hydroxy-20β-acetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (Ia), previously synthesized in this laboratory (2) from hecogenin (VII), was hydrolyzed with methanolic potassium hydroxide to the corresponding dihydroxy acid (I), [m.p.211-212°, $[\alpha]_D^{22}$ -44.2°][2] which was methylated with diazomethane to the methyl ester Ib, m.p. 154-155°, $[\alpha]_D^{25}$ -73.5°. Oxidation with Jones' reagent (3) gave the triketo ester II in 93% yield [m.p. 124-125°, $[\alpha]_D^{22}$ -50.2°]. Preferential ketalisation with ethylene glycol and p-toluenesulfonic acid afforded in 84% yield the diketal ester IIa [m.p. 123.5°-124.5°, $[\alpha]_D^{22}$ -35°] which was reduced with lithium aluminum hydride in tetrahydrofuran, in 76% yield, to 3,20-bis-ethylenedioxy-9,12-seco-11-nor-5α-pregnan-9,12-diol (III), m.p. 154-155°, $[\alpha]_D^{22}$ +8.5°[3]. Its treatment with approximately 4 equivalents of p-toluenesulfonyl chloride in pyridine at 110 to 120° for 4 hrs. and the usual working up gave a mixture of the oxa steroids Vb, Va and V, from which the 11-oxa diketal Vb [m.p. 145-146°, $[\alpha]_D^{22}$ +9.1°, ν_{max}^{KBr} 1099, 1068, 1052 cm^{-1} (C-O-bands)] was isolated and which gave with acetone and p-toluenesulfonic acid (4) in 50% yield from the diol III, 11-oxa-5α-pregnane-3,20-dione (V), m.p. 217-218.5°, $[\alpha]_D^{22}$ +82.2°, ν_{max}^{KBr} 1718 cm^{-1} (3,20-diketone), 1080, 1056, 1037 cm^{-1} (ether bands).

Dehydrogenation with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in refluxing dioxane (5,6) resulted in a mixture of 11-oxa-1,4-pregnadiene-3,20-dione (IVa)(30%), [m.p. 195-196°, $[\alpha]_D^{22}$ +104.3°, λ_{max}^{EtOH} 241 mμ (log ε 4.12), ν_{max}^{KBr} 1718 cm^{-1} (20-ketone), 1673, 1638, 1609 cm^{-1} ($\Delta^{1,4}$-3-ketone) 1091, 1081, 1072 cm^{-1} (ether)] and of Δ^1-11-oxa-5α-pregnene-3,20-dione (Vc) [m.p. 218-219°, $[\alpha]_D^{22}$ + 99.3°, λ_{max}^{EtOH} 227mμ (log ε 3.93), ν_{max}^{KBr} 1710cm^{-1}

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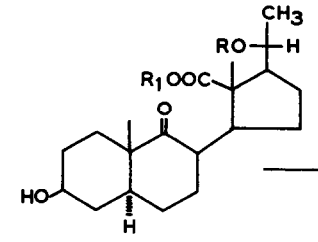
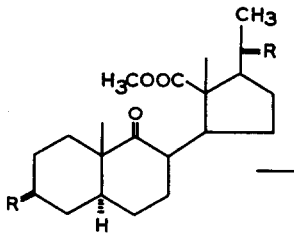
2) If not otherwise stated, rotations were taken in chloroform. Only significant infrared and ultraviolet spectral data are recorded. All new compounds gave satisfactory elemental analyses within 0.3% of the theoretical value); their n.m.r. spectra are compatible with the assigned structures. The detailed n.m.r. analyses will be published in the full paper.

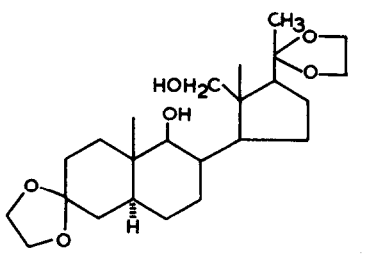
3) The stereochemical assignments, based to a considerable extent on n.m.r. analyses, will be discussed in detail in the full paper. The α-configuration and axial conformation of the 9-hydrogen substituent of compounds of this series are particularly easy to detect in the case of the 12→9 lactone of the 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid, prepared by sodium borohydride reduction of the 3-acetate of keto acid Ia, in which the 9α-hydrogen appears as a doublet, with its center a 3.41 ppm, the coupling constant of which (J = 9.8 cps) is typical of the coupling of two vicinal trans-diaxial protons. This observation is relevant to the stereochemistry of the 11-oxa steroids under discussion, since the lactone - the stereochemistry of which is substantiated also by other considerations - was reduced either with platinum dioxide in the presence of perchloric acid in acetic acid, or with lithium aluminum hydride-boron trifluride, to the corresponding 12-methylene derivative which, upon hydrolysis and oxidation, gave the 11-oxa pregnanedione V. This route to 11-oxa steroids will be the subject of a separate paper. (The n.m.r. spectra were recorded on a Varian A 60 spectrometer, in $CDCl_3$, tetramethylsilane serving as internal standard).



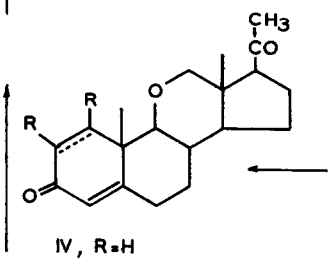
I, R_1=R=H
Ia, R=Ac, R_1=H
Ib, R=H, R_1=CH_3



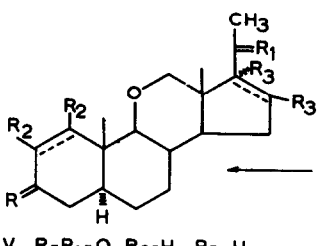
II, R=O
IIa, R= O-CH_2 / O-CH_2



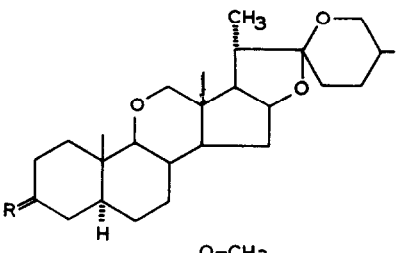
III



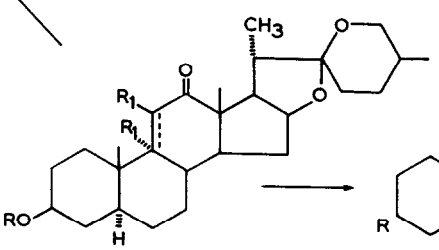
IV, R=H
IVa, R=double bond



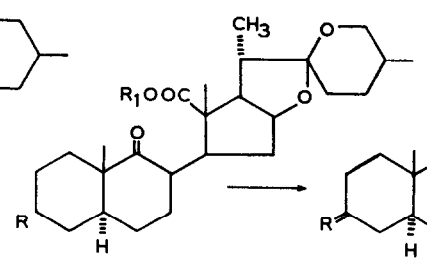
V, R=R_1=O, R_2=H, R_3=H
Va, R=O, R_1= O-CH_2 / O-CH_2, R_2=R_3=H
Vb, R=R_1= O-CH_2 / O-CH_2, R_2=R_3=H
Vc, R=R_1=O, R_2=double bond, R_3=H
Vd, R=R_1=O, R_2=H, R_3=double bond



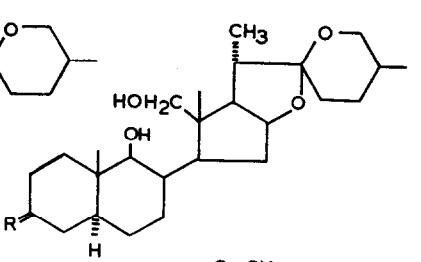
VI, R= O-CH_2 / O-CH_2



VII, R=R_1=H
VIIa, R=Ac, R_1=H
VIIb, R=Ac, R_1=double bond



VIII, R= OH / H, R_1=H
VIIIa, R= OAc / H, R_1=H
VIIIb, R= OH / H, R_1=CH_3
VIIIc, R==O, R_1=CH_3
VIIId, R= O-CH_2 / O-CH_2, R_1=CH_3



IX, R= O-CH_2 / O-CH_2

(20-ketone), 1683 and 1610 cm^{-1} (Δ^1-3-ketone), 1068, 1052, 1036 cm^{-1} (ether)], isolated from the mixture in 4% yield. Renewed dehydrogenation of the portion of the mixture comprising the products without the double unsaturation in positions 1 and 4, raised the yield of the dienone IVa to 43%. The preferential catalytic reduction of this dienone (IVa) with tris-(triphenylphosphine) chloro-rhodium (7,8), following the procedure of Birch (9) [cf. also Djerassi and Gutzwiller (10)] gave in 85% yield the desired 11-oxaprogesterone (IV), m.p. 182.5-184°, $[\alpha]_D^{22}$ +149°, λ_{max}^{EtOH} 238 mμ (log ε 4.13); ν_{max}^{KBr} 1715 cm^{-1} (20-ketone), 1677 and 1622 cm^{-1} (Δ^4-3-ketone), 1090, 1081, 1052 cm^{-1} (ether). The biological activity of this hormone analogue will be reported elsewhere.

In a second series of reactions, the intermediate 11-oxa-5α-pregnane-3,20-dione (V) was synthesized from 9-dehydrohecogenin acetate (VIIb), readily available by selenium dioxide dehydrogenation of hecogenin acetate (VIIa) (11). Ozonolysis in pure ethyl acetate at -30 to -60° gave after alkaline hydrolysis, in 70% yield, 3β-hydroxy-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oic acid (VIII), m.p. 256.5-257.5°, $[\alpha]_D^{22}$ -82.6° (methylcellosolve), ν_{max}^{KBr} 3425 cm^{-1} (broad associated hydroxy bands), 1740 cm^{-1} (acid), 1705 cm^{-1} (9-ketone)[4], which was methylated with diazomethane to the methyl ester VIIIb, m.p. 163.5-164°, $[\alpha]_D^{22}$ -88.5°. Oxidation with Jones' reagent gave the diketo ester VIIIc [m.p. 134-135°; $[\alpha]_D^{22}$ -64°], which was converted, as described above, to the 3-monoketal VIIId, m.p. 215-216°, $[\alpha]_D^{22}$ -76.7°; this was reduced with lithium aluminum hydride to the diol IX, m.p. 222-223°, $[\alpha]_D^{22}$ -56°. Treatment of this diol with p-toluenesulfonyl chloride in pyridine at 85-90° for 3.5 hrs. gave in 76% yield the 11-oxasteroid VI, m.p. 191.5-193°, $[\alpha]_D^{22}$ -87.5°, ν_{max}^{KBr} 1108, 1077, 1054 cm^{-1} (ether bands). The classical degradation of this product, according to Marker's procedure (14)[5], using the experimental method described by Zderic et al. (15), gave in (only) 23% yield Δ^{16}-11-oxa-5α-pregnene-3,20-dione (Vd) [m.p. 281-282°, $[\alpha]_D^{22}$ +50.5°] which was reduced catalytically with palladium on charcoal, in 81% yield, to the 11-oxa-5α-pregnane-3,20-dione (V).

Acknowledgments. We express our high appreciation to Mrs. J. Capitaine for her kind cooperation in some of the experiments and to Mr. D. Capitaine and Mrs. G. Pelletier for devoted technical assistance. Sincere thanks are due to the National Cancer Institute of Canada, the National Research Council of Canada, and to Ayerst Laboratories, Ltd., Montreal, for financial support of this project.

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4) Kutney et al. described the 3-acetate (VIIIa) of this compound (12), whereas we had prepared earlier (13) the 23-bromo derivative thereof.

5) Only one reference is given.

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