Tetrahedron Letters No. 46, pp 4463 - 4464. 0040-4039/79/1108-4463$02.00/0

ANODIC OXIDATION OF RING A-AROMATIC STEROIDS. REGIOSELECTIVE BENZYLIC OXIDATION +

Kurt Ponsold and Helmut Kasch

Academy of Sciences of the GDR, Research Centre of Molecular Biology and Medicine, Central Institute of Microbiology and Experimental Therapy, GDR - 69 Jena, Beutenbergstr. 11

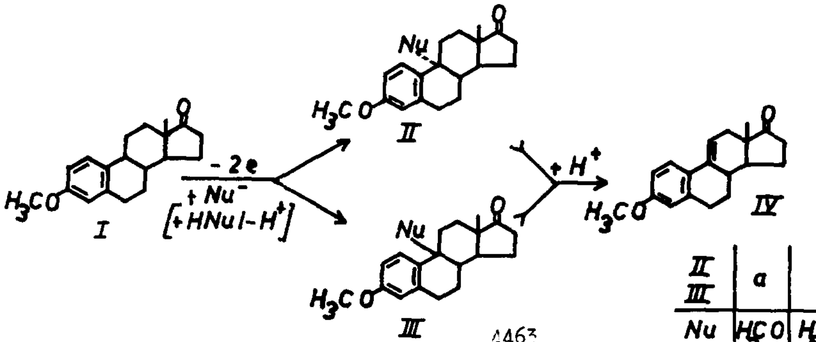
Abstract: A new method for benzylic alkoxylation and hydroxylation of 3-methoxy-estra-1,3,5(10)-trienes (I) is described. 9α- and 9ß-methoxy- and 9α- and 9ß-hydroxy-3-methoxy-estra-1,3,5(10)-trienes (II and III) were prepared by electrochemical oxidation in a methanolic or aqueous solvent supporting electrolyte (SSE).

General pathways for the introduction of various substituents in the benzylic position 9 of estratrienes of type I are not yet known. Only the hydroxy derivative IId was prepared from I by $(Ph_3P)_3RhCl$ /1/ and molecular oxygen or by irradiation in the presence of nitrobenzene /2/. The yields however were only moderate.

We found that the electrochemical oxidation of I in the presence of weak nucleophilic solvents or relatively weak nucleophilic anions is a useful method for synthesis of 9-substituted compounds of type II and III /3/. In this paper we describe in detail the preparation of the methoxy compounds IIa and IIIa as an example for a general procedure.

On electrolysis of I (0,008 mole) in a 0,1 M solution of sodium perchlorate in methanol and methylene chloride (ratio 3 : 1) in the presence of 2,6-lutidine (0,01 mole) we got in nearly quantitative yield a mixture of the isomeric 9-methoxy products, 3,9α-dimethoxy-estra-1,3,5(10)-triene-17-one IIa and 3,9ß-dimethoxy-estra-1,3,5(10)-triene-17-one IIIa (ratio 3 : 2). The electrochemical oxidation was carried out in an undivided cell between two platinum electrodes (working electrode 70 cm^2, cathode 4 cm^2, distance of the electrodes 1,5 cm) at constant current of 800 mA for 40 minutes.

The structure determination of the isolated pure substances IIa and IIIa are based on the following dates. In the ^1H-NMR-spectra the pattern



II III	a	b	c	d	e
Nu	H_3CO	H_5C_2O	i-H_7C_3O	HO	N_3

of the aromatic protons is not altered, there is no proton geminal to the methoxy group. Quantitative transformation of IIa and IIIa into 3-methoxy-estra-1,3,5(10),9(11)-tetraen-17-one IV by treatment with hydrochloric acid in methanol indicates that the stereoisomeric 9-methoxy products must be present.

The configuration of the isomers was elucidated by the different chemical shift of the 13-methyl signals in comparison with known epimeric 9-unsubstituted /4/ and 9-methyl substituted /5/ estratrienes. The results of the ^{1}H-NMR-analysis were fully confirmed by CD-measurements. The α-isomer II showed a positive and the β-isomer a negative Cotton effect at about 228 nm in correspondence with Velluz /6/.

If the electrochemical oxidation was carried out in other primary or secundary alcohols instead of methanol the corresponding 9-alkoxy compounds IIb, c and IIIb, c resulted. But the substance and the current yields are lower as in methanol and decrease with increasing size and branching of the alcohol.

Electrolysis of I in the presence of azide ions in methanolic solution or dimethylformamide yielded a mixture of the isomeric 9-azido compounds IIe and IIIe.

Working in aqueous systems led to the hydroxy-derivatives IId and IIId. We used aqueous acetonitrile or aqueous N,N-dimethylformamide and tetraethylammonium tetrafluoroborate as supporting electrolyte.

The electrochemical benzylic oxidation is not restricted to compound I. Other ethers and esters of estrone and compounds with various substituents in position 17 can also be oxidized.

Acknowledgement: The authors thank Mr. D. Tresselt for ^{1}H-NMR and Dr. Ch. Zimmer for CD analysis.

References

\+ Steroids (64), No. 63, G. Schubert, K. Ponsold, H.G. Hillesheim and M. Koch, Pharmazie, in press

/1/ A.J. Birch and G.S.R. Subba Rao, Tetrahedron Letters, 1968, 2917

/2/ J. Libmann and E. Berman, Tetrahedron Letters, 1977, 2191

/3/ K. Ponsold and H. Kasch, Ger. Offen 2 523 179, ref. C.A. 85, 46943t (1976)

/4/ G.A. Hoyer, K. Junghans and G. Cleve, Chem. Ber., 107, 363 (1974)

/5/ R.V. Coombs, J. Koletar, R. Danna, H. Mah and E. Galantay, J. med. Soc. Perkin I, 1973, 2095

/6/ L. Velluz and M. Legrand, Angew. Chem., 77, 844 (1965)

(Received in Germany 23 July 1979)