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STEREOSELECTIVE OPENING OF RING E IN FUROSTAN SAPOGENINS. AN EFFICIENT ROUTE TO 16,22R,26-HYDROXY STEROIDS [1]

A. G. González, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar and E. Suárez

Department of Organic and Biochemistry, University of La Laguna
Instituto de Investigaciones Químicas, C.S.I.C., Tenerife, Spain

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The growing importance of side chain hydroxylated steroids as biogenetic precursors[2] and biologically active substances (e.g. ecdysones, antheridiol, steroid alkaloids, intermediate products in the mode of action of vitamin D[3-6]) encouraged us to search a route to such compounds starting from 26-hydroxy-furostan sapogenins, which may be prepared by a simple reaction[7] from the corresponding readily available spirostan compounds. The present communication reports the stereoselective opening of ring E in furostan sapogenins which leads to substances that are of use for the aforesaid synthesis.

Reduction of (25R)-5α-spirostan (1) with LAH/$AlCl_3$ gave 2a,[7] which was oxidized with Jones reagent to 2b. This acid was refluxed in Ac_2O being 0·01 N in TsOH for 30 minutes, obtaining an equimolecular mixture (60%) of the isomers 3 and 4 which were separated by column chromatography (SiO_2/20% $AgNO_3$).

Compound 3, $C_{27}H_{42}O_2$, has m.p. 144-146° (MeOH), $[\alpha]_D$ -53°, $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (δ-lactone). Its NMR spectrum does not present signals for vinyl protons, appearing a multiplet at 5·4 ($H\text{-}C_{22}$) and a singlet at 8·93 ($Me\text{-}C_{17}$). The base peak in its MS is attributed to the allylic ion [a] originated by the loss of the side chain. On oxidizing 3 in $CHCl_3$ with m-chloroperbenzoic acid a non-separated mixture of two isomeric epoxides was obtained which by treatment with BF_3-etherate in benzene were transformed into the diene 5, m.p. 187-189°

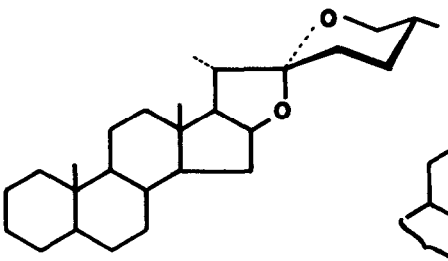
(acetone), $[\alpha]_D$ -191°, λ_{max}^{EtOH} 245 nm (ϵ 11 000), NMR τ 4·6 (2H, m, H-$C_{12,15}$). This led to establish the location of the tetrasubstituted double bond.

In order to determine the configuration at C_{22} the lactone 3 was esterified with MeOH saturated with Na_2CO_3, obtaining 6, m.p. 69-70° (MeOH), $[\alpha]_D$ -20°. Application of the Hudson-Klyne rule[8] to compounds 3 and 6 and of the Horeau method[9] to the C_{22}-OH in the latter indicated that the stereochemistry at C_{22} is R. As a consequence, in 2a and generally in the "dihydrosapogenins" the configuration at this carbon atom, which hitherto had remained undetermined, must be R too.

Compound 3 was also obtained quantitatively by treatment of 2b with BF_3-etherate in Ac_2O at 0° for 30 minutes. The acid-catalyzed opening of ring E follows a Wagner-Meerwein rearrangement, all the atoms involved fulfilling the stereochemical requirements.

The isomer 4, $C_{27}H_{42}O_2$, m.p. 167-169° (MeOH), $[\alpha]_D$ -4°, $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (δ-lactone), shows NMR signals at τ 4·50 (m, $W_{1/2}$ 6 Hz, H-C_{16}) and 5·6 (m, $W_{1/2}$ 18 Hz, H-C_{22}). The base peak in its MS is represented by fragment [b]. Oxidative hydroboration of 4 gave quantitatively 7a, $C_{27}H_{48}O_3$, m.p. 144-145° (acetone/n-hexane), $[\alpha]_D$ +9°. The NMR spectrum of its triacetate 7b, m.p. 138-140° (MeOH), $[\alpha]_D$ -43°, presents signals at τ 4·8 (m, H-C_{16}), 5·15 (m, H-C_{22}) and 6·00 (d, J 6 Hz, 2H-C_{26}) corresponding to the protons geminal to the three acetate groups. 7a was oxidised with Jones reagent and the resulting acid methylated with CH_2N_2 to yield compound 8, m.p. 104-106° (MeOH), $[\alpha]_D$ -154°, which proved to be identical with that obtained by oxidation of 1 with CrO_3/HOAc following the method reported by Barton et al.[10]

When the reaction sequence described above was carried out using the benzyl ether of tigogenin (1; 3β-OH) as starting material, analogous compounds were obtained in comparable yields: 3 (3β-OAc), m.p. 155-157° (MeOH), $[\alpha]_D$ -46°; 4 (3β-OAc), m.p. 159-161° (MeOH), $[\alpha]_D$ -10°; and 7b (3β-OAc), m.p. 188-190° (n-hexane), $[\alpha]_D$ -56°.



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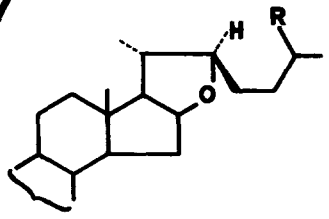
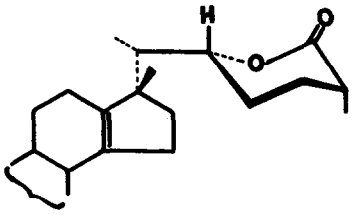


2

a R = CH_2OH

b R = COOH



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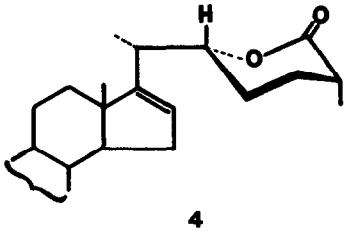

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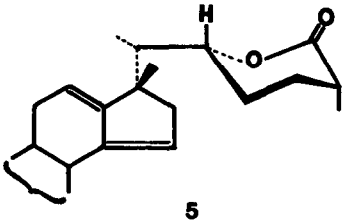

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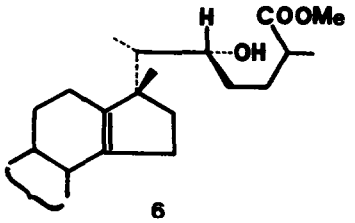

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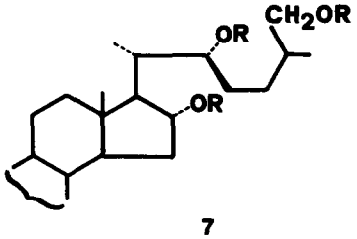
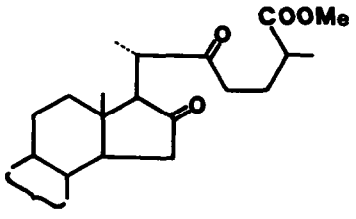


7

a R = H

b R = Ac



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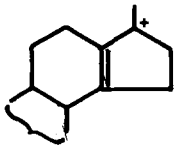
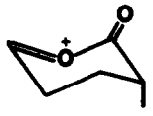


[a]



[b]

All new compounds gave correct elemental analyses. Optical activities were measured in $CHCl_3$ and NMR spectra in $CDCl_3$ (60 MHz).

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REFERENCES

1) Part XXVI in the series "New Sources of Steroid Sapogenins". For Part XXV see A. G. González, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar and E. Suárez, Tetrahedron Letters, 2681 (1974).

2) R. Tschesche, Y. Saito and A. Töpfer, Tetrahedron Letters, 967 (1974).

3) H. Hikino and Y. Hikino in "Progress in the Chemistry of Organic Natural Products", vol. 28, p. 256, Springer-Verlag, Wien, 1970.

4) G. P. Arsenault, K. Biemann, A. W. Barksdale and T. C. McMorris, J. Am. Chem. Soc. 90, 5635 (1968).

5) K. Schreiber in "The Alkaloids", vol. X, p. 1, ed. R. H. F. Manske, Academic Press, New York, 1968.

6) S. J. Halkes and N. P. van Vliet, Rec. Trav. chim. 88, 1080 (1969).

7) G. R. Pettit and W. T. Bowyer, J. Org. Chem. 25, 84 (1960).

8) C. S. Hudson, J. Am. Chem. Soc. 32, 338 (1910). W. Klyne, Chem. and Ind., 1198 (1954).

9) A. Horeau and H. B. Kagan, Tetrahedron 20, 2431 (1964).

10) D. H. R. Barton, Y. D. Kulkarni and P. G. Sammes, J. Chem. Soc. (C), 1149 (1971).