ON CARDIOACTIVE STEROIDS XIV.[1] THE PREPARATION OF (21R)-21METHYL-DIGITOXIN

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Abstract — A high yield direct conversion of digitoxin into (21R)-21methyldigitoxin is described.

In previous communications of this series we have described the application of our "furan methodology" to the synthesis of a variety of cardenolide and bufadienolide analogues.[2] Several of these compounds when tested† in the form of their glucosides turned out to be not only fully active, but displayed a much wider margin of safety than the natural digitalis glycosides currently used in therapy. It next became desirable to attach the natural digitoxin tridigitoxoside sidechain to our best steroid derivatives. It was believed that this would result in a prolongation of the duration of action and a favourable modification of several other pharmacologic parameters. A general solution of this problem is laborious and similar to the total synthesis of digitoxin.[1] However, in one specific case we were able to reach the desired objective in a very simple and highly efficient manner.

One of our best steroids is (21R)-21methyldigitoxigenin[3] which, in the form of its glucoside, is practically equipotent with digitoxin, but shows a 20 times wider margin of safety. We wish to report now the preparation of the tridigitoxoside 5 of this compound.

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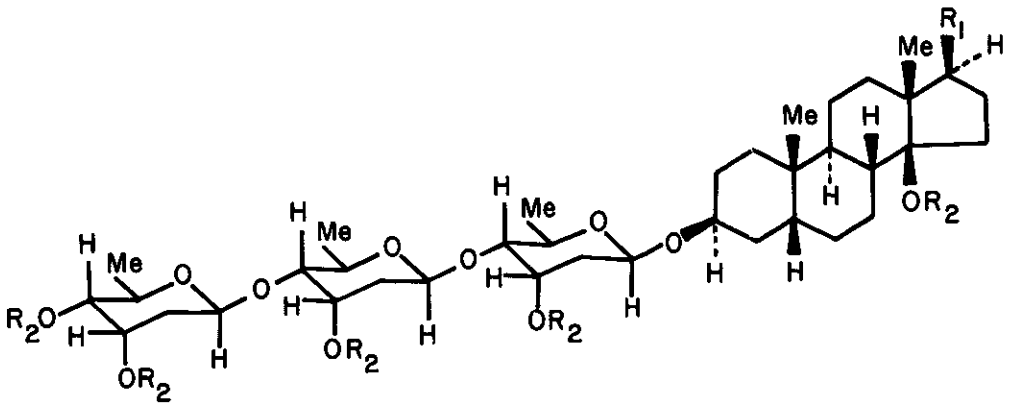
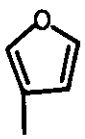
†All pharmacological tests were performed under the direction of Professor Rafael Mendez, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City. The results of these tests are being published by Professor Mendez and his colleagues.

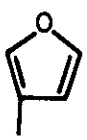
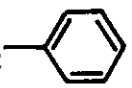
The starting material was the furyl derivative 1[4] easily prepared from digitoxin by reduction with DIBAL. Compound 1 was heated in dioxane with sodium hydride and 18-crown-6 ether for 6 h, followed by addition of an excess of benzyl bromide and another 18 h of reflux. Work-up and chromatography gave the pure perbenzylated compound 2 as a foam, homogeneous in several T.L.C. systems, in a yield of 90%; ir ($CHCl_3$) ν_{max}: no hydroxyl absorption; pmr ($CDCl_3$) δ: 7.30, 7.32, 7.36, 7.38 (m, 25H, aromatic H), 7.14, 7.10, 6.18 (broad s, 1H each, furan), 1.28 (d, J = 6 Hz, 3H, 1 CH_3 in digitoxose), 1.19 (d, J = 6 Hz, 6H, 2 CH_3 in digitoxose), 0.96 (s, 3H, 19-CH_3), 0.86 (s, 3H, 18-CH_3).

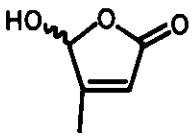
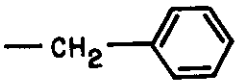
The perbenzylated compound 2 was dissolved in $CHCl_3$ and oxidized with m-chloroperbenzoic acid in the presence of acetic acid and sodium acetate. After work-up the two regioisomeric lactols 3a and 3b were readily separated by chromatography and 3a was used for the next step without any further purification. The yield of 3a and 3b was 92% and the materials were obtained in a ratio 2:1. The regioselectivity of the oxidation is thus much smaller than observed in our digitoxigenin synthesis.[2] The materials 3a and 3b, besides being mixtures of C21-epimers, contain also significant amounts of the corresponding aldehyde tautomers.

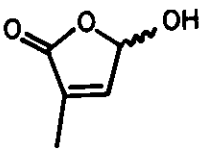
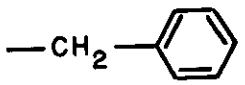
The lactol mixture 3a in THF was cooled to -78°C and treated with an excess of methyllithium for 30 min. The solution was then acidified and worked up. The major epimer 4a was separated by chromatography on silicic acid in a yield of 86%. The product was homogeneous in several T.L.C. systems and remained glassy. We did not succeed to separate the minor epimer 4b as a pure compound. The estimated ratio of 4a/4b was 10:1; ir ($CHCl_3$) ν_{max}: 1706 (C=O), 1625 cm^{-1} (C=C), no hydroxyl absorption; pmr ($CDCl_3$) δ: 7.30, 7.33, 7.35, 7.37 (m, 25H, aromatic H), 5.69 (broad s, 1H, C22-H), 1.36 (d, J = 7 Hz, 3H, C21-CH_3), 1.28 (d, J = 6 Hz, 3H, 1 CH_3 in digitoxose), 1.20 (d, J = 6 Hz, 6H, 2 CH_3 in digitoxose), 1.03 (s, 3H, 18-CH_3), 0.97 (s, 3H, 19-CH_3). The benzylated derivative 4a was hydrogenated in a mixture of ethanol and benzene (2:1) over 10% Pd/C. Preparative T.L.C. on silicic acid gave the pure epimer 5 in a yield of 82%. After crystallization from chloroform-ether, compound 5 melted at 243-245°C; $[\alpha]_D^{24}$ +27.15° ($CHCl_3$); ir ($CHCl_3$) ν_{max}: 3550 (OH), 1710 (C=O), 1630 cm^{-1} (C=C); pmr ($CDCl_3$) δ: 6.16 (broad s, C22-H), 4.90 (m, $W_{\frac{1}{2}}$ = 20 Hz, 4H, 3 anomeric H

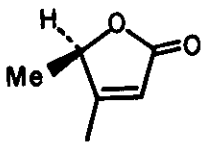
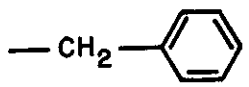


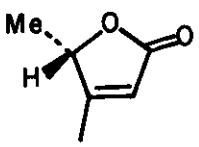
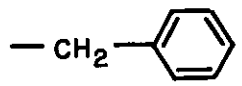
1 R_1 =  , R_2 = H

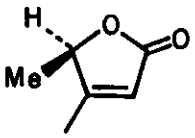
2 R_1 =  , R_2 = 

3a R_1 =  , R_2 = 

3b R_1 =  , R_2 = 

4a R_1 =  , R_2 = 

4b R_1 =  , R_2 = 

5 R_1 =  , R_2 = H

and C21-H), 1.42 (d, J = 7 Hz, 3H, C21-CH_3), 1.29 (d, J = 6 Hz, 3H, CH_3 in digitoxose), 1.23 (d, J = 6 Hz, 6H, 2 CH_3 in digitoxose), 0.93 (s, 3H, 19-CH_3), 0.89 (s, 3H, 18-CH_3).

Mild hydrolysis of 5 (room temperature, *methanol-benzene-0.01M HCl*) *yielded* (21R)-21methyldigitoxigenin (mp 246-247°C), identical in all respects with an authentic sample of this compound.[3] The crystal and molecular structure of our original sample of this material has been solved by E. J. Gabe[5] and thus the (21R) configuration can be assigned to it with certainty. Consequently, the (21R)-21methyldigitoxin structure can be rigorously assigned to our final product 5.

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