ON CARDIOACTIVE STEROIDS VI.[1] THE SYNTHESIS OF 17α-METHYL CARDENOLIDES

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Abstract -- Two methods for the simple synthesis of the $\Delta^{14,15}$-17α-methyl cardenolide 1 are disclosed. This material may be functionalized to a variety of 17α-methyl derivatives for pharmacological testing. As an example, the preparation of 17α-methyl digitoxigenin 20 is described.

In connection with our systematic studies of structure-activity-toxicity relationships in the series of cardioactive steroids, we were interested in the synthesis of 17α-methyl cardenolides. We disclose herein two simple methods for the preparation of the unsaturated lactone 1 and the conversion of this derivative to 17α-methyl digitoxigenin 20.

The starting material for the first method was the furyl derivative 2.[2] Oxidation of the C-15 hydroxyl by μ-oxo-bis(chlorotriphenylbismuth)[3] in CH_2Cl_2 at reflux for 7 h gave the ketone 3[†] (mp 150-152°C) in a yield of 94%; ir ($CHCl_3$) ν_{max}: 1695, 1600 cm^{-1} (conjugated C=O); pmr ($CDCl_3$) δ: 1.03, 1.23 (s, 3H each, 19- and 18-CH_3, respectively), 6.00 (s, 1H, vinylic H).

Most methods currently used for 1-4 additions to conjugated ketones failed with compound 3. We have finally succeeded to prepare compound 4 (mp 126-127°C) in a yield of 81% by treating the ketone 3 with trimethyl aluminum and nickel acetyl acetonate in ether-THF according to Bagnell et al.[4]; ir ($CHCl_3$) ν_{max}: 1730 cm^{-1}

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[†] All compounds gave molecular ions in mass spectroscopy and all spectral data in agreement with the structures assigned to them. All crystalline compounds gave satisfactory values in C/H analysis.

(C=O); pmr ($CDCl_3$) δ: 0.60, 0.98, 1.43 (s, 3H each, 18-, 19- and 17-CH_3, respectively).

The ketone 4 was reduced with $NaBH_4$ in THF and the oily mixture of the epimeric alcohols 5 and 6 was obtained in quantitative yield. It was immediately oxidized to the cardenolides 7 and 8 by our previously described[2] procedure with m-chloroperbenzoic acid followed by $NaBH_4$. The yield of both epimers was 95%. Compounds 7 and 8 were separated by chromatography on silica gel and they were obtained in a ratio 3:1.[††] The major epimer 7 remained oily; ir ($CHCl_3$) ν_{max}: 3610, 3500 (OH), 1790, 1750, 1620 cm^{-1} (conjugated lactone); pmr ($CDCl_3$) δ: 0.93, 1.02, 1.12 (s, 3H each, 3-CH_3), 4.30 (m, 1H, C15α-H).

The C15β-alcohol 7 was treated with methanesulfonyl chloride in pyridine for 30 min at 0°C and for 5 h at 60°C. The 14-15 unsaturated compound 1 (mp 128.5-130°C) was obtained in a yield of 77%; ir ($CHCl_3$) ν_{max}: 1780, 1750, 1625 (conjugated lactone); pmr ($CDCl_3$) δ: 4.80 (d, J = 2 Hz, 2H, allylic H of lactone), 5.23 (broad s, 1H, C15-H), 5.93 (broad s, 1H, vinylic H of lactone).

The second method for the preparation of the derivative 1 was based on the studies of Solo et al. concerning the Diels-Alder addition of steroidal ring D dienes.[5] The diene 10 (mp 53-55°C) was prepared in a yield of 88% by the reaction of the ketone 9[2] with methyl lithium in ether at 0°C, followed by refluxing the resulting tertiary allylic alcohol with hydrochloric acid in acetone; pmr ($CDCl_3$) δ: 1.80 (s, 3H, C17-CH_3), 5.77 (m, 1H, C16-H), 5.90 (m, 1H, C15-H). The diene 10 was heated to 90°C with an excess of ethyl propiolate and a single adduct (mp 103-105°C) 11 was isolated in a yield of 75%; ir ($CHCl_3$) ν_{max}: 1705 cm^{-1} (C=O); pmr ($CDCl_3$) δ: 0.97, 1.03, 1.40 (s, 3H each, 19-, 18- and 17-CH_3, respectively), 6.50 (d, J = 4 Hz, 1H, C16-H), 6.62 (d, J = 4 Hz, 1H, C15-H), 7.53 (s, 1H, H-C=C-C=O).

Selective hydrogenation of the disubstituted double bond in the adduct 11 was achieved with Pd-$CaCO_3$ in benzene. The dihydro derivative 12 (mp 118-120°C) was obtained in a yield of 93%; ir ($CHCl_3$) ν_{max}: 1700 cm^{-1} (CO); pmr ($CDCl_3$) δ: 6.90 (s, 1H, H-C=C-C=O).

The compound 12 was oxidized in a mixture of acetone and water with an excess of

[††]The minor epimer 8 was oxidized with CrO_3-dipy in CH_2Cl_2 and reduced with $NaBH_4$ at 0°C to a 3:1 mixture of 7 and 8. The configuration of the 15-hydroxy group in the major epimer 7 follows from the regiospecific elimination of the corresponding mesylate to yield the Δ 14-15 derivative 1.

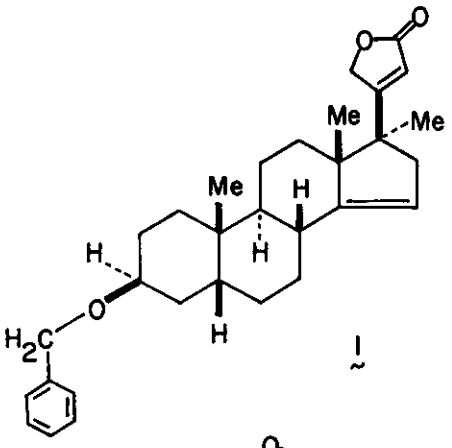
metaperiodate and potassium permanganate. The pure compound 13 was isolated as a foam by chromatography on silica gel using ether-hexane (1:10) as eluent in a yield of 69.3%; ir ($CHCl_3$) ν_{max}: 1750 (-CH=O), 1730 (ester C=O), 1720 cm^{-1} (C=O); pmr ($CDCl_3$) δ: 0.97 (s, 3H, 19-CH_3), 1.27 (s, 6H, C17- and 18-CH_3), 1.00 (t, J = 7 Hz, 3H, CH_2-$\underline{CH}_3$), 4.23 (q, J = 6 Hz, 2H, $\underline{CH}_2$-CH_3), 8.87 (s, 1H, CH=O).

The aldehyde group in compound 13 was oxidized with Jones' reagent at 0°C to a carboxy group. Remarkably the unreactive α-ketoester group remained intact and the carboxyl was immediately subjected to a decarboxylation in dry benzene and pyridine (20:1) with lead tetraacetate and cupric acetate. The pure unsaturated ketoester 14 was isolated by chromatography on silica gel as a foam in a yield of 60%; ir ($CHCl_3$) ν_{max}: 1740 (ester C=O), 1720 cm^{-1} (C=O); pmr ($CDCl_3$) δ: 0.97 (s, 6H, 19- and 18-CH_3), 1.35 (t, J = 7 Hz, 3H, -CH_2-$\underline{CH}_3$), 1.30 (s, 3H, C17-CH_3), 4.33 (q, 2H, J = 6 Hz, -$\underline{CH}_2$-CH_3), 5.10 (broad s, 1H, C15-H).

The configuration of the 17-methyl group in compound 14 follows from the known stereochemistry of the Diels-Alder addition.[cf. 5] It also follows from the correlation with compound 1 and from the comparison of the pmr spectrum of the 17α-methyl digitoxigenin 20 with that of digitoxigenin.

The ketoester 14 was quantitatively reduced with an excess of $LiAlH_4$ in ether and the crude diol was selectively acetylated for 1 h at room temperature in a mixture of dioxane-pyridine and acetic anhydride. The monoacetate 15 (mp 56-58°C) was obtained in a yield of 92%; ir ($CHCl_3$) ν_{max}: 3625 (OH), 1735 cm^{-1} (C=O); pmr ($CDCl_3$) δ: 2.08 (s, 3H, CO-CH_3). Compound 15 was oxidized with Jones' reagent and the oily ketone 16 was purified by preparative tlc on silica gel. It was obtained in a yield of 85%; ir ($CHCl_3$) ν_{max}: 1710 (C=O), 1730 cm^{-1} (CH_3-CO-); pmr ($CDCl_3$) τ: 2.13 (s, 3H, CO-$\underline{CH}_3$), 4.83 (s, 2H, -$\underline{CH}_2$-O-Ac), 5.17 (broad s, 1H, C15-H).

The acetoxy ketone 16 was converted to the alcohol 17 by methanolysis in the presence of potassium carbonate and this material was tetrahydro-pyranylated in methylene chloride in the presence of pyridinium p-toluenesulfonate. The tetrahydro-pyranyl derivative 18 was subjected to a reaction with lithium ethoxy-acetylide in benzene-ether and the crude material thus obtained was stirred with methanolic hydrochloric acid. The product was purified by chromatography and crystallization (mp 129-130°C). It was obtained in an overall yield of 55% from the acetoxy ketone 16 and it was identical by mixed mp, tlc, and all spectral



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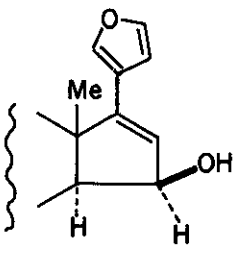

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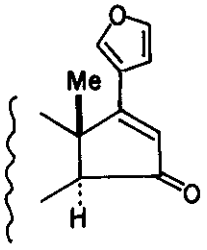

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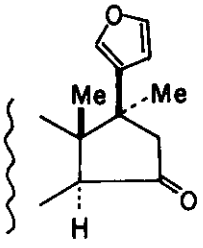

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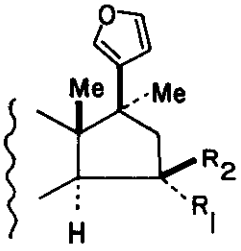
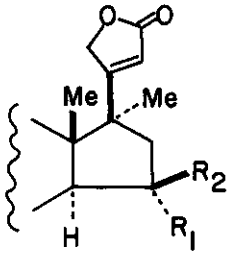


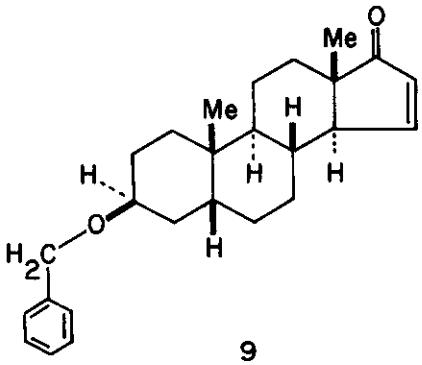
5 R_1=H, R_2=OH

6 R_1=OH, R_2=H



7 R_1=H, R_2=OH

8 R_1=OH, R_2=H



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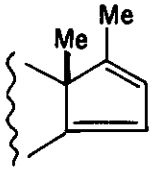

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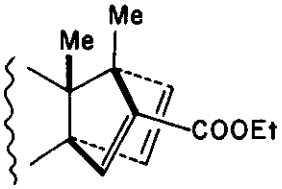

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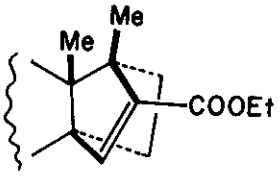

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data with the unsaturated lactone 1. While it is clear that the Diels-Alder approach to compound 1 is less efficient than the furan approach, it is nevertheless of considerable interest. The readily obtainable compound 13 may, for example, serve as starting material for a variety of C14-β carbon substituted cardenolide analogues which we have tried to prepare without much success by other routes.

The conversion of compound 1 to 17α-methyl digitoxigenin 20 was performed as in our previous work,[2] but it proceeded in a poorer yield and with only low stereoselectivity. Compound 1 was treated with NBS in aqueous acetone (10% H_2O) and the resulting bromohydrin was debrominated with Raney nickel in a mixture of methanol and methylene chloride. The benzyl derivative 19 (mp 182-183°C) was obtained in a yield of 35% besides 20% of the 14α-hydroxy derivative and 20% of starting material. The 14α-hydroxy derivative was quantitatively dehydrated to compound 1 and thus the effective yield was somewhat improved; ir ($CHCl_3$) ν_{max}: 3605, 3480 (OH), 1745, 1605 cm^{-1} (unsaturated lactone); pmr ($CDCl_3$) δ: 1.17 (s, 3H, 17α-CH_3), 0.97 (s, 3H, 19-CH_3), 0.92 (s, 3H, 18-CH_3).

Compound 19 was debenzylated with palladium on charcoal in an ethanol-benzene mixture to yield 92% of 17α-methyl digitoxigenin 20 (mp 253-255°C); ir ($CHCl_3$) ν_{max}: 3605, 3450 (OH), 1745, 1605 cm^{-1} (unsaturated lactone); pmr ($CDCl_3$) δ: 5.78 (t, J = 2 Hz, 1H, C22-H), 5.11, 4.97 (2d, J = 2 Hz, 1H each, C21-H_2), 1.17 (s, 3H, C17-CH_3), 0.97 (s, 3H, 19-CH_3), 0.93 (s, 3H, 18-CH_3).

The only feature in the pmr spectrum of compound 20 which is strikingly different from the corresponding spectrum of digitoxigenin (except of course for the presence of the C17-CH_3 singlet) is the pattern due to the two diastereotopic C21-hydrogens. These in the case of digitoxigenin give rise to two doublets at δ = 4.81 and 4.87 (J = 2 Hz). It is believed that differences in the rotational barrier around the C_{17}-C_{20} bond and in the populations of different rotomers may be the cause of the different pmr patterns and it is expected that these different rotational properties will also influence the pharmacologic parameters of compound 20.

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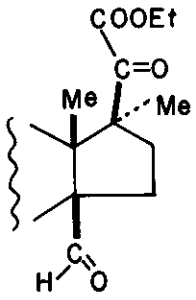

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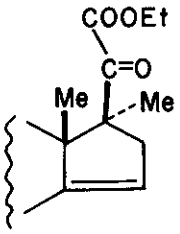

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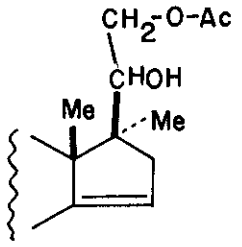

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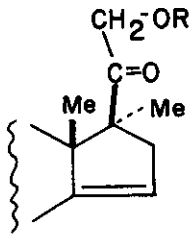
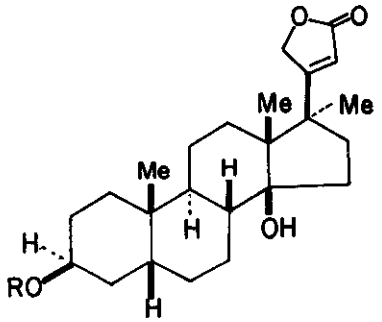


16 R = -CO-Me

17 R = H

18 R = THP



19 R = $-CH_2-C_6H_5$

20 R = H

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