A SIMPLE SYNTHESIS OF CARDENOLIDES AND THEIR LESS TOXIC ISOMERS VIA FURYL INTERMEDIATES

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Abstract - A novel efficient and stereospecific synthesis of digitoxigenine (19) and its isomer (23) via the common intermediate (15) is described.

DISCUSSION

Many years ago one of us (K.W.) proposed a synthesis of cardiac aglycones which would start with tertiary carbinols of the type (I) obtainable by the action of β-furyllithium on suitable steroidal 17-ketones. It was hoped that these compounds could be modified to 17-β,furylsteroids (II). Mechanistic considerations justified the expectation that these furyl intermediates (II) were capable of being oxidized by peracids to normal cardenolides (III) and by N-bromosuccinimide to the cardenolide isomers (IV), respectively.

Model experiments performed on isopropyl furan (V) have shown that this last expectation was indeed correct.[1] The oxidation of a furan may be represented (see formula V) as an attack of an electrophile at the less-hindered α-position, followed by a nucleophilic attack at the remaining α-site. This in the case of NBS lead to the intermediate (IX) which yielded the lactone (X) by elimination of HBr.

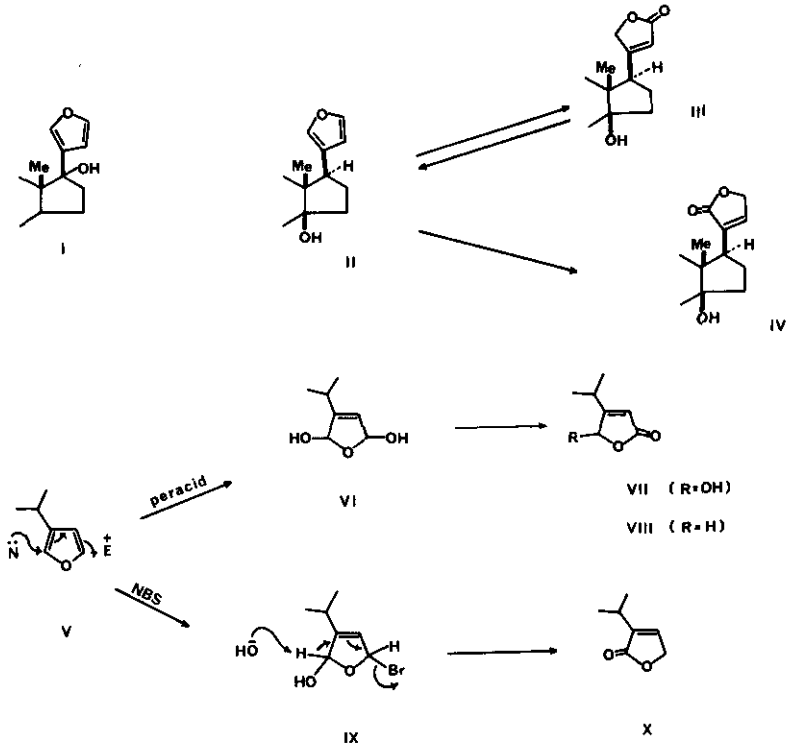
Peracid oxidation proceeded probably via the intermediate (VI) which underwent further oxidation to the hydroxy lactone (VII). This last compound was reduced with $NaBH_4$ to the unsaturated lactone (VIII). It will be shown in the present communication that the yields of all these reactions are capable of considerable improvement.

While the total synthesis of the furyl intermediates (II) from 17-keto steroids was up to the present time never successfully carried out, these compounds were

obtained by hydride reduction of natural cardenolides (III). Moreover, the transformation of the furyl derivatives (II), prepared by reduction from natural cardenolides, yielded as predicted selectively the lactones of the type (III) or (IV).[1] On pharmacological testing the isolactone derivatives (IV) have turned out to display "more rapid onset of action, quick reversibility of toxic effects and a greater margin between therapeutic and toxic doses".[2]

We now wish to disclose a simple and efficient total synthesis of digitoxigenine (19) and its isomer (23) via the furyl derivative (15).

The starting material was the α,β-unsaturated ketone (11) readily prepared in high yield from testosterone (1). The simple and essentially known operations which were used in this preparation are portrayed in Scheme II. The ketone (11) was treated with β-furyllithium[3] in ether and the tertiary carbinol (12) was obtained in a yield of 93%†[I.R. ($CHCl_3$) ν_{max}: 3600 cm^{-1} (OH); N.M.R. ($CDCl_3$) τ: 2.65 (s, 5H, benzyl aromatic), 2.57, 2.78, 3.58 (broad s, 1H each, furyl), 3.91 (d, J = 6, 1H, 15-H), 4.28 (dd, J = 6, 1H, 16-H), 5.52 (s, 2H, benzylic), 6.3 (broad



Scheme I

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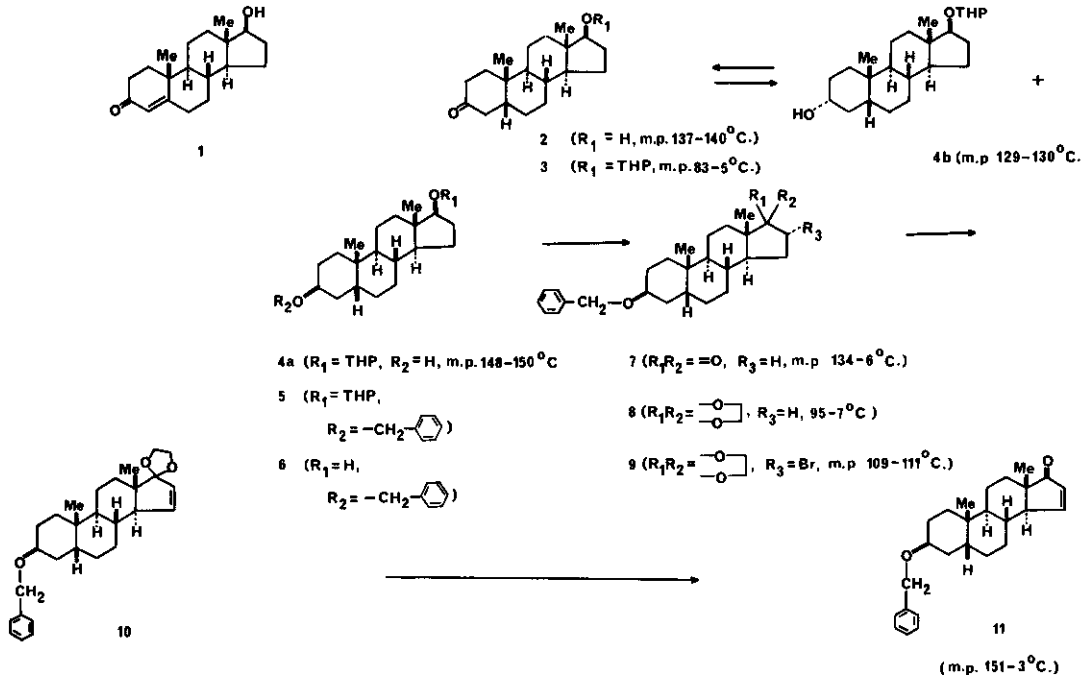
† All compounds gave correct molecular ions in mass spectrometry; all crystalline compounds gave acceptable analyses for carbon and hydrogen.

s, 1H, 3α-H), 8.96 (s, 3H, 19-CH_3), 9.0 (s, 3H, 18-CH_3)]. This material was acetylated with acetic anhydride and pyridine and the crude acetate (13) was subjected to an allylic rearrangement in refluxing aqueous acetone in the presence of calcium carbonate. The resulting secondary allylic alcohol (14) was obtained after chromatography on silica gel in a yield of 87% from (12) [I.R. ($CHCl_3$) ν_{max}: 3605 cm^{-1} (OH), no acetoxy carbonyl absorption; N.M.R. ($CDCl_3$) τ: 2.67 (s, 6H, benzyl aromatic and furyl), 2.48, 3.5 (broad s, 1H each, furyl), 4.08 (d, J = 3, vinylic H), 5.47 (broad s, 1H, 15α-H), 5.51 (s, 2H, benzylic), 6.28 (broad s, 1H, 3α-H), 8.71 (s, 3H, 18-CH_3), 8.93 (s, 3H, 19-CH_3)]. It should be pointed out that the rearrangement was stereospecific and yielded the 15-β hydroxy compound in spite of the clear preference of our system for a nucleophilic attack from the α-side.[4] Hydrogenation of compound (14) with 10% Pd-$CaCO_3$ in ethanol was stereospecific and gave the saturated alcohol (15) (m.p. 109-110°C.) in a yield of 92% after crystallization from ether-hexane [I.R. ($CHCl_3$) ν_{max}: 3605, 3420 cm^{-1} (OH); N.M.R. ($CDCl_3$) τ: 2.63 (s, 6H, benzyl aromatic and furyl), 2.75, 3.68 (broad s, 1H each, furyl), 5.49 (s, 2H, benzylic), 5.65 (t, J = 7, 1H, 15α-H), 6.28 (broad s, 1H, 3α-H), 8.97 (s, 3H, 19-CH_3), 9.21 (s, 3H, 18-CH_3)].

The furyl derivative (15) was treated with m-chloroperbenzoic acid in a mixture of chloroform, acetic acid and sodium acetate. The crude oxidation product which contained mostly the corresponding hydroxy lactone was immediately without isolation reduced in a two phase-system (CH_2Cl_2-H_2O) at room temperature with sodium borohydride for three hours. The pure oily lactone (16) was obtained after chromatography on silica gel in a yield of 87% [I.R. ($CHCl_3$) ν_{max}: 3610, 3480 (OH), 1785, 1750 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.64 (s, 5H, benzyl aromatic), 4.11 (broad s, 1H, 22-H), 5.23 (broad s, 2H, 21-H), 5.48 (s, 2H, benzylic), 5.62 (t, J = 7, 1H, 15α-H), 6.27 (broad s, 1H, 3α-H), 8.97 (s, 3H, 19-CH_3), 9.09 (s, 3H, 18-CH_3)]. Treatment of the hydroxy lactone (16) with mesyl chloride in pyridine yielded 85% of the crystalline 14-15 unsaturated product (17) (m.p. 151-2°C.) [I.R. ($CHCl_3$) ν_{max}: no hydroxy absorption, 1784, 1750 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.67 (s, 5H, benzyl aromatic), 4.11 (t, J = 1, 1H, 22-H), 4.77 (d, J = 2, 1H, 15-vinylic), 5.25 (d, J = 2, 2H, 21-H), 5.49 (s, 2H, benzylic), 6.28 (broad s, 1H, 3α-H), 9.01 (s, 3H, 19-CH_3), 9.18 (s, 3H, 18-CH_3)]. The introduction of the 14-β hydroxyl function was performed by a modification of the method described by Engel and Bach.[5] The olefin (17) was brominated with N-bromoacetamide in an acetic acid-water-acetone mixture and the crude reaction product was

stirred with Ra-Ni in a mixture of methylene chloride, methanol and potassium acetate. Under our conditions the reaction was completely regio- and stereo-specific and gave 3-benzyldigitoxigenine (18) (m.p. 152-3°C.) in a yield of 78% after crystallization from ether-chloroform [I.R. ($CHCl_3$) ν_{max}: 3600, 3450 (OH), 1785, 1748 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.65 (s, 5H, benzyl aromatic), 4.13 (t, J = 2, 1H, 22-H), 5.12 (t, J = 2, 2H, 21-H), 5.5 (s, 2H, benzylic), 6.28 (broad s, 1H, 3α-H), 9.03 (s, 3H, 19-CH_3), 9.11 (s, 3H, 18-CH_3)]. Finally, hydrogenolysis of the benzyl group over Pd-charcoal in an ethanol-benzene mixture yielded 93% of crystalline (m.p. 253-5°C.) digitoxigenine (19), which was identical with the natural compound by mixed melting point, T.L.C. and all spectral data.

In order to synthesize the digitoxigenine isomer (23) the furan intermediate (15) was oxidized with N-bromosuccinimide in a mixture of sodium acetate, water and dioxane and the crude oxidation product was treated with zinc in acetic acid to



Scheme II

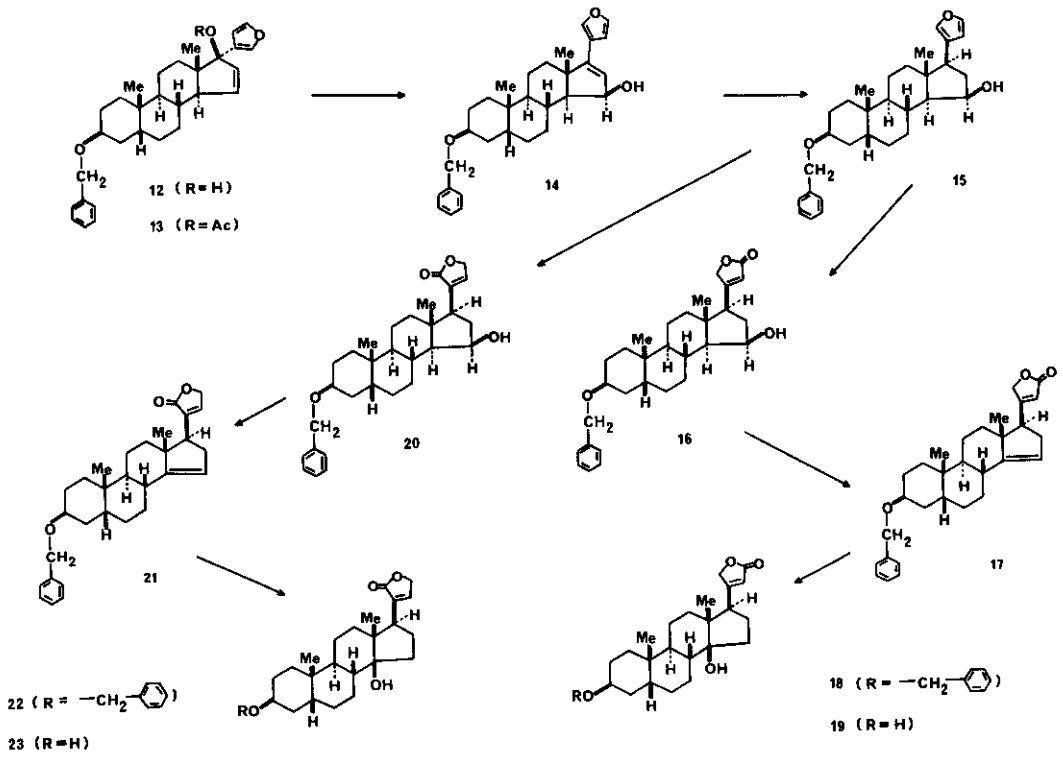
(1)→(2): H_2, $Pd/CaCO_3$, EtOH; (2) → (3): dihydropyrane, PTS, CH_2Cl_2; (3) → (4a) + (4b): sec. butanol, Al t-butoxide, benzene; (4b) → (3): CrO_3/Py, CH_2Cl_2; (4a) → (5): NaH, benzyl bromide, dioxane; (5) → (6): 2% HCl, MeOH: (6) → (7): CrO_3/Py, CH_2Cl_2; (7) → (8): PTS, $HO(CH_2)_2OH$, benzene; (8) → (9): pyridinium bromide perbromide, THF; (9) → (10): DMS, K t-butoxide; (10) → (11): acetone, H_2O, PTS.

reduce the small amount of brominated material. The pure oily lactone (20) was isolated by chromatography on silica gel in a yield of 83% [I.R. ($CHCl_3$) ν_{max}: 3610, 3470 (OH), 1752 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.69 (s, 5H, benzyl aromatic), 2.86 (broad s, 1H, 22-H), 5.25 (broad s, 2H, 23-H), 5.53 (s, 2H, benzylic), 5.72 (t, J = 7, 1H, 15α-H), 6.28 (broad s, 1H, 3α-H), 9.0 (s, 3H, 19-CH_3), 9.17 (s, 3H, 18-CH_3)]. The conversion of the hydroxy lactone (20) to the desired final product (23) was performed in exactly the same manner as the transformation of the isomer (16) to digitoxigenine.

Dehydration of (20) yielded 87% of the Δ-14,15 lactone (21) (m.p. 159-160°C.) [I.R. ($CHCl_3$) ν_{max}: no hydroxy absorption, 1755 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.65 (s, 5H, benzyl aromatic), 2.81 (t, J = 2, 1H, 22-H), 4.76 (d, J = 2, 1H, 15-vinylic), 5.2 (t, J = 2, 2H, 23-H), 5.5 (s, 2H, benzylic), 6.26 (broad s, 1H, 3α-H), 9.01 (s, 3H, 19-CH_3), 9.23 (s, 3H, 18-CH_3)]. Hydroxylation of (21) gave 75% of the benzyl hydroxy lactone (22) (m.p. 212-3°C.) [I.R. ($CHCl_3$) ν_{max}: 3600, 3440 cm^{-1} (OH), 1750 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.67 (s, 6H, benzyl aromatic and 22-H), 5.23 (d, J = 2, 2H, 23-H), 5.51 (s, 2H, benzylic), 6.28 (broad s, 1H, 3α-H), 9.03 (s, 3H, 19-CH_3), 9.16 (s, 3H, 18-CH_3)].

Finally, hydrogenolysis of this last derivative gave the totally synthetic digitoxigenine isomer (23) (m.p. 101-3°C.) in a yield of 90% [I.R. ($CHCl_3$) ν_{max}: 3610, 3445 (OH), 1747 cm^{-1} (>C=O); N.M.R. ($CDCl_3$) τ: 2.67 (broad s, 1H, 22-H), 5.17 (d, J = 2, 2H, 23-H), 5.83 (broad s, 1H, 3α-H), 9.03 (s, 3H, 19-CH_3), 9.16 (s, 3H, 18-CH_3).

Compound (23) was identical in all respects with the same material prepared from natural digitoxigenine.[1] We believe that the simple synthetic operations disclosed in this communication will form an efficient basis for a systematic manipulation of the cardenolide molecule with the objective of achieving a further improvement in its therapeutic parameters.



Scheme III

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