

ON CARDIOACTIVE STEROIDS VII. THE CONVERSION OF DIGITOXIGENIN
TO ISOMERS OF NATURAL BUFALIN AND RESIBUFOGENIN

Franz Josef Jäggi, Thomas Y. R. Tsai, and Karel Wiesner*

Natural Products Research Centre, University of New Brunswick,
Bag Service #45222, Fredericton, New Brunswick, Canada E3B 6E2

Abstract -- A high yield conversion of digitoxigenin I to α -
isobufalin 1 and β -isoresibufogenin 2 is described.

In the first Communication of this series¹ we have described the conversion of digitoxigenin I to the isolactone III via the furan derivative II. The glucoside of compound III was subjected to extensive pharmacological studies^{2,3,4} which have revealed a greater margin of safety and reversibility of toxic effects in comparison with the naturally occurring glycosides of digitalis currently used in therapy. We now wish to disclose a simple conversion of digitoxigenin I to α -isobufalin 1 and β -isoresibufogenin 2. This process has enabled us to prepare efficiently large samples of the corresponding glucosides for pharmacology.⁵

The furan derivative II was benzylated with sodium hydride, 18-crown-6 ether and benzyl bromide in refluxing dioxane for 12 h. The dibenzyl derivative 3 (mp 140-142°C) was obtained in a yield of 88%. An ether solution of compound 3 was first treated for 3 h at -70°C with n-butyl lithium and then with dimethylformamide under ice cooling.

The formyl derivatives 4 and 11 were obtained in a yield of 86% (in a ratio 3:2) and separated by chromatography on silica gel. Compound 4[†] was recrystallized from ether-hexane and melted at 138-139°C; ir (CHCl₃) ν_{\max} : 1670 cm⁻¹ (C=O); pmr (CDCl₃) δ : 9.72 (s, 1H, CH=O), 7.30 (11 H, aromatic + furan α H), 6.30 (d, J = 2 Hz, 1H, furan β H), 4.59, 4.48 (2s, 2H each, benzylic H). Compound 11
.....

[†] All compounds gave correct molecular ions in mass spectrometry and all crystalline compounds gave satisfactory C/H analyses.

melted at 134-135°C (ether-hexane); ir (CHCl₃) ν_{\max} : 1675 cm⁻¹ (C=O); pmr (CDCl₃) δ : 9.08 (s, 1H, CH=O), 7.35 (11 H, aromatic + furan α H), 6.90 (s, 1H, furan β H), 4.60, 4.50 (2s, 2H each, benzylic H).

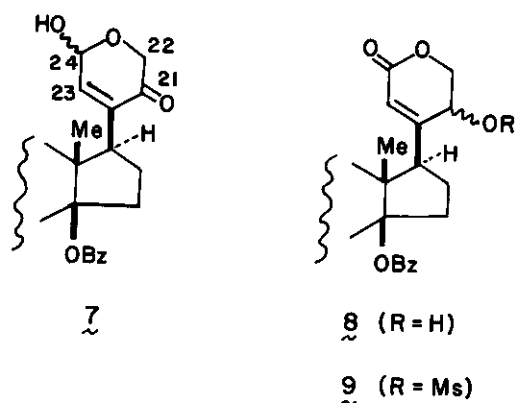
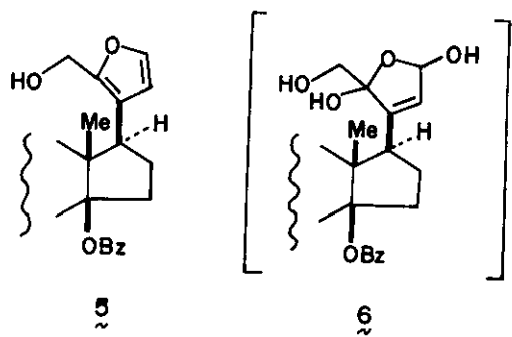
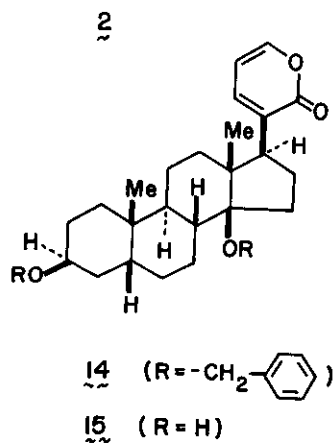
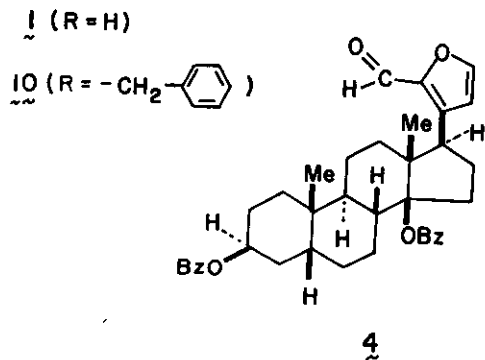
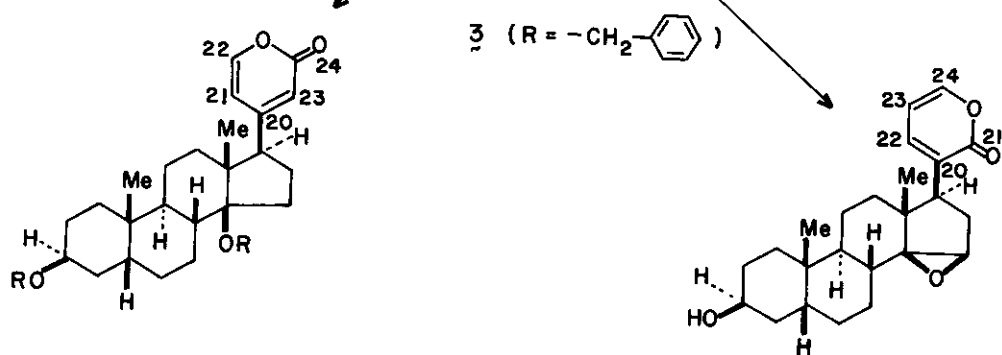
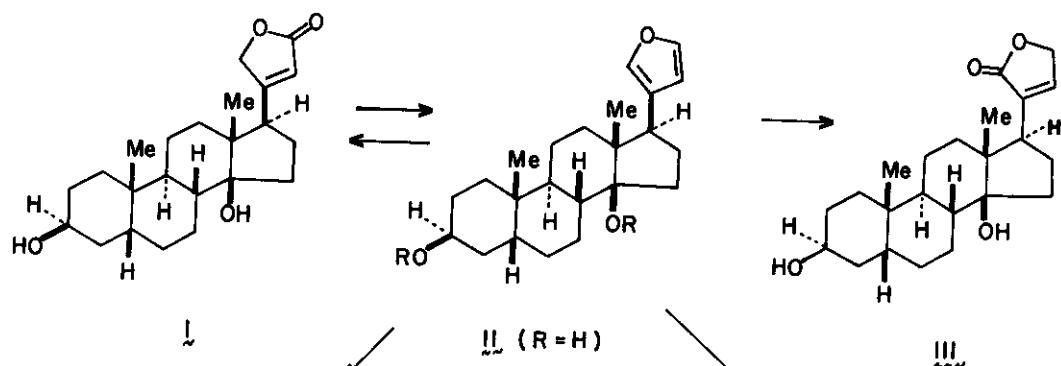
Compound 4 was reduced quantitatively with LiAlH₄ in ether to the oily alcohol 5 [ir (CHCl₃) ν_{\max} : 3605, 3440 cm⁻¹ (OH)] and this material was oxidized in CH₂Cl₂ in the presence of sodium acetate with m-chloroperbenzoic acid. The mixture of epimeric hemiacetals 7 was obtained in a yield of 90%. Presumably the primary oxidation product 6 was immediately transformed into the more stable pyranose form 7; ir (CHCl₃) ν_{\max} : 3590, 3350 (OH), 1685 (C=O), 1640 cm⁻¹ (C=C); uv $\lambda_{\max}^{\text{EtOH}}$: 237 nm (log ϵ = 3.85); pmr (CDCl₃) δ : 7.31 (10 H, aromatic H), 6.62, 6.47 (2d, J = 3 Hz, 1H, C23-H), 5.21, 4.87 (2d, J = 3 Hz, 1H, C24-H), 4.55, 4.47 (2s, 2H each, benzylic H), 3.95 and 4.46 (2d, J = 17 Hz, 2H, C22-H).

The hemiacetal 7 was oxidized in CH₂Cl₂ with CrO₃-diPy and the relatively unstable ketolactone was immediately reduced with an excess of Zn(BH₄)₂ in ether. The oily epimeric hydroxylactones 8 were obtained in a yield of 82%; ir (CHCl₃) ν_{\max} : 3590, 3375 (OH), 1715 (C=O), 1630 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.35, 7.31 (10 H, aromatic H), 5.85, 5.65 (2s, 1H, C23-H), 4.60, 4.49 (2s, 2H each, benzylic H), 4.24, 3.83 (2d, J = 3 Hz, 1H, C22-H).

The hydroxylactone 8 was first mesylated with mesyl chloride and triethylamine in CH₂Cl₂ and the resulting derivative 9 (87%) was heated with DBN in benzene under reflux. The oily homogeneous dibenzyl α -isobufalin 10 was purified by preparative T.L.C. and obtained in a yield of 85%; ir (CHCl₃) ν_{\max} : 1710 (C=O), 1630 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.33 (10 H, aromatic H), 6.88 (d, J = 6 Hz, 1H, C22-H), 6.24 (dd, J = 2,6 Hz, 1H, C21-H), 6.00 (d, J = 2 Hz, 1H, C23-H), 4.60, 4.49 (2s, 2H each, benzylic H).

The dibenzyl derivative 10 was heated under reflux for 2 h in an ethanol-benzene mixture (2:1) with palladium hydroxide on charcoal and cyclohexene.⁶ The product α -isobufalin 11 (mp 128-129°C) was obtained in a yield of 87% after crystallization from ether-CHCl₃; ir (CHCl₃) ν_{\max} : 3610, 3450 (OH), 1715 (C=O), 1635 cm⁻¹ (C=C); uv $\lambda_{\max}^{\text{EtOH}}$: 289 nm (log ϵ = 3.73); pmr (CDCl₃) δ : 7.35 (d, J = 6 Hz, 1H, C22-H), 6.68 (dd, J = 2,6 Hz, 1H, C21-H), 6.10 (d, J = 2 Hz, C23-H), 4.13 (broad s, 1H, 3 α H), 0.96 (s, 3H, 19-CH₃), 0.78 (s, 3H, 18-CH₃).

The transformation of the formyl derivative 11 to the dibenzyl β -isobufalin 14 was accomplished in an exactly analogous manner. Reduction with LiAlH₄ and



oxidation of the resulting primary alcohol with *m*-chloroperbenzoic acid yielded 90% of the mixture of epimeric acetals 12; ir (CHCl₃) ν_{\max} : 3580, 3340 (OH), 1675 cm⁻¹ (C=O); pmr (CDCl₃) δ : 7.33, 7.28 (10 H, aromatic H), 6.03, 5.85 (2s, 1H, C22-H), 5.52, 5.26 (2s, 1H, C21-H), 4.27 (d, *J* = 4 Hz, 2H, benzylic H), 4.48 (s, 2H, benzylic H), 3.90 and 4.43 (2d, *J* = 17 Hz, 2H, C24-H).

Oxidation and reduction of this material gave a mixture of the epimeric hydroxy-lactones 13 in a yield of 80%; ir (CHCl₃) ν_{\max} : 3540, 3400 (OH), 1720 (C=O), 1640 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.31, 7.27 (10 H, aromatic H), 6.40 (d, *J* = 5 Hz, 1H, C22-H), 4.53, 4.58 (d, 2H, benzylic H), 4.47 (3H, benzylic H and C23-H), 4.03 (broad s, 2H, C24-H).

Finally, mesylation and elimination of the mesyloxy group gave dibenzyl β -isobufalin 14 in a yield of 80% in both steps. Compound 14 was recrystallized from ether-chloroform and melted at 169-170°C; ir (CHCl₃) ν_{\max} : 1700 (C=O), 1635 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.33, 7.30 (11 H, aromatic H and C24-H), 7.05 (dd, *J* = 2,7 Hz, 1H, C22-H), 5.65 (dd, *J* = 5,7 Hz, 1H, C23-H), 4.56, 4.49 (2s, 2H each, benzylic H).

Debenzylation of compound 14 by the same method as used for 10 yielded 6% β -isobufalin 15 (mp 160-162°C, ether-chloroform) and 80% of the Δ -14,15 derivative 16 (mp 216-218°C, ether-chloroform). Compound 15: ir (CHCl₃) ν_{\max} : 3600, 3420 (OH), 1695 (C=O), 1625 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.43 (dd, *J* = 2,7 Hz, 1H, C22-H), 7.36 (dd, *J* = 2,5 Hz, 1H, C24-H), 6.22 (dd, *J* = 5,7 Hz, 1H, C23-H). Compound 16: ir (CHCl₃) ν_{\max} : 3610, 3340 (OH), 1705 (C=O), 1630 cm⁻¹ (C=C); pmr (CDCl₃) δ : 7.39 (dd, *J* = 2,5 Hz, 1H, C24-H), 7.24 (dd, *J* = 2,7 Hz, 1H, C22-H), 6.20 (dd, *J* = 5,7 Hz, 1H, C23-H), 5.23 (broad s, 1H, C15-H).

We attempted to convert the Δ -14,15 derivative 16 to β -isobufalin 15 using the modified method with NBS and Raney nickel.^{cf. 7} However, in this case the intermediate bromohydrin eliminated hydrobromic acid and yielded β -isoresibufogenin 2 before hydrogenolysis of the bromine could occur.^{††} Compound 2 was obtained in a yield of 60% after crystallization from hexane-CH₂Cl₂ and melted at 229-231°C; ir (CHCl₃) ν_{\max} : 3605, 3350 (OH), 1700 (C=O), 1630 cm⁻¹ (C=C);

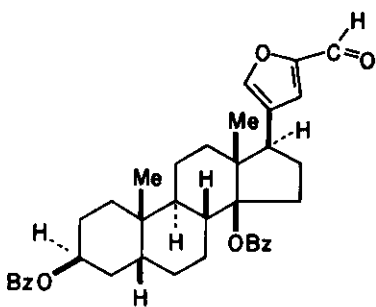
EtOH
uv λ_{\max} : 295 nm (log ϵ = 3.75); pmr (CDCl₃) δ : 7.53 (dd, *J* = 2,7 Hz, 1H,

.....

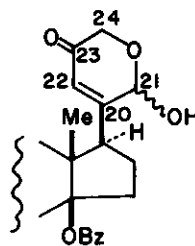
†† An analogous Δ -14,15 derivative in the α -isobufalin series was readily converted to compound 1 under the same conditions.

C22-H), 7.33 (dd, $J = 2,5$ Hz, 1H, C24-H), 6.20 (dd, $J = 5,7$ Hz, 1H, C23-H), 4.13 (broad s, 1H, 3 α -H), 3.58 (broad s, 1H, 15- α H), 1.00 (s, 3H, 19-CH₃), 0.85 (s, 3H, 18-CH₃).

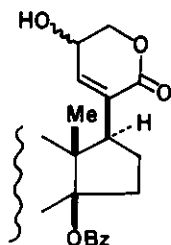
The total synthesis of α -isobufalin and β -isoresibufogenin from testosterone was also completed and will be reported in a separate paper.



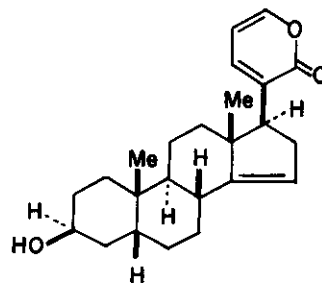
II



12



13



16

ACKNOWLEDGEMENTS

The financial support of the Natural Sciences and Engineering Research Council of Canada, the Canadian Heart Foundation and Advance Biofactures Corporation, New York, is gratefully acknowledged.

REFERENCES

1. J. M. Ferland, Y. Lefebvre, R. Deghenghi, and K. Wiesner, Tetrahedron Letters, 1966, No. 39, 3617.
2. R. Mendez, G. Pastelin, and E. Kabela, J. Pharmacol. Exp. Ther., 1974, 188, 189.
3. J. I. Gliklich, R. Gaffney, M. R. Rosen, and B. F. Hoffmann, Eur. J. Pharmacol., 1975, 32, 1.
4. C. R. Ross and N. I. Pessah, Eur. J. Pharmacol., 1975, 33, 223.
5. The results of the pharmacological studies of all our derivatives will be published in due course by Professor Rafael Mendez and his collaborators.
6. S. Hanessian, T.-J. Liak, and B. Vanasse, Synthesis, 1981, 396.
7. T. Y. R. Tsai, A. Minta, and K. Wiesner, Heterocycles, 1979, 12, 1397.

Received, 11th December, 1981