FURAN TO PYRONE CONVERSIONS

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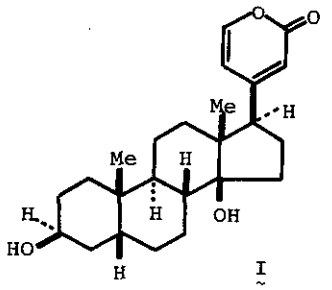
Abstract -- Conversions of the furyl derivatives 2, 3 and 6 to the α-pyrones 10 and 16 have been studied. These techniques are applicable in conjunction with our "cardenolide furan methodology" to the synthesis of bufalin III and γ-isobufalin IV, as well as to a variety of other synthetic problems.

In 1979 we have reported a new and very efficient methodology for the synthesis of cardenolides from steroidal C_{17} ketones.[1] This technique involved the setting up of a furyl group in the C_{17}-β position with a simultaneous creation of a "handle" which made it possible to introduce very simply the C_{14}-β hydroxyl. A high yield oxidation of the furyl group to an unsaturated lactone completed the synthesis.

In order to use this methodology for the synthesis of the bufadienolides a high yield furan to pyrone transformation has to be substituted for the furan to cardenolide oxidation. We have recently described one such transformation which has enabled us to prepare α-isobufalin I and β-isoresibufogenine II from digitoxigenin[2] and by total synthesis.[3] The preparation of natural bufalin III and γ-isobufalin IV requires, however, entirely different furan to pyrone transformations. These have now been worked out on model compounds and we wish to disclose them in the present Communication.†

†Our ability to do research has been restricted by an administrative decision and it is not quite clear when the corresponding total synthesis will be implemented.



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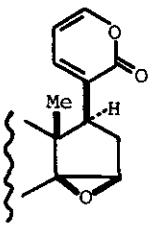

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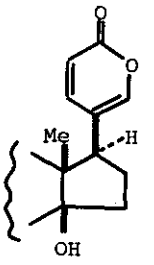

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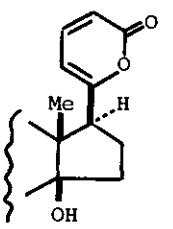

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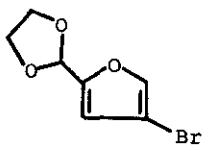

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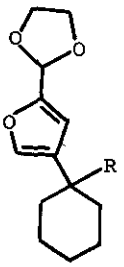

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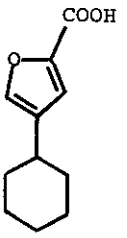
2 R = H



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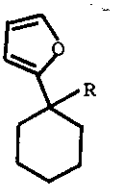
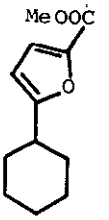


4 R = OH
5 R = H



6

The starting materials 2, 3 and 6 were prepared by simple and well-known methods which will not be discussed in detail. The bromofuryl acetal V[4] was lithiated and the resulting β-furyl lithium derivative was treated with cyclohexanone. The tertiary alcohol 1 thus obtained gave by dehydration and hydrogenation the acetal 2. This compound by deacetalization and oxidation yielded the carboxylic acid 3. Treatment of cyclohexanone with α-furyl lithium gave the tertiary alcohol 4 which was dehydrated and hydrogenated to the α-cyclohexylfuran 5. Lithiation of this material and treatment with methyl chloroformate yielded the ester 6.

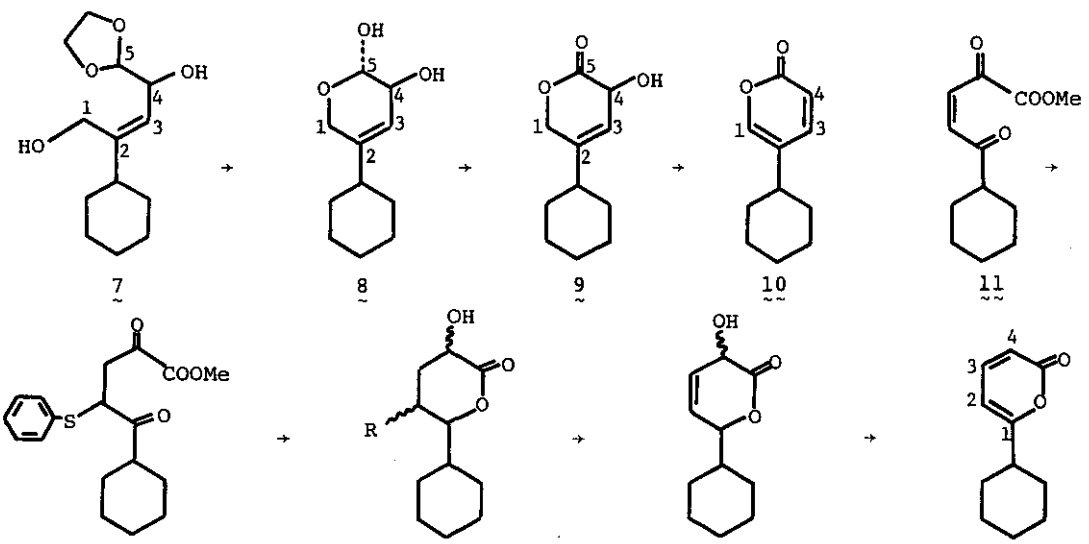
The acetal 2 was dissolved in CH_2Cl_2 and irradiated in the presence of meso-tetraphenylporphine (0.4%) for 1 h with a 100 Watt high pressure mercury lamp at -70°C while oxygen was bubbled through the solution. The resulting endoperoxide solution was treated with an excess of dimethylsulfide, evaporated to dryness, taken up in aqueous THF and 2N NaOH and reduced with an excess of $NaBH_4$. Work-up and purification by chromatography yielded 85% of the pure oily acetal 7;[††] ir ($CHCl_3$) ν_{max}: 3600, 3450 cm^{-1} (OH); pmr ($CDCl_3$) δ: 4.00 (br

[††]All compounds yielded correct molecular ions in mass spectrometry and all spectral data compatible with the structures assigned to them. All crystalline compounds yielded acceptable C/H analyses.

s, 4H, O-CH_2-CH_2-O), 4.10 (br s, 2H, C_1-H), 4.28-4.60 (m, 1H, C_4-H), 4.88 (d, J = 4 Hz, 1H, C_5-H), 5.38 (d, J = 8 Hz, 1H, C_3-H).

The diol-acetal 7 was heated under reflux in a mixture of THF and 3N HCl for 4 h. The hemiacetal 8 (presumably the diequatorial trans diastereomer, mp 70-72°C) was isolated by crystallization from ether-pentane in a yield of 96%. Compound 8 was heated under reflux with Ag_2CO_3 on Celite in benzene. The hydroxy lactone 9 (mp 82-83°C) was isolated in a yield of 70% by preparative tlc and crystallization from ether-hexane; ir ($CHCl_3$) ν_{max}: 3550 (OH), 1730 cm^{-1} (CO); pmr ($CDCl_3$) δ: 3.33 (bs, 1H, OH), 4.50-4.90 (m, 3H, C_1-H + C_4-H), 5.73 (dd, J = 2,1 Hz, 1H, C_3-H). A mixture of the hydroxy lactone 9 and triethylamine was cooled on the ice-bath and treated with mesyl chloride. The α-pyrone 10 was isolated by preparative tlc and crystallization from ether-hexane (mp 35-36°C) in a yield of 85%; ir ($CHCl_3$) ν_{max}: 1730, 1710, 1635 cm^{-1} (pyrone); uv : λ_{max}^{EtOH} = 298 nm (log ε = 3.74); pmr ($CDCl_3$) δ: 6.26 (d, J = 10 Hz, 1H, C_4-H), 7.18-7.38 (m, 2H, C_1-H + C_3-H).

The carboxylic acid 3 was subjected to sensitized oxygen addition, followed by reductive work-up exactly as described for the acetal 2. Preparative tlc on silica gel, followed by crystallization yielded 65% of the already described hydroxy lactone 9.



The sensitized oxygen addition to the ester 6 was performed as described for compound 2. After 2 h dimethylsulfide was added and the mixture was allowed to stand at -70°C for 30 min. The pure diketone 11 was isolated by chromatography on silica gel in a yield of 72%; ir ($CHCl_3$) ν_{max}: 1737, 1718, 1690, 1603 cm^{-1} (ester, ketones, double bond); pmr ($CDCl_3$) δ: 3.86 (s, 3H, OCH_3), 6.52 (d, J = 12 Hz, 1H, vinylic H), 6.83 (d, J = 12 Hz, 1H, vinylic H).

The diketone 11 was stirred for 10 min at -15°C in THF with sodium thiophenoxide. The pure oily diketone 12 was isolated by chromatography on silica gel in a yield of 86.2%; ir ($CHCl_3$) ν_{max}: 1722, 1700 cm^{-1} (CO); pmr ($CDCl_3$) δ: 3.20 (d, J = 5 Hz, 1H, CHHCO), 3.42 (d, J = 9 Hz, 1H, CHHCO), 3.84 (s, 3H, OCH_3), 4.24 (dd, J = 5,9 Hz, CHS), 7.37 (s, 5H, aromatic H).

The diketone 12 was reduced with $NaBH_4$ in methanol, the resulting diol ester was saponified with 0.5 N NaOH and the dihydroxy acid was lactonized by heating with p-toluenesulfonic acid in benzene. Chromatography on silica gel yielded 71% of the oily hydroxy lactone 13; ir ($CHCl_3$) ν_{max}: 3550 (OH), 1730 cm^{-1} (CO); pmr ($CDCl_3$) δ: 3.60-3.90 (m, 1H, CH(OH)CO), 4.10-4.30 (m, 1H, CH-O-CO), 4.50-5.00 (m, 1H, CH-S), 7.20-7.70 (m, 5H, aromatic H).

The sulfide 13 was oxidized with m-chloroperbenzoic acid in CH_2Cl_2, the excess of peracid was destroyed by addition of methyl sulfide and the sulfoxide 14 was heated under reflux in toluene for 1.5 h. Chromatography on silica gel yielded 57% of the oily hydroxy lactone 15; ir ($CHCl_3$) ν_{max}: 3550 (OH), 1730 cm^{-1} (CO); pmr ($CDCl_3$) δ: 4.50-4.90 (m, 2H, CHOH, CHOCO), 6.00 (br s, 2H, vinylic H).

Mesylation of the hydroxy lactone 15 and elimination of the mesyloxy group was performed as described for compound 9. The α-pyrone 16 (mp 39-40°C) was isolated by chromatography on silica gel and crystallization from acetone-hexane; ir ($CHCl_3$) ν_{max}: 1720, 1630, 1550 cm^{-1} (pyrone); uv: λ_{max}^{EtOH} = 301 nm (log ε = 3.56); pmr ($CDCl_3$) δ: 5.97 (d, J = 6 Hz, 1H, C_2-H), 6.16 (d, J = 9.5 Hz, 1H, C_4-H), 7.30 (dd, J = 6,9.5 Hz, 1H, C_3-H).

We have naturally tried to reduce the diketo ester 11 to a dihydroxy ester which could be converted directly to the hydroxy lactone 15. However, in this system a simultaneous reduction of the ester group could not be avoided.

ACKNOWLEDGEMENTS

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