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THE SYNTHESIS OF THE RINGS A/B IN WITHAFERIN A AND OTHER WITHANOLIDES*

M. Weissenberg, E. Glotter and D. Lavie

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

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A recent communication on the synthesis of the A/B rings moiety of withaferin A[1], prompted us to report our own approach to this probelm which is markedly different, and led to the successful preparation of the title derivatives. This study follows a detailed chemical investigation performed earlier in our laboratory[2] on the isolation and characterisation of several withanolides[2b], a group of naturally occurring C_{28} steroidal lactones identified in some species of Solanaceae[3]. Interest in the different physiological activities of withaferin A (1a)[4] led us to consider synthetic routes for the construction of the characteristic A/B rings system found in withanolides. The present communication deals with the partial synthesis of four withanolide like substitution patterns (1-4) in the cholestane (1b-4b), 17β-acetoxyandrostane (1c-4c) and 20β-acetoxypregnane (1d-2d) series.

The sequence in the cholestane series starts with compound 5b obtained in two steps from cholesterol[5]. Catalytic hydrogenation (5% Pd-$CaCO_3$ in benzene) of 5b produced quantitatively the epoxy-enone 6b m.p. 118-120° which upon treatment with $LiAlH_4$ yielded the unsaturated diol 7b; peracid epoxidation gave stereoselectively the α-epoxide 8b. Selective acetylation at C-3 followed by mild oxidation at C-1 and elimination on alumina, yielded the epoxy-enone 9b (overall yield 70% from 5b). The trans junction of the A/B rings in 9b was proved by the positive solvent shift ($\Delta CDCl_3/C_6H_6$ + 11.5 Hz) experienced in the nmr spectrum by the C-10 Me[6].Opening of the epoxide ring of 9b in acidic conditions and subsequent acetylation led to compound 10b (75%), m.p. 125-126°, nmr $\Delta CDCl_3/C_6H_6$ + 6 Hz. Dehydration of 10b ($SOCl_2$ in pyridine) followed by mild hydrolysis of the 4-acetate, gave quantitatively 2b, m.p. 125-127°, nmr δ ($CDCl_3$) 6.82 (3-H, dd, J=10 and 4.5 Hz), 6.05 (6-H, t), 5.99 (2-H, dd, J=10 and < 1 Hz), 4.64 (4-H, dd, J=4.5 and < 1 Hz), 1.45 (19-H, s)

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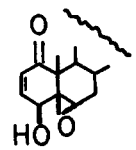

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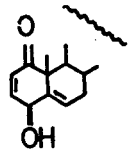

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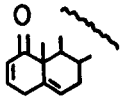

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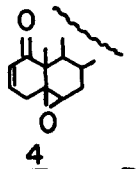

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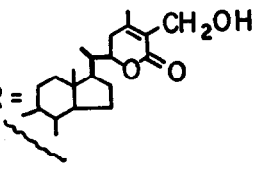

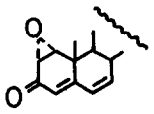

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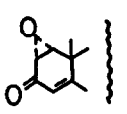

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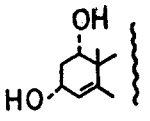

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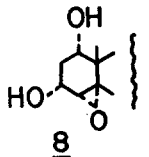

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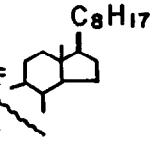

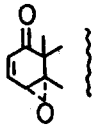

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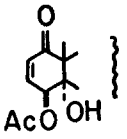

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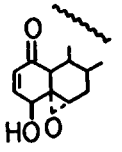

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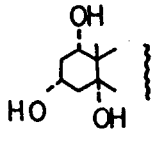

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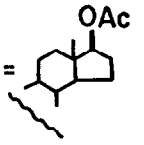

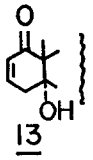

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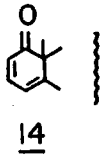

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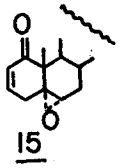

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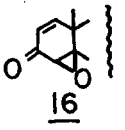

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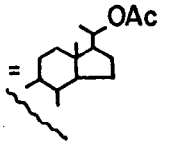

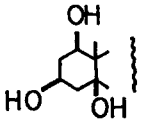

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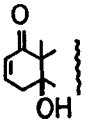

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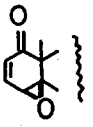

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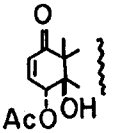

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and 0.71 (18-H, s). The corresponding androstane and pregnane derivatives were prepared using a similar set of reactions; compounds 2b, 2c (m.p. 198-200°) and 2d (m.p. 85-87°) have the A/B rings structure appearing in the withanolide 2a[3].

Stereoselective peracid epoxidation of 2b afforded quantitatively the β-epoxide 1b, m.p. 223-225° $[\alpha]_D$ + 40° (c, 0.63, $CHCl_3$), M^+ 414, nmr δ ($CDCl_3$) 6.96 (3-H, q, J=10 and 6 Hz), 6.22 (2-H, d, J=10 Hz), 3.75 (4-H, d, J=6 Hz) 3.23 (6-H, d, J=2.5 Hz), 1.40 (19-H, s) and 0.67 (18-H, s); the large downfield solvent shift ($\Delta CDCl_3/C_6H_6$ - 14 Hz) of the C-10 Me is in agreement with the boat conformation assigned to ring A in withaferin A by solvent shifts[6] and X-ray[7] analysis. Similarly 1c, m.p. 248-250°, and 1d have been prepared; they all have the A/B rings moiety of withaferin A[2a]. When the peracid epoxidation was done on the acetate derivative of 2b, a 2:1 mixture of α- and β-epoxides was obtained from which the α-epoxide only could be isolated. Following hydrolysis 11b was obtained, m.p. 185-187°, $[\alpha]_D$ + 102° (c, 0.5, $CHCl_3$), nmr $\Delta CDCl_3/C_6H_6$ + 5 Hz.

In another set of reactions, compound 6b was converted to the triol 12b by a procedure developed in the androstane series[8] and including first reduction with $NaBH_4$, then stereoselective peracid epoxidation followed by treatment with $LiAlH_4$, in an overall yield of 75%. Selective acetylation at C-3 followed by mild oxidation at C-1 and subsequent elimination on alumina gave the enone 13b, m.p. 132-133°, nmr $\Delta CDCl_3/C_6H_6$ + 12 Hz, $\Delta CDCl_3/C_5H_5N$ - 3 Hz (70% yield from 12b). Dehydration of 13b ($SOCl_2$ in pyridine) led to a 2:1 mixture of the dienone 14b[9] and 3b, easily separated to give pure 3b, m.p. 102-103°, $[\alpha]_D$ - 26.5° (c, 0.8, $CHCl_3$), λ_{max}^{EtOH} 222 nm(ε 8800), nmr δ ($CDCl_3$) 6.80 (3-H, dq, J=10, 4.5 and 2.5 Hz), 5.90 (2-H, dq, J=10, 2.5 and < 1 Hz), 5.61 (6-H, m), 1.23 (19-H, s) and 0.70 (18-H, s); 3c has been similarly prepared, m.p. 156-158°. Compounds 3b and c have the A/B rings structure encountered in withanolides F, G, H, J, L, and M[2d], and in physalins B and C[10]. Further peracid epoxidation of 3b led to a 2:1 mixture of the α- and β-epoxides 15b and 4b, which was separated to give 15b, m.p. 121-123°, nmr $\Delta CDCl_3/C_6H_6$ + 17 Hz and 4b, m.p. 114-115°, M^+ 398, nmr δ ($CDCl_3$) 6.82 (3-H, dq, J=10, 5 and 2 Hz), 6.03 (2-H, dd, J=10 and 3 Hz), 3.12 (6-H, d, J=2.1 Hz), 1.24 (19-H, s) and 0.67 (18-H, s), $\Delta CDCl_3/C_6H_6$ - 4 Hz; in a similar way compounds 15c (m.p. 181-183°) and 4c (m.p. 192-193°) were prepared. The compounds 4b-c have the A/B rings moiety found in withanolide E[2d] and jaborosalactone A[11]. In both the cholestane and androstane series, the major product of this epoxidation was found to be the α-epoxide; the β-epoxide was predominant in our previous experiments done on the peracid epoxidation of withanolide L having the system 3, however, with an additional Δ^{14}[2d].

The related compounds 17b-20b have been prepared through a similar sequence starting from 16b. The triol 17b was converted to the enone 18b (m.p. 194-196°, nmr $\Delta CDCl_3/C_5H_5N$ - 22 Hz) using the same sequence as described for 12 ⟶ 13. Dehydration of 18b ($SOCl_2$ in pyridine) gave exclusively 14b. Peracid epoxidation of 14b afforded stereoselectively the β-epoxide 19b, m.p. 155-157°, nmr $\Delta CDCl_3/C_6H_6$ - 5 Hz. The epoxide ring in 19b was opened as described

above for 9 ⟶ 10 to give 20b, m.p. 170-172°, nmr $\Delta CDCl_3/C_6H_6$ - 8 Hz. The preparation of these pairs of isomers by independent sequences constitutes as well additional proof for the configurational assignments based on the nmr data.

Further details on chemical and biological studies will be given in forthcoming publications.

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