# An Unusual D-Homo-rearrangement of a 14α,17β,20α-Trihydroxywithanolide. Crystal and Molecular Structure of 5-Hydroxy-14α,17α-epoxy-17β-methyl-5β-D-homoandrostan-1,17a-dione

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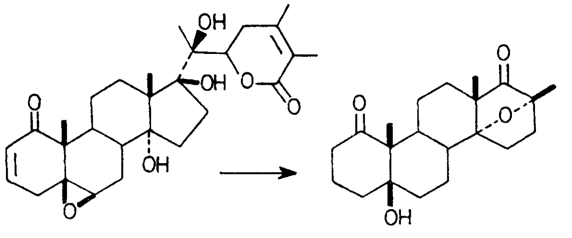
*Summary* Cleavage of the C(20)–C(22) bond in a derivative of withanolide E (**1**), followed by oxidation, afforded the D-homoandrostane derivative (**2**), whose structure was determined by *X*-ray analysis; the mechanistic aspects of this unusual rearrangement are discussed.

17-HYDROXYPREGNAN-20-ONES are known[1] to rearrange under alkaline conditions or in the presence of Lewis acids to give D-homoandrostan-17-one derivatives; the only exception is that of 17α-hydroxypregnan-20-ones, yielding under the influence of Lewis acids, D-homoandrostan-17a-one derivatives.



(1) (2)

In elucidating the structure of withanolide E (**1**),[2] a sequence of reactions involving the reductive opening of the lactone ring and subsequent cleavage of the C(20)–C(22) glycol was performed. Instead of the expected 14α, 17β-dihydroxypregnan-20-one derivative, a monoketone $C_{21}H_{32}O_4$,‡ m.p. 231 °C, $[\alpha]_D$ + 135°, $\nu_{max}$ (KBr) 1753 cm$^{-1}$, was obtained (main component). This was further oxidised to the diketone (**2**), $C_{21}H_{30}O_4.H_2O$, m.p. 215 °C, $[\alpha]_D$ + 33°, $\nu_{max}$ (KBr) 1754 and 1701 cm$^{-1}$.

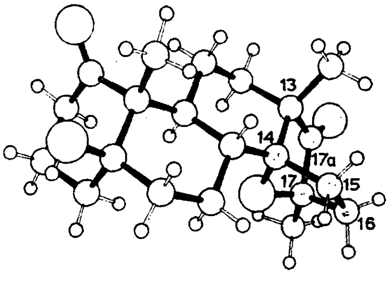


FIGURE. *X*-Ray structure of compound (**2**).

The structure of compound (**2**), *M* 364·4, was determined by *X*-ray analysis. *Crystal data*: monoclinic, space group $P2_1$; $a$ = 10·438(7), $b$ = 13·027(2), $c$ = 7·270(2) Å, $\beta$ = 92·21(6)°; $U$ = 987·8 Å$^3$; $Z$ = 2; $D_m$ = 1·24, $D_c$ = 1·23 g cm$^{-3}$. Intensity data (2283 reflections) were collected with Mo-$K_\alpha$ radiation by the balanced filter technique on a Siemens automatic diffractometer controlled by an IBM

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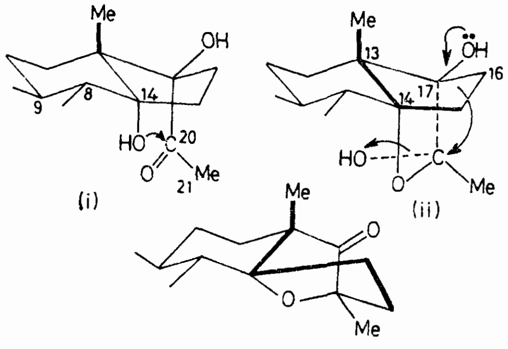
‡ Elemental analyses are by high resolution mass spectrometry.

1800 on-line computer. The structure was solved by the MULTAN[3] computer programme to $R = 0{\cdot}06$, weighted $R = 0{\cdot}085$. According to this analysis (Figure), rings A, B, and C are in the chair conformation, and the six-membered ring D is in a boat conformation. C(13), C(14), and C(15) point upwards, whereas C(16), C(17), and C(17a) point downwards; C(14) and C(17) are connected by the oxygen bridge.



(i) (ii) (iii)

It is noteworthy that the intermediate pregnan-20-one derivative rearranges even in the exceedingly mild conditions (acetone solution containing $HIO_4$ or $NaIO_4$) under which the reaction was performed. The unusual mechanistic aspect of this arrangement is that the expansion of ring D takes place by migration of the C(16)–C(17) bond rather than that of the C(13)–C(17) bond as normally occurring with 17β-hydroxypregnan-20-one derivatives.[1] This transformation (i → iii) is suggested to occur through the transient formation of a hemiacetal (ii) in which the C(16)–C(17) bond is correctly oriented for migration.

In order to prove that the rearrangement is indeed triggered by the 14α-OH group, the reaction was also performed with the related 5α,6β-dihydroxy-14-ene obtained from (**1**) by treatment with $H_2SO_4$ in acetone. Reduction of this compound with $LiAlH_4$ followed by oxidative cleavage with $HIO_4$ afforded the expected 17β-hydroxypregn-14-en-20-one.

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[1] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' ch. 5.11, and references cited therein, Elsevier, Amsterdam, 1968.

[2] D. Lavie, I. Kirson, E. Glotter, D. Rabinovich, and Z. Shakked, *J.C.S. Chem. Comm.*, 1972, 877.

[3] G. Germain, P. Main, and M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.