Intramolecular 1,2-Hydride Shift in the Rearrangement of Steroidal 16β-Hydroxy-17-ones to 17β-Hydroxy-16-ones

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Isotopic labelling experiments using [16α-^{2}H]-3β,16β-dihydroxy-5α-androstan-17-one (**1**) show that an intramolecular 1,2-hydride shift mechanism is operative in its rearrangement to the corresponding 17β-hydroxy-16-one with both base and acid.

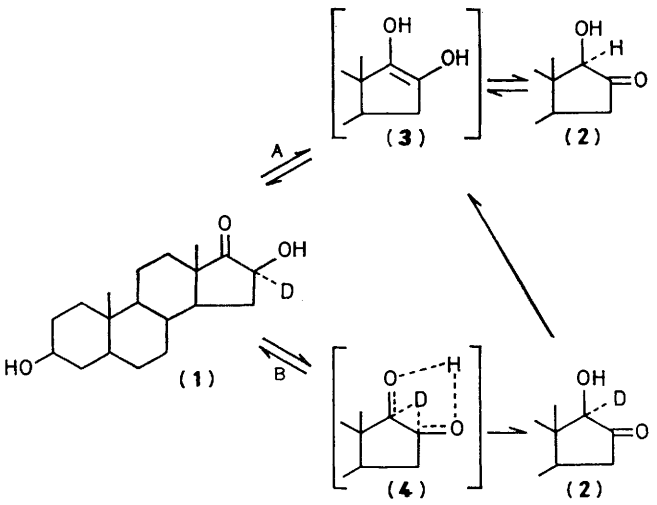
Steroidal 16β-hydroxy-17-ones isomerize to the most stable ketol, the 17β-hydroxy-16-one, with both base and acid. Two mechanisms are feasible for the acid-catalysed rearrangement. One is the conventional enolization mechanism[1] where the 17-oxo-function can give the enediol intermediate (**3**), and the ketonization may then give either the original ketol, the 16β-epimer, or the rearranged ketol, the 17β-epimer (mechanism A, Scheme 1). The alternative mechanism B[2] involves an intramolecular stereospecific 1,2-hydride shift. In order to decide unambiguously as to which is the actual mechanism we employed the 16α-deuterio-16β-epimer (**1**) as a substrate; we reasoned that the primary product would be 17α-deuterium labelled to the same extent as the starting compound with mechanism B, and would not retain the isotope with the mechanism A.

The isomerization of the dihydroxy-5α-androstanone (**1**) to (**2**) was explored under basic and acidic conditions. Treatment of the 16α-deuterio-ketol (**1**), m.p. 188—193 °C, 90 atom % ^{2}H, which was synthesized in three steps from [16,16-^{2}H]-3β-hydroxy-5α-androstan-17-one by literature methods,[2-4] with H_2SO_4 or NaOH in aqueous MeOH at room temperature caused the rearrangement. The deuterium content of the ketols (**1**) and (**2**), which were isolated and purified by repeated crystallization, was analysed by mass and ^{1}H n.m.r. spectro-

Table 1. Analysis of the deuterium content of the ketols (**1**) and (**2**).

	Conditions		Relative amount of product (%)[a]		^{2}H-Content (atom %)[b]	
	Base or acid	Time	(**1**)	(**2**)	(**1**)	(**2**)
(i)	3 M-H_2SO_4[c]	10 days	58	42	91	63
(ii)	3 M-H_2SO_4[c]	20 days	40	60	90	36
(iii)	1 M-NaOH[d]	3 h	0	100	—	16
(iv)	1 M-NaOH[d]	1 h	0	100	—	46
(v)	0.025 M-NaOH[d]	1 h	31	69	89	65
(vi)	0.025 M-NaOH[d]	7 h	<1	>99	—	57

[a] The relative amounts were determined by measuring the peak height of the C-18 angular methyl resonance in the ^{1}H n.m.r. spectrum of the reaction mixtures without isolation. ^{1}H N.m.r. ($CDCl_3$): (**1**) δ 0.93 (3H, s); (**2**) δ 0.73 (3H, s). [b] The deuterium content was determined by mass spectral analysis (*m/e* 306 and 307, M^+). [c] To a solution of [16α-^{2}H]-(**1**) (90 atom % ^{2}H; 100 mg) in MeOH (14 ml) was added 3 M-H_2SO_4 (6 ml). [d] To a solution of [16α-^{2}H]-(**1**) (90 atom % ^{2}H, 100 mg) in 75% aqueous MeOH (10 ml) was added 1.0 ml of the NaOH solution.



Scheme 1

scopy (Table 1). These spectra showed 16—65% of deuterium-labelling at the 17α-position of the product (**2**) while the isotope was completely retained in the recovered substrate (**1**). Thus, we were unable to distinguish between the two mechanisms directly as we had hoped initially. However, the deuterium content of the ketol (**2**) was lower in experiments using a longer reaction time or more drastic conditions, and when the 17α-deuterio-compound (**2**) (57 atom %) was treated with NaOH under conditions (iv), *ca.* 30% of the deuterium was lost from the ketol (**2**). This demonstrates that the 17α-deuterio-compound initially formed is probably of high stereochemical purity, but that enolisation through the 16-oxo-function may result in loss of label.

The deuterium-labelling at the 17α-position of the ketol (**2**) shows that the enolization mechanism previously formulated should be discounted and the intramolecular 1,2-hydride shift mechanism is operative in the rearrangement of 16β-hydroxy-17-ones to 17β-hydroxy-16-ones with both base and acid.

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References

1 For example: J. Fishman, *J. Am. Chem. Soc.*, 1960, **82**, 6143; T. Nambara and J. Fishman, *J. Org. Chem.*, 1962, **27**, 2131; D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 388.
2 W. S. Johnson, B, Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, 1957, **79**, 1991.
3 L. Tokes, R. L. LaLonde, and C. Djerassi, *J. Org. Chem.*, 1967, **32**, 1012.
4 F. A. Kincl, *J. Steroid Biochem.*, 1976, **7**, 419.