The Relative Stabilities of *cis*- and *trans*-A/B-1,6-Dioxo-steroids

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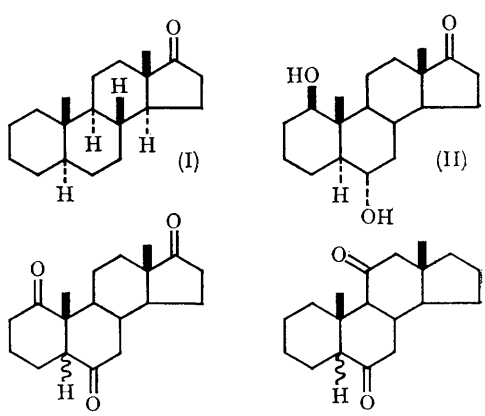
DURING microbiological studies of steroid transformations, 17-oxo-5α-androstane (I) was found to give a dihydroxy-ketone (II). Oxidation of this metabolite afforded a triketone which was shown to be 1,6,17-trioxo-5α-androstane (III). (This structure, first suggested by the positions and solvent-dependence of the angular methyl groups' n.m.r. signals,[1] was confirmed by mass-spectrometric examination and by chemical relationships within a series of products obtained from hydroxylating 5α-androstane monoketones.)

With refluxing methanolic potassium hydroxide the triketone gave an isomer in 82% yield. While a 5β-1,6,17-trioxo-structure (IV) appeared probable for the latter, the n.m.r. data were inconclusive. [From the scanty relevant information in the literature,[2] the C-19 and C-18 protons' signals of structure (IV) would be predicted to occur at τ 8·89 and 9·12 in deuterochloroform solution. With the C-19 protons' resonance the difference from the observed value is greater than is usual for the signals of di- and tri-oxo-5α-androstanes.[1]] However, structure (IV) was established by Huang-Minlon reduction of the triketone to 5β-androstane.

A similar base-induced isomerisation has also been observed with 1,6-dioxo-5α-androstane.



(III) 5α-H
(IV) 5β-H

(V) 5α-H
(VI) 5β-H

With mono-ketones the *trans*-A/B-6-oxo-compounds are more stable than their *cis*(5β)-isomers.[3]

TABLE

τ-Values, C-19 and C-18 protons, of 1,6,17-trioxoandrostanes

	5α-Compound (III)		5β-Compound (IV)	
	19	18	19	18
CCl_4	8·89	9·15	9·01	9·17
$CDCl_3$	8·84	9·13	8·95	9·13
C_6H_6	9·29	9·53	9·04	9·63
C_5H_5N	8·92	9·24	8·89	9·27

However, models show that introduction of a 1-oxo-function into the *trans*-system causes a severe non-bonded repulsion with the 11α-hydrogen, an interaction which is relieved in the *cis*-form. This effect clearly supervenes in the 1,6-diketones, the *cis*-A/B-compounds being the more stable.* The presence of a 1-oxo-group by itself is probably sufficient to reverse the normal stability relationship, the 6-oxo-group merely facilitating isomerisation by providing an intermediate (the Δ^5-enol) which is formed under mild conditions.

A similar interaction would be expected between the 11-oxo-group and the 1β-hydrogen of 6,11-dioxo-5α-androstane (V). However, isomerisation to the 5β-diketone (VI) would create an equivalent repulsion involving the 1α-hydrogen. The observation that the 5α-6,11-diketone does not isomerise shows that the normal stability order (*trans* > *cis*) is restored in this system.

(*Received, July 11th*, 1966; *Com.* 479.)

* Professor D. Lavie has kindly informed us that 1,4-dioxo-steroids are also more stable with the *cis*-A/B-ring junction.

[1] P. C. Cherry, W. R. T. Cottrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.*, in the press.
[2] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964.
[3] See, *inter alia*, N. L. Allinger, M. A. Darooge, and R. B. Hermann, *J. Org. Chem.*, 1961, **26**, 3626; D. N. Jones and D. K. Kime, *J. Chem. Soc.* (*C*), 1966, 846.