

Totally Synthetic Steroid Heterocycles. Part 3.¹ Stereochemical Course of Oxidation of Sulphur in 16-Thia-8,14-didehydro-D-homoestrone 3-Methyl Ether and its Derivatives

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The stereochemistry of oxidation at sulphur of the steroidal systems 16-thia-8,14-didehydro-D-homoestrones (1a—e) was studied with the oxidants sodium metaperiodate and *m*-chloroperbenzoic acid. The configurational assignments of the α - and β -oxides obtained are based on i.r. (intramolecular hydrogen bonding) and n.m.r. data. The direction and degree of stereoselectivity in the oxidation contrasts with that observed for thians. A marked directive effect is observed for peracid oxidation of the α -hydroxy-sulphide (1b), leading to the α -oxide (2b) in a highly stereoselective manner.

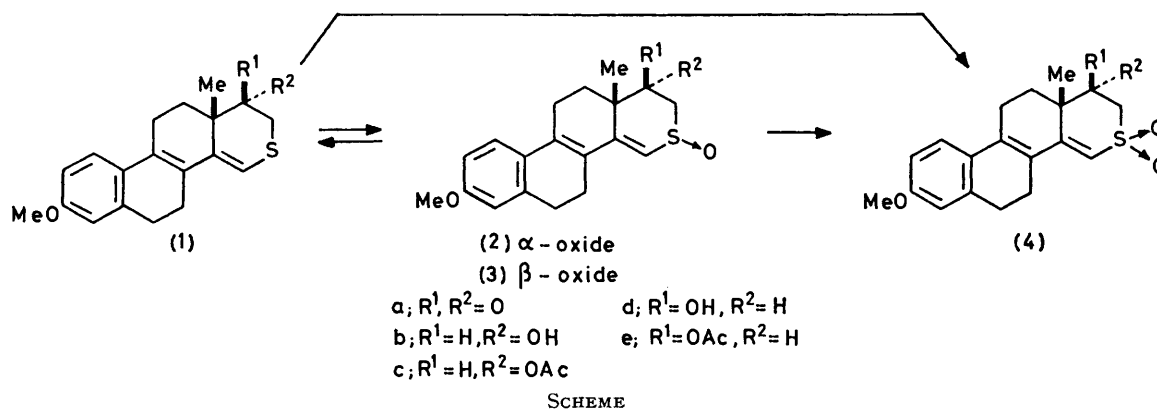
IN Part 1,² we described the synthesis of the tetracyclic intermediates (I) of 16-thia-D-homoestrogens. In at-

¹ Part 2, T. Terasawa and T. Okada, preceding paper.

tempting further stepwise reduction of the double bond system, we observed that these compounds are very

² T. Terasawa and T. Okada, *J.C.S. Perkin I*, 1978, 576.

resistant to catalytic hydrogenation under the usual conditions, probably due to a poisoning effect of sulphur acid, oxidation led directly to the sulphones (4) in almost 70% yield. The sulphones were obtained quantitatively



atom. To overcome this difficulty, we initially considered use of the sulfoxides (2) and (3) and sulphones (4) as substrates. We now report oxidations of the steroidal sulphides (1a—e). The stereochemical aspects

from the corresponding sulfoxides (2) and (3). The sulfoxide isomers were separated by preparative t.l.c.

Configurational Assignments.—The assignment of configuration at sulphur of the sulfoxides obtained was

TABLE I
Spectral data of sulfoxides and sulphones

Compound ^a	M.p. (°C)	$\lambda_{\max.}$ (EtOH)/nm (e)	$\nu_{\max.}/\text{cm}^{-1}$ (CHCl ₃) ^b			δ (CDCl ₃) ^c		
			OH	CO	S→O	13-Me	15-H	17a-H (J/Hz)
(2a)	173—175	348 (27 300)		1 713	1 034	1.29(s) (-0.08)		
(3a)	178—180	351 (27 300)		1 713	1 036	1.53 (s) (0.16)		
(2b)	182—186	341.5 (31 300)	3 378		1 057 1 040	1.00 (s) (0.01)	6.72 (s)	
(2c)	204—213	343 (31 200)		1 744 1 730	1 041 1 028	1.03 (s) (-0.04)	6.66 (s)	5.11 (t, J 3.5)
(3b)	200—205	337.5 (30 900)	3 617 3 309		1 038 1 013	1.25 (s) (0.26)	6.42 (s)	
(3c)	203—212	340 (30 800)		1 737	1 038 1 018	1.33 (s) (0.26)	6.40	5.16
(2d)	200—206	343 (28 700)	3 617 3 344		1 032 1 013	1.04 (s) (0.02)	(d, J 2) 6.47(s)	(q, J 5.5, 2)
(2e)	210—215	344.5 (30 400)		1 747	1 028	1.10 (s) (0)	6.52 (s)	5.63 (q, J 9, 6.5)
(3d)	187—191	338.5 (28 600)	3 613		1 020 1 012	1.24 (s) (0.22)	6.27 (s)	
(3e)	184—187	341 (30 500)		1 747	1 028 1 018	1.31 (s) (0.21)	6.31	4.89
(4a)	172—173	345 (27 600)		1 728	1 312 1 138 1 123	1.49 (s) (0.12)	(d, J 1.5)	(q, J 13, 3)
(4b)	237—240	335.5 (28 500)			1 295 1 136 1 118	1.18 (s) (0.19)		
(4d)	213—215	336.5 (28 800)			1 291 1 139 1 120	1.16 (s) (0.14)		

^a All new compounds gave satisfactory elemental analyses. ^b Dilute solution. ^c Values in parentheses refer to substituent effects based on the parent sulphides.

are of particular interest in the absence of comparable results.

For this purpose, oxidation of sulphides was carried out using sodium metaperiodate and *m*-chloroperbenzoic acid. When the sulphides (1) were carefully oxidized with an equimolar amount or a slight excess of oxidants, there resulted isomeric mixtures of the sulfoxides (2) and (3). With two mol. equiv. of the per-

made on the basis of the spectral data summarized in Table I. For example, in the n.m.r. comparison of the acetoxy-sulfoxides (2e) and (3e), the signal for the axial 17 α -proton of the former appears at lower field (0.74 p.p.m.) than for the latter. Also, the 13-Me protons of the α -oxide (2e) resonate at higher field (0.21 p.p.m.) than those of the β -oxide (3e). These results are consistent with the assigned configuration based on the known

acetylene-type anisotropic effect of the sulphur-oxygen bond,³ suggesting *cis*- and *trans*-relationships between 17 α -H and the sulphur-oxygen bond in sulphoxides (2e) and (3e), respectively. The same conclusions were drawn from an n.m.r. study using the shift reagent, Eu(dpm)₃.⁴ The stereochemistry of the sulphoxide alcohols (2d) and (3d) was confirmed by chemical correlation with the corresponding acetates (2e) and (3e). The configurations of the sulphoxides (2b) and (3b) [also (2c) and (3c)] could be determined by physical comparison with (2d) and (3d) [also (2e) and (3e)]. The i.r. spectrum of a dilute solution of the β -oxide (3b) in chloroform exhibits a free OH (3 617 cm⁻¹) and associated OH band (3 309 cm⁻¹), while that of the α -oxide (2b) shows only one intramolecularly bonded OH band (3 378 cm⁻¹) indicating that the sulphur-oxygen bond is *cis* to the α -oriented OH group. Other data recorded in Table I also supported the assigned structures. In particular, the n.m.r. signals for 13-Me of the α -oxides commonly occur at higher field (0.2–0.3 p.p.m.) than those of the corresponding β -oxides. Also, the signals for 15-H appear at lower field (0.2–0.3 p.p.m.) in the α -oxides compared with the β -oxides. These results are also consistent with the general anisotropic effect of the sulphur-oxygen bond. Furthermore, there is a substituent effect by the α - and β -oxides on the chemical shift of the 13-Me protons (*ca.* 0 and 0.24 p.p.m., respectively). On this basis, the configurations of the oxo-sulphoxides (2a) and (3a) were deduced.

Oxidations.—The stereochemical results of oxidation to sulphoxides are summarized in Table 2. Since all

TABLE 2
Stereochemical outcome of sulphur oxidation

Compound (1)	Method ^a	Product ratio ^b		Isolated yield (%)	
		α -S→O	β -S→O	(2)	(3)
(a)	A	1:1.8		26.5	31.9
	B	1:2.0		23.8	32.5
(b)	A	1:1.5		24.3	67.4
	B	9.2:1		73.5	6.3
(c)	A	1:2.2		27.5	64.8
	B	1.1:1		45.4	36.2
(d)	A	1.5:1		73.4	20.8
	B	2.2:1		58.4	14.0
(e)	A	1:1.2		29.9	35.9
	B	1.2:1		54.2	40.3

^a See Experimental section. ^b Estimated from the n.m.r. spectrum of the crude mixture.

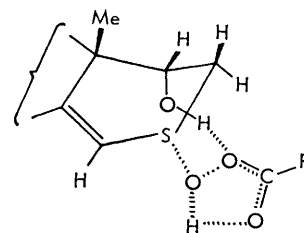
pairs of isomeric sulphoxides isolated are found not to be isomerized under the conditions employed, the isomer distribution is believed not to be governed by thermodynamic control. Johnson and McCants⁵ suggested that in 4-substituted thians periodate oxidation is governed by product development control, whereas peracid oxidation is determined by steric approach control. The identical direction and degree of stereoselectivity for

³ K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Comm.*, 1966, 759.

⁴ R. R. Fraser and Y. Y. Wigfield, *Chem. Comm.*, 1970, 1471.

⁵ C. R. Johnson and D. McCants, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1109.

both oxidations of sulphoxides (1a or d) contrasts with the above results for thians. Examination of our data also reveals that the isomer ratio is unaffected by the nature of the 17 α -substituent, as suggested by a comparison of the cases (1c and e). Thus, we cannot offer, at the moment, a satisfactory explanation for the stereochemical results. Of particular interest is the remarkable stereoselectivity of peracid oxidation of the α -hydroxy-sulphide (1b) leading to a marked predominance of the α -oxide. This result is probably attributable to a directive effect by the hydroxy-group, as shown in the Figure. Participation of a neighbouring hydroxy-



Suggested transition state for peracid oxidation of sulphide (1b)

group in influencing the stereoselectivity of peracid oxidation is well known.⁶ This orientation effect is no longer apparent in peracid oxidation of the acetoxy-sulphide (1c).

Finally, we examined whether the parent sulphides can be easily restored from the corresponding sulphoxides and sulphones. The sulphoxides (2b and d) were treated with sodium borohydride by stirring at room temperature in aqueous alcohol in the presence of cobalt chloride to give smoothly the sulphides (1b and d), respectively, in 65–75% yield.⁷ However, all our attempts to deoxygenate the sulphones proved unpromising. Lithium aluminium hydride reduction of sulphone (4e) in tetrahydrofuran, even at low temperatures, effected elimination and hydrogenolysis of the 17 α -oxygen function, while the sulphonyl group remained unaffected.

EXPERIMENTAL

For general directions see ref. 2.

Oxidation to Sulphoxides.—*General methods.* (A) Sodium metaperiodate. A solution of sodium metaperiodate (0.4 mmol) in water (2 ml) was added to an ice-cold solution of the sulphide (0.3 mmol) in methanol (15 ml) (for the alcohols) or 1:1 or 2:1 methanol-acetone (15 ml) (for the ketone and acetates). The mixture was stirred at room temperature for 20 h.

(B) *m*-Chloroperbenzoic acid. A solution of *m*-chloroperbenzoic acid (0.3 mmol) in dichloromethane (2 ml) was added dropwise at 0° to a stirred solution of the sulphide (0.3 mmol)

⁶ For recent examples for hydroxy-olefins, see (a) M. Mousseron-Canet and J.-C. Guilleux, *Bull. Soc. chim. France*, 1966, 3853; (b) M. Mousseron-Canet, B. Labeeuw, and J.-C. Lanet, *Compt. rend.*, 1966, **262**, 1438; (c) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Letters*, 1967, 5261; (d) D. H. R. Barton and Y. Houmier, *J.C.S. Perkin I*, 1972, 919; For a similar example for hydroxy-sulphides, see (e) C. A. Kingsbury, *J. Org. Chem.*, 1972, **37**, 102.

⁷ D. W. Chasar, *J. Org. Chem.*, 1971, **36**, 613.

in dichloromethane (3 ml). The solution was stirred at room temperature for 1–2 h.

Isolation of Sulphoxides.—The reaction mixture was poured into water and extracted with dichloromethane. After the usual work-up, the residue obtained was purified by preparative t.l.c. (1 : 1 or 2 : 1 chloroform–acetone for the alcohols and the acetates; 2 : 1 benzene–ethyl acetate for the ketone) to separate the epimeric sulphoxides. Product ratios and yields of the isolated sulphoxides are listed in Table 2. The sulphoxide alcohols were acetylated with acetic anhydride and pyridine in the usual manner. All the

sulphoxides were crystallized from dichloromethane–ether or acetone.

Preparation of Sulphones.—As for oxidation to sulphoxides, sulphide or sulphoxide was oxidized with a slight excess of *m*-chloroperbenzoic acid in dichloromethane. The sulphones thus obtained were directly, or after purification by preparative t.l.c., crystallized from dichloromethane–ether. Physical data of the sulphoxides and sulphones are summarized in Table 1.

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