Totally Synthetic Steroid Heterocycles. Part 2.[1] Stereochemistry of Hydride Reduction of 16-Oxa- and 16-Thia-8,14-didehydro-D-homoestrone 3-Methyl Ether and Related Compounds

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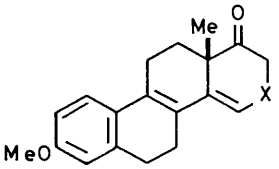
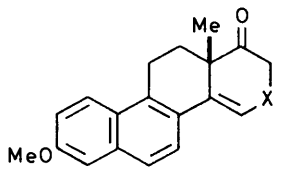
The stereochemistry of carbonyl reduction of 16-oxa- and 16-thia-8,14-didehydro-D-homoestrone derivatives (1)—(3) was studied using various hydrides. Some related compounds (4)—(8) were also examined for comparison. The observed stereochemical results are tentatively interpreted in terms of control of steric approach to the ring carbonyls in different conformations by the ring heteroatoms involved. Ring deformation caused by introduction of a sulphur atom often reverses the steric course of carbonyl reduction in steroids.

STERIC modifications of a carbocyclic framework by insertion of heteroatoms may influence various reactions commonly used for carbocycles. In Part 1,[1] we described the synthesis of the 16-oxa- and 16-thia-D-homoestrogens (1)—(3). Lithium aluminium hydride

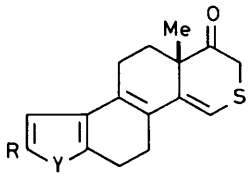


(1) R = Me
(2) R = Et

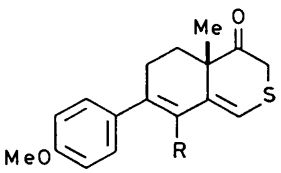
a; X = S
b; X = O



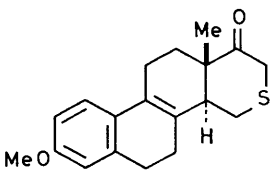
(3)



(4) R = H, Y = S
(5) R = CH_3, Y = O



(6) R = H
(7) R = Et



(8)

(LAH) reduction of heterocyclic ketones of type (1) demonstrated that there were substantial changes in stereochemistry upon introduction of a ring heteroatom. We observed that hydride reduction of the thia-ketone (1a) gave the 17aα-ol preferentially, while the oxa-ketone (1b) afforded the 17aβ-ol exclusively. The steric course observed for the hydride reduction of the thia-compound (1a) is inconsistent with the generalization[2] that steroidal 17(or 17a)-ketones usually undergo nucleophilic attack preferentially from the less hindered α-side. In order to explore this observation, we decided to examine in more detail the carbonyl reduction of the heterocyclic ketones (1)—(3) and that of the related compounds (4)—(8).

Various hydrides other than LAH were also used under standard conditions. The stereoselectivity for reduction seemed to be unaffected by solvents and temperatures. The results are summarized in Table 1. The preference for formation of the α-ol was observed for various reductions of the thia-compounds (3)—(7), closely similar in structure to compound (1a). In contrast, the 18-homologue (2) and the oxa-compound (3b) were almost exclusively reduced to the β-ol. The stereoselectivity of reduction of the thia-ketone (1a) decreased when LAH was replaced by its alkoxy-derivatives or by sodium borohydride, but a distinct preference for the α-ol was still retained. However, use of sodium bis-(2-methoxyethoxy)aluminium hydride demonstrated a profound effect, eventually reversing the product ratio in favour of the β-ol. Furthermore, this reagent improved the stereoselectivity favouring the β-ol in the case of the 18-homologue (2a). It seemed that the unusual behaviour of hydride reduction might be limited to unsaturated thiacyclic ketones of types (1)—(7) but we have found recently that compound (8) also gives the corresponding α-ol predominantly.

A number of factors may govern the stereochemistry of these reductions. We first supposed that a metal chelate complex properly situated between the ring sulphur atom and the incipient hydroxy-function might play an important role in directing the steric course of carbonyl reduction of the thia-ketones, leading to predominant formation of the α-oriented alcohols. However, this seemed unlikely from the fact that the 18-homologue (2a) is not subject to similar steric control. Alternatively, we thought that there might be electronic interactions[3] between the carbonyl group and the sulphur atom, which could affect the stereochemistry of reduction. As a measure of sulphur participation, the i.r. carbonyl frequencies in various solvents of different polarities were evaluated for the thia-ketone (1a), the

[1] Part 1, T. Terasawa and T. Okada, *J.C.S. Perkin I*, 1978, 576.

[2] (*a*) D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 131 and references cited therein; (*b*) S. N. Ananchenko, V. Y. Limanov, V. N. Leonov, V. N. Rzheznikov, and I. V. Torgov, *Tetrahedron*, 1962, **18**, 1355.

[3] B. T. Buzzi, P. R. Olivato, R. Rittner, C. Trufen, H. Viertler, and B. Wladislaw, *J.C.S. Perkin II*, 1975, 1294.

oxa-ketone (1b), and the corresponding carbocyclic compound.[4] However, these comparative data gave no clear evidence for the existence of a polar interaction.

Although other possible polar factors should not be excluded, steric control of approach of the hydride species is probably of major importance. Inspection of Dreiding models shows that introduction of a sulphur relative to an oxygen atom deforms the six-membered ring to a great extent, due to variation of bond lengths and angles.* The deformation alters the ring geometry so as to bend the carbonyl oxygen down. Thus, a significant difference in spatial environment around the carbonyl function is brought about between the oxa- and thia-rings. This can be represented by the dihedral angles (ϕ) about the C(13)–C(17a) bond, which are estimated from the Dreiding models as illustrated in the Figure.

In agreement with our results, the steric requirement in the oxa-ketones favours hydride attack from the α-side, leading to the β-oriented equatorial alcohol exclusively. On the other hand, the β-side becomes less hindered with increasing ϕ by 35° in the case of the thia- relative to the oxa-ketones, despite the presence of the

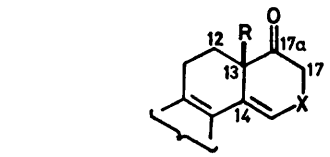
TABLE 1

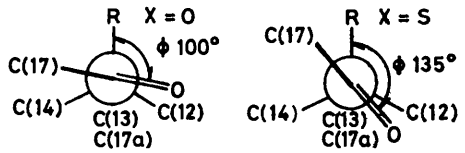
Stereochemical outcome of hydride reduction

Ketone	Hydride	Conditions	α-OH : β-OH *	Yield (%) *
(1a)	LAH	THF (r.t.)	4.4 : 1	92.6
	$NaBH_4$	MeOH (0—5°)	2.5 : 1	96.3
	$LiAlH(Bu^tO)_3$	THF (r.t.)	2.7 : 1	97.6
	$LiAlH(MeO)_3$	THF (0—5°)	2.0 : 1	86.0
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH (r.t.)	1 : 2.9	87.9
(2a)	LAH	THF (r.t.)	1 : 6.1	92.1
	$NaBH_4$	EtOH–THF (r.t.)	1 : 5.2	97.3
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH (r.t.)	1 : 19.5	89.8
(1b)	LAH	THF (r.t.)	β only	70.5
(2b)	LAH	THF (r.t.)	β only	89.7
(3a)	LAH	THF (r.t.)	1.4 : 1	88.0
(3b)	LAH	Et_2O–THF (r.t.)	β only	70.5
(4)	$NaBH_4$	EtOH–THF (r.t.)	2.3 : 1	85.9
(5)	$NaBH_4$	EtOH–THF (r.t.)	2.2 : 1	70.5
(6)	LAH	THF (r.t.)	1.4 : 1	88.0
	$NaBH_4$	MeOH (r.t.)	1.9 : 1	98.3
(7)	LAH	THF (r.t.)	1.9 : 1	45.0
(8)	LAH	THF (r.t.)	3.2 : 1	87.4
	$NaAlH_2(OCH_2CH_2OCH_3)_2$	PhH–THF (r.t.)	1.3 : 1	96.7

r.t. = Room temperature.

* Isolated.





Conformations and dihedral angles about the C(13)–C(17a) bond for compounds (1)—(7)

TABLE 2

Spectral data for alcohols and acetates from hydride reduction

Starting ketone		Alcohol M.p. (°C)	Alcohol $\nu(CCl_4)$/cm^{-1} [d]	Acetate M.p. (°C)	Acetate δ($CDCl_3$) [e] (*J*/Hz)
(1a)	α [a]	140—142	3 553	136—137	4.98 (t, *J* 3)
	β [a]	140—141	3 632	162.5—164	5.06 (q, *J* 5, 10.5)
(1b)	β [a]	140.5—142	3 633	161—164	5.00 (q, *J* 5, 10)
(2a)	α [a]	112.5—114	3 554	Oil	5.27 (t, *J* 3)
	β [a]	100—101.5	3 631	103—105	5.12 (q, *J* 6, 10.5)
(2b)	β [a]	105.5—107	3 632	104—106	5.07 (q, *J* 6, 10)
(3a)	α [b]	175—177	3 550	169.5—171	5.08 (q, *J* 2, 4)
	β [b]	216—218	3 630	210.5—213	5.14 (q, *J* 4.5, 10.5)
(3b)	β [b]	194—196	3 632	183—185	5.06 (q, *J* 5, 10.5)
(4)	α [c]	127—128	3 552	116—118	4.95br (t, *J* 3)
	β [c]	94—97	3 630	115—117	5.03 (q, *J* 5, 10.5)
(5)	α [c]	127—130	3 548	121—123	5.09br (t, *J* 4)
	β [c]	154—157	3 630	187—189	5.13 (q, *J* 4, 11)
(6)	α [c]	109—110	3 552		
	β [c]	129—130.5	3 631		
(7)	α [c]	Oil	3 548		
	β [c]	Oil	3 631		
(8)	α [c]	137—139	3 528	159—161	4.78 (t, *J* 3)
	β [c]	142—144	3 631	180—181.5	4.89 (q, *J* 6, 9)

[a] Ref. 1. [b] This work. [c] T. Terasawa and T. Okada, to be published. [d] OH band. [e] C*H*OAc signal.

* C–X bond lengths are often appreciably different from C–C distances: C–O 1.43, C–C 1.54, C–S 1.82 Å. The variation in bond angles is less important for oxygen but the C–S–C angle of *ca.* 100° is substantially different from the near-tetrahedral angles found in other heterocyclic compounds.

[4] T. Terasawa and M. Takasuka, unpublished data.

13-alkyl substituent. In this situation, hydride attack produces predominantly the α-oriented axial alcohol. An increase in the steric bulk of the reducing agent as well as the angular substituent may influence the course of reduction, shielding and restricting β-approach. This is exemplified in the reduction of the thia-ketones (1a) and (2a) with various hydrides. The stereochemical results for reduction of compound (8) (ϕ 130°) may be similarly interpreted. However, a detailed examination of the data presented in Table 1 suggests that accessibility of hydrides to the carbonyl group from either the α- or the β-side depends on a delicate steric balance. This fact reflects the limitations of the purely steric argument.

The configurations of the epimeric alcohols obtained in this study were determined from i.r. (intramolecular hydrogen bonding) and n.m.r. data of the acetates (Table 2).

EXPERIMENTAL

General details are given in Part 1.[1]

Reduction of 3-*Methoxy*-16-*thia*-D-*homoestra*-1,3,5(10),6,-8,14-*hexaen*-17a-*one* (3a).—To an ice-cold stirred solution of the thia-ketone (3a) (103.5 mg, 0.33 mmol) in dry tetrahydrofuran (8 ml), lithium aluminium hydride (19 mg, 0.5 mmol) was added in small portions. Stirring was continued for 30 min at room temperature. The mixture was poured into ice-cold water and extracted with dichloromethane. The usual work-up left a crystalline residue which was purified by preparative t.l.c. (9 : 1 benzene–ethyl acetate with double development), giving the 17aα-ol (less polar) (52.4 mg, 50.8%) and the 17aβ-ol (more polar) (38.3 mg, 37.1%); product ratio 1.4 : 1. Analytical samples were obtained by two crystallizations from dichloromethane–ether or acetone. The 17aα-*ol* had m.p. 175—177°, $\nu_{max.}$ (dilute CCl_4) 3 550 cm^{-1} (bonded OH); $\lambda_{max.}$ (EtOH) 227, 249, 271.5sh, 280, 311.5, and 321sh nm (ε 24 300, 20 900, 20 300, 22 500, 29 900, and 27 600); δ($CDCl_3$) 1.04 (3 H, s, 13-Me), 3.89 (3 H, s, OMe), 6.57br (1 H, s, 15-H), and 7.0—7.9 (5 H, m, ArH); *m/e* 312 (M^+) (Found: C, 72.85; H, 6.45; S, 10.3. $C_{19}H_{20}O_2S$ requires C, 73.05; H, 6.45; S, 10.25%). The *acetate* was prepared from acetic anhydride–pyridine as a crystalline solid, m.p. 169.5—171° (dichloromethane–ether); $\nu_{max.}$ ($CHCl_3$) 1 739sh, 1 730 (OAc), 1 623, 1 604, 1 582, and 1 502 cm^{-1} (aromatic); δ($CDCl_3$) 1.13 (3 H, s, 13-Me), 2.09 (3 H, s, OAc), 3.90 (3 H, s, OMe), 5.08 (1 H, q, *J* 2 and 4 Hz, 17a-H), 6.69br (1 H, s, 15-H), and 7.0—7.9 (5 H, m, ArH). The 17aβ-*ol* had m.p. 216—218°, $\nu_{max.}$ (dilute CCl_4) 3 630 cm^{-1} (free OH); $\lambda_{max.}$ (EtOH) 228, 248, 272sh, 279.6, 309, and 317sh nm (ε 24 400, 21 900, 22 400, 24 800, 26 600, and 25 000); *m/e* 312 (M^+) (Found: C, 72.8; H, 6.4; S, 10.2%). The *acetate* had m.p. 210.5—213°, $\nu_{max.}$ ($CHCl_3$) 1 742, 1 727 (OAc), 1 627, 1 600, 1 580, and 1 497 cm^{-1} (aromatic); $\lambda_{max.}$ (EtOH) 227.5, 247.5, 270, 278.5, 307.5, and 318 nm (ε 23 800, 22 100, 24 000, 26 800, 27 100, and 24 900); δ($CDCl_3$) 1.14 (3 H, s, 13-Me), 2.14 (3 H, s, OAc), 3.90 (3 H, s, OMe), 5.14 (1 H, q, *J* 4.5 and 10.5 Hz, 17a-H), 6.51br (1 H, s, 15-H), and 7.0—7.9 (5 H, m, ArH).

Reduction of 3-*Methoxy*-16-*oxa*-D-*homoestra*-1,3,5(10),6,-8,14-*hexaen*-17a-*one* (3b).—To a cold stirred solution of the oxa-ketone (3b) (90 mg, 0.3 mmol) in dry ether (6 ml) and dry tetrahydrofuran (4 ml), lithium aluminium hydride (12 mg, 0.3 mmol) was added in small portions. The mixture was stirred at room temperature for 10 min, quenched with ice–water, and extracted with 3 : 1 ether–dichloromethane. The usual work-up left a foam which was triturated with dichloromethane–ether, giving the 17aβ-ol (46.8 mg) as a crystalline solid, m.p. 193—197°. The residue was purified by preparative t.l.c. (4 : 1 benzene–ethyl acetate with triple development) to yield a second crop of the 17aβ-ol (15.9 mg), m.p. 195—197° (dichloromethane–ether); total yield 70.5%. Recrystallization from dichloromethane–ether gave an analytical sample, m.p. 194—196°, $\nu_{max.}$ (dilute CCl_4) 3 632 cm^{-1} (free OH); $\lambda_{max.}$ (EtOH) 220, 247sh, 256.5, 265, 282, 292, and 304 nm (ε 19 100, 28 300, 39 400, 41 600, 13 800, 22 100, and 19 500); *m/e* 296 (M^+) (Found: C, 76.85; H, 6.8. $C_{19}H_{20}O_3$ requires C, 77.0; H, 6.8%). The *acetate* was prepared from acetic anhydride–pyridine as a crystalline solid, m.p. 183—185° (dichloromethane–ether), $\nu_{max.}$ ($CHCl_3$) 1 736 (OAc), 1 630, 1 601, 1 567, and 1 507 cm^{-1} (aromatic); $\lambda_{max.}$ (EtOH) 220, 248sh, 255.5, 264, 281.5, 291.5, and 303 nm (ε 16 800, 32 000, 43 800, 46 700, 14 100, 19 200, and 19 000); δ($CDCl_3$) 1.15 (3 H, s, 13-Me), 2.13 (3 H, s, OAc), 3.89 (3 H, s, OMe), 5.06 (1 H, q, *J* 5 and 10.5 Hz, 17a-H), 6.94 (1 H, s, 15-H), and 7.0—7.9 (5 H, m, ArH).

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