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SELENIUM DIOXIDE OXIDATION OF STEROIDAL 1,4-DIEN-3-ONES. A SIMPLE AND CONVENIENT ROUTE TO 6-HYDROXYCORTICOSTEROIDS

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ABSTRACT: A convenient one-step procedure for the chemical synthesis of 6-hydroxycorticosteroids involving allylic oxidation by selenium dioxide is described.

6β-Hydroxylation is one of the major pathways in the metabolism of corticosteroids. In studying the metabolism of synthetic corticosteroids, we had to synthesize a variety of 6-hydroxycorticosteroids and their analogs to serve as reference compounds. In general, synthesis of 6-hydroxylated steroids had been carried out by two alternative routes: (a) auto-oxidation or peracid oxidation of 3-alkoxy-3,5-dienes and

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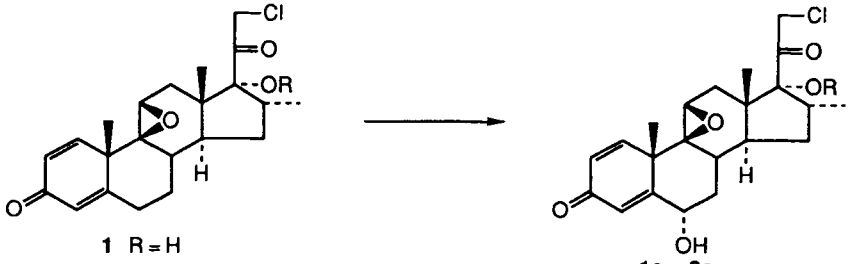
subsequent 1,2-dehydrogenation[1] or (b) peracid oxidation of 3-alkoxy-1,3,5-trienes.[2] Usually, mixtures of 6α- and 6β-epimers are obtained and subjected to chromatographic separation.

Direct introduction of the 14α-hydroxy function by allylic oxidation of steroidal 7-en-6-ones with selenium dioxide in dioxane was reported by A. Zürcher and his coworkers.[3] This oxidation has been utilized by many research groups[4] to synthesize ecdysone and its analogs.

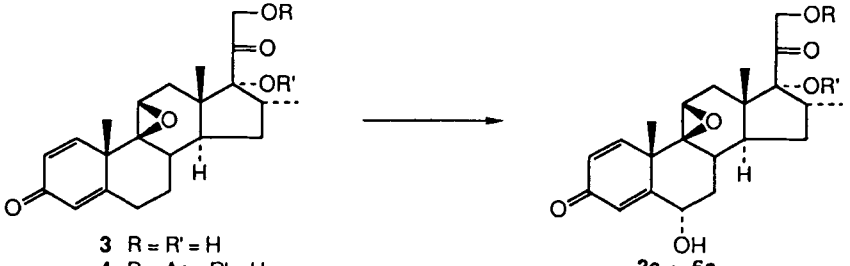
We have recently found that selenium dioxide oxidation can also be applied to a straightforward introduction of the 6-hydroxy group in steroidal 1,4-dien-3-ones. We report here a stereospecific one-step preparation of the 6-hydroxy derivatives of corticosteroids and related compounds. As substrates, mometasone,[5] betamethasone, dexamethasone, and prednisolone derivatives were considered. Our results for the allylic oxidations are summarized in Table I and the ^1H NMR data of 6-hydroxysteroids prepared are listed in Table II.

In most cases, allylic hydroxylation was effected simply by heating a stirred suspension of the steroid and an excess of selenium dioxide in an appropriate solvent, giving invariably moderate to good yields of the 6-alcohols. However, when an unprotected primary hydroxy group was present, the yield of the expected product was inevitably reduced due to secondary oxidation. Dioxane or n-butyl acetate was the solvent of choice. Sometimes, aromatic hydrocarbon, acetic acid, DMSO, or diglyme was also used. The reaction conditions required and the yields were largely dependent on the substitution



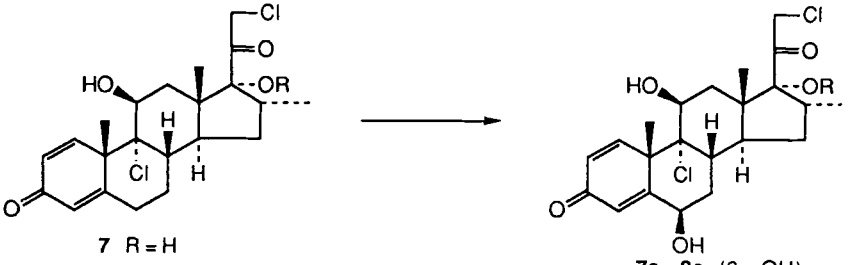
1 R = H
2 R = COFu (α)

1a, 2a
1b, 2b (6β-OH)



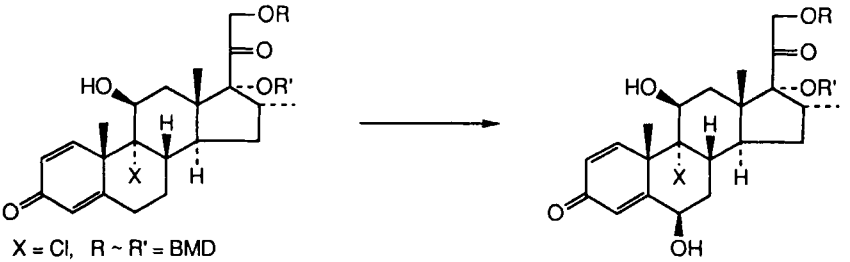
3 R = R' = H
4 R = Ac, R' = H
5 R = TBDMS, R' = H
6 R = R' = Acetonide

3a ~ 6a
3b (6β-OH)



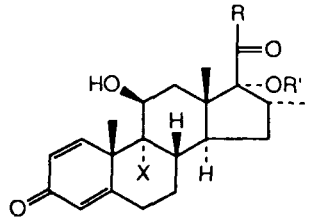
7 R = H
8 R = COFu (α)

7a, 8a (6α-OH)
7b, 8b

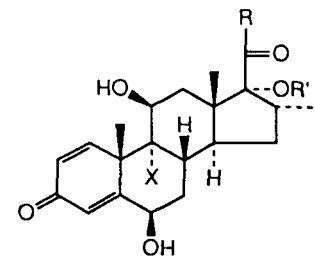


9 X = Cl, R ~ R' = BMD
10 X = Cl, R = Ac, R' = H
11 X = Cl, R = Ac, R' = COFu (α)
12 X = Br, R = Ac, R' = H
13 X = F, R = R' = COEt (16β-Me)

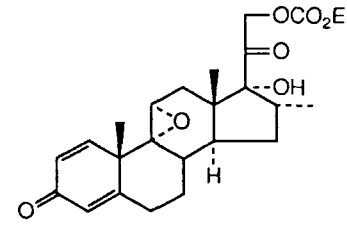
10a (6α-OH)
9b ~ 13b



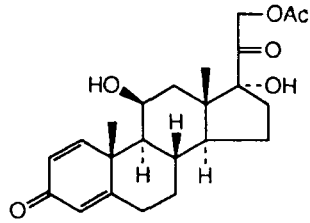
14 X = Cl, R = CO_2Me, R' = H
15 X = Br, R = CO_2Me, R' = H
16 X = Cl, R = CO_2Me, R' = COFu (α)
17 X = Br, R = CO_2Me, R' = COFu (α)
18 X = Cl, R = OMe, R' = H
19 X = Br, R = OMe, R' = H
20 X = Cl, R = OMe, R' = COFu (α)



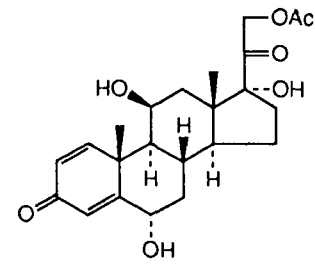
14 b ~ 20 b



22



21



21a

mode at the 9- and 11-positions of substrates. In the 9β,11β-oxides, the hydroxylation was completed within a few hours with about a molar excess of the oxidant at a temperature below 100°C. For the 9α,11β-halohydrins, a longer time, a higher temperature, and/or a larger excess of the reagent were usually necessary. Contrary to expectation, the allylic oxidation did not proceed very smoothly in a prednisolone series of compounds having no 9-substituent. No conditions could improve the low yield of the 6-alcohol accompanied by more polar by-

Table I. Allylic Oxidation of Steroidal 1,4-dien-3-ones

Substrate	SeO_2 (eq)	Solvent	Conditions	Product	Yield (%)[a]
1	3.0	Dioxane	80°C, 1 h	**1a**	65.6
2	3.0	Dioxane	80°C, 1 h	**2a**	92.8
3	3.0	Dioxane	80°C, 1 h	**3a**	33.5
4	1.5	Dioxane	80°C, 2 h	**4a**	88.3
	2.0	Dioxane	80°C, 2 h		87.6[b]
	2.0	n-BuOAc	90°C, 2 h		85.5
	2.0	Benzene	90°C, 2 h		77.6
	4.0	HOAc	80°C, 3 h		63.6
5	3.0	Dioxane	80°C, 1 h	**5a**	83.6
6	3.0	Dioxane	80°C, 1 h	**6a**	92.6
7	8.0	Dioxane	110°C, 18 h	**7b**	61.7
	8.0	n-BuOAc	110°C, 18 h		43.3
8	6.0	Dioxane	100°C, 39 h	**8b**	73.7
	8.0	n-BuOAc	110°C, 25 h		51.7
	8.0	Diglyme	110°C, 24 h		53.2
	8.0	DMSO	110°C, 20 h		11.2
9	8.0	Dioxane	80°C, 4.5 h	**9b**	62.9
10	6.0	Dioxane	100°C, 30 h	**10b**	65.7
11	6.0	Dioxane	110°C, 24 h	**11b**	73.0
12	3.0	Dioxane	100°C, 28 h	**12b**	68.0
13	3.0	Dioxane	100°C, 72 h	**13b**	44.2[b]
	6.0	Dioxane	100°C, 46 h		38.0
	3.0	Diglyme	140°C, 5 h		30.5
14	6.0	Dioxane	100°C, 30 h	**14b**	72.9
15	3.0	Dioxane	100°C, 24 h	**15b**	76.0
16	6.0	Dioxane	100°C, 30 h	**16b**	66.0
17	6.0	Dioxane	110°C, 27 h	**17b**	68.3
18	6.0	Dioxane	100°C, 24 h	**18b**	67.2
19	3.0	Dioxane	100°C, 24 h	**19b**	67.1
20	6.0	Dioxane	100°C, 46 h	**20b**	82.1
21	3.0	Dioxane	100°C, 72 h	**21a**	20.1[c]
	6.0	Dioxane	90°C, 48 h		20.3
	8.0	Dioxane	110°C, 28 h		21.5

[a] Isolated. [b] Added as H_2SeO_3. [c] Added in portions at 24-h intervals.

products with recovery of the starting steroid. It is particularly noteworthy that the present hydroxylation occurred stereospecifically and the product was obtained as a single isomer for all substrates we examined. The orientation of the 6-hydroxy group to be introduced was also found to be closely related to the substitution mode at the 9-position. 9α,11β-Halohydrins **7-20** gave all the 6β-alcohols, while the 6α-alcohols were obtained for 9β,11β-oxides[6] **1-6**. The 6α-isomer was formed again in the case of a prednisolone derivative (e.g. **21**) carrying no substituent at the 9-position.

The stereostructures of the compounds obtained were established as follows. Oxide-ring cleavage with HCl converted compounds **1a** and **2a** to **7a** and **8a**, respectively. The latter compounds were shown to be 6-epimeric with **7b** and **8b**, derived from the direct oxidation of **7** and **8**. Similarly, **4a** was transformed to **10a** epimeric with **10b**. On the other hand, mild treatment of **7b**, **8b**, and **10b** with dil NaOH led to **1b**, **2b**, and **3b**, respectively, which were 6-epimeric on each other with **1a**, **2a**, and **3a**. Comparison of the ^{1}H NMR of these epimeric pairs enabled configurational assignment of the 6-hydroxy groups.[7] For all the compounds prepared, the 19-H signal revealed a downfield shift by 0.18 ppm due to a 1,3-diaxial interaction with the 6-OH in the 6β-alcohols compared to the 6α-alcohols. Alternatively, a downfield shift (~0.3 ppm) was observed for the 4-H signal in the 6α-series relative to the 6β-series, which could be ascribed to the steric interaction between the 4-H and the 6-OH.[8] The 6-H signal in the 6α-series also appeared downfield (~0.15 ppm) with a more split pattern caused by the additional diaxial

Table II. ^{1}H NMR Data for 6-Hydroxysteroids Prepared

Compd.	Solv.[a]	δ (ppm)			Compd.	Solv.[a]	δ (ppm)		
		19-H	4-H	6-H			19-H	4-H	6-H
1a(α)[b]	A	1.41	6.48	4.71	**10a**(α)[b]	B	1.66	6.46	4.55
1b (β)	E	1.59	6.48	4.59	**10b** (β)	B	1.85	6.16	4.42
2a (α)	A	1.43	6.57	4.73	**11b** (β)	A	1.84	6.22	4.54
2b (β)	A	1.62	6.54	4.69	**12b** (β)	B	1.89	6.16	4.42
3a (α)	C	1.41	6.50	4.57	**13b** (β)	A	1.75	6.22	4.56
3b (β)	B	1.59	6.48	4.59	**14b** (β)	B	1.83	6.17	4.43
4a (α)	B	1.41	6.48	4.65	**15b** (β)	A	1.88	6.21	4.51
5a (α)	A	1.43	6.55	4.72	**16b** (β)	H	1.86	6.21	4.47
6a (α)	A	1.39	6.50	4.70	**17b** (β)	F	1.88	6.21	4.45
7a (α)	D	1.65	6.50	4.55	**18b** (β)	B	1.83	6.17	4.43
7b (β)	D	1.83	6.17	4.42	**19b** (β)	A	1.87	6.21	4.51
8a (α)	C	1.67	6.50	4.60	**20b** (β)	G	1.85	6.20	4.46
8b (β)	C	1.85	6.20	4.46	**21a** (α)	B	1.45	6.36	4.54
9b (β)	B	1.86	5.85	4.34					

[a] See Experimental. [b] Config. of 6-OH.

coupling with one of the 7-H's, compared to that in the 6β-series.[8] Ultimately, configurations of the introduced hydroxy groups were confirmed by X-ray analyses of compounds **7b** and **8a**.[9]

Selenium dioxide oxidation can be useful for the direct 6-hydroxylation of steroidal 4-en-3-ones.[10] Although the mechanism of this reaction is still not clear,[11] the above results strongly suggest that 6-hydroxylation always occurred with β-stereochemistry for the 9α-halo derivatives of corticosteroids. This means that the present oxidation offers a useful synthetic route to the 6β-hydroxy metabolites of 9α-halogenated corticosteroids and their derivatives.

Experimental

Mps were determined on a calibrated Yanagimoto Micro Melting Point Apparatus. Nuclear magnetic resonance spectra (NMR) were taken on a Varian VXR-200 200 MHz spectrometer using tetramethylsilane as an internal standard. Precoated TLC plates (SILICA GEL F-254, 20 x 20 x 0.05 cm, Merck) were used for preparative thin-layer chromatography. All new compounds were characterized spectroscopically and showed satisfactory elementary analyses.

Abbreviations used are: TBDMS = $SiMe_2t$-Bu; BMD = bismethylenedioxy; Fu = furoyl; Solvent A = $CDCl_3$; B = $CDCl_3$-CD_3OD (9:1); C = $CDCl_3$-CD_3OD (6:1); D = $CDCl_3$-CD_3OD (4:1); E = $CDCl_3$-CD_3OD (19:1); F = $CDCl_3$-CD_3OD (15:2); G = $CDCl_3$-CD_3OD (7:1); H = $CDCl_3$-CD_3OD (5:3).

General Procedure for Allylic Oxidations

A stirred suspension of a steroidal 1,4-dien-3-one (0.1 mmol) and selenium dioxide (0.15-0.4 mmol for a 9β,11β-oxide, 0.3-0.8 mmol for a 9α,11β-halohydrin) was heated at 80-140°C for 1-72 h in an appropriate solvent (mostly dioxane, n-BuOAc, sometimes benzene, acetic acid, DMSO, or diglyme). The reaction was monitored by TLC. After the reaction was complete, the mixture was filtered through a short column of silica gel and then or directly purified by preparative TLC (benzene-EtOAc mixtures), giving a crystalline analytically pure material.

Preparation of 9β,11β-Oxides 1b, 2b, and 3b

(1b) -- Compound **7b** (44.3 mg, 0.1 mmol) was dissolved in methanol (44 ml) and 0.01 N NaOH (44 ml) was added. The resulting mixture was stirred at room temperature for 15 min, then diluted with

cold water, and extracted with dichloromethane. The extract was washed with aq saline, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (Cy-EtOAc, 1:1) and gave pure **1b** (22.8 mg, 56.0%).

(**2b**) -- Similarly, compound **8b** (66.3 mg, 0.12 mmol) was treated with 0.01 N NaOH (66 ml) in methanol (66 ml) for 5 min. Preparative TLC (Chf-An, 4:1) of the product gave pure **2b** (23.7 mg, 38.5%).

(**3b**) -- As described above, compound **10b** (233.5 mg, 0.5 mmol) in methanol (234 ml) was treated with 0.01 N NaOH (234 ml) for 2.5 h. The product was purified by preparative TLC (Cy-EtOAc, 1:2) to obtain pure **3b** (124.6 mg, 64.2%).

Preparation of 9α,11β-Halohydrins 7a, 8a, and 10a

(**7a**) -- Compound **1a** (61 mg, 0.15 mmol) was dissolved in dioxane (3 ml). Conc HCl (0.5 ml) was added dropwise to the stirred mixture cooled to 12-14°C. Stirring was continued at the same temperature for 0.5 h. The mixture was extracted with chloroform. The extract was washed with satd $NaHCO_3$ solution and aq saline, dried, and evaporated. The product was purified by preparative TLC (Bz-EtOAc, 1:1) to obtain pure **7a** (33.4 mg, 50.2%).

(**8a**) -- Similarly, compound **2a** (25 mg, 0.05 mmol) in 3 ml of dioxane was treated with conc HCl at 13-15°C for 20 min. The product was purified by preparative TLC (Chf-An, 2:1) to obtain pure **8a** (25.1 mg, 93.4%).

(**10a**) -- Compound **4a** (43 mg, 0.1 mmol) was dissolved in dioxane (2 ml) containing acetic acid (0.5 ml). To the above mixture cooled to

12-13°C was added dropwise conc HCl (0.5 ml) with stirring. After 20 min, the mixture was worked up as described above. The product was purified by preparative TLC (Bz-EtOAc, 1:2) to yield pure **10a** (28.1 mg, 60.2%).

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5. 9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione, See (a) Shapiro, E. L., Gentles, M. J., Tiberi, R. L., Popper, T. L., Berkenkopf, J., Lutsky, B., and Watnick, A. S., J.

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6. In relation to this, the 9α,11α-oxide **22** was subjected to allylic oxidation (3.0 eq SeO_2, dioxane, 100°C, 42 h), but no product was obtained.
7. For 6-substituted Δ4-3-ketosteroids: (a) Collins, D. J. and Hobbs, J. J., Tetrahedron Lett., 1963, 197. (b) Okamoto, T. and Kawazoe, Y., Chem. Pharm. Bull., 1963, 11, 643.
8. In 9β,11β-oxides, however, the differences were small and irregular, presumably because of B-ring distortion and different degrees of long-range shielding by the oxide ring system, e.g. **1a**: δ 4.71 (ddd, 1H, J = 10, 5, and 1.5 Hz, 6β-H), 6.48 (t, 1H, J = 1.5 Hz, 4-H); **1b**: δ 4.50 (ddd, 1H, J = 10, 5, and 1.5 Hz, 6α-H), 6.48 (t, 1-H, J = 1.5 Hz, 4-H); **7a**: δ 4.55 (ddd, 1H, J = 10, 5, and 1.5 Hz, 6β-H), 6.50 (t, 1H, J = 1.5 Hz, 4-H); **7b**: δ 4.42 (t, 1H, J = 2 Hz, 6α-H), 6.17 (t, 1H, J = 2 Hz, 4-H).
9. Details of the X-ray analyses will be reported elsewhere.
10. Similarly, the 1,2-dihydro derivatives of betamethasone 21-acetate, dexamethasone 17-propionate 21-acetate (3.3 eq SeO_2, dioxane, 80°C, 2.5 h), and betamethasone 17,21-dipropionate (3 eq SeO_2, dioxane, 110°C, 2.5 h) were converted to the corresponding 6β-alcohols in 22%, 23%, and 25% yields, respectively.
11. If the 6-hydroxylation reaction can be rationalized by assuming initial formation of an ene product, e.g. the 5-ene-4-seleninic acid, followed by its [2,3]-sigmatropic rearrangement, the stereochemistry may be determined by the orientation of the 4-seleninic group first introduced in the ene reaction. See also Sharpless, K. B. and Lauer, R. F., J. Am. Chem. Soc., 1972, 94, 7154.

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