Tetrahedron Letters,Vol.24,No.9,pp 917-920,1983 0040-4039/83/090917-04$03.00/0
Printed in Great Britain

REMOTE SUBSTITUENT EFFECT ON THE REGIOSELECTIVITY IN THE BAEYER-VILLIGER OXIDATION OF 5α-CHOLESTAN-6-ONE DERIVATIVES[1]

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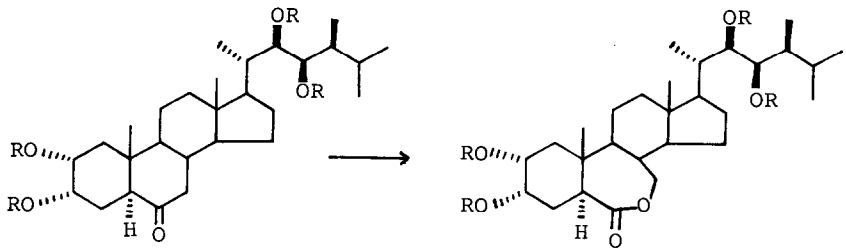
Abstract: The regioselectivity in the Baeyer-Villiger oxidation of 5α-cholestan-6-one derivatives was markedly affected by the substituents at C-1, 2 or 3 position which were located at γ or δ position from the reaction center C-6.

It is well known that in the Baeyer-Villiger oxidation the migratory aptitude of alkyl groups with retention of their configurations falls into the order of reactivity: t-Bu > iso-Pro > Et > Me, as expected from their relative abilities to stabilize an electron-deficient transition state. It was reported that in the case of 5α-cholestan-6-one this migratory aptitude holded true; the 6-oxalactone was obtained as a major product upon the oxidation. On the other hand, introduction of acetoxyl or halogen at 3β position affected the regioselectivity of the Baeyer-Villiger oxidation, and the 7-oxalactones were obtained as major products.[2] This unusual regioselectivity of the oxidation was investigated only in the case of 5α-cholestan-6-ones with some substituents at 3β position.

During the course of our synthesis[3] of a new plant growth hormone, brassinolide(4), and its possible biosynthetic precursor the 6-ketone(3), which were recently isolated and identified in some higher plants,[4,5,6] we also observed the similar unusual phenomenon in the oxidation of 2α,3α,22,23-tetraacetoxy-5α-ergostan-6-one(1); C-7 carbon (primary) migrated more readily than C-5 carbon (secondary) affording the 7-oxalactone(2) with ca. 90% regioselectivity.[3] This pronounced high selectivity can be ascribed to the effect of not only 3α-acetoxyl group but also 2α-acetoxyl group. In this communication, we wish to report the remote substituent effect on the regioselectivity in the Baeyer-Villiger oxidation of 5α-cholestan-6-one derivatives with substituents at C-1, 2 or 3 position.

In order to clarify the factors affecting this abnormal selectivity, 5α-cholestan-6-one derivatives with substituents at 1α, 2α, 2β, 3α, and 3β positions as shown in Table I were synthesized from cholesterol,[7] and the



1 R = Ac

3 R = H

2 R = Ac

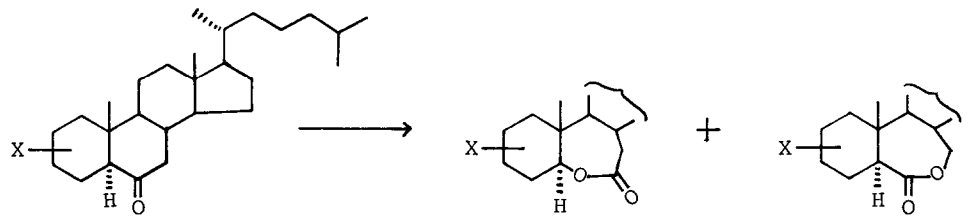
4 R = H

regioselectivity was investigated. These ketones were treated with 7 equivalent of trifluoroperacetic acid[8] in dichloromethane in the presence of disodium hydrogen phosphate at 20°C. The reaction was monitored by thin layer chromatography. When the starting material was disappeared (ca. 1h), the reaction mixture was submitted to the usual workup to give a mixture of 6-oxa- and 7-oxalactone in almost quantitative yield. Both regioisomers were easily separated by column chromatography or preparative thin layer chromatography and their structures were assigned by proton magnetic resonance spectra.[9] The results were summarized in Table I.

Upon the oxidation, the compounds(21 and 5) with methyl or hydrogen at 3β position gave the 6-oxa- and 7-oxalactones in ratios of 80 : 20 and 70 : 30, respectively. These results were in good agreement with the generally accepted migratory aptitude of alkyl groups. However, when a electron-withdrawing group such as hydroxyl, acyloxyl or sulfonyloxyl was present at 1α, 2α, 2β, 3α, or 3β position, the ratio of 7-oxa- to 6-oxalactone was remarkably increased and 7-oxalactones were obtained as major products. This trend was increased to some extent with the introduction of a strong electron-withdrawing group like trifluoroacetyloxyl or p-toluenesulfonyloxyl (entry, 11, 12, 15, 16, 19, 20, 27, 28, 31, and 32). The position and configuration of substituents do not seem to have great effect on the regioselectivity as shown in Table I. The effect was observed accumulatively, as examplified by the compounds with 2α,3α-dihydroxyl or diacetoxyl group (33 and 34). Another new finding in the present work is that the acetoxyl substituent not directly attached to the steroid ring system exhibited weaker effect on the regioselectivity than the one on the steroid ring system as evidenced in the case of the compounds (6 and 22) which possess acetoxyl group at δ position apart from the reaction center C-6. This might be a reflection of the rigid σ framework of the steroidal skeleton that facilitates the transmission of through-bond electronic effect. The effect of electron-withdrawing substituents at C-1, 2 or 3 position on the regioselectivity must come from the conformational factor in the transition state as well

as the inductive effect of the substituents.

In order to understand this phenomenon, further investigation is in progress in connection with so-called long range effect in a steroid ring system.[10]



6-ketones 6-oxalactones 7-oxalactones

Table 1. Regioselectivity in the Baeyer-Villiger Oxidation of 5α-Cholestan-6-one Derivatives

		X	6-oxa : 7-oxa*			X	6-oxa : 7-oxa*
3α	(5)	H	70 : 30	3β	(21)	Me	80 : 20
	(6)	CH_2OAc	50 : 50		(22)	CH_2OAc	45 : 55
	(7)	OH	36 : 64		(23)	OH	37 : 63
	(8)	OMe	38 : 62		(24)	OMe	36 : 64
	(9)	OAc	40 : 60		(25)	OAc	39 : 61
	(10)	OBz	38 : 62		(26)	OBz	33 : 67
	(11)	OTFA	30 : 70		(27)	OTFA	28 : 72
	(12)	OTs	28 : 72		(28)	OTs	25 : 75
2α	(13)	OH	22 : 78	2β	(29)	OH	35 : 65
	(14)	OAc	30 : 70		(30)	OAc	30 : 70
	(15)	OTFA	17 : 83		(31)	OTFA	25 : 75
	(16)	OTs	20 : 80		(32)	OTs	27 : 73
1α	(17)	OH	31 : 69		(33)	2α,3α-di$(OH)_2$	8 : 92
	(18)	OAc	25 : 75		(34)	2α,3α-di$(AcO)_2$	14 : 86
	(19)	OTFA	16 : 84				
	(20)	OTs	14 : 86				

The ratios were determined by ^{1}H-NMR analysis and also by weights of the isolated compounds.

Acknowledgement: This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.

References and Notes

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8. The similar regioselectivities of the oxidation were also observed with m-chloroperbenzoic acid. But the reactions proceeded very slowly.
9. In all cases the 6-oxalactones were more polar than the 7-oxalactones in TLC. In ^{1}H-NMR($CDCl_3$) 6-oxalactones exhibited characteristic signals at ca. 4.2-4.5 ppm as double doublet(5α-H) and at ca. 2.3-2.5 ppm as multiplet ($7\text{-}H_2$), while 7-oxalactones showed signals at ca. 2.7-3.1 ppm as double doublet(5α-H) and at ca. 4.0-4.1 ppm as multiplet($7\text{-}H_2$).
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(Received in Japan 8 November 1982)