C-25 Hydroxylation of Cholesterol Derivatives

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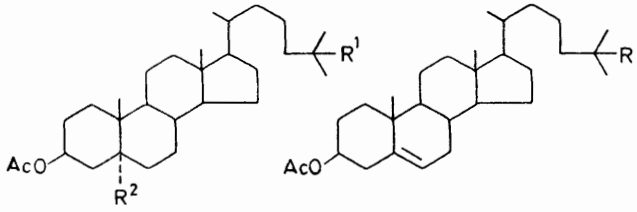
Summary Irradiation of saturated cholestane derivatives with peracetic acid resulted in hydroxylation at the 25- and 5α-positions; this method is used for the synthesis of 25-hydroxycholesterol.

INTEREST in 25-hydroxylated cholesterol derivatives has recently been stimulated by the discovery that 1,25-dihydroxy-vitamin D_3[1] is the active metabolite of this vitamin.



	(1)	(3)	(5)	(6)	(7)	(8)		(2)	(4)
R^1	H	OH	H	OH	OAc	$OCOCl_3$	R	H	OH
R^2	H	H	OH	OH	OH	OH			

We report here on a simple synthesis of the 25-hydroxycholestanyl and 25-hydroxycholesteryl 3β-acetates (**3**) and (**4**). The salient feature of this synthesis is the direct hydroxylation with peracetic acid which was first used for hydroxylation of tertiary carbon atoms by Heywood *et al.*,[2] and was recently adapted by us for the introduction of hydroxy-groups into the androstane skeleton.[3]

Irradiation in quartz tubes of a 5% solution of 3β-acetoxycholestane (**1**) containing 10 mol equiv. of peracetic acid (40% in acetic acid) with a 300 nm external light source overnight, resulted in 60% of the starting material and a mixture of oxygenated products, the major ones being the 25-hydroxy-(**3**)[4] and 5α-hydroxy-cholestanes (**5**) in 37·5 and 30% yield, respectively.

To prepare the 25-hydroxycholesterol (**4**) it was necessary to protect the double bond of cholesterol by transforming it into its 5α-hydroxy-derivative (**5**). This was treated with peracetic acid under the same conditions, resulting in 50% conversion into hydroxylated products, the main one being the 5α,25-diol (**6**) (38%). Partial acylation (heating with Ac_2O–pyridine) or trichloroacylation [treatment with $(CCl_3CO)_2O$] led to the corresponding 3β,25-diesters, (**7**) and (**8**), which were converted into the 25-hydroxycholesterol[4] (**4**), with acetic and toluene-*p*-sulphonic acids, followed by hydrolysis.

In addition to the above products we have isolated from hydroxylation of (**1**) and (**2**) small amounts of the respective 14-, 17-, and 20-hydroxy-derivatives.

The formation of 5α- and 25-hydroxycholestane derivatives indicates the steric availability of these two centres to methyl radicals[3] as compared with the other five tertiary positions. The steric effect of the side chain is probably responsible for the small extent of attack at C-14 which in the case of androstane derivatives, is as reactive as C-5.[3]

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[4] L. F. Fieser, W. Y. Huang, and B. K. Bhattacharya, *J. Org. Chem.*, 1957, **22**, 1380.