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THE DETERMINATION OF THE ABSOLUTE CONFIGURATION AT C_{23} IN 23-HYDROXYLANOSTEROL

A TRITERPENE FUNGAL METABOLITE OF THE *BASIDIOMYCETE SCLERODERMA* AURANTIUM PERS—AND ITS C_{23} EPIMER

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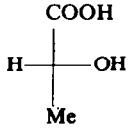
Abstract—The absolute configuration at C_{23} in the naturally occurring 23-hydroxylanosterol has been deduced to be *S*, and in its C_{23} epimer to be *R*, by correlation of their molecular rotations and that of lanosterol with those of *R*(−) and *S*(+) 4-methylpent-3-en-2-ol.

THE isolation and identification of 23ξ-hydroxylanosterol has been described.[1] We have now deduced the absolute configuration at C_{23} by standard correlation techniques. The absolute configuration at each chiral centre in the molecule is now known.

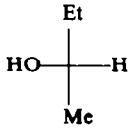
It has been suggested[2] that the steroid (and presumably the triterpenoid) nucleus plus part of the side chain can be regarded as being similar to an Et group for the purposes of considering the rotary contributions of chiral centres in the side chain. On this basis, the ideal acyclic analogues of the side chain of our 23-hydroxylanosterol (and its epimer) would be the *R* and *S* forms of 2-methylhex-2-en-4-ol. Unfortunately the resolution of this secondary alcohol has never been carried out. The next lower homologue—2-methylpent-2-en-4-ol has been resolved by Duveen and Kenyon.[3]

The absolute configurational relationship between (−)-lactic acid (**1**) and (+)-butanol-2 (**2**) has been demonstrated[4] and it has been established that (*S*) secondary alcohols of the structure (**3**) are dextrorotatory.[5,6] It thus appears certain that secondary alcohols of the same absolute configuration will have rotations of the same sign. The saturated analogue of 2-methylpent-2-en-4(*S*)-ol(4) corresponds to structure **3** (R = i:Bu). The introduction of the double bond into the latter structure does not alter the absolute configuration at the chiral centre; we could therefore deduce that 2-methylpent-2-en-4(*S*)-ol would be dextrorotatory.



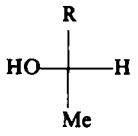
R(−)-lactic acid

1

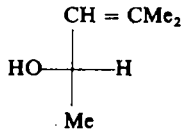


S(+)-butanol-2

2



3



4

R = Et, n-C_3H_7 to n-C_7H_{15}-
i-Pr-, i-Bu-, t-Bu-
neo-C_5H_{11}

Recently, Landor, Miller and Tatchell[7, 8] verified that (+)-2-methylpent-2-en-4-ol has the *S* configuration and that its enantiomer has the *R* configuration.

These enantiomers of 2-methylpent-2-en-4-ol were therefore adopted as the acyclic analogues of our 23-hydroxylanosterol and its C_{23} epimer. The latter had been obtained by CrO_3-pyridine oxidation of the naturally occurring diol to the corresponding lanost-8,24-dien-3, 23-dione;[1] reduction of this dione with excess LAH in ether yielded a mixture of the two diols epimeric at C_{23}. The epimers are separated by PLC and the least polar is identical to the naturally occurring diol. The more polar diol has IR, NMR and mass spectra identical to the naturally occurring diol and differs only in rotation, m.p. and polarity.

TABLE 1

	$[\alpha]_D^{20}$	M_D	ΔM_{D_1}	ΔM_{D_2}	Ref
(1) 2-Methylpent-2-en-4-ol *R*	−4·01	−4·01			3, 8
(2) 2-Methylpent-2-en-4-ol *S*	+4·01	+4·01			3, 7
(3) 23-Hydroxylanosterol (nat. occurring)	+73	+322			
			+75		
(4) Lanosterol	+58	+247			
				−13	
(5) 23-Hydroxylanosterol (C_{23} epimer of 3)	+53	+234			

ΔM_{D_1} = M_D of 3 − M_D of 4
ΔM_{D_2} = M_D of 5 − M_D of 4

The rotations of the diols, lanosterol and the acyclic analogues are collected in Table 1. The molecular rotation differences are also given. It will be noted that ΔM_{D_1} (M_D of the naturally occurring diol—M_D lanosterol) is positive and that ΔM_{D_2} (M_D of the C_{23} epimer—M_D lanosterol) is negative. Comparing the sign of these differences with the sign of the M_D values for *S* and *R* 2-methylpent-2-en-4-ol which are positive and negative respectively, we conclude that the natural diol is *S* at C_{23} and that its epimer is *R* at this centre.

The older system of Plattner[9] for describing the configurations at chiral centres in the side chain uses the letters α and β. Using this system, 23*S*-hydroxylanosterol would be 23β-hydroxylanosterol, its C_{23} epimer would be 23α-hydroxylanosterol.

It must be pointed out that the specific rotation quoted in Table 1 for the naturally occurring diol is not the same as that given earlier. The values for this diol and its

epimer were found to be concentration dependent, varying from +66 to +73° and from +56 to +53° respectively over the concentration range *c*, 0·3 to 1·0. These variations do not of course invalidate the method of determination of configuration, for ΔM_{D_1} is always positive and ΔM_{D_2} is always negative. Barton and Cox[10] found that variations of 2° or 3° were common, the variation of 7° seems unusually large.

In the LAH reduction of lanost-8,24-dien-3, 23-dione, the naturally occurring diol was obtained in 55% yield (of total diol) and its C_{23} epimer in 45% yield. Two more experiments result in the same yields. As the same work up procedure was used (separation by PLC) we assume that experimental losses are the same for both epimers. The excess of one epimer may be explained by differences in steric hindrance to the approach of the reducing agent to the two faces of the C_{23} ketone group. From a study of a Courtaulds molecular model we conclude that approach to one face (β) of the C_{24} ketone group is slightly hindered by the C_{21} Me group; the other face (α) is not so hindered. Attack on this least hindered (α) face leading to the C_{23}β-alcohol predominates though only to a small extent. One would only expect a slight predominance due to the small size of the attacking reagent.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage apparatus and are uncorrected. Rotations were determined for $CHCl_3$ solutions at 20° on a photoelectric polarimeter. Thick layer chromatography (PLC) was carried out on unactivated silica gel (Merck Kieselgel $PF_{254+366}$) supported on glass with a stationary phase thickness of 2 mm, the developing solvent being benzene-ethyl acetate (9:1).

The reduction of lanost-8,24-diene-3,23-dione. The dione (200 mg, purified by PLC) in Na dried ether (30 ml) was added slowly to a slurry of LAH (80 mg) in dry ether (15 ml) over 10 min followed by heating under reflux for 1·5 hr. Excess hydride was then destroyed by the cautious addition of water followed by dilution with water. Vigorous shaking was followed by ether extraction (3 ×), the ether layer was dried over Na_2SO_4, evaporated and the residue taken up in EtOAc and applied to a PLC plate.

The plate was developed twice and inspection under UV light showed the presence of two intense bands which were recovered and eluted with EtOAc. The least polar band yielded a diol as long needles (81 mg) from EtOAc m.p. 157–159°, $[\alpha]_D^{20}$ +73° (*c*, 1·00). (Found: C, 81·4: H, 11·4. $C_{30}H_{50}O_2$ requires: C, 81·5; H, 11·3%), which was identical with the naturally occurring lanost-8,24-diene-3β,23-diol. The other band yielded the C-23 epimeric diol as fine needles (65 mg) from methanol m.p. 140–142°, $[\alpha]_D^{20}$ +53° (*c*, 1·00). (Found: C, 81·1; H, 11·6. $C_{30}H_{50}O_2$ requires: C, 81·5; H, 11·3%).

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