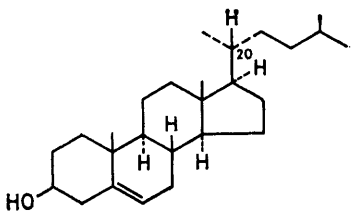
The Configuration at C-20 of a Natural Δ^5-C_{26}-Sterol

By JOHN M. JOSEPH and WILLIAM R. NES
(*Department of Biological Sciences, Drexel University, Philadelphia, Pennsylvania* 19104)

Summary The (20*R*)- and (20*S*)-epimers of halosterol, a naturally occurring C_{26}-analogue of cholesterol, have been synthesized; the (20*R*)-epimer was identical with and the (20*S*)-epimer different from the sterol derived from the naturally occurring 22-dehydro derivative.

THE analogue (26,27-bisdemethylcampesterol, 24,24-dimethylchol-5-en-3β-ol) of cholesterol in which the side chain has been shortened by one CH_2-group is naturally occurring[1] and called halosterol.[1] In the case of the $\Delta^{7,22}$-analogue (asterosterol) from starfish, the configuration at C-20 is known[2] to be the same as in cholesterol which is the same as in sterols of algae, fungi, and tracheophytes.[3] However, the opposite configuration has been found in a steroidal carboxylic acid found in a marine organism.[4] In order to study this configurational problem further, we have synthesized both (20*R*)-halosterol and its (20*S*)-epimer. The synthetic sequence was analogous to the preparation from pregnenolone of cholesterol and 20-isocholesterol except that isopentyl bromide was used in the Grignard reaction. Dehydration of the 20-hydroxy-derivatives was followed by 3,5-cyclosteroid rearrangement, hydrogenation, and retrorearrangement yielding a mixture (40% from pregnenolone) of halosterol [(20*R*)-isomer, m.p. 152—153 °C,



Halosterol

R.R.T.† 0·78] and 20-isohalosterol (m.p. 137—139 °C, R.R.T.† 0·69) in a ratio of 59:41, as shown by g.l.c. The isomers were separated by chromatography on alumina. The mass spectra were consistent with the assigned structures, but no attempt to distinguish between the isomers from their metastable ions[5] was made. The (20*S*)-epimer moved faster in both adsorption and gas–liquid chromatography as also happens with the epimers of cholesterol. Inversion from the (20*R*)- to the (20*S*)-configuration results in a consistent change in the R.R.T.† by a factor of 0·9, and the ^{1}H n.m.r. spectra of epimers of cholesterol and halosterol also showed consistent differences. Inversion of the configuration in the cholesterol,[3] halosterol, and other[4] cases is accompanied by an upfield shift of 0·10 p.p.m. in the signal from the C-21 protons. The spectrum (360 MHz) of the (20*R*)-epimer of halosterol showed peaks at δ 0·673 (s, 18-H_3), 1·006 (s, 19-H_3), 0·906 (d, J 6·5 Hz, 21-H_3), and 0·865 and 0·849 (each d, J 6·5 Hz, *gem*-Me_2), and the (20*S*)-epimer showed peaks at δ 0·674 (s, 18-H_3), 1·004 (s, 19-H_3), 0·805 (d, J 6·5 Hz, 21-H_3), and 0·865 and 0·869 (each d, J 6·5 Hz, *gem*-Me_2). The separation between the two doublets for the side-chain *gem*-dimethyl groups is greater in both cases for the (20*R*)-epimer: 1·5 Hz for cholesterol and 0·0 Hz for 20-isocholesterol; 6·0 Hz for halosterol and 2·5 Hz for 20-isohalosterol. It is also interesting that with the shorter side chain the separation between the doublets is increased.

Metayer and Barbier[6] prepared halosteryl acetate (m.p. 136—138; $[\alpha]_D$ − 42·8°) from the natural 22-dehydrohalosterol. The acetates of our samples had m.p. 136—137 °C, $[\alpha]_D^{26}$ −46·1° ($CHCl_3$), and R.R.T.† 0·84 for the (*R*)-epimer and m.p. 104—106 °C, $[\alpha]_D^{26}$ −59·4° ($CHCl_3$) and R.R.T.† 0·74 for the (*S*)-epimer. In the cholesterol series inversion of the configuration from (20*R*) to (20*S*) also is accompanied by a negative shift in $[\alpha]_D^{26}$ (−39·6 to −56·2°, respectively, as the free alcohols).

It is clear from these physical constants that the natural Δ^5-C_{26}-series has the same configuration as does cholesterol and other natural sterols.‡ As will be reported elsewhere only the (20*R*)-epimer of halosterol underwent protozoan metabolism, as is also true in the C_{27}-series.[7]

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† R.R.T. is retention time relative to cholesterol in g.l.c. on 1% XE-60 at 235 °C.

‡ By the Sequence Rule this configuration is *R* for the sterols lacking a Δ^{22}-bond and *S* for the Δ^{22}-derivatives. However, in both cases the H-atom at C-20 is α-oriented (in front when C-22 is to the right) by the modified α,β-convention for the side chain (W. R. Nes, *Adv. Lipid Res.*, 1977, **15**, 240).

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