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# Synthesis of [21-$^2$H]- and [22-$^2$H]-Derivatives of 23,24,25,26,27-Pentanorcholesterol and 23,24,25,26,27-Pentanordihydrolanosterol and the Stereochemical Significance of the Deuterium Spin-Lattice Relaxation Times*

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We report the synthesis of some analogs at the 21- or 22-methyl group of 23,24,25,26,27-pentanorcholesterol (3$\beta$-hydroxybisnorchol-5-ene) and 23,24,25,26,27-pentanordihydrolanosterol, together with the results of deuterium relaxation time measurements. The latter measurements are expected to cast light on the stereochemistry of the isopropyl side chain, since the deuterium relaxation time is determined by anisotropic intramolecular rotation.

As a first step for the synthesis of deuterated compounds, isomerization of (20*S*)-3$\beta$-acetoxybisnorchol-5-en-22-al was performed according to the procedure of Barton *et al.* to afford an equilibrium mixture of the epimers at C-20. The epimeric mixture was oxidized with chromium trioxide in acetic acid. Upon column chromatography of the products on Sephadex LH-20, the 20*R*-carboxylic acid was eluted first with chloroform, followed by the 20*S*-epimer. After treatment of the carboxylic acids with ethyl chloroformate and triethylamine in tetrahydrofuran, reduction of the products with sodium borohydride afforded the corresponding hydroxy compound, and subsequent phosphoryl chloride treatment in pyridine gave the corresponding chloro compounds. Upon lithium aluminum hydride reduction, each chloro compound afforded the same product, 3$\beta$-hydroxybisnorchol-5-ene (I). The $^1$H NMR spectrum of I showed two doublets at 0.93 and 0.84 ppm, indicating a chemical shift difference between the 21- and 22-methyl groups. When lithium aluminum deuteride instead of lithium aluminum hydride was used as the reducing reagent in the last step of the reactions, 22-chloro- and 21-chloro compounds afforded the corresponding deuterated compounds, IIa and IIb, respectively. The $^1$H NMR signals at 0.84 and 0.93 ppm, which correspond to the chemical shifts of the deuterated 22- and 21-methyl groups, respectively, decreased. The $^2$H NMR chemical shifts expressed in ppm, are essentially the same as those of the analogous $^1$H compound. The second stage of the present studies was the synthesis of the same type of compounds in the lanosterol series; they were 23,24,25,26,27-pentanordihydrolanosterol and its 22- and 21-deuterated compounds (Va and Vb). A solution of 3$\beta$-acetoxy-23,24,25,26,27-penta-

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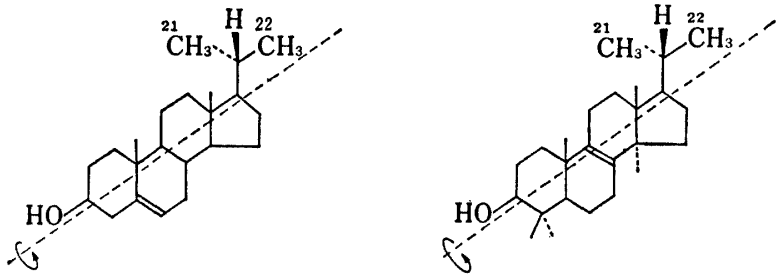
norlanost-8-en-22-al was reduced with sodium borohydride and the resulting alcohol was chlorinated with phosphoryl chloride in pyridine to give the 22-chloro compound (XIa). Lithium aluminum hydride reduction of XIa gave 23,24,25,26,27-pentanordihydrolanosterol. On the other hand, reduction of XIa with lithium aluminum deuteride afforded the 22-deuterated compound (Va). The methyl ester of 3$\beta$-acetoxy-23,24,25,26,27-pentanorlanost-8-en-22-oic acid was subjected to isomerization of C-20 according to the procedure of Hayatsu. A solution of the methyl ester in diethylene glycol containing 12.5% potassium hydroxide was refluxed, and after acetylation of the products, column chromatography on Sephadex LH-20 afforded the 20*R*-carboxylic acid (Xb) and 20*S*-carboxylic acid (Xa) in 28 and 32% yields, respectively. Xb thus obtained was transformed to the chloro compound and then into the deuterated compound (Vb) by hydrogenation with lithium aluminum deuteride. The $^2H$ NMR spectra of Va and Vb showed signals at 0.90 ppm without any difference between the deuterated 21- and 22-methyl groups.

Generally, the $^2H$ spin-lattice relaxation time ($T_1$) is greatly affected by the anisotropic tumbling of the molecule, which is usually a rigid, rod-like molecule. The relaxation behavior of $^2H$ is dominated by a quadrupolar mechanism and therefore is indicative of the molecular dynamics (internal and/or overall) at the position of substitution. This makes interpretation of relaxation data much simpler for $^2H$ than for $^1H$ or $^{13}C$. We examined the $^2H$ $T_1$'s of IIa and IIb, as shown in Figure 1. In view of the molecular geometry, it may be possible to treat the molecular tumbling motion in solution as that




IIa: 22-$CH_2D$ 0.14 sec
IIb: 21-$CH_2D$ 0.19 sec

Va: 22-$CH_2D$ 0.15 sec
Vb: 21-$CH_2D$ 0.16 sec

Fig. 1. The Deuterium Spin-lattice Relaxation Times of the [21-$^2H_1$]- and [22-$^2H_1$]-Derivatives of 23,24,25,26,27-Pentanorcholesterol and 23,24,25,26,27-Pentanordihydrolanosterol

of a symmetrical top, the principal axis being the dotted line across the steroid skeleton. Thus, the C–$^2H$ vector of the deuterated 22-methyl group of IIa would be close to the principal axis compared with that of the deuterated 21-methyl group of IIb. The $T_1$ value of the deuterated 21-methyl group should be longer than that of the 22-methyl group, since the $T_1$ value of the latter is mainly influenced by the rather longer correlation time for the motion around the axis perpendicular to the principal axis. It should be

emphasized here that the longer $T_1$ value is caused by a shorter correlation time, while the shorter $T_1$ value is caused by a longer correlation time. This expectation is consistent with the experimental results, giving $T_1$ values of 0.14 and 0.19 sec for IIa and IIb, respectively. Undoubtedly, this result arises because the ratio of internal rotation around the C-17—C-20 bond is much slower than $1/T_1$ ($\sim$5 sec). Therefore the methyl groups in question have restricted orientation, in agreement with the view of Nes *et al.* rather than the arguments of Gut *et al.* on the stereochemistry of sterols at C-20.

On the other hand, we found that there appears to be no significant difference in the $T_1$ values of methyl groups between Va and Vb (0.15 and 0.16 sec, respectively). As indicated by CPK models, the molecular shapes of Va and Vb exhibit a swelling, mainly due to the presence of three more methyl groups at the 4, 4 and 14 positions. Therefore, it is likely that the similarity of 21- and 22-$^2$H $T_1$ values arises from the rather isotopic nature of the tumbling motion, in contrast to that of IIa and IIb.

The present discussion should provide a useful basis for considering the relationship between stereochemistry and anisotropic motion in the field of steroid chemistry.