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CONFIGULATION AT C-23 IN 5β-CHOLESTANE-3α,7α,12α,23-TETROL EXCRETED BY PATIENTS WITH CEREBROTENDINOUS XANTHOMATOSIS

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The configuration at C-23 in 5β-cholestane-3α,7α,12α,23-tetrol, one of the bile alcohols isolated from the bile and feces of patients with cerebrotendinous xanthomatosis, has been determined by X-ray crystallography to be 23R.

KEYWORDS——bile alcohols, X-ray analysis, absolute configuration, cerebrotendinous xanthomatosis, structure determination

In the currently accepted pathway of cholic acid biosynthesis from cholesterol, side chain cleavage is thought to proceed via 26-hydroxylation of 5β-cholestane-3α,7α,12α-tetrol.[2] In the patients with rare inherited disease cerebrotendinous xanthomatosis (CTX) this 26-hydroxylation capacity is defective[3] and consequently large amounts of bile alcohols have been found in their bile and feces. These bile alcohols have been conclusively identified as 5β-cholestane-3α,7α,12α,23ξ-tetrol,[4,5] 5β-cholestane-3α,7α,12α,24α-tetrol,[4] 5β-cholestane-3α,7α,12α,24β-tetrol,[4] 5β-cholestane-3α,7α,12α,25-tetrol,[6] 5β-cholestane-3α,7α,12α,23ξ,25-pentol,[7,8] and 5β-cholestane-3α,7α,12α,24α,25-pentol.[8] To clarify the biological significance of the 23-hydroxylated bile alcohols in the CTX patients the elucidation of the configurations at C-23 in these bile alcohols is indispensable.

The configurations of 23-hydroxyl groups in 5β-cholestane-3α,7α,12α,23ξ-tetrol and 5β-choletane-3α,7α,12α,23ξ,25-pentol, have been assigned as 23β (23R)[5] and 23β (23S),[7] respectively, based on the differences of molecular rotations. But the configurations are still under discussion because Dayal *et al*,[9] using circular dichroism spectroscopy, has proposed the assignment opposite to the previous one for 5β-cholestane-3α,7α,12α,23ξ,25-pentol.

In order to determine the absolute configuration as well as the molecular structure of 5β-cholestane-3α,7α,12α,23ξ-tetrol, a single crystal X-ray analysis was undertaken. The tetrol crystallized in the monoclinic crystal class with a=12.696 (4), b=7.934 (2), c=13.436 (4) Å, and β=108.92 (2)°. All unique diffraction intensities with $2\theta<50.0°$ were collected by a ω-scan mode on a Syntex R3 four-circle diffractometer with graphite monochromated MoKα radiation (0.7107 Å). Of the 2431 theoretically possible reflections, 1949 (80.2%) were judged to be observed after correction for Lorentz and polarization effects. The distribution of normalized structure factors for

observed reflections indicated the noncentrosymmetric space group $P2_1$, and the density ($\rho_{calcd.}$: 1.18 g /cm^3) showed the presence of one formula unit of 5β-cholestane-3α,7α,12α,23ξ-tetrol per asymmetric unit (Z=2). A phasing model which was obtained from the program MULTAN[10] was refined using Syntex XTL program system. Full-matrix least-squares refinements with anisotropic temperature factors for the non-hydrogen atoms and isotropic ones for the hydrogen atoms converged to the final R factor of 0.046 for 1949 reflections. Figure 1 shows a perspective drawing of the molecular structure. From the relative configuration obtained by X-ray analysis it is now concluded that the configuration at C-23 of the tetrol is R.

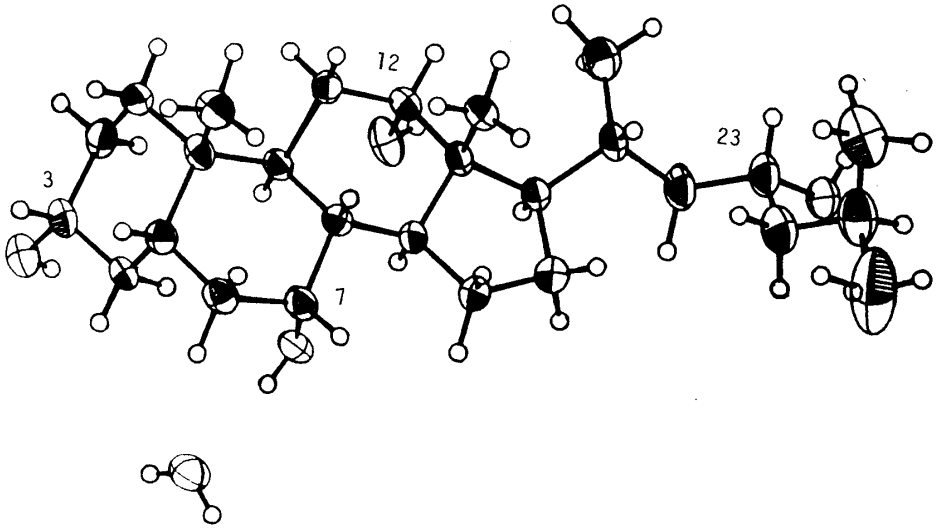

Figure 1.

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