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Metabolism of 27-Nor-24, 25-dihydrolanosterol and 23, 24, 25, 26, 27-Pentanordihydrolanosterol by Rat Liver Homogenate Preparations*

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We have previously shown that lanosterol analogs with both a side chain longer than the hexanor analog and the normal configuration at C-20 are potent inhinitors of cholesterol biosynthesis from lanosterol. This finding prompted us to determine whether these lanosterol analogs can be metabolized as substrates. For this purpose we prepared the tritum-labeled 27-nor-24,25-dihydrolanosterol (**1b**) and 23,24,25,26,27-pentanordihydrolanosterol (**2b**), and examined their metabolism in preparations of rat liver *in vitro* (Chart 1).

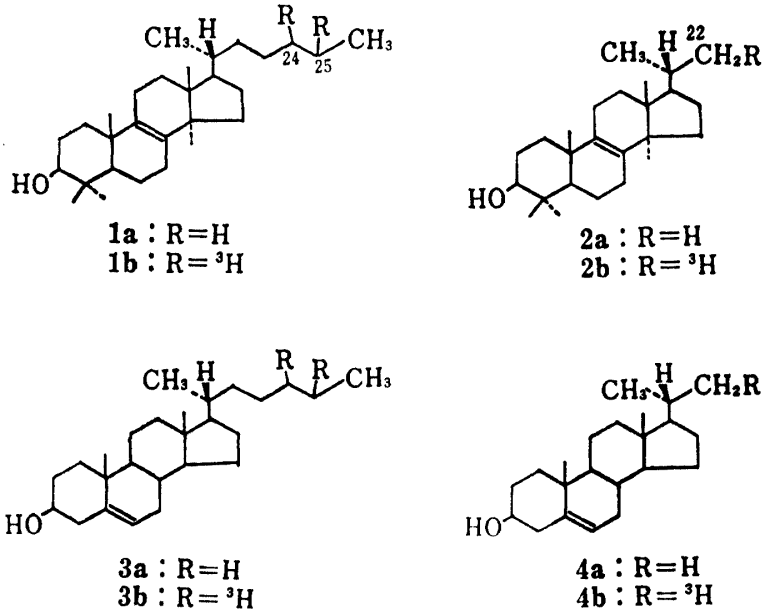


Chart 1.

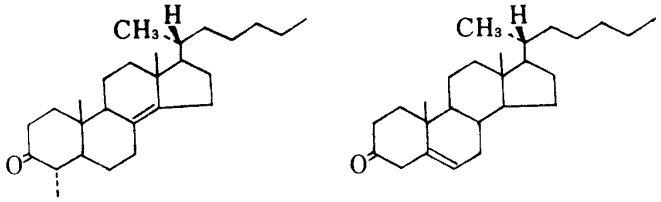
First, [22-^{3}H]-23,24,25,26,27-pentanordihydrolanosterol was incubated with S-10, and after TLC of the products (which is capable of separating 4,4-demethyl sterol, 4-monomethyl sterol, 4,4-dimethyl sterol and sterone), a portion of the 4,4-demethyl sterol fraction was cocrystallized with 23,24,25,26,27-pentanorcholesterol (**1a**). However, radioactivity indicative of the formation of **4a** was not detected in the sample. The 4,4-demethyl sterol fraction was cocrystallized with 23,24,25,26,27-pentanordihydrolanosterol (**2a**), and it was found that 87.5% of the starting material had remained unchanged in the incubation.

* 本報は *Chem. Pharm. Bull.*, **30**, 628 (1982) に報告.

The radioautograph of incubation products of [24,25-^{3}H]-27-nor-24,25-dihydrolanosterol showed five bands (A-1, A-2, B, C, D) which corresponded to 4-monomethyl sterones and 4,4-demethylsterones, 4,4-dimethyl sterols, 4-monomethyl sterols, and 4,4-demethyl sterols, respectively as judged from their chromatographic properties. The eluate from band B was cocrystallized with 40 mg of 27-nor-24,25-dihydrolanosterol (**1a**) to a constant specific activity (1.05×10^6 dpm/mg), suggesting 42.6% recovery of the starting material. Similarly, the eluate from band D was cocrystallized with 27-norcholesterol (**3a**, 100 mg); the specific activity of the crystals remained constant during four recrystallization, that is, 7.24×10^4, 6.29×10^4, 6.68×10^4, and 6.27×10^4 dpm/mg, corresponding to 6.5% transformation of the 27-noranalog into 27-norcholesterol. The eluate from the sterone fraction (A-2) was cocrystallized with 50 mg of 27-norcholest-5-en-3-one (**9**) to a constant specific activity, suggesting 2.3% conversion to 27-nor-cholest-5-en-3-one.

In order to obtain further information on the metabolites, parallel incubations of S-10 with unlabeled 27-nor-24,25-dihydrolanosterol (**1a**) were performed on a large scale. After TLC separation of the products, the eluates from each fraction were analyzed by GC-MS. Peaks lacking in blank experiments were found in eluates from the lanosterol fraction, cholesterol fraction and sterone fraction. The new peak in the lanosterol fraction coincided with the starting material. The new peak in the cholesterol fraction coincided with 27-norcholesterol (**3a**). Next, the new peak in the sterone fraction corresponding to band A-1 was analyzed by GC-MS, and the metabolite was tentatively assigned as 4α-methyl-27-norcholest-8(14)-en-3-one by comparison of the MS fragmentation patterns of Δ^7, $\Delta^{8(14)}$, and Δ^{14} derivatives of 4α-methylcholestan-3-one.

Consequently, the structure of the metabolite of the A-1 band in the isotope experiments was determined to be 4α-methyl-27-nor-cholest-8(14)-en-3-one (**11**) (Chart 2). To our knowledge, this 4α-methyl-$\Delta^{8(14)}$-sterone analog is the first of its type obtained as a metabolite of lanosterol analogs.



11 **9**

Chart 2

Further, it is interesting to note that 8(14)-unsaturated sterols have implicated in the processes of demethylation at C-14 in sterol biosynthesis.

In summary, we found that 27-nor-24,25-dihydrolanosterol is metabolized to 27-norcholesterol, but the pentanor analog of dihydrolanosterol is not metabolized to the corresponding analog of cholesterol. The structure of the side chain thus appears to have a strong influence on the metabolism of lanosterol analogs.