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1α-HYDROXYLATION OF CHOLESTEROL AND THE RELATED 3-HYDROXYSTEROIDS[1]

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For the preparation of 1,25-dihydroxycholecalciferol which is "tissue-active" form of Vitamin D_3 in the intestine,[2,3] 1α-hydroxycholesterol or its related 1,3-dihydroxysteroid could be an important intermediate. We have uncovered a general procedure of the introduction of a hydroxyl group at 1α-position of cholesterol and the related 3-hydroxysteroids.

The procedure is constituted of three steps from 3-keto-$\Delta^{1,4}$-steroids, and the following examples[4] serve to provide a basis for evaluation of its wide scope.

In the first step in our procedure, the 3-keto-$\Delta^{1,4}$-steroids (1a and 1b) were converted to the 3-keto-$\Delta^{1,5}$-steroids (2a and 2b) via the deconjugation procedure using t-BuOK in DMSO,[5] followed by treatment with ice-water and extraction with $CHCl_3$. Since cholesta-1,5-diene 3-one (2a) is extremely sensitive to aqueous alkaline solution and regenerates the 1,4-diene (1a), the work-up of the product should be carried out quickly in ice-cooled conditions. $NaBH_4$ reduction of the 3-keto-$\Delta^{1,5}$-steroid (2a or 2b) in methanol at 0° then gave the corresponding 3-hydroxy-$\Delta^{1,5}$-steroid (3a or 3b) in good yield. More conveniently, the reduction could be applied directly to the crude product of the deconjugation reaction, by which the yield of 3a was raised up to 50% based on 1a.

Support for beta-configuration of the newly formed 3-hydroxy function was

provided by the selective reduction of the 1,2-double bond in 3a or 3b with palladium on charcoal in dioxane, for cholesterol or dehydroepiandrosterone (obtained after saponification of the 17-ethyleneketal function) was obtained.

The final step in the procedure is achieved by hydroboration of 3 in THF at room temperature for 1 hr by 0.8 mole equivalent of 1M-solution of diborane in THF,[6] followed by the alkaline-peroxide oxidation.

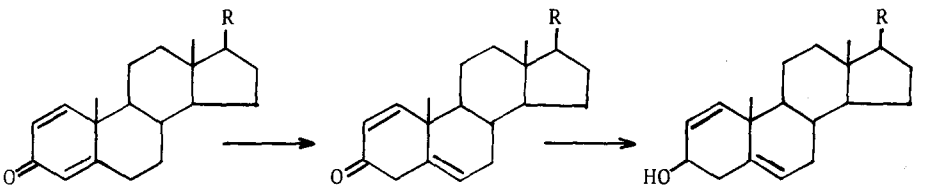
By chromatography on alumina, the oxidation products from 3a or 3b produced, respectively, first the starting material 3 (25-30%) and then two isomeric dihydroxy compounds 4a or 4b (negative to periodic acid-oxidation) and 5a or 5b (positive to periodic acid-oxidation) each in ca. 15% yield.

Introduction of the hydroxy group at 1α or 2α position of these steroids is reasonably assumed from the steric factors in the course of hydroboration[7] and it was actually verified from nmr spectroscopic studies[8] and chemical reactions on these products that the more strongly absorbed on alumina to be the 2α,3β-dihydroxy isomer (5a or 5b) and the other one to be the 1α,3β-dihydroxy isomer (4a or 4b).

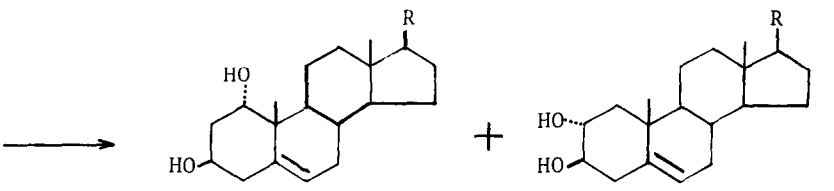
For example, the lower field bands in the nmr spectrum of 4a consists of a narrow multiplet for 1β-H (τ 6.20; $W_{1/2}$ 8 Hz), a broad multiplet for 3α-H (τ 6.10; $W_{1/2}$ 24 Hz), and a doublet for 6-H (τ 4.45, J=5 Hz). The nmr spectrum of 5a showed, in the same region, a one proton triplet of doublets (τ 6.40, J=9 and 3 Hz) and a one proton quartet (τ 6.74, J=9 Hz) indicating the presence of two vicinal axial methine protons bonded to OH function as well as a one olefinic proton doublet for 6-H (τ 4.65, J=4 Hz).

Though the melting point of 4a did not agree with that of 1α-hydroxycholesterol reported by Kodicek et al.,[9] the catalytic hydrogenation of 4a in the presence of a mixed catalyst of Pd/C and PtO_2 afforded the dihydro compound 6a (mp 152-154°) identical in all respects to 1α,3β-dihydroxy 5α-cholestane reported by Shoppee et al.[10,11] The structure of 5a was also determined unequivocally, since its dihydro derivative (mp 202-204°, $[\alpha]_D$ +12° (CH_3OH): diacetate, mp 109-110°) was identical in all respects to 2α,3β-dihydroxy 5α-cholestane reported by the same authors.[12]

Acid hydrolyses of the ketals (4b and 5b) afforded the corresponding 17-keto-



a: R= C_8H_{17} 2a, mp 105-109°(50%) 3a, mp 135-136°(65%)
1 b: R= -O-CH_2-CH_2-O- 2b, mp 154-157°(70%) 3b, mp 134-138°(80%)
c: R= =O



4a, mp 154-156°(ca. 15%) 5a, mp 191-194°(ca. 15%)
4b, mp 194-197°(ca. 15%) 5b, mp 122-126°(ca. 15%)
4c, mp 261-266° 5c, mp 98-100°

compounds (4c and 5c), whose nmr spectra were in good accordance with the proposed structures. Furthermore, 4c ($[\alpha]_D$ +24°(C_2H_5OH): diacetate, mp 219-222°) was identical in all respects to 1α-hydroxydehydroepiandrosterone obtained by the microbiological 1α-hydroxylation of dehydroepiandrosterone.[13]

By the use of an excess of BH_3/THF (≳1.5 mole equivalent), at least two trihydroxy derivatives were obtained; while the use of the reagent less than 0.8 mole equivalent reduced the yields of the diols and resulted in the predominant recovery of the starting materials.

This general procedure for introduction of 1α-hydroxy group into 3-oxygenated steroids has also been successfully applied to progesterone series.

We are currently investigating the syntheses of 1,25-dihydroxycholecalciferol and its related compounds by the use of this procedure.

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10) The physical data of 1α-hydroxycholesterol are shown in the Table:

source	elemental composition	melting point	$[\alpha]_D$
Pelc and Kodicek[9]	$C_{27}H_{46}O_2 \cdot 1/2\ H_2O$	195-200°	0 ± 1° (CH_3OH)
the present work	$C_{27}H_{46}O_2$	154-156°	+4° (CH_3OH)

By private communication from Drs. Morisaki and Ikekawa to one (C.K.) of the present authors, we noticed that the research group at Tokyo Institute of Technology also synthesized 1α-hydroxycholesterol, whose physical data were consistent with ours. We thank Dr. Morisaki for this information.

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