[Chem. Pharm. Bull.]
31(3) 907-911 (1983)

Synthesis of (22*R*)- and (22*S*)-22-Hydroxylanosterols¹⁾

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(Received August 28, 1982)

Epoxidation of (22*E*)-3 β -acetoxylanosta-8,22-dien-24-one (**1**) afforded the 22,23-epoxides (**2**) which were led to (22*R*)-22-hydroxylanosterol (**7a**) predominantly and (22*S*)-22-hydroxylanosterol (**8a**) as a minor product in a few steps. The epimeric relationship of **7a** and **8a** was confirmed by Jones oxidation of **7a** to give the 3,22-diketone compound (**9**), which furnished mainly (22*S*)-22-hydroxylanosterol (**8a**) on hydride reduction.

Keywords—(22*R*)-22-hydroxylanosterol; (22*S*)-22-hydroxylanosterol; lanosta-8,24-diene-3,22-dione; hydrazine hydrate; pyrazole compound; inotodiol

We have recently shown¹⁾ that some lanosterol analogs with modified side chains inhibit cholesterol biosynthesis from lanosterol. In this connection, 22-hydroxylated lanosterol analogs were required for the investigation of the biological activity. (22*R*)-22-Hydroxylanosterol (inotodiol),²⁾ which was isolated from the birch fungus *Inonotus obliquus*, has been synthesized by Poyser *et al.*²⁾ This paper describes the synthesis of (22*R*)- and (22*S*)-22-hydroxylanosterols.

The starting material, (22*E*)-3 β -acetoxylanosta-8,22-dien-24-one (**1**, Chart 1) in this study, was prepared from lanosterol according to the published procedure.³⁾ Reaction of **1** with H₂O₂ in an alkaline solution gave the epoxy compounds (**2**) which exhibited one spot on thin layer chromatography (TLC). As epoxidation of this type is reported^{4,5)} to give the (22*S*, 23*R*)-epoxy compound, the main component of **2** is expected to have the (22*S*, 23*R*)-configuration although four stereoisomers are possible in keto epoxides. Treatment of **2** with hydrazine hydrate^{4,6)} in EtOH gave an undesired nitrogen-containing compound. The structure of the latter compound was assumed to be **3a** or **3b** from its mass spectrum (MS) (m/z 494, M⁺), ele-

Chart 1

recrystallized from MeOH to give colorless needles of **5a, b**, mp 212–213°C. *Anal.* Calcd for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.90; H, 10.44. MS m/z : 500 (M^+), 485, 467, 407, 43 (base peak). PMR δ (ppm): 0.73 (3H, s, 18-CH₃), 1.00 (3H, s, 19-CH₃), 1.12 (6H, d, 26- and 27-CH₃, $J=6.5$ Hz), 2.03 (3H, s, 3-OCOCH₃), 2.40–2.72 (3H, m, 23-H₂ and 25-H), 4.03–4.25 (1H, m, 22-H), 4.40–4.64 (1H, m, 3-H).

3 β ,22 ξ -Diacetoxylanosta-8-en-24-one (6a, b)—**5a, b** was acetylated with Ac₂O–pyridine as usual to give **6a, b**. Recrystallization from MeOH gave colorless needles of **6a, b**, mp 213–214°C. *Anal.* Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 74.83; H, 9.95. MS m/z : 542 (M^+), 482, 467 (M^+-75 , base peak), 407. PMR δ (ppm): 0.70 (3H, s, 18-CH₃), 1.00 (3H, s, 19-CH₃), 1.08 (6H, d, 26- and 27-CH₃, $J=6.5$ Hz), 1.96 (3H, s, 22-OCOCH₃), 2.03 (3H, s, 3-OCOCH₃), 2.28–2.84 (3H, m, 23-H₂ and 25-H), 4.36–4.60 (1H, m, 3-H), 5.24–5.50 (1H, m, 22-H).

(22R)-3 β ,22-Diacetoxylanosta-8,24-diene (7b) and (22S)-3 β ,22-Diacetoxylanosta-8,24-diene (8b)—NaBH₄ (0.1 g) was added to a solution of **6a, b** (0.1 g) in MeOH–tetrahydrofuran (12 ml, 5:1) and the mixture was stirred at room temperature for 2 h. The usual work-up afforded the crystalline alcohol. This crude alcohol was dissolved in pyridine (5 ml), then POCl₃ (2 ml) was added, and the mixture was refluxed for 1 h. After usual work-up, the brown residue was chromatographed on silica gel (20 g). Elution of the *Rf* 0.22 fraction (developed with benzene) with benzene gave a solid (70 mg) which was recrystallized from MeOH to give colorless platelets of **7b**, mp 152–154°C (lit.²⁾ 153.5–155.5°C). *Anal.* Calcd for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.20; H, 10.65. MS m/z : 526 (M^+), 511, 466, 451, 391, 109 (base peak), 69, 43. PMR δ (ppm): 0.69 (3H, s, 18-CH₃), 1.00 (3H, s, 19-CH₃), 1.61 (3H, s, 26- or 27-CH₃), 1.67 (3H, s, 26- or 27-CH₃), 2.00 (3H, s, 22-OCOCH₃), 2.03 (3H, s, 3-OCOCH₃), 4.36–4.60 (1H, m, 3-H), 4.80–5.20 (2H, m, 22- and 24-H). $[\alpha]_D^{17.5} + 47^\circ$ ($c=1.0$, CHCl₃) (lit.²⁾ $[\alpha]_D^{17} + 45^\circ$).

Further elution of the *Rf* 0.11 fraction with benzene gave a solid (5 mg) which was recrystallized from MeOH to give colorless needles of **8b**, mp 143–146°C. *Anal.* Calcd for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.41; H, 10.19. MS m/z : 526 (M^+), 511, 466, 451 (M^+-75 , base peak), 391, 109, 69, 43. PMR δ (ppm): 0.68 (3H, s, 18-CH₃), 1.00 (3H, s, 19-CH₃), 1.62 (3H, s, 26- or 27-CH₃), 1.68 (3H, s, 26- or 27-CH₃), 2.01 (3H, s, 22-OCOCH₃), 2.03 (3H, s, 3-OCOCH₃), 4.40–4.64 (1H, m, 3-H), 4.86–5.16 (2H, m, 22- and 24-H).

(22R)-22-Hydroxylanosterol (7a)—**7b** was hydrolyzed with 10% methanolic KOH under reflux for 10 h. After usual work-up, the residue was recrystallized from MeOH to give colorless needles of **7a**, mp 188–190°C (lit.²⁾ mp 189–191.5°C). *Anal.* Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.06; H, 11.48. MS m/z : 442 (M^+), 427, 409, 391, 372, 109, 99 (base peak), 69. PMR δ (ppm): 0.72 (3H, s, 18-CH₃), 0.81 (3H, s, 31-CH₃), 0.88 (3H, s, 32-CH₃), 0.98 (3H, s, 30-CH₃), 0.99 (3H, s, 19-CH₃), 1.65 (3H, s, 26- or 27-CH₃), 1.73 (3H, s, 26- or 27-CH₃), 3.12–3.36 (1H, m, 3-H), 3.56–3.80 (1H, m, 22-H), 5.08–5.32 (1H, m, 24-H). $[\alpha]_D^{17.5} + 58^\circ$ ($c=0.5$, CHCl₃) (lit.²⁾ $[\alpha]_D^{20} + 59^\circ$).

(22S)-22-Hydroxylanosterol (8a)—**8b** was hydrolyzed with 10% methanolic KOH under reflux for 10 h. After usual work-up, the residue was recrystallized from MeOH to give colorless needles of **8a**, mp 132–134°C. *Anal.* Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 80.94; H, 11.42. MS m/z : 442 (M^+), 427, 409, 391, 372, 109, 99, 69 (base peak). PMR δ (ppm): 0.70 (3H, s, 18-CH₃), 0.81 (3H, s, 31-CH₃), 0.91 (3H, s, 32-CH₃), 0.98 (3H, s, 30-CH₃), 0.99 (3H, s, 19-CH₃), 1.64 (3H, s, 26- or 27-CH₃), 1.72 (3H, s, 26- or 27-CH₃), 3.12–3.36 (1H, m, 3-H), 3.56–3.80 (1H, m, 22-H), 5.08–5.32 (1H, m, 24-H). $[\alpha]_D^{17.5} + 44^\circ$ ($c=0.5$, CHCl₃).

Oxidation of 7a—Jones reagent (0.1 ml) was added to a solution of **7a** (10 mg) in acetone (5 ml), and the mixture was stirred for 15 min at 0°C. After usual work-up, the residue was chromatographed on silica gel (5 g). Elution with methylene chloride gave a solid (5 mg) which was recrystallized from MeOH to give colorless needles of lanosta-8,24-diene-3,22-dione (**9**), mp 84–85°C. *Anal.* Calcd for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 81.91; H, 10.45. MS m/z : 438 (M^+), 423, 369, 355, 341, 69 (base peak), 57, 55. PMR δ (ppm): 0.73 (3H, s, 18-CH₃), 0.92 (3H, s, 32-CH₃), 1.06, 1.08, and 1.11 (3H each, singlet each, 19-, 30- or 31-CH₃), 1.63 (3H, s, 26- or 27-CH₃), 1.76 (3H, s, 26- or 27-CH₃), 3.04–3.22 (2H, br d, 23-H₂, $J=7$ Hz), 5.20–5.44 (1H, m, 24-H).

Reduction of 9—NaBH₄ (10 mg) was added to a solution of **9** (10 mg) in MeOH (5 ml) and the reaction mixture was stirred for 1 h at room temperature. After usual work-up, the residue was chromatographed on silica gel (1 g). Elution with methylene chloride gave a solid (8 mg) which was analyzed by GLC and exhibited two peaks corresponding to **7a** and **8a** in a ratio of 1:2. A part of the residue (6 mg) was acetylated as usual and the products were separated by chromatography on silica gel to give **7b** (2 mg) and **8b** (4 mg).

Acknowledgement The authors are indebted to Professor S. Okuda of the Institute of Applied Microbiology, University of Tokyo, for elemental analyses. This work was supported in part by a grant from Mishima Kaiun Memorial Foundation.

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