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4. Katsumi Tanabe, Rinji Takasaki, and Ryozo Hayashi : Steroid Series. VI.[1] Synthesis of B-Norsteroids. (2).

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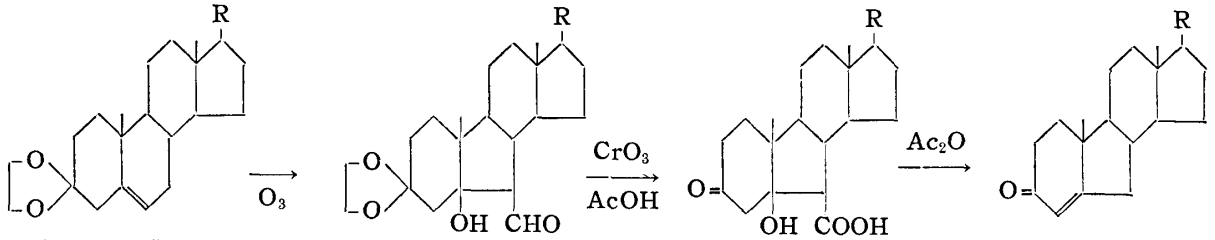
In a preceding paper[2] it was shown that 5β-hydroxy-6β-formyl-B-norsteroid cyclic 3-(ethylene acetal) (II) can be prepared, in addition to 5β,6β-epoxysteroid cyclic 3-(ethylene acetal), by the action of ozone on the cyclic ethylene acetal of Δ^4-3-oxosteroid. The present paper deals with the conversion of (II) into Δ^4-3-oxo-B-norsteroid (IV).



(Ia) R = C_8H_{17}
(Ib) R = -C(O,O)-CH_3
(Ic) R = <O,O>
(IIa) R = C_8H_{17}
(IIb) R = $COCH_3$
(IIc) R = <O,O>
(IIIa) R = C_8H_{17}
(IIIb) R = $COCH_3$
(IIIc) R = O
(IVa) R = C_8H_{17}
(IVb) R = $COCH_3$
(IVc) R = O

On treatment of 6β-formyl-B-nor-5β-cholestan-5-ol (IIa) with chromium trioxide in acetic acid, it afforded, with concomitant hydrolysis of acetal group, 3-oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (IIIa) of m.p. 185° (decomp.), $[\alpha]_D$ +12.2°, which proved identical with that obtained by oxidation of 3β,5-dihydroxy-B-nor-5β-cholestane-6β-carboxylic acid with chromium trioxide in acetic acid.[1] Thus, the β-configuration at C-5 and C-6 in (IIIa) was established. The acid (IIIa) was found to eliminate readily elements of water and carbon dioxide when heated in acetic anhydride to afford the known B-norcholest-4-en-3-one[3] (IVa) of m.p. 67~67.5°, $[\alpha]_D$ +3.9°, UV λ_{max} : 240 mμ (ε 16,600).

Oxidation of 5-hydroxy-6β-formyl-B-nor-5β-pregnane-3,20-dione cyclic 3-(ethylene acetal) (IIb) and 5-hydroxy-6β-formyl-B-nor-5β-androstane-3,17-dione bis(ethylene acetal) (IIc) gave the corresponding carboxylic acid, 5-hydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxylic acid (IIIb), m.p. 177° (decomp.), and 5-hydroxy-3,17-dioxo-B-nor-5β-androstane-6β-carboxylic acid (IIIc) of m.p. 174° (decomp.), respectively. (IIIb) and (IIIc) were then converted to B-norpregn-4-ene-3,20-dione (IVb) of m.p. 145~146°, λ_{max} 239 mμ (ε 16,250), and B-norandrost-4-ene-3,17-dione (IVc) of m.p. 142~143°, λ_{max} 239.5 mμ (ε 15,200), respectively. The latter compound was partialy reduced with sodium borohydride to 17β-hydroxy-B-norandrost-4-en-3-one as shown in a preceding paper.[1]

Experimental[*2]

3-Oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic Acid (IIIa)—To a solution of 5-hydroxy-6β-formyl-B-nor-5β-cholestan-3-one cyclic 3-(ethylene acetal) (IIa; 1.78 g.) in AcOH (60 cc.), a solution of CrO_3 (1.0 g.) in 90% AcOH (20 cc.) was added under ice-cooling. After the mixture was kept at room

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*2 All m.p.s are uncorrected. Rotations were measured in $CHCl_3$.
1) Part V : This Bulletin, **9**, 12 (1961).
2) Part IV of this series : This Bulletin, **9**, 7 (1961).
3) W. G. Dauben, G. J. Fonken : J. Am. Chem. Soc., **78**, 4736 (1956). Reported constants are : m.p. 61.1~62.2°, $[\alpha]_D$ +30.2°, and $\lambda_{max}^{heptane}$ 235 mμ (ε 14,900).

temperature for 5.5 hr., the excess reagent was decomposed by addition of 2 cc. of MeOH. After removal of the solvent under a reduced pressure, the residue was extracted with Et_2O. The extract was washed with water, dried, and the solvent was evaporated, leaving 1.2 g. of a crystalline mass. Recrystallization from hydr. Me_2CO gave 5-hydroxy-B-nor-5β-cholestan-3-one-6β-carboxylic acid (IIIa) as needles, m.p. 185° (decomp.), $[\alpha]_D^{28}$ +12.2° (c=0.49). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.85; H, 10.06. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1745 (COOH), 1715 (3-CO).

5-Hydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxylic Acid (IIIb)—A solution of CrO_3 (260 mg.) in 90% AcOH (8 cc.) was added to a solution of 5-hydroxy-6β-formyl-B-nor-5β-pregnane-3,20-dione cyclic 3-(ethylene acetal) (IIb; 500 mg.) in AcOH (20 cc.). After 5.5 hr. at room temperature the excess reagent was decomposed with MeOH and the solvent was evaporated under a reduced pressure. The greenish solid residue was dissolved in CH_2Cl_2, the solution was washed with water, and dried. Evaporation of the solvent gave 388 mg. of 5-hydroxy-B-nor-5β-pregnane-3,20-dione-6β-carboxylic acid (IIIb), which was recrystallized from hydr. Me_2CO to needles of m.p. 177° (decomp.), $[\alpha]_D^{28.5}$ +10.7° (c=0.93). *Anal.* Calcd. for $C_{21}H_{35}O_5$: C, 69.58; H, 8.34. Found: C, 69.33; H, 8.22. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1725 (COOH), 1695 (20-CO).

5-Hydroxy-B-nor-5β-androstane-3,17-dione-6β-carboxylic Acid (IVc)—A solution of CrO_3 (78 mg.) in 90% AcOH (8 cc.) was added to a solution of 5-hydroxy-6β-formyl-B-nor-5β-androstane-3,17-dione 3,17-bis(ethylene acetal) (IIc; 500 mg.) in AcOH (20 cc.). The mixture was kept at room temperature for 5.5 hr. and MeOH (1 cc.) was added to decompose the excess reagent. The solvent was evaporated at a reduced pressure to leave a greenish residue, which was dissolved in a mixture of Et_2O-AcOEt (1:4). The solution was washed with water and dried, and the solvent was evaporated at a reduced pressure to give 380 mg. of a syrupy residue, which was recrystallized from benzene-Me_2CO to afford 5-hydroxy-3,20-dioxo-B-nor-5β-androstane-6β-carboxylic acid (IIIc) as prisms of m.p. 174° (decomp.), $[\alpha]_D^{27}$ +37.5° (c=0.32). *Anal.* Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.18; H, 8.20. IR ν_{max}^{KBr} cm^{-1}: 3500~3120 (OH), 1760 (17-CO), 1720 (COOH).

B-Norcholest-4-en-3-one (IVa)—A solution of 3-oxo-5-hydroxy-B-nor-5β-cholestane-6β-carboxylic acid (IIIa; 300 mg.) in Ac_2O (30 cc.) was refluxed for 2.5 hr. Evaporation of the solvent under a reduced pressure left a pale yellow syrup, which was chromatographed on alumina. Elution with benzene-petr. ether (3:2), after evaporation of the solvent, afforded 83 mg. of crystalline solid melting at 58~60°, which was rechromatographed on alumina. Elution with the same mixture of solvents gave B-norcholest-4-en-3-one (IVa), which, after recrystallization from MeOH-Me_2CO, melted at 67~67.5°, $[\alpha]_D^{27}$ +3.9° (c=1.02). *Anal.* Calcd. for. $C_{27}H_{44}O$: C, 84.26; H, 11.42. Found: C, 84.40; H, 11.08. UV λ_{max}^{EtOH}: 240 mμ (ε 16,600). IR ν_{max}^{KBr} cm^{-1}: 1680, 1640 (Δ^4-3-CO).

B-Norpregn-4-ene-3,20-dione (IVb)—A solution of 5-hydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxylic acid (IIIb; 70 mg.) in Ac_2O (5 cc.) was refluxed for 2.5 hr. The solvent was evaporated under a reduced pressure and the resulting pale yellow syrupy residue was chromatographed on alumina. Elution with benzene afforded 44 mg. of B-norpregn-4-ene-3,20-dione (IVb), m.p. 140~142.5°. One recrystallization from petr. ether gave white rhombics of m.p. 145~146°, $[\alpha]_D^{27}$ +65.2° (c=0.92). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.19; H, 9.20. UV λ_{max}^{EtOH}: 239 mμ (ε 16,250). IR ν_{max}^{KBr} cm^{-1}: 1695 (20-CO), 1678, 1640 (Δ^4-3-CO).

B-Norandrost-4-ene-3,17-dione (IVc)—A solution of 5-hydroxy-3,17-dioxo-B-nor-5β-androstane-6β-carboxylic acid (IVb; 91 mg.) in Ac_2O (5 cc.) was refluxed for 2.5 hr. Removal of the solvent under a reduced pressure afforded a pale yellow residue, which was chromatographed on alumina. Elution with benzene gave 55 mg. of crystalline material, which was recrystallized from petr. ether to white plates of m.p. 142~143°, $[\alpha]_D^{27}$ +60.2° (c=1.3). *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.30; H, 8.90. UV λ_{max}^{EtOH}: 239.5 mμ (ε 15,200). IR ν_{max}^{KBr} cm^{-1}: 1750 (17-CO), 1667, 1637 (Δ^4-3-CO).

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Summary

5β-Hydroxy-6β-formyl-B-norsteroid cyclic 3-(ethylene acetals) (IIa, b, c) in the cholestane, pregnane, and androstane series were oxidized to the corresponding carboxylic acids (IIIa, b, c) with concomitant hydrolysis of acetal group. The carboxylic acids were then converted into B-norcholest-4-en-3-one (IVa), B-norpregn-4-ene-3,20-dione (IVb), and B-norandrost-4-ene-3,17-dione (IVc) on heating in acetic anhydride.

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