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176. Hiroko Hasegawa, Shigeo Nozoe, and Kyosuke Tsuda : Stereochemistry of Steroids containing Aromatic A-Ring. II.[*1,1)] Reaction of 9α,11α-Epoxyestrone.[*2]

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The previous paper[1)] of this series reported that the epoxide (III) obtained by the oxidation of 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one acetate (I) with perbenzoic acid is identical with the epoxide obtained by alkali treatment of the bromohydrin (II) derived from I and that this substance is 9α,11α-epoxide.

The present paper describes the steric structure of the estratriol,[1)] obtained during the reductive cleavage of this epoxide (III) with lithium aluminum hydride, as well as the configuration of hydrogen atom in 9-position of the 3-hydroxyestra-1,3,5(10)-triene-11,17-dione[1)] obtained during the treatment of III with acid or alkali, and the stability of the B/C ring junction in the steroids containing aromatic A-ring.

The reduction of the epoxide (III) with lithium aluminum hydride in tetrahydrofuran gave estratriol[1)] (IVa), m.p. 250°, which on acetylation formed triacetate (IVc), proving the compound (IVa) to be 3,11,17-triol. Methylation of IVa with dimethyl sulfate afforded methyl ether (IVb), m.p. 145~146°. Magerlein and Hogg[2)] have synthesized estra-1,3,5(10)-triene-3,11α, 17β-triol[3)] from methyl 11α-hydroxy-3-oxopregna-1,4,17(20)-*cis*-trien-21-oate[2)] by its pyrolysis, followed by ozonization and then reduction, whose methyl ether had m.p. 144~145°. Since they had the same melting points, thus in order to confirm their identity, an oxidation of methyl ether (IVb) was attempted with chromic anhydride in pyridine, which gave two products, 11,17-diketone (Vb) and 11-hydroxy-17-one (VIb). On the other hand, 11β-hydroxyestrone methyl ether prepared by Hogg's procedure[2)] was oxidized with chromic anhydride in pyridine to a compound which was identical with Vb by the mixed melting point and comparison of their infrared spectra.

Since the inversion of the configuration at the α-position of carbonyl group has been now considered not to occur under oxidative condition with chromic anhydride in pyridine, the hydrogen atom at 9-position of IVa has α-orientation.

In general, the mechanism[4)] of the reductive cleavage of epoxide ring with lithium aluminum hydride has been considered to be S_N2 type reaction. However, the formation of a compound with 11α-hydroxy and 9α-hydrogen configuration by the cleavage of 9α,11α-epoxide with lithium aluminum hydride is thought to be due to the attack of the hydride from the α-side at 9-position through a stabilized benzyl cation.

Partial acetylation of the triol (IVa) afforded a 3-monoacetate (IVd), whose oxidation with chromic anhydride in pyridine gave 11α-hydroxyestrone 3-acetate (VId).

Treatment of the epoxide (III) with dry hydrogen chloride gas in chloroform afforded the corresponding chlorohydrin (VIIIa), whose acetylation formed a diacetate (VIIIb), suggesting the structure of 9ξ-chloro-11α-hydroxy compound. On the other hand, the

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[*1] This paper constitutes Part XLII of a series entitled "Steroid Studies" by K. Tsuda.

[*2] This paper will constitute a part of the dissertation to be submitted by H. Hasegawa in partial fulfilment of the requirements for the Doctor's degree.

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same treatment in methanol did not give a chlorohydrin but formed a phenol (IXa),[1] which possessed no chlorine. Since infrared spectrum of this product showed the absorption of five- and six-membered ring ketones, it seemed that a fission of the epoxide ring[5,6] took place to form a 11-keto compound.

In order to confirm this point, 11β-hydroxyestrone[2] (VIIIa) was oxidized with Killiani's reagent to afford 3-hydroxyestra-1,3,5(10)-triene-11,17-dione (Va), which was clearly different from the product (IXa). Treatment of diketone (Va) with potassium hydroxide in methanol gave the compound (IXa), which indicated that with the alkaline treatment the hydrogen at 9-position of Va was converted to β-configuration. Thus the structure of IXa was assigned as 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione. Treatment of epoxide (III) with alkali in methanol also gave IXa. The methylation of IXa with diazomethane afforded the amorphous methyl ether.

The nuclear magnetic resonance spectra of C-9 hydrogens of Va and IXa were shown in Fig. 1.*4 The coupling constants[7] between the C-9 hydrogens and the C-8 hydrogens of Va and IXa, 9 c.p.s. and 3 c.p.s., respectively, agree with the B/C-*trans* juncture of Va and with the B/C-*cis* juncture of IXa.

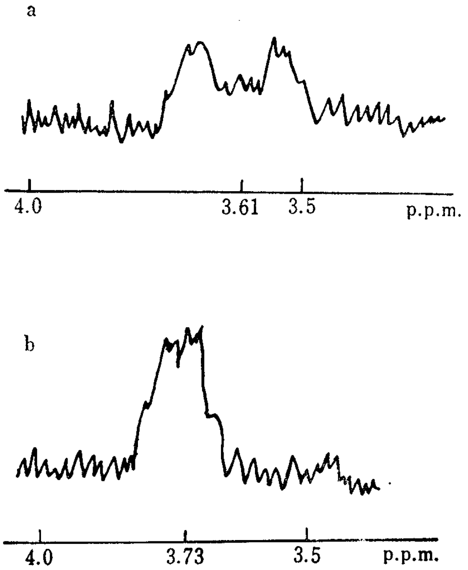

Fig. 1. Nuclear Magnetic Resonance spectra of C-9 Hydrogens

a : 3-Hydroxyestra-1,3,5(10)-triene-11,17-dione (Va)
b : 3-Hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione (IXa)

In general, the steroid skeleton is the most stable when its ring juncture has the *trans-anti-trans* conformation. Elks, *et al.*,[8] however, have reported that the hydrolysis of 1-methyl-3,11-diacetoxy-1,3,5(10),9(11)-tetraene compound gave a mixture of the two C-11 carbonyl compounds, in which the isomer possessing B/C-*cis* juncture was main product.

The easy conversi on of 9α-H of 3-hydroxyestra-1,3,5(10)-triene-11,17-dione (Va) to 9β-H (IXa) clearly shows that even this compound which does not possess CH_3 group at C-1 position and has B/C-*cis* juncture is more stable than B/C-*trans* juncture.

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*4 The NMR spectra were measured in pyridine with tetramethylsilane as internal standard, using a Varian A-60 instrument. All chemical shifts were reported in p.p.m. as δ-value.

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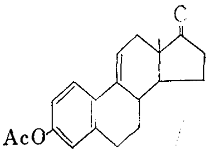

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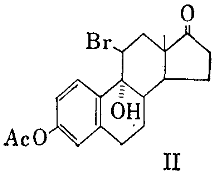

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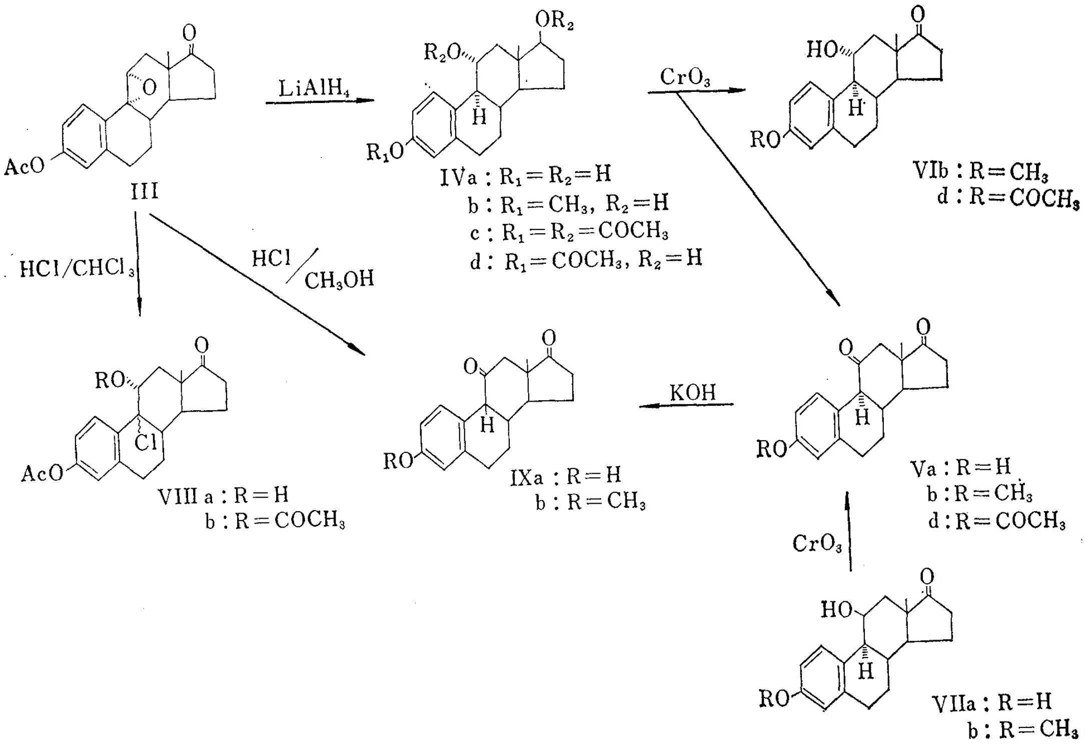

Cahrt 1.

Experimental*[5]

Estra-1,3,5(10)-triene-3,11α,17β-triol (IVa)——To a solution of 900 mg. of 3-acetoxy-9α,11α-epoxyestra-1,3,5(10)-triene-17-one (Ⅲ) in 60 ml. of tetrahydrofuran was added 900 mg. of $LiAlH_4$. The mixture was refluxed for 24 hr. and after cooling, the excess reagent was decomposed by the addition of Me_2CO. The solvent was removed by distillation and 5% HCl was added to the residue. The resulting precipitate was filtered to give 513 mg. of IVa, m.p. 240~243° (decomp.). The analytical sample was prepared with recrystallization from Me_2CO, m.p. 249~250°, $[\alpha]_D$ −48°(c=1.09). UV : λ_{max} 279 mμ (ε 1930). IR ν_{max} cm^{-1} : 3405, 3190, 1620, 1591, 1500. *Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found : C, 74.88; H, 8.38.

3-Methoxyestra-1,3,5(10)-triene-11α,17β-diol (IVb)——To a stirred solution of 200 mg. of IVa in 15 ml. of EtOH was added 0.75 ml. of NaOH solution (10 g. of NaOH in 15 ml. of H_2O) and then 1 ml. of dimethyl sulfate dropwisely. After repeating the addition of NaOH solution and dimethyl sulfate three times, the reaction mixture was stirred for 15 min. The solvent was removed, washed with H_2O and dried to give 150 mg. of material. Recrystallization from Et_2O gave 90 mg. of IVb, m.p. 145~146°, $[\alpha]_D$ −44°(c=1.00). UV λ_{max} mμ (ε) : 277 (1600), 283 (1470). IR ν_{max} cm^{-1} : 3545, 3280~3180, 1612, 1577, 1497. *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found : C, 75.54, H, 8.60.

3-Methoxyestra-1,3,5(10)-triene-11,17-dione (Vb) and 3-Methoxy-11α-hydroxyestra-1,3,5(10)-trien-17-one (VIb)——To a solution of 150 mg. of IVb in 2 ml. of pyridine was added 1.5 ml. of pyridine-CrO_3 complex (containing 150 mg. of CrO_3) and the mixture was allowed to stand at room temperature for 3 hr. It was poured into ice water and extracted with Et_2O. The ethereal solution was washed successively with 5% HCl, saturated Na_2CO_3 solution and H_2O. The extract was dried and evaporated to

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*[5] All melting points were uncorrected. Optical rotations were measured in dioxane. Infrared spectra were obtained with Nujol and ultraviolet spectra were measured in methanol.

leave a solid residue. The residue was triturated with Et_2O and Et_2O soluble and insoluble portions were separated. Recrystallization of insoluble part from Me_2CO afforded 9 mg. of Vb, m.p. 185° (soften), 200° (decomp.). This compound was identified by mixture melting point and infrared spectral comparison with Vb, prepared by oxidation of VIIb.

The Et_2O soluble part was chromatographed over 3 g. of silica gel and eluted with Et_2O-benzene (1:99~1:2) to give 63 mg. of crude VIb. Recrystallization from Et_2O afforded 29 mg. of the analytical sample, m.p. 153~156°, $[\alpha]_D$ +24° (c=1.00). UV λ_{max} mμ (ε): 277 (1880), 283 (1680). IR ν_{max} cm^{-1}: 3540, 1730, 1608, 1583, 1500. *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.03; H, 8.04.

3-Methoxyestra-1,3,5(10)-triene-11,17-dione (Vb) from VIIb——To a solution of 100 mg. of 3-methoxy-11β-hydroxyestra-1,3,5(10)-trien-17-one (VIIb)[2] in 2 ml. of pyridine was added 1 ml. of pyridine CrO_3 complex (containing 100 mg. of CrO_3) and the mixture was allowed to stand at room temperature for 3 hr. The reaction mixture was poured into ice water and extracted with Et_2O. The ethereal solution was washed successively with HCl, saturated $NaHCO_3$ solution and H_2O, and dried over anhyd. Na_2SO_4. The solvent was removed and the resulting residue was recrystallized from Me_2CO three times to give 8 mg. of Vb, m.p. 184° (softed) 201° (decomp.). UV λ_{max} mμ: 277 (ε 1880), 284 (shoulder). IR ν_{max} cm^{-1}: 1743, 1715, 1612, 1582, 1502. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.25; H, 7.45.

Estra-1,3,5(10)-triene-3,11α,17β-triol Triacetate (IVc)——A solution of 100 mg. of IVa in 0.5 ml. of pyridine and 0.5 ml. of Ac_2O was allowed to stand at room temperature for 15 hr. and then poured into ice water. The resulting precipitate was filtered and dried. Recrystallization from Et_2O gave 78 mg. of IVc, m.p. 132~135°, $[\alpha]_D$ −110° (c=1.12). IR ν_{max} cm^{-1}: 1755, 1728. *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.38; H, 7.26.

Estra-1,3,5(10)-triene-3,11α,17β-triol 3-Acetate (IVd)——A solution of 157 mg. of IVa in 2 ml. of pyridine and 76 mg. of Ac_2O was allowed to stand at room temperature for 15 hr. The mixture was poured into ice water and extracted with Et_2O. The ethereal solution was washed successively with 5% HCl, saturated $NaHCO_3$ solution and H_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent was removed by distillation to give 147 mg. of solid. Recrystallization afforded IVd, m.p. 154~155°. UV λ_{max} mμ (ε): 266 (536), 274 (445). IR ν_{max} cm^{-1}: 3300, 1763, 1583, 1493. *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.82; H, 7.89.

3,11α-Dihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate (VId)——To a 0.5 ml. of pyridine-CrO_3 complex (containing 50 mg. of CrO_3) was added a solution of 50 mg. of IVd in 1.5 ml. of pyridine. The mixture was allowed to stand at room temperature for 3.5 hr., then poured into ice water and extracted with Et_2O. The ethereal solution was washed successively with 5% HCl, saturated $NaHCO_3$ solution andH_2O .The extract was dried over anhyd. Na_2SO_4 and the solvent was removed. The residue was recrystallized from Et_2O to give 14 mg. of VId, m.p. 156~158°. UV: λ_{max} 266 mμ (ε 565). IR ν_{max} cm^{-1}: 3520, 1768, 1740, 1603, 1583, 1488. *Anal.* Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.29; H, 7.41.

9ξ-Chloro-3,11α-dihydroxyestra-1,3,5(10)-trien-17-one 3-Acetate (VIIIa)——To a solution of 300 mg. of III in 6 ml. of $CHCl_3$ was introduced dry HCl gas at −7° for 2 hr. During this time, the solution changed its color to light yellow. The $CHCl_3$ solution was washed with cold saturated $NaHCO_3$ solution, and then H_2O. The solution was dried over anhyd. Na_2SO_4 and the solvent was removed *in vacuo* to give 330 mg. of powder. Recrystallization from Et_2O gave 83 mg. of VIIIa, m.p. 115° (soften), 133° (decomp.). IR ν_{max} cm^{-1}: 3550, 1753, 1736, 1613, 1585, 1493. *Anal.* Calcd. for $C_{20}H_{23}O_4Cl$: C, 66.20; H, 6.39. Found: C, 66.24; H, 6.44.

9ξ-Chloro-3,11α-dihydroxy-1,3,5(10)-trien-17-one Diacetate (VIIIb)——A solution of 70 mg. of chlorohydrin (VIIIa) in 1 ml. of pyridine and 1 ml. of Ac_2O was allowed to stand at room temperature for 24 hr., then poured into ice water. The resulting precipitate was filtered to afford 34 mg. of crude material, m.p. 137~159°. Recrystallization from Et_2O gave 20 mg. of VIIIb, m.p. 149~159°. IR ν_{max} cm^{-1}: 1766, 1747, 1613, 1587, 1493. *Anal.* Calcd. for $C_{22}H_{25}O_5Cl$: C, 65.26; H, 6.22; Cl, 8.76. Found: C, 65.36; H, 6.26; Cl, 8.94.

3-Hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione (IXa)——To a solution of 1.2 g. of III in 25 ml. of MeOH was introduced dry HCl gas at −5° for 1.5 hr. A cooled saturated $NaHCO_3$ solution was added to the methanolic solution to give precipitate. Filtration of it gave 840 mg. of IXa, m.p. 201~205°. Recrystallization from Et_2O prepared the analytical sample, m.p. 204~207° (decomp.), $[\alpha]_D$ +282° (c=1.07). UV: λ_{max} 282 mμ (ε 2070). IR ν_{max} cm^{-1}: 3360, 1730, 1700, 1611, 1502. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.93; H, 6.88.

3-Hydroxyestra-1,3,5(10)-triene-11,17-dione (Va)——To a solution of 500 mg. of 3,11β-dihydroxyestra-1,3,5(10)-trien-17-one (VIIa) prepared by the method of Hogg and Magerlein[2] in 20 ml. of Me_2CO was added dropwise 1.03 ml. of Kiliani solution (530 mg. of CrO_3 in 4.0 ml. of H_2O and 0.45 ml. of conc. H_2SO_4) at room temperature. The reaction mixture was poured into H_2O, and extracted with Et_2O. The ethereal solution was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation and recrystallization from Me_2CO afforded Va, m.p. 199~203°. $[\alpha]_D$ +374° (c=0.97). UV λ_{max} mμ: 279 (ε 1950), 285 (shoulder). IR ν_{max} cm^{-1}: 3350, 1740, 1715, 1610, 1510. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.08; H, 7.08.

3-Hydroxyestra-1,3,5(10)-triene-11,17-dione Acetate (Vd)——To a solution of 200 mg. of 11β-hydroxyestrone 3-acetate (VIId)[2] in 10 ml. of Me_2CO was added 0.37 ml. of Kiliani solution. After addition of small amount of aq. $NaHCO_3$, the mixture was poured into H_2O. Filtration and recrystallization from Me_2CO gave 50 mg. of Vd, m.p. 156~161°, $[\alpha]_D$ +326° (c=1.03). UV λ_{max} mμ (ε): 267 (609), 274 (580). IR ν_{max} cm^{-1}: 1761, 1738, 1714, 1606, 1583, 1496. *Anal.* Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.56; H, 6.81.

3-Methoxy-9β-estra-1,3,5(10)-triene-11,17-dione (IXb)——To a solution of 300 mg. of 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione (IXa) in 30 ml. of MeOH was added an excess of solution of diazomethane in Et_2O and the mixture was allowed to stand at room temperature for 14 hr. Removal of the solvent afforded 293 mg. of amorphous product. It was chromatographed over silica gel 12 g. and eluted with petr. ether-benzene (3:7) to give 100 mg. of amorphous product (IXb). UV λ_{max} mμ (ε): 279.7 (1830), 286.8 (1610). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1744, 1710, 1610, 1577. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.12; H, 7.39.

Isomerization of Va to IXa——A solution of 105 mg. of Va in 15 ml. of 1% MeOH-KOH was refluxed for 70 min. under nitrogen atmosphere. The solution was neutralized with AcOH and MeOH was removed to give precipitate. The filtration of the precipitate afforded 83 mg. of material, m.p. 192~199°. Recrystallization from Et_2O gave 51 mg. of IXa. The result of the thin layer chromatography with elution solvent, benzene-Me_2CO (9:1), showed that the mother liquor contained only a little of Va.

Alkaline Treatment of IXa——A solution of 30 mg. of IXa in 5 ml. of 1% MeOH-KOH was refluxed 70 min. The solution was neutralized with AcOH and the solvent was removed. The resulting precipitate was filtered to give 13 mg. of starting material, m.p. 205~208°. The result of the thin layer chromatography with above solvent system showed that Va was not contained in it.

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Summary

The reduction of 3-hydroxy-9α,11α-epoxyestra-1,3,5(10)-trien-17-one (III) with lithium aluminum hydride gave estra-1,3,5(10)-triene-3,11α,17β-triol. The reaction of III with hydrogen chloride in methanol yielded 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione (IXa). On the other hand, the reaction in chloroform afforded 9ξ-chloro-3,11α-dihydroxyestra-1,3,5(10)-trien-17-one (VIIIa). With alkali 3-hydroxyestra-1,3,5(10)-triene-11,17-dione (Va) is converted into 9β-isomer (IXa).

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