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120. Toshio Nambara and Kohichi Hirai : Reactions of the 16-Double Bond of 5α,14β-Androst-16-ene.

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In the course of our studies on the Zimmermann reaction in connection with the stereochemistry of steroids, an interest in the ring juncture of C/D-*cis* steroid prompted us to explore the reactivities of double bond in ring D. The present paper deals with the observations on the stereospecific behaviour of 16-double bond of 14β-steroid towards epoxidation and catalytic hydrogenation.

The first project was directed to the epoxidation of 5α,14β-androst-16-ene with perbenzoic acid. Recently, the satisfactory methods of preparing Δ^{16} compound from the corresponding 17-oxosteroid have been reported by several groups.[1~3] The authors have adopted Caglioti's method, that is, the reduction of *p*-tosylhydrazone of 17-ketone with lithium aluminum hydride for the synthesis of 5α,14β-androst-16-en-3β-ol (Ⅲa).

The starting material, 3β-acetoxy-5α,14β-androstan-17-one (Ⅰ), prepared from dehydroisoandrosterone acetate by the method of St. André, *et al.*,[4] was converted to *p*-tosylhydrazone (Ⅱ) by refluxing with *p*-tosylhydrazine in methanol and submitted to the reduction with lithium aluminum hydride in tetrahydrofuran without isolating Ⅱ. The crude product was chromatographed on alumina, and the expected compound (Ⅲa), m.p. 138~140°, was isolated in 20% yield, together with a small amount of unknown product, m.p. 114~115°. The yield of the latter obtained was so low that insufficient material was available for further work. Examination of infrared spectrum and color reaction with tetranitromethane showed the presence of double bond in Ⅲa, and catalytic hydrogenation of Ⅲa over palladium-on-charcoal afforded 5α,14β-androstan-3β-ol (Ⅳ), m.p. 149~150°.[5] In comparison with the saturated compound hereby obtained, an attempt to prepare Ⅳ by way of desulfurization of 17-dithioketal was made. Employing ethanedithiol and boron trifluoride[6] in glacial acetic acid, Ⅰ was converted to 17,17-ethylenedithio derivative (Ⅴb), m.p. 190~191°, and subjected further to hydrolysis and desulfurization with freshly prepared Raney nickel W-2. However, the result of gas chromatography[7] revealed that the product obtained was unexpectedly a mixture of Ⅲa and Ⅳ in the ratio of *ca.* 1:1, and the mixture could not be separated successfully. It should be noted that Δ^{16} compound was produced from 17-dithioketal by desulfurization even when the activated Raney nickel was used.[1,8] Transformation of Ⅰ to Ⅱ did not proceed in satisfactory yield and the reasonable amount of 5α,14β-androstane-3β,17α-diol was recovered by chromatographic separation of the reduction product.

Treatment of acetate (Ⅲb), m.p. 86°, prepared by ordinary acetylation of Ⅲa with perbenzoic acid in chloroform gave the product, m.p. 120° exclusively. The newly obtained compound, whose elemental analysis confirmed the formula of 16,17-epoxide,

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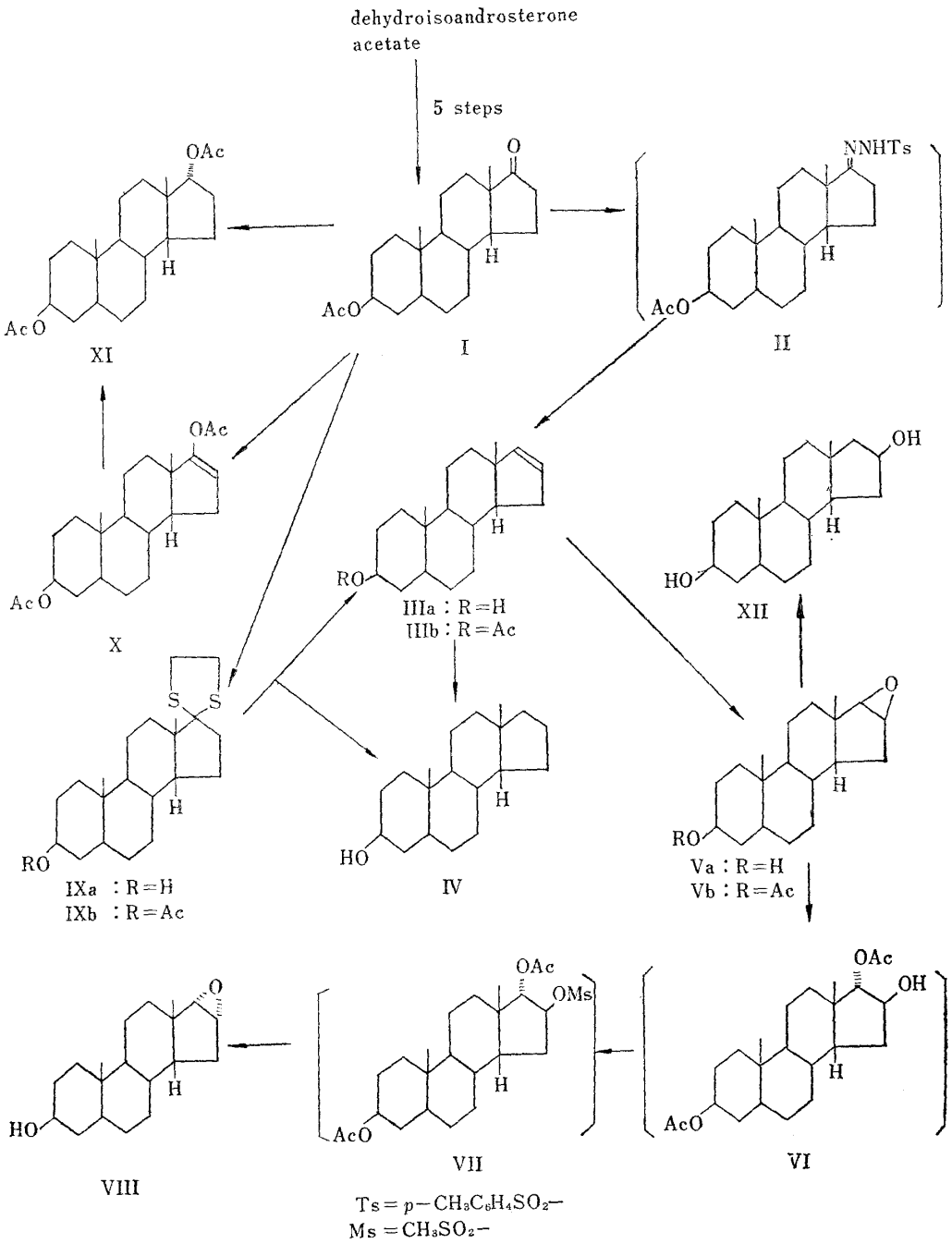
was different from the authentic 16α,17α-epoxide[9] according to the usual criteria (melting point, rotation and infrared spetrum). The orientation of 16β,17β-epoxide (Vb) has been further proved by the following sequence. Ring opening of the epoxide with acetic acid produced 5α,14β-androstane-3β,16β,17α-triol 3,17-diacetate (VI) where the configuration at C-16 and C-17 was tentatively assigned on the basis of analogous reaction. Reductive cleavage of Vb with lithium aluminum hydride afforded 5α,14β-androstane-3β,16β-diol (XII), m.p. 173°, the structure of which was characterized by comparison with the isomeric 5α,14β-androstane-3β,17β-diol.[4] Then, VI was converted to its 16β-mesylate (VII) with methanesulfonyl chloride in pyridine. When VII was refluxed in methanolic potassium hydroxide solution, followed by chromatographic separation, a crystalline



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material was isolated as a main product, and it proved to be identical in all respects with 16α,17α-epoxy-5α,14β-androstan-3β-ol (Ⅷ),*2 obtained by the sequence leading from 16β-halo-17α-hydroxy derivative.[9] In the previous paper dealing with 16,17-ketol rearrangement of 5α,14β-androstane,[10] it was reported that epoxidation of enol acetate, derived from 16- and 17-ketone, with perbenzoic acid gave the corresponding 16β,17β-epoxide, respectively. In those cases, however, the epoxide was submitted to further elaboration without isolation, and the configuration of the intermediate epoxide has not been conclusively proved.

Then, an examination was tried on the catalytic hydrogenation of the double bond of 5α,14β-androst-16-ene-3β,17-diol diacetate (X) over palladium-on-charcoal. By the usual treatment of reaction mixture, 5α,14β-androstane-3β,17α-diol diacetate (Ⅺ), whose structure was confirmed by comparison with the authentic sample, was isolated as a single product almost quantitatively. The formation of 17α-acetoxy substituent was also indicative of selective β-side attack of the reagent.

It is sufficiently substantiated in the literature[11~14] that in the case of usual 14α-C/D-*trans* steroid, epoxidation of 16-double bond with per-acids is initiated by the rear side of α-route to form 16α,17α-epoxide and catalytic hydrogenation of 17-substituted Δ^{16} compound to yield 17β-substituent. These reactions could take place on the less hindered α-side of the molecule, probably because of non-bonded interaction of the angular C-18 methyl group with the β-face of carbon 16 and 17. It has now been clarified that in the case of 14β-C/D-*cis* steroid, both perbenzoic acid and hydrogen attack the β-side of steroid molecule preferentially. These results coincide well with the previous observations, that is, 16,17-ketol rearrangement[7] and kinetically controlled bromination of 17-oxo steroid[6] in 14β series. It is of particular interest that owing to the concave nature of C/D ring juncture, ring D of 14β-*cis* steroid shows behaviour different from that of 14α-*trans* steroid. Further studies on the stereochemistry of ring D in connection with the Zimmermann reaction of ketosteroids are being conducted in our laboratory.

Experimental*3

3β-Acetoxy-5α,14β-androstan-17-one *p*-Tosylhydrazone (II)——A mixture of 3β-acetoxy-5α,14β-androstan-17-one (I) (500 mg.) and *p*-tosylhydrazine (450 mg.) dissolved in MeOH (60 ml.) was refluxed for 10 hr. After evaporation of the solvent, the oily residue was obtained, and attempted crystallization was unsuccessful, therefore the crude product was submitted to further transformation without purification.

Reduction of II with Lithium Aluminum Hydride——To a solution of above-mentioned oily product, dissolved in tetrahydrofuran (30 ml.) was added $LiAlH_4$ (1.5 g.) portionwise and the reaction mixture was refluxed for 15 hr. After careful addition of moist Et_2O under cooling, followed by an acidification with 5% H_2SO_4, the organic layer was separated, washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the oily residue obtained was chromatographed on alumina (20 g.).

Elution with hexane-benzene (5:5) gave a semisolid product (40 mg.). Recrystallization from hexane gave colorless prisms, m.p. 114~115°.

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*2 Infrared spectra comparison was carried out by Mrs. Beatrice S. Gallagher to whom the authors' thanks are due.

*3 All melting points are uncorrected and all rotations were measured in $CHCl_3$ solution. For thin-layer chromatography (TLC) Silica Gel G (Merck, Co., Ltd.) was employed as an adsorbent.

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NII-Electronic Library Service

Elution with benzene-Et_2O (8:2 and 7:3) gave 101 mg. of 5α,14β-androst-16-en-3β-ol (IIIa). Recrystallization from Me_2CO afforded colorless needles, m.p. 136~138°. The analytical sample melted at 138~140°. $[\alpha]_D^{14.2}$ +89.4° (c=0.47), IR: $\nu_{max}^{CCl_4}$ 1609 cm^{-1} (C=C). With tetranitromethane IIIa showed pale yellow coloration. *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.90; H, 11.40.

Elution with Et_2O and recrystallization from aq. MeOH gave 5α,14β-androstane-3β,17α-diol (136 mg.) as colorless leaflets, m.p. 184° (literature 188~189°).[4]

5α,14β-Androst-16-en-3β-ol Acetate (IIIb)——A solution of IIIa (100 mg.), dissolved in Ac_2O (0.4 ml.) and pyridine (1 ml.), was allowed to stand at room temperature for 24 hr. Usual work-up and recrystallization from MeOH gave IIIb (89 mg.) as colorless needles, m.p. 86°, $[\alpha]_D^{16}$ +54.7° (c=0.53). *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.91, H, 10.22.

5α,14β-Androstan-3β-ol (IV)——A solution of IIIa (5 mg.), dissolved in EtOH (5 ml.), was shaken with 5% Pd-C (5 mg.) in the stream of H_2 for 20 hr. at room temperature under atmospheric pressure. After removal of the catalyst, the filtrate was concentrated to afford a crystalline product. Recrystallization from hexane gave IV (4.5 mg.) as colorless needles, m.p. 149~150° (literature 148~150°),[5] $[\alpha]_D^{16}$ +48.6° (c=0.50). *Anal.* Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.36; H, 11.38.

17,17-Ethylenedithio-5α,14β-androstan-3β-ol Acetate (IXb)——A solution of I (50 mg.), ethanedithiol (0.2 ml.) and BF_3-Et_2O (0.2 ml.), dissolved in glacial AcOH (3 ml.), was allowed to stand at room temperature for 24 hr. The reaction mixture was diluted with Et_2O, washed with *N* NaOH, H_2O and dried over anhyd. Na_2SO_4. Upon evaporation of the solvent, a crystalline product was obtained. Recrystallization from EtOH gave IXb (42 mg.) as colorless needles, m.p. 190~191°, $[\alpha]_D^{14.5}$ +46.2° (c=1.65). *Anal.* Calcd. for $C_{23}H_{36}O_2S_2$: C, 67.62; H, 8.88. Found: C, 67.66; H, 8.77.

17,17-Ethylenedithio-5α,14β-androstan-3β-ol (IXa)——A solution of IXb (50 mg.), dissolved in 5% MeOH-KOH (10 ml.), was refluxed for 1 hr. Upon concentration of the reaction mixture, the crystalline residue was obtained. Recrystallization from MeOH gave IXa (42 mg.) as colorless needles, m.p. 220~223°, $[\alpha]_D^{14.5}$ +49.5° (c=0.78). *Anal.* Calcd. for $C_{21}H_{34}OS_2$: C, 68.80; H, 9.32. Found: C,69.15; H, 9.14.

Desulfurization of IXa with Raney Nickel——A solution of IXa (250 mg.), dissolved in EtOH (35 ml.), was refluxed with freshly prepared Raney Ni W-2 (6 g.) for 11 hr. After a removal of the catalyst, the filtrate was concentrated to afford crystalline residue. By fractional crystallization from MeOH starting material (22 mg.) was recovered unchanged. Upon concentration of mother liquor, the crystalline residue (120 mg.) was obtained. Gas chromatography of the acetylated product employing Nitrile Silicone (XF 1105) as the stationary phase revealed that the desulfurization product substantially consisted of IIIa and IV in a ratio of *ca.* 1:1. On usual catalytic hydrogenation over 5% Pd-C, the mixture was converted completely to IV. Recrystallization from hexane gave IV as colorless needles, m.p. 145~146°.

16β,17β-Epoxy-5α,14β-androstan-3β-ol Acetate (Vb)——To a solution of IIIb (89 mg.), dissolved in $CHCl_3$ (20 ml.) was added $CHCl_3$ solution (1.2 ml.) of perbenzoic acid (0.355*M*). Being allowed to stand for 24 hr. at room temperature, the reaction mixture was washed with cold *N* NaOH, H_2O and then dried over anhyd. Na_2SO_4. After evaporation of the solvent, the oily product obtained was submitted to chromatography on alumina (4 g.). Elution with hexane-benzene (8:2 and 5:5) and recrystallization from MeOH gave Vb (65 mg.) as colorless leaflets, m.p. 119.5~120°, $[\alpha]_D^{15.5}$ +48.5° (c=0.52). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.65; H, 9.65.

16β,17β-Epoxy-5α,14β-androstan-3β-ol (Va)——A solution of Vb (12.5 mg.) dissolved in 5% MeOH-KOH (5 ml.) was refluxed for 1 hr. Upon concentration of the reaction mixture, the crystalline residue was obtained. Recrystallization from Me_2CO-hexane gave Va (9.5 mg.) as colorless needles, m.p. 115°, $[\alpha]_D^{15}$ +19.5° (c=0.26). *Anal.* Calcd. for $C_{19}H_{30}O_2 \cdot \frac{1}{2}H_2O$: C, 76.02; H, 10.47. Found: C, 75.64; H, 9.97. Reacetylation of Va with use of Ac_2O and pyridine in the usual manner afforded Vb.

5α,14β-Androstane-3β,16β-diol (XII)——To a solution of Vb (20 mg.), dissolved in tetrahydrofuran (6 ml.) was added $LiAlH_4$ (20 mg.) and the solution was refluxed for 6 hr. After decomposition of the excess reagent by usual treatment, the reaction mixture was extracted with Et_2O. The organic layer separated was washed and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a crystalline residue. Recrystallization from Me_2CO-hexane afforded XII (18 mg.) as colorless needles, m.p. 171~172°. The analytical sample melted at 173°. $[\alpha]_D^{18.5}$ +20.0° (c=0.40). Mixed melting point on admixture with 5α,14β-androstane-3β,17β-diol (m.p. 170~171°)[4] showed distinct depression. *Anal.* Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.63; H, 11.43.

Conversion of Vb to 16α,17α-Epoxy-5α,14β-androstan-3β-ol (VIII)——A solution of Vb (40 mg.) dissolved in glacial AcOH (1.5 ml.) was refluxed for 2 hr. The reaction mixture was concentrated to the small volume, and the residue was extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue obtained was submitted to chromatography on alumina (2 g.). Elution with hexane-benzene (5:5) and benzene gave oily product (VI) (37.2 mg.). TLC of VI with use of benzene-Et_2O (8:2) as developing solvent, and conc. H_2SO_4 as coloration reagent was indicative of single product (Rf 0.34). To a solution of VI dissolved in pyridine (0.15 ml.) was added methanesulfonyl chloride (0.04 ml.) and the reaction mixture was allowed to stand at 0° overnight. The reaction mixture was diluted with Et_2O, and washed with 5% $NaHCO_3$,

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N HCl and H_2O successively. After evaporation of the solvent, the residue obtained was chromatographed on alumina (2 g.). Elution with hexane–benzene (5:5 and 3:7) gave oily product (Ⅶ) (39 mg.) as a main fraction. TLC of Ⅶ with use of benzene–Et_2O (8:2) as developing solvent, and conc. H_2SO_4 as coloration reagent was indicative of sole product (Rf 0.50). A solution of Ⅶ dissolved in 5% MeOH–KOH (5 ml.) was refluxed for 6 hr. After an usual work-up, the oily product obtained was chromatographed on alumina (1.5 g.). Elution with hexane–benzene (3:7) and recrystallization from Me_2CO–hexane gave Ⅷ (8.3 mg.) as colorlss needles, m.p. 133°. Comparison with the authentic sample (literature 135~137°)[9] proved the compound to be identical in every respect.

Hydrogenation of Androst-16-ene-3β,17-diol Diacetate (X)——A solution of X (30 mg.) dissolved in EtOH (10 ml.) was shaken with 5% Pd-C (15 mg.) for 12 hr. in the stream of H_2 at room temperature under atmospheric pressure. After a removal of the catalyst by filtration, the filtrate was concentrated to give crystalline residue. Recrystallization from aq. MeOH afforded 5α,14β-androstane-3β,17-diol diacetate (Ⅺ) (24 mg.), m.p. 109°. Mixed melting point and IR spectrum comparison with the authentic sample[4] proved it to be identical in all respects.

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Summary

Epoxidation and catalytic hydrogenation of the 16-double bond of 5α,14β-androst-16-ene were examined. It was concluded that in the C/D *cis*-14β-steroid, the reagents could attack the less hindered β-side of the molecule, presumably because of the cage-like structure of C/D-ring juncture.

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