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Toshio Nambara and Kazuhiro Imai: Chemistry of C-17-Substituted 5α,14β-Androst-15-ene.*1

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In the preceding paper,[1] it was reported that in 14β-steroids the reagent would attack 16-double bond from the less hindered β-side. The interest in unusual situation of ring D prompted us further to examine the influence of C/D-*cis* fusion on the reactivity of 15-double bond. The present paper describes some findings obtained during the attempt to prepare 5α,14β-androst-15-en-3β-ol starting from 3β-hydroxy-5α-androst-14-en-17-one acetate (Ib).[2]

For this purpose the initial project was directed to the synthesis of 3β-hydroxy-5α,14β-androst-15-en-17-one (IIa). According to the method reported by Sondheimer, *et al.*,[3] Ib was isomerized by refluxing with sodium hydroxide in *tert*-butanol. In actuality, migration of double bond took place in ca. 30% yield but difficulties were encountered in quantitative separation of resultant Δ^{15}-compound (IIa) from unchanged Δ^{14}-isomer (Ia) by means of column chromatography. Isolation of the desired compound, however, was attained with success by acetylation of the crude product followed by preparative thin-layer chromatography on silica gel and in consequence, 3β-hydroxy-5α,14β-androst-15-en-17-one acetate (IIb), m.p. 98.5~100°, was obtained in satisfactory yield.

In the present case, conjugated double bond being vulnerable against nucleophilic reagent,[4] the usual methods to reduce steroidal ketone to methylene seemed to be unfavorable. Hence the project for removal of oxygen function at C-17 was focused on the indirect method by way of 17-hydroxy derivative, and IIb was submitted to reduction with sodium borohydride in methanol. Unfortunately, 5α,14β-androst-15-ene-3β,17α-diol 3-acetate (III) could not be isolated, but on usual acetylation 3β, 17α-diacetate (Vb), m.p. 85~89°, was afforded as a crystalline derivative. Retention of double bond at C-15, 16 in III was confirmed by the fact that the starting compound (IIb) was recovered upon oxidation with manganese dioxide. In addition, configuration of 17-hydroxyl group was rationalized by leading to the saturated compound (VIb), which proved to be identical with the authentic sample. These results revealed that sodium borohydride would attack 17-oxo group preferentially from the β-side to yield 17α-hydroxy compound. It is to be noted that in 14β-series Δ^{15}-17-ketone as well as isolated 17-ketone are reduced to the corresponding 17α-hydroxy derivative probably because cage-like structure of C/D-fusion shields the α-side.[2,5,6] Then, chlorination of III was undertaken with use of thionyl chloride in benzene. Nevertheless, unexpected compound, m.p. 243~246°, was afforded as main product, which seemed to be 17α-yl-sulfite according to the elemental analysis and infrared spectrum.

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1) T. Nambara, K. Hirai: This Bulletin, **12**, 836 (1964).
2) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, C. R. Scholz: J. Am. Chem. Soc., **74**, 5506 (1952).
3) F. Sondheimer, S. Burstein, R. Mechoulam: *Ibid.*, **82**, 3209 (1960).
4) E. W. Cantrall, R. Littell, S. Bernstein: J. Org. Chem., **29**, 64 (1964).
5) T. Nambara, J. Fishman: *Ibid.*, **26**, 4569 (1961); **27**, 2131 (1962).
6) T. Nambara, M. Yano: This Bulletin, **13**, 1004 (1965).

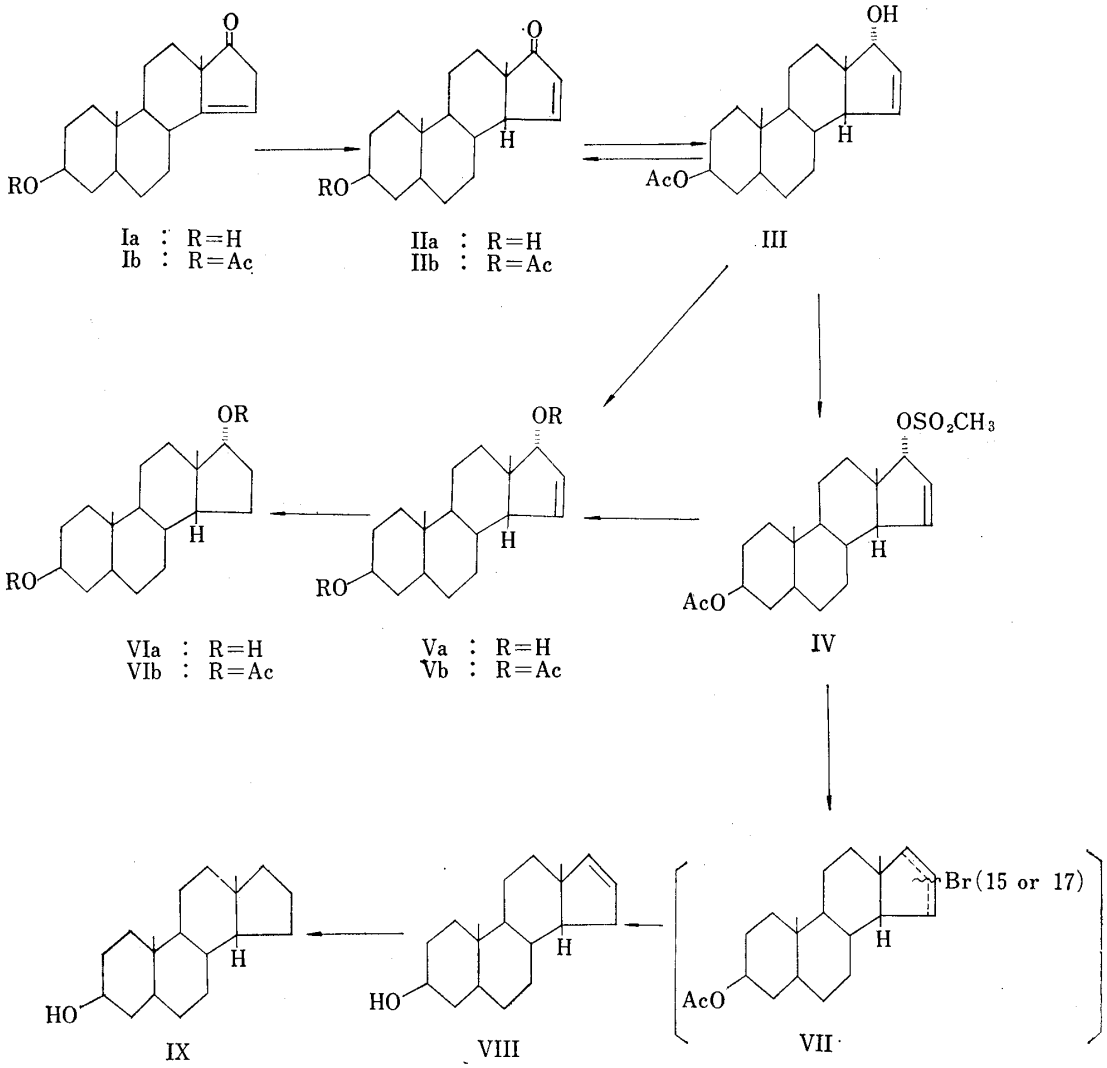

Chart 1.

Accordingly, the first project was changed in such a way that the desired compound would be prepared through Δ^{15}-17-sulfonate. On usual work-up with methanesulfonyl chloride in pyridine Ⅲ was converted to methanesulfonate (Ⅳ), m.p. 157~160°. However, when treated with lithium aluminum hydride in tetrahydrofuran for removal of mesyloxy group, Ⅳ was converted to 5α,14β-androst-15-ene-3β,17α-diol (Va), m.p. 186~188°. The structure of Va was established by leading to the known Ⅵb by usual acetylation and catalytic hydrogenation. Therefore transformation of Ⅳ into 17-halide and subsequent dehalogenation were attempted. The methanesulfonate (Ⅳ) being refluxed in acetone containing sodium iodide, halogenation was somewhat difficult, but the reaction employing lithium bromide in butanone[7] proceeded with ease. The crude product obtained was further submitted to dehalogenation without isolating allylic bromide (Ⅶ) because of insufficient amount available. When Ⅶ was treated with lithium aluminum hydride in tetrahydrofuran, reduction occurred with loss of halogen furnishing unsaturated compound (Ⅷ), which was in turn led to the known 5α,14β-androstan-3β-ol (IX) by catalytic hydrogenation over palladium-on-charcoal. Contrary to the expectations, however, Ⅷ was found to be 5α,14β-androst-16-en-3β-ol on the basis of usual criteria (mixed melting point, infrared spectrum and thin-layer

7) N. L. Wendler, R. P. Graber, G. G. Hazen : Tetrahedron, **3**, 144 (1958).

chromatography).

The migration of double bond took place though it is ambiguous whether it did at the initial step or at the subsequent one. Allylic rearrangement in ring system has been observed on the analogous examples involving nucleophilic substitution reaction of sulfonate or metal hydride reduction of halide.[8] Now it is noteworthy that 14β-androst-15-ene was isomerized with formation of 16-double bond through these reactions. This finding appears to be in good accord with the previous observation that enolization of 16-ketone is directed predominantly toward C-17 rather than C-15.[5,9] These properties may be interpreted in terms of conformational stability of ring D having Δ^{15} or Δ^{16}, but the plausible explanation for the preference of 16-double bond must await further informations concerning the spatial arrangement of *cis*-linked ring D.*3

Studies on allylic rearrangement in ring D are being extended to C/D-*trans* steroid and will be reported in near future.*4

Experimental*5

3β-Hydroxy-5α,14β-androst-15-en-17-one Acetate (IIb)—— i) To a solution of Ib (700 mg.) dissolved in *tert*-BuOH (50 ml.) was added 2*N* KOH (50 ml.) and the mixed solution was refluxed in the stream of N_2 for 1 hr. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with 5% HCl, H_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent the residue (ca. 700 mg.) obtained was treated with Ac_2O (3.5 ml.) and pyridine (7 ml.). The resultant oily product (ca. 730 mg.) which consisted of the two isomeric 3-acetates, was applied to TLC plate (20×20 cm.) and chromatographed using hexane-ether (1:1) as developing solvent and I_2 as staining reagent. The adsorbent of the spot (Rf 0.40) corresponding to IIb was collected and eluted with ether. Recrystallization from aq. MeOH gave IIb (150 mg.) as colorless leaflets. m.p. 98.5~100°, $[\alpha]_D^{18.0}$ +28.1° (c=0.58). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.26. Ib exhibited a spot at Rf 0.63 on the chromatogram and was recovered in the same manner. ii) Isomerization of Ib was carried out in the same manner as described in i) and the crude product obtained was chromatographed on Al_2O_3. Elution with benzene-ether (9:1) and recrystallization of the eluate from hexane-acetone gave IIa as colorless needles. m.p. 131~132°. (reported m.p. 132~135°[3]). Then, IIa (90 mg.) was dissolved in Ac_2O (0.45 ml.) and pyridine (0.9 ml.) and the solution was allowed to stand at room temperature overnight. The reaction mixture was treated in the usual way and the crude product obtained was recrystallized from aq. MeOH to give IIb (60 mg.) as colorless leaflets. m.p. 98.5~100°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

5α,14β-Androst-15-ene-3β,17α-diol 3-Acetate (III)——To a solution of IIb (57mg.) in MeOH (2 ml.) was added $NaBH_4$ (20 mg.) under cooling in H_2O. After standing at room temperature for 3 hr. the reaction mixture was acidified with glacial AcOH (0.05 ml.), diluted with ice-water and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and concentrated to give oily product (III) (46 mg.), which was submitted to further work without purification.

A solution of III (10 mg.) in benzene (1 ml.) was refluxed with activated MnO_2 (30 mg.) for 6 hr. Upon removal of MnO_2 by filtration and concentration of the filtrate, oily product (5.3 mg.) was obtained. By means of preparative TLC IIb was isolated and it proved to be entirely identical with the authentic sample by IR spectra comparison.

Reaction of III with Thionyl Chloride—— To a solution of III (45 mg.) in benzene (5 ml.) was added $SOCl_2$ (0.2 ml.) under ice-cooling and the mixed solution was allowed to stand at room temperature for 2 hr. The reaction mixture was diluted with ether and washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent crystalline product (38 mg.) was obtained. Recrystallization from ace-

*3 Chinn reported that 3β-hydroxy-13α-androst-5-ene-16,17-dione exists in Δ^{15}-enol form where ring C would probably be in either boat- or twist-conformation.[10]

*4 Note added in proof: The sodium borohydride reduction of 14β-hydroxyandrosta-4,15-diene-3,17-dione, which resulted in disappearance of Δ^{15}-double bond along with formation of 17α-hydroxyl group, has just been reported (M. Tanabe, D. F. Crowe: J. Org. Chem., **30**, 2776 (1965)).

*5 All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. For thin-layer chromatography (TLC) silica gel G (E. Merck Co.) was used as an adsorbent.

8) P. B. D. de la Mare: "Molecular Rearrangements," Ed. by P. de Mayo, vol. 1, 27 (1963), Interscience Publ., New York.
9) T. Nambara, M. Katō: This Bulletin, **13**, 78 (1965).
10) L. J. Chinn: J. Org. Chem., **29**, 3304 (1964).

tone gave bis (3β-acetoxy-5α,14β-androst-15-en-17α-yl) sulfite as colorless prisms. m.p. 243~246°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1270 (S=O). *Anal.* Calcd. for $C_{42}H_{62}O_7S \cdot 2H_2O$: C, 67.52; H, 8.91. Found : C, 67.95; H, 9.14.

5α,14β-Androst-15-ene-3β,17α-diol 3-Acetate 17-Methanesulfonate (IV)—— To a solution of III (70 mg.) in pyridine (1 ml.) was added CH_3SO_2Cl (0.12 ml.) under ice-cooling, and the mixture was allowed to stand at room temperature overnight. After dilution with ether (100 ml.) the solution was washed with 5% $NaHCO_3$, 5% HCl and H_2O successively, and dried over anhyd. Na_2SO_4. The extract was concentrated to give oily residue (ca. 60 mg.), which was in turn chromatographed on Al_2O_3 (2 g.). Elution with hexane-benzene (1:1) and recrystallization of the eluate from acetone-hexane afforded IV (42 mg.) as colorless needles. m.p. 157~160°, $[\alpha]_D^{18.0}$ +13.8° (c=0.29). *Anal.* Calcd. for $C_{22}H_{34}O_5S$: C, 64.36; H, 8.35. Found : C, 64.18; H, 8.56.

5α,14β-Androst-15-ene-3β,17α-diol (Va)—— To a solution of IV (42 mg.) in tetrahydrofuran (6 ml.) was added $LiAlH_4$ (60 mg.) and the reaction mixture was boiled under reflux for 8 hr. After careful addition of moist ether under cooling, followed by acidification with 5% H_2SO_4, organic layer was separated, washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent oily residue obtained was chromatographed on Al_2O_3 (2 g.). Elution with benzene and recrystallization of the eluate from acetone gave Va (13 mg.) as colorless leaflets. m.p. 186~188°, $[\alpha]_D^{17.9}$ +50.8° (c=0.39, MeOH). *Anal.* Calcd. for $C_{19}H_{30}O_2 \cdot H_2O$: C, 73.98; H, 10.46. Found : C, 73.75, 74.15; H, 10.99, 10.94.

5α,14β-Androst-15-ene-3β,17α-diol Diacetate (Vb)—— III (25 mg.) was dissolved in Ac_2O (0.13 ml.) and pyridine (0.25 ml.) and the solution was allowed to stand at room temperature overnight. On usual work-up the crude product obtained was chromatographed on Al_2O_3 (2 g.). Elution with hexane-benzene (5:5 to 2:8) and recrystallization of the eluate from aq. MeOH gave Vb (10 mg.) as colorless leaflets. m.p. 85~89°, $[\alpha]_D^{20.2}$ +34.2° (c=0.37). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found : C, 73.39; H, 9.46.

5α,14β-Androstane-3β,17α-diol Diacetate (VIb)——A solution of Vb (10 mg.) dissolved in EtOH (10 ml.) was shaken with 5% Pd/C (5 mg.) for 20 hr. in the stream of H_2 at room temperature under atmospheric pressure. After removal of catalyst by filtration the filtrate was concentrated to give crystalline product. Recrystallization from aq. MeOH gave VIb (6 mg.) as colorless leaflets. m.p. 99.5~102.5°. Mixed melting point on admixture with the authentic sample[2] showed no depression and IR spectra of the two samples were entirely identical.

5α,14β-Androst-16-en-3β-ol (VIII)——A solution of IV (65 mg.) in $CH_3COC_2H_5$ (20ml.) containing LiBr (2 g.) was refluxed for 3 hr. On evaporation of solvent *in vacuo* oily residue (61 mg.) was obtained. To the solution of this crude product (VII) in tetrahydrofuran (20ml.) was added $LiAlH_4$ (100 mg.) and the mixed solution was refluxed for 10 hr. After careful addition of moist ether followed by acidification with 5% H_2SO_4, organic layer was washed with H_2O, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue obtained was chromatographed on Al_2O_3 (3 g.). Elution with benzene-ether (8:2) and recrystallization of the eluate from acetone-hexane gave VIII (15 mg.) as colorless needles. m.p. 132~133°. *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found : C, 82.98; H, 11.07. Mixed melting point, IR spectra and TLC comparison showed it to be identical with the authentic sample.[1]

Catalytic Hydrogenation of VIII—— An ethanolic solution of VIII (8.3 mg.) was shaken with 5% Pd/C (4 mg.) in the stream of H_2 for 20 hr. at room temperature under atmospheric pressure. After removal of catalyst by filtration the filtrate was concentrated to give crystalline product. Recrystallization from hexane gave IX as colorless prisms. m.p. 145~148°. Mixed melting point and IR spectra comparison showed it to be identical with the authentic sample.[1]

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