This oil was refluxed in a mixture of acetic acid (10 ml.) and conc. HCl (10 ml.) for 6 hr. After the evaporation of the solvents under reduced pressure, $H_2O$ was added to the residue and an aqueous solution was made alkaline with NaOH pellets and extracted with ether. The ether extract was washed with satd. NaCl solution and then dried over anhyd. $K_2CO_3$. The evaporation of ether under $N_2$ atmosphere gave yellow oil (0.2 g.) which was treated with pyridine (2 ml.) and benzoyl chloride (8 drops). After kept standing overnight, the reaction mixture was poured onto ice and extracted with ether. The ether extract was washed successively with 10%HCl, satd. NaCl solution, satd. $NaHCO_3$ solution and satd. NaCl solution, dried over $Na_2SO_4$ and after removal of the solvent, yielded a pale yellow oil which solidified on standing for 2 days in dessicator. Recrystallization twice from benzene and hexane gave light pale yellow needles, m.p. 119~120.5°. A mixed melting point with N-benzoyl-α-phenethylamine (V) obtained from the Beckmann rearrangement showed no depression. The IR spectrum of this sample was essentially superimposable with that of V.

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## Summary

When the chloride (Ⅲ) of N-phthaloyl-α-methylphenylglycine submitted to the Friedel-Crafts reaction, it was found that abnormal reaction occurred and α-phthalimidostyrene (Ⅳ) was obtained in good yield. Moreover, in the course of the demonstration of this structure, the structure of geometrical isomers of α-methyldeoxybenzoin oxime was established.

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## 133. Toshio Nambara and Mutsuji Yano*1 : Chemistry of C-16-Oxygenated 5α,14β-Androstanes.*2

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In the extension of our previous studies on conformation analysis of 14β-steroid, we wish to report the observations concerning metal hydride reduction of 16-oxo group and ring opening of 16β,17β-epoxide with hydrogen bromide.

The initial project was directed to reduction of 16-oxo-14β-steroid with use of metal hydride. 3β,17α-Dihydroxy-5α,14β-androstan-16-one diacetate (Ⅱ), prepared from 14β-isoandrosterone acetate (Ⅰ) in several steps,[1,2] was submitted to reduction with lithium aluminum hydride in ether. Treatment under mild condition gave 5α,14β-androstane-3β,16α,17α-triol (Ⅲa) as the sole product, which in turn was converted to acetonide (Ⅳa), m.p. 178~180°, and further to its 3-acetate (Ⅳb), m.p. 149~151°. It is sufficiently substantiated that of four possible 16,17-ketols in 14β-series 17α-hydroxy-16-ketone is the

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2) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, C. R. Scholz : J. Am. Chem. Soc., **74**, 5506 (1952).

most stable one, whose 17$\alpha$-hydroxyl group is incapable of being epimerized during the course of the reaction.[1] Acetonide formation was indicative of the presence of *cis*-glycol structure in IIIa and in consequence, assignment of $\alpha$ configuration to the introduced hydroxyl group at C-16 was rationalized. Isopropylidene residue of IVb was readily removed by acid hydrolysis and the resultant 3-monoacetate (IIIb) was transformed to 3$\beta$,16$\alpha$,17$\alpha$-triacetate (IIIc), m.p. 102~103°, with acetic anhydride and pyridine. In addition, examination was made on sodium borohydride reduction of II in dimethylformamide. Unfortunately, the reduction product could not be isolated in a crystalline state, but subsequent acetylation furnished the corresponding triacetate, which was identical with that prepared through lithium aluminum hydride reduction described above. In these cases, however, experimental findings would not necessarily be plausible explanation for the stereospecific reaction of metal hydride against 16-oxo group, since

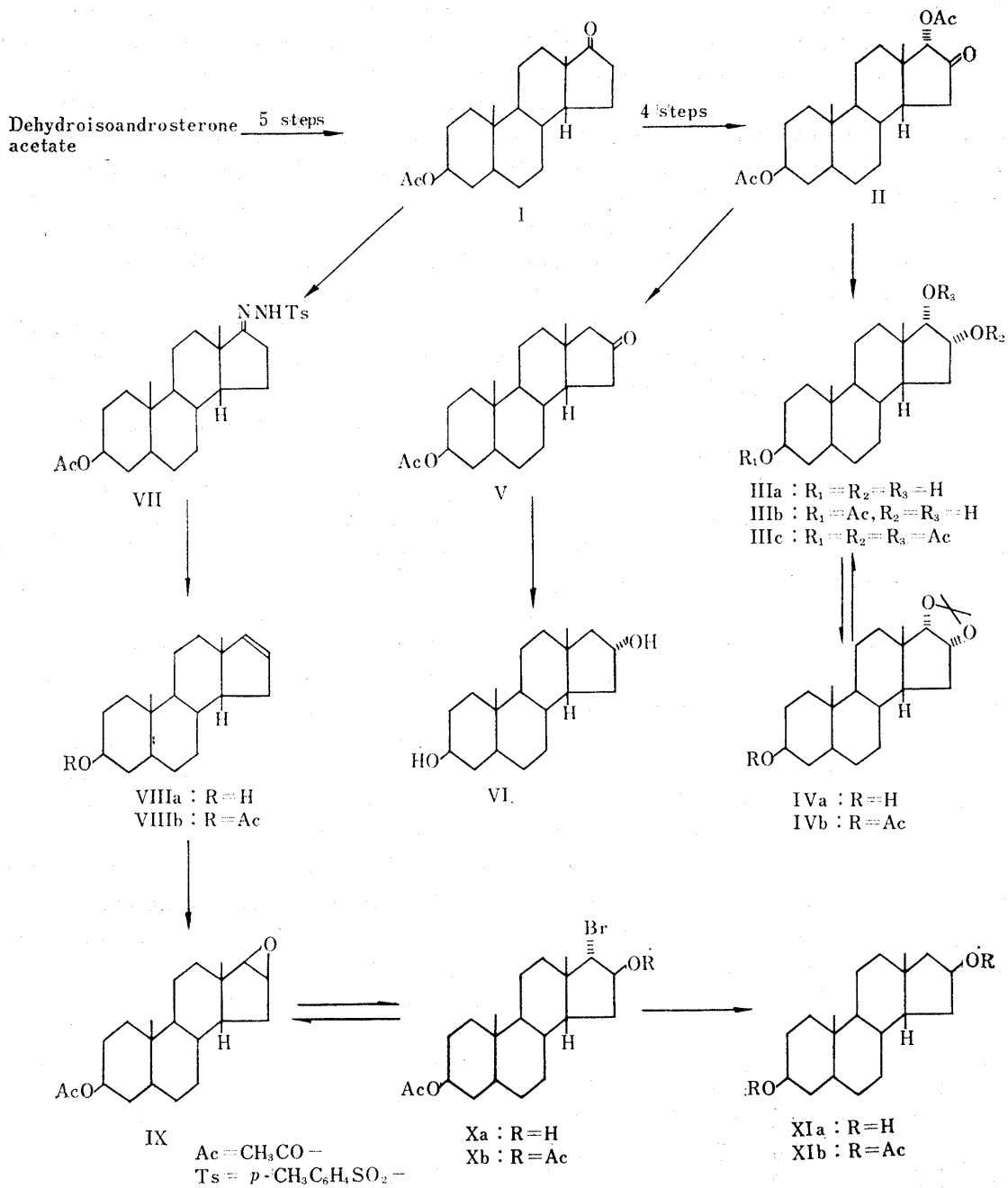


Chart 1.

17α-substituent would possibly present steric interaction to the approach of the reagent from rear side of the molecule.[3] Accordingly, reduction of 3β-hydroxy-5α,14β-androstan-16-one acetate (V) with lithium aluminum hydride was also examined. Thereupon, 5α,14β-androstane-3β,16α-diol (VI), m.p. 169~171°, was provided as the single product, whose structure was confirmed by differentiating from its C-16-epimer, that is, 5α,14β-androstane-3β,16β-diol (XIa).[4] These observations suggest that attack of the reagent would take course preferentially from the less hindered β-side to C-16 with formation of 16α-hydroxy derivative. It should be now emphasized that in 14β-steroids influence of cage-like structure of C/D-*cis* fusion would be still effective for the reaction of 16-ketone, the result being in good accord with the earlier finding on the reaction of 17-oxo-14β-steroid.[1,2,5]

Then, ring cleavage of 16β,17β-epoxide with hydrogen bromide was undertaken. The starting material for this purpose, 5α,14β-androst-16-en-3β-ol (VIIIa), has been previously synthesized in these laboratories utilizing the method proposed by Caglioti, *et al.*[4,6] Namely I was transformed to *p*-tosylhydrazone (VII) and then submitted to reductive cleavage with lithium aluminum hydride. However, condensation with *p*-tosylhydrazine took place only in poor yield and the crude product was further elaborated without isolating the intermediate *p*-tosylhydrazone. This time, therefore, the first project was focused on establishing the suitable conditions to improve the yield of VII. As a result of some attempts it was found that in the presence of catalytic amount of acetic acid, condensation reaction proceeded fairly well, and *p*-tosylhydrazone (VII), m.p. 151~153°, was successfully obtained in the crystalline state. In the same manner as reported in the preceding paper, VII was treated with lithium aluminum hydride to give 5α,14β-androst-16-en-3β-ol (VIIIa) in 70% yield, which was further converted to the desired 16β,17β-epoxy-5α,14β-androstan-3β-ol acetate (IX).

Treatment of IX with hydrogen bromide in acetic acid furnished a crystalline product, m.p. 118~120°, which was, however, resistant to acetylation and chromic acid oxidation, and was supposed to be 16,17-bromohydrin acetate by the usual criteria. The structure of this unexpected product was elucidated to be 17α-bromo-5α,14β-androstane-3β,16β-diol diacetate (Xb) in the following way.[7] Refluxing with methanolic potassium hydroxide followed by acetylation yielded again IX, whereas catalytic hydrogenation over palladium-on-barium carbonate gave rise to debromination furnishing 5α,14β-androstane-3β,16β-diol diacetate (XIb), m.p. 164~166°, which proved to be identical with the diacetate of known 5α,14β-androstane-3β,16β-diol.[4] It is quite surprising that even on brief exposure to hydrogen bromide in the presence of acetic acid Xb was afforded as the major product. The initially produced bromohydrin would be further transformed to 16-acetate with much ease. At the present time we cannot account for the reactivity hereby observed, but the situation seems to be analogous to facile acetylation of 16β-hydroxyl group of gitoxigenin.[8] When chloroform solution of IX was shaken with aqueous hydrobromic acid vigorously, bromohydrin (Xa) was successfully provided. The resultant product was separated by thin-layer chromatography employing silica gel G and was characterized by leading to Xb by usual acetylation. Nevertheless difficulties were encountered in isolating the desired bromohydrin by means of alumina chromatography. When Xa was passed through a column of alumina, dehydro-

3) J. Fajkoš, *et al.* : Collection Czechoslov. Chem. Communs., **26**, 64, 1118 (1961).
4) T. Nambara, K. Hirai : This Bulletin, **12**, 836 (1964).
5) T. Nambara, J. Fishman : J. Org. Chem., **26**, 4569 (1961). See also L. F. Fieser, M. Fieser : "Steroids" p. 268, Reinhold Publ. Co., New York (1959).
6) L. Caglioti, M. Magi : Tetrahedron, **19**, 1127 (1963).
7) L. F. Fieser, R. Ettore : J. Am. Chem. Soc., **75**, 1700 (1953).
8) W. Neumann : Ber., **70**, 1547 (1937).

bromination occurred readily to provide again 16β,17β-epoxide. That elimination of hydrogen bromide can be effected only by contact with alumina has already been shown in some instances, where the reaction takes place due to the extremely favorable geometrical alignment of the reaction centers.[9] In the present case it seemed very likely that facile dehydrobromination proceeded in such a way that steric hindrance of bulky bromine atom at C-17 would be relieved on the concave side of C/D-*cis* fusion.

Further studies on conformation of ring D of 5α,14β-androstan-16-one are being conducted in these laboratories and will be reported in near future.

## Experimental*4

**Reduction of 3β,17α-Dihydroxy-5α,14β-androstan-16-one Diacetate (II) with Lithium Aluminum Hydride**——To a solution of II (30 mg.) in ether (5 ml.) was added $LiAlH_4$ (50 mg.) portionwise under cooling in ice-bath and the mixture was allowed to stand at room temperature for 2 hr. The reaction mixture was diluted with moist ether, acidified with 5% $H_2SO_4$, washed with $H_2O$, and dried over anhyd. $Na_2SO_4$. On evaporation of solvent the crystalline residue (19 mg.) was obtained. To the solution of crude product dissolved in acetone (5 ml.) was added conc. $H_2SO_4$ (0.05 ml.) and the mixed solution was allowed to stand overnight at room temperature. The reaction mixture was neutralized with $KHCO_3$ solution, concentrated *in vacuo* almost to dryness. The residue thus obtained was dissolved in ether and treated in the usual manner. Recrystallization from MeOH gave 16,17-isopropylidene-5α,14β-androstane-3β,16α,17α-triol (IVa) (16 mg.) as colorless needles. m.p. 178~180°, $[\alpha]_D^{19.6}$ +33.3° (c=0.21). *Anal.* Calcd. for $C_{22}H_{36}O_3 \cdot H_2O$: C, 72.09; H, 10.45. Found: C, 72.12; H, 10.16.

**16,17-Isopropylidene-5α,14β-androstane-3β,16α,17α-triol 3-Acetate (IVb)**——A solution of IVa (12 mg.) dissolved in $Ac_2O$ (0.15 ml.) and pyridine (0.3 ml.) was allowed to stand at room temperature overnight. Usual treatment of the reaction mixture followed by recrystallization from MeOH gave IVb (10 mg.) as colorless leaflets. m.p. 149~151°, $[\alpha]_D^{19.6}$ +40.0° (c=0.30). *Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.60; H, 9.68.

**Reduction of 3β,17α-Dihydroxy-5α,14β-androstan-16-one Diacetate (II) with Sodium Borohydride**——To a solution of II (50 mg.) in $HCON(CH_3)_2$ (1.5 ml.) was added aq. solution (0.5 ml.) of $NaBH_4$ (50 mg.) and the reaction mixture was allowed to stand at room temperature for 2 hr. After decomposition of the excess reagent with AcOH the resultant product was extracted with $CHCl_3$, washed with NaCl-saturated $H_2O$ and dried over anhyd. $Na_2SO_4$. The $CHCl_3$ extract was concentrated to give the semisolid residue (51 mg.). The crude product was treated with $Ac_2O$ (0.4 ml.) and pyridine (1 ml.) in the usual manner and was chromatographed on $Al_2O_3$ (3 g.). Elution with hexane-benzene (7:3) and benzene afforded 5α,14β-androstane-3β,16α,17α-triol triacetate (IIIc) (38 mg.). Recrystallization from aq. MeOH gave IIIc as colorless leaflets. m.p. 102~103°, $[\alpha]_D^{18.0}$ +61.0° (c=0.32). *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.11; H, 8.65.

**Hydrolysis of 16,17-Isopropylidene-5α,14β-androstane-3β,16α,17α-triol 3-Acetate (IVb)**——A solution of IVb (6 mg.) dissolved in 5% methanolic $H_2SO_4$ (1 ml.) was allowed to stand at room temperature for 20 hr. The reaction mixture was neutralized with $KHCO_3$ and concentrated *in vacuo* to give the oily residue. The crude product was dissolved in ether, washed with $H_2O$, dried over anhyd. $Na_2SO_4$ and concentrated. Treatment of the oily residue with $Ac_2O$ and pyridine in the usual manner afforded the semisolid product, which in turn was chromatographed on $Al_2O_3$ (1 g.). Elution with hexane-benzene (5:5 and 3:7) and recrystallization from aq. MeOH gave IIIc (3 mg.) as colorless leaflets. m.p. 97~101°. Mixed melting point on admixture with the sample obtained through $NaBH_4$ reduction of II showed no depression.

**5α,14β-Androstane-3β,16α-diol (VI)**——To a solution of 3β-hydroxy-5α,14β-androstan-16-one acetate (V) (30 mg.) in ether (5 ml.) was added $LiAlH_4$ (50 mg.) portionwise under cooling in ice-bath and the reaction mixture was allowed to stand at room temperature for 2 hr. The mixture was diluted with moist ether, acidified with 5% $H_2SO_4$, washed with $H_2O$ and dried over anhyd. $Na_2SO_4$. Upon evaporation of solvent the crystalline product was obtained. Recrystallization from hexane-acetone gave VI (24 mg.) as colorless needles. m.p.169~171°, $[\alpha]_D^{24.1}$ +31.8° (c=0.60). Mixed melting point on admixture with 5α,14β-androstane-3β,16β-diol (XIa) (m.p. 171~172°)[4] showed distinct depression. *Anal.* Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.45; H, 11.10.

**3β-Hydroxy-5α,14β-androstan-17-one Acetate *p*-Tosylhydrazone (VII)**——To a solution of 3β-hydroxy-5α,14β-androstan-17-one acetate (I) (960 mg.) in MeOH (100 ml.) were added *p*-tosylhydrazine (710 mg.) and

*4 All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise stated. TLC plate was prepared and activated according to the Stahl's procedure using silica gel G (E. Merck Co.) as adsorbent.

9) G. H. Ott, T. Reichstein: Helv. Chim. Acta, **26**, 1799 (1943).

AcOH (0.5 ml.), and the solution was boiled under reflux for 6 hr. The reaction mixture was concentrated *in vacuo* to give the crystalline product. Recrystallization from aq. MeOH gave Ⅶ (1.210 g.) as colorless needles. m.p. 151~153°, $[\alpha]_D^{24.1}$ +86.3° (c=0.40). *Anal.* Calcd. for $C_{28}H_{40}O_4N_2S$: C, 67.17; H, 8.05; N, 5.60. Found: C, 67.56; H, 8.08; N, 5.56.

**5α,14β-Androst-16-en-3β-ol (VIIIa)**[4]——To a solution of Ⅶ (1.210 g.) in tetrahydrofuran (100 ml.) was added $LiAlH_4$ (2.4 g.) and the reaction mixture was boiled under reflux for 10 hr. After usual treatment of the reaction mixture the oily product obtained was chromatographed on $Al_2O_3$ (20 g.). Elution with benzene–ether (8:2 and 7:3) and recrystallization from acetone gave Ⅷa (467 mg.) as colorless needles. m.p. 136~138°.

**17α-Bromo-5α,14β-androstane-3β,16β-diol Diacetate (Xb)**——16β,17β-Epoxy-5α,14β-androstan-3β-ol acetate (Ⅸ) (40 mg.) was dissolved in AcOH (1 ml.) and HBr-saturated AcOH (0.1 ml.), and the solution was allowed to stand at room temperature for 24 hr. The reaction mixture was diluted with ether, washed with cold 5% $NaHCO_3$, $H_2O$ and dried over anhyd. $Na_2SO_4$. After evaporation ofsolvent the residue obtained was chromatographed on $Al_2O_3$ (3 g.). Elution with hexane–benzene (8:2 and 6:4) and recrystallization form MeOH gave Xb (43 mg.) as colorless needles. m.p. 118~120°, $[\alpha]_D^{16.3}$ +57.3° (c=0.34). *Anal.* Calcd. for $C_{23}H_{35}O_4Br$: C, 60.65; H, 7.75. Found: C, 61.21; H, 7.67.

**5α,14β-Androstane-3β,16β-diol Diacetate (XIb)**——i) 5α,14β-Androstane-3β,16β-diol (XIa) (22 mg.) was dissolved in $Ac_2O$ (0.2 ml.) and pyridine (0.5 ml.) and the solution was allowed to stand at room temperature for 24 hr. Usual treatment of the reaction mixture followed by recrystallization from aq. MeOH gave XIb (21 mg.) as colorless needles. m.p. 165~167°, $[\alpha]_D^{18.4}$ +27.0 (c=0.48). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.32; H, 9.29.

ii) A solution of Xb (12 mg.) dissolved in EtOH (4 ml.) was shaken with 5% $Pd/BaCO_3$ (50 mg.) in a stream of $H_2$ under the atmospheric pressure for 24 hr. After removal of catalyst the filtrate was concentrated *in vacuo* to furnish the crystalline residue. Recrystallization from aq. MeOH gave XIb (7 mg.) as colorless needles. m.p.164~166°. Mixed melting point and IR spectra comparison prove it to be identical with the sample obtained in i).

**17α-Bromo-5α,14β-androstane-3β,16β-diol 3-Acetate (Xa)**——To a solution of Ⅸ (45 mg.) in $CHCl_3$ (2.5 ml.) was added 48% HBr (1.3 ml.) and the mixed solution was stirred vigorously for 20 hr. The reaction mixture was diluted with $CHCl_3$, washed with $H_2O$ and dried over anhyd. $Na_2SO_4$. Upon evaporation of solvent the oily residue (58 mg.) was obtained, a part of which (42 mg.) was submitted to the preparative thin-layer chromatography employing benzene–ether (9:1) as developing solvent. The adsorbent corresponding to Rf value 0.25~0.33 was collected and eluted with ether to give the oily product (Xa) (18 mg.). According to the thin-layer chromatography using the same solvent system it consisted of the sole compound showing single spot at Rf 0.29. Usual acetylation of Xa (10 mg.) with $Ac_2O$ (0.08 ml.) in pyridine (0.2 ml.) followed by recrystallization from MeOH afforded Xb (6 mg.) as colorless needles, m.p. 115~118°. Mixed melting point on admixture with the authentic sample showed no depression.

**16β,17β-Epoxy-5α,14β-androstan-3β-ol Acetate(IX). i) Treatment of Xb with Methanolic Potassium Hydroxide**——A solution of Xb (35 mg.) dissolved in 5% methanolic KOH (6 ml.) was boiled under reflux for 2 hr. The reaction mixture was concentrated *in vacuo* and the resultant oily residue was extracted with ether, washed with $H_2O$ and dried over anhyd. $Na_2SO_4$. After evaporation of solvent the crystalline product obtained was treated with $Ac_2O$ (0.2 ml.) in pyridine (0.4 ml.) in the usual manner. Recrystallization from MeOH gave Ⅸ (13 mg.) as colorless needles. m.p. 115~118°. Mixed melting point and IR spectra comparison proved it to be entirely identical with the authentic sample.

**ii) Treatment of Xa with Alumina**——A solution of Xa (15 mg.) dissolved in hexane–benzene (1:1) was adsorbed on $Al_2O_3$ (2 g.) packed in a column and was allowed to stand overnight. Elution with benzene (80 ml.) followed by recrystallization from MeOH gave Ⅸ (9 mg.) as colorless needles. m.p. 116~119°. Mixed melting point and IR spectra comparison proved it to be entirely identical with the authentic sample.

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## Summary

In connection with the studies on conformation of ring D of 5α,14β-androstane, metal hydride reduction of 16-ketone and ring opening of 16β,17β-epoxide with hydrogen bromide were examined. It was clarified that in 14β-series metal hydride would attack 16-oxo group from the less hindered β-side to yield 16α-hydroxy compound. The ring cleavage of 16β,17β-epoxide with hydrogen bromide afforded 17α-bromo-16β-hydroxy derivative, which was readily acetylated in the presence of acetic acid and was converted again to the epoxide only by contact with alumina.

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