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164. Shunsaku Noguchi, Masayuki Imanishi, and Katsura Morita : Synthesis of 20α-Hydroxy-16-oxosteroids and the C-20 Configuration of $\Delta^{17(20)}$-16-Oxosteroids.*1

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In a previous paper[1] we reported a modified degradation of the diosgenin side chain to give pregn-5-ene-3β,16β,20α-triol and 5α-pregnane-3β,16β,20α-triol. Acetylation of the 16,20-acetonides[2] of these triols followed by acid hydrolysis gave the corresponding 3β-acetoxypregn-5-ene-16β,20α-diol (Ia)[2] and 3β-acetoxy-5α-pregnane-16β,20α-diol (Ib),[2] respectively. These 16β,20α-diols (Ia and Ib) were further oxidized with CrO_3-H_2SO_4 reagent[3] in acetone to give 16,20-dioxosteroids (IIa and IIb), which were useful intermediates for synthesis of steroid[16,17-*c*]pyrazoles.[2] In the present paper we describe a selective oxidation of 16β,20α-dihydroxysteroid (I) at the 16-position to 20α-hydroxy-16-oxosteroid (III) and also discuss the C-20 configuration of isomeric $\Delta^{17(20)}$-16-oxosteroids (V and VI) obtainable from III (Chart 1).

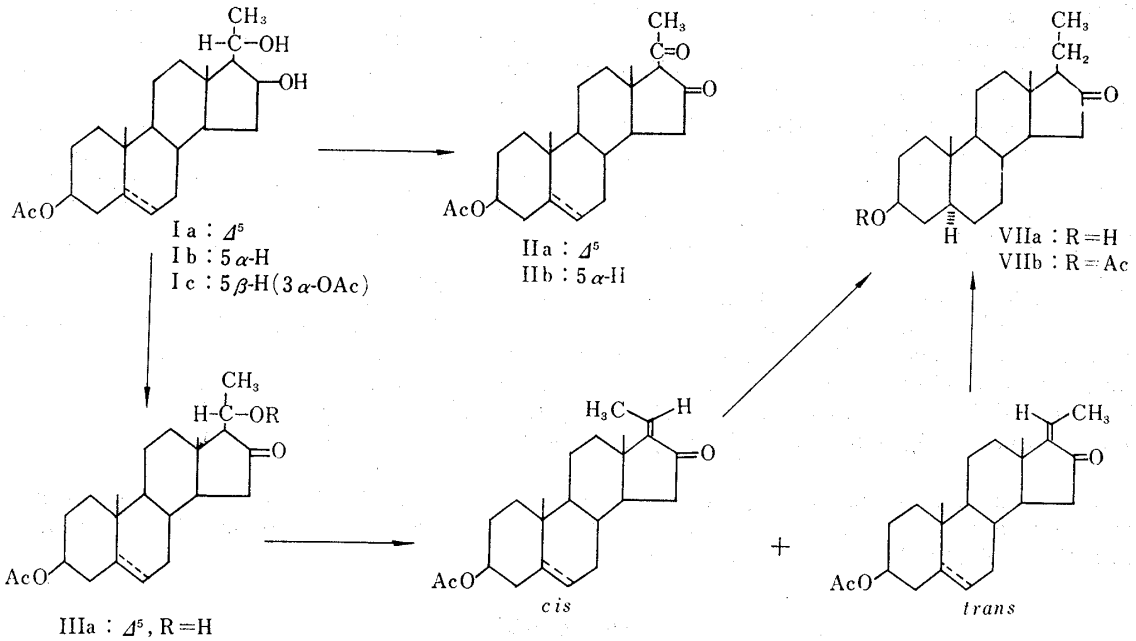

Chart 1.

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1) K. Morita, S. Noguchi, H. Kono, T. Miki : This Bulletin, **11**, 90 (1963).
2) K. Morita, S. Noguchi, K. Hiraga, T. Kishi, H. Nawa, T. Miki : *Ibid.*, **11**, 144 (1963).
3) C. Djerassi, R. R. Engle, A. Bowers : J. Org. Chem., **21**, 1548 (1956). And see also K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon : J. Chem. Soc., **1946**, 39.

In 1961, Brown, *et al.*[4] reported a mild oxidation of primary or secondary alcohols with $Na_2Cr_2O_7$-H_2SO_4 reagent in ether. This oxidation procedure offered special promise for the synthesis of ketones capable of undergoing further reaction under the usual oxidation conditions. We applied this procedure to the oxidation of 16β,20α-diols (Ia and Ib) and found that the 16β-hydroxyl group was selectively oxidized. An improved yield was obtained when a mixture of ether-benzene-tetrahydrofuran (20:1:1) was used as a solvent in place of ether in the reaction.

By this procedure Ia and Ib gave 3β,20α-dihydroxypregn-5-en-16-one 3-acetate (IIIa) and 3β,20α-dihydroxy-5α-pregnan-16-one 3-acetate (IIIb) in 60% yield. Similarly, oxidation of 5β-pregnane-3α,16β,20α-triol 3-acetate (Ic), which was synthesized from 16β,20α-isopropylidenedioxypregn-4-en-3-one (VII) or 5β-spirostan-3α-ol (XI) *via* 16β,20α-isopropylidenedioxy-5β-pregnan-3α-ol (X) according to the scheme (Chart 2), gave 3α,20α-dihydroxy-5β-pregnan-16-one 3-acetate (IIIc) in a comparative yield (Chart 1).

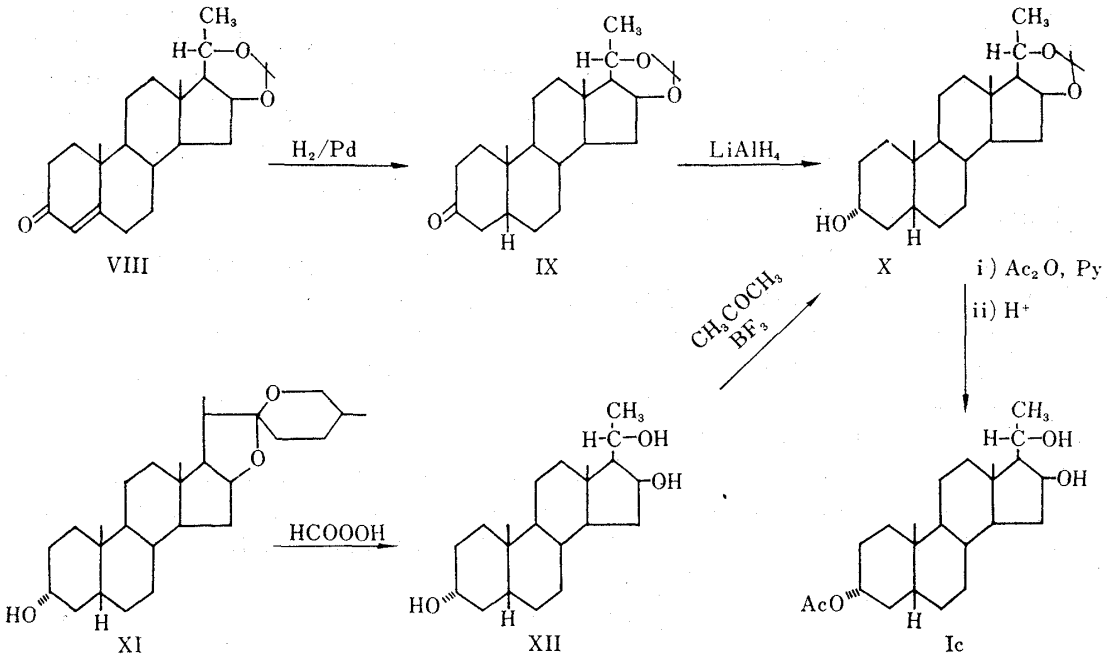


Chart 2.

That the oxidation took place only at the 16-position was demonstrated by the infrared spectrum of the product (III), which showed a characteristic five-membered absorption band at 5.75~5.80 μ.

The facility in oxidation of the 16β-hydroxyl group compared with the 20α-hydroxyl would be, in some degree, attributable to a steric acceleration due to the 1,3-interaction between the 18-angular methyl group and the 16β-hydroxyl group.

III have a β-hydroxy-ketone system, and hence the hydroxyl group should be readily eliminated to form an α,β-unsaturated system. As a matter of fact, when IIIa and IIIb were treated with tosyl chloride in pyridine, the corresponding 17-ethylene compounds, 3β-acetoxypregna-5,17(20)-dien-16-one (Va+VIa) and 3β-acetoxy-5α-pregn-17(20)-en-16-one (Vb+VIb) were obtained.

More smooth elimination to give the same products took place when their 20α-acetates (IVa, IVb, and IVc) were allowed to pass through a column of unwashed alumina. Treatment of III and IV with alkali such as potassium bicarbonate or carbonate in aqueous methanol also gave the 17-ethylene compounds. In every aforementioned reaction, the product was a mixture of *cis* and *trans* isomers*[3] (V and VI), and the mixture could

4) H.C. Brown, C.P. Garg : J. Am. Chem. Soc., 83, 2952 (1961).

be separated by chromatography on silica gel to give pure isomers.

The configuration at C-20 of 17-ethylene compounds (V and VI) was established on the basis of the nuclear magnetic resonance spectra, wherein a quartet associated with the C-20 vinyl hydrogen appeared at 5.7 p.p.m.*4 in one isomer, while in the other at 6.5 p.p.m.*4 The latter was therefore assigned *cis* isomer (V), because deshielding at the 20-hydrogen by the 16-carbonyl group should be more enhanced in the *cis* isomer (V) than in the *trans* isomer (VI). Upon catalytic reduction both isomers (Vb and VIb) gave an identical reduction product, 3β-acetoxy-5α-pregnan-16-one (VIIb).

When the reaction products (V and VI) obtained under various conditions were analyzed by gas chromatography, the ratio of *cis* (V) and *trans* (VI) isomers varied to a considerable extent according to the type of reactions. For example, treatment of III with tosyl chloride in pyridine gave a *cis* 1.5:*trans* 1 mixture, alkaline treatment of III or IV a *cis* 1:*trans* 1 mixture and alumina column treatment of IV a *cis* 2.5:*trans* 1 mixture. That alumina treatment of IV predominantly results in the *cis* isomer (V) would be explained by a *cis*-elimination mechanism (Chart 3).

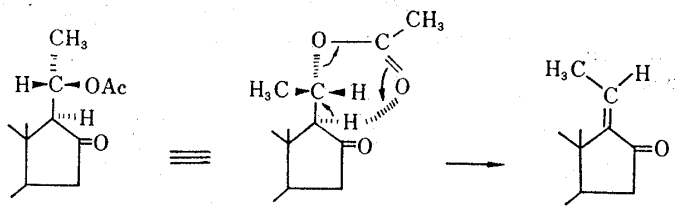


Chart 3.

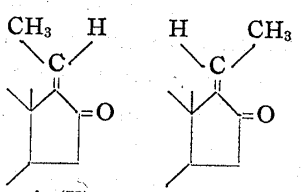
Huang-Minlon, *et al.*[5] obtained an isomer of 3β-hydroxypregna-5,17(20)-dien-16-one by treatment of 3β-hydroxy-16α,17α-epoxypregn-5-en-20-one with hydrazine followed by manganese dioxide oxidation, but they did not state the stereochemistry of the compound. Very recently, Sciaky, *et al.*[6] also obtained Va and VIa by treatment of 3β-hydroxy-16α,17α-epoxypregn-5-en-20-one acetate with hydrazine followed by the Oppenauer oxidation and discussed the C-20 configurations of Va and VIa on the basis of molecular rotation, infrared spectra and chromatographic behaviors. The present conclusion on the structural assignment of the C-20 configuration on the basis of the nuclear magnetic resonance spectra are in agreement with their conclusion.

Experimental*5

16β,20α-Isopropylidenedioxy-5β-pregnan-3-one (IX)——To a solution of 5.0 g. of 16β,20α-isopropylidenedioxypregn-4-en-3-one[2] (VIII) in 250 ml. of MeOH was added a solution of 500 mg. of KOH in 15 ml. of MeOH and the mixture was hydrogenated with H_2 over 2.5 g. of 5% Pd-C catalyst at room temperature. The catalyst was filtered and the filtrate was neutralized with AcOH and the solvent was evaporated under reduced pressure. The resulting residue was recrystallized from MeOH to give 3.8 g. of IX, m.p. 155~157°. *Anal.* Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.38; H, 10.33.

5β-Pregnane-3α,16β,20α-triol (XII)——To a suspension of 2.5 g. of 5β-spirostan-3α-ol (XI) in 120 ml. of 80% HCOOH was added 10 ml. of 30% H_2O_2 and the mixture was warmed on a steam bath to keep the temperature at 40~50° for 2 hr., during this period the crystals dissolved to a clear solution. After a further addition of 5 ml. of 30% H_2O_2, the solution was kept at 40~50° for another one hour. The

*3 Of the epimeric 17-ethylene compounds, *trans* isomer (VI) is the one in which the C-21 methyl group is pointing away from the C-18 methyl. (L. F. Fieser, M. Fieser : Experientia, **4**, 285 (1948)).



cis (V) *trans* (VI)

*4 Taken in $CDCl_3$ solution with TMS as internal reference on a Varian A-60 spectrometer (δ-value).

*5 All melting points are uncorrected.

5) Huang-Minlon, Chung-Tungshun : Tetrahedron Letters, **1961**, 666.

6) R. Sciaky, F. Facciano : Gazz. chim. ital., **93**, 1014 (1963).

reaction mixture was concentrated under reduced pressure to a volume of 40 ml. and then poured onto ice. The resulting precipitates were collected and washed with H_2O to give the crude formate of XII. To a solution of the crude formate in 60 ml. of MeOH was added 5 ml. of 20% aq. KOH and the mixture was refluxed on a steam bath for 0.5 hr. After neutralizing with dil. HCl, the solution was diluted with H_2O and concentrated under reduced pressure to give a crystalline product, which was collected and washed with H_2O. This product was recrystallized from AcOEt to give 1.6 g. of XII, m.p. 187~190°. *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.54; H, 10.83.

16β,20α-Isopropylidenedioxy-5β-pregnan-3α-ol (X)——a) To a stirred solution of 7.0 g. of IX in 600 ml. of anhyd. Et_2O was added dropwise a solution of 3.0 g. of $LiAlH_4$ in 100 ml. of anhyd. Et_2O. After stirring for 0.5 hr., dil. H_2SO_4 was added to decompose the excess of the reagent and then the organic layer was separated, washed successively with dil. H_2SO_4 and H_2O and dried over Na_2SO_4. After evaporation of the solvent, the resulting residue was recrystallized from AcOEt to give 6.0 g. of X, m.p. 155~159°. *Anal.* Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.45; H, 10.27.

b) A suspension of XII in Me_2CO was treated with 2 drops of 37% BF_3 in Et_2O and the mixture was stirred at room temperature for 1 hr., during this period crystals of XII dissolved. After an addition of one drop of pyridine, the reaction mixture was concentrated to a volume of 10 ml. and diluted with H_2O. The resulting precipitates were collected and washed with H_2O to give 350 mg. of X, which was recrystallized from AcOEt, m.p. 157~159°.

5β-Pregnane-3α,16β,20α-triol 3-Acetate (Ic)——Acetylation of 5.0 g. of X with Ac_2O and pyridine and recrystallization of the product from MeOH furnished 4.5 g. of 16β,20α-isopropylidenedioxy-5β-pregnan-3α-ol acetate, m.p. 172~173°. *Anal.* Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.92; H, 9.71.

To a solution of the acetate (4.5 g.) in 15 ml. of AcOH was added 5 ml. of H_2O and the mixture was heated on a steam bath for 20 min. and then diluted with H_2O. The resulting precipitates were collected and washed with H_2O to give 4.0 g. of Ic, m.p. 213~215°. *Anal.* Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.22; H, 9.82.

3β,20α-Dihydroxypregn-5-en-16-one 3-Acetate (IIIa)——To a stirred solution of 25 g. of pregn-5-ene-3β,16β,20α-triol 3-acetate (Ia) in 75 ml. of tetrahydrofuran, 75 ml. of benzene and 1500 ml. of Et_2O was added dropwise 37 ml. of aq. $Na_2Cr_2O_7$–H_2SO_4 reagent[4] (A solution of 20.0 g. of $Na_2Cr_2O_7 \cdot 2H_2O$ and 15 ml. of conc. H_2SO_4 diluted with H_2O to a volume of 100 ml.) over a period of 4.5 hr. at 25°. The solution was treated with MeOH to decompose the excess chromic acid and the organic layer was washed with aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from MeOH to give 14 g. of IIIa, m.p. 188~190°, $[\alpha]_D^{22}$ −160° (c=0.5, EtOH), IR λ_{max}^{Nujol} μ: 2.88, 5.74, 5.79. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H. 9.15. Found: C, 73.57; H, 9.18.

3β,20α-Diacetoxypregn-5-en-16-one (IVa)——A mixture of 5.0 g. of IIIa, 50 ml. of pyridine and 50 ml. of Ac_2O was heated on a steam bath for 1 hr. and poured onto ice. The resulting precipitates were collected, washed with H_2O and recrystallized from MeOH to give 4.5 g. of IVa, m.p. 193~195°, IR λ_{max}^{Nujol} μ: 5.74, 5.80. *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.97; H, 8.61.

3β,20α-Dihydroxy-5α-pregnan-16-one 3-Acetate (IIIb)——Oxidation of Ib with aq. $Na_2Cr_2O_7$–H_2SO_4 reagent, according to the procedure for the preparation of IIIa, and recrystallization of the resulting product from MeOH afforded an analytical sample of IIIb, m.p. 225~227°, $[\alpha]_D^{22}$ −101° (c=0.32, EtOH), IR λ_{max}^{Nujol} μ: 2.88, 5.75, 5.80. *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.06; H, 9.51.

3β,20α-Diacetoxy-5α-pregnan-16-one (IVb)——Acetylation of IIIb with Ac_2O and pyridine was carried out by the usual method. Recrystallization of the product from MeOH afforded IVb, m.p. 187~189°, IR λ_{max}^{Nujol} μ: 5.73, 5.78. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.03; H, 9.13.

3α,20α-Diacetoxy-5β-pregnan-16-one (IVc)——Ic was oxidized with aq. $Na_2Cr_2O_7$–H_2SO_4 reagent according to the procedure for the preparation of IIIa. The resulting noncrystalline product was acetylated with Ac_2O and pyridine by the usual method and the crude acetate was recrystallized from MeOH to give an analytical sample of IVc, m.p. 197~201°. IR λ_{max}^{Nujol} μ: 5.74, 5.76. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.54; H, 9.33.

3β-Acetoxypregna-5,17(20)-*cis*-dien-16-one (Va) and 3β-Acetoxypregna-5,17(20)-*trans*-dien-16-one (VIa)——A solution of 1.0 g. of IVa in 30 ml. of benzene was passed through a column of 100 g. of alumina and the column was then eluted with 2 L. of benzene–Et_2O (3:1). The eluates were combined and the solvent was removed under reduced pressure. The resulting product (a mixture of Va and VIa) was dissolved in $CHCl_3$ and chromatographed on 800 g. of silica gel. Elution with $CHCl_3$ gave the *trans* isomer (VIa), which was recrystallized from MeOH, m.p. 143~144°, $[\alpha]_D^{22}$ −216° (c=0.6, EtOH), UV: λ_{max}^{EtOH} 243 mμ (ε 9,100), IR λ_{max}^{KBr} μ: 5.80, 5.85, 6.10, 8.07.

Further elution with the same solvent gave the *cis* isomer (Va), which was recrystallized from MeOH, m.p. 161~162°, $[\alpha]_D^{21}$ −186° (c=0.5, EtOH), UV: λ_{max}^{EtOH} 243 mμ (ε 9,410), IR λ_{max}^{Nujol} μ: 5.73, 5.77, 6.04, 8.05. *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 76.99; H, 9.01.

Acetylation of 3β-hydroxypregna-5,17(20)-dien-16-one, which was prepared by the Huang-Minlon method,[5] afforded the acetate, which was confirmed to be identical with the *cis* isomer (Va) by the comparison of the IR and NMR spectra.

3β-Acetoxy-5α-pregn-17(20)-*cis*-en-16-one (Vb) and 3β-Acetoxy-5α-pregn-17(20)-*trans*-en-16-one (VIb)——IVb was treated with alumina as described in the case of IVa and the resulting product (a mixture of Vb and VIb) was chromatographed on a column of silica gel. Elution with $CHCl_3$ gave firstly the *trans* isomer (VIb), which was recrystallized from MeOH, m.p. 166~167°, $[\alpha]_D^{22}$ −139°(0.7, EtOH), UV : λ_{max}^{EtOH} 243 mμ (ε 9,000), IR λ_{max}^{Nujol} μ : 5.75, 5.83, 6.07, 8.08, 9.10.

Continued elution with the same solvent gave the *cis* isomer (Vb), which was recrystallized from MeOH, m.p. 182~183°, $[\alpha]_D^{21}$ −112°(c=0.9, EtOH), UV : λ_{max}^{EtOH} 243 mμ (ε 9,500), IR λ_{max}^{Nujol} μ : 5.73, 5.79, 6.05, 8.03, 8.38. *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found : C, 76.91; H, 9.51.

Elimination Reactions of the 20α-Hydroxyl Group——a) TsCl-pyridine : To a solution of 50 mg. of IIIa in 1.0 ml. of pyridine was added 50 mg. of TsCl and the mixture was heated on a steam bath for 4 hr. The mixture was diluted with H_2O and resulting precipitates were collected and washed with H_2O to give 43 mg. of a crystalline product, which was proved to be a 1.5:1 mixture of *cis* (Va) and *trans* (VIa) by the gas chromatographic analysis (Stationary phase, 3% SE-30 on chromosorb W, at 230°, N_2 flow rate 35 ml./min.). IIIb also gave a similar result.

b) $KHCO_3$: To a solution of 50 mg. of IIIa in 2.5 ml. of MeOH was added 0.5 ml. of 10% aq. $KHCO_3$ and the mixture was heated under reflux on a steam bath for 2.5 hr. The reaction solution was diluted with H_2O and resulting precipitates were collected and washed with H_2O to give 31 mg. of a crystalline product, which was proved to be a 1.5:1 mixture of *cis* and *trans* isomers (3-hydroxy compounds) by the gas chromatographic analysis. IIIb, IVa and IVb also gave similar results.

c) K_2CO_3 : To a solution of 50 mg. of IIIa in 2.5 ml. of MeOH was added 0.5 ml. of 5% aq. K_2CO_3 and the mixture was heated under reflux on a steam bath for 1 hr. The reaction solution was diluted with H_2O and resulting precipitates were collected and washed with H_2O to give 35 mg. of a crystalline product, which was proved to be a 1.0~1.5:1 mixture of *cis* and *trans* isomers (3-hydroxy compounds) by the gas chromatographic analysis. IIIb, IVa and IVb also gave similar results.

d) Al_2O_3 : A solution of 50 mg. of IVa was passed through a column of 5.0 g. of alumina and then the column was eluted with 100 ml. of benzene and 100 ml. of benzene-Et_2O (3:1). The product (44 mg.) was proved to be a 2.5:1 mixture of *cis* (Va) and *trans* (VIa) by the gas chromatographic analysis. IVb also gave similar results.

3β-Acetoxy-5α-pregnan-16-one (VIIb) and 3β-Hydroxy-5α-pregnan-16-one (VIIa)——a) From Vb : A solution of 500 mg. of Vb in 50 ml. of MeOH was shaken with H_2 over 500 mg. of 5% Pd-C catalyst at room temperature. After uptake of the calculated volume of H_2, the catalyst was removed and the filtrate was concentrated under reduced pressure. The resulting residue was recrystallized from MeOH to give 350 mg. of VIIb, m.p. 156~158°; IR λ_{max}^{Nujol} μ : 5.78, 8.08. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found : C, 76.38; H, 10.06.

To a solution of 200 mg. of VIIb in 4 ml. of MeOH was added 0.4 ml. of 10% aq. K_2CO_3 and the mixture was heated under reflux on a steam bath for 0.5 hr. After acidification with AcOH, the reaction solution was diluted with H_2O and concentrated under reduced pressure until crystals deposit. The product was collected, washed with H_2O and recrystallized from Et_2O to give 120 mg. of VIIa, m.p. 157~158°, IR λ_{max}^{Nujol} μ : 2.86, 5.79. *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found : C, 79.19; H, 10.60.

b) From VIb : VIb was hydrogenated with H_2 over Pd-C catalyst as described in the case of Vb. The resulting product was confirmed to be identical with a specimen obtained in (a) by the mixed melting point determination and comparison of the IR spectra.

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Summary

Treatment of 16β,20α-dihydroxysteroids, Ia, Ib, and Ic, with $Na_2Cr_2O_7$-H_2SO_4 reagent in ether-benzene-tetrahydrofuran resulted in a selective oxidation of the 16-hydroxyl group to afford 20α-hydroxy-16-oxosteroids, IIIa, IIIb, and IIIc. IIIa, IIIb, and the 20-acetates, IVa and IVb, were treated with TsCl, $KHCO_3$, K_2CO_3 or alumina to afford a mixture of *cis* and *trans* 17(20)-16-oxosteroids (V and VI). The C-20 configuration of the isomers, V and VI, was established on the basis of the nuclear magnetic resonance spectra.

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