164. Shunsaku Noguchi, Masayuki Imanishi, and Katsura Morita:
Synthesis of 20α-Hydroxy-16-oxosteroids and the C-20
Configuration of Δ^{17(20)}-16-Oxosteroids.\textsuperscript{a1}

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In a previous paper\textsuperscript{11} 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\textsuperscript{20} of these triols followed by acid hydrolysis gave the corresponding
3β-acetoxypregn-5-ene-16β,20α-diol (Ia)\textsuperscript{21} and 3β-acetoxy-5α-pregnane-16β,20α-diol
(Ib),\textsuperscript{22} respectively. These 16β,20α-diols (Ia and Ib) were further oxidized with CrO\textsubscript{3}-
H\textsubscript{2}SO\textsubscript{4} reagent\textsuperscript{23} in acetone to give 16,20-dioxosteroids (IIa and IIb), which were useful
intermediates for synthesis of steroid[16,17-c]pyrazoles.\textsuperscript{3} In the present paper we descibe
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 Δ^{17(20)}-16-
oxosteroids (V and VI) obtainable from III (Chart 1).

![Chart 1.](image-url)

\textsuperscript{a1} This paper constitutes Part XXXII of Takeda Laboratories' series entitled "Steroids"; Part XXXI:
This Bulletin, 12, 1180 (1964).
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\textsuperscript{1} K. Morita, S. Noguchi, H. Kono, T. Miki: This Bulletin, 11, 90 (1963).
\textsuperscript{3} C. Djerassi, R. R. Engle, A. Bowers: J. Org. Chem., 21, 1548 (1956). And see also K. Bowden,
In 1961, Brown, et al.\textsuperscript{4} reported a mild oxidation of primary or secondary alcohols with Na$_2$Cr$_2$O$_7$-H$_2$SO$_4$ 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 16\(\beta\),20\(\alpha\)-diols (Ia and Ib) and found that the 16\(\beta\)-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 3\(\beta\),20\(\alpha\)-dihydroxypregn-5-en-16-one 3-acetate (Ila) and 3\(\beta\),20\(\alpha\)-dihydroxy-5\(\alpha\)-pregnan-16-one 3-acetate (IIB) in 60\% yield. Similarly, oxidation of 5\(\beta\)-pregnane-3\(\alpha\),16\(\beta\),20\(\alpha\)-triol 3-acetate (Ic), which was synthesized from 16\(\beta\),20\(\alpha\)-isopropylidenedioxypregn-4-en-3-one (I\(\text{III}\)) or 5\(\beta\)-spirostan-3\(\alpha\)-ol (I\(\text{IV}\)) via 16\(\beta\),20\(\alpha\)-isopropylidenedioxy-5\(\beta\)-pregnan-3\(\alpha\)-ol (I\(\text{V}\)) according to the scheme (Chart 2), gave 3\(\alpha\),20\(\alpha\)-dihydroxy-5\(\beta\)-pregnan-16-one 3-acetate (I\(\text{VI}\)) in a comparative yield (Chart 1).

![Chart 2](image)

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

The facility in oxidation of the 16\(\beta\)-hydroxyl group compared with the 20\(\alpha\)-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 16\(\beta\)-hydroxyl group.

I\(\text{II}\) have a \(\beta\)-hydroxy-ketone system, and hence the hydroxyl group should be readily eliminated to form an \(\alpha\),\(\beta\)-unsaturated system. As a matter of fact, when I\(\text{IIa}\) and I\(\text{Iib}\) were treated with tosyl chloride in pyridine, the corresponding 17-ethylene compounds, 3\(\beta\)-acetoxypregna-5,17(20)-dien-16-one (I\(\text{Va}\)+I\(\text{Vla}\)) and 3\(\beta\)-acetoxy-5\(\alpha\)-pregn-17(20)-en-16-one (I\(\text{Vb}\)+I\(\text{Vlb}\)) were obtained.

More smooth elimination to give the same products took place when their 20\(\alpha\)-acetates (I\(\text{Va}\), I\(\text{Vb}\), and I\(\text{Vc}\)) were allowed to pass through a column of unwashed alumina. Treatment of I\(\text{II}\) and I\(\text{IV}\) 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\textsuperscript{5a} (V and VI), and the mixture could

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.* in one isomer, while in the other at 6.5 p.p.m.* 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 (V). Upon catalytic reduction both isomers (Vb and VIb) gave an identical reduction product, 3β-acetoxy-5α-pregn-16-one (VII).

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 V predominantly results in the cis isomer (V) would be explained by a cis-elimination mechanism (Chart 3).

Huang-Minlon, et al., obtained an isomer of 3β-hydroxyxypregn-5,17(20)-dien-16-one by treatment of 3β-hydroxy-16α,17α-epoxyxypregn-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., also obtained Va and VIA by treatment of 3β-hydroxy-16α,17α-epoxyxypregn-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**

16β,20α-Isopropylidenedioxy-5β-pregn-3-one (IX)—To a solution of 5.0 g. of 16α,20α-isopropylidenedioxyxypregn-4-en-3-one (VII) 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 H₂ 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 K, m.p. 155~157°. Anal. Calcd. for C₂Hy₅O₂: C, 78.96; 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 5α-spirostan-3α-ol (XI) in 120 ml. of 80% HCOOH was added 10 ml. of 30% H₂O₂ 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 50% H₂O₂ the solution was kept at 40~50° for another one hour. The

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*3 Of the epimeric 17-ethylene compounds, trans isomer (V) 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)).

*4 Taken in CDCl₃ solution with TMS as internal reference on a Varian A-60 spectrometer (δ-value).

*5 All melting points are uncorrected.

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 H₂O to give the crude formate of XI. 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 H₂O and concentrated under reduced pressure to give a crystalline product, which was collected and washed with H₂O. This product was recrystallized from AcOEt to give 1.6 g. of XI, m.p. 187~190°. Anal. Calcd. for C₇₅H₃₈O₇: C, 74.95; H, 10.78. Found : C, 74.54; H, 10.83.

16β,20α-Isopropylidenedioxy-5α-pregn-3α-ol (X)—a To a stirred solution of 7.0 g. of X in 600 ml. of anhyd. Et₂O was added dropwise a solution of 3.0 g. of LiAlH₄ in 100 ml. of anhyd. Et₂O. After stirring for 0.5 hr., dil. H₂SO₄ was added to decompose the excess of the reagent and then the organic layer was separated, washed successively with dil. H₂SO₄ and H₂O and dried over Na₂SO₄. 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 C₇₅H₃₈O₇: C, 76.65; H, 10.71. Found : C, 76.45; H, 10.27.

b) A suspension of XI in Me₂CO was treated with 2 drops of 37% BF₃ in Et₂O 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 H₂O. The resulting precipitates were collected and washed with H₂O to give 350 mg. of X, which was recrystallized from AcOEt, m.p. 157~159°.

5β-Pregnane-3α,16β,20α-triol 3-Acetate (Ie) —Acetylation of 5.0 g. of X with Ac₂O and pyridine and recrystallization of the product from MeOH furnished 4.5 g. of 16β,20α-isopropylidenedioxy-5β-pregn-3α-ol acetate, m.p. 172~173°. Anal. Calcd. for C₇₅H₃₈O₇: C, 74.80; 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 H₂O and the mixture was heated on a steam bath for 20 min. and then diluted with H₂O. The resulting precipitates were collected and washed with H₂O to give 4.0 g. of Ic, m.p. 213~215°. Anal. Calcd. for C₇₅H₃₈O₇: C, 72.97; H, 10.12. Found : C, 73.22; H, 9.82.

3β,20α-Dihydroxy-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 EtO was added dropwise 37 ml. of aq. Na₂CrO₄·H₂SO₄ reagent⁴ (A solution of 20.0 g. of Na₂CrO₄·2H₂O and 15 ml. of conc. H₂SO₄ diluted with H₂O 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. NaHCO₃ and H₂O, dried over Na₂SO₄ and evaporated. The residue was recrystallized from MeOH to give 14 g. of IIIa, m.p. 188~190°, [α]D²⁰⁻160° (c=0.5, EtOH), IR λ_{max} μ : 2.88, 5.74, 5.79. Anal. Calcd. for C₇₅H₃₈O₇: C, 73.76; H, 9.15. Found : C, 73.57; H, 9.18.

3β,20α-Diacetoxy-5-en-16-one (IVa)—A mixture of 5.0 g. of IIIa, 50 ml. of pyridine and 50 ml. of Ac₂O was heated on a steam bath for 1 hr. and poured onto ice. The resulting precipitates were collected, washed with H₂O and recrystallized from MeOH to give 4.5 g. of Na, m.p. 193~195°, IR λ_{max} μ : 5.74, 5.80. Anal. Calcd. for C₇₅H₃₈O₇: C, 72.08; H, 8.71. Found : C, 71.97; H, 8.61.

3β,20α-Dihydroxy-5α-pregn-16-one 3-Acetate (IIIb)—Oxidation of Ib with aq. Na₂CrO₄·H₂SO₄ 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°, [α]D²⁰⁻101° (c=0.32, EtOH), IR λ_{max} μ : 2.88, 5.75, 5.80. Anal. Calcd. for C₇₅H₃₈O₇: C, 73.36; H, 9.64. Found : C, 73.06; H, 9.51.

3β,20α-Diacetoxy-5α-pregn-16-one (IVb)—Acetylation of Eb with Ac₂O and pyridine was carried out by the usual method. Recrystallization of the product from MeOH afforded Nb, m.p. 187~189°, IR λ_{max} μ : 5.73, 5.78. Anal. Calcd. for C₇₅H₃₈O₇: C, 71.74; H, 9.15. Found : C, 72.03; H, 9.13.

3α,20α-Diacetoxy-5β-pregn-16-one (IVc)—Ic was oxidized with aq. Na₂CrO₄·H₂SO₄ reagent according to the procedure for the preparation of IIIa. The resulting noncrystalline product was acetylated with Ac₂O 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} μ : 5.74, 5.76. Anal. Calcd. for C₇₅H₃₈O₇: C, 71.74; H, 9.15. Found : C, 71.54; H, 9.33.

3β-Acetoxy-pregna-5,17(20)-cisdien-16-one (Va) and 3β-Acetoxy-pregn-5,17(20)-trans-dien-16-one (Va)—A solution of 1.0 g. of Na 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-Et₂O (3:1). The eluates were combined and the solvent was removed under reduced pressure. The resulting product (a mixture of Va and Vb) was dissolved in CHCl₃ and chromatographed on 800 g. of silica gel. Elution with CHCl₃ gave the trans isomer (Va), which was recrystallized from MeOH, m.p. 143~144°, [α]D²⁰⁻216° (c=0.6, EtOH), UV : λ_{max} μ 243 mµ (ε 9,410), IR λ_{max} μ : 5.80, 5.85, 6.10, 8.07.

Further elution with the same solvent gave the cis isomer (Vb), which was recrystallized from MeOH, m.p. 161~162°, [α]D²⁰⁻186° (c=0.5, EtOH), UV : λ_{max} μ 243 mµ (ε 9,410), IR λ_{max} μ : 5.73, 5.77, 6.04, 8.05. Anal. Calcd. for C₇₅H₃₈O₇: 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, 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-pregnan-17(20)-cis-en-16-one (Vb) and 3β-Acetoxy-5α-pregnan-17(20)-trans-en-16-one (VB) — Vb was treated with alumina as described in the case of Va and the resulting product (a mixture of Va and Vb) was chromatographed on a column of silica gel. Elution with CHCl₃ gave firstly the trans isomer (Vb), which was recrystallized from MeOH, m.p. 166~167°, [α]₀²⁰ = 133° (0.7, EtOH), UV: λ max 243 mp (ε 9,000), IR μ max : 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°, [α]₀²⁰ = 112° (c = 0.9, EtOH), UV: λ max 243 mp (ε 9,500), IR μ max : 5.73, 5.79, 6.05, 8.05, 8.38. Anal. Calcd. for C₂₃H₃₈O₃: C, 77.65; 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 Illa 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 H₂O and resulting precipitates were collected and washed with H₂O to give 43 mg. of a crystalline product, which was proved to be a 1:5:1 mixture of cis (Va) and trans (Vb) by the gas chromatographic analysis (Stationary phase, 3% SE-30 on chromosorb W, at 230°, N₂ flow rate 35 ml./min.). Vlb also gave a similar result.

b) K₂CO₃: To a solution of 50 mg. of Illa in 2.5 ml. of MeOH was added 0.5 ml. of 10% aq. K₂CO₃ and the mixture was heated under reflux on a steam bath for 2.5 hr. The reaction solution was diluted with H₂O and the resulting precipitates were collected and washed with H₂O 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. Vlb, Va and Vb also gave similar results.

c) K₂CO₃: To a solution of 50 mg. of Illa in 2.5 ml. of MeOH was added 0.5 ml. of 5% aq. K₂CO₃ and the mixture was heated under reflux on a steam bath for 1 hr. The reaction solution was diluted with H₂O and the resulting precipitates were collected and washed with H₂O 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. Vlb, Va and Vb also gave similar results.

d) Al₂O₃: A solution of 50 mg. of Va 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-Et₂O (3:1). The product (44 mg.) was proved to be a 2.5:1 mixture of cis (Va) and trans (Vb) by the gas chromatographic analysis. Vlb 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 H₂O over 500 mg. of 5% Pd-C catalyst at room temperature. After uptake of the calculated volume of H₂, 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 μ max : 5.78, 8.08. Anal. Calcd. for C₂₉H₄₆O₃: 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. K₂CO₃ 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 H₂O and concentrated under reduced pressure until crystals deposit. The product was collected, washed with H₂O and recrystallized from Et₂O to give 120 mg. of VIIa, m.p. 157~158°, IR μ max : 2.86, 5.79. Anal. Calcd. for C₂₉H₄₆O₃: C, 79.19; H, 10.76. Found: C, 79.19; H, 10.60.

b) From Vb: Vb was hydrogenated with H₂ 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.

The authors express their deep gratitude to Dr. S. Tatsunoa, Director of these Laboratories, for his kind encouragement, to Dr. Y. Abe for his guidance. Thanks are also due to Mr. H. Kamio for spectral determinations and Mr. M. Kan for elemental analysis.

Summary

Treatment of 16β,20α-dihydroxysteroids, Ia, Ib, and Ic, with Na₂Cr₂O₇-H₂SO₄ reagent in ether-benzene-tetrahydrofuran resulted in a selective oxidation of the 16-hydroxyl group to afford 20α-hydroxy-16-oxosteroids, Illa, Illb, and Illc. Ilia, Illb, and the 20-acetates, Na and Nb, were treated with TsCl, K₂CO₃, K₂HPO₄ 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.

(Received June 3, 1964)