Summary

In view of the finding that 5α-pregnane-3β,5,6β,16β,20α-pentol (POL) shows an interesting sodium excreting activity similar to that of SEF in the animal test, a number of polyoxygenated pregnanes possessing the hydroxyl or the carbonyl groups at the positions of C-3, C-5, C-6, C-16, and C-20 were synthesized. Syntheses of 3β,5,6β,16α-tetrahydroxy-5α-pregnan-20-one——a hybrid compound of POL and SEF——was also described.

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20. Hayao Nawa, Masao Uchibayashi, Akira Okabori, Katsura Morita, and Takuichi Miki : Synthesis of Polyhydroxysteroids. III.*1 Synthesis of Pregnanetetrols. (1).

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In connection with the studies on the relationship between the structure and the biological activities of 5α-pregnane-3β,5,6β,16β,20α-pentol (POL), an effort has been directed to the investigation of the minimum structural requirements for the activity. This paper deals with the syntheses of five tetrahydroxy analogs which lack either the 5- or the 16-hydroxyl group of POL, namely 5α-pregnane-3β,5,6β,20α-tetrol (IIIa) and its C-20-epimer (IV), 5α-pregnane-3β,6β,16β,20α-tetrol (VIIIa) and its and C-6-epimer (XIa), and the C-20-epimer of XIa i. e. 5α-pregnane-3β,6α,16β,20β-tetrol (XIII).

For the synthesis of compounds IIIa and IV, 3β,5,6β-trihydroxy-5α-pregnan-20-one (II) was selected as an intermediate as shown in Chart 1. Compound II has been pre-

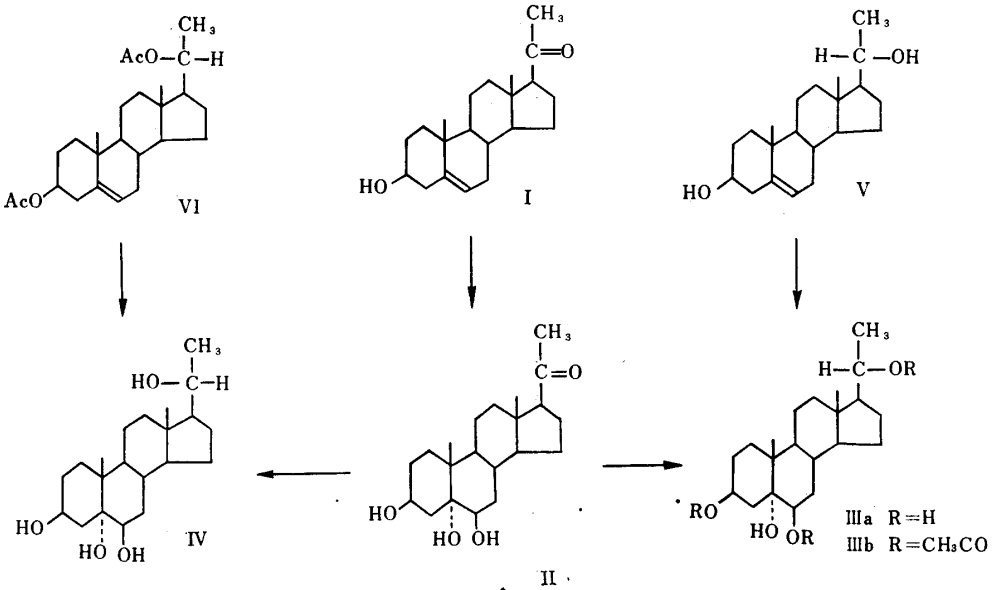

Chart 1.

*1 Part XXVII of Takeda Laboratories' Series entitled "Steroids"; Part XXVI : This Bulletin, **11**, 95 (1963).

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viously prepared by the opening of the epoxide ring of 5,6α-epoxy-3β-hydroxy-5α-pregnan-20-one[1] or by the X-ray irradiation on 3β-hydroxypregn-5-en-20-one (I).[2]

In the present study, the compound II was easily obtained by the treatment of the acetate of I with hydrogen peroxide in acetic acid.

Reduction of II with sodium in ethanol afforded 5α-pregnane-3β,5,6β,20α-tetrol (IIIa) as a crystalline hydrate, whose structure was confirmed by the conversion to the acetate (IIIb). The 20-epimer of IIIa, 5α-pregnane-3β,5,6β,20β-tetrol (IV), were then obtained by the reduction of II with sodium borohydride in methanol. The compounds IIIa and IV thus synthesized were also obtainable by the respective treatment of previously described pregn-5-ene-3β,20α-diol (V)[3] and pregn-5-ene-3β,20β-diol diacetate (VI)[4] with hydrogen peroxide in formic acid.

Synthesis of 5-desoxy-POL (VIII) and its 6-epimer (XI) was conducted by starting with β-chlorogenin (VIIa) and chlorogenin (Xa), both of which have been prepared by Marker and his co-workers[5] by stereospecific reduction of chlorogenone derived from diosgenin. Present experiments revealed that chlorogenone was converted to β-chlorogenin in better yield by treatment with sodium borohydride than by catalytic hydrogenation over platinum oxide reported by Marker. It was also found that the melting point of β-chlorogenin diacetate (VIIb), 175~177°, prepared by the authors was much higher than the recorded value of 118~120°,[5] though VIIb gave the identical infrared spectrum with the one reported in the literature.

As is shown in Chart 2, the compounds VIIa and Xa, and their acetates (VIIb and Xb) were subjected respectively to the oxidative cleavage of the sapogenin side chain with hydrogen peroxide in formic acid, and the desired 5α-pregnane-3β,6β,16β,20α-tetrol (VIIIa) and 5α-pregnane-3β,6α,16β,20α-tetrol (XIa) were obtained. Structures of these

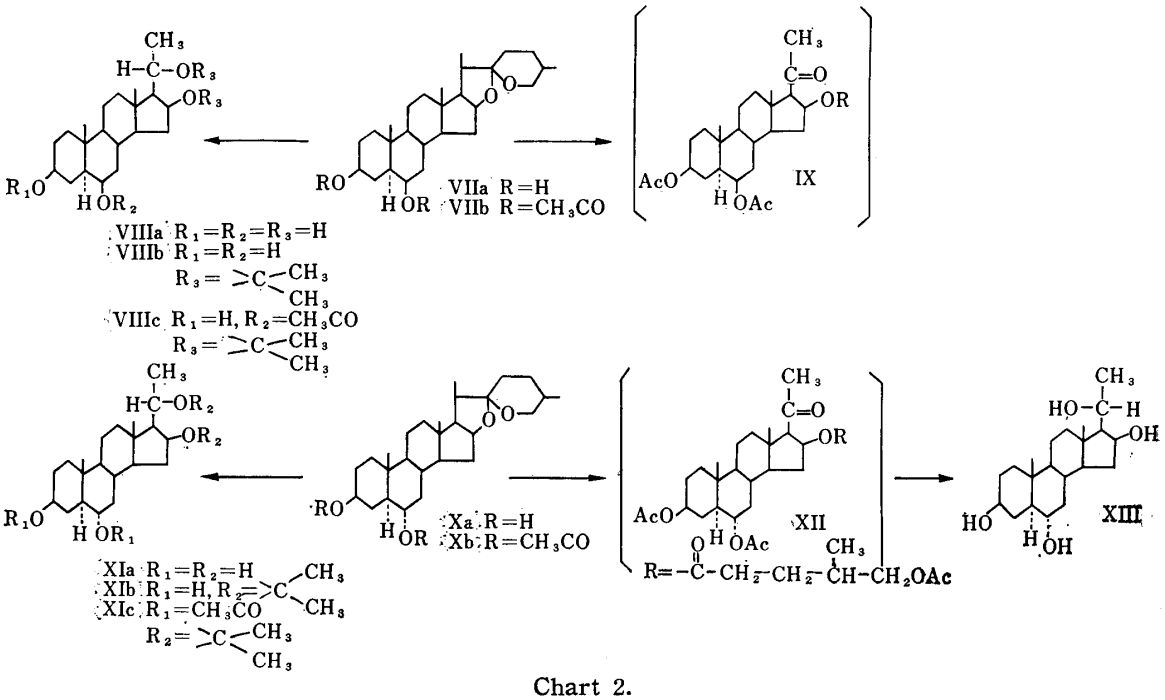

Chart 2.

1) M. Ehrenstein, T. O. Stevens : J. Org. Chem., **6**, 908 (1941).
2) M. Keller, J. Weiss : J. Chem. Soc., **1950**, 2709.
3) R. E. Marker, H. M. Crooks, Jr., E. L. Wittbecker : J. Am. Chem. Soc., **63**, 777 (1941).
4) P. Wieland, K. Miescher : Helv. Chim. Acta, **32**, 1922 (1949); W. Klyne, E. Miller : J. Chem. Soc., **1950**, 1972.
5) R. E. Marker, E. M. Jones, D. L. Turner : J. Am. Chem. Soc., **62**, 2537 (1940).

products were confirmed by the formation of 16β,20α-isopropylidenedioxy derivatives (VIIIb and XIb), and their monoacetate (VIIIc) or diacetate (XIc). The latter two compounds were easily reversible to VIIIa and XIa by hydrolysis with dilute acid.

Synthesis of compounds, the C-20-stereoisomers of VIIIa and XIa was finally attempted. Respective conversion of β-chlorogenin diacetate (VIIb) and chlorogenin diacetate (Xb) into the pseudo compounds, followed by oxidation and splitting the side chain afforded the 20-keto compounds (IX and XII). Reduction of XII with lithium aluminum hydride yielded 5α-pregnane-3β,6α,16β,20β-tetrol (XIII) as expected, while treatment of IX with the same reagent resulted in isolation of VIIIb as the only crystalline product. It was clear therefore that the reduction of the 20-keto group in IX did not show any expected stereospecificity.

Experimental*3

3β,5,6β-Trihydroxy-5α-pregnan-20-one (II)——Two grams of 3β-acetoxypregn-5-en-20-one (acetate of I) was heated with a mixture of 2 cc. of 30% H_2O_2 and 100 cc. of AcOH on a water-bath for 2 hr. Concentration of the reaction mixture to a volume of 5 cc. and an addition of ice water gave pasty mass, which was separated by decantation and washed with water. The product was dissolved in a mixture of 2 g. of KOH in 6 cc. of water and 40 cc. of MeOH and reflexed for 1 hr. After an addition of 5 cc. of water and 2 cc. of AcOH, the solution was concentrated to remove MeOH under vacuum. On treatment with a few amounts of Me_2CO, the residue was crystallized (0.7 g.). Recrystallization from MeOH gave colorless needles, m.p. 250~253°; $[\alpha]_D^{21}$ +59°(c=0.51, $CHCl_3$: MeOH=75:25). *Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found : C, 71.67; H, 9.65.

5α-Pregnane-3β,5,6β,20α-tetrol (IIIa)——a) To a boiling solution of 5 g. of II in 500 cc. of EtOH was added 25 g. of Na in small pieces. After the Na was dissolved, 100 cc. of water and 65 cc. of AcOH were added, and the mixture was concentrated to remove EtOH under vacuum. The precipitates were collected, washed with water, and dried over Na_2SO_4. The product was dissolved in 500 cc. of pyridine and 25 cc. of Ac_2O and allowed to stand overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was chromatographed over 200 g. of Florisil. Elution with a solvent pair of CH_2Cl_2 and AcOEt (9 : 1) yielded about 1.5 g. of crystals which were heated under reflux with 3 g. of KOH, 15 cc. of water, and 70 cc. of MeOH for 1 hr. After an addition of 15 cc. of water and 1.1 cc. of AcOH, MeOH was removed and the resulting precipitate was filtered up, washed with water, and dried over Na_2SO_4. Recrystallization from MeOH and from Me_2CO gave 0.8 g. of colorless needles, m.p. 224~225°; $[\alpha]_D^{23}$ −9°(c=0.49, $CHCl_3$: MeOH=88:12). *Anal.* Calcd. for $C_{21}H_{36}O_4 \cdot \frac{1}{2}H_2O$: C, 69.62; H, 10.31. Found : C, 69.95; H, 10.43.

b) A mixture of 780 mg. of pregn-5-ene-3β,20α-diol (V) in 5 cc. of 30% H_2O_2 and 50 cc. of 85% HCOOH was kept at 70~75° for 2 hr. The mixture was concentrated to a volume of 10 cc. and treated with ice water. The precipitates were taken up by filtration. washed with water, and dissolved in 6 cc. of water and 35 cc. of MeOH containing 1.5 g. of KOH. The solution was heated on a water bath for 1 hr., then mixed with 5 cc. of water and 1.4 cc. of AcOH and concentrated under vacuum. The residue was recrystallized from MeOH and from Me_2CO yielding 400 mg. of colorless needles, m.p. 225°. *Anal.* Calcd. for $C_{21}H_{36}O_4 \cdot \frac{1}{2}H_2O$: C, 69.62; H, 10.31. Found : C, 69.60; H, 10.15. This compound was confirmed to be identical with the sample obtained in (a) by mixed melting point determination and comparison of IR spectrum.

5α-Pregnane-3β,5,6β,20α-tetrol 3,6,20-triacetate (IIIb)——Acetylation of 50 mg. of IIIa with 5 cc. of pyridine and 3 cc. of Ac_2O was effected in the usual manner. Recrystallization of the product from MeOH furnished colorless thin plates, m.p. 202~204°. *Anal.* Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found : C, 67.97; H, 8.66.

5α-Pregnane-3β,5,6β,20β-tetrol (IV)——a) To a solution of 5 g. of II in 500 cc. of MeOH was added 1 g. of $NaBH_4$ in small portions with stirring at room temperature. The mixture was stirred at the same temperature for 3 hr. and left overnight. After an addition of 150 cc. of water, the mixture was acidified with conc. H_2SO_4 and concentrated to remove MeOH under vacuum. The precipitate was collected, washed with water, and dried over Na_2SO_4. The crude product was dissolved in MeOH and after a separation of a few insoluble substance by filtration the solution was evaporated. The residue was dissolved in 70 cc. of pyridine and 40 cc. of Ac_2O and left overnight. After evaporation of the solvents, the resulting syrup was chromatographed over 100 g. of Florisil. Elution with a

*3 All m.p.s are uncorrected. All pure substances prepared were examined by infrared spectrum.

solvent mixture of CH_2Cl_2 and AcOEt (9 : 1) gave about 2 g. of crystats which were heated under reflux with 3 g. of KOH, 15 cc. of water, and 70 cc. of MeOH for 1 hr. After an addition of 15 cc. of water and 1.1 cc. of AcOH, the mixture was concentrated to give precipitates, which were filtered up and dried over Na_2SO_4. Crystallization from MeOH afforded 1 g. of colorless prisms, m.p. 274～276°; $[\alpha]_D^{22}$ $-13.5\pm2.5°$ (c=0.38, $CHCl_3$: MeOH=67:33). *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found : C, 71.70; H, 10.20.

b) A mixture of 2.02 g. of pregn-5-ene-3β,20β-diol diacetate (VI) in 10 cc. of 30% H_2O_2 and 100 cc. of 85% HCOOH was maintained at 70～75° for 2 hr. The mixture was concentrated to a volume of 10 cc. and treated with ice water. The solid deposited was collected and washed with water. The product was dissolved in 15 cc. of water and 70 cc. of MeOH containing 3 g. of KOH and heated on a water bath for 1 hr. The solution was mixed with 15 cc. of water and 1.1 cc. of AcOH, and concentrated to remove MeOH under vacuum. The precipitates were filtered up, washed with water, and dried over Na_2SO_4. By the treatment of the solid obtained with about 40 cc. of Me_2CO colored contaminants was dissolved away. The insoluble portion was recrystallized from MeOH to give 0.8 g. of colorless, transparent prisms, which soften at 100° and melt at 273～274°. The material dried *in vacuo* at 120° for 6 hr. is opaque and shows the melting point of 274～276. *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found : C, 71.86; H, 10.30. This product was confirmed to be identical with the sample prepared in (a) by mixed melting point determination and comparison of IR spectrum.

β-Chlorogenin (VIIa)——To a solution of 4.3 g. of chlorogenone in 600 cc. of MeOH was added 7.6 g. of $NaBH_4$ in small portions with stirring at room temperature. The mixture was stirred at the same temperature for 1 hr., left for 24 hr. and then refluxed for 2 hr. The solution was mixed with 150 cc. of water, acidified with conc. H_2SO_4, and evaporated to remove MeOH under vacuum. The resulting mixture of the product in water was extracted with Et_2O, and the extract was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from Me_2CO yielded 2.9 g. of colorless needles, m.p. 241～244°. *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found : C, 75.33; H, 10.12.

β-Chlorogenin Diacetate (VIIb)——A 3.2 g. sample of β-chlorogenin was acetylated with 60 cc. of pyridine and 30 cc. of Ac_2O in the conventional way. Recrystallization of the product from MeOH furnished 2.96 g. of colorless prisms which softened at 150～155° and melted at 175～177°. *Anal.* Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found : C, 72.19; H, 9.25.

5α-Pregnane-3β,6β,16β,20α-tetrol (VIIIa)——a) A solution of 2 g. of VIIa in 10 cc. of 30% H_2O_2 and 100 cc. of 85% HCOOH was heated at 70° for 2 hr. and concentrated to a volume of 50 cc under vacuum. On addition of 500 cc. of water to the solution, precipitates deposited were taken up by filtration and hydrolyzed under reflux with 5 g. of KOH, 20 cc. of water, and 80 cc. of MeOH. The reaction mixture was diluted with water, neutralized with dil. HCl, and concentrated. The crystalline residue was collected, washed with water, and dried over Na_2SO_4. Recrystallization from Me_2CO-CCl_4 gave 1.2 g. of colorless prisms, m.p. 236～237°. *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found : C, 71.67; H, 10.04.

b) A solution of 3.1 g. of VIIb in 20 cc. of 30% H_2O_2 and 200 cc. of 99% HCOOH was kept 70° for 2 hr. and concentrated to a volume of 50 cc under vacuum. Similar treatments as (a) afforded 1.9 g. of crystals, m.p. 235～238°.

c) To a solution of 300 mg. of 16β,20α-isopropylidenedioxy-5α-pregnane-3β,6β-diol (VIIIb) in 20 cc. of EtOH was added 20 cc. each of 10% HCl and EtOH, and mixture was refluxed for 30 min. An addition of water, neutralization with aq. KOH followed by the evaporation of EtOH furnished crystalline precipitates, which were filtered up, washed with water, and dried over Na_2SO_4. Recrystallization from MeOH-Me_2CO yielded 200 mg. of crystals, m.p. 235～238°. The products obtained in (b) and (c) were both identical with the sample prepared in (a) confirmed by comparison of IR spectrum and mixed melting point determination.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,6β-diol (VIIIb)——An addition of 0.1 cc. of 37% BF_3 etherate to a suspension of 230 mg. of VIIa in 30 cc. of Me_2CO resulted in a clear solution which was allowed to stand at room temperature for 30 min. After an addition of 1 cc. of pyridine, the solution was concentrated under vacuum and the residue was mixed with water. The precipitates were collected, washed with water, and dried over Na_2SO_4. Recrystallization from MeOH-Me_2CO afforded 210 mg. of colorless prisms, m.p. 262～264°. *Anal.* Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found : C, 73.20; H, 10.35.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,6β-diol 6-acetate (VIIIc)——A 600 mg. portion of VIIIb was heated at 80° with a mixture of 20 cc. of pyridine and 10 cc. of Ac_2O for 3 hr. and treated in the usual manner. Since crystallization of the product was unsuccessful, it was heated under reflux with a mixture of 500 mg. of KOH in 1 cc. of water and 70 cc. of MeOH for 3 hr. After usual treatments the crystalline product (450 mg.) was recrystallized from Me_2CO to give colorless needles, m.p. 190～191°. *Anal.* Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found : C, 71.66; H, 9.70. The IR spectrum was compatible with the structure.

5α-Pregnane-3β,6α,16β,20α-tetrol (XIa)——A solution of 3.7 g. of Xa in 20 cc. of 30% H_2O_2 and 200 cc. of 99% HCOOH was heated at 70° for 2 hr. and concentrated to a volume of 50 cc. under vacuum. On addition of 400 cc. of water to the mixture, precipitates deposited were collected and hydrolyzed under reflux with 10 g. of KOH, 40 cc. of water, and 160 cc. of MeOH. The reaction mixture was diluted with water, neutralized with dil. HCl, and concentrated to remove MeOH under vacuum. The crystalline residue was filtered up, washed completely with water, and dried over Na_2SO_4. Recrystallization from MeOH-Me_2CO yielded 2.5 g. of colorless prisms, m.p. 262~264°. *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.22; H, 10.39.

b) A solution of 0.96 g. of Xb in 10 cc. of 30% H_2O_2 and 100 cc. of 99% HCOOH was heated at 70° for 2 hr. and concentrated to a volume of 50 cc. under vacuum. Similar treatments to (a) gave 0.59 g. of crystals, m.p. 262~264°.

c) To a solution of 250 mg. of 16β,20α-isopropylidenedioxy-5α-pregnane-3β,6α-diol (XIb) in 20 cc. of EtOH was added a mixture of 20 cc. each of 10% HCl and EtOH and refluxed for 30 min. The mixture was diluted with water, neutralized with aq. KOH, and concentrated to remove EtOH under vacuum. The crystalline precipitates were collected, washed with water, dried over Na_2SO_4, and recrystallized from MeOH-Me_2CO to furnish 170 mg. of crystals, m.p. 262~264°.

Identity of the products obtained by the methods (a), (b), and (c) was proved by mixed melting point and IR spectrum.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,6α-diol (XIb)——A suspension of 120 mg. of XIa in 20 cc. of Me_2CO was mixed with one drop of conc. HCl. Stirring and warming in a water bath resulted in a clear solution which was left at room temperature for 30 min. Addition of one drop of pyridine and concentration *in vacuo* afforded a crystalline residue which was filtered up, dried over Na_2SO_4, and recrystallized from MeOH-Me_2CO. The product was obtained as colorless prisms, m.p. 268~270°, weighing 100 mg. *Anal.* Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.56; H, 10.05.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,6α-diol diacetate (XIc)——A sample of 240 mg. of XIb was treated with 5 cc. of Ac_2O and 10 cc. of pyridine at 80° for 3 hr. By the usual treatment, the product was recrystallized from MeOH to give 220 mg. of colorless prisms, m.p. 167~169°. *Anal.* Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.41; H, 9.34.

An attempt to obtain 5α-Pregnane-3β,6β,16β,20β-tetrol from β-Chlorogenin Diacetate (VIIb): Formation of 16β,20α-Isopropylidenedioxy-5α-pregnane-3β,6β-diol (VIIIb)——Ten grams of VIIb was gently refluxed with 0.5 g. of pyridine hydrobromide in 20 cc. of Ac_2O for 3.5 hr. After a dilution with 100 cc. of AcOH, the reaction mixture was kept at 11~13°, to which was added a mixture of 4 g. of CrO_3 5 cc. of water, and 15 cc. of AcOH with in 15 min. After stirring for further 15 min. at the same temperature, then later for 30 min. at room temperature, the mixture was treated with 10 cc. of water containing 2.5 g. of $NaHSO_3$ and evaporated under vacuum. The residue was mixed with water and extracted with Et_2O, which was washed with aq. Na_2CO_3 and water, dried over Na_2SO_4, and evaporated. The syrupy residue was dried completely over P_2O_5.

The crude 3β,6β,16β-trihydroxy-5α-pregnan-20-one 3,6-diacetate 16-(4-methyl-5-acetoxy valerate) (IX) thus obtained was dissolved, without further purification, in 300 cc. of Et_2O and the solution was added dropwise to a mixture of 7.5 g. of $LiAlH_4$ in 500 cc. of Et_2O with stirring at room temperature. After stirring for 2 hr. at room temperature, the mixture was left overnight and then refluxed gently for 8 hr. The excess of $LiAlH_4$ was decomposed by the addition of 10 cc. of water, and the reaction mixture was treated with 300 cc. of 5% H_2SO_4 and evaporated *in vacuo* to remove Et_2O. The insoluble product was collected, washed with water, and dissolved in 170 cc. of hot MeOH. Seperating from a few insoluble materials, the mother liquor was evaporated to dryness.

The residue (6 g.) was acetylated with 140 cc. of pyridine and 80 cc. of Ac_2O at 80° for 3 hr. The mixture was evaporated under vacuum and the residual thick paste was chromatographed over 200 g. of Florisil. Elution with CH_2Cl_2 gave 4.62 g. of syrup, which was re-chromatographed over 100 g. of the same absorbent. After washing with 200 cc. of benzene, the column was developed with 200 cc. of benzene-AcOEt mixtures (95 : 5, 90 : 10, 85 : 15), which eluted 3.54 g. of a non-crystalline substance.

The above product was heated under reflux with 5 g. of KOH in 30 cc. of water and 120 cc. of MeOH for 2 hr. Addition of 6 cc. of AcOH, concentration *in vacuo* followed by addition of water afforded an oil which was dried under vacuum. The oily material was dissolved in 150 cc. of Me_2CO and stirred with 0.5 cc. of 37% BF_3 etherate for 1 hr. at room temperature. After addition of 0.5 cc. of pyridine, the mixture was evaporated and the residue was dissolved in dil. MeOH. On standing, crystals separated (1.45 g.) were purified by recrystallization from MeOH-Me_2CO to give colorless prisms, m.p. 260~262°. This compound was found identical with VIIIb prepared by the other route by mixed melting point and IR spectrum.

The non-crystalline fraction (ca. 1 g.) separated from the crystals was re-acetylated and chromatographed over 30 g. of Florisil. Fractions (780 mg.) eluted by CH_2Cl_2 were again hydrolyzed. No crystalline substance was detected in the hydrolyzate remained as an oil.

5α-Pregnane-3β,6α,16β,20β-tetrol (XIII)——A solution of 5 g. of Xb and 0.25 g. of pyridine hydrobromide in 10 cc. of Ac_2O was heated under gentle reflux for 3.5 hr. and diluted with 60 cc. of AcOH. To this solution was added at 11~13° a mixture of 2 g. of CrO_3 in 2.5 cc. of water and 7.5 cc. of AcOH within 15 min. After stirring at room temperature for 40 min., the reaction mixture was treated with aq. $NaHSO_3$ (1.25 g.) and evaporated under vacuum. The residue was mixed with water and extracted with benzene, which was washed with aq. Na_2CO_3 and water, dried over Na_2SO_4, and evaporated. The syrupy residue was dried completely over P_2O_5.

The crude 3β,6α,16β--trihydroxy-5α-pregnan-20-one 3,6-diacetate 16-(4-methyl-5-acetoxyvalerate) (XII) thus obtained was dissolved, without further purification, in 100 cc. of Et_2O and the solution was added dropwise to a mixture of 3.75 g. of $LiAlH_4$ in 200 cc. of Et_2O at room temperature. The reaction mixture was stirred for 8 hr. at the same temperature and refluxed for 3 hr. Usual treatments yielded a powdery product which was acetylated with 70 cc. of pyridine and 40 cc. of Ac_2O at 80° for 3 hr. The mixture was poured into water and the powdery acetate obtained was chromatographed over 100 g. of Florisil. Elution with CH_2Cl_2 gave 1.9 g. of thick paste which was rechromatographed with 30 g. of the same absorbent. After washing with benzene, the column was developed with benzene-AcOEt (95 : 5) which eluted 1 g. of non-crystalline fractions.

This substance was hydrolyzed under reflux with 0.5 g. of KOH in 1.5 cc. of water and 40 cc. of MeOH for 2 hr. Treatment of the reaction mixture in the usual way and recrystallization from Me_2CO and then from MeOH-Me_2CO afforded 850 mg. of colorless prisms, m.p. 242~244°; $[\alpha]_D^{20}$ +34° (c=0.36, $CHCl_3$+10% MeOH). *Anal.* Calcd. for $C_{21}H_{35}O_4 \cdot {}^6/_5H_2O$: C, 68.62; H, 10.33. Found : C, 68.62; H, 10.22.

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Summary

5α-Pregnane-3β,5,6β,20α-tetrol (IIIa), 5α-pregnane-3β,5,6β,20β-tetrol (IV), 5α-pregnane-3β,6β,16β,20α-tetrol (VIIIa), 5α-pregnane-3β,6α,16β,20α-tetrol (XIa), and 5α-pregnane-3β,6α,16β,20β-tetrol (XIII) were synthesized according to the schemes shown in Chart 1 and Chart 2.

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21. Masanobu Terasaka,*1 Kazuko Yamamoto (neé Narahashi),*1 and Yutaka Kawazoe*2 : Alkaloids of Root-bark of *Orixa japonica* Thunb. XII.*3 Nuclear Magnetic Resonance Study of N-Methylorixidinine, N-Methylisoorixidinine, and N-Methylorixidine.

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The structures of N-methylorixidinine, N-methylisoorixidinine, and N-methylorixidine, derived from orixine,[1] have been proposed on chemical and spectroanalytical evidences as I, III, and V, respectively, as shown in Chart 1.[2] It will be shown in this paper that the analysis of the nuclear magnetic resonance spectra of these com-

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*3 Part XI. K. Narahashi : This Bulletin, **10**, 792 (1962).
1) M. Terasaka : *Ibid.*, **8**, 523 (1960).
2) K. Narahashi : *Ibid.*, **10**, 792 (1962).