UDC 547.92.07

19. Takuichi Miki, Katsura Morita, Shunsaku Noguchi, Toyokazu Kishi, Kentaro Hiraga, and Hayao Nawa : Synthesis of Polyhydroxysteroids. II.*1 Syntheses of Isomeric 5α-Pregnane-3,5,6,16,20-pentols and Related Compounds.

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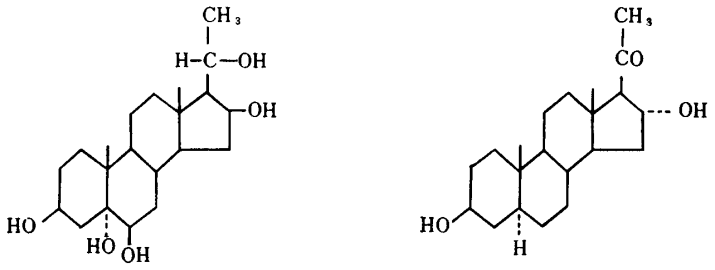
In view of the finding that 5α-pregnane-3β,5α,6β,16β,20α-pentol (POL)[1] shows an interesting sodium excreting activity similar to that of Ciba's SEF[2] in the animal test employing adrenalectomized rats and that the structure of both substances is of close similarity, syntheses of a number of polyhydroxypregnanes possessing the hydroxyl or the carbonyl groups at positions C-3, C-5, C-6, C-16, and C-20 were attempted in our Laboratories.

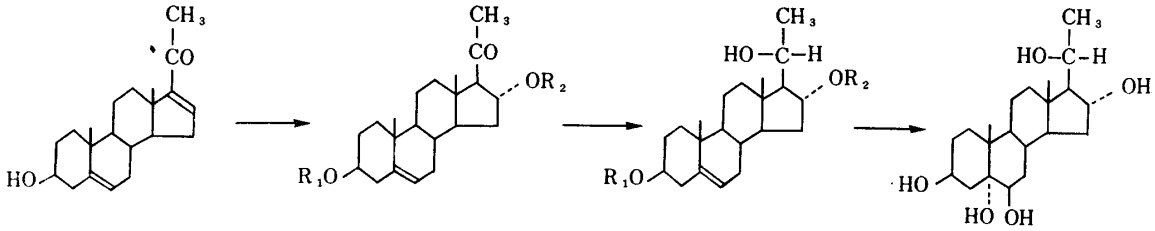


POL SEF

Chart 1.

In this paper, the syntheses of these polyhydroxy pregnanes from diosgenin as well as an alternative synthesis of SEF are described.

The physiological activities of these steroids will be reported elsewhere by Nakao *et al.* 3β-Hydroxypregna-5,16-diene-20-one (I), which has been obtained from diosgenin by the modified Marker's method,[3] was treated with a small amount of sodium ethoxide



(I)

(IIa) R_1=OH, R_2=$CH_2C_6H_5$
(IIb) R_1=Ac, R_2=$CH_2C_6H_5$
(IIc) R_1=Ac, R_2=H
(IId) R_1=Ac, R_2=Ac

(IIIa) R_1=Ac, R_2=H
(IIIb) R_1=Ac, R_2=Ac

(IV)

Chart 2.

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*1 This paper constitutes Part XXVI of Takeda Laboratories' series entitled "Steroids"; Part XXV: This Bulletin, **11**, 90(1963).

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1) T. Nakao, K. Hiraga, T. Saito, Y. Murayama : Jikeikai Medical Journal., **6**, 1-6 (1959).
2) R. Neher, P. Desaulles, E. Vischer, P. Wieland, A. Wettstein : Helv. Chim. Acta, **41**, 1667 (1958).
3) A.F.B. Cameron, R.M. Evans, J.C. Hamlet, J.S. Hunt, P.G. Jones, A.G. Long : J. Chem. Soc., **1955**, 2807.

in purified benzyl alcohol to yield 3β-hydroxy-16α-benzyloxypregn-5-en-20-one (IIa),[4] which was acetylated and the resulting 3-acetate IIb was subjected to hydrogenolysis giving 3β,16α-dihydroxypregn-5-en-20-one 3-acetate (IIc)[5] It was, however, hydrolyzed to dehydro-SEF in poor yield under the usual hydrolytic conditions, and hence the approach to the synthesis of SEF by this route proved to be unsatisfactory.

Then an attempt was made on reduction of 3β-formyloxy-16α,17α-epoxypregn-5-en-20-one (Vb) with chromous acetate.[6]

The formyl ester Vb, which was obtained from the free alcohol Va by the reaction of phosgene-dimethylformamide complex,[7] was treated with chromous acetate in acetic acid to yield 3β,16α-dihydroxypregn-5-en-20-one 3-formate (VIIb). It was hydrolyzed smoothly to free alcohol VIIa, which was finally hydrogenated to SEF by the catalytic hydrogenation.

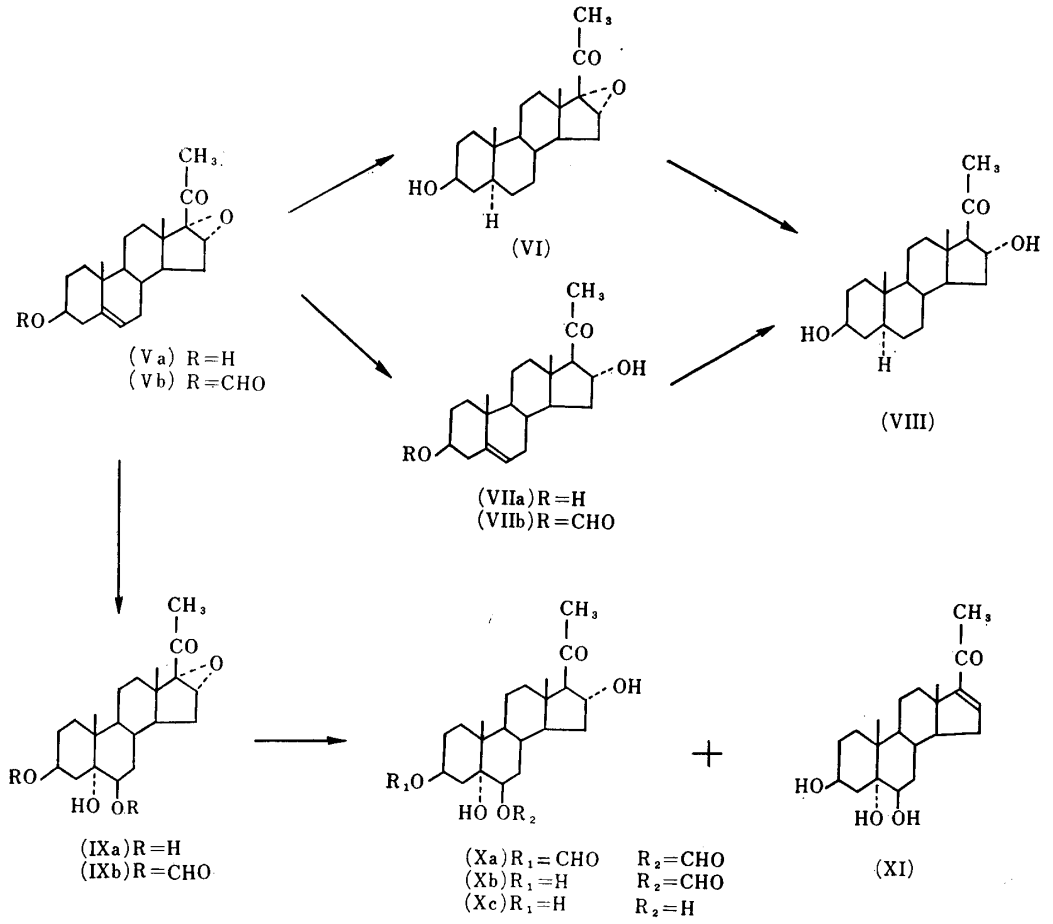

Chart 3.

Treatment of 16α,17α-epoxy-3β-formyloxypregn-5-en-20-one (Vb) with hydrogen peroxide in 85% formic acid at room temperature gave 16α,17α-epoxy-3β,5,6β-trihydroxy 5α-pregnan-20-one 3,6-diformate (IXb), which, on reduction with chromous acetate, afforded 3β,6β-diformyloxy-5,16α-dihydroxy-5α-pregnan-20-one (Xa). On hydrolysis with methanol-potassium hydrogen carbonate at room temperature Xa afforded a mono-formyl ester, to which was assigned the 6β-formyloxy structure Xb.

4) H. Hirschmann, F.B. Hirschmann, M.A. Daus : J. Am. Chem. Soc., **74**, 539 (1952).
5) H. Hirschmann, F.B. Hirschmann, J.W. Corcoran : J. Org. Chem., **20**, 572 (1955).
6) W. Cole, P.L. Julian : *Ibid.*, **19**, 131 (1954).
7) K. Morita, S. Noguchi, M. Nishikawa : This Bulletin, **7**, 896 (1959).

The free alcohol Xc was obtained by the hydrolysis under a slightly vigorous condition employing potassium carbonate in place of potassium hydrogen carbonate.

In order to obtain an isomer of POL, II c was subjected to reduction with sodium borohydride followed by performic acid oxidation and hydrolysis to yield 5α-pregnane-3β,5,6β,16α,20β-pentol (IV).

In another route of our syntheses to the epimeric 5α-pregnanepentols, diosgenin XII was employed as the starting material. XII was converted to the diosone diacetate [3β,16β-dihyroxypregn-5-en-20-one 3-acetate 16-(4-methyl-5-acetoxyvalerate)], which was reduced with lithium aluminum hydride to yield pregn-5-ene-3β,16β,20β-triol (XIVa).[8]

An attempt to oxidize XIVa with hydrogen peroxide in 85% formic acid was unsuccessful owing to an extremely sparing solubility of XIVa in the solvent. However, the triacetate XIVb underwent successful oxidation, followed by saponification to yield 5α-pregnane-3β,5,6β,16β,20β-pentol (XV), which is the epimer of POL at C-20.

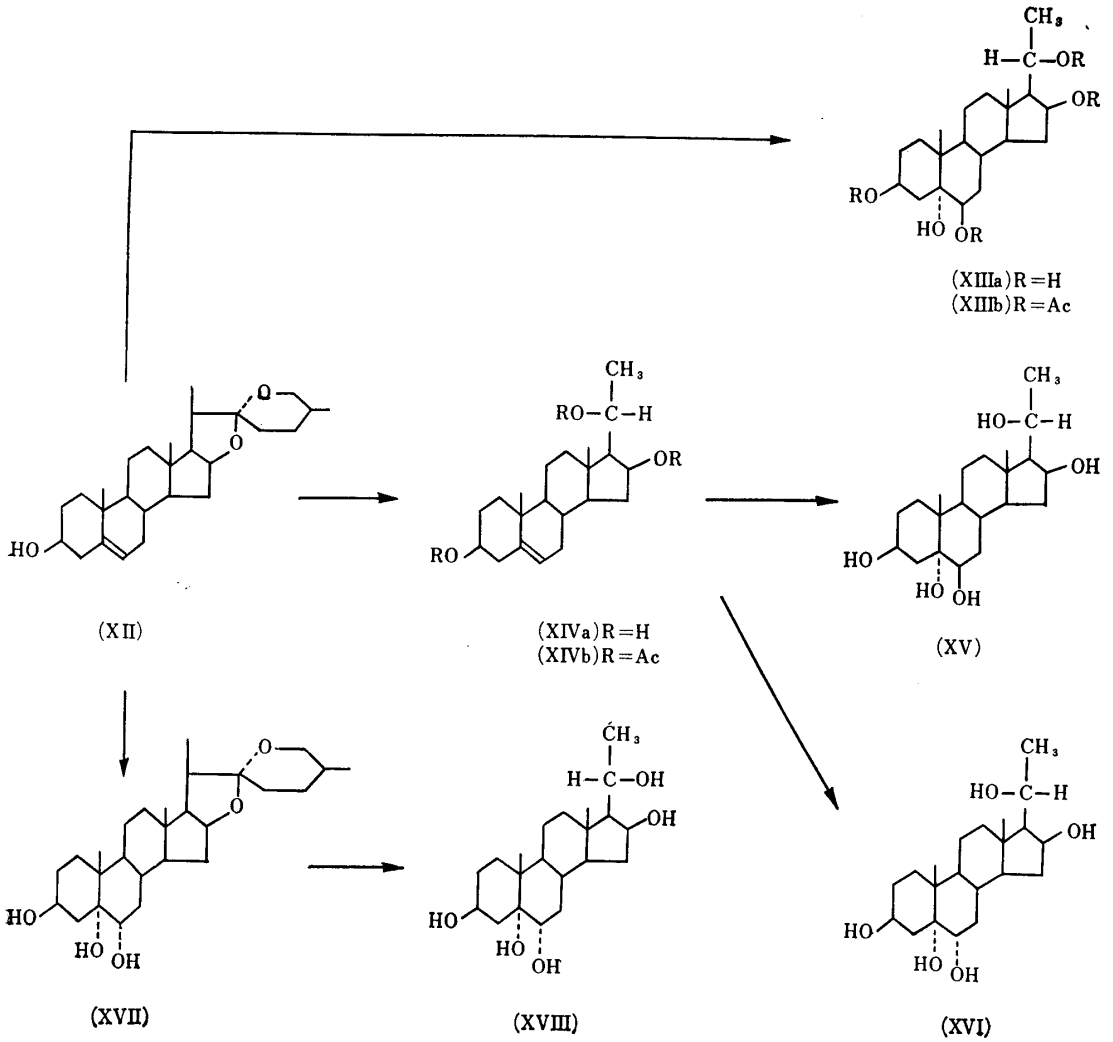

Chart 4.

Another epimer XVI of POL isomeric at both C-6 and C-20 was obtained by *cis*-hydroxylation of XIVb with osmium tetroxide followed by hydrolysis.

The C-6 epimer XVIII of POL was prepared from 5α,25D-spirostan-3β,5,6α-triol (XVII)

8) B. Löken, S. Kaufmann, G. Rosenkranz, F. Sondheimer : J. Am. Chem. Soc., 78, 1738 (1956).

by the usual procedure of oxidative elimination of the sapogenin side chain with performic acid followed by hydrolysis.

An attempt to prepare XVIII from 3β,16β,20α-triacetoxypregn-5-ene[9] by osmium tetroxide oxidation followed by saponification was unsuccessful, for no steroid-osmium tetroxide adduct precipitated on prolonged standing of the reaction mixture.

Thus the four epimeric 5α-pregnane-3β,5,6,16β,20-pentols (POL=XIIIa), (XV), (XVI), XVIII and 5α-pregnane-3β,5,6β,16α,20β-pentol (IV) as well as 3β,5,6β,16α-tetrahydroxy-5α-pregnan-20-one (Xc), which is considered to be a hybrid compound of POL and SEF,

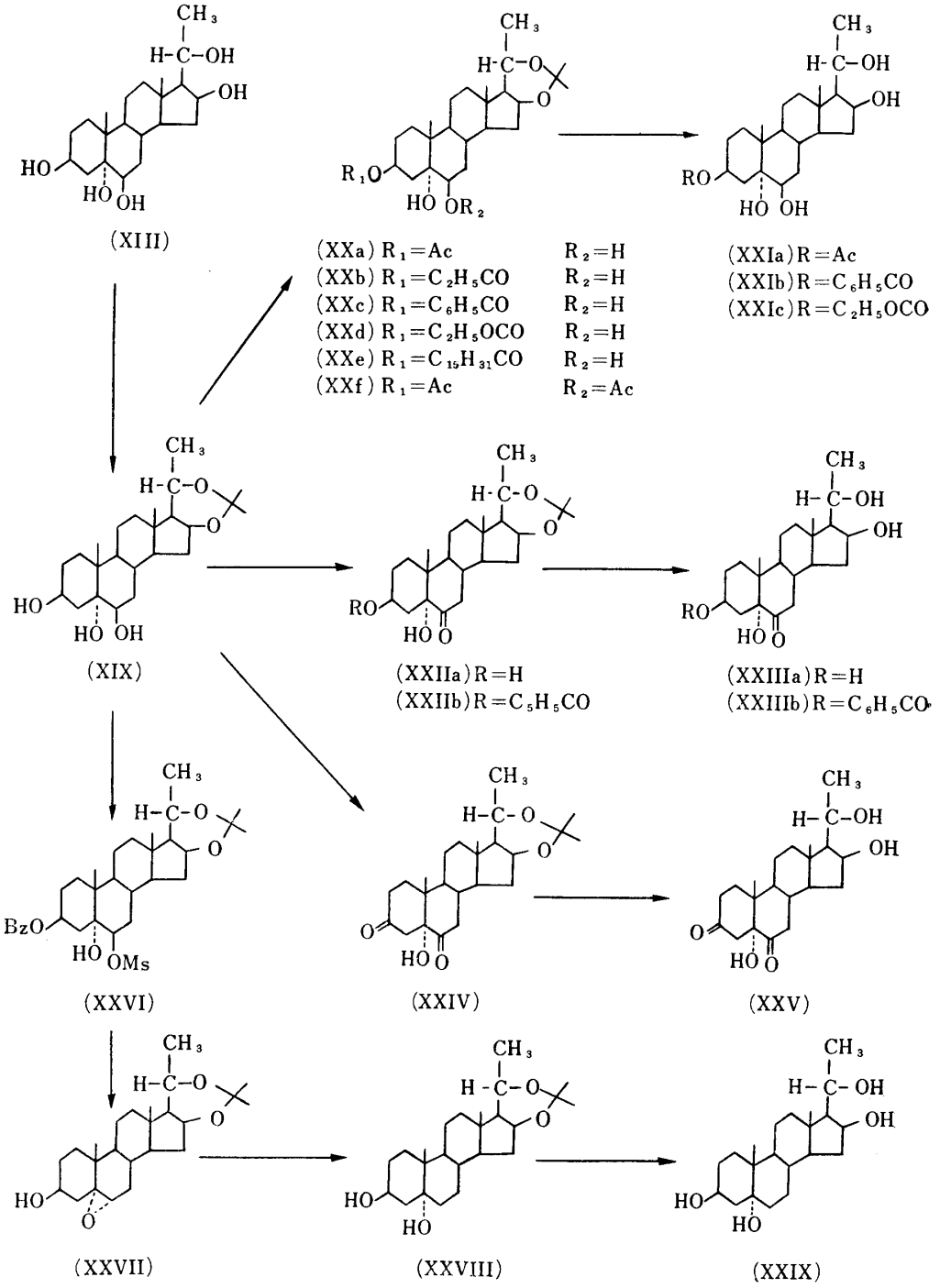

Chart 5.

9) Part XXV of this series. This Bulletin, **11**, 90 (1963).

have been synthesized; the physiological evaluation of these compounds being undertaken by Nakao and co-workers.

It is worthwhile to note that these pregnanepentols show a property of giving hydrated crystal, from which the water is particularly difficult to be removed under an ordinary drying condition. However, the anhydrous pentols were obtained by repeating the following procedure : A solution of the hydrated crystals in methanol and carbon tetrachloride was boiled on a steam bath at an atmospheric pressure to distil off the solvents and water under azeotropic condition.

Further syntheses of polyoxygenated pregnanes were carried out starting from POL XIIIa which was prepared by performic acid oxidation of XII as follows : On treatment with acetone and a small amount of boron trifluoride etherate, POL XIIIa afforded the 16β,20α-acetonide (XIX),*3 which was esterified with a number of acid anhydrides or acid chlorides under various conditions to yield the 3-monoesters or the 3,6-diesters. The acetonides of these esters, on heating with aqueous acetic acid, were converted to the 16β,20α-diols.

Oxidation of XIX with NBS afforded the monoketone XXIIIa, whereas chromic acid oxidation of XIX in pyridine at an elevated temperature gave the diketone XXIV; both ketones were hydrolyzed (to XXIIIa and XXV) by boiling with aqueous acetic acid.

When the acetonide XIX was benzoylated and then treated with methanesulfonyl chloride in pyridine, the principal product was XXVI, which was hydrolyzed to α-epoxide XXVII (with alkali in methanol).

The α-epoxy structure of XXVII was confirmed by converting this into XXIX, which was also prepared from 5α,25D-spirostan-3β,5-diol*4 by performic acid oxidation followed by hydrolysis.

Experimental*5

3β-Hydroxy-16α-benzyloxypregn-5-en-20-one acetate (IIb)——3β-Acetoxy-16α-benzyloxypregn-5-en-20-one (IIb) (m.p. 131~132°) was obtained from 3β-hydroxypregna-5,16-dien-20-one (I) by the method reported by H. Hirschmann *et al.*[4] *Anal.* Calcd. for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found C, 77.37; H, 8.77.

3β,16α-Dihidroxypregn-5-en-20-one 3-acetate (IIc)——A mixture of 5.0 g. of IIb and 1.65 g. of 5% Pd-C in 1,000 cc. of 99% EtOH were shaken in an atmosphere of H_2 for 45 min. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The crystalline residue dissolved in CH_2Cl_2-hexane mixture was chromatographed over Celite-silica (1 : 1). Elution with benzene-Et_2O (2 : 1) afforded firstly a substance melting at 135~145° and later (IIc). Recrystallization of the latter from benzene raised the m.p. to 167~169°; yield 1.7 g. (42%). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found : C, 73.51; H, 9.11.

3β,16α-Dihydroxypregn-5-en-20β-ol diacetate (IIIb)——One gram of IIc was acetylated with Ac_2O and pyridine as usual and the resulting IId (m.p. 170~173°) was dissolved in 30 cc. of MeOH. To this was added 0.5 g. of $NaBH_4$ and the solution allowed to stand overnight in an ice-box separating colorless needles, which were collected and recrystallized from MeOH; yield 0.5 g.; m.p. 184~186°. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.77; H, 9.09. Found : C, 71.49; H. 9.26.

5α-Pregnane-3β,5,6β,16α,20β-pentol (IV)——To a solution of 0.8 g. of IIc in 50 cc. of MeOH was added 0.4 g. of $NaBH_4$ and the mixture was allowed to stand overnight at room temperature. Addition of 50 cc. of water and concentration under reduced pressure gave a crystalline residue, m.p. 220~230° (decomp.); IIIa. The crude IIIa dissolved in 20 cc. of 85% HCOOH was treated with 2 cc. of 30% H_2O_2 and the mixture was kept for 2 hr. at room temperature.

Water was added and the precipitate was hydrolyzed with K_2CO_3 in aq. MeOH. After acidification with *N* HCl, the mixture was extracted with AcOEt and the organic layer was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization from AcOEt with addition of CCl_4 and

*3 Pregnane-16β,20α-diols form the cyclic metadioxane compounds; details of this novel reaction will be described in the subsequent paper (part V?).

*4 5α,25D-spirostan-3β,5-diol was prepared from diosgenin α-oxide by the known method. (Pl. A. Plattner, H. Heusser, M. Feuer : Helv. Chim. Acta, **32**, 587 (1949)).

*5 All melting points are uncorrected.

evaporation of the solvent under azeotropic condition*6 gave IV melting at 264~266° (decomp.); yield 0.3 g. (38% from IIc), which was demonstrated by elemental analysis to contain ¼ mole of water of crystallization. *Anal.* Calcd. for $C_{21}H_{36}O_5 \cdot \frac{1}{4}H_2O$: C, 67.65; H, 9.64. Found : C, 67.68; H, 9.72.

16α,17α-Epoxy-3β-hydroxy-5α-pregnan-20-one (VI)——Va (3.7 g.) dissolved in 100 cc. of AcOH was shaken with 1 g. of 5% Pd-C in an atmosphere of H_2. When 280 cc. of H_2 was consumed within 30 min., the rate of reaction decreases rapidly.

After shaking for another hour, the catalyst was filtered and the filtrate evaporated afforded VI, melting 175~181°. Recrystallization from MeOH raised the m.p. to 183~184°; yield, 2.0 g.

3β,16α-Dihydroxypregn-5-en-20-one (VIIa)——A solution of 15 g. of 3β-formyloxy-16α,17α-epoxypregn-5-en-20-one (Vb)[7] in 300 cc. of AcOH was shaken in an atmosphere of CO_2 with 30 g. of chromous acetate.

After 48 hr., water was added and the mixture was extracted three times with CH_2Cl_2 and the combined extract was washed with water, dried and evaporated giving crystalline product, which was dissolved in CH_2Cl_2, passed through a column of Florisil and evaporated to give 8.0 g. of crude VIIb.

This crude ester was hydrolyzed with K_2CO_3 in MeOH at room temperature affording 6.0 g. of VIIa melting at 237~242°. Recrystallization from MeOH raised the m.p. to 241~243°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found : C, 75.75; H, 9.70.

3β,16α-Dihydroxy-5α-pregnan-20-one (VIII)——VIIa (400 mg.) in AcOH was reduced with Pd-C, H_2 at room temperature, giving 300 mg. of VIII melting at 250~252°.

Identity with an authentic specimen was confirmed by the mixed m.p. determination and the comparison of IR specrtra.

16α,17α-Epoxy-3β,5,6β-trihydroxy-5α-pregnan-20-one 3,6-diformate (IXb)——To a suspension of 20 g of 16α,17α-epoxy-3β-formyloxypregn-5-en-20-one (Vb) in 20 cc. of 85% HCOOH was added 2 cc. of 30% H_2O_2 and the mixture was allowed to stand at 30° for 1.5~2.0 hr. with occasional shaking, during which a clear solution was resulted. Water was added to the solution and the precipitated crystals of IXb were filtered, washed with water and crystallized from MeOH; yield 1.1 g.; m.p. 244~247°.

Recrystallization from MeOH raised the m.p. to 246~248°. *Anal.* Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found : C, 65.68; H, 7.57.

Hydrolysis of IXb with K_2CO_3 in aq. MeOH afforded the free alcohol IXa melting at 223~225°. *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found : C, 69.04; H, 8.64.

3β,5,6β,16α-Tetrahydroxy-5α-pregnan-20-one 3,6-diformate (Xa)——A solution of 2.4 g. of the epoxide IXb in 500 cc. of AcOH was reduced with ca. 10 g. of chromous acetate as described with VIIa. The crude reaction product was recrystallized from MeOH to afford 1.1 g. of Xa melting at 237~239°. *Anal.* Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found : C, 65.32; H, 8.18.

Partial hydrolysis of Xa with $KHCO_3$ in aq. MeOH at room temperature furnished the monoformyl ester Xb melting at 249~251°. *Anal.* Calcd. for $C_{22}H_{34}O_6$: C, 67.05; H, 8.71. Found : C, 66.91; H, 8.76.

Further hydrolysis of Xb with K_2CO_3 afforded 3β,5,6β,16α-tetrahydroxy-5α-pregnan-20-one (Xc) melting at 232~235°. *Anal.* Calcd. for $C_{21}H_{34}O_5 \cdot H_2O$: C, 65.61; H, 9.44. Found : C, 66.21; H, 9.44.

3β,5,6β-Trihydroxy-5α-pregn-16-en-20-one (XI)——A solution of 1.1 g. of IXa in 150 cc. of AcOH was reduced with chromous acetate at room temperature for 24 hr.

The reaction mixture was diluted with water and extracted three times with 150 cc. portions of AcOEt.

The extracts were combined, washed with water, dried and evaporated affording 0.5 g. of crystals melting at 219~221°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found : C, 72.33; H, 9.48.

5α-Pregnane-3β,5,6β,16β,20α-pentol (POL) (XIIIa)——A suspension of 10 g. of diosgenin XII in a mixture of 200 cc. of 85% HCOOH and 20 cc. of 30% H_2O_2 was warmed at 70~80° for 1 hr. During this period, XII went into solution. About one-half of the solvent was removed *in vacuo* and then water was added to the solution. The precipitate deposited was collected and washed with water to give the formate of XIIIa, which was dissolved in 200 cc. of MeOH, treated with a solution of 5 g. of KOH in 10 cc. of water, and the solution was refluxed for 1 hr. After cooling, the alkaline solution was acidified with AcOH, evaporated *in vacuo*, and the residue was washed with water to give 6.5 g. of crude XIIIa, m.p. 245~250°. Recrystallization from MeOH-H_2O raised the m.p. to 250~252°. *Anal.* Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found : C, 68.51; H, 9.72.

XIIIa was acetylated with Ac_2O in pyridine to form the tetraacetate XIIIb, m.p. 216~218°. *Anal.* Calcd. for $C_{29}H_{44}O_9$: C, 64.90; H, 8.26. Found : C, 65.13; H, 8.19.

3β,16β,20β-Trihydroxy-pregn-5-ene 3,16,20-triacetate (XIVb)——XIVb (m.p. 141~143°) was prepared by $LiAlH_4$ reduction ofdiosone diacetate [3β,16β-dihydroxypregn-5-en-20-one 3-acetate 16-(4-methyl-5-acetoxyvalerate)] according to Löken, *et al.*,[8] followed by acetylation.

5α-Pregnane-3β,5,6β,16β,20β-pentol (XV)——To a solution of 500 mg. of XIVb in 10 cc. of 99% HCOOH was added 1 cc. of 30% H_2O_2. The solution was allowed to stand at room temperature for

*6 See also the procedure for (XV).

1 hr. and then warmed at 40~50° for another hour. After cooling, a large volume of water was added, and the resulting precipitate was collected and washed with water to give 500mg. of the formate of XV. The crude formate was hydrolyzed, as described, in the case of XIII, to give 280 mg. of crude XV, needless, m.p. 290°. Crude XV was dissolved in a small volume of MeOH, diluted with a large volume of CCl_4 and the solution was boiled on a steam bath in an atmospheric pressure to distil water off under azeotropic condition. This pro cedure was repeated to give a pure crystalline XV, prisms, m.p. 290°. *Anal.* Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found : C, 68.71; H, 9.79.

5α-Pregnane-3β,5,6α,16β,20β-pentol (XVI)——To a solution of 650 mg. of XIVb in 0.5 cc. of pyridine and 65 cc. of anhyd. Et_2O was added 500 mg. of OsO_4 and the solution was maintained in dark place at room temperature for 7 days. The Et_2O was decanted and the black precipitate was refluxed for for 4 hr. with 25 cc. of EtOH, 20 cc. of water and 2 g. of Na_2SO_3. After filtration and washing the precipitate repeatedly with EtOH, the combined filtrate and washings were concetrated *in vacuo*. Water was added to this, and the crystals were filtered, washed with water and hydrolyzed by refluxing with 20 cc. of MeOH, 200 mg. of KOH and 1 cc. of water to yield the hydrate of XVI, m.p. 280° (decomp.), 300 mg. Recrystallization of the hydrate from MeOH-CCl_4 by the similar procedure as described with XV gave anhyd. XVI, m.p. 255~258° (decomp.). *Anal.* Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found : C, 68.47; H, 9.89.

5α,25D-Spirostan-3β,5,6α-triol (XVII)——A mixture of 2.0 g. of XII, 2.0 cc. of pyridine, 200 cc. of anhyd. Et_2O and 1.5 g. of OsO_4 was maintained in dark place at room temperature for 7 days and the resulting precipitate was worked up as similar as the case of XVI, giving 1.2 g. of crude XVII, m.p. 248~252°. One crystallization from AcOEt raised the m.p. to 249~252°. *Anal.* Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found : C, 71.99; H, 9.97.

5α-Pregnane-3β,5,6α,16β,20α-pentol (XVIII)——A solution of 500 mg. of XVII in 10 cc. of 85% HCOOH was treated with 1 cc. of 30% H_2O_2 and the mixture was heated at 60~70° for 1 hr. After cooling, the solution was diluted with water and the resulting precipitate was collected, dissolved in 5 cc. of MeOH, treated with a solution of 0.3 g. of KOH in 0.5 cc. of water and allowed to stand at room temperature overnight. The alkaline solution acidified with dil. HCl was concentrated *in vacuo* to give 250 mg. of crude XVIII, m.p. 260~265° (decomp.). Recrystallization from MeOH-CCl_4 by the similar procedure described in the preparation of XV gave an amorphous solid, m.p. 230° (decomp.), which was demonstrated by the elemental analysis to contain one-half mole of water of crystallization. *Anal.* Calcd. for $C_{21}H_{36}O_5 \cdot \frac{1}{2}H_2O$: C, 66.81; H, 9.88. Found : C, 66.84; H, 9.60.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5,6β-triol (XIX)——To a suspension of 35 g. of XIII in 500 cc. of Me_2CO was added 2 cc. of 37% BF_3 in Et_2O, and the mixture was stirred at room temperature for 1 hr. During this period crystals of XIII dissolved and leaflet crystals were separated, which were collected, washed with Me_2CO and dried to give 35 g of XIX melting at 260~265°. The analytical sample was prepared by the recrystallization from large volume of MeOH, dimethylformamide or pyridine; m.p. 268~269°. *Anal.* Calcd. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found : C, 70.31; H, 9.84.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5,6β-triols 3-acylate] (XXa-e)——(XXa-e) were prepared by following procedure : to a solution of 16β,20α-isopropylidenedioxy-5α-pregnane-3β,5,6β-triol (XIX) in pyridine was added a calculated amount of the acid anhydride or chloride and the solution was allowed to stand at room temperature. After 2 hr., the reaction mixture was poured into water and the product was collected and recrystallized.

Table I. 16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5,6β-triols 3-acytate

Compd. No.	R_1	R_2	m.p. (°C)	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
XXa	CH_3CO	H	265	$C_{26}H_{42}O_6$	69.33	9.71	69.04	9.82
XXb	CH_3CH_2CO	H	255	$C_{27}H_{44}O_6$	69.79	9.55	69.70	9.83
XXc	C_6H_5CO	H	271	$C_{31}H_{44}O_6$	72.65	8.59	72.16	8.31
XXd	C_2H_5OCO	H	260	$C_{27}H_{44}O_7$	68.95	9.36	68.70	9.33
XXe	$C_{16}H_{31}CO$	H	161	$C_{40}H_{70}O_6$	74.25	10.91	73.96	10.83

Table II. 5α-Pregnane-3β,5,6β,16β,20α-pentols 3-acylate

Compd. No.	R_1	R_2	m.p. (°C)	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
XXIa	CH_3CO	H	252	$C_{23}H_{38}O_6$	67.32	9.27	67.24	9.08
XXIb	C_6H_5CO	H	285	$C_{28}H_{40}O_6$	71.20	8.48	71.16	8.33
XXIc	C_2H_5OCO	H	260	$C_{24}H_{40}O_7$	65.73	8.73	65.46	8.99

5α-Pregnane-3β,5,6β,16β,20α-pentol 3-acylate (XXIa-c)——XXIa-c were prepared by the following procedure : a suspension of 1 g. of XX in 20 cc. of AcOH and 5 cc. of water was heated on a steam bath for 2 hr. After cooling, water was added and the crystals of XXI were filtered, dried and recrystallized.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5,6β-triol 3,6-diacetate (XXf)——To a solution of 3 g. of (XIX) in 20 cc. of pyridine was added 4.5 cc. of Ac_2O and the solution was heated on a steam bath for 6 hr. After cooling, water was added and the crystals of XXf were collected, dried and recrystallized from benzene to yield 2.5 g. of colorless crystals melting at 275°. *Anal.* Calcd. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00. Found : C, 68.56; H, 8.74.

3β,5-Dihydroxy-16β,20α-isopropylidenedioxy-5α-pregnan-6-one (XXIIa)——A 100 cc. separatory funnel charged with 1 g. of XIX, 25 cc. of Et_2O, 13 cc. of MeOH, 3.5 cc of water and 0.46 g. of NBS was shaken for a few minutes to make the solution effective. On addition of water, the bulk of the diolone XXIIa separated from the reaction mixture as colorless crystals. The water phase was tapped off and the suspension in Et_2O washed with $NaHSO_3$ solution, alkali and then water. The ketone XXIIa was then collected and recrystallized from benzene to yield 0.5 g. of colorless needles melting at 259°. Successive concentration of the mother liquor afforded additional crops amounting to 0.2 g. *Anal.* Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.36. Found : C, 70.62; H, 9.45.

Elimination of Me_2CO moiety from XXIIa was effected by the usual method affording the diol XXIIIa, m.p. 272°. *Anal.* Calcd. for $C_{21}H_{34}O_5$: C, 68.85; H, 9.29. Found : C, 68.89; H, 9.45.

3β-Benzoyloxy-5-hydroxy-16β,20α-isopropylidenedioxy-5α-pregnan-6-one (XXIIb)——A solution of 2 g. of 3β-benzoyloxy-16β,20α-isopropylidenedioxy-5α-pregnane-5,6β-diol (XXc) in 20 cc. of pyridine was treated with CrO_3 (1.2 g.). The reaction mixture was stirred at room temperature for 3 hr., poured into water and extracted with benzene. The benzene extract was washed with water, dried, evaporated and the residue was recrystallized from benzene to yield 1.5 g. of colorless crystals melting at 286°. *Anal.* Calcd. for $C_{31}H_{42}O_6$: C, 72.94; H, 8.24. Found : C, 73.17; H, 8.43.

Elimination of Me_2CO moiety from XXIIb was effected by the usual method affording the diol XXIIIb, m.p. 285°. *Anal.* Calcd. for $C_{28}H_{38}O_6$: C, 71.48; H, 8.08. Found : C, 71.58; H, 8.39.

5-Hydroxy-16β,20α-isopropylidenedioxy-5α-pregnane-3,6-dione (XXIV)——A solution of 2 g. of XIX in 20 cc. of pyridine was treated with CrO_3 (2.4 g.). The reaction mixture was stirred for 20 hr. at 60~70°, poured into water and extracted with benzene. The benzene extract was washed with water, dried, evaporated and the residue was recrystallized from benzene to yield 1.5 g. of colorless crystals melting at 272°. *Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.28; H, 8.91. Found : C, 71.02; H, 8.90.

Elimination of Me_2CO moiety from XXIV was effected by the usual method affording the diol XXV, m.p. 236°. *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.23; H, 8.79. Found : C, 68.94; H, 8.98.

3β-Benzoyloxy-16β,20α-isopropylidenedioxy-5α-pregnan-5,6β-diol 6-methanesulfonate (XXVI)——To a solution of 6.8 g. of XXc in 68 cc. of pyridine was gradually added 6.8 g. of methanesulfonylchloride with external cooling. The solution was allowed to stand in an ice-box overnight, then 3 hr. at room temperature, and poured into water. The precipitate was filtered, recrystallized from $CHCl_3$ yielding 5.8 g. of colorless amorphous compound decomposing at 183°. *Anal.* Calcd. for $C_{32}H_{46}O_8S$: C, 65.08; H, 7.79; S, 5.42. Found : C, 64.55; H, 7.26; S, 4.72.

5,6α-Epoxy-16β,20α-isopropylidenedioxy-5α-pregnan-3β-ol (XXVII)——To a solution of 3.5 g. of XXVI in 220 cc. of EtOH was added 2.2 g. of KOH and the solution was refluxed for 2 hr. After evaporation of EtOH, the residue was extracted with Et_2O, washed with *N* HCl and with water, dried over Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from Me_2CO to yield 1.1 g. of colorless crystals melting at 241°. *Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.85; H, 9.74. Found : C, 74.28; H, 9.48.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5-diol (XXVIII)——A solution of 1.5 g. of XXVII in 50 cc. of Et_2O and 100 cc. of benzene was added dropwise at room temperature to a stirred solution of 0.5 g. of $LiAlH_4$ in 100 cc. of Et_2O and stirring was continued for 2 hr. at 40~45°. To a cooled reaction mixture was added 250 cc. of water. The precipitate was filtered and extracted with MeOH. After removal of the solvent, the residue was recrystallized from MeOH giving 1 g. of colorless crystals, m.p. 272°. *Anal.* Calcd. for $C_{24}H_{40}O_4$: C, 73.47; H, 10.20. Found : C, 73.35; H, 10.04.

Elimination of Me_2CO moiety from XXVIII was effected by the usual method affording the diol XXIX, m.p. 225°. *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.51; H, 10.23. Found : C, 71.85; H, 10.32.

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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-

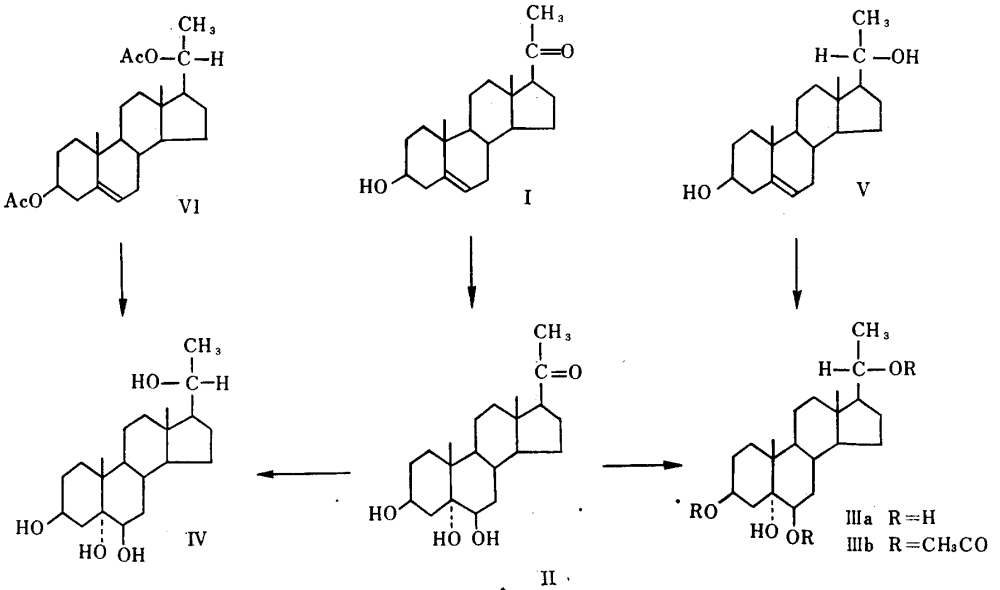

Chart 1.

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

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