CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 11 No. 2 February 1963

UDC 547.92.07 : 577.176.5

23. Hayao Nawa, Masao Uchibayashi, Akira Okabori, Katsura Morita, and Takuichi Miki : Synthesis of Polyhydroxysteroids. IV.*1 Syntheses of Pregnanetetrols. (2).

(*Research Laboratories, Takeda Chemical Industries, Ltd.**2)

In a continuation of the efforts to investigate the minimum structural requirements for the biological activities of 5α-pregnane-3β,5,6β,16β,20α-pentol (POL), this paper deals with the syntheses of tetrahydroxy analogs which lack the 6-hydroxyl group of POL, namely 5α-pregnane-3β,5,16β,20α-tetrol (VIa) and its 20-epimer 5α-pregnane-3β,5,16β,20β-tetrol (VIII).

The key intermediate which may leads to the desired substances VIa and VIII appeared to be 5α,25D-spirostane-3β,5-diol (Va). It is known that when treated with N-bromosuccinimide, the axiale C-6-hydroxyl of cholestane-3β,5α,6β-triol is preferentially oxidized.[1] This selective oxidation with N-bromosuccinimide was applied to 5α,25D-spirostane-3β,5,6β-triol (I)[2] prepared from diosgenin, and 3β,5-dihydroxy-5α,25D-spirostan-6-one (II) was obtained, the structure of which was confirmed by formation of the oxime.

Since the Wolff-Kishner reduction of 5α-hydroxy-6-keto steroids has been known to afford 5-ene compound,[3] this reaction was not applicable to the preparation of compound Va by eliminating the 6-keto group of II. By analogy with the case of 3β-hydroxycholestan-6-one,[4] an attempt was made to convert II by treatment with ethanedithiol into the 6-ethylenethioketal derivative and desulfurate with Raney nickel to compound V. The reaction of compound II with ethanedithiol, however, resulted in the recovery of II probably owing to the steric interference of the 5-hydroxyl group.

For synthesis of compound V, another route was then studied employing 5,6α-epoxy-5α,25D-spirostan-3β-ol (IVa) as an intermediate. This compound has been synthesized by Burn and his collaborators[6] from diosgenin by the action of monoperphthalic acid, though any yield has not been mentioned. For the present purpose the following route appeared to be more attractive.

Fieser and his co-workers[4] reported that ethyl chloroformate (cathyl chloride) was

---

*1 This paper constitutes Part XXVIII of Takeda Laboratories' Series entitled "Steroids;" Part XXVII : This Bulletin, **11**, 103 (1963).

*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (那波速男, 内林政夫, 岡堀 滉, 森田 桂, 三木卓一).

1) L.F. Fieser, S. Rajagopalan : J. Am. Chem. Soc., **71**, 3938 (1949).
2) D.H.R. Barton, C.H. Robinson : J. Chem. Soc., **1954**, 3045; H. Heymann, L.F. Fieser : J. Am. Chem. Soc., **73**, 5252 (1951).
3) H. Hauptmann, M.M. Campos : J. Am. Chem. Soc., **74**, 3179 (1952); L.F. Fieser : *ibid.*, **76**, 1945 (1954).
4) L.F. Fieser, J.E. Herz, M.W. Klohs, M.A. Romero, T. Utne : *Ibid.*, **74**, 3309 (1952).
5) A. Fürst, F. Koller : Helv. Chim. Acta, **30**, 1454 (1947).
6) D. Burn, B. Ellis, V. Petrow, I.A. Stuart-Webb, D.M. Williamson : J. Chem. Soc., **1957**, 4092.

an excellent reagent for selective acylation of the 3β-hydroxyl in cholestane-3β,5α,6β-triol. Treatment of compound I with ethyl chloroformate gave 3β-ethoxycarbonyloxy-5α,25D-spirostane-5,6β-diol (IIIa) as expected.

Fürst and Koller[5] prepared 5α,6α-epoxycholestan-3β-ol in good yield by the reaction of cholestane-3β,5α,6β-triol 3-acetate with mesyl chloride (methanesulfonyl chloride) followed by the treatment of the 6-mesylate with potassium hydroxide in methanol. When compound IIIa was allowed to react with mesyl chloride in pyridine in order to obtain the 6-mesyl compound IIIb, the product was found, by analysis and infrared spectrum, to be a mixture of the expected IIIb and 3β-ethoxycarbonyloxy-5,6α-epoxy-5α,25D-spirostane (IVb). The mixture was chromatographed through a Florisil column and 3β-ethoxycarbonyloxy-5α,6α-epoxide IVb was isolated as the only elutable product in good yield. The mesylate IIIb contained in the mixture was therefore considered to have been transformed to the 5α,6α-epoxide IVb during the chromatography. Further, refluxing the above-mentioned mixture of IIIb and IVb with potassium hydroxide in methanol directly furnished 3β-hydroxy-5α,6α-epoxide IVa in good yield. Compound IVa was identified by comparison of its infrared spectrum with that of an authentic sample prepared by Burn *et al.*[6] The acetyl derivative IVc also confirmed the structure of IVa. Treatment of IVa with ethyl chloroformate afforded compound IVb which was used for identification of the same compound isolated from the above-mentioned column chromatography.

As is known, a 5α,6α-epoxide ring of steroidal compounds suffers reductive cleavage by lithium aluminum hydride to yield the corresponding 5α-hydroxy compounds. The lithium aluminum hydride reduction of compound IVa was effected satisfactorily to give 5α,25D-spirostane-3β,5-diol (Va) in higher yield. The monoacetate Vb prepared by usual procedures of acetylation exhibits in the infrared spectrum a well-separated two-peaked band (5.75 and 5.85 μ) in addition to a free hydroxyl band at 2.90 μ. This apparent anomaly of the acetate band remains to be studied further. An attempt to open the epoxide ring of IVa by hydrogenation over platinum catalyst in acetic acid was unsuccessful with a recovery of the unchanged material.

The key intermediates Va and Vb thus synthesized were subjected respectively to the treatment with hydrogen peroxide in formic acid under as milder condition[8] as possible to effect oxidative splitting of the sapogenin side chain, and the desired 5α-pregnane-3β,5,16β,20α-tetrol (VIa) was obtained. The structure of the product VIa was confirmed by conversion to the acetate VIb and 16β,20α-acetonide VIc. The latter derivative was further identified by comparison with an authentic sample prepared by another route.[9] When vigorous conditions were applied to the above oxidative cleavage of the side chain, 5α-pregnane-3β,5,6β,16β,20α-pentol (POL) was separated from the reaction mixture as a single crystalline product, which was identified as its 16,20-acetonide. This product might have been produced as a result of facile dehydration of the C-5-hydroxyl group and the subsequent hydroxylation of the double bond formed similary to the preparation of POL from diosgenin.

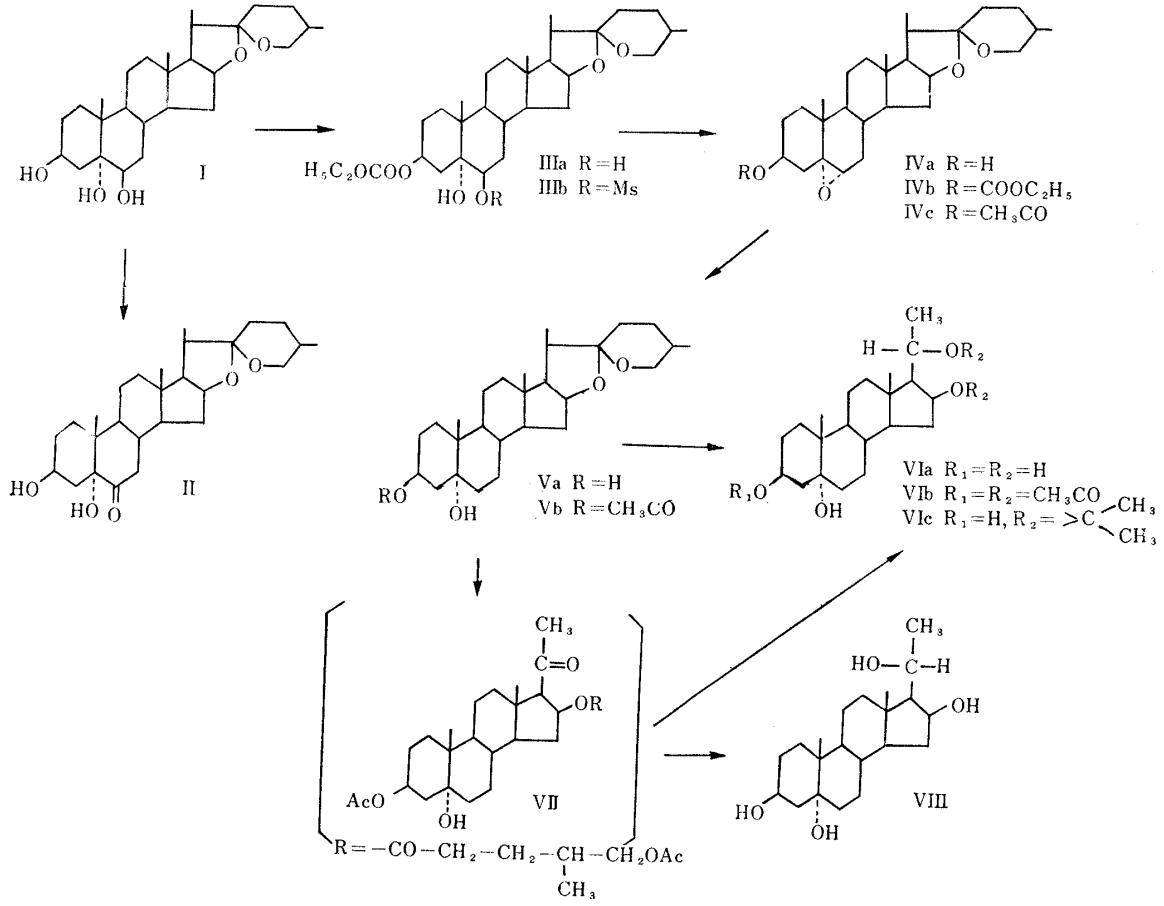
Synthesis of 5α-pregnane-3β,5,16β,20β-tetrol (VIII), an epimer of compound VIa with regard to the C-20-hydroxyl group, was conducted by conversion of V to the pseudo compound and oxidative cleavage of the side chain, followed by lithium aluminum hydride reduction of the resulting 16-valeryloxy-20-keto compound.

The first crystalline product isolated from the reaction mixture was identified as pregn-5-ene-3β,16β,20β,-triol by the comparison with an authentic specimen.[9] The non-crystalline portion from the above reaction mixture was acetylated and chromato-

7) Pl. A. Plattner, H. Heusser, M. Feuer : Helv. Chim. Acta, **32**, 587 (1949).
8) Part XXV of this series : This Bulletin, **11**, 90 (1963).
9) Part XXVI of this series : This Bulletin, **11**, 95 (1963).

graphed through Florisil column to separate into two fractions. Fraction eluted by methylene chloride gave pregn-5-ene-3β,16β,20α-triol triacetate which was identified by comparison with an authentic sample.[9]

These two 5-ene compounds were thought to have been produced by the reactions involving dehydration of the 5-hydroxyl group during the side-chain degradation. The other fraction, obtained by elution with methanol-containing methylene chloride, was subjected to re-chromatography followed by alkaline hydrolysis, and the desired 5α-pregnane-3β,5,16β,20β-tetrol (VIII) was obtained. From the above results it became clear that the lithium aluminum hydride reduction of the 20-keto group did not proceed stereospecifically and afforded both the 20α- and 20β-hydroxy compounds.



Experimental[*3]

3β,5-Dihydroxy-5α,25D-spirostan-6-one (II)——A solution of 2.6 g. of 5α,25D-spirostane-3β,5α,6β-triol (I) in 50 cc. of dioxane was diluted with 4.5 cc. of water, cooled to 25° and treated with 1.09 g. of N-bromosuccinimide under stirring. In the course of 10 min. the color changed to yellow, orange, and yellow. After stirring for 30 min. the mixture was poured into ice water and decolorized by addition of aq. $NaHSO_3$. The mixture was then extracted with $CHCl_3$ and the extract was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The residue was crystallized from MeOH to give 1.5 g. of colorless needles, m.p. 237~240°. Repeated crystallization from MeOH gave material of analytical quality, m.p. 247~250°; $[\alpha]_D^{24}$ −105°(c=0.40, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{42}O_5 \cdot H_2O$: C, 69.79; H, 9.54. Found : C, 69.93; H, 9.74.

Oxime of Compound II——A 380 mg. portion of II was treated with 300 mg. of hydroxylamine hydrochloride in a mixture of 6 cc. of EtOH and 2 cc. of pyridine in the usual manner. Recrystallization of the product from Me_2CO yielded fine-granular crystals, m.p. 276~278°. *Anal.* Calcd. for $C_{27}H_{43}O_5N$: N, 3.03. Found : N, 2.86.

[*3] All melting points are uncorrected. All pure substances prepared were examined by infrared spectrum.

3β-Ethoxycarbonyloxy-5α,25D-spirostane-5,6β-diol (IIIa)——A solution of 1.0 g. of I in 15 cc. of dioxane and 1.6 cc. of pyridine was cooled with ice and treated dropwise with 2.0 cc. of ethyl chloroformate. On standing for 1 hr. at room temperature, 25 cc. of water and 1 cc. of conc. HCl were added and the mixture heated for 30 min. on a boiling water-bath and then cooled. The precipitates were taken up by filtration, washed well with water, and recrystallized twice from Me_2CO. The product was obtained as colorless needles, m.p. 246~247°, weighed 700 mg.; $[\alpha]_D^{24}$ −83°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}O_7$: C, 69.20; H, 9.29. Found: C, 69.44; H, 9.44.

5α,6α-Epoxy-5,25D-spirostan-3β-ol (IVa)——a) A mixture of 5.0 g. of IIIa and 3.38 cc. of methanesulfonyl chloride in 50 cc. of pyridine was allowed to stand at 0° for 20 hr. and later at room temperature for 3 hr. The mixture was poured into ice water and the precipitate was filtered up, washed with water, and dried over Na_2SO_4. The crude product thus obtained, which was a mixture of 3β-ethoxycarbonyloxy-6β-mesyloxy-5α,25D-spirostan-5α-ol (IIIb) and 3β-ethoxycarbonyloxy-5,6α-epoxy-5α,25D-spirostane (IVb) as stated below, was refluxed with 4.2 g. of KOH in 600 cc. of MeOH for 3 hr. The solution was mixed with 5 cc. of AcOH, concentrated to a volume of 50 cc., and mixed with water. The crystalline product was taken up by filtration and recrystallized from MeOH to give 3.0 g. of colorless needles, m.p. 215~218°. Further recrystallization from the same solvent raised the m.p. to 220~221.5°, which was not depressed on admixture with the sample prepared in b).

b) A solution of 1.05 g. of IVb and 0.5 g. of KOH in 40 cc. of MeOH and 1.5 cc. of water was refluxed for 2 hr. After an addition of 0.5 cc. of AcOH and 20 cc. of water, the mixture was concentrated to remove MeOH under vacuum, and cooled. The crystals separated were recrystallized twice from MeOH to give 0.83 g. of colorless needles, m.p. 220~221°; $[\alpha]_D^{20}$ −130°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{42}O_4 \cdot \frac{1}{2}H_2O$: C, 73.76; H, 9.85. Found: C, 73.81; H, 9.87. The IR spectrum of the product was completely identical with an authentic spectrum of Burn's preparation (m.p. 208~209°, $[\alpha]_D^{26}$ −136°).[6]

3β-Ethoxycarbonyloxy-5,6α-epoxy-5α,25D-spirostane (IVb)——a) A mixture of 1.98 g. of IIIa and 1.34 cc. of methanesulfonyl chloride in 20 cc. of pyridinewas treated in a similar way to the case of a) in IVa. The crude product was recrystallized from Me_2CO to yield 1.5 g. of colorless granules, m.p. 178~181° (decomp.). The material obtained after two more recrystallizations showed m.p. 180~183°(decomp.). Found: C, 69.73; H, 9.19. These analytical data and the IR spectrum indicated that the material was obviously a mixture of IIIb and IVb.

The mixture was chromatographed over 50 g. of Florisil and eluted with CH_2Cl_2. The eluted substance was recrystallized from Me_2CO to give 0.82 g. of colorless needles, m.p. 193~195°; $[\alpha]_D^{20}$ −115°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22; O, 19.10. Found: C, 71.81; H, 9.22; O, 18.96. Elution of the column with CH_2Cl_2–MeOH (9:1) afforded 0.07 g. of the starting material IIIa.

b) To a solution of 200 mg. of IVa in 5 cc. of pyridine was added 1 cc. of ethyl chloroformate dropwise with cooling. The mixture was allowed to stand at room temperature for 1 hr. and poured onto ice. The crystals were purified by recrystallization from Me_2CO and 150 mg. of colorless needles was obtained, m.p. 188~190°. The product was identified with the sample prepared in a) by mixed melting point determination and comparison of IR spectrum.

5,6α-Epoxy-5α,25D-spirostane-3β-ol Acetate (IVc)——A solution of 250 mg. of IVa in 10 cc. of pyridine and 5 cc. of Ac_2O was kept at 80° for 3 hr., concentrated under vacuum and mixed with water. Recrystallization of the crystalline precipitates twice from MeOH-$CHCl_3$ gave 200 mg. of colorless needles, m.p. 232~234°; $[\alpha]_D^{20}$ −119°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.37; H, 9.43.

5α,25D-Spirostane-3β,5-diol (Va)——To a mixture of 2.75 g. of $LiAlH_4$ in 500 cc. of Et_2O was added dropwise a solution of 5.5 g. of IVa in 100 cc. of tetrahydrofuran at room temperature and the mixture stirred for 5 hr. at the same temperature. After an addition of 20 cc. of AcOEt and dil·HCl to the mixture, the organic layer was taken up, washed with aq. Na_2CO_3 and with water, and dried over Na_2SO_4. Distillation of the solvent and recrystallization of the residue from MeOH yielded 4.0 g. of colorless scales, m.p. 254~256°; $[\alpha]_D^{20}$ −69°(c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.74; H, 10.13.

5α,25D-Spirostane-3β,5α-diol 3-Acetate (Vb)——A 300 mg. portion of Va, 10 cc. of pyridine, and 5 cc. of Ac_2O were treated in the conventional way. Recrystallization of the product from MeOH furnished 200 mg. of colorless needles, m.p. 238~240°. IR λ_{max}^{Nujol} μ: 2.90 (OH), 5.75, 5.85 (acetate). *Anal.* Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; $COCH_3$, 9.06. Found: C, 73.67; H, 9.82; $COCH_3$, 9.26.

5α-Pregnane-3β,5,16β,20α-tetrol (VIa)——a) A solution of 0.5 g. of Va in 8 cc. of ethylene chloride, 10 cc. of 99% HCOOH, and 1.1 cc. of 30% H_2O_2 was warmed at 50° for 30 min. The mixture was concentrated under vacuum and the syrupy residue was refluxed for 1.5 hr. with 0.5 g. of KOH in 3 cc. of water and 50 cc. of MeOH. After an addition of 0.5 cc. of AcOH and 10 cc. of water, the mixture was concentrated under vacuum. The precipitate thus formed was filtered up and recrystal-

lized from Me_2CO-MeOH. The product was obtained as colorless granules, m.p. 222~225°, weighed 0.25 g. *Anal.* Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.87; H, 10.60.

b) A solution of 400 mg. of IVb in 7 cc. of ethylene chloride was treated with 9 cc. of 99% HCOOH and 1 cc. of 30% H_2O_2 at 50° for 30 min. The mixture was worked up in a similar manner to a) and 200 mg. of colorless granules was obtained, m.p. 220°, which was proved to be identical with the sample prepared in a) by mixed melting point determination and comparison of IR spectrum.

5α-Pregnan-3β,5,16β,20α-tetrol 3,16,20-Triacetate (VIb)——A solution of 170 mg. of VIa in 10 cc. of pyridine and 6 cc. of Ac_2O was heated at 80° for 2 hr. After a concentration of the mixture and addition of water, the solid obtained was recrystallized from Me_2CO to give 170 mg. of colorless needles, m.p. 206~207°; $[\alpha]_D^{20}$ +20° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.43, H, 8.65.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5-diol (VIc)——A suspension of 100 mg. of VIa in 35 cc. of Me_2CO was mixed with 4 drops of 37% BF_3 etherate and stirred at 30° for 2.5 hr. The needles were filtered up and recrystallized from $CHCl_3$-MeOH to give 80 mg. of colorless scales, m.p. 268~272°. The product showed no depression in melting point on admixture with an authentic sample (m.p. 265~268°) described in other place.[9] The IR spectrum of both samples were superimposable.

16β,20α-Isopropylidenedioxy-5α-pregnane-3β,5,6β-triol——A solution of 2.0 g. of Va in 200 cc. of 99% HCOOH and 20 cc. of 30% H_2O_2 was heated at 70~75° for 2 hr., concentrated under vacuum, and mixed with water. The syrup obtained was washed with water and then refluxed for 1 hr. with 4 g. of KOH in 20 cc. of water and 80 cc. of MeOH. After an addition of 4 cc. of AcOH, the red-colored solution was concentrated under vacuum until resinous mass appeared, which was separated by filtration. The filtrate was concentrated again to white precipitates. The resinous mass was scratched in the presence of a small volume of water and partially solidified. This solid portion (300 mg.) and the white precipitate (700 mg.) were combined and subjected to recrystallization from MeOH in vain. A sample of 300 mg. of this material was suspended in 20 cc. of Me_2CO and stirred with 2 drops of 37% BF_3 etherate for 1 hr. at room temperature. After an addition of 2 drops of pyridine, the reaction mixture was evaporated, and the residue was washed with water and recrystallized from MeOH-Me_2CO and from Me_2CO. The product thus obtained as colorless scales, m.p. 255~261°, was confirmed to be identical with authentic 16β,20α-isopropylidenedioxy-5α-pregnane-3β,5,6β-triol (POL acetonide) by comparison of IR spectrum.

5α-Pregnane-3β,5,16β-tetrol (VIII)——A solution of 7.7 g. of Va in 50 cc. of Ac_2O was refluxed for 1.5 hr. After an addition of 0.5 g. of pyridine hydrobromide, the solution was refluxed gently for further 4 hr. The reaction mixture was concentrated under vacuum to a volume of about 25 cc., diluted with 77 cc. of AcOH, and cooled to 11~13°. To this solution was added at the same temperature a mixture of 3.7 g. of CrO_3, 4 cc. of water, and 18 cc. of AcOH with stirring in the course of 30 min. After stirring for another 30 min. at room temperature, the reaction mixture was treated with 15 cc. of water containing 2 g. of $NaHSO_3$ and evaporated under vacuum. The residue was mixed with water and extracted with Et_2O, which was washed successively with water, aq. Na_2CO_3, and water, dried over Na_2SO_4, and evaporated.

The syrup thus obtained was dried over P_2O_5 and dissolved in 400 cc. of Et_2O. The solution was added dropwise to a mixture of 6.9 g. of $LiAlH_4$ in 300 cc. of Et_2O with stirring at room temperature. After stirring for 5 hr. at room temperature, the mixture was left overnight and then refluxed for 3.5 hr. An excess of $LiAlH_4$ was decomposed by careful addition of 20 cc. of water, and the reaction mixture was treated with 350 cc. of 5% H_2SO_4 and subjected to evaporate Et_2O under vacuum. The insoluble product was taken up by filtration, washed with water, and dissolved in 450 cc. of hot MeOH. On concentration of the solution, white precipitates deposited were collected by filtration and washed with a few volume of cold MeOH. Recrystallization from MeOH yielded 0.4 g. of colorless granules, m.p. 280°. This was identical in IR spectrum with pregn-5-ene-3β,16β,20β-triol (m.p. 290°) obtained by the different experiment.[9]

The mother liquor was evaporated and the residual thick paste was acetylated with 120 cc. of pyridine and 70 cc. of Ac_2O at 80° for 3 hr. The mixture was evaporated under vacuum and the residue (ca. 6 g.) was chromatographed over 200 g. of Florisil. Elution with CH_2Cl_2 gave 2.98 g. of syrup. Further elution with a solvent pair of CH_2Cl_2-MeOH (8:2) yielded 1.55 g. of non-crystalline material. The former fraction crystallized on treatment with MeOH to afford 0.6 g. of colorless scales melting at 173~186°. Recrystallization from MeOH raised the m.p. to 194~197°. *Anal.* Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.15; H, 8.75. This product was identical in IR spectrum with pregn-5-ene-3β,16β,20α-triol triacetate (m.p. 196~198°) prepared by another route.[9]

The latter fraction in the above column-chromatography was re-chromatographed over 30 g. of Florisil. After washing with CH_2Cl_2, elution was continued with mixtures of CH_2Cl_2-AcOEt (9:1, 8:2, 6:4). Fractions eluted by these solvent mixtures were combined and evaporated to give 1.39 g. of syrup, which was hydrolyzed with 0.7 g. of KOH in 50 cc. of MeOH and 2 cc. of water under reflux

for 1.5 hr. After an addition of 0.7 cc. of AcOH, the mixture was concentrated to remove MeOH under vacuum and the residue was solidified on standing. Filtration and washing with water furnished 1 g. of white powder. On purification of this material from MeOH-Me_2CO, the major portion remained as an oil and only few amounts of crystals were isolated. Recrystallization from MeOH gave colorless needles, m.p. 270°. *Anal.* Calcd. for $C_{21}H_{36}O_4 \cdot \frac{1}{2}H_2O$: C, 69.62; H, 10.31. Found : C, 69.83; H, 10.28.

The authors express their deep gratitude to Dr. S. Kuwada, Director of these Laboratories, for his encouragement and to Drs. T. Matsukawa and Y. Abe for their helpful advices.

Thanks are also due to Mr. M. Kan for elemental analyses and to Mr. H. Nakamachi for optical measurements.

Summary

5α-Pregnane-3β,5,16β,20α-tetrol (VIa) and 5α-pregnane-3β,5,16β,20β-pentol (VIII) were synthesized according to the scheme shown in the Figure.

(Received February 19, 1962)

UDC 547.92.07 : 543.422.4

24. Katsura Morita, Shunsaku Noguchi, Kentaro Hiraga, Toyokazu Kishi, Hayao Nawa, and Takuichi Miki : Synthesis of Polyhydroxysteroids. V.*1 Preparation and Infrared Spectra of 16β,20α-Isopropylidenedioxysteroids.

(*Research Laboratories, Takeda Chemical Industries, Ltd.**2)

In the previous paper[1] authors described a novel method for the side chain cleavage of diosgenin *via* the chlorinated intermediates to give pregn-5-ene-3β,16β,20α-triol (I) in overall yield of 60~70%.

A selective protection of a hydroxyl group or groups was hence desired in order to make use of this triol as a useful starting material. For this purpose an attempt was made on the formation of a cyclic derivative between two hydroxyl groups at C-16β and 20α, for diosgenin involves a furan ring at this site of the molecule.

On treatment with acetone and a few drops of borontrifluoride-ether solution, the triol I furnished, in a quantitative yield, the acetonide IIa, which was readily hydrolyzed by boiling in aqueous acetic acid to the triol (I). The isomeric 16β,20β-diol[2] and 16α,20β-diol,[2] however, gave no cyclic compound under similar conditions. The failure of the acetonide formation would be due to a steric reason.

In pursuing our work concerned with the preparation of polyhydroxysteroids, a number of 16β,20α-isopropylidenedioxysteroids were prepared. These compounds were generally obtained from 16β,20α-diol in the pregnane series by the reaction with acetone in the presence of a small amount of borontrifluoride-ether solution. It is

---

*1 This paper constitutes Part XXIX of Takeda Laboratories' series entitled "Steroids;" Part XXVIII : This Bulletin, **11**, 139 (1963).

*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (森田 桂, 野口俊作, 平賀謙太郎, 貴志豊和, 那波速男, 三木卓一).

1) Part XXV : This Bulletin, **11**, 90 (1963).

2) Part XXVI : This Bulletin, **11**, 95 (1963).