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Hydroboration of Steroidal-1,5-dien-3β-ols: A General Procedure for the Introduction of a Hydroxyl Group at 1α-Position of the 3-Oxygenated Steroids

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The procedure used for the preparation of 1α-hydroxycholesterol from cholesta-1,4-dien-3-one was applied to 17,17-ethylenedioxyandrosta-1,4-dien-3-one and 20,20-ethylenedioxypregna-1,4-dien-3-one. The successful results described in this paper serve to provide a basis for evaluation of wide scope of this procedure for the introduction of a hydroxyl group at 1α-position of 3-oxygenated steroid derivatives.

The procedure consists of three steps starting from 3-keto-$\Delta^{1,4}$-steroids available readily from 3-oxygenated steroids: 1) deconjugation to 3-keto-$\Delta^{1,5}$-steroids, 2) reduction with metalhydride to 3β-hydroxy-$\Delta^{1,5}$-steroids, and 3) hydroboration to 1α,3β-dihydroxy-Δ^{5}-steroids.

This paper also includes definite identification of the final and intermediate compounds in the procedure and interpretation of their mass and nuclear magnetic resonance spectroscopic behaviors.

It is now generally accepted that vitamin D must be hydroxylated on C-25 position in the liver[2,3] and subsequently on C-1 position in the kidney,[4] before it can function on bone and intestine. The resulting metabolite, 1α,25-dihydroxycholecalciferol [1α,25-$(OH)_2$-D_3] is the most potent form of vitamin D known[5,6] and is active in anephric animals.[7,8] Recently, this metabolite was synthesized in DeLuca's laboratory[9] and its success promised well for the treatment of renal osteodystrophy and hypoparathyroidism.

Further experiments showed that 5,6-*trans* isomer of cholecalciferol[10] as well as dihydrotachysterol[11] (DHT), both of which have similar structure in regard to the geometry of the hydroxy function on C-1 position, sustained their biological response in anephric animals.

These results suggest an absolute importance of the α-hydroxy function on C-1 position for the initiation of the biological activities of vitamin D.

Very recently, an analog of 1α,25-$(OH)_2$-D_3: 1α-hydroxycholecalciferol (1α-OH-D_3) was synthesized in DeLuca's laboratory[12] for the first time and then by several research groups[13–15]

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2) G. Ponchon, A.L. Kennan, and H.F. DeLuca, *J. Clin. Invest.*, **48**, 2032 (1969).
3) M. Horsting and H.F. DeLuca, *Biochem. Biophys. Res. Commun.*, **36**, 251 (1969).
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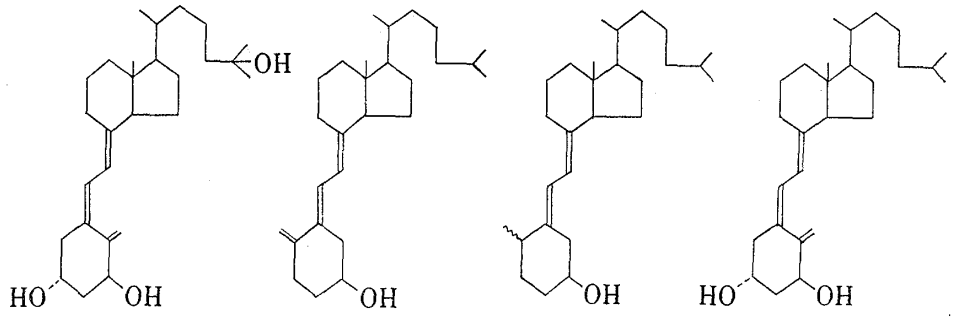
13) D.H.R. Barton, R.H. Hesse, M.M. Pechet, and E. Rizzardo, *J. Am. Chem. Soc.*, **95**, 2748 (1973).
14) A. Fürst, L. Leber, W. Meier, and K. Pfoertner, *Helv. Chim. Acta*, **56**, 1708 (1973).
15) R.G. Harrison, B. Lythgoe, and P.W. Wright, *Tetrahedron Letters*, **1973**, 3649.



1α,25-(OH)$_2$-D$_3$ 5,6-*trans*-D$_3$ DHT 1α-OH-D$_3$

including ours.[16] DeLuca's and our groups further showed independently that 1α-OH-D$_3$ had comparable biological activity to 1α,25-(OH)$_2$-D$_3$ in the stimulation of intestinal calcium transport and bone mineral mobilization in normal and anephric rats,[12,16] and thus demonstrated firmly an absolute importance of the 1α-hydroxy function.

These works suggest not only that 1α-OH-D$_3$ is expected to be extremely useful in clinical medicine, but also that the finding of a general procedure of the introduction of a hydroxyl group at 1α-position of cholesterol or its derivatives (*e.g.*, 25-hydroxycholesterol) is an urgent need for the preparation of these active vitamin D derivatives (1α-OH-D$_3$, 1α,25-(OH)$_2$-D$_3$, and their derivatives).[17]

The present paper deals with a general synthetic route leading to the 1α-hydroxy-Δ^5-steroids from readily available 3-keto-$\Delta^{1,4}$-steroids. The procedure consists of three steps from the latter compounds[18] which are readily obtainable from the 3-ketosteroids or their analogs by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[19] Since the successful application of this procedure to the synthesis of 1α-hydroxycholesterol and its subsequent transformation to 1α-OH-D$_3$ have already been reported in detail,[16] an application of this procedure to androsta-1,4-diene-3,17-dione (Ia) and pregna-1,4-diene-3,20-dione (IIa) will be described here. Since we employ a strong basic condition in the first step in our procedure, it is more convenient to protect the isolated keto-functions as ethylene ketal in order to avoid the undesirable self-condensation reactions. The selective ethylene ketal formations of Ia and IIa were made by treating these compounds in reflux benzene with ethylene glycol in the presence of a small amount of *p*-toluene sulfonic acid. The derived 17,17-ethylenedioxyandrosta-1,4-dien-3-one (Ib) and 20,20-ethylenedioxypregna-1,4-dien-3-one (IIb) were used as the starting materials.

In the first step in our procedure, the 3-keto-$\Delta^{1,4}$-steroids (Ib and IIb) were converted to the 3-keto-$\Delta^{1,5}$-steroids (III and IV) *via* the deconjugation procedure using *t*-BuOK in dimethylsulfoxide[20] (DMSO), followed by treatment with ice-water and extraction with

16) C. Kaneko, S. Yamada, A. Sugimoto, Y. Eguchi, M. Ishikawa, T. Suda, M. Suzuki, S. Kakuta, and S. Sasaki, *Steroids*, **23**, 75 (1974).

17) The similar experiments aiming to find out new methods for the introduction of 1α-hydroxyl group into steroids as well as to synthesize the active vitamin D$_3$ metabolite [1α,25-(OH)$_2$–D$_3$] and the related metabolites are in progress by Drs. Ikekawa and Morisaki's group at Tokyo Institute of Technology. See for 1α-hydroxycholesterol: *a*) M. Morisaki, K. Bannai, and N. Ikekawa, *Chem. Pharm. Bull.* (*Tokyo*), **21**, 1853 (1973); for 1α,25-dihydroxycholesterol; *b*) M. Morisaki, J. Rubio-Lightbourn, N. Ikekawa, and T. Takeshita, *Chem. Pharm. Bull.* (Tokyo), **21**, 2568 (1973): and for 24,25- and 25,26-dihydroxycholesterols; *c*) M. Seki, J. Lubio-Lightbourn, M. Morisaki, and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2783 (1973).

18) A preliminary report of this procedure has been published: C. Kaneko, S. Yamada, A. Sugimoto, M. Ishikawa, S. Sasaki, and T. Suda, *Tetrahedron Letters*, **1973**, 2339.

19) *a*) R. Owyang, in "Steroid Reactions," ed. by C. Djerassi, Holden-Day Inc., San Francisco, 1963, p. 229; *b*) C.C. Beard, in "Organic Reactions in Steroid Chemistry," ed. by J. Fried and J.A. Edwards, Van Nortrand Reinhold Co., N.Y., 1972, p. 308.

20) E. Shapiro, L. Weber, E.P. Oliveto, H.L. Herzog, R. Neri, S. Tolksdorf, M. Tanabe, and D.F. Crowe, *Steroids*, **8**, 461 (1966).

benzene-ethyl acetate. The 3-keto-$\Delta^{1,5}$-steroids were then reduced to the 3β-hydroxy-$\Delta^{1,5}$-steroids (V and VI) with $NaBH_4$ in methanol at 0° or more preferably with $Ca(BH_4)_2$ in ethanol below −10° and this step corresponds to the second step in the procedure. More conveniently, the reduction could be applied directly to the crude products of the deconjugation reactions, by which the yields of the 3β-hydroxy-$\Delta^{1,5}$-steroids (V and VI) were 65—75% based on the 3-keto-$\Delta^{1,4}$-steroids (Ib and IIb).[21] The configurational assignments in compounds, V and VI, were supported by the respective nuclear magnetic resonance (NMR) spectra which showed a broad multiplet ($W_{1/2}$: 20 Hz) at around 5.8 τ for the axial 3α-proton.

Confirmation of *beta*-configuration of the newly formed 3-hydroxy function in V was provided by the selective reduction of the 1,2-double bond with palladium on charcoal in dioxane. The product obtained after hydrolysis of the 17-ethylene ketal function was proved to be identical in all respects with dehydroepiandrosterone (VIIa). The same catalytic reduction of 3-hydroxy-cholesta-1,5-diene obtained from cholesta-1,4-dien-3-one by the deconjugation and subsequent metal-hydride reduction also afforded cholesterol identical with an authentic sample.[16,18]

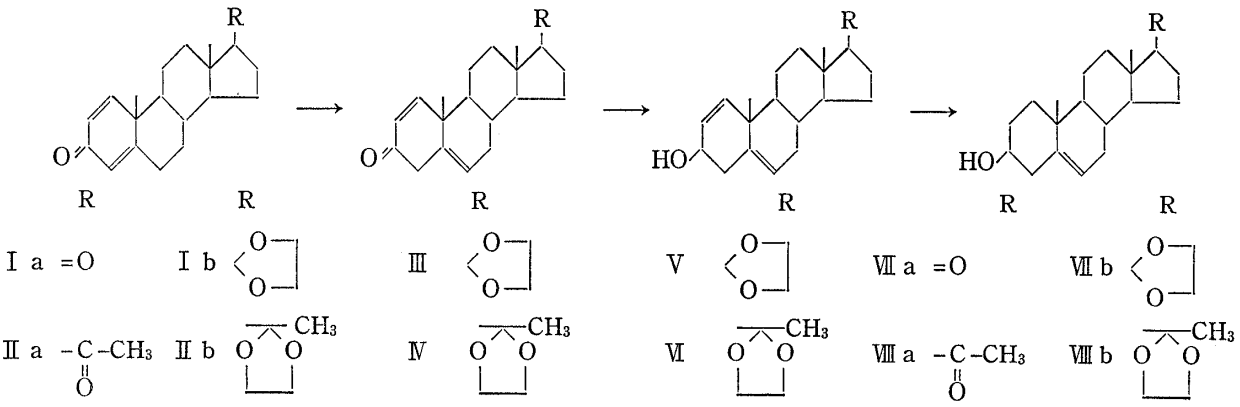


Chart 1

The final step in the procedure is achieved by hydroboration of the 3β-hydroxy-$\Delta^{1,5}$-steroids (V and VI) in tetrahydrofuran (THF) at room temperature for 1 hr by 0.8 mole equivalent of 1 M solution of diborane in THF,[22] followed by the oxidation with alkaline hydrogen peroxide.

By chromatography on alumina, the oxidation products from V or VI yielded, respectively, first the starting material (20—25%) and then two isomeric dihydroxy compounds, IXb or Xb (15—20%) and XIb or XIIb (20—25%).

Introduction of the hydroxyl group at 1α- or 2α-position of these steroids is reasonably assumed from the steric factors in the course of hydroboration[23,24] and it was actually verified from NMR spectroscopic studies and chemical reactions on these products that the more strongly adsorbed on alumina to be the 2α,3β-dihydroxy isomer (XIb and XIIb) and the other one to be the 1α,3β-dihydroxy isomer (IXb and Xb).

21) The 3β-hydroxy-$\Delta^{1,5}$-steroids were also obtained from the related 3-keto-$\Delta^{1,5}$-steroids by the reduction using $LiAlH_4$ or $LiAlH(OBu)_3$: *a*) R. Wiechert, O. Engelfried, U. Kerb, H. Laurent, and H. Muller, *Chem. Ber.*, **99**, 1118 (1966); *b*) M. Tanabe and D.F. Crowe, *Tetrahedron*, **23**, 2115 (1967).

22) *a*) H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 5832 (1959); *b*) Z. Zweifel, K. Nagase, and H.C. Brown, *ibid.*, **84**, 183 (1962); *c*) G. Zweifel and H.C. Brown, *Organic Reactions*, **13**, 33 (1963).

23) Diborane reacts with a disubstituted olefin much faster than with a trisubstituted one; see for example, H.C. Brown, "Hydroboration," W.A. Benjamin Inc., 1962.

24) Sondheimer, and Nussim found that cholest-1-ene reacted with diborane to give, after oxidation, 1α- and 2α-ols and confirmed the attack of reagent from the unhindered rear side: F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961). See also S. Wolfe, M. Nussim, Y. Mayer, and F. Sondheimer, *ibid.*, **24**, 1034 (1959).

The structure determination of the hydroboration products (IXb and XIb) has been carried out in the following way. The specific introduction of a hydroxyl group at A ring in these products is supported by the presence of only one vinylic proton signal at around 4.5 τ region in each compound (IXb and XIb).[25] The spectrum of IXb showed further two proton signals at around 6.0 τ ($W_{1/2}\simeq 20$ Hz; H_3) and at 6.2 τ ($W_{1/2}\simeq 8$ Hz; H_1), but their exact half widths could not be determined by the presence of the strong signal due to methylene protons in the ketal group (6.14 τ, s, 4H).

The ketal groups at C-17 in IXb and XIb were readily eliminated by the mild acid hydrolysis affording 1α- and 2α-hydroxydehydroepiandrosterone (IXa and XIa), respectively.

The lower field bands in the NMR spectrum of XIa consist of a one proton triplet of doublets at 6.38 τ (J=9.5 and 5 Hz) and a one proton quartet at 6.72 τ (J=9.5 Hz) indicating the presence of two vicinal axial methine protons bonded to hydroxy function as well as one olefinic proton doublet at 4.60 τ for H_6 (J=5 Hz).

The structure of IXa was confirmed unequivocally, since its physical properties were identical in all respects with 1α-hydroxydehydroepiandrosterone obtained from the microbiological hydroxylation of dehydroepiandrosterone.[26]

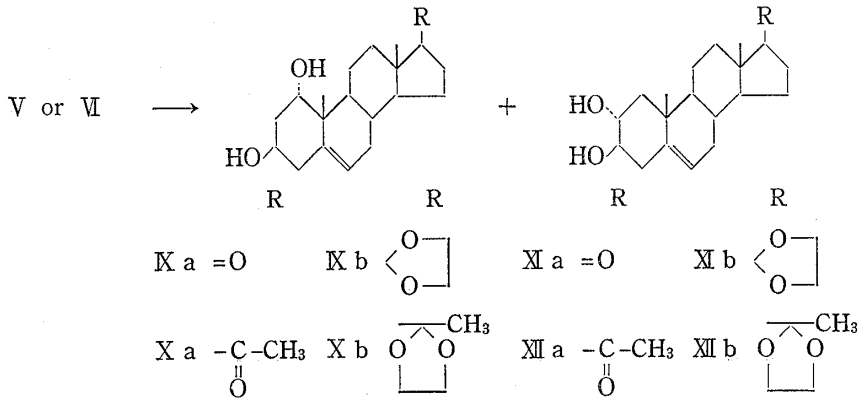


Chart 2

Concerning to the mass spectra of these two diols and their 17-ketal derivatives, it seems worthy to note that the 1α-hydroxy derivatives (IXa and IXb) showed M-18 (H_2O) peaks more intensely than the molecular ion peaks, while the relative intensities of these two peaks were reversed in the 2α-hydroxy derivatives (XIa and XIb). In accordance with the structures deduced as above, this fragmentation indicates that the newly introduced hydroxyl groups in the former compounds (IXa and IXb) are axially oriented (1α-configuration) and thus eliminated much easier under these conditions than the equatorially oriented 2α-hydroxy functions in the latter compounds (XIa and XIb). In the mass spectra of the corresponding diacetates, the molecular ion peak of the acetate of IXa could no longer be observed, and the M-60 (CH_3COOH) peak appeared as the parent peak though XIa still showed the molecular ion peak.

The NMR spectra of Xb and XIIb obtained from VI by the same reaction sequence were in good accordance with the assigned structures and the parent peak in the mass spectrum of Xb corresponded to M-15 (CH_3) ion, while that of XIIb coincided with the molecular ion though in very weak intensity.

The fact that cholesta-1,4-dien-3-one also afforded 1α- and 2α-hydroxy derivatives of cholesterol in the same reaction sequence[16,18] demonstrates clearly that both the regio- and stereo-selectivities observed in the hydroboration of the androsta-1,5-dien-3β-ol (V) and the

25) In the hydroboration of this and the related compounds (*e.g.*, cholesta-1,5-dien-3β-ol), the third diols were also obtained, whose structures have not been determined as yet. *cf.* reference 16.

26) R.M. Dodson, A.G. Goldkamp, and R.D. Muir, *J. Am. Chem. Soc.*, **82**, 4026 (1960).

pregna-1,5-dien-3β-ol (VI) are quite general phenomenon in the related $\Delta^{1,5}$-steroids and seems to exclude the participation of the 3β-hydroxy group in this reaction.[27]

By the use of an excess of BH_3–THF ($\geq$1.5 mole equivalent), at least two trihydroxy derivatives were obtained, while the use of the reagent less than 0.8 mole equivalent reduced the yields of the diols and resulted in the predominant recovery of the starting materials.

As described in the experimental in detail, when the deconjugation reaction was applied to 17- or 20-keto compounds (Ia and IIa) having no protective group, predominant products were undesired self-condensation products and the yields of the desired deconjugation products were poor.

We are currently investigating the use of an alkylborane instead of diborane and the protection of 3β-hydroxy function of V and VI in the final step in order to see how these alterations affect the results of the hydroxylation reaction.

Experimental[28]

17,17-Ethylenedioxyandrosta-1,5-dien-3-one (III)——To a solution of 17,17-ethylenedioxyandrosta-1,4-dien-3-one (Ib, 5 g) in 100 ml of DMSO (distilled before use after dehydration over CaH_2) was added finely powdered *t*-BuOK (prepared from 2.5 g of potassium), and the solution was stirred for 1 hr at 10°. The reaction mixture was poured into ice-water and extracted with 1 liter of benzene–ethyl acetate (1 : 2 v/v). Water and the solvent employed were previously saturated with CO_2 by the addition of dry ice. The organic layer was washed with ice water several times and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* below 35° gave 4.5 g of semi-crystalline residue. Recrystallization of the small portion (450 mg) of this residue from methanol gave 17,17-ethylenedioxyandrosta-1,5-dien-3-one (III), mp 154—157° (350 mg; 70%); λ_{max}^{EtOH} 227 nm (log ε=4.03), ν_{max}: 1690 cm^{-1}. NMR ($CDCl_3$): 3.05 (d, J=10 Hz, 1H), 4.15 (d, J=10 Hz, 1H), 4.60 (d, J=4 Hz, 1H), 6.15 (s, 4H), 6.70 and 7.15 (an AB quartet, J=17 Hz, 2H). Mass Spectrum *m/e*: 328 (M^+). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.63; H, 8.74.

17,17-Ethylenedioxyandrosta-1,5-dien-3β-ol (V)——The crude semi-crystalline residue (4.05 g) obtained above was dissolved in 250 ml of methanol, and to this solution was added 2.5 g of $NaBH_4$ in 100 ml of water under ice-cooling and stirring. After kept stirring for 1 hr at 0°, the excess of $NaBH_4$ was decomposed by adding 200 ml of 50% aqueous acetone. After the solution was kept standing at room temperature overnight, the crystals deposited were filtered, washed thoroughly with water and dried under vacuum. Recrystallization from methanol afforded 2.4 g of V. Evaporation of acetone followed by extraction with CH_2Cl_2 gave 600 mg of the residue. This was combined with the above mother liquor and the whole was chromatographed on alumina with $CHCl_3$. About 400 mg of V was obtained. The combined yield of V was 63% based from Ib, mp 134—138°. Mass Spectrum *m/e*: 330. NMR ($CDCl_3$): 4.26 (broad d, J=10 Hz, 1H), 4.56 (d, J=10 Hz, 1H), 4.64 (m, 1H), 5.87 (d.d, J=10 and 7 Hz, 1H), 6.16 (s, –OCH_2CH_2O–). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.18; H, 9.29.

The use of $Ca(BH_4)_2$ instead of $NaBH_4$ raised the yield of V from Ib to 75%. The detailed procedure of this method was reported already in ref. 16 in the preparation of cholesta-1,5-dien-3β-ol from cholesta-1,5-dien-3-one. By mild acid hydrolysis, V gave 3β-hydroxyandrosta-1,5-dien-17-one, mp 131—133° in a quantitative yield. The latter compound was then reduced to dehydroepiandrosterone (mp 138—140°) by catalytic hydrogenation with 10% Pd/C in methanol (The reduction was terminated at the point of 1 mole equivalent hydrogen-uptake).

Hydroboration of 17,17-ethylenedioxyandrosta-1,5-dien-3β-ol (V)——To a solution of 17,17-ethylenedioxyandrosta-1,5-dien-3β-ol (V, 1 g) in dry THF (30 ml) was added 1.6 ml of 1M diborane solution (pre-

27) Contrary to the hydroborations described above, the methylenation of $\Delta^{1,5}$-3β-hydroxysteroids with iodomethylzinc iodide reagent proceeds through preferential β-face attack of the reagent to give 1β,2β-methylene-3β-hydroxy-Δ^5-steroids. The complex formation of the reagent with the hydroxyl group followed by intramolecular transfer of methylene has been suggested: *a*) E.P. Blanchard and H.E. Simmons, *J. Am. Chem. Soc.*, **86**, 1337 (1964); *b*) H.E. Simmons, E.P. Blanchard, and R.D. Smith, ibid., **86**, 1347 (1964).

28) The melting points were determined in a capillary tube and are uncorrected. The infrared spectra were recorded in KBr pellets on DS-403 and IR-S JASCO spectrometers and ultraviolet (UV) spectra were determined on a Hitachi model-323. The NMR spectra were obtained in the specified solvents on a C-60 HL JEOL (60 Mc.p.s.) and the chemical shifts are given in τ-units. Mass spectra were recorded on a Hitachi-model RMU-7M double focus mass spectrometer using all cases a direct sample insertion into the ion source. Optical rotation values were measured by Yanagimoto model OR-10 direct reading polarimeter.

pared as described in ref. 21*c*) and the solution was kept standing for 30 min at room temperature. The excess of diborane was decomposed by addition of water (2 ml). To this solution was added 3N NaOH (10 ml) and 30% H_2O_2 (10 ml) and the whole was stirred for 2 hr at room temperature. Extraction with $CHCl_3$ and evaporation after drying over $MgSO_4$ gave the residue (900 mg), which was chromatographed on alumina. Elution with $CHCl_3$ gave a small amount of the starting material (V). Elution with 1% methanol–$CHCl_3$[29] gave after recrystallization from methanol 17,17-ethylenedioxyandrost-5-ene-1α,3β-diol (IXb), 155 mg, mp 194—197°. NMR ($CDCl_3$): 4.45 (m, H_6), 5.9—6.3 (m, H_3,H_1, and $-OCH_2CH_2O-$). Mass Spectrum *m/e*: 348 (M^+). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.30; H, 9.33.

Elution with the same solvent then afforded 17,17-ethylenedioxyandrost-5-ene-2α,3β-diol (XIb), 210 mg, mp 122—126° (from methanol). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.35; H, 9.30.

1α,3β-Dihydroxyandrost-5-en-17-one (IXa)——To a solution of IXb (100 mg) in methanol (10 ml) was added 10 ml of 5% aq. HCl and the whole was stirred at room temperature for 3 hr and then at 50° for 1 hr. The resulting solution was diluted with $CHCl_3$, washed with excess of 5% aq. Na_2CO_3 and then with water, dried over $MgSO_4$ and evaporated. Recrystallization from excess of methanol gave 1α,3β-dihydroxyandrost-5-en-17-one (IXa, 75 mg) as colorless prisms, mp 261—266°. $[\alpha]_D^{20}$: +23.5° (methanol). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.83; H, 9.42. Mass Spectrum *m/e*: 304 (M^+), 286 (the intensity of the latter peak is stronger than that of the former).

Treatment of IXa with Ac_2O and pyridine in the usual manner followed by recrystallization from methanol gave the diacetate, mp 219—221°. Mass Spectrum *m/e*: M−60 as the parent peak, 286, 268. NMR ($CDCl_3$): 4.46 (broad d, J=5 Hz, 1H), 4.96 (t, J=2.5 Hz, 1H), 5.10 (d.d, J=10 and 5 Hz, 1H), 8.0 (s, 6H). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found, C, 71.08; H, 8.37.

2α,3β-Dihydroxyandrost-5-en-17-one (XIa)——By the hydrolysis in the same manner as described above, XIb afforded XIa, mp 98—100°. NMR ($CDCl_3$): 4.60 (d, J=5 Hz, 1H), 6.38 (t.d, J=9.5 and 5 Hz, 1H), 6.72 (q, J=9.5 Hz, 1H). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.75; H, 9.39.

20,20-Ethylenedioxypregna-1,5-dien-3β-ol (VI)——20,20-Ethyllenedioxypregna-1,4-dien-3-one (IIb), mp 183—184°, was converted to VI in *ca.* 50% yield by the same manner as described in the transformation of Ib to V.[30] mp 135—140° (methanol). Mass Spectrum *m/e*: 358 (M^+), 343 (M−15 as base peak). NMR ($CDCl_3$): 4.26 (d.d, J=10 and 2 Hz, 1H), 4.58 (d, J=10 Hz, 1H), 4.64 (m, 1H), 5.83 (d.d, J=10 and 7 Hz, 1H), 6.12 (s, $-OCH_2CH_2O-$). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05, H, 9.56. Found: C, 77.21, H, 9.63.

Hydroboration of 20,20-Ethylenedioxypregna-1,5-dien-3β-ol (VI)——By the hydroboration reaction performed under the same conditions described in the transformation of V to IXb and XIb, the compound (VI) gave Xb (18%), XIIb (20%) together with small amounts of the starting material (VI) and the mixture of triols.

20,20-Ethylenedioxypregne-5-en-1α,3β-diol (Xb), mp 158—163° (acetone–ether). Mass Spectrum *m/e*: 361 (M−15 as parent peak), 358 (M−18). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.53; H, 9.56.

This compound gave 1α,3β-dihydroxypregn-5-en-20-one in good yield after hydrolysis by 5% aq. HCl and methanol, mp 232—236° (methanol–ether). Mass Spectrum *m/e*: 332 (M^+), 314 (M-18) [the intensity of the latter is much stronger than that of the former]. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.59; H, 9.84.

20,20-Ethylenedioxypregn-5-ene-2α,3β-diol (XIIb), mp 205—206° (methanol). Mass Spectrum *m/e*: 376 (M^+), 361 (M−15 as base peak). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.40; H, 9.60. NMR ($CDCl_3$): 4.58 (broad s, 1H), 6.10 (b.s, 4H), 6.0—6.9 (m, 2H).

This was hydrolyzed to 2α,3β-dihydroxypregn-5-en-20-one in good yield by the method as described above, mp 195—196° (methanol). Mass Spectrum *m/e*: 332 (M^+), 314 (M−18) [the intensities of both peaks were almost the same]. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.81; H, 9.64.

3β,20-Dihydroxypregna-1,5-diene——To the solution of pregna-1,4-diene-3,20-dione (IIa: 2 g) in 70 ml of DMSO was added finely powdered *t*-BuOK (prepared from 1.5 g of potassium) and the solution was stirred for 30 min at 0°. The reaction mixture was poured into excess of ice-water and extracted with $CHCl_3$. After the usual work-up, the residue was dissolved in 20 ml of ether and to this was added 100 ml of methanol. To this solution was added 1.5 g of $NaBH_4$ in 60 ml of H_2O under ice-cooling. After kept stirring for 1 hr at 0°, the excess of $NaBH_4$ was decomposed by addition of acetone. Acetone was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2 and dried over $MgSO_4$. The residue after evaporation of the solvent was chromatographed over alumina to give 700 mg of 3β,20-dihydroxypregna-1,5-diene, mp 192—197° (methanol). NMR ($CDCl_3$): 4.23 (d, J=10 Hz, 1H), 4.47 (d, J=10 Hz, 1H), 4.60 (d, J=5 Hz, 1H), 5.82 (d.d, J=10 and 6 Hz, 1H), 6.30 (m, 1H), 8.77 (d, J=6 Hz, 3H), 8.90 and 9.23 (s, each 3H). Mass Spectrum *m/e*: 316 (M^+). *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.53; H, 10.40.

29) The first eluate from this solvent system afforded a small amount of another diol, mp 156—159° (methanol): Mass Spectrum *m/e* 348 (M^+), whose structure has not been determined as yet.

30) 20,20-Ethylenedioxypregna-1,5-dien-3-one (IV) obtained by the deconjugation reaction melted between 152—168° after recrystallization from methanol.

Hydroboration of 3β,20-Dihydroxypregna-1,5-diene——Hydroboration of 3β,20-dihydroxypregna-1,5-diene (1 g) obtained above was carried out in 30 ml of dry THF with 2 ml of 1M diborane solution. The crude addition product was then oxidized with alkaline-hydrogen peroxide as described in the hydroboration of V. The residue obtained after $CHCl_3$ extraction was chromatographed over alumina. Elution with 1% methanol–$CHCl_3$ gave a small amount of the starting material (*ca.* 10%). Elution with 2% methanol–$CHCl_3$ gave after recrystallization from acetone 1α,3β,20-trihydroxypregn-5-ene (140 mg), mp 196—204°. Mass Spectrum *m/e*: 334 (M^+), 316 (The intensity of the latter is much stronger than that of the former).

Elution with the same solvent then gave the other ene-triol (90 mg), mp 212—219° (acetone–ether), Mass Spectrum *m/e*: 334 (M^+), whose structure is now under investigation.

Elution with 5% methanol–$CHCl_3$ gave 2α,3β,20-trihydroxypregn-5-ene (200 mg), mp 235—240° (methanol). Mass Spectrum *m/e*: 334 (M^+), 316: the intensity of each peak was almost the same. *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.37; H, 10.38.

By acetylation in the usual way, the triacetate (mp 190—193°, Mass Spectrum *m/e*: 400 as the parent peak) was obtained. NMR ($CDCl_3$): 4.60 (d, $J=5$ Hz, 1H), 4.90 (m, 1H), 5.1—5.4 (m, 2H), 8.0 (s, 9H).

Elution from 20—40% methanol–$CHCl_3$ afforded an appreciable amount of the tetraol mixture.

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