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Further Preparation of Steroidal Diosphenols. I. Synthesis of Some 4,4-Dimethyl-2-hydroxy-3-oxo-1-ene Steroids in Androstane and Pregnane Series

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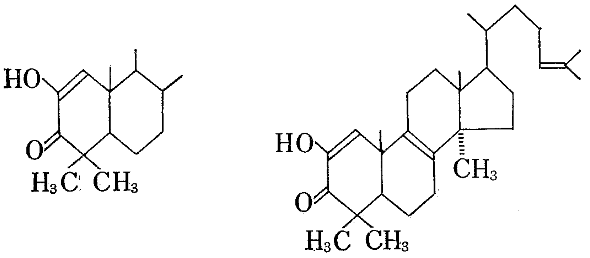
Some 2-hydroxy-3-oxo-4,4-dimethyl-1-ene steroids and two 4-hydroxy-3-oxo-2,2-dimethyl-4-ene steroids were prepared in order to obtain anti-tumor substances against sex hormone dependent cancer such as breast cancer and prostatic cancer. These diosphenols were synthesized by the autoxidation of the corresponding 3-oxo steroids in the presence of potassium *tert*-butoxide in *tert*-butanol.

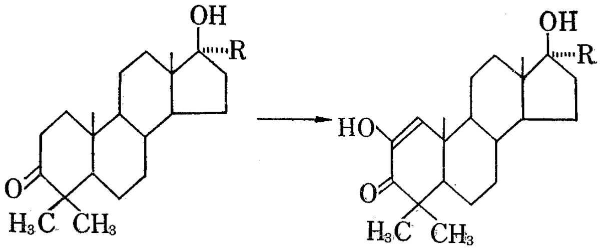
Some diosphenols having the partial structure I in ring A of steroids have been prepared in order to examine anti-tumor activities[2] and it has been described that 2-hydroxylanosta-1,8,24-trien-3-one (II) shows anti-tumor activity on cheek-pouch test.[3] On the other hand, many steroid hormones were used as therapies against hormone dependent cancer such as advanced breast cancer and prostatic cancer, and some of them were found to be effective.[4] If any therapeutic steroid having less or no hormonal effect and more anti-tumor potency is developed, such a material will surely bring much benefits for the therapy. From this point of view, further preparations of diosphenols and the examination of their activities were very interesting for us. This paper describes synthesis and biological activities of diosphenols, which have the partial structure I or related structure in ring A and various substituents in ring B, C and D.



I

II

Chart 1



IIIa : R = H,5-ene
IIIb : R = CH_3,5-ene
IIIc : R = H,5α
IIId : R = CH_3,5α

IVa : R = H,5-ene
IVb : R = CH_3,5-ene
IVc : R = H,5α
IVd : R = CH_3,5α

Chart 2

Although various synthetic methods of a diosphenol are reported,[2] all diosphenols in this paper were prepared by autoxidation of 3-oxo steroids in potassium *tert*-butoxide in *tert*-butanol

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[1] Location: *a) Shimosakunobe, Kawasaki-shi*; *b) Tsukiji, Chuo-ku, Tokyo.*

[2] H. Mori, V.S. Gandhi, and E. Schwenk, *Chem. Pharm. Bull.* (*Tokyo*), 10, 842 (1962).

[3] E. Schwenk, *Drug Res.* (Arzneim.-Forsch.), 12, 1143 (1962).

[4] G. Pincus and E.P. Vollmer, "Biological Activities of Steroids in Relation to Cancer," Academic Press, N. Y., 1960.

developed by Barton and his co-workers.[5] The known 4,4-dimethyl-3-oxo steroids[6] IIIa, IIIb, IIIc and IIId were readily converted into the corresponding diosphenols IVa, IVb, IVc and IVd. Among these diosphenols, IVa has been already prepared in the above-mentioned literature[2] by different route from IIIa through 2-oximino compound, but it was found that the autoxidation of IIIa is much better method in this case.

IVa was introduced into diacetate (Va) by treatment with acetic anhydride and pyridine at room temperature, whereas 17-mono acetate (Vb) was obtained by reflux with acetic acid, the structure of which was instantly supported from ultraviolet spectrum data, showing that the wave length of the absorption of 17-mono acetate (Vb) was 271 mμ, that of diacetate (Va) being 236 mμ.[7] This observation is very reasonable from the fact that the reaction of estradiol with carboxylic acid at reflux temperature gives estradiol 17-mono acylate,[8] that is, the acylation rate of an enol or phenol hydroxyl group is very slow in comparison with that of secondary alcoholic hydroxyl group under this condition. The diacetate (Va) was oxidized with sodium dichromate in acetic acid and acetic anhydride[9] gave the corresponding 7-oxo compound (VIa), which on hydrolysis with hydrochloric acid gave the free diosphenol (VIb). Jones oxidation of IVa led to 17-oxo diosphenol (VIIa), which was also obtainable from 4,4-dimethyl-5-androstene-3,17-dione (VIII) by autoxidation.

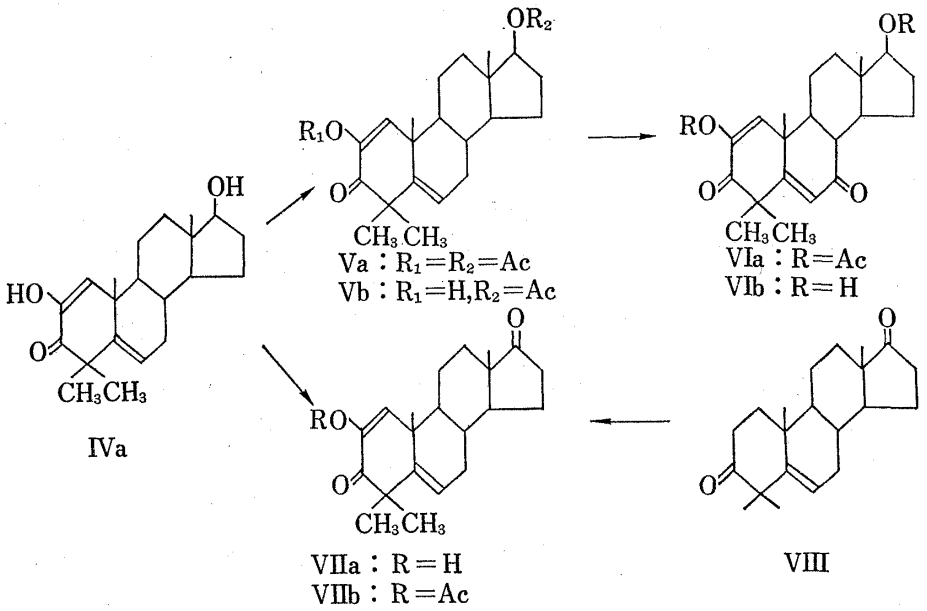

Chart 3

11β,17β-Dihydroxy-4-androsten-3-one (IX) was methylated by the usual manner developed by Woodward and his co-workers[10] (methyl iodide-potassium *tert*-butoxide in *tert*-butanol) to give the corresponding 4,4-dimethyl compound (X), from which the diosphenol (XI) was obtained by autoxidation. Methylation of 20-ethylene ketals of progesterone,[11] 17α-hydroxyprogesterone[12] and 21-acetoxyprogesterone[13] (XIIa, XIIb and XIIc) by the same way afforded the corresponding 4,4-dimethyl compounds, XIIIa, XIIIb and XIIIc.

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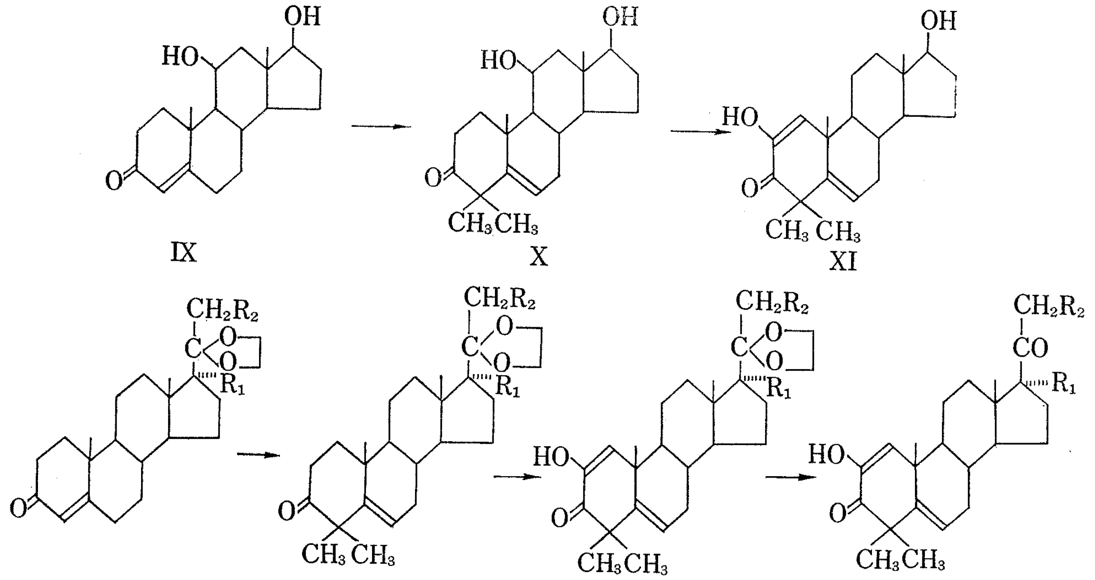
[5] D.H.R. Barton, S.K. Pradham, S. Sternhell, and J.F. Templeton, *J. Chem. Soc.*, **1961**, 255.
[6] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).
[7] E.T. Stiller and O. Rosenheim, *J. Chem. Soc.*, **1938**, 353.
[8] M. Hosoi and H. Mori, *Yakugaku Zasshi*, **76**, 847 (1956).
[9] C.W. Marshall, R.E. Ray, I. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6308 (1957).
[10] R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A.I. Ives, and R.B. Kelly, *J. Chem. Soc.*, **1957**, 1131.
[11] M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).
[12] P.L. Julian, E.W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).
[13] F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1956).

The autoxidation of 4,4-dimethyl compounds, XIIIa, XIIIb and XIIIc followed by careful acidification of the reaction products led to the correponding diosphenols (XIVa, XIVb and XIVc), which on hydrolysis with acid gave the desired diosphenols, XVa, XVb and XVc.

Methylation of cortisol BMD (XVI)[14] with the usual method was undertaken without satisfactory result on account of low solubility in *tert*-butanol. Tetrahydrofuran was found



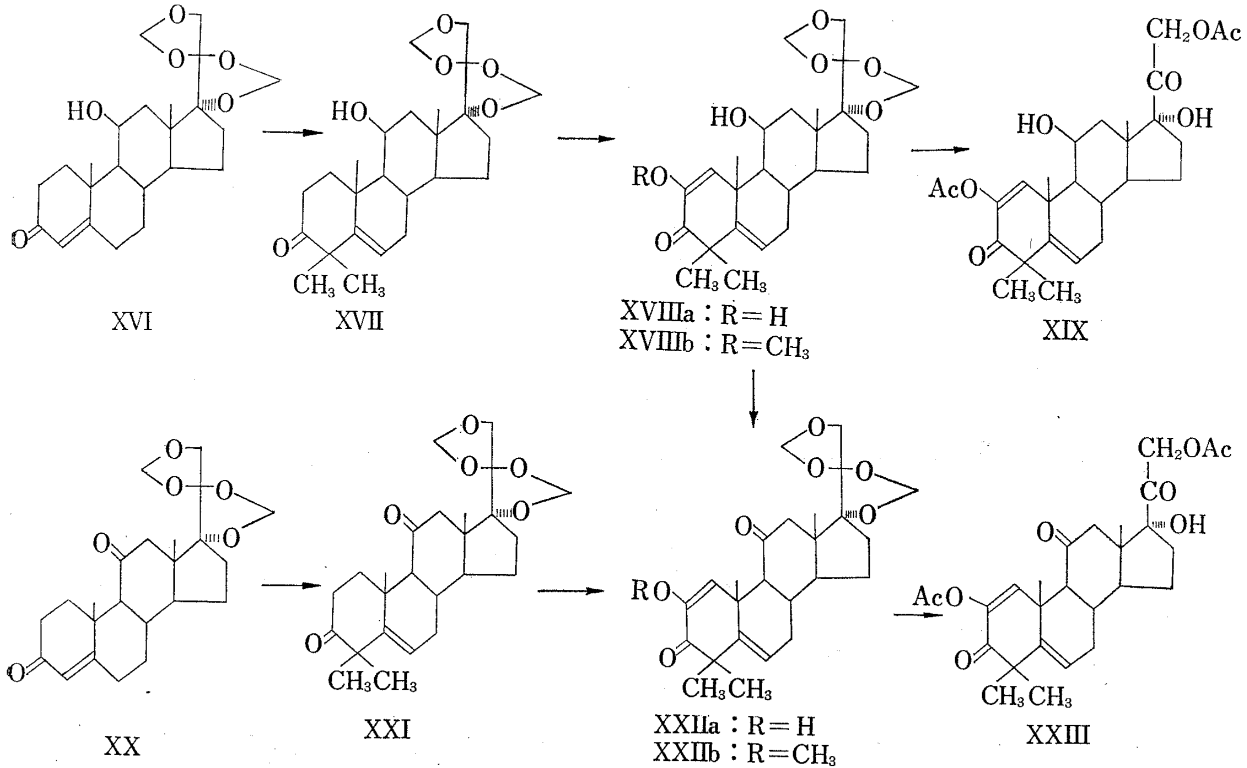
XIIa : $R_1=R_2=H$
XIIb : $R_1=OH, R_2=H$
XIIc : $R_1=H, R_2=OAc$

XIIIa : $R_1=R_2=H$
XIIIb : $R_1=OH, R_2=H$
XIIIc : $R_1=H, R_2=OH$

XIVa : $R_1=R_2=H$
XIVb : $R_1=OH, R_2=H$
XIVc : $R_1=H, R_2=OH$

XVa : $R_1=R_2=H$
XVb : $R_1=OH, R_2=H$
XVc : $R_1=H, R_2=OH$

Chart 4



XVIIIa : R=H
XVIIIb : $R=CH_3$

XXIIa : R=H
XXIIb : $R=CH_3$

Chart 5

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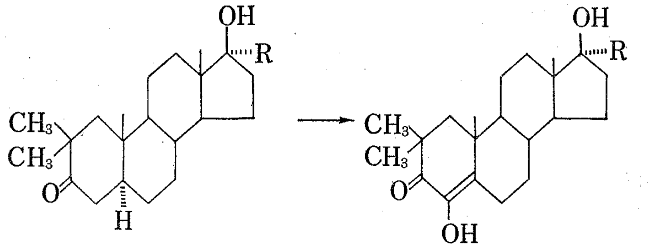
[14] R.E. Beyler, R.M. Moriarty, F. Hoffman, and L.H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

to be a good solvent in this reaction, that is, cortisol BMD (XVI) was introduced into 4,4-dimethyl compound (XVII) in satisfactory yield by methyl iodide–potassium *tert*-butoxide in *tert*-butanol and tetrahydrofuran. The autoxidation of XVII was also proceeded smoothly by using tetrahydrofuran as a solvent to give the diosphenol BMD (XVIIIa). Cortisone BMD (XX)[14] was introduced into 4,4-dimethyl compound (XXI) and the diosphenol BMD (XXIIa) by the same procedures. The possibility that methylation or autoxidation at C-12 or C-9 would occur was ruled out from the following transformations. The diosphenols (XVIIIa and XXIIa) were treated with dimethyl sulfate in alkali to give 2-methyl ethers (XVIIIb and XXIIb) respectively. The oxidation of XVIIIb with chromium trioxide gave 11-oxo compound (XXIIb), the infrared spectrum of which was identical with that of 2-methyl ether (XXIIb) obtained above. The hydrolysis of XVIIIa and XXIIa by 50% acetic acid followed by acetylation with acetic anhydride and pyridine gave the diosphenol diacetates (XIX and XXIII) respectively.

The autoxidation of 2,2-dimethyl-5α-3-oxo steroids,[15] XXIVa and XXIVb, in the usual way afforded the corresponding diosphenols, XXVa and XXVb, respectively.



XXIVa : R = H
XXIVb : R = CH_3

XXVa : R = H
XXVb : R = CH_3

Chart 6

Anti-mammary-tumor activities were measured by the inhibition of growth of testosterone responsive mammary adenocarcinomas of C3H/Heston female mice, the result of which was already reported by Takatani, *et al.*[16] Most diosphenols prepared in this paper were found to be effective in this test. The diosphenol (IVa) was submitted to clinical test against advanced breast cancer and could be used as an effective agent in some cases without any side effect, the details of which was described in the paper.[16]

Experimental[17]

General Procedure of Autoxidation——K (2.0 g) was dissolved in *tert*-BuOH (100 ml) and 4,4-dimethyl-3-oxo steroid (1.0 g) was added. The solution or suspension was shaken in O_2 atmosphere until 1.0—1.2 equivalent volume O_2 was absorbed, and poured into ice-cold water. After acidification with 10% HCl or AcOH, the product was isolated by filtration or extraction with ether, and recrystallized from suitable solvent. Sometimes it was very effective to purify a desired diosphenol that the solution of a diosphenol was shaken with 20% KOH, and the resulting K salt (soluble in 20% KOH in some cases and insoluble in other cases) was again converted into the diosphenol by acid.

2,17β-Dihydroxy-4,4-dimethyl-1,5-androstadien-3-one (IVa)——17β-Hydroxy-4,4-dimethyl-5-androsten-3-one (IIIa, mp 192—198°, not completely pure, 20 g) was autoxidized as described above. After alkaline treatment, the diosphenol (IVa, 13.05 g), mp 155—157° was obtained by recrystallization from MeOH, which was identical with an authentic sample in all respects.

2,17β-Dihydroxy-4,4,17-trimethyl-1,5-androstadien-3-one (IVb)——17β-Hydroxy-4,4,17-trimethyl-5-androsten-3-one (IIIb, 5.0 g) was autoxidized as described above, and after alkaline treatment, the product was recrystallized from aqueous MeOH to give the diosphenol (IVb, 1.3 g), mp 154—157°. Further recrystallization from MeOH afforded an analytical sample as colorless needles. mp 154—157°, $[\alpha]^{20}_{D}$ +25° (c=1.00), UV λ_{max} (ε) 273 mμ (9500). *Anal.* Calcd. for $C_{22}H_{32}O_3 \cdot \frac{1}{2}H_2O$: C, 74.96; H, 9.51. Found: C, 75.16; H, 9.48.

2,17β-Dihydroxy-4,4-dimethyl-5α-androst-1-en-3-one (IVc)——17β-Hydroxy-4,4-dimethyl-5α-androst-1-en-3-one (IIIc, 2.0 g) was autoxidized as decribed above. Recrystallization from ether afforded the

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[15] H.J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

[16] O. Takatani, S. Kumaoka, O. Abe, N. Sakauchi, R. Sato, and H. Mori, *Endocrinogia Japonica*, **14**, 195 (1967).

[17] All melting points were uncorrected. Optical rotations were measured in chloroform solution, and ultraviolet spectrum in methanol solution unless otherwise stated.

diosphenol (IVc, 1.2 g), mp 171—174°. Further recrystallization from ether gave an analytical sample as colorless prisms. mp 171—175°, $[\alpha]_D^{25}$ +27°(c=1.18), UV λ_{max} (ε) 270 mμ (9000). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.78; H, 9.56.

2,17β-Dihydroxy-4,4,17-trimethyl-5α-androst-1-en-3-one(IVd)——17β-Hydroxy-4,4,17-trimethyl-5α-androstan-3-one (IIId, 0.65 g) was autoxidized as described above. Recrystallization from acetone afforded the diosphenol (IVd, 0.39 g), mp 173—176°. An analytical sample was obtained by chromatography on Florisil and recrystallization from MeOH of the fraction eluted by benzene as colorless prisms. mp 175—177°, $[\alpha]_D^{25}$ +19°(c=0.98), UV λ_{max} (ε) 270 mμ (9100). *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.29; H, 9.96.

2,17β-Diacetoxy-4,4-dimethyl-1,5-androstadien-3-one (Va)——A solution of 2,17β-dihydroxy-4,4-dimethyl-1,5-androstadien-3-one (IVa, 1.0 g) in C_5H_5N (20 ml) and Ac_2O (5.0 ml) was allowed to stand for 2 days, and poured into 10% HCl. Precipitates were collected by filtration, washed with 5% Na_2CO_3 and water, and dried. Recrystallization from MeOH afforded the diacetate (Va, 0.93 g), mp 132—136°. An analytical sample was obtained by further recrystallization from MeOH as colorless prisms. mp 137—140°, $[\alpha]_D^{23}$ +18° (c=1.00), UV λ_{max} (ε) 236 mμ (7300). *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.39; H, 8.33.

17β-Acetoxy-2-hydroxy-4,4-dimethyl-1,5-androstadien-3-one (Vb)——A solution of 2,17β-dihydroxy-4,4-dimethyl-1,5-androstadien-3-one (IVa, 1.0 g) in AcOH (40 ml) was refluxed for 3 hr, and poured into water. Precipitates were collected by filtration, washed with water, 5% Na_2CO_3 and water, and dried. Recrystallization from acetone gave the acetate (Vb, 0.7 g), mp 188—194°. An analytical sample was obtained by further recrystallization from acetone as colorless needles. mp 197—199°, $[\alpha]_D^{25}$ +51° (c=1.00), UV λ_{max} (ε) 271 mμ (7700). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.99; H, 8.69.

2,17β-Diacetoxy-4,4-dimethyl-1,5-androstadiene-3,7-dione (VIa)——To a solution of 2,17β-diacetoxy-4,4-dimethyl-1,5-androstadien-3-one (Va, 2.8 g) in AcOH (16.8 ml) and Ac_2O (5.6 ml) was added solid $Na_2Cr_2O_7$ (2.8 g) at room temperature. The reaction mixture was stirred for 4 hr, stood at room temperature for 24 hr, and poured into water. Precipitates were collected by filtration and washed with water. Recrystallization from MeOH afforded VIa (1.9 g), mp 176—178°. $[\alpha]_D^{25}$ +24°(c=1.61). UV λ_{max} (ε) 236 mμ (14400). *Anal.* Calcd. $C_{25}H_{32}O_6$: C, 75.73; H, 8.14. Found: C, 75.63; H, 8.08.

2,17β-Dihydroxy-4,4-dimethyl-1,5-androstadiene-3,7-dione (VIb)——A solution of the diacetate (VIa, 5.0 g) in MeOH (100 ml) and 10% HCl (10 ml) was refluxed for 3 hr, and poured into water. Precipitates were collected by filtration, washed with water and dried. Recrystallization from MeOH afforded VIb (2.2g), mp 229—234°. Further recrystallization from MeOH gave an analytical sample as colorless prisms. mp 231—233°, $[\alpha]_D^{23}$ +60°(c=1.00, MeOH), UV λ_{max} (ε) 237 mμ (15800). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.98; H, 8.24.

2-Hydroxy-4,4-dimethyl-1,5-androstadiene-3,17-dione (VIIa)——a) From IVa: To an ice-cold solution of IVa (5.0 g) in acetone (100 ml) was added 8N CrO_3 solution (5.0 ml),[18] and after standing for 3 min the resulting suspension was poured into water. Precipitates were collected by filtration, washed with water and dried. Recrystallization from MeOH gave VIIa (2.25 g), mp 179—183°. An analytical sample was obtained by further recrystallization from MeOH as colorless prisms. mp 180—183°, $[\alpha]_D^{25}$ +124°(c=1.55), UV λ_{max} (ε) 270 mμ (6800). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.62; H, 8.78.

The acetate (VIIb) was obtained by usual acetylation with C_5H_5N and Ac_2O. mp 245—250° (from $CHCl_3$-MeOH), $[\alpha]_D^{20}$ +86° (c=1.00), UV λ_{max} (ε) 234 mμ (8900). *Anal.* Caclcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.47; H, 8.18.

b) From VIII: The autoxidation of VIII (4.2 g) by the procedure described above afforded VIIa (1.75g), mp 177—182°, identical with the sample obtained above.

11β,17β-Dihydroxy-4,4-dimethyl-5-androsten-3-one (X)—— MeI (1.3 ml) was dropwise added to a solution of 11β,17β-dihydroxy-4-androsten-3-one (IX, 1.0 g) in *tert*-BuOH (20 ml) in which K (0.5 g) was dissolved beforehand, and stirring was continued for 7 hr at 16—20°. The reaction was taken place in N_2 atmosphere. The resulting suspension was poured into water and *tert*-BuOH was distilled out *in vacuo*. Precipitates were collected by filtration, washed with water, and dried. Recrystallization from acetone gave the dimethyl compound (X, 0.3 g), mp 251—258°. $[\alpha]_D^{31}$ −13° (c=0.47, dioxane). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.41; H, 9.92.

2,11β,17β-Trihydroxy-4,4-dimethyl-1,5-androstadien-3-one (XI)——11β,17β-Dihydroxy-4,4-dimethyl-5-androsten-3-one (X, 1.1 g) was autoxidized as described above. Recrystallization from acetone-EtOH afforded XI (0.33 g), mp 226.5—228° as colorless needles. $[\alpha]_D^{20}$ +75° (c=1.00), UV λ_{max} (ε) 270 mμ (9500). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.73; H, 8.75.

20,20-Ethylenedioxy-2-hydroxy-4,4-dimethyl-1,5-pregnadien-3-one (XIVa)——20,20-Ethylenedioxy-4,4-dimethyl-5-pregnen-3-one (XIIIa, 4.7 g), which was prepared from progesterone 20-ethylene ketal (XIIa) by the procedure described in U.S. Patent,[19] was autoxidized as decsribed above (AcOH must be

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[18] A solution of CrO_3 (26.72 g) in H_2SO_4 (23 ml) diluted with H_2O at a volume of 100 ml was used.

[19] U.S. Patent 3120516 (1964).

used for acidification). Recrystallization from acetone gave the diosphenol (XIVa, 1.7 g), mp 180—182°, as colorless prisms. $[\alpha]_D^{19}$ $+72°$ $(c=1.00)$, UV $\lambda_{\max}$ (ε) 272 mμ (7100). *Anal.* Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.98; H, 9.07.

2-Hydroxy-4,4-dimethyl-1,5-pregnadiene-3,20-dione (XVa)——The ethylene ketal (XIVa, 0.7 g) was dissolved in AcOH (100 ml) and water (30 ml) and the solution was allowed to stand at room temperature for 3 days. Water was added and precipitates were collected by filtration, washed with water and dried. Recrystallization from MeOH afforded the diosphenol (XVa, 0.4 g), mp 160—163°, as colorless prisms. $[\alpha]_D^{20}$ $+10°$ $(c=1.00)$, UV $\lambda_{\max}$ (ε) 271 mμ (7000). *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.44; H, 9.04.

17α-Hydroxy-20,20-ethylenedioxy-4,4-dimethyl-5-pregnen-3-one (XIIIb)——MeI (13 ml) was dropwise added to a solution of 17α-hydroxy-20,20-ethylenedioxy-4-pregnen-3-one (XIIb, 14.0 g) in *tert*-BuOH (250 ml) in which K (4.0 g) was dissolved, and stirring was continued for 3 hr at room temperature in N_2 atmosphere. The suspension was poured into water, and the resulting precipitates were collected by filtration, washed with water, and dried. Recrystallization from acetone afforded 4,4-dimethyl compound (XIIIb, 7.0 g), mp 232—234°. Further recrystallization from acetone gave an analytical sample as colorless prisms. mp 232—234°, $[\alpha]_D^{20}$ $-23°$ $(c=1.00)$. *Anal.* Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.65; H, 9.38.

2,17α-Dihydroxy-20,20-ethylenedioxy-4,4-dimethyl-1,5-pregnadien-3-one (XIVb)——The dimethyl compound (XIIIb, 6.5 g) was autoxidized as described above. The product was chromatographed on silica gel and the diosphenol (XIVb) was eluted by benzene. Recrystallization from acetone afforded an analytical sample (1.7 g) as colorless prisms. mp 185—188°, $[\alpha]_D^{21}$ $+40°$ $(c=1.00)$, UV $\lambda_{\max}$ (ε) 272 mμ (8300). *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.48; C, 9.03.

2,17α-Dihydroxy-4,4-dimethyl-1,5-pregnadiene-3,20-dione (XVb)——A solution of the diosphenol ethylene ketal (XIVb, 1.0 g) in MeOH (30 ml) and 8% H_2SO_4 (3.0 ml) was refluxed for 30 min, and poured into water. The resulting precipitates were collected by filtration, washed with water and dried. Recrystallization from acetone gave the diosphenol (XVb, 0.45 g), mp 185—187°. Further recrystallization from acetone afforded an analytical sample as colorless prisms. mp 192—194°, $[\alpha]_D^{20}$ $+47°$ $(c=1.00)$, UV $\lambda_{\max}$ (ε) 272 mμ (7700). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.72; H, 8.48.

21-Hydroxy-20,20-ethylenedioxy-4,4-dimethyl-5-pregnen-3-one (XIIIc)——21-Acetoxy-20,20-ethylenedioxy-4-pregnen-3-one (XIIc, 0.45 g) was methylated as shown in the preparation of XIIIb. Recrystallization from MeOH afforded XIIIc (0.20 g), mp 170—175°. An analytical sample was obtained by further recrystallisation from MeOH as colorless prisms. mp 183—185°, $[\alpha]_D^{18}$ $+19°$ $(c=1.21)$. *Anal.* Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.89; H, 9.42.

2,21-Dihydroxy-4,4-dimethyl-1,5-pregnadiene-3,20-dione (XVc)——The dimethyl compound (XIIIc, 1.0 g) was autoxidized as described above. A solution of the crude diosphenol (XIVc) in acetone (50 ml) and 10% HCl (5 ml) was refluxed for 1 hr, and poured into water. Precipitates were collected by filtration and washed with water. After drying, recrystallization from iso-PrOH afforded the diosphenol (XVc, 0.22 g), mp 139—142°. An analytical sample was obtained by further recrystallization from iso-PrOH as colorless prisms. mp 140—142°, $[\alpha]_D^{18}$ $+136°$ $(c=1.20)$, UV $\lambda_{\max}$ (ε) 272 mμ (7900). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.50; H, 8.68.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-4,4-dimethyl-5-pregnen-3-one (XVII)——To a solution of 17α,20;20,21-bismethylenedioxy-11β-hydroxy-4-pregnen-3-one (XVI, 1.0 g) in tetrahydrofuran (26 ml) was added *tert*-BuOH (26 ml) in which K (0.8 g) was beforehand dissolved, and the resulting solution was stirred for 30 min. MeI (2.8 ml) was dropwise added over a period of 30 min and stirring was continued for additional 2.5 hr. The reaction was taken place in N_2 atmosphere. The resulting suspension was poured into water and the product was extracted with CH_2Cl_2-ether mixture. The organic layer was washed with 10% HCl, 5% Na_2CO_3 and water, and dried (Na_2SO_4). The removal of the solvent left a crystalline material, which on recrystallization from acetone-CH_2Cl_2 afforded the dimethyl compound (XVII, 0.46 g), mp 254—260°. An analytical sample was obtained by further recrystallization from the same solvent as colorless cubes. mp 264—268°, $[\alpha]_D^{25}$ $-117°$ $(c=0.99)$. *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.72; H, 8.51.

17α,20;20,21-Bismethylenedioxy-2,11β-dihydroxy-4,4-dimethyl-1,5-pregnadien-3-one (XVIIIa)——A solution of the dimethyl compound (XVII, 0.2 g) in tetrahydrofuran (20 ml) and *tert*-BuOH (28 ml) in which K (0.68 g) was beforehand dissolved was stirred vigorously in O_2 atmosphere for 1.5 hr at room temperature. Water was added, and after acidification with 10% HCl, precipitates were collected by filtration, washed with water, and dried. Recrystallization from MeOH afforded the diosphenol (XVIIIa, 0.095 g), mp 227—232°. Further recrystallization from MeOH gave an analytical sample as colorless prisms. mp 232–235°, $[\alpha]_D^{25}$ $+78°$ $(c=0.91)$, UV $\lambda_{\max}$ (ε) 271 mμ (8200). *Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.27; H, 7.73.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-2-methoxy-4,4-dimethyl-1,5-pregnadien-3-one (XVIIIb)——To a solution of the diosphenol (XVIIIa, 0.2 g) in MeOH (20 ml) and Me_2SO_4 (1.2 ml) was dropwise added 25% KOH (4 ml). After stirring for 30 min, water was added and the precipitates were collected by filtration, washed and dried. Recrystallization from MeOH gave the methyl ether (XVIIIb, 0.15 g), mp 213—216°. An analytical sample was obtained by further recrystallization from MeOH as colorless needles. mp 218—220.5°, $[\alpha]_D^{25}$ $-42°$(c=2.03), UV λ_{max} (ε) 265 mμ (6900). *Anal.* Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 68.36; H, 8.15.

2,21-Diacetoxy-11β,17α,dihydroxy-4,4-dimethyl-1,5-pregnadiene-3,20-dione (XIX)——17α,20;20,21–Bismethylenedioxy–2,11β–dihydroxy–4,4–dimethyl–1,5–pregnadien–3–one (XVIIIa, 0.2 g) was heated with 50% AcOH (20 ml) under reflux for 6 hr in N_2 atmosphere. The solvent was removed by distillation *in vacuo*, and the residue was dissolved in C_5H_5N (5 ml) and Ac_2O (5 ml). After standing overnight, water was added, and precipitates were collected by filtration, washed with 10% HCl, 5% Na_2CO_3 and water, dried, and chromatographed on alumina (4 g). The product eluted with CH_2Cl_2–ether was recrystallized from acetone–*n*–hexane to yield the diosphenol diacetate (XIX, 0.041 g), which on recrystallization from the same solvent afforded an analytical sample as colorless needles. mp 220—224.5°, $[\alpha]_D^{25}$ $+29°$ (c=0.95), UV λ_{max} (ε) 233 mμ (8600). *Anal.* Cacld. for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43. Found: C, 66.32; H, 7.15.

17α,20;20,21-Bismethylenedioxy-4,4-dimethyl-5-pregnene-3,11-dione (XXI)——17α,20;20,21–Bismethylenedioxy–4–pregnene–3,17–dione (XX, 5.0 g) was methylated as described in the preparation of XVII. Recrystallization from acetone gave the dimethyl compound (XXI, 3.9 g), mp 245—248°. An analytical sample was obtained by further recrystallization from acetone as colorless needles. mp 246.5—249.5°, $[\alpha]_D^{28}$ $-73°$ (c=0.94). *Anal.* Cacld. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.70; H, 7.80.

17α,20;20,21-Bismethylenedioxy-2-hydroxy-4,4-dimethyl-1,5-pregnadiene-3,11-dione (XXIIa)——The dimethyl compound (XXI, 2.0 g) was autoxidized by using tetrahydrofuran (200 ml), *tert*–BuOH (200 ml) and K (6.0 g). The solution was poured into water and the resulting yellow solution was acidified by 10% HCl. Precipitates were collected by filtration, washed with water and dried. Recrystallization from acetone gave the diosphenol (XXIIa, 0.52 g), mp 243—249°. Further recrystallization from acetone afforded an analytical sample as colorless prisms. mp 253—257°, $[\alpha]_D^{24}$ $+15°$(c=0.99), UV λ_{max} (ε) 271 mμ (7400). *Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.54; H, 7.14.

17α, 20; 20, 21-Bismethylenedioxy-2-methoxy-4, 4-dimethyl-1, 5-pregnadiene-3, 11-dione (XXIIb)——a) From XXIIa: The diosphenol (XXIIa, 0.052 g) was methylated as described in the preparation of XVIIIb. Recrystallization from acetone gave the methyl ether (XXIIb, 0.034 g), mp 267—270°. An analytical sample was obtained by further recrystallization from acetone as colorless prisms. mp 270—273°, $[\alpha]_D^{31}$ $+4°$ (c=0.31), UV λ_{max} (ε) 265 mμ (7500). *Anal.* Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.38; H, 7.42.

b) From XVIIIb: A solution of CrO_3 (0.05 g) in AcOH (2 ml) containing water was added to a solution of the diosphenol methyl ether (XVIIIb, 0.05 g) in AcOH (3 ml), and after standing for 15 min at room temperature, water was added. Precipitates were collected by filtration, washed with water and dried. Recrystallization from acetone afforded colorless prisms, the infrared spectrum of which was identical with that of the compound prepared from XXIIa.

2,21-Diacetoxy-17α-hydroxy-4,4-dimethyl-1,5-pregnadiene-3,11,20-trione (XXIII)——The hydrolysis and the acetylation of the diosphenol (XXIIa, 0.2 g) were made by the same procedure described in the preparation of XIX. The product was chromatographed on alumina (4 g). The fraction eluted by CH_2Cl_2–ether (1:1) was recrystallized from MeOH to give the diosphenol diacetate (XXIII, 0.066 g). Further recrystallization from MeOH afforded an analytical sample as colorelss prisms. mp 195—198°, $[\alpha]_D^{31}$ $+5°$ (c=0.81), UV λ_{max} (ε) 233 mμ (9100). *Anal.* Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04. Found: C, 66.58: H, 7.21.

4,17β-Dihydroxy-2,2-dimethyl-4-androsten-3-one (XXVa)——17β–Hydroxy–2,2–dimethyl–5α–androstan–3–one (XXIVa, 2.0 g) was autoxidized as described above. Recrystallization from acetone–*n*–hexane gave the diosphenol (XXVa, 0.9 g), mp 168—171°. Further recrystallization from the same solvent afforded an analytical sample as colorless prisms. mp 171—173°, $[\alpha]_D^{27}$ $+49°$ (c=1.09), UV λ_{max} (ε) 277 mμ (12500). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.61; H, 9.81.

4,17β-Dihydroxy-2,2,17-trimethyl-4-androsten-3-one (XXVb)——17β–Hydroxy–2,2,17–trimethyl–5α–androstan–3–one (XXIVb, 1.0 g) was autoxidized as described above. Recrystallization from acetone–*n*–hexane gave the diosphenol (XXVb, 0.52 g), mp 149—153°. An analytical sample was obtained by further recrystallization from the same solvent as colorless needles. mp 158—161°, $[\alpha]_D^{27}$ $+31°$ (e=1.01), UV λ_{max} (ε) 278 mμ (12400). *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.34; H, 9.89.

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