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Synthesis of 14β-Pregnanes. II.[1] Nuclear Magnetic Resonance Sepctroscopic Evidence for the Conformation of the C-Rings in C/D *cis*-11β,12β-Oxygenated Pregnanes[2]

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The synthesis of C/D *cis* 11β,12β-oxygenated pregnane derivatives from 3β,12β-diacetoxy-5α,25D-spirostan-11-one (II) *vis* dienone (V) is described. Nuclear magnetic resonance studies indicated the possible conformation of the C-ring in C/D-*cis* pregnane is not a boat but a chair form.

Nuclear magnetic resonance (NMR) studies on conformation of the C-rings in some C/D-*trans* steroids have been made by several workers who examined signal peaks of the protons attached to the substituent-bearing atoms.[4] Recently, Shoppee, *et al.*,[5] reported that the C-ring of digacetigenin (I) was the boat form owing to the very facile hydrolysis of the secondary 12β-acetoxyl group with methanolic potassium hydrogen carbonate at 20°, and that its D-ring was in a plane form. In this paper, we describe the synthesis of 11β, 12β-oxygenated 14β-pregnanes and NMR spectroscopic evidence for the conformations of their C-rings.

3β,12β-Diacetoxy-5α,25D-spirostan-11-one (II) was converted into 3β,11β,12β-triacetoxy-5α-pregn-16-en-20-one (III) according to the procedures by Zderic, *et al.*,[6,7] and Cameron, et al.,[7] and by hydrogenation with 5% palladium-charcoal in methanol, this product afforded the saturated triacetate (IV), which had no absorption due to the α,β-unsaturated ketone system in its infrared (IR) and ultraviolet (UV) spectra, and had a positive Cotton effect in optical rotatory dispersion(ORD)curve. Treatment of III with bis(bromomethyl)hydantoin-γ-collidine furnished 3β,11β,12β-triacetoxy-5α-pregna-14,16-dien-20-one (V). The structure of V was shown from its IR absorptions at 1750, 1240, 1220 (acetate), and 1650 and 1530 cm^{-1} (conj. dienone system), its UV absorption at 301 mμ (log ε=4.13), and its NMR signals τ 7.68 (3H) due to a methyl ketone, and τ 3.75 (1H, triplet,[8] J=2 cps) and τ 2.72 (1H, doublet, J=2 cps) due to vinyl protons. Epoxidation of V with monoperphthalic acid afforded 14β,15β-epoxy-pregn-16-en-20-one (VI), which was converted into 3β,11β,12β-trihydroxy-14β,15β-epoxy-5α, 17-isopregnan-20-one (XIII), having a stable configuration[9] of the 17-side chain with a C/D *cis* juncture. Treatment of VI with sulfuric acid in dioxan furnished 14β,15α-diol (VII), and,

1) Part I: H. Mitsuhashi and M. Fukuoka, *Chem. Pharm. Bull.* (Tokyo), **14**, 809 (1966).
2) A part of this work was presented at the 31st Annual Meeting of the Hokkaido Branch, Pharmaceutical Society of Japan, Sapporo, Feb. 1967.
3) Location: *Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido.*
4) K. Tori, T. Tomita, H. Hazaki, M. Narisada, and W. Nagata, *Chem. Pharm. Bull.* (Tokyo), **11**, 956 (1963); D.H. Williams and N.S. Bhacca, *J. Am. Chem. Soc.*, **86**, 2742 (1964).
5) C.W. Shoppee, N.W. Hughes, R.E. Lack, and B.C. Newman, *Tetrahedron Letters*, **1967**, 3171.
6) J.A. Zderic, H. Carpis, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 446 (1960).
7) A.F.B. Cameron, R.M. Evans, J.C. Hamlet, J.S. Hunt, P.G. Jones, and A.G. Long, *J. Chem. Soc.*, **1955**, 2807.
8) The triplet signal was observed for the C-15 proton of 3β,12β-dihydroxy-5α-pregna-14,16-dien-20-one 3-monoacetate, and 3β-acetoxy-5α-pregna-14,16-diene-11,20-diene (D. Satoh and S. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 248 (1967).
9) H. Mitsuhashi, T. Nomura, and M. Fukuoka, *Steroids*, **4**, 483 (1964).

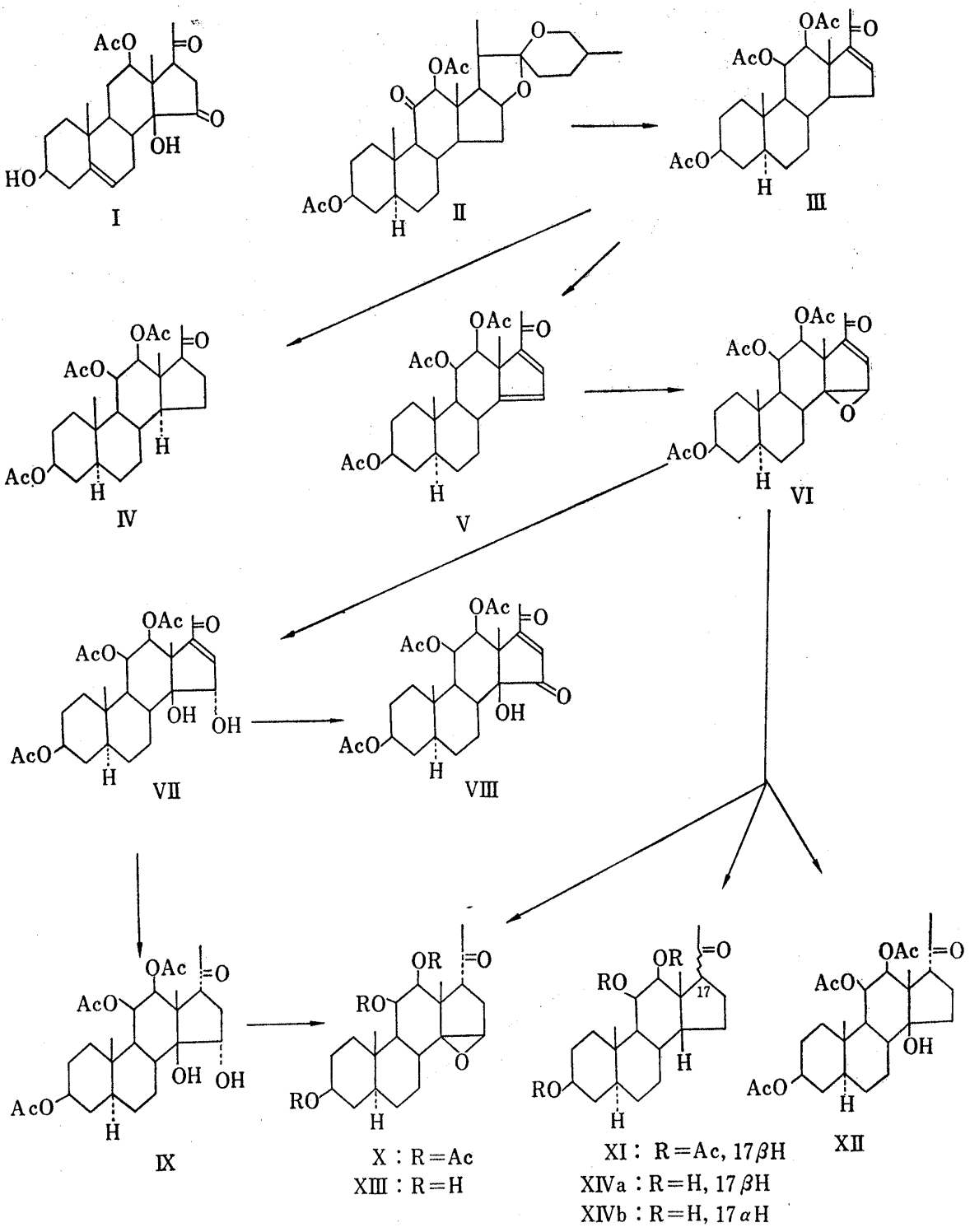


Chart 1

as we reported,[1,10] the following data suggest that the cleavage of the 14β,15β-epoxide of VI afforded a 14β,15α-*trans*-diol grouping. The IR spectrum of VII showed bands at 3590, 3520(OH), 1740, 1720, 1240(acetate), 1675 and 1610 cm^{-1} (conj. open-chain ketone system), and the UV spectrum showed a maximum at 230 mμ (log ε=3.90) due to the α,β-unsaturated ketone system. The NMR signal of the C-15 and C-16 hydrogens occurred as two doublets (J=3 cps) and the configuration at C-14 and C-15 was justified by the ORD curve very similar

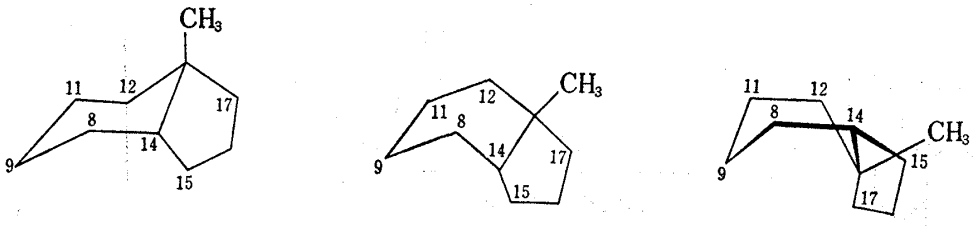
10) M. Fukuoka and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 2007 (1967).

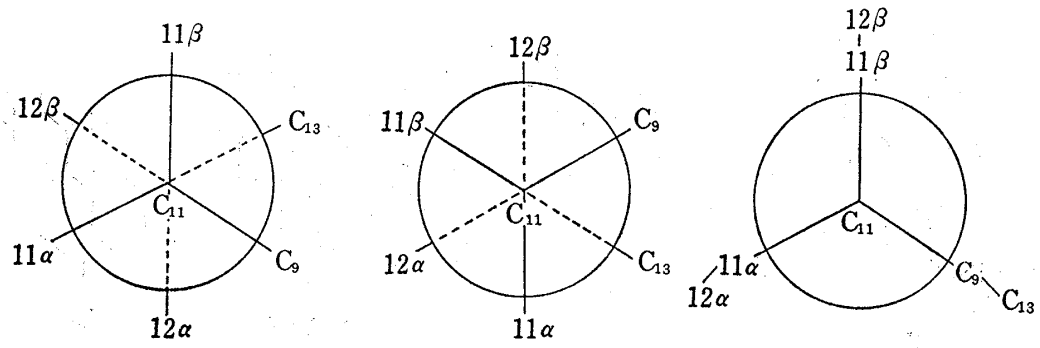
to that of the Δ^{16}-pregnene-14β,15α-diol derivatives[1,10,11] and further justified by conversion of VII into 3β,11β,12β-triacetoxy-14β,15β-epoxy-5α,17-isopregnan-20-one (IX).

VII was oxidized with chromium trioxide in acetic acid to 3β,11β,12β,14β-tetrahydroxy-5α-pregn-16-ene-15,20-dione 3,11,12-triacetate (VIII), which showed IR absorptions at 3590 (OH), 1740, 1240 (acetate), 1720 (conj. 5-membered ring ketone) and 1685 cm^{-1} (conj. open-chain ketone), UV absorption at 246.5 mμ (log ε 3.93), and NMR signals of C-21 methyl group (τ, 7.62) and C-16 proton (1H, singlet, τ, 3.51).

By hydrogenation with 5% palladium–charcoal in methanol, VII afforded the saturated diol (IX) which had a negative Cotton effect in its ORD curve and furnished the saturated 14β,15β-epoxide (X) by dehydration with phosphorus chloride in pyridine. Catalytic hydrogenation of VI afforded X together with XI and XII, and three reduction products (X, XI, and XII) showed the naegtive Cotton effect. Two of the reduction products, X and XI, were hydrolysed with methanol in the presence of alkali to give XIII and XIVa, with a negative Cotton effect, and XIVb with a positive Cotton effect.

Since we have succeeded in synthesizing C/D *cis* 11β,12β-oxygenated pregnanes, we shall hereby discuss the conformation of the C-rings of series of compounds, which exist in any of the conformations a chair form (A) or a boat form (B or C). The Newmann projections, along the C_{11}–C_{12} bond, corresponding to three conformations are shwon below the perspective diagrams.





calcd. coupling constants (cps)	calcd. coupling constants (cps)	calcd. coupling constants (cps)
$\phi_{11\alpha,12\alpha}$ 60° J=2.5	$\phi_{11\alpha,12\alpha}$ 60° J=2.5	$\phi_{11\alpha,12\alpha}$ 0° J=10
$\phi_{11\beta,12\alpha}$ 180° J=16	$\phi_{11\beta,12\alpha}$ 60° J=2.5	$\phi_{11\beta,12\alpha}$ 60° J=2.5

Fig. 1

The conformation of the C-ring may be determined from the coupling constants given in Table 1, and a comparison of the coupling constants of 11α,12β-oxygenated pregnanes[12]

11) 3β,12β,14β,15α-Tetrahydroxy-5α-pregn-16-en-20-one 3,15-diacetate and 3,12,15-triacetate also had a negative Cotton effect.

12) R. Tschesche, M. Baumgarth, and P. Welzel, *Tetrahedron*, 23, 249 (1967).

13) K.L. Williamson and W.S. Johnson, *J. Am. Chem. Soc.*, 83, 4623 (1961).

Table I

Compd.	19-CH_3	18-CH_3	21-CH_3	11-H (triplet) J=cps	12α-H(doublet) J=cps	16-H (J=cps)	15-H (J=cps)
III	8.96	9.08	7.76	4.44 J=3.1, 2.5	5.00 J=3.1	3.34	
IV	9.10	9.00	7.91	4.38 J=3.0, 2.6	5.20 J=3.0		
V	9.03	8.53	7.68	4.47 J=3.0, 2.6	5.71 J=3.0	2.72 (d, 2)	3.75 (t, 2)
VI	9.14	8.44	7.80	4.50 J=3.3, 2.1	5.40 J=3.3	3.17 (d, 1)	6.13 (d, 1)
VII	9.17	8.56	7.69	4.48 J=3.0, 2.6	5.38 J=3.0	3.21 (d, 3)	4.92 (d, 3)
VIII	9.18	8.52	7.62	4.55 J=3.0, 2.5	5.48 J=3.0	3.51	
IX	9.15	8.42	7.71	4.36 J=3.1, 2.5	4.94 J=3.1		5.80 (q, 6.7, 3.0)
X	9.13	8.37	7.77	4.30 J=3.0, 2.5	5.60 J=3.0		6.45
XI	9.16	8.45	7.77	4.38 J=3.0, 2.6	5.45 J=3.0		
XII	9.16	8.48	7.78	4.43 J=3.0, 2.5	5.56 J=3.0		
XV	9.05	8.55	7.83	4.83 J=9.0, 9.5	5.13 J=9.0		
XVI	9.03	8.50	7.82	4.71 J=9.5, 10.0	5.30 J=9.5		
XVII	9.05	8.58	7.83	4.83 J=10.0, 9.5	5.24 J=10.0		

d: doublet q: quartet
XV=3β,11α,12β-triacetoxy-5α,14α,17-isopregnan-20-one[11]
XVI=3β,11α,12β-triacetoxy-14β,15β-epoxy-5α,17-isopregnan-20-one[11]
XVII=3β,11α,12β-triacetoxy-14β-hydroxy-5α,17-isopregnan-20-one[11]

(XV to XVII) and that calculated from the dihedral angles by the Williamson–Johnson version[13] of the Karplus equation indicated that the conformation of the C-rings was that near projection, as a chair form (A).

Experimental[14]

3β,11β,12β-Triacetoxy-5α-pregnan-20-one (IV)——The enone (III) (70 mg) was hydrogenated in the presence of 5% Pd–C (50 mg) in MeOH (10 ml). Upon isolation, recrystallization from acetone–diisopropyl ether yielded a dihydro derivative (IV) (30 mg), mp 134—137°, ORD (c=1.0, MeOH): $[\alpha]_{265}$ (trough)–1400°, $[\alpha]_{306}$ (peak) +1300°, IR ν_{max}^{Nujol} cm^{-1}: 1745, 1240 (–OCO–), 1710 (CO). *Anal.* Calcd. for $C_{27}H_{40}O_7$ (mol. wt., 476.59): C, 68.04; H, 8.46. Found: C, 68.27; H, 8.40. MS (mass spectrum) (m/e): 476 (M^+), 433, 418, 416, **374, 356**, 341, 314.

3β,11β,12β-Triacetoxy-5α-pregna-14,16-dien-20-one (V)——The enone (III) (1.7 g) and bis(bromomethyl)hydantoin (0.72 g) in dry CCl_4 (40 ml) were heated under reflux for 30 min. After filtration, the solvent was removed *in vacuo*. The residue was treated with γ-collidine (5 ml) at 150° for 45 min in N_2 atmosphere. The solution was poured into H_2O and the product extracted with ether. The ether layer was washed with 5% HCl, $NaHCO_3$, and H_2O, dried over Na_2SO_4, and the solvent removed. Recrystallization of the residue from ether–hexane gave V (1.1 g), mp 160—162°, $[\alpha]_D^{18}$ +312.5° (c=0.80, $CHCl_3$), UV λ_{max}^{EtOH} mμ (log ε): 301 (4.13), IR ν_{max}^{Nujol} cm^{-1}: 1750, 1240 (–OCO–), 1650 (conj. CO), 1530 (conj. C=C). *Anal.* Calcd. for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.56; H, 7.66.

3β,11β,12β-Triacetyoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (VI)——To a solution of the dienone (V) (210 mg) in absolute $CHCl_3$ (2 ml) was added a solution of monoperphthalic acid (132 mg) in ether (3 ml), and the mixture was allowed to stand at room temperature for 5 days. After decomposition of the excess peracid, the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and the solvent removed. The residue was separated into the dienone (V) (105 mg) and the epoxide (VI) by preparative thin-layer chromatography PTLC (Kieselguhr HF_{254} benzene–ether=1:1 system). Recrystallization from ether–hexane gave VI (96.5 mg), mp 129.5—131.5°, $[\alpha]_D^{20}$ +108.1° (c=0.85, $CHCl_3$), UV λ_{max}^{EtOH} mμ (log ε): 242 (3.71), IR ν_{max}^{Nujol} cm^{-1}: 1750, 1240 (–OCO–), 1665 (conj. CO), 1590 (conj. C=C), ORD: (c=0.15, dioxan). $[\alpha]_{270}$ (trough) −1000°, $[\alpha]_{363}$ (peak) +800°. *Anal.* Calcd. for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43, Found: C, 66.36; H, 7.32.

14) All melting points were measured with a Kofler Hot Stage Microscope and are uncorrected. Optical rotatory dispersion (ORD) curves were run with a Jasco Model ORD/UV-5. NMR spectra were determined at 60 Mc in $CDCl_3$ solution containing tetramethylsilane as an internal reference, using Hitachi Model H-60, and the mass spectra on Hitachi Mass Spectrometer Model RMU-60 equipped with direct inlet system Model MG-150.

3β,11β,12β,14β, 15α-Pentahydroxy-5α-pregn-16-en-20-one 3,11,12-Triacetate (VII)——To a solution of the unsaturated epoxide (VI) (513 mg) in dioxan (20 ml), was added 2N H_2SO_4 (2.5 ml), and the mixture was allowed to stand at room temperature for 16 hr. After isolation in the same way[1] as above, the products were separated into the epoxide (VI) (251 mg) and the diol (VII) by PTLC (diisopropyl ether–acetone–AcOEt=10:1:1). VII was recrystallized from acetone–diisopropyl ether, 210.9 mg, mp 275—279°, $[\alpha]_D^{23}$ +136.3° (c=0.66, $CHCl_3$), UV λ_{max}^{EtOH} mμ (log ε): 230 (3.90), IR ν_{max}^{Nujol} cm^{-1}: 3590, 3520 (OH), 1740, 1720, 1240 (broad) (–OCO–) 1675 (conj. CO), 1610 (conj. C=C), ORD: (c=0.73, dioxan), $[\alpha]_{300}$ (peak) +4000°, $[\alpha]_{370}$ (trough) −334°. *Anal.* Calcd. for $C_{27}H_{38}O_9$: C, 64.01; H, 7.56. Found: C, 63.83; H, 7.53.

3β,11β,12β,14β-Tetrahydroxy-5α-pregn-16-ene-15,20-dione 3,11,12-Triacetate (VIII)——To VII (117 mg) in AcOH (10 ml) was added a solution of 4.5% CrO_3–AcOH (0.5 ml) and the mixture was stood at room temperature for 17 hr. After decomposition of the excess CrO_3, extraction with CH_2Cl_2, and the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and solvent removed. Recrystallization from diisopropyl ether gave VIII, (93.4 mg), mp 194.5—195.5°; $[\alpha]_D^{25}$ −40.0° (c=1.95, $CHCl_3$), UV λ_{max}^{EtOH} mμ (log ε): 246.5 (3.93), IR ν_{max}^{Nujol} cm^{-1}: 3590 (OH), 1740, 1240 (broad), 1685 (conj. CO). *Anal.* Calcd. for $C_{27}H_{36}O_9$: C, 64.27; H, 7.19. Found; C, 64.38; H, 7.27.

3β,11β,12β,14β,15α-Pentahydroxy-5α,17-isopregnan-20-one 3,11,12-Triacetate (IX)——The unsaturated diol (VII) (200 mg) was hydrogenated in the presence of 5% Pd–C (100 mg) in MeOH (50 ml). The product was isolated, and purification by PTLC developed several times, gave the amorphous IX. ORD: (c=0.18, MeOH), $[\alpha]_{266}$ (peak) +1304.3°, $[\alpha]_{308}$ (trough) −1304.0° $[\alpha]_{589}$ −10.8°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1735, 1245 (–OCO–), 1710 (CO). *Anal.* Calcd. for $C_{27}H_{40}O_9$: C, 63.76; H 7.93. Found: C, 63.51; H, 8.00.

Hydrogenation of 3β,11β,12β-Triacetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one——a) With Pd-$BaSO_4$ Catalyst: The unsaturated epoxide (VI) (71 mg) was hydrogenated over 5% Pd–$BaSO_4$ (97 mg) in EtOH (8 ml). The product was isolated into three compounds (X, XI, and XII) by PTLC, which was developed several times 3β,11β,12β-triacetoxy-14β,15β-epoxy-5α,17-isopregnan-20-one (X); Recrystallized from hexane; 21.5 mg, mp 109—110°. ORD: (c=0.23, MeOH), $[\alpha]_{260}$ (peak) +1026.7°, $[\alpha]_{303}$ (trough) −602.7°, $[\alpha]_{589}$ −27.7°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1240 (–OCO), 1710 (CO). *Anal.* Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H,7.81. Found; C, 66.29; H, 7.62.

3β,11β,12β-Triacetoxy-5α,14β,17-isopregnan-20-one (XI) : Recrystallized from ether–diisopropyl ether; 28.9 mg, mp 205—206°, ORD (c=0.21, MeOH), $[\alpha]_{260}$ (peak) +1390.4°, $[\alpha]_{303}$ (trough) −1097.6°, $[\alpha]_{589}$ −73.2° IR ν_{max}^{Nujol} cm^{-1}: 1735 (broad), 1245, 1220 (–OCO–), 1695 (CO). *Anal.* Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.30; H, 8.25.

3β,11β,12β,14β,-Tetrahydroxy-5α,17-isopregnan-20-one 3,11,12-Triacetate (XII) : Purification by PTLC, developed several times amorphous (8.30 mg). ORD: (c=0.21, MeOH), $[\alpha]_{256}$ (peak) +1129.4°, $[\alpha]_{301}$ (trough) −1030.6°, $[\alpha]_{589}$ −127.1°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1730 (broad), 1245, 1220 (–OCO–), 1710 (CO). Mass Spectrum Calcd. for $C_{27}H_{40}O_8$: mol. wt., 492.59. Found: *m/e* 492 (M^+), 464, 432, 429, 414, 389, 372, 371, 351.

b) With Adams Catalyst: The unsaturated epoxide (VI) (500 mg) was hydrogenated over PtO_2 (221 mg) in EtOH (60 ml). Isolation as in (a) gave X (204.5 mg), and XI (195 mg).

Dehydration of the Saturated Diol (IX)——$POCl_3$ (1 ml) was added to an ice-cold solution of IX (113 mg) in dry pyridine (4 ml) and stored at −5° for 17 hr. After isolation in the usual manner, the product was passed through neutral Al_2O_3 (1 g) and recrystallization from hexane gave X (62.5 mg), mp 109—110°, mix. mp 109—110° with the compound obtained by hydrogenation of VI.

Hydrolysis of 3β,11β,12β-Triacetoxy-14β,15β-epoxy-5α,17-isopregnan-20-one (X)——The saturated epoxide (X) (125 mg) was hydrolyzed by refluxing in 5% methanolic KOH solution (6 ml) for 5 hr. The mixture was diluted with H_2O and extracted with ether. Recrystallization of the extract (66.7 mg) from acetone–diisopropyl ether yilded XIII (56.3 mg), mp 122—124°. ORD: (c=0.18, MeOH), $[\alpha]_{256}$ (peak) +1408.5°, $[\alpha]_{300}$ (trough) −833.8°, IR ν_{max}^{Nujol} cm^{-1}: 3450 (broad) (OH), 1698 (CO). *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found; C, 68.88; H, 9.02.

Hydrolysis of 3β,11β,12β-Triacetoxy-5α,14β,17-isopregnan-20-one (XI)——XI (80 mg) was hydrolyzed in 5% methanolic KOH solution (3 ml) at a room temperature for 17 hr. The mixture was separated into two bands by chromatography and eluted with AcOEt. Recrystallization of the less polar product from acetone–diisopropyl ether yielded XIVa 28.1 mg, mp 106—108°, ORD: (c=0.1, MeOH), $[\alpha]_{258}$(peak) +1541.7° $[\alpha]_{302}$ (trough) −925.7°, $[\alpha]_{589}$+42.8°, IR ν_{max}^{Nujol} cm^{-1}: 3450 (broad) (OH), 1695 (CO). *Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.04; H, 9.81. Recrystallization of the polar product from AcOEt yielded 12 mg of XIVb, mp 217—220°. ORD: (c=0.15, MeOH), $[\alpha]_{265}$ (trough) −1400,° $[\alpha]_{308}$ (peak) +1400°, $[\alpha]_{589}$ +60.3°, IR ν_{max}^{Nujol} cm^{-1}: 3450 (broad) (OH), 1695 (CO). *Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.98; H, 9.74.

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