# A New Steroid with an Unnatural Configuration: 8α,14β-Progesterone

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A modified Wolf-Kishner reduction of certain 5α,8α,14β-11-oxo steroids gave the corresponding 11-deoxy steroids with the same stereochemistry, and the introduction of a double bond at $C_4$—$C_5$ leads to 8α,14β-progesterone. The structure and configuration of this compound are discussed on the basis of its physical properties. Its unnatural backbone stereochemistry was established by transformations from the 8α,14β-1,4-diene derivative to the known 8α,14β-estrone.

The demonstration by Westerhof of differences in the biological activity of steroids which feature unnatural backbone stereochemistry has led to the preparation of a variety of such compounds.[1] Although racemic 8α,14β-estrone[2] was prepared by the total synthetic method, no 8α,14β-steroid of the pregnane series has yet been reported on. In view of the current interest in progesterone analogs,[3] we would like to report the synthesis of 8α,14β-progesterone (**7**).

The reduction of 11-oxo-5α,8α,14β-spirostan-3β-ol[4] (**1a**) by a modified Wolf-Kishner procedure, developed in our laboratory[5] for the reduction of highly-hindered ketones, followed by acetylation, led to 8α,14β-spirostan 3β-acetate (**2a**, $R_1$=Ac). Side-chain degradation then gave the 16-pregnene derivative (**3a**, R=OAc), which, on hydrogenation over a palladium-charcoal catalyst, followed by saponification, yielded the 5α,8α,14β-pregnane derivative (**3b**, R=OH). Compound **3b** (R=OH) was also obtained using the technique described above for spirostan-series compounds, starting from the 11-oxo-8α,14β-pregnane derivative (**1b**, $R_2$=H).

The partial saponification of the 3β,20β-diacetoxy pregnane derivative, followed by the oxidation of the 3-hydroxyl derivative, provided the 3-ketone (**4a**, $X_1$,$X_2$=H). The subsequent introduction of the $C_4$–$C_5$ double bond was effected in the following way: the treatment of 2ξ,4ξ-dibromo-3-ketone (**4a**, $X_1$,$X_2$=Br) with lithium salts in *N*,*N*-dimethylformamide, and selective hydrogenation with the ruthenium complex[6]

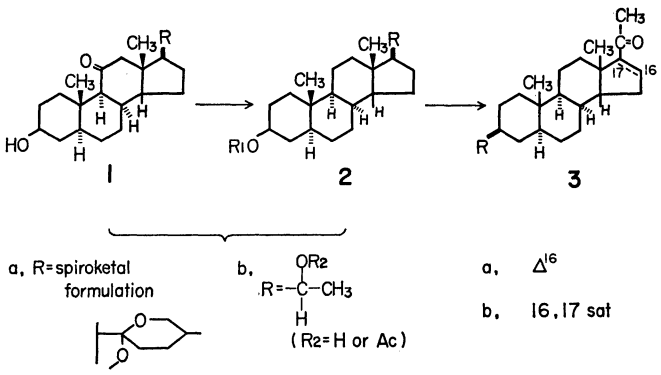



Fig. 1.

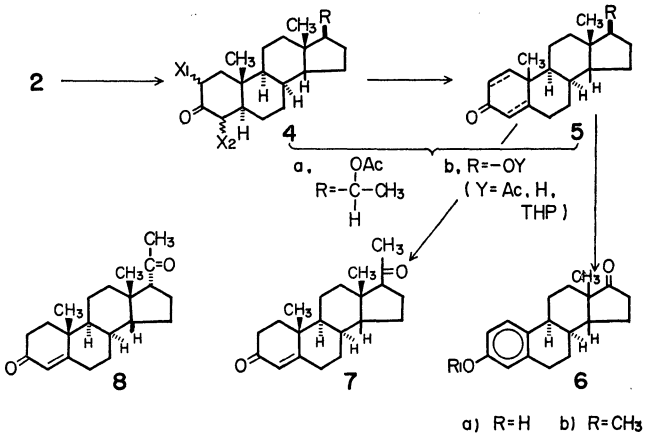



Fig. 2.

of the resulting 1,4-diene-3-ketone (**5a**, $\Delta^{1,4}$), gave the 20β-acetoxy-4-ene-3-ketone derivative (**5a**, $\Delta^4$). This compound, on hydrolysis subsequent to its oxidation, led to the 17β-acetyl derivative (**7**) (predominating) and the 17α-isomer (**8**). These configurations were supported by the circular dichroism data (Table 1). In **7**, a positive Cotton effect appears at 288 nm, in agreement with the 17β-configuration of

TABLE 1. COTTON EFFECT OF UNNATURAL PROGESTERONE AND NATURAL PROGESTERONE

| | Circular dichroism (Molecular ellipticity) |
|---|---|
| **7** | $[\theta]_{253}$ −12160, $[\theta]_{288}$ +8510, $[\theta]_{325}$ +5600 |
| **8** | $[\theta]_{253}$ −11200, $[\theta]_{280}$ −3050, $[\theta]_{325}$ +7210 |
| Progesterone | $[\theta]_{240sh}$ +18700, $[\theta]_{286}$ +13320, $[\theta]_{325}$ −4100 |

The spectra were measured in methanol.

1) a) E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kassnnar, E. Diczfalusy, and K. C. Tillinger, *Nature*, **186**, 168 (1960); b) The nonphotolytic route has been reported: M. Uskokovic, J. Jacobelli, P. Philion, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966); c) E. Farkas, J. M. Owen, and D. J. O'Toole, *J. Org. Chem.*, **34**, 3023 (1969); d) P. Crabbe, A. Cruz, and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968); e) R. Bucourt, D. Hainait, J. -C. Gase, and G. Nominé, *Tetrahedron Lett.*, **1968**, 5093.

2) C. Rufer, E. Schröder, and H. Gibian, *Ann. Chem.*, **705**, 211 (1967), and the references cited there in.

3) Dr. T. Miyake of our laboratory has discussed (in R. I. Dorfman, ed., "Hormone Research. V," Academic Press, New York, N. Y. (1966), pp. 59—145) the relation between the structure and the physiological activity of progestational steroids.

4) C. Djerassi, W. Frick, G. Rosenkrazz, and F. Sondheimer, *J. Amer. Chem. Soc.*, **75**, 3496 (1953); C. Djerassi, A. J. Manson, and A. Segoloff, *J. Org. Chem.*, **21**, 490 (1956); C. Djerassi, H. Bendas, and A. Segaloff, *ibid.*, **21**, 1056 (1956).

5) W. Nagata and H. Itazaki, *Chem. Ind.* (London), **1964**, 1194.

6) S. Nishimura and K. Tsuneda, This Bulletin, **42**, 852 (1969).

the side chain of progesterone; **8** was shown to have the 17α-configuration by its negative Cotton effect in the same region.[7]

The positive Cotton effect for the $n$—$\pi^*$ transition of the α,β-unsaturated ketone, at *ca.* 325 nm, and the negative effect for the $\pi$—$\pi^*$ (253 nm) showed **7** and **8** to have identical 8α and 14β ring junctures. The natural configuration, as in progesterone, is characterized by a negative Cotton effect at 325 nm and a positive one at the $\pi$—$\pi^*$ transition. This evidence indicates the stereochemistry of **7**, though it is not complete.

The Baeyer-Villiger oxidation of **3b** (R=OH) with trifluoroperacetic acid, followed by the oxidation of the $C_3$-hydroxy group with Jones's reagent, afforded **4b** ($X_1$,$X_2$=H, Y=Ac) after alkaline hydrolysis had given 17β-ol (**4b**, $X_1$,$X_2$=H, Y=H). This ketone was dibrominated with bromine in acetic acid, giving the dibromide, which, on subsequent treatment with lithium carbonate and lithium bromide, gave the 1,4-dien-3-one (**5b**, Y=H, $\Delta^{1,4}$). The corresponding tetrahydropyranyl ether (**5b**, Y=THP, $\Delta^{1,4}$) was obtained by the standard method. The reductive aromatization of **5b** (Y=THP, $\Delta^{1,4}$) by Dryden's method,[8] followed by the oxidation of 17-hydroxyl, provided 8α,14β-estrone (**6a**), identified with an authentic specimen of 8α,14β-estrone[2] by a comparison of the IR, mass, and NMR spectra. The methyl ether (**6b**) was also identical with an authentic specimen. Thus, we confirmed the assigned stereochemistry of 8α,14β in our synthetic compounds.

## Experimental

The melting points are corrected. The UV spectra were obtained using a Hitachi EPS 3-T spectrophotometer, while a Nihon-Bunko DS-201B spectrophotometer was used for the IR spectra. The NMR spectra were obtained on a Varian A-60 spectrometer, with TMS as the internal standard, and the mass spectra were taken with a Hitachi RML-6 spectrometer. The optical rotations were measured in 1% EtOH-$CHCl_3$ with a Perkin Elmer Polarimeter 141.

*1. (25R)-8α,5α,14β-Spirostan-3β-ol (**2a**, $R_1$=H).* A mixture of 1.0 g of (25*R*)-5α,8α,14β-spirostan-3β-ol-11-one (**1a**),[4] 9.5 g of 80% hydrazine hydrate, 1.8 g of hydrazine dihydrochloride, and 52 m*l* of triethylene glycol was heated at 130°C for 1.5 hr. After adding 4.5 g of potassium hydroxide pellets, the temperature was raised to 210°C by distilling the low-boiling material out. After 3.5 hr, the reaction mixture was diluted with water and extracted with methylene chloride. The methylene chloride solution was washed with water and dried, and the solvent was evaporated. The crystalline residue was then recrystallized from methanol to give **2a** ($R_1$=H) (0.73 g); mp 168—172°C. A pure sample melted at 169—173°C, $[\alpha]_D^{23}$ −95.5° (c 0.18); NMR τ: 9.21 (27-C$\underline{H_3}$), 9.05 (21-C$\underline{H_3}$), 8.98 (18-C$\underline{H_3}$), 9.13 (19-C$\underline{H_3}$).

Found: C, 77.7; H, 10.6%. Calcd for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6%.

*2. 5α,8α,14β-Pregn-16-en-20-one 3β-Acetate(**3a**, R=-OAc).*[9] The 5α,8α,14β-tigogenine compound (**2a**, $R_1$=H) (0.75 g) was refluxed for 12.5 hr with 60 m*l* of acetic anhydride and 0.45 g of pyridine hydrochloride. The mixture was then cooled, diluted with 12 m*l* of acetic acid and 18 m*l* of water, and added to 0.3 g of chromic anhydride in 6 m*l* of 90% acetic acid while being stirred at 15—20°C. After standing at 25°C for 3 hr, the solution was treated first with 0.2 m*l* of 37% formaldehyde and then with 0.65 g of sodium acetate. The stirred suspension was then heated on a water bath for 1 hr, cooled, and diluted with water. After being extracted with ether, the ether solution was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed[10] on alumina (20 g, Wohlem activity II). Elution with benzene-petroleum ether (4 : 1) and benzene afforded 16-ene (**3a**, R=−OAc) (0.32 g) as plates (from acetone); mp 146—147°C, $[\alpha]_D^{21}$ +56.1° (*c* 0.3).

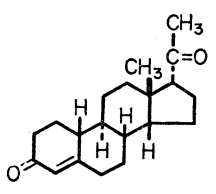
Found: C, 77.2; H, 9.6%. Calcd for $C_{23}H_{34}O_3$: C, 77.1; H, 9.6%. IR ($CCl_4$) $cm^{-1}$: 1745 (3β-acetate), 1670 (20-ketone), 1615 ($\Delta^{16}$). NMR τ: 9.06 (19-C$\underline{H_3}$), 8.81 (18-C$\underline{H_3}$), 8.00 (3β-C$\underline{H_3}$COO), 7.75 (21-C$\underline{H_3}$), 3.40 ($\Delta^{16}$-olefin, t, $J \fallingdotseq 4$ Hz).

*3. 3β-Hydroxy-5α,8α,14β-pregnan-20-one (**3b**, R=-OH).* A solution of 0.22 g of $\Delta^{16}$-ene (**3a**, R=−OAc) in 20 m*l* of ethyl acetate was shaken with a 5% palladium-charcoal catalyst under a hydrogen atmosphere for 15 min. After the removal of the catalyst and the evaporation of the solvent under reduced pressure, a crude acetate was obtained. The saponification of this acetate with 0.2 g of potassium carbonate in ethanol, followed by recrystallization from ether-petroleum ether, gave 0.18 g of **3b** (R=-OH); mp 125—130°C. Analytical samples were recrystallized from methanol; mp 134°C, $[\alpha]_D^{21}$ +82.8° (*c* 0.3).

Found: C, 78.9; H, 10.8%. Calcd for $C_{21}H_{34}O_2$: C, 79.1; H, 10.8%. IR ($CHCl_3$) $cm^{-1}$: 3600 (3β-OH), 1700 (20-ketone). NMR τ: 9.16 (18-C$\underline{H_3}$), 9.06 (19-C$\underline{H_3}$), 7.91 (21-C$\underline{H_3}$). CD (*c* 0.009, MeOH): $[\theta]_{291}$+7630. Mass: 318 (M·).

*4. 3β,20β-Dioxy-5α,8α,14β-pregnane (**2b**, $R_1$, $R_2$=H).* In view of the facile alkaline isomerization at C-14 of 11-oxo-8-ene steroids, the preparation of 11-oxo-14β-pregn-8-en-3β-ol was carried out under Djerassi's conditions:[4] a solution of 12.7 g of 3β,20β-diacetoxy-5α-pregn-8-ene-11-one[11] was refluxed for 40 minutes with 1.2 *l* of 5% methanolic potassium hydroxide. After concentration *in vacuo*, dilution with water, extraction with methylene chloride, evaporation and recrystallization from methanol, we obtained 9.1 g of 11-oxo-5α,14β-pregn-8-en-3β,20β-diol with a mp of 198—202°C; $[\alpha]_D^{26.2}$+152° (*c* 1.0); UV $\lambda_{max}^{MeOH}$ 248 nm (ε 9200); CD (*c* 0.01, $CH_3Cl$): $[\theta]_{385}$ 0, $[\theta]_{355}$ −1480, $[\theta]_{330}$ −1230, $[\theta]_{246.5}$ +25600; NMR ($CDCl_3$) τ: 8.88 (18-C$\underline{H_3}$ and 19-C$\underline{H_3}$), 8.81 (d, $J \fallingdotseq 7$ Hz, 21-C$\underline{H_3}$).

Found: C, 75.9; H, 9.6%. Calcd for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7%.




NMR 18-$CH_3$ 77, 21-$CH_3$ 128

CD(in dioxane): $[\theta]_{376}$ 0, $[\theta]_{356}$ −1520, $[\theta]_{342}$ −3630, $[\theta]_{330}$ −4620, $[\theta]_{304}$ −4690, $[\theta]_{286}$ −4690, $[\theta]_{260}$ −610

7) G. Snatzke, H. Pieper, and R. Tshesche, *Tetrahedron*, **20**, 107 (1964). Another example favorable to the present discussion is given by P. Crabbe *et al.*, Ref. 1d.

8) H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Amer. Chem. Soc.*, **86**, 742 (1964); S. Hayakawa, Y. Kanematsu, and T. Fujiwara, *Biochem. J.*, **115**, 249 (1969).

9) *Cf.* G. P. Mueller, *Nature*, **181**, 771 (1958).

10) T. Reichstein and C. W. Schoppee, *Discuss. Faraday Soc.*, **1949**, 305.

11) E. R. H. Jones and D. A. Wilson, *J. Chem. Soc.*, **1965**, 2933.

The catalytic hydrogenation of this 14β-8-en-11-oxo compound (9.1 g) was carried out in 280 m*l* of ethanol in an 86-atm autoclave with 4.0 g of 5% palladium-charcoal for 48 hr. Subsequent recrystallization from ether-petroleum ether gave 6.7 g of **1b** ($R_2$=H); mp 170—173°C; $[\alpha]_D^{23}$+12.0° (*c* 0.35); NMR τ: 9.00 (18-C$\underline{H_3}$), 8.96 (19-C$\underline{H_3}$), 8.85 (d, *J*≒8 Hz, 21-C$\underline{H_3}$); CD (MeOH): $[\theta]_{303}$ −6416.

Found: C, 75.3; H, 10.1%. Calcd for $C_{21}H_{34}O_3$: C, 75.4; H, 10.2%.

**1b** ($R_2$=H) (6.8 g) was reduced to the corresponding 11-deoxo derivative (**2b**, $R_1$,$R_2$=H) in a 79% yield by a modified Wolf-Kishner reduction, heating with 54 g of 80% hydrazine hydrate and 10.4 g of hydrazine dihydrochloride in 320 m*l* of triethylene glycol at 130°C for 1.5 hr. After adding 34.5 g of potassium hydroxide, the temperature was raised to 210°C, as in Exp. 1. After cooling, the reaction was worked up as usual. The recrystallization from acetone led to **2b** ($R_1$=H) (4.8 g) with a mp of 170—173°C. Three recrystallizations from acetone afforded an analytical sample with a mp of 185°C; $[\alpha]_D^{25.8}$ +28.1° (*c* 0.5); NMR τ: 9.10 (19-C$\underline{H_3}$), 9.03 (18-C$\underline{H_3}$), 8.85 (d, *J*≒7 Hz, 21-C$\underline{H_3}$).

Found: C, 78.9; H, 11.3%. Calcd for $C_{21}H_{30}O_2$: C, 78.7; H, 11.3%.

*5. 3,20-Dioxo-5α,8α,14β-pregnane (**3b**, R=O).* The oxidation of 0.70 g of **3b** (R=−OH) with 0.3 m*l* of Jones's reagent in 0.15 m*l* of acetone at room temperature produced **3b** (R=O) (0.54 g), with a mp of 133—135°C. Recrystallization from methanol then led to the analytical sample; mp 138°C; $[\alpha]_D^{29}$+115.5° (*c* 0.23); IR ($CCl_4$) $cm^{-1}$: 1705; NMR τ: 9.11 (18-C$\underline{H_3}$), 8.86 (19-C$\underline{H_3}$), 7.86 (21-C$\underline{H_3}$); CD (*c* 0.001, MeOH): $[\theta]_{325}$ −3926.

Found: C, 79.7; H, 9.9%. Calcd for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2%.

The same product was obtained when the oxidation of **2b** ($R_1$,$R_2$=H) was carried out with stirred chromium trioxide-acetic acid; the mixed melting point and the IR spectra proved to be identical.

The 3,20-dioxo compound (**3b**, R=O) (0.18 g) obtained above was reduced by stirring with 20 mg of sodium borohydride in 20 m*l* of ethanol for 30 min at room temperature; the mixture was then treated as usual to afford 0.14 g of **2b** ($R_1$,$R_2$=H), which was identical with the sample of 3β,20β-diol obtained in Exp. 4.

*6. 3β,20β-Diacetoxy-5α,8α,14β-pregnane (**2b**, $R_1$,$R_2$=Ac).* The free 3β,20β-diol **2b** ($R_1$,$R_2$=H) (0.5 g) in 2.5 m*l* of acetic anhydride and 50 m*l* of pyridine was warmed on a water-bath for 1.5 hr. After dilution with water, filtration, and recrystallization from acetone, we obtained 0.44 g of the diacetate (**2b**, $R_1$,$R_2$=Ac) with a mp of 102—104°C; $[\alpha]_D^{26.8}$ +38.2° (*c* 0.9).

Found: C, 74.4; H, 9.8%. Calcd for $C_{25}H_{40}O_4$: C, 74.2; H, 9.9%. IR ($CCl_4$) $cm^{-1}$: 1735—1740; NMR τ: 9.16 (19-C$\underline{H_3}$), 9.08 (18-C$\underline{H_3}$), 8.83 (d, *J*≒7 Hz, 21-C$\underline{H_3}$), 8.00 (C$\underline{H_3}$COO).

*7. 20β-Acetoxy-5α,8α,14β-pregnan-3-one (**4a**, $X_1$,$X_2$=H).* The partial saponification of the diacetate (**2b**, $R_1$,$R_2$=Ac) in 120 m*l* of 90% methanol with 1.9 g of potassium carbonate gave, after stirring for 2.5 hr at room temperature and dilution with water, 3.5 g of **2b** ($R_1$=H, $R_2$=Ac) with a mp of 112—116°C. Further recrystallization from methanol afforded an analytical sample with a mp of 121°C; $[\alpha]_D^{26.8}$ +46.5° (*c* 0.52); IR (Chf) $cm^{-1}$: 3690, 3600 (3β-OH), 1725 (20β-acetate); NMR τ: 9.18 (19-C$\underline{H_3}$), 9.08 (18-C$\underline{H_3}$), 8.83 (d, *J*=7 Hz, 21-C$\underline{H_3}$), 8.00 (C$\underline{H_3}$COO).

Found: C, 76.1; H, 10.3%. Calcd for $C_{23}H_{38}O_3$: C, 76.2; H, 10.5%.

A mixture of Jones's reagent (1.2 eq.) was added to a solution of 3.2 g of the above 3β-ol **2b** ($R_1$=H, $R_2$=Ac) in 15 m*l* of acetone over a 3-min period, and then the whole mixture was immediately poured into a large volume of ice water. The precipitate was extracted with ether, washed, and dried, and the solvent was removed. Recrystallization from acetone then afforded 3.3 g of **4a** ($X_1$,$X_2$=H); mp 140—141°C; $[\alpha]_D^{26.9}$+71.9° (c, 0.12), IR (Chf) $cm^{-1}$: 1715 (3-ketone), 1735 (acetate); NMR τ: 9.13 (18-C$\underline{H_3}$), 8.88 (19-C$\underline{H_3}$), 8.81 (d, *J*=7 Hz, 21-C$\underline{H_3}$), 8.00 (C$\underline{H_3}$COO); CD (*c* 0.003, dioxane): $[\theta]_{330}$ 0, $[\theta]_{294}$+3635, $[\theta]_{250}$+117, $[\theta]_{218}$+5360.

Found: C, 76.7; H, 9.8%. Calcd for $C_{23}H_{36}O_3$: C, 76.6; H, 10.0%.

*8. 20β-Acetoxy-8α,14β-pregna-1,4-dien-3-one (**5a**, $\Delta^{1,4}$).* One gram of the 3-ketone (**4a**, $X_1$,$X_2$=H) was brominated in 70 m*l* of acetic acid (containing one drop of hydrogen bromide-acetic acid) with 950 mg of bromine in 20 m*l* of acetic acid. The color disappeared in 10 min, after which the solution was left to stand for 1 hr. The addition of water precipitated the crude 2ξ,4ξ-dibromo-3-ketone (**4a**, $X_1$,$X_2$=Br), which was dried and refluxed for 3 hr in 45 m*l* of *N*,*N*-dimethylformamide with 0.7 g of lithium bromide and 1.2 g of lithium carbonate, avoiding moisture. Most of the solvent was thus evaporated off, and the concentrate was diluted with 2*N*-hydrochloric acid. After extraction with methylene chloride, the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by tlc,[12] using benzene-ethyl acetate (9 : 1) as the developing solvent, to give 0.40 g of **5a** ($\Delta^{1,4}$). An analytical sample was recrystallized three times from ether - *n*-hexane; mp 165°C; $[\alpha]_D^{26.9}$ +220.2° (*c* 0.5); IR (Chf) $cm^{-1}$: 1730 (acetate), 1655, 1620, 1600 ($\Delta^{1,4}$-3-ketone); UV $\lambda_{max}^{MeOH}$ 247 mμ (ε 12360); CD: (*c*, 0.001, MeOH) $[\theta]_{345}$+15200, $[\theta]_{320}$+7600, $[\theta]_{299}$+15200, $[\theta]_{273}$ 0, $[\theta]_{255}$−16000; NMR τ: 9.08 (18-C$\underline{H_3}$), 8.83 (d, *J*≒7 Hz, 21-C$\underline{H_3}$), 8.70 (19-C$\underline{H_3}$), 8.00 (C$\underline{H_3}$COO–), 3.96 (d. d., *J*≒2 Hz, $C_4$–H), 3.80 (d, *J*≒3 Hz, $C_2$–H), 3.00 (d, *J*≒10 Hz, $C_1$–H).

Found: C, 77.4; H, 9.1%. Calcd for $C_{23}H_{32}O_3$: C, 77.5; H, 9.0%.

*9. 20β-Acetoxy-8α,14β-pregn-4-en-3-one (**5a**, $\Delta^4$).* 1,4-Diene-3-one (0.13 g) was hydrogenated with 0.1 g of the ruthenium complex in 20 m*l* of benzene at 40°C under an hydrogen pressure of 88 atm for 1 hr. The residue thus obtained was then separated by tlc, using benzene-ethyl acetate (4 : 1) as the developing solvent, to give 98 mg of **5a** ($\Delta^4$). An analytica sample was recrystallized from ether-petroleum ether; mp 84°C; $[\alpha]_D^{27}$+145.3° (*c* 0.4); IR (Chf) $cm^{-1}$: 1725 (acetate), 1655, 1600 (4-en-3-one); NMR τ: 8.75 (19-C$\underline{H_3}$), 8.81 (d, *J*≒7 Hz, 21-C$\underline{H_3}$), 8.74 (19-C$\underline{H_3}$), 8.00 (C$\underline{H_3}$COO), 4.25 (t, *J*≒2 Hz, 4H); CD (*c* 0.003, MeOH): $[\theta]_{332}$+12660, $[\theta]_{316}$+8180, $[\theta]_{282}$+8310, $[\theta]_{262.5}$ 0, $[\theta]_{245}$−15510, $[\theta]_{229}$ 0, $[\theta]_{217}$+14800.

Found: C, 77.0; H, 9.5%. Calcd for $C_{23}H_{34}O_3$: C, 77.1; H, 9.5%.

*10. 8α,14β-Pregn-4-en-3-one (**7**) and 8α,14β,17α-pregn-4-en-3-one (**8**).* A solution of 0.90 g of 20β-acetyl-4-en-3-one (**5a**, $\Delta^4$) dissolved in 40 m*l* of ether was added to a solution of 0.5 g of lithium aluminum hydride in 30 m*l* of ether, and the mixture was stirred at room temperature for 30 min. The mixture was then cooled, and the excess lithium aluminum hydride was decomposed by the addition of water. On a usual work-up, a syrupy residue was obtained. To a solution of 0.7 g of chromium trioxide in 20

12) For preparative and analytical tlc, silicagel G or GF (E. Merck Co.) was used as the adsorbent.

ml of pyridine, we then added, at 10—15°C, a solution of the syrupy residue in 13 ml of the same solvent. After the reaction mixture had been allowed to stand for 2 hr, the usual work-up gave 0.85 g of a mixture of **7** and **8**, which were separated by tlc. By using a developing solvent (benzene-ethyl acetate, 3 : 1), we obtained 0.71 g of **7** (recrystallization from ether-petroleum ether) with a mp of 78°C; $[\alpha]_D^{24}$ +98°C (*c* 0.8). NMR τ: 9.10 (18-C$\underline{H}_3$), 8.75 (19-C$\underline{H}_3$), 7.90 (21-C$\underline{H}_3$), 4.25 (t, $J\fallingdotseq 2$ Hz, 4H).

Found: C, 80.0; H, 9.6%. Calcd for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6%.

We also obtained **8** (28 mg). It was recrystallized from acetone gave an analytical sample; mp 101°C, $[\alpha]_D^{23.5}$ +38° (*c* 0.5). NMR τ: 8.78 (18-C$\underline{H}_3$), 8.68 (19-C$\underline{H}_3$), 7.86 (21-C$\underline{H}_3$), 4.25 (t, $J\fallingdotseq 2$ Hz, 4H).

Found: C, 80.3; H, 9.3%. Calcd for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6%.

*11. Oxidation of **3b** (R=-OH) with Peroxytrifluoroacetic Acid.* Into a mixture of 0.20 ml of 90% hydrogen peroxide and 30 ml of methylene dichloride at 0°C, we stirred 1.5 ml of trifluoroacetic anhydride over a period of 10 min. The mixture was further stirred for five minutes and then transferred to a dropping funnel and stirred drop by drop, into an ice-cold solution of 1.2 g of **3b** (R=OH) in 60 ml of methylene chloride containing 3.8 g of disodium hydrogen phosphate. The mixture was allowed to stand at room temperature under stirring for 1 hr, and then water was added to dissolve the salt. An organic layer was separated and washed with 2 N sodium thiosulfite. After drying, the solvent was removed to give a crystalline residue, **4b** ($X_1$,$X_2$=H, Y=Ac); mp 121—123°C. An analytical sample showed a mp of 125°C, $[\alpha]_D$+79° (*c* 0.9).

Found: C, 75.7; H, 9.5%. Calcd for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7%.

The saponification of 0.70 g of **4b** ($X_1$,$X_2$=H, Y=Ac) with 700 mg of potassium hydroxide in 16 ml of methanol for 30 min, followed by recrystallization from aq. methanol, produced 0.52 g of **4b** ($X_1$,$X_2$=H, Y=H); mp 138—141°C. Analytical sample: mp 142—143.5°C; $[\alpha]_D$+65° (*c* 0.5).

Found: C, 78.6; H, 10.4%. Calcd for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4%.

*12. 8α,14β-Estrone (**6a**) and Its 3-Methyl Ether (**6b**).* The 1,4-dien-3-one (**5b**, $\Delta^{1,4}$) was prepared as has been described above. A solution of 0.20 g of **4b** ($X_1$,$X_2$ and Y=H) in 10 ml of acetic acid (containing one drop of hydrogen bromide-acetic acid) was treated with a solution of 0.10 g of bromine in 2.0 ml of acetic acid at room temperature for 20 min. After an additional 30 min's stirring at 45—50°C, the reaction mixture was diluted. The extract was made neutral by washing it with 2 N sodium bicarbonate and water; then it was evaporated to dryness to yield a crude dibromoketone. The dehydrobromination of the crude dibromoketone (0.21 g) with 0.17 g of lithium bromide and 0.21 g of lithium carbonate in 8.5 ml of refluxing *N,N*-dimethylformamide under a $N_2$ gas stream for 1.5 hr gave the 1,4-dien-3-one compound. The products were separated by tlc. Development with benzene - ethyl acetate (4 : 1) gave crystalline fraction (74 mg); repeated crystallizations from ether - petroleum ether gave **5b** (Y=H, $\Delta^{1,4}$); mp 92—93°C; $[\alpha]_D^{24}$+48° (*c* 0.7), IR (Chf) $cm^{-1}$: 1655, 1628, 1600 ($\Delta^{1,4}$-3-ketone). UV $\lambda_{max}^{MeOH}$ 248 nm (ε 12100); CD (*c* 0.0004, MeOH): $[\theta]_{390}$ +13400, $[\theta]_{315}$ +4530, $[\theta]_{299}$+14310, $[\theta]_{268}$ 0, $[\theta]_{250}$−10410, $[\theta]_{225}$ 0; NMR τ: 9.03 (18-C$\underline{H}_3$), 8.70 (19-C$\underline{H}_3$), 3.98 (d, d., $J\fallingdotseq 2$ Hz, 4-H), 3.75 (d, $J\fallingdotseq 4$ Hz, 2H), 3.00 (d, $J\fallingdotseq 10$ Hz, 1H).

Found: C, 79.4; H, 9.4%. Calcd for $C_{19}H_{26}O_2$: C, 79.7; H, 9.2%.

A solution of 0.10 g of **5b** (Y=H, $\Delta^{1,4}$) in 4 ml of dihydropyran was treated with 0.5 ml of a dihydropyran-anhydrous hydrogen chloride solution (10%) by ice-cooling. After 1.5 hr, the mixture was poured into 30 ml of aq. saturated sodium bicarbonate and thoroughly extracted with ether. The organic layer was washed with water and evaporated *in vacuo* to give a residue, which was then purified by tlc. Development with benzene - ethyl acetate (9 : 1) gave 75 mg of the 17ξ-tetrahydropyranyl compound (**5b**, Y=THF, $\Delta^{1,4}$) as an oil. A solution of 60 mg of biphenyl and 0.1 ml of diphenylmethane in 2 ml of freshly-distilled tetrahydrofuran was refluxed under an argon stream with 30 mg of lithium metal with stirring. After this mixture had cooled, into the resulting dark-green solution the above **5b** in 1.5 ml of tetrahydrofuran was slowly stirred under an argon stream, after which the reaction mixture was refluxed for 15 min. The excess of lithium was then decomposed by the addition of methanol and acidified with diluted hydrochloric acid. After the hydrocarbon had been removed by steam distillation, the product was extracted with methylene dichloride. The organic layer was washed with water, dried over anhydrous sodium sulfate, and then evaporated to dryness. The residue was purified ay tlc (elution, benzene - ethyl acetate, 1 : 1) to give a phenolic substance (28.5 mg), which could not be crystallized. This was immediately oxidized with Jones's reagent (0.4 ml) in 4 ml of acetone; subsequent crystallizations from ethanol gave 20.4 mg of **6a** with a mp of 207—213°C. An analytical sample was recrystallized 2 times from ethanol; mp 215—219°C, $[\alpha]_D^{23}$ +11.5° (*c* 0.8). IR (Chf) $cm^{-1}$: 3600, 3000, 1730, 1605, 1500, 860, 820. (The IR coincided well with the IR of Rufer's sample); NMR τ: 8.85 (18-C$\underline{H}_3$), 3.44 (1H), 3.29 (3H), 2.97 (4H) ($\Delta\tau$ 1,4 ppm, 0.47).[13]

Found: C, 80.0; H, 8.20%. Calcd for $C_{18}H_{22}O_2$: C, 79.9; H, 82.0%.

*3-Methyl Ether (**6b**).* This was prepared by the dimethyl sulfate - 2 N potassium hydroxide treatment of **6a** and was crystallized from methanol; it exhibited a mp of 146—147°C; $[\alpha]_D^{23}$ +14.5° (*c* 0.8, dioxane).

Found: C, 80.1; H, 8.5%. Calcd for $C_{19}H_{24}O_2$: C, 80.2; H, 8.5%. IR (Chf) $cm^{-1}$: 2995, 2920, 2850, 1730, 1610, 1510, 845. Mass spectrum: 284 (M·), 256, 225, 199, 186, 173, 160, 140, 134. The samples of **6a** and **6b** were proven to be identical with authentic samples of *dl*-8α,14β-estrone and its 3-methyl ether (IR spectra, mass spectra, and thin-layer chromatographic behavior).

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13) The assignment of the B/C *cis* fusion in **6a** is supported by the small $\Delta\tau$ 1,4-value of 0.47 ppm in NMR (see W. Nagata, T. Terasawa, and K. Tori, *J. Amer. Chem. Soc.*, **86**, 3746 (1964).)