ene chloride (freshly distilled over calcium hydride); 56 ml. of ethylene glycol, 2.8 g. of selenium dioxide and 280 mg. of *p*-toluenesulfonic acid monohydrate were added, and the resulting suspension was stirred at room temperature for 96 hours. The mixture was partitioned between methylene chloride and water, and the organic extract was washed further with bicarbonate solution and again with water. Drying, concentration and crystallization from hexane gave 2.4 g. of product, m.p. 181–184°. An analytical sample had m.p. 190–191°, $[\alpha]^{26}D$ +87.5°, $\lambda_{max}^{CHCl_3}$ at 5.92 μ.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.55; H, 10.45.

6α-Methyl-20β-hydroxy-allopregnan-3-one 3-Ethylene Ketal (VIII).—Dioxolane VII (517 mg.) was dissolved in a solution of 30 ml. of tetrahydrofuran and 36 ml. of methanol. The solution was cooled to 0°, and 225 mg. of sodium borohydride was added. After standing for one hour, 25 ml. of 50% aqueous acetic acid was added. The solution was concentrated *in vacuo* until the steroid precipitated out. The material was filtered and chromatographed over Florisil. The benzene eluates were combined and crystallized from ethanol to give 335 mg., m.p. 169–172°. An analytical sample had m.p. 169–172°; λ_{max}^{Nujol} at 2.92, 6.10, 9.18 μ.

Anal. Calcd. for $C_{24}H_{40}O_3 \cdot H_2O$: C, 73.05; H, 10.73. Found: C, 73.13; H, 10.58.

6α-Methyl-20β-hydroxy-allopregnan-3-one (IXa).—The dioxane VIII (200 mg.) was dissolved in 20 ml. of methanol, 2 ml. of 8% sulfuric acid was added, and the solution was refluxed under a stream of nitrogen for 40 minutes. Water (100 ml.) was added, and the resulting precipitate was filtered and washed well with water. Recrystallization from methylene chloride–ethanol gave 96 mg., m.p. 170–174°. An analytical sample had m.p. 178–180°, $[\alpha]^{26}D$ +24°; λ_{max}^{Nujol} at 2.92, 5.94 μ; optical rotation: $[\alpha]_{700}$ +17°, $[\alpha]_{589}$ +21°, $[\alpha]_{310}$ +656°, $[\alpha]_{290}$ −390°, $[\alpha]_{287.5}$ −114.9°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.64; H, 10.88.

An acetate IXb was prepared in the usual manner. Crystallization from methylene chloride–hexane gave a material having m.p. 170–171°, $[\alpha]^{26}D$ +53°; λ_{max}^{Nujol} at 5.80, 5.86, 8.05 μ; rotatory dispersion in methanol (<0.29): $[\alpha]^{24}_{589}$ 52.4; optical rotation: $[\alpha]_{650}$ +41°, $[\alpha]_{589}$ +52°, $[\alpha]_{315}$ +810°, $[\alpha]_{280}$ −200°, $[\alpha]_{275}$ −100°; see Fig. 1.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.28; H, 10.23.

6α-Hydroxymethyl-allopregnane-3β,20β-diol (IIc). A. From 3β,20β-Dihydroxy-Δ⁵-pregnene (Ib).—Diol Ib (25 g.) was subjected to hydroformylation as described in the preparation of aldehyde VI, but at 200°. After cooling, a straw-colored crystalline precipitate (23.6 g.) was filtered off and washed with benzene. Recrystallization from methanol gave 7.8 g., m.p. 239–241°. The analytical sample has m.p. 241–243°, $[\alpha]^{25}D$ +16.1° (dioxane), λ_{max}^{Nujol} at 3.10 μ.

Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.33; H, 11.26.

B. From 6α-Hydroxymethyl-allopregnane-3β,20β-diol 3,20-Diacetate (IIa).—Diacetate IIa (348 mg.) was refluxed for 3 hours in 25 ml. of a 5% methanolic solution of potassium hydroxide. The solution was concentrated *in vacuo* to 10 ml., 50 ml. of water was added, and the suspension was extracted with ethyl acetate. The extract was washed with water until neutral, and concentrated until crystallization started. Filtration gave 191 mg. of material (m.p. 236–239°) identical with that described above.

BLOOMFIELD, N. J.
PITTSBURGH, PENNA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Preparation of 6-Methyl Steroids by the "Oxo Reaction"

BY P. F. BEAL, M. A. REBENSTORF AND J. E. PIKE

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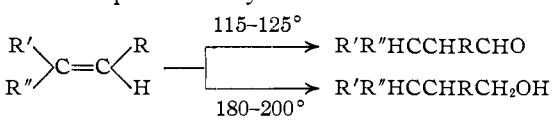
The "oxo reaction" has been applied to the steroidal 5,6-double bond. Reaction with 3β-acetoxy-5-pregnen-20-one yielded 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one which was converted to 6α-methylprogesterone and 6α-methyl-5α-pregnane-3,20-dione. The stereochemistry of the product was assigned on the basis of lithium–ammonia reduction and optical rotatory dispersion studies.

The discovery that introduction of a methyl group at positions 2 and 6 markedly influenced the activities of certain adrenal steroids,[1] led us to investigate alternate means of methylating the steroidal nucleus.

Introduction of aldehyde or hydroxymethyl groups has been effected by addition of the elements of formaldehyde or methanol across the double bond of simple olefins by the "oxo reaction."[2]



The olefin is treated with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl. The new carbon generally adds to the less substituted end of the double bond. Whether an aldehyde or an alcohol is produced depends upon the temperature at which the reaction is effected.

Either a hydroxymethyl or an aldehyde group introduced into the steroid nucleus by this reaction appeared suitable for conversion to a methyl group.

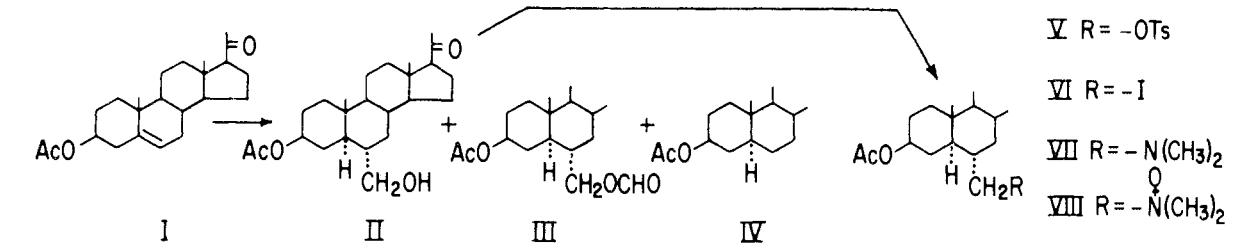
Cholesterol has been hydroformylated to yield a steroidal aldehyde.[3] As the double bond is sometimes isomerized by the "oxo" conditions, this aldehyde was of indefinite structure. The present investigation was directed toward the effect of hydroxymethylation conditions on the steroidal 5,6-double bond.

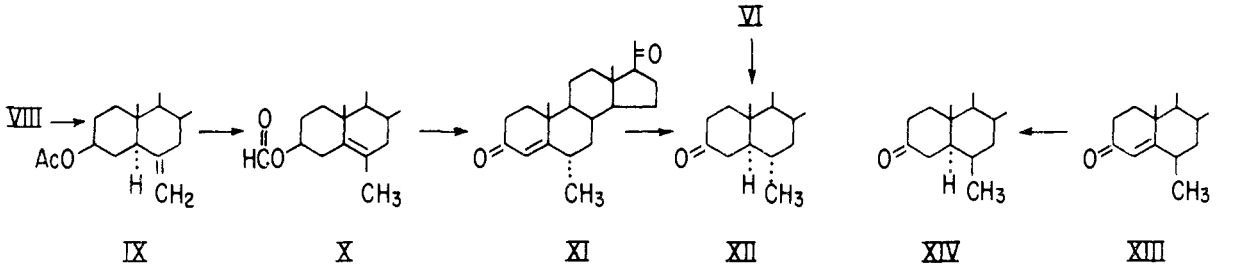
When a toluene solution of 3β-acetoxy-5-pregnen-20-one was subjected to equal pressures of carbon monoxide and hydrogen, 91 kg./cm.² total pressure, at 180° in the presence of either dicobalt octacarbonyl or cobalt carbonate (in the latter case the catalyst is formed *in situ*[2]) a new compound which proved to be 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one (II) was isolated in yields of 60–65%. This also was accom-

(1) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955); G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

(2) I. Wender, H. W. Sternberg and M. Orchin, "Catalysis," Vol. 5, Chapter 2, Reinhold Publishing Corp., New York, N. Y., 1957; M. Orchin and I. Wender, "Encyclopedia of Chemical Technology," Vol. 9, Interscience Encyclopedia, Inc., New York, N. Y., pp. 699–712, 1952.

(3) Private discussion with Dr. I. Wender of U. S. Bureau of Mines.





panied by small amounts of the formate of the hydroxymethylated steroid III and 3β-acetoxy-5α-pregnan-20-one (IV), in which the 5,6-double bond was merely saturated.

Reaction of II with triphenyl phosphite methiodide[4] yielded 3β-acetoxy-6α-iodomethyl-5α-pregnan-20-one (VI). Treatment of VI with dimethylamine afforded 3β-acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one (VII) which was then oxidized[5] with hydrogen peroxide to yield 3β-acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one N-oxide (VIII). This N-oxide decomposed[5] smoothly at temperatures just above its melting point to give 3β-acetoxy-6-methylene-5α-pregnan-20-one (IX). Very strong infrared absorption at 889 cm.$^{-1}$ indicated the presence of the terminal methylene group. Compound IX was then isomerized by treatment with formic acid to 3β-formyloxy-6-methyl-5-pregnen-20-one (X). Infrared absorption of this compound at 1190 and 1182 cm.$^{-1}$ indicated that ester interchange had occurred at the 3-position in the presence of formic acid. Oppenauer oxidation[6] of X yielded the known 6α-methylprogesterone.[7,8] Thus hydroxymethylation occurred at the 6-position in the major reaction product.

Reduction of VI with lithium aluminum hydride, followed by oxidation of the product with pyridine–chromium trioxide complex[9] gave a methylpregnanedione (XII). For comparison compounds, 6α- and 6β-methylprogesterone[7,8] were reduced with lithium and ethanol in liquid ammonia and then reoxidized with the pyridine–chromic acid complex to yield different methyl pregnanediones. On the basis that the lithium reduction of the double bond introduces an axial hydrogen at C-5 to form the more stable *trans* A/B configuration,[10] the structures of these compounds have been assigned as 6α-(XII) and 6β-(XIV) methyl-5α-pregnane-3,20-dione. The optical rotatory dispersion curves of both compounds were characteristic of the *trans* A/B ring juncture.[11] The dione obtained from the hydroxymethylation product was identical by infrared absorption, melting point, mixed melting point and optical rotation with 6α-methylallopregnane-3,20-dione (XII). The structure of II is thus assigned as 3β-acetoxy-6α-hydroxymethylallopregnan-20-one. Therefore the oxo reaction under hydroxymethylation conditions appears to take place *via* a *cis* addition.

Tosylation of II with pyridine and *p*-toluenesulfonyl chloride yielded 3β-acetoxy-6α-tosyloxymethylallopregnane-20-one (V). Reaction of V with sodium formate gave a 6-formyloxy compound (III) identical by melting point and infrared absorption with the reaction by-product previously mentioned.

The second by-product (IV) was identical by melting point, mixed melting point and infrared absorption with an authentic sample of 3β-acetoxyallopregnan-20-one.

These same hydroxymethylation conditions were applied to β-sitosterol to yield a hydroxymethylated product, the structure of which has been assigned as 6α-hydroxymethylsitostanol, by analogy with the above work.

Experimental

Hydroxymethylation of 3β-Acetoxy-5-pregnen-20-one (I) with Dicobalt Octacarbonyl.—A 500-ml. Magne-Dash[12] autoclave was charged with 30.0 g. of 3β-acetoxy-5-pregnen-

(4) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

(5) A. C. Cope, T. T. Foster and P. H. Towle, THIS JOURNAL, **71**, 3929 (1949).

(6) H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 816 (1956).

(7) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(8) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

(9) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1955).

(10) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(11) Private communication, W. A. Struck and R. L. Houtman, these laboratories.

(12) A magnetically agitated high pressure autoclave manufactured by Autoclave Engineers, Erie, Penna.

3-one, 450 ml. of toluene and 4.5 g. of dicobalt octacarbonyl.[13] The autoclave was sealed and flushed three times with carbon monoxide. Carbon monoxide was admitted to 42 kg./cm.^{2} and then the pressure was brought to 88 kg./cm.^{2} with hydrogen. The reaction was heated at 180° with agitation for 18 hours. The cold pressure drop was 20 kg./cm.^{2} The reaction mixture was removed from the autoclave and the toluene removed under reduced pressure. The residue was dissolved in 250 ml. of 3A ethyl alcohol and the solution refluxed until the catalyst was decomposed. Filtration through Celite removed the cobalt residue. The alcohol was removed under reduced pressure. The residue was recrystallized from acetone–Skellysolve B[14] to yield 20.7 g. of crude product melting 125–140°. Chromatography of a 2.0-g. portion over Florisil[15] furnished a fraction eluted with 10% acetone–Skellysolve B. This fraction was recrystallized from Skellysolve B–acetone to yield 0.18 g. of 3β-acetoxy-6α-formyloxymethyl-5α-pregnane-20-one, melting 134–135°; ν_{max}^{Nujol} 1716, 1697, 1244 and 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 73.74; H, 9.15. Found: C, 73.75; H, 8.86.

Elution with 20% acetone–Skellysolve B removed 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one (II), which was recrystallized from acetone-Skellysolve B to yield 1.65 g. of crystals melting 149–151°; ν_{max}^{Nujol} 3500, 1722, 1688, 1242, 1226 and 1212 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.81; H, 9.82.

Chromatography of the mother liquors of the initial recrystallization furnished 1.86 g. of 3β-acetoxy-5α-pregnan-20-one eluted with 5% acetone–Skellysolve B. A sample melted 141–144° after recrystallization from aqueous methanol. The 10% eluates afforded an additional 1.86 g. of III. The 20% eluates yielded 4.24 g. of impure II, identical to the analytical sample by infrared absorption.

Hydroxymethylation of 3β-Acetoxy-5-pregnen-20-one (I) in the Presence of Cobalt Carbonate.—A 500-ml. Magne-Dash autoclave was charged with 10.0 g. of 3β-acetoxy-5-pregnen-20-one, 150 ml. of toluene and 1.5 g. of cobalt carbonate. After flushing three times with carbon monoxide, the carbon monoxide pressure was raised to 46 kg./cm.^{2} and the total pressure was brought to 93 kg./cm.^{2} with hydrogen. The reaction was heated at 180° with agitation for 12 hours. The cold drop was 24 kg./cm.^{2}. The gases were vented and the reaction mixture removed from the autoclave. The toluene was removed under reduced pressure. The residue was dissolved in 200 ml. of refluxing 3A alcohol. After standing overnight the mixture was filtered through Celite. The solvent was removed under reduced pressure and the residue recrystallized from Skellysolve B–acetone to yield a crystalline product (7.2 g.) melting 130–145°. A 2-g. sample of this product was chromatographed over Florisil and a single peak of 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one was eluted with 20% acetone–Skellysolve B. Recrystallization of this eluate afforded 1.51 g. of product melting 144–148°.

3β-Acetoxy-6α-tosyloxymethyl-5α-pregnan-20-one (V).—A solution of 4.1 g. of 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one and 4.0 g. of *p*-toluenesulfonyl chloride i n 22 ml. of pyridine was allowed to stand overnight at room temperature. The mixture was diluted with ice-water and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid and then with saturated sodium bicarbonate. After the solvent was removed, the residue was chromatographed over Florisil and eluted with 10% acetone–Skellysolve B. When this eluate had evaporated to about one-third its original volume the crystalline product which had separated was removed by filtration to yield 3.91 g. of 3β-acetoxy-6α-tosyloxymethyl-5α-pregnan-20-one (V) melting 95–105°; ν_{max}^{Nujol} 1730, 1700, 1597, 1495, 1364, 1178, 1249, 1230, 841 and 311 cm.$^{-1}$. Evaporation of the filtrate yielded an additional 1.0 g. of crude V.

Anal. Calcd. for $C_{31}H_{44}O_6S$: S, 5.88. Found: S, 5.75.

(13) I. Wender, H. Steinberg, S. Metlin and M. Orchin, "Inorganic Syntheses," Vol. V, McGraw-Hill Book Co., Inc., New York, N. Y., 1957, p. 190.

(14) A saturated hydrocarbon fraction, b.p. 64–70°.

(15) A synthetic magnesia–silica gel made by the Floridin Co., Warren, Pa.

3β-Acetoxy-6α-formyloxymethyl-5α-pregnan-20-one (III).—A mixture of 1.0 g. of 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one, 1.0 g. of *p*-toluenesulfonyl chloride and 5 ml. of pyridine was allowed to stand at room temperature for 44 hours. The mixture was decomposed by addition of ice and the product extracted with methylene chloride. After washing and solvent removal the residue was dissolved in 22 ml. of 3A alcohol, 0.75 ml. of water and 0.3 g. of sodium formate. The mixture was refluxed for 16 hours and then the solvent was removed under reduced pressure. After extraction with methylene chloride, the product was chromatographed over Florisil. A partially crystalline product was eluted with 5% acetone–Skellysolve B. Recrystallization of a sample of the eluate from acetone–Skellysolve B yielded crystals melting 135–137°. The infrared absorption spectrum of this material was identical to that of III, isolated from the hydroxymethylation reaction.

3β-Acetoxy-6α-iodomethyl-5α-pregnan-20-one (VI).—A mixture of 5.0 g. triphenylphosphite methiodide and 3.06 g. of 3β-acetoxy-6α-hydroxymethyl-5α-pregnan-20-one (II) in 6 ml. of methyl iodide was heated at reflux with stirring for 90 minutes. The solution was cooled to room temperature and the excess methyl iodide removed under a stream of nitrogen. The residue was partitioned between water and methylene chloride and extracted twice with methylene chloride. The combined extracts were washed thoroughly with water and dried over sodium sulfate. The solvent was removed under reduced pressure and 20 ml. of methanol was added to the residue to effect crystallization. Filtration yielded 2.68 g. of VI melting 160–166° with decomposition; ν_{max}^{Nujol} 1718, 1695 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{37}IO_3$: C, 57.60; H, 7.45; I, 25.36. Found: C, 57.50; H, 7.67; I, 25.10.

3β-Acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one (VII).—A mixture of 4.0 g. of 3β-acetoxy-6α-iodomethyl-5α-pregnan-20-one and 15 ml. of dimethylamine was sealed in a Parr bomb and heated on a steam-bath for 70 minutes. The bomb was cooled and opened. The excess dimethylamine was allowed to evaporate. The product was partitioned between methylene chloride and water. The aqueous layer was made alkaline with 10% sodium hydroxide. The solvent was removed and the product was chromatographed over Florisil. The 20–30% acetone–Skellysolve B eluates afforded 2.24 g. of a partially crystalline product of sufficient purity for the next step. An analytical sample of VII was prepared by recrystallization of a portion of the eluate from Skellysolve B, yielding crystals melting 118–119°; ν_{max}^{Nujol} 2760, 1720, 1695 and 1235 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}NO_3$: C, 74.77; H, 10.38; N, 3.35. Found: C, 74.85; H, 10.31; N, 3.40.

3β-Acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one N-oxide (VIII).—A solution of 1.77 g. of 3β-acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one in 5 ml. of methanol was cooled in an ice-bath and 2.5 ml. of 30% aqueous hydrogen peroxide was added. The mixture became nearly solid, so a further 10 ml. of methanol was put in. The mixture was removed from the ice-bath and after 10 minutes of stirring at room temperature a clear solution resulted. After stirring for 18 hours at room temperature the mixture was heated until refluxing commenced and then cooled in an ice-bath. A small amount of a slurry of manganese dioxide in methanol was added and then stirring was continued at room temperature until decomposition of hydrogen peroxide was complete. The mixture was filtered and the solvent was removed under reduced pressure. The residue was partitioned between methylene chloride and water and the solvent removed under reduced pressure. The product was chromatographed over Florisil. The methanol eluate contained 0.57 g. of the monohydrate of 3β-acetoxy-6α-dimethylaminomethyl-5α-pregnan-20-one N-oxide, a sample of which melted at 114–117° with decomposition at 130° after recrystallization from Skellysolve B; ν_{max}^{Nujol} 3580, 3500, 3350, 3170, 1707, 1697, 1252 and 1232 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{43}NO_4.H_2O$: C, 69.14; H, 10.04; N, 3.10. Found: C, 69.01; H, 9.98; N, 3.41.

3β-Acetoxy-6-methylene-5α-pregnan-20-one (IX).—The crude crystalline amine oxide VIII (3.84 g.) was heated in a wax-bath at 130–140° at 20 mm. for 30 minutes. After this time gas evolution had nearly ceased. The residue (3.22 g.) was leached with several portions of boiling Skelly-

solve F[16] and then chromatographed over Florisil. The 4 and 5% acetone–Skellysolve B eluates removed 2.28 g. of 3β-acetoxy-6-methylene-5α-pregnan-20-one from the column. Recrystallization from Skellysolve F yielded 1.27 g. of IX melting 113–117°; ν_{max}^{Nujol} 1722, 1701, 1644, 1235, 1024 and 886 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.72.

3β-Formyloxy-6-methyl-5-pregnen-20-one (X).—A solution of 1.17 g. of 3β-acetoxy-6-methylene-5α-pregnan-20-one in 10 ml. of 98% formic acid was stirred at room temperature for 90 minutes with no apparent change. The mixture then was heated on the steam-bath for 20 minutes. The reaction mixture became deep purple. The solvent was removed under reduced pressure and the residue neutralized with excess sodium bicarbonate and extracted with methylene chloride. The product was chromatographed over Florisil and eluted with 4% acetone–Skellysolve B to yield 0.91 g. of a crystalline product. A sample of the product was recrystallized from Skellysolve B to yield crystals of X melting 158–160°. The infrared absorption spectrum indicated that ester interchange had occurred to give the 3β-formate; ν_{max}^{Nujol} 1721, 1693, 1190, 1182 and 925 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.92; H, 9.29.

6α-Methylprogesterone (XI).—A solution of 73 mg. of 3-formyloxy-6-methyl-5-pregnen-20-one (X), 5 ml. of xylene and 0.75 ml. cyclohexanone was heated to reflux, then 0.1 g. of aluminum isopropoxide was added and the mixture allowed to reflux for 45 minutes. The flask was cooled and the mixture diluted with ice. The reaction mixture was distilled under reduced pressure to remove the solvents and then extracted with methylene chloride. The product was chromatographed over Florisil. The starting material (X, 8 mg.) was eluted with 5% acetone–Skellysolve B. The acetone eluate of the column contained 18 mg. of 6α-methylprogesterone. The infrared spectrum of this material was identical to that of an authentic sample. Recrystallization from aqueous methanol yielded crystals melting 116–119°.

6α-Methyl-5α-pregnane-3,20-dione (XII).—A solution of 1.5 g. of 3β-acetoxy-6α-iodomethyl-5α-pregnan-20-one in 50 ml. of benzene was added with stirring to a suspension of 3.0 g. of lithium aluminum hydride in 50 ml. of ether. The mixture was heated with stirring at reflux for 5.5 hours and then cooled. The excess hydride was decomposed by the successive addition of ethyl acetate, ethanol, water and dilute hydrochloric acid. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and dilute sodium thiosulfate solution, and the solvent removed under reduced pressure. The crude reduction product was dissolved in 20 ml. of pyridine and oxidized with a mixture of 2.0 g. of chromium trioxide and 20 ml. of pyridine. After the usual work-up the product was filtered through a short Florisil column. The crystalline material thus obtained was combined and twice recrystallized from acetone–Skellysolve B to give 0.161 g. of 6α-methyl-5α-pregnane-3,20-dione melting 152–153°. Mixed melting point with a specimen of XII, prepared from 6α-methylprogesterone, was also 152–153° and the infrared spectra of the two samples were identical.

The combined mother liquors from the above crystallizations were triturated with ether to afford an additional 0.30 g. of XII melting 140–148°.

6α-Methyl-5α-pregnane-3,20-dione (XII).—A solution of 2.2 g. of 6α-methylprogesterone in 90 ml. of absolute ethanol was added with stirring to 500 ml. of liquid ammonia. Addition of 13.8 g. of lithium wire was made as rapidly as possible. After the addition was complete, the ammonia was allowed to evaporate, water was added and the mixture extracted with benzene. Solvent removal after washing the extract with water and drying with sodium sulfate gave the crude diol as an oil. This was oxidized directly by dissolving in 25 ml. of pyridine and adding to a mixture of 2.5 g. of chromium trioxide and 25 ml. of pyridine. After standing overnight, water and 1:1 benzene–ether was added. The suspended solid was removed by filtration through Supercel, the organic layer separated and the aqueous layer re-extracted with 1:1 benzene–ether. The combined extracts were washed with water, dried and the solvent removed under reduced pressure. Toluene was added and the solvent again removed under reduced pressure to remove the pyridine. The residue in benzene was filtered, chromatographed over 10 g. of Florisil and the crystalline material obtained recrystallized from acetone–Skellysolve B to give 0.98 g. of XII melting 147–150°. Further recrystallization from the same solvent raised the melting point to 151–153°; ν_{max}^{Nujol} 1700, 1600 cm.$^{-1}$; optical rotatory dispersion in dioxane (*c* 0.101): $[\alpha]_{589}$ +119°, $[\alpha]_{315}$ +2635°, $[\alpha]_{285}$ −188°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.06; H, 10.36.

6β-Methyl-5α-pregnane-3,20-dione (XIV).—A solution of 2.5 g. of 6β-methylprogesterone in 70 ml. of absolute ethanol was added dropwise with stirring to a solution of 11.9 g. of lithium wire in 500 ml. of liquid ammonia. When the addition was complete, an additional 5.0 g. of lithium and 40 ml. of ethanol was added to ensure complete reduction. The ammonia was allowed to evaporate, water added and the organic material extracted twice with 1:1 benzene–ether. The combined organic layers were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue dissolved in 25 ml. of pyridine. The crude diol was oxidized overnight at room temperature with 2.5 g. of chromium trioxide and 25 ml. of pyridine. Water and 1:1 benzene–ether were added and the suspended solid removed by filtration through Super-cel. The organic layer was separated and the solvent removed under reduced pressure. The pyridine was removed by addition of toluene and then concentration under reduced pressure. After filtration of a benzene solution of the residue through 10 g. of Florisil, the crystalline product was recrystallized from acetone–Skellysolve B to give 0.95 g. of XIV melting 177–181°. A second recrystallization raised the melting point to 179–181°; ν_{max}^{Nujol} 1705, 1693 cm.$^{-1}$; the infrared spectrum of the 6α- and 6β-isomers were not identical; optical rotatory dispersion in dioxane (*c* 0.100): $[\alpha]_{589}$ + 100°, $[\alpha]_{315}$ +2644, $[\alpha]_{285}$ −359°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.25; H, 10.22.

The nuclear magnetic resonance spectra of the 6α- and 6β-methyl-5α-pregnane-3,20-diones confirmed the stereochemistry at C_6. These were run by George Slomp of these laboratories and will be submitted for publication in THIS JOURNAL.

Hydroxymethylation of Sitosterol. Preparation of 6α-Hydroxymethyl Sitostanol.—A 500-ml. Magne-Dash autoclave was charged with 10.35 g. of sitosterol, 150 ml. of toluene and 1.0 g. of $Co_2(CO)_8$ catalyst. The autoclave was flushed three times with carbon monoxide, the carbon monoxide pressure raised to 56 kg./cm.^{2} and then the pressure brought to 112 kg./cm.^{2} with hydrogen. The autoclave was heated with agitation for 6 hours at 180°. The cold drop was 9 kg./cm.^{2} The reaction mixture was removed from the autoclave and 4.62 g. of product removed by filtration. Recrystallization from 3A alcohol yielded 4.0 g. of 6α-hydroxymethylsitostanol melting 208–210°; ν_{max}^{Nujol} 3280, 1052 and 1031 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.63; H, 11.68.

Chromatography of the filtrate over Florisil afforded an additional 1.75 g. of the product.

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(16) A saturated hydrocarbon fraction, b. p. 35–58°.