

[JOINT CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF THE SCHERING CORPORATION AND THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES]

Hydroformylation of the Steroid Nucleus: A Novel Method for the Preparation of 6 α -Methylsteroids

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Hydroformylation of 3 β ,20 β -dihydroxy- Δ^5 -pregnene (I) yielded a 6 α -hydroxymethyl-allosteroid, as proved by correlation with 6 α -methylprogesterone. The allo ring juncture was assigned on the basis of optical rotatory dispersion, stereospecific reduction and Zimmermann color rates.

The hydroformylation (Oxo) reaction has generally been applied to simple molecules,² though some natural products have been successfully converted to aldehydes and alcohols containing one more carbon atom.³ The successful application of this reaction to cholesterol,^{4a} coupled with current interest in methylated derivatives of steroidal hormones,^{4b} led us to subject a simple steroid to the action of carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl.

When 3 β ,20 β -diacetoxy- Δ^5 -pregnene (Ia, Chart I)⁵ was exposed to these gases in the presence of dicobalt octacarbonyl at 195°, a substance having an additional hydroxymethyl group was obtained. It was formulated as 6 α -hydroxymethylallopregnane-3 β ,20 β -diol 3 β ,20 β -diacetate (IIa) on the basis of its properties and the reactions to be described. The substance did not give a color with tetranitromethane, indicating loss of unsaturation, and its infrared spectrum showed the presence of free hydroxyl. Saponification led to triol IIC, and acetylation of either IIa or IIC gave triacetate IIb.

To prove the structure of II the following correlation was effected: The diacetate IIa was treated with *p*-toluenesulfonyl chloride and the resulting tosylate IID was reduced with lithium aluminum hydride to methyl-diol III, and further oxidized to methyl-dione IV. This same substance also was obtained by reduction, with lithium in liquid ammonia, of the double bond in the known 6 α -methylprogesterone (V).^{6,7} Hence, the hydroxymethyl group in the new series must be located in the 6 α -position.

The stereochemistry of the hydrogen at C-5 is

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

(3) J. C. Lo Cicero and R. T. Johnson, THIS JOURNAL, **74**, 2094 (1951); A. Rosenthal and D. Read, *Can. J. Chem.*, **35**, 788 (1956); C. Bordenca, Abstracts of Papers, Meeting American Chemical Society, New York, N. Y., September 1957, p. 16p.

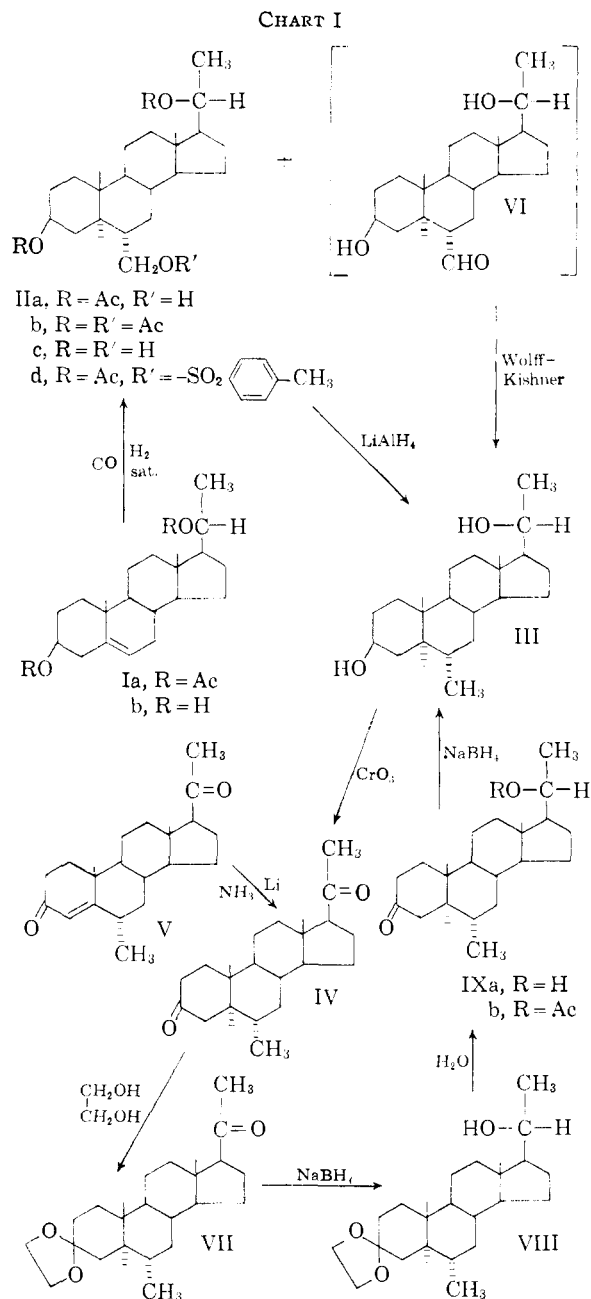
(4) (a) S. Friedman, S. Metlin and I. Wender, unpublished work of U. S. Bureau of Mines. Although the yield from hydroformylation of cholesterol was high, neither the position of the entering group nor the stereochemistry of the product was investigated; (b) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955); G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanzel, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

(5) R. B. Turner and D. M. Voitle, *ibid.*, **73**, 2283 (1957).

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

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

not unequivocally established by the manner of its preparation from 6 α -methylprogesterone. To be



sure, metal reduction of an α,β -unsaturated ketone always yields the more stable stereoisomer at

the β -carbon atom.⁸ However, though the allo configuration is undoubtedly the more stable one in the simple pregnane series, it need not be when the steroid nucleus is substituted at C-6.⁹

The fact that an allopregnane derivative had indeed been obtained became clear from the following observations: Preferential ketalization of IV at C-3¹⁰ gave monoketal VII and reduction of the surviving carbonyl at C-20 with sodium borohydride with subsequent removal of the protecting group gave IXa and a corresponding acetate IXb.¹¹

Both compounds showed a positive single Cotton effect curve in optical rotatory dispersion measurements¹² characteristic for such allo compounds, e.g., cholestanone (see Fig. 1).

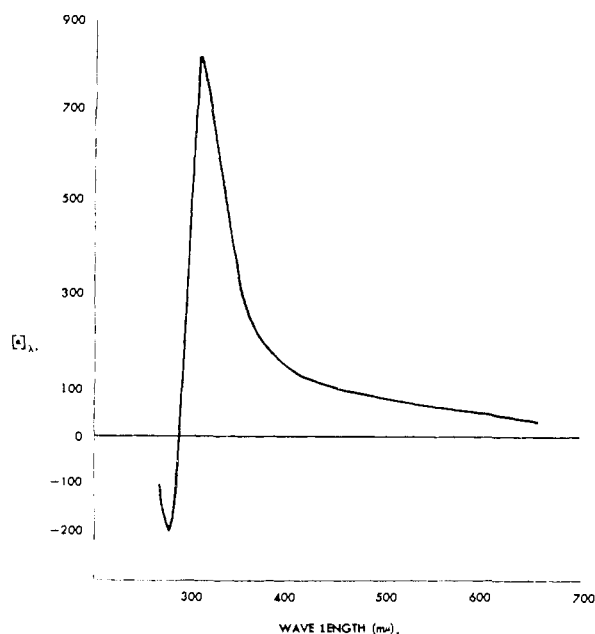


Fig. 1.—Rotatory dispersion of 6 α -methyl-20 β -acetoxy-allopregnan-3-one (VIIIb) (c 0.29 g./100 ml. CHCl₃, $T = 26^\circ$) (IXb).

Furthermore, reduction of IXa with sodium borohydride yielded the 3 β -hydroxy compound III in high yield. Since such a reduction is expected to give predominantly the equatorial alcohol,¹³ again an allo AB ring junction would have to be assigned. Finally, quantitative Zimmermann color reaction rate measurements for IXa gave a

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

(9) However, upon reduction with lithium in liquid ammonia 4-methyl- Δ^4 -stigmasten-3-one gave 4 α -methylstigmastan-3-one (AB *trans*); cf. Y. Mazur, A. Weizmann and F. Sondheimer, *THIS JOURNAL*, **80**, 1007 (1958).

(10) E. P. Oliveto, H. Q. Smith, C. Gerold, L. Weber, R. Rausser and E. B. Hershberg, *ibid.*, **77**, 2224 (1955).

(11) The 20 β -configuration is assigned from the mode of preparation and from differences in molecular rotation; see D. K. Fukushima and E. D. Meyer, *J. Org. Chem.*, **23**, 174 (1958).

(12) We wish to thank Dr. Carl Djerassi of Wayne State University and Dr. Charles Sweeley of the National Heart Institute for obtaining these curves. For leading references, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 1955 (1957).

(13) W. G. Dauben, G. J. Fonken and D. S. Noyce, *THIS JOURNAL*, **78**, 2579 (1956). We wish to thank Dr. Dauben for suggesting this course.

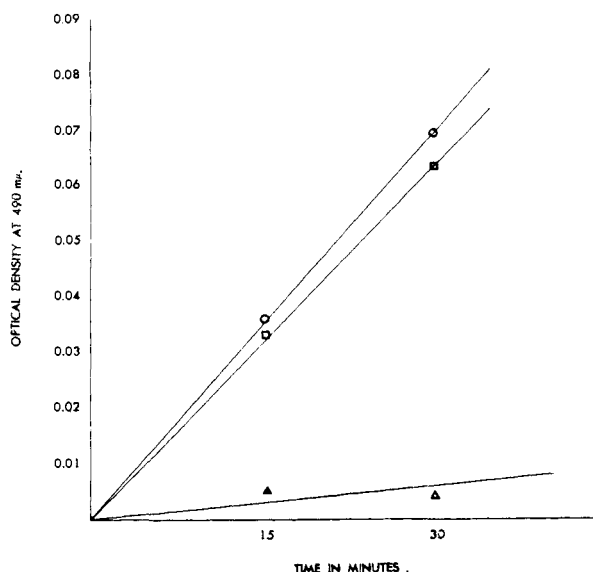


Fig. 2.—Zimmermann color reaction of 100 γ of: cholestan-3-one (5 α -H), A, \square ; coprostan-3-one (5 β -H), B, Δ ; and of 86 γ of 6 α -methyl-20 β -hydroxy-allopregnan-3-one (IXa), C, O.

curve characteristic of an allo-3-ketone¹⁴ (see Fig. 2).

The Oxo reaction also was carried out on the parent diol Ib, and the expected homologous triol IIc was isolated. When an attempt was made, however, to prepare aldehyde VI by lowering the reaction temperature to 135 $^\circ$, a mixture of starting material Ib, triol IIc and aldehyde VI (indicated by an infrared absorption at 5.83 μ) was obtained. The new aldehyde could not be purified chromatographically as it was largely destroyed, and a more indirect proof of its existence had to be adopted. The reaction mixture was treated with semicarbazide hydrochloride. Subsequent chromatography gave (1) unreacted starting material Ib, and (2) a mixture of triol IIc and the semicarbazone of VI. When this mixture was reduced by the Wolff-Kishner method, the resulting methyl compound III, identical with the material described earlier, could be separated easily from triol IIc.

It is significant that hydroformylation of a steroid molecule gives essentially only one product. Although it is true that reaction at the 5,6 double bond would be expected to give predominantly the 6-hydroxymethyl compound,¹⁵ double bonds are easily isomerized under hydroformylation conditions with the formyl group adding to the most accessible carbon atoms.¹⁶ Thus the 5,6-double bond might be expected to isomerize to the 6-7 position and hydroformylation to occur at both C-6 and C-7. While the failure to isolate the C-6- β and C-7 substituted products does not ex-

(14) We are indebted to Prof. D. H. R. Barton for suggesting this method. For technique, see A. M. Bongiovanni, W. R. Eberlein and P. Z. Thomas, *J. Clin. Endocrin. Metab.*, **17**, 331 (1957).

(15) I. Wender, J. Feldman, S. Metlin, B. H. Gwynn and M. Orchin, *THIS JOURNAL*, **77**, 5760 (1955).

(16) Internal olefins isomerize to terminal olefins and addition of the formyl group occurs chiefly at the two end carbon atoms; see I. Wender, S. Metlin, S. Ergun, H. W. Sternberg and H. Greenfield, *ibid.*, **78**, 5401 (1956).

clude the possibility that some may have been formed as minor products, the formation of only one isomer as a major product indicates that hydroformylation of complex molecules is stereospecific.

Acknowledgment.—We wish to thank Drs. Barton, Dauben and Meinwald for their kind interest, and Drs. Herzog, Robinson and Hershberg for their helpful discussions.

Experimental¹⁷

Apparatus and Reagents.—The hydroformylation reactions were carried out in a standard American Instrument Co. half-liter stainless steel rocking autoclave with a free space of 492 ml. The equipment has been described previously.¹⁸ The synthesis gas (1H₂:1CO) was manufactured and compressed at the Bureau of Mines. All solvents were reagent grade.

6 α -Hydroxymethyl-allopregnane-3 β ,20 β -diol 3,20-Diacetate (IIa).—A solution of 44 g. of 3 β ,20 β -diacetoxy- Δ^5 -pregnene (Ia) and 8 g. of dicobalt octacarbonyl¹⁹ in 220 ml. of toluene was heated to 200° for 4 hours with 3500 p.s.i.g. of synthesis gas in an autoclave. The reaction mixture was removed from the autoclave and refluxed until the catalyst was decomposed and very little color remained. The solution was filtered and the toluene evaporated, leaving 36 g. of crude product. Recrystallization from acetone-hexane gave 26 g., m.p. 168–170° (transition 107–108°); analytical sample, 172–174°, $[\alpha]_{25}^{20} +23.2^\circ$; $\lambda_{\text{max}}^{\text{CO}}$ at 2.92, 5.78, 8.08 μ .

Anal. Calcd. for C₂₈H₄₂O₅: C, 71.85; H, 9.74. Found: C, 71.52; H, 9.71.

6 α -Hydroxymethyl-allopregnane-3 β ,20 β -diol Triacetate (IIb).—This compound was prepared in the usual manner (pyridine-acetic anhydride) either from the triol IIc (see below) or the diacetate IIa. Crystallization from pentane gave an analytical sample, m.p. 128–129°, $[\alpha]_{25}^{20} +33.9^\circ$; $\lambda_{\text{max}}^{\text{CO}}$ 5.78, 8.10 μ .

Anal. Calcd. for C₂₈H₄₄O₆: C, 70.55; H, 9.31. Found: C, 70.44; H, 9.51.

6 α -Tosyloxymethyl-allopregnane-3 β ,20 β -diol Diacetate (IIId).—Crude hydroxy-diacetate IIa (3.9 g.) was dissolved in 60 ml. of freshly distilled pyridine and cooled to 0°. To this solution, 8.6 g. of *p*-toluenesulfonyl chloride was added, and the resulting solution was allowed to stand overnight. It was then poured into a solution of 1.4 l. of water and 70 ml. of concd. hydrochloric acid. The mixture was extracted with ether, and the extract washed with aqueous sodium bicarbonate and water, dried, and concentrated. Crystallization from hexane gave 3.16 g. of the tosylate, m.p. 167–169°. An analytical sample melted at 169° (transition points at 121° and 154°), $[\alpha]_{25}^{20} +23.9^\circ$, $\lambda_{\text{max}}^{\text{CO}}$ at 225 m μ (ϵ 12,000); $\lambda_{\text{max}}^{\text{NH}}^{\text{OH}}$ at 5.78, 6.25, 6.70, 8.05 μ .

Anal. Calcd. for C₃₃H₄₆O₇S: S, 5.54. Found: S, 5.43.

6 α -Methyl-allopregnane-3 β ,20 β -diol (III). A. From 6 α -Tosyloxymethyl-allopregnane-3 β ,20 β -diol Diacetate (IIId).—The preceding tosylate IIId (3.16 g.) was dissolved in 60 ml. of dry tetrahydrofuran and added dropwise, with stirring and cooling, to a suspension of 8.0 g. of lithium aluminum hydride in 50 ml. of the same solvent. After the initial reaction had subsided, the temperature was raised to reflux for 18 hours. Excess reagent was destroyed with acetone, and the complex was decomposed with 200 ml. of 15% aqueous hydrochloric acid. The material was extracted with methylene chloride and the extract washed with aqueous sodium bicarbonate and water. Drying, concentration, and crystallization from isopropyl ether gave 1.05 g., m.p. 201–202°. A second crop, 180 mg., m.p. 199–201°, was obtained from the mother liquors. An analytical sample had m.p. 202–203°, $[\alpha]_{25}^{20} +8.9^\circ$, $\lambda_{\text{max}}^{\text{NH}}^{\text{OH}}$ at 3.10 μ .

(17) All melting points were taken on a Kofler block. Rotations were carried out in a 1-dm. tube at a concentration of ca. 1% in chloroform, unless otherwise specified. Analyses and spectral data were obtained by the Microanalytical and Physical Chemistry Departments of the Schering Corp.

(18) I. Wender, R. Levine and M. Orchin, *THIS JOURNAL*, **72**, 4375 (1950).

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

Anal. Calcd. for C₂₂H₃₈O₂: C, 78.98; H, 11.45. Found: C, 79.11; H, 11.45.

B. From 6 α -Methyl-20 β -hydroxy-allopregnan-3-one (IXa).—Monoketone IXa (see below), 65 mg., was dissolved in 8 ml. of methanol, cooled to 0°, and 45 mg. of sodium borohydride was added. After one hour, 6 ml. of 50% aqueous acetic acid was added and the solution concentrated *in vacuo* to a 5-ml. volume. The resulting precipitate (66.1 mg., $[\alpha]_{25}^{20} 8.1^\circ$) was filtered, dried, and recrystallized from isopropyl ether to give 37.9 mg. of substance identical with diol III ($[\alpha]_{25}^{20} +8.6^\circ$) prepared as above.

C. Via 6 α -Formyl-allopregnane-3 β ,20 β -diol (VI) from 3 β ,20 β -Dihydroxy- Δ^5 -pregnene (Ib).—A solution of 25 g. of Ib and 5 g. of dicobalt octacarbonyl¹⁹ in 200 ml. of toluene was heated to 125–135° for 4 hours with 3500 p.s.i.g. of synthesis gas in an autoclave. The resultant slurry was filtered and washed with benzene to give 20 g. of crystalline material. Infrared spectral analysis indicated the presence of unreacted starting material as well as of aldehyde.

This crude material (4.4 g.) and 1.76 g. of semicarbazide were dissolved in 240 ml. of methanol, and a small amount of pyridine hydrochloride was added. The solution was heated to reflux for 1.5 hours, 100 ml. of water added, and the mixture concentrated *in vacuo* to about 100 ml. The resulting white precipitate (5.4 g.) was filtered and chromatographed on 250 g. of Florisil. From the benzene-ether (3:1) eluates, 2.4 g. of starting material Ib (m.p. 209–210°) was isolated. Eluates with methylene chloride-methanol (9:1) gave a mixture of semicarbazone from aldehyde VI as well as triol IIc; infrared bands at 3.06, 5.96, 6.04 and 6.30 μ . This mixture was used directly in the Wolff-Kishner reaction now to be described.

A solution of 0.98 g. of potassium hydroxide in 40 ml. of diethylene glycol was heated to 200° and the mixture of semicarbazone and triol described above was added. Immediate vigorous evolution of gas was observed. The temperature was raised to 250° and kept there for 1.5 hours. After cooling, 300 ml. of ice-water containing 1.8 ml. of concentrated hydrochloric acid was added, and the aqueous phase was extracted with methylene chloride. The organic extract was washed with water, dried, and concentrated to an oily residue (1.3 g.). The latter was chromatographed on alumina. From the ether-methylene chloride (4:1) eluates, 378 mg. of III was isolated after recrystallization from isopropyl ether. This material had m.p. 199–201°, $[\alpha]_{25}^{20} +8.9^\circ$ and did not, upon admixture, depress the melting point of material obtained as described above.

6 α -Methyl-allopregnane-3,20-dione (IV). A. From 6 α -Methyl-allopregnane-3 β ,20 β -diol (III).—Diol III (1.05 g.) was dissolved in 180 ml. of acetone distilled over potassium permanganate, and this solution was titrated at room temperature, with stirring, to a permanent yellow color with 8 N Kiliani acid (26.72 g. of chromic oxide, 23 ml. of concentrated sulfuric acid, made up to 100 ml. with water). The color change was observed after the addition of 3.80 ml. The suspension was stirred for another 5 minutes and then poured into 800 ml. of ice-water. The precipitate was recrystallized from acetone-hexane to give 761 mg., m.p. 147–149°. An analytical sample had m.p. 152–153°, $[\alpha]_{25}^{20} +111.7^\circ$, $\lambda_{\text{max}}^{\text{NH}}^{\text{OH}}$ at 5.85 μ .

Anal. Calcd. for C₂₂H₃₄O₂: C, 79.95; H, 10.37. Found: C, 79.83; H, 10.16.

B. From 6 α -Methylprogesterone (V).—6 α -Methylprogesterone^{6,7} (275 mg.) was dissolved in 40 ml. of anhydrous ether, cooled to –80° and added to a solution of 300 mg. of lithium metal in 200 ml. of liquid ammonia. The mixture was stirred for 5 minutes and then 5 g. of ammonium chloride was added in one portion. The ammonia then was allowed to evaporate at room temperature, and 100-ml. portions each of water and methylene chloride were added to the residue. The two layers were separated, the aqueous phase was further extracted with methylene chloride, and the combined organic extracts were washed with water to neutrality. Drying and concentration gave an oily residue that was chromatographed over 10 g. of alumina. The hexane-benzene (8:2) eluates were combined to give 42.9 mg., m.p. 152–154°, $[\alpha]_{25}^{20} +113.0^\circ$, identical by mixed melting point test and infrared spectrum with the material obtained from the Oxo reaction. Further eluates with hexane-benzene (1:1 and 1:4) gave, after chromic acid oxidation, another 56.3 mg. of the desired dione IV.

6 α -Methyl-allopregnane-3,20-dione 3-Ethylene Ketal (VII).—Dione IV (2.8 g.) was dissolved in 100 ml. of methyl-

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°, $[\alpha]_{26D}^{25} + 87.5^\circ$, $\lambda_{max}^{CHCl_3}$ 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.

6 α -Methyl-20 β -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.

6 α -Methyl-20 β -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°, $[\alpha]_{26D}^{25}$

+24°; λ_{max}^{Nujol} at 2.92, 5.94 μ ; optical rotation: $[\alpha]_{700}^{25} + 17^\circ$, $[\alpha]_{589}^{25} + 21^\circ$, $[\alpha]_{310}^{25} + 656^\circ$, $[\alpha]_{290}^{25} - 390^\circ$, $[\alpha]_{287.5}^{25} - 114.9^\circ$.

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°, $[\alpha]_{26D}^{25} + 53^\circ$; λ_{max}^{Nujol} at 5.80, 5.86, 8.05 μ ; rotatory dispersion in methanol (<0.29): $[\alpha]_{24.89}^{25} + 52.4^\circ$; optical rotation: $[\alpha]_{650}^{25} + 41^\circ$, $[\alpha]_{589}^{25} + 52^\circ$, $[\alpha]_{315}^{25} + 810^\circ$, $[\alpha]_{280}^{25} - 200^\circ$, $[\alpha]_{275}^{25} - 100^\circ$; 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.

6 α -Hydroxymethyl-allopregnane-3 β ,20 β -diol (IIc). A. From 3 β ,20 β -Dihydroxy- Δ^5 -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°, $[\alpha]_{26D}^{25} + 16.1^\circ$ (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 6 α -Hydroxymethyl-allopregnane-3 β ,20 β -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.

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

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

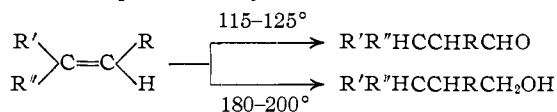
BY P. F. BEAL, M. A. REBENSTORF AND J. E. PIKE

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The "oxo reaction" has been applied to the steroidal 5,6-double bond. Reaction with 3 β -acetoxy-5-pregnen-20-one yielded 3 β -acetoxy-6 α -hydroxymethyl-5 α -pregnan-20-one which was converted to 6 α -methylprogesterone and 6 α -methyl-5 α -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 substi-

tuted 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 3 β -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 3 β -acetoxy-6 α -hydroxymethyl-5 α -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.