

**$\Delta^{3,5}$ -Pregnadiene-3,17 $\alpha$ ,21-triol-11,20-dione 3,17,21-Triacetate (IXb).**—A stirred suspension of cortisone acetate (VIIIb) (10 g.) in acetic anhydride (500 cc.) containing *p*-toluenesulfonic acid monohydrate (7.0 g.) was kept at room temperature for 72 hours (after 1 hour a complete solution was obtained). The reaction mixture was then added with stirring to 3.5 kg. of ice and water. After keeping overnight at 5° filtration afforded a product (10.25 g.), m.p. 123–128°, which after one crystallization from methanol containing a few drops of pyridine yielded  $\Delta^{3,5}$ -pregnadiene-3,17 $\alpha$ ,21-triol-11,20-dione triacetate (IXb) (7.0 g.), m.p. 158–161°. The analytical sample had m.p. 168–169°,  $[\alpha]_D -65^\circ$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  234 m $\mu$ ,  $\epsilon$  20,890.

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{34}\text{O}_8$ : C, 66.65; H, 7.04. Found: C, 66.56; H, 7.08.

**6 $\beta$ -Nitro- $\Delta^4$ -pregnene-17 $\alpha$ ,21-diol-3,11,20-trione 17,21-Diacetate (6 $\beta$ -Nitrocortisone Diacetate) (Xb).**—Fuming nitric acid (75 cc.) was added over 2 hours with good stirring to a suspension of  $\Delta^{3,5}$ -pregnadiene-3,17 $\alpha$ ,21-triol-11,20-dione 3,17,21-triacetate (IXb) (10 g.) in anhydrous ether (300 cc.) at 0°. Most of the steroid had dissolved after this time. The solution was then stirred at 0° for a further 2 hours when ice-water (400 cc.) was added in one portion. Ethyl acetate (250 cc.) was then added and the combined organic phase was washed with cold 5% sodium bicarbonate solution until the alkaline solution just turned brown and then several times with water. The dried solution ( $\text{Na}_2\text{SO}_4$ ) was evaporated *in vacuo* at 40° and the residue crystallized from ethyl acetate-ether to afford 6 $\beta$ -nitrocortisone 17,21-diacetate (Xb) (3.97 g.), m.p. 220–223°,  $[\alpha]_D -56^\circ$ , and a second crop (960 mg.), m.p. 219–223°. The analytical sample from ethyl acetate-hexane had m.p. 226–228°,  $[\alpha]_D -57^\circ$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  226–228 m $\mu$ ,  $\epsilon$  11,480;  $\lambda_{\text{max}}^{\text{KBr}}$  1748 (sh.), 1735, 1710, 1680, 1625 and 1555 cm $^{-1}$ ; rotatory dispersion curve (*c* 0.0615 in dioxane):  $[\alpha]_{700} -30.9^\circ$ ,  $[\alpha]_{650} -9.75^\circ$ ,  $[\alpha]_{589} -37.4^\circ$ ,  $[\alpha]_{425} -102.5^\circ$ ,  $[\alpha]_{400} -73.2^\circ$ ,  $[\alpha]_{302.5} -3340^\circ$ .

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{31}\text{O}_9\text{N}$ : C, 61.34; H, 6.38; N, 2.86. Found: C, 61.70; H, 6.55; N, 2.79.

**6 $\alpha$ -Nitrocortisone (XIb).**—6 $\beta$ -Nitrocortisone diacetate (Xb) (500 mg.) was added to a solution of potassium hydroxide (100 mg.) in methanol (5 cc.) at 0° and stirred for 2 hours under nitrogen. The steroid dissolved readily and after 90 minutes a precipitate began to settle out. After acidification with acetic acid the solution was heated to dissolve the precipitate and then concentrated and finally careful addition of water afforded 6 $\alpha$ -nitrocortisone (XIb) (220 mg.), m.p. 215–220°, raised by crystallization from

methanol to 230–232°,  $[\alpha]_D +149^\circ$  (dioxane);  $\lambda_{\text{max}}^{\text{KBr}}$  3450, 1710, 1670, 1625 and 1550 cm $^{-1}$ ;  $\lambda_{\text{max}}^{\text{EtOH}}$  228–230 m $\mu$ ,  $\epsilon$  14,130; rotatory dispersion curve (*c* 0.0560):  $[\alpha]_{700} +100^\circ$ ,  $[\alpha]_{589} +150^\circ$ ,  $[\alpha]_{415} +2,390^\circ$ ,  $[\alpha]_{300} +1,535^\circ$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{27}\text{O}_7\text{N}$ : C, 62.21; H, 6.71; N, 3.46. Found: C, 61.95; H, 6.63; N, 3.31.

**Pregnane-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triol-20-one 3-Acetate 6-Nitrate (XIII).**—Fuming nitric acid (5.0 cc.) was added with stirring to a solution of 5 $\alpha$ ,6 $\alpha$ -oxidopregnane-3 $\beta$ -ol-20-one 3-acetate (XII) (1.0 g.) in anhydrous ether (30 cc.) at 0°. After keeping at 0–5° for 17 hours the precipitate which had settled out was removed by filtration to afford pregnane-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triol-20-one 3-acetate 6-nitrate (XIII) (650 mg.), m.p. 182–186°, raised by several crystallizations from methanol to 194–196°,  $[\alpha]_D -37^\circ$ ;  $\lambda_{\text{max}}^{\text{KBr}}$  3425, 1730, 1695 and 1640 cm $^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{29}\text{H}_{35}\text{O}_7\text{N}$ : C, 63.14; H, 8.06; N, 3.20. Found: C, 63.02; H, 7.99; N, 3.28.

A solution of XIII (500 mg.) in acetone (50 cc.) was treated with an excess of 8 *N* chromic acid<sup>24</sup> at 15° for 5 minutes.

Addition of water and filtration afforded unchanged starting material in high yield.

**Treatment of Pregnane-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triol-20-one 3-Acetate 6-Nitrate (XIII) with Alkali.**—Potassium hydroxide (100 mg.) was added to a solution of the nitrate ester XIII (250 mg.) in methanol (12 cc.) and heated under reflux in an atmosphere of nitrogen for 45 minutes. After neutralization with acetic acid, addition of ice-water and filtration afforded 5 $\alpha$ ,6 $\alpha$ -oxidopregnane-3 $\beta$ -ol-20-one (XIV) (170 mg.), m.p. 183–185°, raised by crystallizations from ethyl acetate-hexane to 185–187°,  $[\alpha]_D -5^\circ$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{33}\text{O}_3$ : C, 75.86; H, 9.70; O, 14.44. Found: C, 75.54; H, 9.79; O, 14.82.

Acetylation of this product (acetic anhydride-pyridine, 16 hours, 20°) afforded 5 $\alpha$ ,6 $\alpha$ -oxidopregnane-3 $\beta$ -ol-20-one 3-acetate (XII), m.p. 167–168°, undepressed on admixture with an authentic sample,  $[\alpha]_D +14^\circ$ ,  $\lambda_{\text{max}}^{\text{KBr}}$  1737 and 1708 cm $^{-1}$ . The infrared spectra were identical.

*Anal.* Calcd. for  $\text{C}_{29}\text{H}_{35}\text{O}_4$ : C, 73.76; H, 9.15; O, 17.09. Found: C, 74.05; H, 8.87; O, 17.40.

(24) See for example A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

## Steroids. CXI.<sup>1</sup> Studies in Nitro Steroids. Part 3.<sup>1</sup> The Synthesis of 21-Nitroprogesterone<sup>2</sup>

By A. BOWERS AND H. J. RINGOLD

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20-Dihydrodesoxicorticosterone (IV) was prepared from desoxycorticosterone acetate (I) by sodium borohydride reduction of its derived 3-cycloethylene-ketal II. Cleavage of IV with periodic acid gave 17 $\beta$ -formyl- $\Delta^4$ -androstene-3-one (V). Condensation of V with nitromethane and a final oxidative step afforded 21-nitroprogesterone (VII).

In recent years an increasing amount of empirical evidence has accumulated which indicates that introduction of certain atoms or groups or further unsaturation in key positions throughout the steroid nucleus leads to an enhancement or a desirable modification of the biological activity. Notable among these modifications has been the introduction of a fluorine atom at C-9( $\alpha$ ),<sup>3</sup> C-12( $\alpha$ ),<sup>4</sup> C-21<sup>5</sup> and C-6( $\alpha$ ).<sup>6</sup>

(1) Steroids CX and Part 2, A. Bowers, L. C. Ibañez and H. J. Ringold, *This Journal*, **81**, 3707 (1959).

(2) Presented by A. B. at the Steroids and Natural Products Section of the Gordon Research Conference, August, 1958.

(3) (a) J. Fried and E. F. Sabo, *This Journal*, **76**, 1455 (1954);

In every case these fluorinated steroid hormones exhibited increased biological activity when com-

(b) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *ibid.*, **77**, 1068 (1955).

(4) (a) J. E. Herz, J. Fried and E. F. Sabo, *ibid.*, **78**, 2017 (1956);

(b) D. Taub, R. D. Hoffsommer and N. L. Wendler, *ibid.*, **78**, 2912 (1956).

(5) (a) P. Tannhauser, R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 2658 (1956); (b) J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *ibid.*, **78**, 4812 (1956).

(6) (a) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); (b) A. Bowers and H. J. Ringold, *This Journal*, **80**, 4423 (1958);

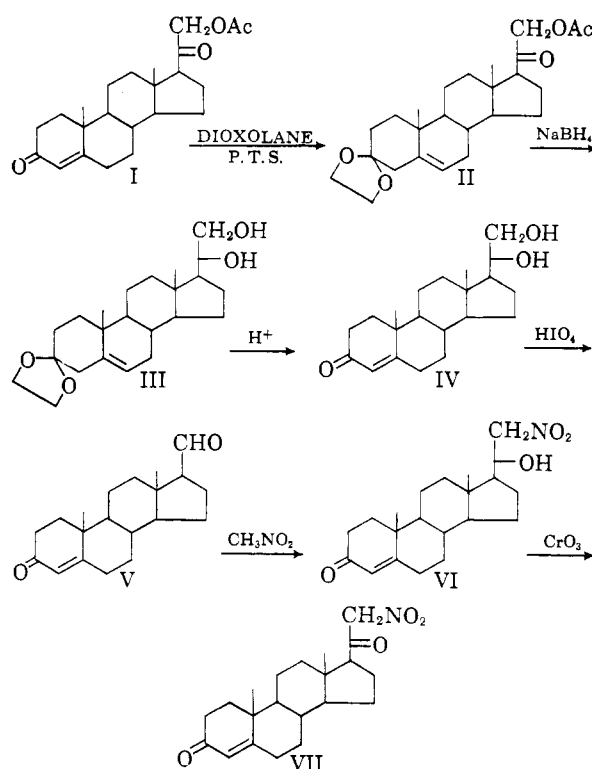
(c) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

pared with the *nonfluorinated parent compound*. The reason for the enhancement effect of the fluorine atom is not clear, but it is undoubtedly partially connected with its high electronegativity<sup>7</sup> and small size. It was thus of considerable interest to establish whether this increase in biological activity was an inherent feature of the fluorine atom or whether substitution of other powerful electronegative groups would have a similar effect. In this connection we have recently synthesized a series of 6 $\alpha$ -nitro steroid hormones<sup>1,8</sup> and as a continuation of these studies we report the synthesis of 21-nitroprogesterone.<sup>9</sup>

Our initial attempts were directed toward a direct displacement at C-21 of desoxycorticosterone tosylate or 21-iodoprogesterone with sodium nitrite in dimethylformamide. Kornblum and his colleagues<sup>10</sup> have utilized this reaction successfully with many saturated aliphatic primary and secondary halides, but we were unable to isolate any 21-nitroprogesterone from our experiments.

Our second approach was indirect and involved the partial degradation of the C-17 side chain to the 17-formyl compound V which was then condensed with nitromethane. A final oxidative step afforded 21-nitroprogesterone (VII).

A suitable starting material was desoxycorticosterone acetate (I) which by the dioxalane method<sup>11</sup> was smoothly converted into the 3-cycloethylene-ketal II in 61% yield.<sup>12</sup> Reduction at C-20 of this monoketal (II) with sodium borohydride was attended by concomitant hydrolysis of the C-21 acetate group to afford  $\Delta^5$ -pregnene-20 $\beta$ ,21-diol-3-monocycloethylene-ketal<sup>13</sup> (III). Cleavage of the ketal with dilute sulfuric acid in methanol<sup>14</sup> afforded the corresponding  $\Delta^4$ -3-ketone<sup>15</sup> IV. Periodic acid cleavage of the C-20,21-glycol system of IV gave the aldehyde V in good yield. The condensation of aldehydes with nitromethane is a reaction well known in carbohydrate chemistry<sup>16</sup> and using essentially the conditions of Sowden and Fischer<sup>16</sup> the 17 $\beta$ -formyl compound V was condensed with nitromethane to afford 21-nitro-20-dihydroprogesterone (VI). We were not able, however, to effect



this condensation in better than 15% yield. In the infrared VI displayed a strong band at 1550  $\text{cm}^{-1}$  characteristic of a nitro group attached to a saturated carbon atom.<sup>17</sup> The C-20 hydroxyl group of VI proved very resistant to oxidation, presumably due to the general steric hindrance to approach of the reagent and also to hydrogen bonding of the C-20 hydroxyl group with the C-21 nitro group. For example, VI was recovered unchanged after treatment with an excess of 8 *N* chromic acid in acetone solution<sup>18</sup> for 3–5 minutes at 20°. A successful oxidation was finally carried out by extending the reaction time to 1 hour when 21-nitroprogesterone (VII) was isolated in 69% yield. In the infrared VII displayed bands at 1720 (20-ketone), 1650 and 1612  $\text{cm}^{-1}$  ( $\Delta^4$ -3-ketone) and 1550  $\text{cm}^{-1}$  (C-21 nitro group).

In contrast to 21-fluoroprogesterone,<sup>5a,9</sup> 21-nitroprogesterone was progestationally inactive in the guinea pig copulatory assay (subcutaneous route) at dose levels where progesterone gave a 100% response.<sup>19</sup>

### Experimental<sup>20</sup>

**$\Delta^5$ -Pregnene-21-ol-20-one-3-cycloethylene-ketal 21-Acetate (II).**—A solution of desoxycorticosterone acetate (I) (15 g.) in dioxalane<sup>11</sup> (200 cc.) (cycloethylene-ketal of methyl ethyl ketone) containing *p*-toluenesulfonic acid monohy-

(17) For an excellent account of the infrared spectra of nitro compounds see J. F. Brown, *ibid.*, **77**, 6341 (1955).

(18) See for example A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemm, *J. Chem. Soc.*, 2548 (1953).

(19) Biological assays by Endocrine Laboratories, Madison, Wisc.

(20) Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. We are grateful to Dr. L. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin-Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(7) It was pointed out recently<sup>4a</sup> that the enhancement of adrenocortical activity by introduction of a 9 $\alpha$ -substituent is paralleled by the electronegativity of the substituent; being greatest with the fluorine atom.

(8) A. Bowers, M. B. Sanchez and H. J. Ringold, *THIS JOURNAL*, **81**, 3702 (1959).

(9) 21-Fluoroprogesterone has been reported to possess between 2–4 times the progestational activity of progesterone; cf. ref. 5a.

(10) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham, *THIS JOURNAL*, **78**, 1497 (1956).

(11) H. J. Dauben, B. Löken and H. J. Ringold, *ibid.*, **76**, 1359 (1954).

(12) This compound was first prepared in lower yield by the benzene-ethylene glycol-*p*-toluenesulfonic acid method; cf. R. Antonucci, S. Bernstein, R. Lenhard, K. H. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(13) The 20 $\beta$ -configuration was assigned on the basis of the known steric course of the borohydride reduction of C-20 ketones; cf. D. K. Fukushima and E. D. Meyer, *ibid.*, **23**, 174 (1958), and references cited therein.

(14) W. S. Allen, S. Bernstein and R. Littell, *THIS JOURNAL*, **76**, 6116 (1954).

(15) This compound has been prepared previously by a four-step sequence from  $\Delta^5$ -pregnene-3 $\beta$ ,21-diol-3-one 21-acetate; cf. M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 171 (1938).

(16) See, for example, J. C. Sowden and H. O. L. Fischer, *THIS JOURNAL*, **69**, 1963 (1947).

drate (300 mg.) was distilled at such a rate that 75 cc. of distillate was collected in 4 hours. A further 75 cc. of dioxane was then added to the reaction mixture and the distillation continued at the same rate for a further 4 hours. After cooling in ice the product was removed by filtration. One crystallization from ethyl acetate containing a few drops of pyridine afforded the monoketal II (10.3 g.), m.p. 195–201°,  $\lambda_{\text{max}}^{\text{EtOH}}$  240–242 m $\mu$ ,  $\epsilon$  724. This material was used without further purification.

The analytical sample had m.p. 207–209°,  $[\alpha]_D +49^\circ$ , and did not exhibit selective absorption in the ultraviolet; lit.<sup>12</sup> m.p. 206–208°,  $[\alpha]_D +42.5^\circ$ .

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{36}\text{O}_5$ : C, 72.08; H, 8.71. Found: C, 71.98; H, 8.55.

**$\Delta^5$ -Pregnene-20 $\beta$ ,21-diol-3-cycloethylene-ketal (III).**—Sodium borohydride (5 g.) in water (20 cc.) was added to a solution of the 3-cycloethylene-ketal of desoxycorticosterone acetate (II) (7.2 g.) in methanol (300 cc.). After keeping at room temperature for 20 hours the solution was concentrated *in vacuo* to 50 cc. and then diluted with ice-water. Filtration of the precipitate afforded  $\Delta^5$ -pregnene-20 $\beta$ ,21-diol-3-cycloethylene-ketal (III) (6.7 g.), m.p. 208–211°, raised by several crystallizations from methanol to 218–220°,  $[\alpha]_D \pm 0^\circ$ .

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{36}\text{O}_4 \cdot \frac{1}{2}\text{CH}_3\text{OH}$ : C, 71.90; H, 9.54. Found: C, 72.35; H, 9.75.

**$\Delta^4$ -Pregnene-20 $\beta$ ,21-diol-3-one (IV).**—Dilute sulfuric acid (8% v./v.) (60 cc.) was added to a solution of  $\Delta^5$ -pregnene-20 $\beta$ ,21-diol-3-cycloethylene-ketal (III) (12.9 g.) in methanol (200 cc.) and the solution was heated under reflux for 45 minutes. After neutralization with sodium carbonate solution (5%) the solution was concentrated to approximately 100 cc. and then diluted with ice-water. Filtration and crystallization of the product from acetone afforded  $\Delta^4$ -pregnene-20 $\beta$ ,21-diol-3-one (IV) (8.6 g.), m.p. 163–165°, raised by several crystallizations from acetone to 169–170°,  $[\alpha]_D +111^\circ$ ; lit.<sup>15</sup> reports m.p. 166–167°,  $[\alpha]_D +93^\circ$  (ethanol).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{32}\text{O}_3$ : C, 75.86; H, 9.70. Found: C, 75.82; H, 9.76.

**17 $\beta$ -Formyl- $\Delta^4$ -androstene-3-one (V).**—Periodic acid (2.1 g.) was added with stirring to a solution of  $\Delta^4$ -pregnene-20 $\beta$ ,21-diol-3-one (IV) (3.3 g.) in anhydrous dioxane (200 cc.) under nitrogen. After 3 hours at room temperature the solution was added to ice-water (2 l.). Filtration afforded 17 $\beta$ -formyl- $\Delta^4$ -androstene-3-one (V) (2.42 g.), m.p. 143–145°. This product was used for the subsequent step with-

out further purification. The analytical sample from ether hexane had m.p. 149–151°,  $[\alpha]_D +178^\circ$ ; lit.<sup>21</sup> m.p. 151–153°,  $[\alpha]_D +159^\circ$  (dioxane).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{28}\text{O}_2$ : C, 80.49; H, 8.78. Found: C, 80.25; H, 8.91.

**21-Nitro- $\Delta^4$ -pregnene-20-ol-3-one (VI).**—Sodium methoxide (1.8 g.) was added to a solution of 17 $\beta$ -formyl- $\Delta^4$ -androstene-3-one (V) (1.8 g.) in absolute ethanol (50 cc.) containing nitromethane (1.8 cc.) in an atmosphere of nitrogen. After stirring for 16 hours at room temperature the reaction mixture was diluted with ether (300 cc.). Filtration afforded a semi-solid product which was suspended with stirring in 2 *N* hydrochloric acid (100 cc.) for 30 minutes.

The oily suspension was then extracted with ether and the combined ether extracts were washed with water and dried ( $\text{Na}_2\text{SO}_4$ ). The product obtained after removal of the ether was adsorbed from benzene-hexane (50:50, 200 cc.) onto Florisil (125 g.). Elution with benzene-ether (80:20, 1200 cc.) afforded after one crystallization from benzene 21-nitro- $\Delta^4$ -pregnene-20-ol-3-one (VI) (280 mg.), m.p. 183–190°, raised by further crystallizations from benzene to 195–202° (200 mg.). The analytical sample from benzene had m.p. 197–199°,  $[\alpha]_D +112^\circ$ ;  $\lambda_{\text{max}}^{\text{EtOH}}$  1660, 1620 and 1550  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{31}\text{O}_4\text{N}$ : C, 69.77; H, 8.65; N, 3.88. Found: C, 69.42; H, 8.61; N, 3.49.

**21-Nitroprogesterone (VII).**—Chromic acid<sup>18</sup> (0.2 cc. of 8 *N*; theory 0.13 cc.) was added to a solution of 21-nitro- $\Delta^4$ -pregnene-20-ol-3-one (VI) (185 mg.) in acetone (15 cc.) at 20°. After 40 minutes at room temperature an additional 0.1 cc. of 8 *N* chromic acid was added and the solution kept for a further 10 minutes. Water was then added and filtration afforded 21-nitroprogesterone (VII) (161 mg.), m.p. 165–175°, raised by one crystallization from methanol to 185–189° (129 mg.). The analytical sample had m.p. 197–199° (from aqueous acetone),  $[\alpha]_D +270^\circ$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  240 and 312–316 m $\mu$ ,  $\epsilon$  19,000 and 813, changed upon addition of 1 drop of 5% sodium hydroxide solution to  $\lambda_{\text{max}}$  240 and 332–334 m $\mu$ ,  $\epsilon$  20,400 and 18,600;  $\lambda_{\text{max}}^{\text{EtOH}}$  1720, 1650, 1612 and 1550  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{29}\text{O}_4\text{N}$ : C, 70.17; H, 8.13; N, 3.90. Found: C, 70.44; H, 7.96; N, 3.77.

(21) K. Miescher, F. Hunziker and A. Wettstein, *Helv. Chim. Acta*, **23**, 400 (1940), report the preparation of V essentially by the same method which we employed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

## Steroids. CXVIII.<sup>1</sup> 6-Methyl Derivatives of 17 $\alpha$ -Hydroxyprogesterone and of Reichstein's Substance "S"

By H. J. RINGOLD, J. PEREZ RUELAS, E. BATRES AND CARL DJERASSI

RECEIVED DECEMBER 20, 1958

$\Delta^5$ -Pregnene-3 $\beta$ ,17 $\alpha$ -diol-20-one (I) was converted into 6 $\alpha$ -methyl-17 $\alpha$ -acetoxyprogesterone (VIIb), the key reaction involving methylmagnesium bromide cleavage of the 5 $\alpha$ ,6 $\alpha$ -oxido-20-ketal II. Synthesis of the 1-dehydro, 6-dehydro and 1,6-bisdehydro derivatives of VIIb as well as the preparation of 6 $\alpha$ -methyl "S" is described. Some of the new compounds exhibit exceptional oral progestational activity.

The addition of a 6 $\alpha$ -methyl substituent to the steroid nucleus has been reported<sup>2–6</sup> in certain cases

(1) Paper CXVII. J. S. Mills, A. Bowers, C. Casas Campillo, C. Djerassi and H. J. Ringold, *THIS JOURNAL*, **81**, 1264 (1959).

(2) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanz, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

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

(4) A. David, F. Hartley, D. R. Millson and V. Petrow, *J. Pharm. and Pharmacol.*, **9**, 929 (1957).

(5) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, *THIS JOURNAL*, **80**, 2904 (1958).

(6) J. A. Campbell, J. C. Babcock and J. A. Hogg, *ibid.*, **80**, 4717 (1958).

to favorably influence biological activity. Spero, *et al.*,<sup>2</sup> reported the effect of 6-methyl substitution in the cortical hormones series while a communication<sup>3</sup> from these laboratories noted the effect of 6-alkyl substitution in the testosterone and progesterone series. Petrow and co-workers<sup>4</sup> and Campbell, Babcock and Hogg<sup>5</sup> found that the oral progestational activity of 17 $\alpha$ -ethynyltestosterone derivatives was increased by 6 $\alpha$ -methyl substitution. Recently, a communication of the Upjohn group<sup>6</sup> appeared describing the synthesis, from 17 $\alpha$ -hydroxyprogesterone, of 6 $\alpha$ -methyl-17 $\alpha$ -acetoxy-