drate (300 mg.) was distilled at such a rate that 75 cc. of distillate was collected in 4 hours. A further 75 cc. of dioxalane 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°, $\lambda_{max}^{EtOH}$ 240–242 mμ, ε 724. This material was used without further purification.

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

*Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.98; H, 8.55.

**Δ⁵-Pregnene-20β,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 Δ⁵-pregnene-20β,21-diol-3-cycloethylene-ketal (III) (6.7 g.), m.p. 208–211°, raised by several crystallizations from methanol to 218–220°, $[\alpha]D \pm 0°$.

*Anal.* Calcd. for $C_{23}H_{36}O_4 \cdot {}^1/_2CH_3OH$: C, 71.90; H, 9.54. Found: C, 72.35; H, 9.75.

**Δ⁴-Pregnene-20β,21-diol-3-one (IV).**—Dilute sulfuric acid (8% v./v.) (60 cc.) was added to a solution of Δ⁵-pregnene-20β,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 Δ⁴-pregnene-20β,21-diol-3-one (IV) (8.6 g.), m.p. 163–165°, raised by several crystallizations from acetone to 169–170°, $[\alpha]D$ +111°; lit.[15] reports m.p. 166–167°, $[\alpha]D$ +93° (ethanol).

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.82; H, 9.76.

**17β-Formyl-Δ⁴-androstene-3-one (V).**—Periodic acid (2.1 g.) was added with stirring to a solution of Δ⁴-pregnene-20β,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 17β-formyl-Δ⁴-androstene-3-one (V) (2.42 g.), m.p. 143–145°. This product was used for the subsequent step without further purification. The analytical sample from ether hexane had m.p. 149–151°, $[\alpha]D$ +178°; lit.[21] m.p. 151–153°, $[\alpha]D$ +159° (dioxane).

*Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 80.49; H, 8.78. Found: C, 80.25; H, 8.91.

**21-Nitro-Δ⁴-pregnene-20-ol-3-one (VI).**—Sodium methoxide (1.8 g.) was added to a solution of 17β-formyl-Δ⁴-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 ($Na_2SO_4$). 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-Δ⁴-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°; $\lambda_{max}^{KBr}$ 1660, 1620 and 1550 cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{31}O_4N$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.42; H, 8.61; N, 3.49.

**21-Nitroprogesterone (VII).**—Chromic acid[18] (0.2 cc. of 8 *N*; theory 0.13 cc.) was added to a solution of 21-nitro-Δ⁴-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°, $\lambda_{max}^{EtOH}$ 240 and 312–316 mμ, ε 19,000 and 813, changed upon addition of 1 drop of 5% sodium hydroxide solution to $\lambda_{max}$ 240 and 332–334 mμ, ε 20,400 and 18,600; $\lambda_{max}^{KBr}$ 1720, 1650, 1612 and 1550 cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{29}O_4N$: 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.[1] 6-Methyl Derivatives of 17α-Hydroxyprogesterone and of Reichstein's Substance "S"

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

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Δ⁵-Pregnene-3β,17α-diol-20-one (I) was converted into 6α-methyl-17α-acetoxyprogesterone (VIIb), the key reaction involving methylmagnesium bromide cleavage of the 5α,6α-oxido-20-ketal II. Synthesis of the 1-dehydro, 6-dehydro and 1,6-bisdehydro derivatives of VIIb as well as the preparation of 6α-methyl "S" is described. Some of the new compounds exhibit exceptional oral progestational activity.

The addition of a 6α-methyl substituent to the steroid nucleus has been reported[2–6] in certain cases to favorably influence biological activity. Spero, *et al.*,[2] reported the effect of 6-methyl substitution in the cortical hormones series while a communication[3] from these laboratories noted the effect of 6-alkyl substitution in the testosterone and progesterone series. Petrow and co-workers[4] and Campbell, Babcock and Hogg[6] found that the oral progestational activity of 17α-ethynyltestosterone derivatives was increased by 6α-methyl substitution. Recently, a communication of the Upjohn group[5] appeared describing the synthesis, from 17α-hydroxyprogesterone, of 6α-methyl-17α-acetoxy-

(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. Hanze, 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).

progesterone (VIIb), a potent progestational agent. Previous to that communication we had synthesized VIIb by a different route and this paper describes our synthesis as well as the conversion of 6α-methyl-17α-hydroxyprogesterone (VIIa) and its 17-acetate into new 6-methyl derivatives, several of which possess tremendously potentiated oral progestational activity.

Our synthesis proceeded from $\Delta^5$-pregnene-3β,-17α-diol-20-one acetate[7a,b] (I). Treatment with ethylene glycol, benzene and *p*-toluenesulfonic acid in the conventional manner afforded the C-20 cycloethylene ketal II which was converted to the 5α,6α-oxide III by treatment with perbenzoic acid in chloroform solution. The cleavage of a 5α,6α-oxide with methylmagnesium halide to yield the 6β-methyl-5α-hydroxy compound was first demonstrated by Madaeva and co-workers,[8] This reaction has since served as the key step in the preparation of a number of 6-methyl hormone analogs.[2-6,9-11] Thus, three-hour reaction of III with methylmagnesium bromide in boiling benzene followed by ammonium chloride decomposition of Grignard reagent and chromatography of the crude product, yielded the 6β-methyl-5α-hydroxy ketal (IV), the 3-acetate group having been removed by the reagent. Methanol–sulfuric acid hydrolysis[12] of the C-20 ketal gave 6β-methyl-pregnane-3β,5α,17α-triol-20-one (V) which was oxidized with chromium trioxide in pyridine[13] to the 3-keto-5α-hydroxy compound VI. Treatment of the latter with concentrated hydrochloric acid in acetic acid for 18 hours at room temperature resulted in dehydration at C-5 and concomitant inversion of the 6β-methyl compound to the equatorial 6α-methyl-17α-hydroxyprogesterone (VIIa). The stability of VIIa to further acid or base treatment as well as rotatory dispersion studies conclusively established the 6α-methyl configuration. Acetylation at C-17 with acetic anhydride–acetic acid–*p*-toluenesulfonic acid according to the general conditions of Turner[14] yielded 6α-methyl-17α-acetoxyprogesterone (VIIb) accompanied by some of the 3-enol acetate-17-acetate XII. Reduction of the 17-acetylation time to one hour minimized enol acetate formation. Constants for VI, VIIa and VIIb were in good general agreement with those reported in the preliminary communication of the Upjohn group.[5]

Oxidation of 6α-methyl-17α-acetoxyprogesterone with selenium dioxide[15a,b,c,d] in *t*-butyl alcohol[15b,c] gave the $\Delta^1$-dehydro compound VIII, $\lambda_{max}$ 244 mμ, while chloranil oxidation of the $\Delta^4$-3-keto

(7) (a) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941); (b) P. L. Julian, E. W. Meyer and I. Ryden, THIS JOURNAL, **72**, 367 (1950).

(8) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 436 (1939); *C. A.*, **33**, 9309 (1939); O. S. Madaeva, M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 213 (1940); *C. A.*, **34**, 7292 (1940).

(9) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958).

(10) See G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957), and earlier references therein.

(11) The Grignard cleavage of a 6α,7α-epoxide and preparation of 6β-methyl estrogens is described by E. Velarde, J. Iriarte, H. J. Ringold, C. Djerassi, Steroids CXIII, *J. Org. Chem.*, **24**, 311 (1959).

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

(13) R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns and L. H. Sarett, *ibid.*, **75**, 1707 (1953).

(14) R. B. Turner, *ibid.*, **75**, 3489 (1953).

(15) (a) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **21**, 239 (1956); (b) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); (c) S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. Van Dorp, *Rec. trav. chim.*, **75**, 475 (1956); (d) K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957).

compound in ethyl acetate–acetic acid[16] yielded the $\Delta^{4,6}$-dienone IX, $\lambda_{max}$ 289 m$\mu$. Dehydrogenation of IX with selenium dioxide then yielded the $\Delta^{1,4,6}$-trienone X; $\lambda_{max}$ 228, 253 and 304 m$\mu$.

Of further interest was the conversion of 6$\alpha$-methyl - 17$\alpha$ - hydroxyprogesterone to 6$\alpha$ - methyl "S" since microbiological C-11 hydroxylation of the latter would lead to the 6-methyl cortical hormones, The 21-hydroxylation of VII, yielding 6$\alpha$-methyl "S" 21-acetate (XIa), was readily accomplished by our chemical procedure[17] involving C-21 iodination with iodine–calcium oxide in methanol–tetrahydrofuran followed by potassium acetate–acetone acetoxylation of the crude 21-iodo compound, Acid-catalyzed acetylation of XIa yielded the 17,21-diacetate (XIb).

In an earlier paper,[18] it was shown that an axial 6$\beta$-methyl group greatly affects the rotatory dispersion curve of a $\Delta^4$-3-ketone while the equatorial 6$\alpha$-epimer hardly plays any role. In agreement with the above chemical conclusions is the rotatory dispersion curve of 17$\alpha$-hydroxy-6$\alpha$-methylprogesterone (VIIa) (Fig. 1) which resembles closely

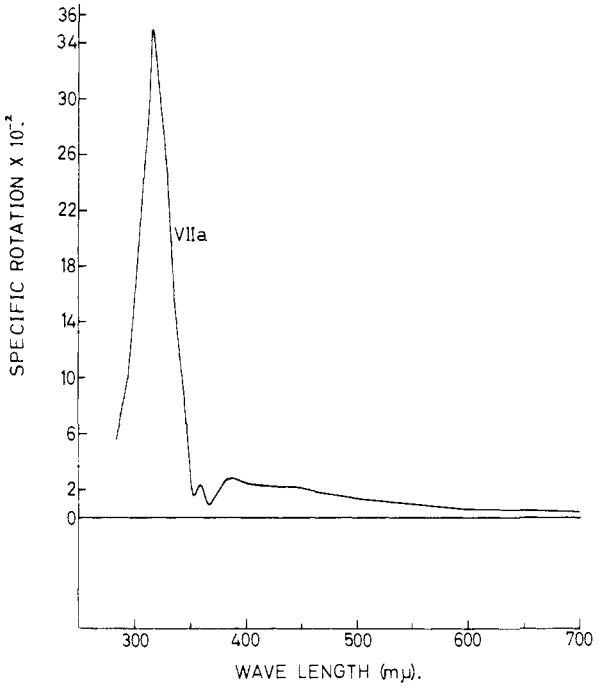


Fig. 1.

that of progesterone,[19] thus supporting the presence of an equatorial substituent at C-6. The amplitude[20] of the curve is reduced upon acetylation at C-17 (VIIb) and this—coupled with the hypsochromic shift of the main dispersion peak[20]—is again consistent with our earlier observation[21] on the effect of acetylation of a 17$\alpha$-hydroxy group in a 17$\alpha$-hydroxy-20-keto steroid.

**Biological Activity.**[22]—Evaluation of VIIb in the Clauberg assay, oral route, (Table I) with 19-nor-17$\alpha$-ethynyltestosterone[23] (Norlutin) as the standard confirmed that, in the experimental animal, 6$\alpha$-methyl-17$\alpha$-acetoxyprogesterone (VIIb) is a compound of high progestational potency[4] exhibiting two to three times the activity of the standard. Of theoretical importance was the determination of the effect of additional unsaturation in VIIb. We have found (unpublished data) that the progestational activity of 1-dehydroprogesterone and 1-dehydro-17$\alpha$-ethynyltestosterone is slightly less than that of the parent compound in each case while Wettstein[24] reported that 6-dehydroprogesterone is a weaker agent than progesterone. Thus, it was surprising to find that 1 - dehydro - 6$\alpha$ - methyl - 17$\alpha$ - acetoxyprogesterone (VIII), in the Clauberg assay, oral route, was 2.5 to 4× more active than the $\Delta^4$-3-ketone VIIb (see Table I), while the 6-dehydro compound IX was also found to be considerably more active than VIIb.

Also of interest was the finding that 6$\alpha$-methyl "S" diacetate (XIb) is a potent progestational agent exhibiting somewhat greater activity than 19-nor-17$\alpha$-ethynyltestosterone. The parent compound "S" 17,21-diacetate also exhibited low but definite activity in the Clauberg assay.

TABLE I

ORAL PROGESTATIONAL ACTIVITY—CLAUBERG ASSAY

| Compound | Relative activity |
|---|---|
| 17$\alpha$-Ethynyl-19-nortestosterone | 1 |
| 6$\alpha$-Methyl-17$\alpha$-acetoxyprogesterone | 2–3 |
| 1-Dehydro-6$\alpha$-methyl-17$\alpha$-acetoxyprogesterone | 8 |
| 6-Dehydro-6-methyl-17$\alpha$-acetoxyprogesterone | 12[a] |
| 1,6-Bisdehydro-6-methyl-17$\alpha$-acetoxyprogesterone | 10 |
| 6$\alpha$-Methyl "S" 17,21-diacetate | 1.5 |

[a] The slope of the dose–response curve of this compound differed greatly from the others and the relative activity varied from 4 to 18. Our best estimate of activity is 12× norethynyltestosterone.

## Experimental[25]

**20-Cycloethylenedioxy-$\Delta^5$-pregnene-3$\beta$,17$\alpha$-diol 3-Acetate** (II).—A mixture of 17$\alpha$-hydroxypregnenolone 3-acetate (I)[7] (49 g.), ethylene glycol (45 ml.), benzene (1.3 l.) and *p*-toluenesulfonic acid.1$H_2O$ (3 g.) was boiled for 16 hours with continuous separation of water. The cooled solution, after potassium carbonate wash, was evaporated to dryness and then subjected to chromatographic purification on 1.8 kg. of neutral alumina. The hexane–benzene (1:4), benzene and benzene–ether (4:1) fractions yielded 33.2 g. (61%) of II, m.p. 187–189°. Recrystallization from acetone yielded the analytical specimen, m.p. 194–195°, $[\alpha]D$ −66°.

*Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.65; H, 8.97.

**5$\alpha$6$\alpha$-Oxido-20-cycloethylenedioxyallopregnane-3$\beta$,17$\alpha$-diol 3-Acetate** (III).—The ketal II (35 g.) was added to a cold solution of perbenzoic acid (1.3 equiv.) in 300 ml. of

(16) This modification of the chloranil oxidation of A. J. Agnello and G. D. Laubach, THIS JOURNAL, **79**, 1257 (1957), was developed by Dr. A. Bowers of these laboratories.

(17) H. J. Ringold and G. Stork, *ibid.*, **80**, 250 (1958).

(18) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958).

(19) E. W. Foltz, A. E. Lippman and C. Djerassi, *ibid.*, **77**, 4359 (1955).

(20) For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(21) C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(22) Bioassays by The Endocrine Laboratories, Madison, Wisc.

(23) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954).

(24) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

(25) Melting points are uncorrected. Rotations were determined in chloroform unless noted otherwise and ultraviolet absorption spectra in 95% ethanol solution. Infrared spectra were determined with a Perkin–Elmer model 21 spectrophotometer. We are grateful to Dr. L. Throop for determination of rotations and spectral data.

chloroform, the reaction mixture briefly stirred and then allowed to stand at room temperature for 48 hours before pouring into a solution of sodium carbonate (30 g.) in water (2 l.). The organic phase was separated, washed with water to neutrality, dried and evaporated. The residue was chromatographed on 1.2 kg. of neutral alumina, the chloroform eluate yielding, after crystallization from acetone, 14 g. (39%) of α-epoxide (III), m.p. 218–220°. Further crystallization from acetone raised the melting point to 221–223°, $[\alpha]_D$ −67°.

*Anal.* Calcd. for $C_{25}H_{38}O_6 \cdot C_3H_6O$: C, 68.26; H, 9.00. Found: C, 68.27; H, 8.69.

**6β-Methyl-20-cycloethylenedioxyallopregnane-3β,5α,17α-triol (IV).**—A solution of 5.5 g. of III in 250 ml. of thiophene-free benzene was treated with 27.5 ml. of 4 *N* methylmagnesium bromide in ether and the mixture boiled, with the exclusion of moisture, for 3 hours. The cooled mixture was cautiously treated with excess aqueous ammonium chloride solution and the crude product isolated by ethyl acetate extraction. The residue in benzene was adsorbed on 200 g. of alkaline alumina whereupon elution with methylene chloride–acetone and acetone yielded 2.17 g. of the 6β-methyl ketal IV (a solvate), m.p. 171°, $[\alpha]_D$ −31°.

*Anal.* Calcd. for $C_{24}H_{40}O_5 \cdot C_3H_6O$: C, 69.49; H, 9.94. Found: C, 69.49; H, 9.60.

**6β-Methylallopregnane-3β,5α,17α-triol-20-one (V).**—A solution of 2.33 g. of ketal IV in 70 ml. of methanol and 7 ml. of 8% (v./v.) sulfuric acid,[10] after boiling for 40 minutes, was concentrated to *ca.* 20 ml. *in vacuo* and poured into water yielding 1.57 g. (75%) of V, m.p. 242–246°. Three recrystallizations from acetone gave material of m.p. 251–252°, $[\alpha]_D$ −45°.

*Anal.* Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.59; H, 9.98.

**6β-Methylallopregnane-5α,17α-diol-3,20-dione (VI).**—The triol V (1.37 g.) in pyridine (14 ml.) was added with stirring to the complex[13] prepared from 1.37 g. of chromium trioxide in 14 ml. of pyridine. After 16 hours standing at 25° the mixture was diluted with ethyl acetate, filtered through filter-aid, the residue extracted with hot ethyl acetate and the combined solutions washed successively with 10% hydrochloric acid, water, 10% sodium carbonate and water. Concentration and cooling of the dried ethyl acetate solution deposited VI which was filtered and washed with cold ether; yield 0.635 g. (47%), m.p. 266–268°. Recrystallization from acetone lowered the melting point to 263–264°, $[\alpha]_D$ +12° (dioxane); $\lambda_{max}^{KBr}$ 1685, 1705 cm.$^{-1}$ (reported[5] m.p. 274–279°, $[\alpha]_D$ −6° (chloroform)).

*Anal.* Calcd. for $C_{22}H_{34}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.08; H, 9.52. Found: C, 72.31; H, 9.23.

**6α-Methyl-17α-hydroxyprogesterone (VIIa).**—A stirred suspension of VI (200 mg.) in 25 ml. of glacial acetic acid was allowed to react with 1 ml. of concentrated hydrochloric acid (solution was complete after 5 hours). After 18 hours, salt water was added precipitating 180 mg. of VII, m.p. 210–212°. Crystallization from acetone–ether raised the m.p. to 218–221.5°, $[\alpha]_D$ +75°; $\lambda_{max}$ 242 mμ, ε 15,200; $\lambda_{max}^{KBr}$ 1600, 1660, 1695 cm.$^{-1}$ (reported[5] m.p. 220–223.5°, $[\alpha]_D$ +75°, $\lambda_{max}$ 241 mμ, ε 16,150); R.D. (*c* 0.077 and 0.015 in dioxane): $[\alpha]_{700}$ +42°, $[\alpha]_{589}$ +79°, $[\alpha]_{390-367.5}$ +284°, $[\alpha]_{367.5}$ + 84°, $[\alpha]_{357.5}$ +224°, $[\alpha]_{352.5}$ +175°, $[\alpha]_{315}$ +3513°, $[\alpha]_{255}$ +553°, $[\alpha]_{275}$ +753°.

*Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.85; H, 9.48.

**6α-Methyl-17α-acetoxyprogesterone (VIIb).**—A solution of VIIa (500 mg.), *p*-toluenesulfonic acid·$H_2O$ (500 mg.), acetic acid (25 ml.) and acetic anhydride (5 ml.) after one hour reaction at room temperature was poured into water and stirred until the excess anhydride had hydrolyzed. Isolation of the product by ethyl acetate extraction and crystallization of the residue from acetone–ether gave 360 mg. of 17-acetate VIIb, m.p. 195–197°, raised by further crystallization from the same solvent pair to 207–209°, $[\alpha]_D$ +66°, $\lambda_{max}$ 241 mμ, ε 15,500; $\lambda_{max}^{KBr}$ 1250, 1600, 1670, 1730 cm.$^{-1}$; R.D. (*c* 0.088 and 0.017 in dioxane): $[\alpha]_{700}$ +14°, $[\alpha]_{589}$ +39°, $[\alpha]_{400-397.5}$ +135°, $[\alpha]_{367.5}$ −83°, $[\alpha]_{360}$ −21°, $[\alpha]_{352.5}$ −80°, $[\alpha]_{310}$ +2947°, $[\alpha]_{280}$ +311° (reported[5] m.p. 205–209°, $[\alpha]_D$ +56°, $\lambda_{max}$ 240 mμ, ε 15,950). Chromatography of the mother liquors furnished a few mg. of the enol acetate XIII.

*Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.55, Found; C, 74.17; H, 9,20; O, 16,48.

**6-Methyl-Δ$^{3,5}$-pregnadiene-3,17α-diol-20-one Diacetate (XII).**—When VIIa was treated as above but with extension of the acetylation time to 3 hours, crystallization of the residue from acetone–methanol gave the enol acetate 17-acetate XIII, m.p. 160–162°, $[\alpha]_D$ −146°; $\lambda_{max}$ 244 mμ, ε 19,950; $\lambda_{max}^{KBr}$ 1205, 1250, 1630, 1660, 1740 cm.$^{-1}$. Chromatographic purification of the mother liquors gave a low yield of VIIb.

*Anal.* Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.11; H, 8.21.

**6α-Methyl-Δ$^{1,4}$-pregnadien-17α-ol-3,20-dione Acetate (VIII).**—A stirred mixture of VIIb (300 mg.), selenium dioxide (180 mg.), pyridine (0.06 ml.) and anhydrous *t*-butyl alcohol (20 ml.) was boiled for 30 hours in a nitrogen atmosphere, cooled and filtered through filter-aid, the residue being washed with hot ethyl acetate. The solution was evaporated to dryness *in vacuo*, the residue redissolved in ethyl acetate, the solution washed with water and again evaporated. Chromatography of the oily residue on 15 g. of neutral alumina, yielded in the hexane–benzene (1:1.4) fraction, 180 mg, of Δ$^{1,4}$-dienone VIII, m.p. 230–232°. The analytical sample, from acetone–hexane (needles), melted at 235–237°, $[\alpha]_D$ +16°; $\lambda_{max}$ 244 mμ, ε 14,100; $\lambda_{max}^{KBr}$ 1600, 1620, 1660, 1730 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; O, 16.65. Found: C, 74.61; H, 8.66; O, 16.39,

**6-Methyl-Δ$^{4,6}$-pregnadien-17α-ol-3,20-dione Acetate (IX).**—A mixture of 6α-methyl-17α-acetoxyprogesterone (VIIb) (1 g.), chloranil (2 g.), ethyl acetate (25 ml.) and acetic acid (5 ml.) was boiled under nitrogen for 10 hours[14] and then poured into water. The mixture was repeatedly extracted with ethyl acetate and then the combined extracts washed with cold 10% sodium hydroxide until the alkaline wash was colorless and finally with water to neutrality. Concentration of the dried solution and crystallization of the residue from acetone–ether gave 590 mg. of crude IX, m.p, 198–204°, Recrystallization from the same solvents gave the analytical specimen, m.p, 218–220°, $[\alpha]_D$ +11°; $\lambda_{max}$ 289 mμ, ε 24,000; $\lambda_{max}^{KBr}$ 1580, 1625, 1660, 1710, 1730 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; O, 16.65. Found: C, 74.94; H, 8.41; O, 16.49.

**6-Methyl-Δ$^{1,4,6}$-pregnatrien-17α-ol-3,20-dione Acetate (X).**—The Δ$^{4,6}$-dienone IX (570 mg.) was oxidized with selenium dioxide as described for the preparation of VIII. Chromatography gave in the benzene–hexane (1:1) fractions, 310 mg, of X, m.p. 224°. Recrystallization from acetone–ether raised the melting point to 225–227°, $[\alpha]_D$ −38°; $\lambda_{max}$ 228, 253 and 304 mμ, ε 13,500, 9,120 and 11,700; $\lambda_{max}^{KBr}$ 1575, 1600, 1655, 1710, 1725 cm.$^{-1}$.

*Anal,* Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.01; H, 8.12.

**6α-Methyl-Δ$^4$-pregnene-17α,21-diol-3,20-dione Acetate (XIa).**—A solution of 6α-methyl-17α-hydroxyprogesterone (VIIa)(2 g.) in aged[21] tetrahydrofuran (15 ml.) and methanol (9 ml.) was treated successively with single portions of iodine (3 g.) and finely-powdered C.P. calcium oxide (3 g.). By means of a magnetic stirrer and without external cooling or heating the mixture was vigorously stirred for 3 hours. At the end of this period[27] the almost colorless mixture was poured with stirring into 500 ml. of ice-water containing 1 g. of sodium thiosulfate. Glacial acetic acid (10 ml.) was added, the mixture stirred for a few minutes and the crude 21-iodo compound isolated by methylene chloride extraction. The extract, after being washed to neutrality with water, was dried over sodium sulfate and evaporated to dryness *in vacuo* at room temperature or below. The residue

(26) Best results are obtained in this reaction with tetrahydrofuran containing a peroxide content equivalent to 0.01 g. of iodine per ml. of tetrahydrofuran. "Aging" is most readily accomplished by distilling tetrahydrofuran from calcium oxide and then allowing the solvent, in an open wide-mouthed colorless glass vessel, to be exposed to direct sunlight for several days. Fresh and aged tetrahydrofuran may be combined to give the proper peroxide content.

(27) For optimum yield the reaction mixture should be precipitated within a short time after disappearance of the iodine color.

was taken up in acetone (50 ml.), potassium acetate (5 g.) was added and the mixture boiled for 20 hours. The acetone was distilled, water was added and the product extracted with methylene chloride. After removal of solvent, the crude product was dissolved in methanol (25 ml.) and a solution of sodium bisulfite (1 g.) in water (15 ml.) added and the mixture boiled for one hour. The solution was then concentrated *in vacuo*, water was added and the crude XIa (an oil) isolated by methylene chloride extraction. Chromatography of the oil on 200 g. of neutral alumina gave in the benzene–ether (4:1) fractions, 670 mg. of XIa, m.p. 188–190°. Acetone recrystallization gave the analytical specimen, m.p. 195–196.5°, $[\alpha]D$ +135°; $\lambda_{max}$ 241 mμ, ε 15,500; $\lambda_{max}^{KBr}$ 1230, 1590, 1640, 1710, 1740 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51; O, 19.88. Found: C, 71.64; H, 8.40; O, 19.83.

**6α-Methyl-Δ$^4$-pregnene-17α,21-diol-3,20-dione Diacetate (XIb).**—A solution of XIa (760 mg.), glacial acetic acid (50 ml.), acetic anhydride (13 ml.) and *p*-toluenesulfonic acid·$1H_2O$ (760 mg.) was allowed to stand for one hour at 25° before pouring into ice-water. When the excess anhydride had hydrolyzed the product was extracted with ethyl acetate and the extract washed to neutrality with bicarbonate and water. Evaporation of solvent and crystallization of the residue from acetone–ether gave 260 mg. of 17,21-diacetate XIb, m.p. 203–204°. Recrystallization from acetone–hexane yielded material of m.p. 216–218°, $[\alpha]D$ +51°; $\lambda_{max}$ 241 mμ, ε 16,600; $\lambda_{max}^{KBr}$ 1230, 1600, 1660, 1720, 1740 cm.$^{-1}$.

*Anal.* Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.48; H, 8.13.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

# Synthesis of Amino Sugars by Reduction of Hydrazine Derivatives; D- and L-Ribosamine, D-Lyxosamine[1-3]

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A number of amino sugar derivatives have been synthesized through the reduction of the hydrazino compounds derived from the replacement, with probable Walden inversion of *p*-tolylsulfonyloxy groups with hydrazine, Methyl 3,4-*O*-isopropylidene-2,*O*-*p*-tolylsulfonyl-β-D-arabinopyranoside, 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-xylofuranose, 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose, methyl 3,5-*O*-isopropylidene-2-*O*-*p*-tolylsulfonyl-α,β-D-xylofuranoside and methyl 3,4-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside, have been converted by this method to amino sugar derivatives. A derivative of a diamino sugar is described. Crystalline D(and DL)-ribosamine (2-amino-2-deoxyribose) and D-lyxosamine (2-amino-2-deoxy-D-lyxose) are reported as hydrochlorides.

It has been shown that the reduction of sugar phenylhydrazones provides a convenient method for the synthesis of certain monosaccharide derivatives containing a primary amino group.[4] In a previous publication,[3] the reduction of hydrazino compounds, obtained by replacement of a *p*-tolylsulfonyloxy group with hydrazine, has been utilized for the synthesis of amino sugars. Peat and Wiggins[5] have shown that ammonolysis of a *p*-tolylsulfonyloxy group proceeds through an intermediate epoxide when a suitably situated hydroxyl group is available. This results in retention of configuration at the original site of the *p*-tolylsulfonyloxy group because of two successive Walden inversions at this point. The same spatial considerations apply to hydrazinolysis as shown by the identity of the end products.

In the case of 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucofuranose, wherein the *p*-toluenesulfonate is not adjacent to any free hydroxyl group, Lemieux and Chu[6] have proved that ammonolysis, or hydrazinolysis, of the *p*-tolylsulfonyloxy group proceeds with Walden inversion to yield a derivative of 3-amino-3-deoxy-D-allose. We have likewise proved that hydrazinolysis of 3,4-*O*-isopropylidene-2-*O*-*p*-tolylsulfonyl-β-L-arabinopyranoside proceeds with Walden inversion since the crystalline, unsubstituted amino sugar hydrochloride, m.p. 142–148 dec., $[\alpha]D$ −15.6 → +6.7° (water), is not identical with that obtained[7] by the definitive C5–C6 degradation of 2-amino-2-deoxy-D-galactose to 2-amino-2-deoxy-L-arabinose hydrochloride, m.p. 153–155° dec., $[\alpha]D$ +174 → +115° (water), according to the procedure established for the synthesis of 2-amino-2-deoxy-D-xylose from 2-amino-2-deoxy-D-glucose by Wolfrom and Anno.[8] Since only two possibilities are involved, this allows the 2-amino-2-deoxy-L-ribose configuration to be assigned to the 2-amino-2-deoxy-α-L-pentose hydrochloride, $[\alpha]^{22}D$ +6.7° (water, equilibrium), previously reported.[3] It is established by comparison with the 2-amino-2-deoxy-D-xylose hydrochloride, dec. 165–167°, $[\alpha]D$ +40° (final), obtained by Wolfrom and Anno,[8] that the hydrazino group on C2 of the D-xylose derivatives herein described also entered with Walden inversion, resulting in 2-amino-2-deoxy-α-D-lyxose hydrochloride, dec. 148–155°, $[\alpha]D$ +54 → −36° (water).

The present work is concerned with the synthesis of amino sugars prepared from *p*-toluenesulfonate derivatives of D-arabinose, D-xylose and D-galactose. It should be noted that the interest in the synthesis and investigation of the amino sugars is considerably enhanced by the isolation of a variety of useful antibiotics such as streptomycin, carbomycin, erythromycin,[9] puromycin,[10] strepto-

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(2) Reported in part in *Abstract Papers Am. Chem. Soc.*, **134**, 11D (1958).

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