Registry No.—**1**, 21333-80-2; **2**, 21371-69-7; **3**, 21343-09-9; **14**, 21343-10-2; **15**, 21343-11-3; **16**, 21371-70-0; *N*-benzyloxycarbonylsarcosine *p*-nitrophenyl ester, 16879-76-8.

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The Synthesis of 17-Deoxy-17-α and -17β 20-pregnynes and -20-pregnenes

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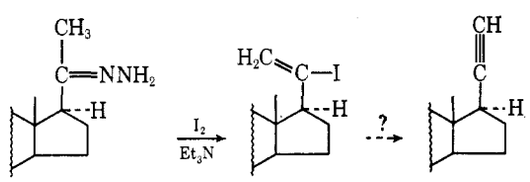
A variety of 17-deoxy-17α- and -17β-20-pregnynes, pregnenes, and pregnanes were prepared from 20-iodo-Δ^{20} steroids by base-catalyzed dehydrohalogenation. The mechanism of the elimination reaction from 20-iodo-Δ^{20} steroids to pregn-20-ynes is discussed.

Many pharmacologically active steroids contain the 17α-ethynyl-17β-hydroxy moiety (usually introduced by addition of a metal acetylide to a 17-keto steroid), and partial or complete reduction of the ethynyl group also produces compounds with biological activity.[1] Removal of the oxygen function at C-3 in many steroids enhances the original activity,[2] and it was of interest to see the effect of a similar loss in 17α-substituted 17β-hydroxy steroids. We, therefore, sought to prepare a series of 17-ethynyl-17-deoxy steroids and some simple reduction products.

Our synthetic approach made use of a reaction discovered by Barton some years ago,[3] but largely neglected since then. The reaction involves the treatment of a ketone hydrazone (*e.g.*, that of a 20-keto steroid) with iodine in the presence of triethylamine to afford high yields of vinyl iodide (*e.g.*, a Δ^{20}-20-iodo steroid). We felt that such a vinyl iodide should be

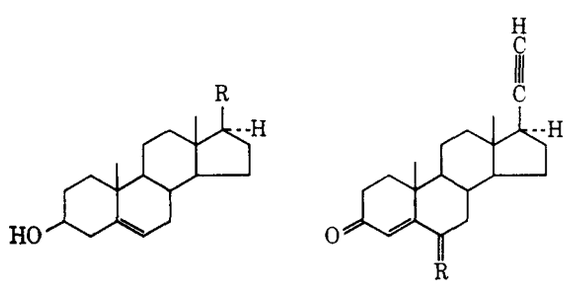


easily convertible, upon treatment with base, to the corresponding ethynyl compound. To test this idea, we decided to prepare some 17β-ethynyl steroids from readily obtainable 17β-acetyl (20-keto) steroids.

The starting material for this preliminary work was pregnenolone, which was converted to its hydrazone (hydrazine, triethylamine) and thence to the vinyl iodide (I) with iodine–triethylamine in tetrahydrofuran. This material was converted, upon refluxing with potassium hydroxide in methanol, to the acetylene II in 88% yield. The structure determination was made on the basis of infrared and nuclear magnetic resonance spectral data. The orientation of the ethynyl side chain was shown to be β (see below). The iodide I was also converted to the 17β-vinyl compound III by sodium–alcohol reduction.

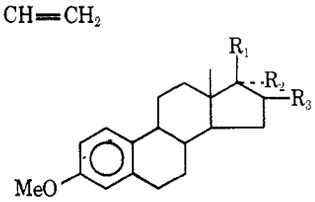
The desired conjugated ketone IV was prepared from II in 60% yield by Oppenauer oxidation. Jones oxidation afforded the undesired enedione V.

Since the above synthetic route to 17-ethynyl-17-deoxy steroids proved successful, we decided to prepare a few compounds in the A-ring aromatic series. The 20 ketone in this series was prepared *via* the 17-ethylidene compound,[4] by photosensitized oxygenation and dehydration,[5] and hydrogenation. This material was

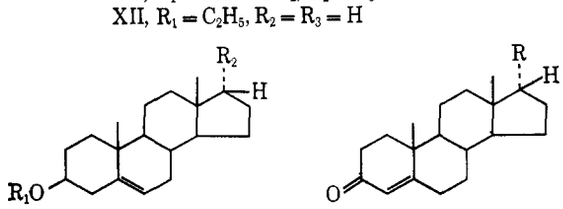


I, R = C(I)=CH$_2$
II, R = C≡CH
III, R = CH=CH$_2$

IV, R = H,H
V, R = O



VI, R_1, R_2 = O, R_3 = H
VII, R_1, R_2 = CHCH$_3$, R_3 = H
VIII, R_1 = COCH$_3$, R_2, R_3 = double bond
IX, R_1 = COCH$_3$, R_2 = R_3 = H
X, R_1 = C≡CH, R_2 = R_3 = H
XI, R_1 = CH=CH$_2$, R_2 = R_3 = H
XII, R_1 = C_2H_5, R_2 = R_3 = H



XIII, R_1 = R_2 = COCH$_3$
XIV, R_1 = H, R_2 = C(I)=CH$_2$
XV, R_1 = H, R_2 = C≡CH
XVI, R_1 = H, R_2 = CH=CH$_2$

XVII, R = C_2H_5
XVIII, R = C≡CH
XIX, R = CH=CH$_2$
XX, R = C_2H_5

(1) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 518–521, 556–558.
(2) M. S. deWinter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959).
(3) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962).
(4) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).
(5) A. M. Krubiner, G. Saucy, and E. P. Oliveto, *ibid.*, **33**, 3548 (1968).

converted, *via* the hydrazine and vinyl iodide, to the 17β-ethynyl (X) and 17β-vinyl (XI) steroids in high yield. Hydrogenation of X with platinum in ethyl acetate–acetic acid afforded the 17-ethyl compound XII, identical with that obtained by hydrogenating VII. Since the latter hydrogenation would be expected to occur from the α face of the molecule to give a 17β-ethyl group, this proves the 17β configuration of the ethynyl group in X and, by analogy, in II and IV.

Finally, to prepare a true 17-deoxy analog of the active 17α-ethynyl-17β-hydroxy steroids, a 17α-20-keto steroid was required as starting material. The hydrazone of 17α-pregnenolone acetate[6] could be prepared with or without the use of triethylamine without epimerization at C-17 to the more stable 17β configuration. The acetate group at C-3 was saponified in this step. The hydrazone obtained was different from that prepared from pregnenolone, as evidenced by its physical properties and spectra. Conversion to the iodide XIV proceeded smoothly, and the material also was different from iodide I. We felt that the subsequent dehydrohalogenation reaction would give some clues as to the exact pathway of acetylene formation. If the proton at C-21 were being lost, one would proceed directly to the acetylene with no opportunity for epimerization at C-17. However, if the C-17 β proton were lost, the intermediate allene would be expected to rearrange to the acetylene by protonation of C-17 from the α side to afford II. When the reaction was performed, only 17α-ethynyl compound XV was formed. There was no trace of any II present. Again, compound XV exhibited different physical and spectral properties than II. Compound XIV was also converted to XVI by sodium–alcohol reduction, and XVI was hydrogenated (Pd–C, ethanol) to XVII. Compounds XV, XVI, and XVII were converted to XVIII, XIX, and XX, respectively, by Oppenauer oxidation.[7]

Experimental Section[8]

Pregnenolone hydrazone.—A mixture of 20.0 g of pregnenolone, 75 ml of triethylamine, 15 ml of 85% hydrazine hydrate, and 200 ml of ethanol was refluxed for 4 hr. After cooling, the reaction mixture was poured into water. The precipitated material was filtered and washed well with water to afford 19.37 g of product, mp 229–232° (lit.[3] mp 205–215°).

20-Iodopregna-5,20-dien-3β-ol (I).—The above hydrazone (19.37 g) in a mixture of dry THF (1 l.) and triethylamine (500 ml) was treated dropwise under nitrogen with a solution of 36 g of iodine in 100 ml of THF. The iodine color disappeared upon addition, and gas evolution was noted. About halfway through the addition, a precipitate of triethylamine hydriodide formed. At the end of the addition, the iodine color did not fade anymore. After stirring for 1 hr, the reaction mixture was concentrated *in vacuo*, dissolved in methylene chloride, washed with 2 *N* hydrochloric acid and 5% sodium thiosulfate solution, and dried. The crude, oily product obtained after removal of the solvent crystallized upon standing. After recrystallization from aqueous ethanol, there was obtained 12.4 g of light tan product, mp 135–136.5° (lit.[3] mp 142–144°).

3β-Hydroxypregn-5-en-20-yne (II).—20-Iodopregna-5,20-dien-3β-ol (9.38 g) was added to a solution of 30 g of potassium hydroxide in 350 ml of ethanol, and the mixture was refluxed for 4 hr. After cooling, most of the alcohol was removed *in vacuo*, water was added, and the mixture was acidified with 6 *N* hydrochloric acid. After ether extraction, drying, and removal of the solvent, a tan solid was obtained. Two recrystallizations from aqueous ethanol afforded 4.16 g of material, mp 166–168.5°. A second crop of 1.63 g was also obtained: ir ν_{max} 3610 and 3310 cm^{-1}; nmr δ 0.80 (s, 3H), 1.01 (s, 3H), 2.05 (s, 1H), and 5.42 (m, 1H).

The analytical sample was recrystallized from ether–petroleum ether (bp 30–60°): mp 167.0–168.5°; $[\alpha]^{25}D$ −14.6°.

Anal. Calcd for $C_{21}H_{30}O$ (mol wt 298.49): C, 84.50; H, 10.13. Found: C, 84.46; H, 10.41.

3β-Hydroxypregna-5,20-diene (III).—Sodium (7 g) was added portionwise to a solution of 1.0 g of 20-iodopregna-5,20-dien-3β-ol in 55 ml of ethanol. The mixture was refluxed for 3 hr, most of the ethanol was removed *in vacuo*, water was added, and the mixture was acidified with 6 *N* hydrochloric acid. After ether extraction, drying, charcoal treatment, and removal of the ether, the residual white plates were recrystallized from aqueous ethanol to afford 608 mg of product, mp 117–118.5°; ir ν_{max} 910 and 3620 cm^{-1}; nmr δ 0.60 (s, 3H), 1.01 (s, 3H), 4.90 (m, 1H), 5.03 (broad s, 1H), 5.75 (broad m, 1H), and 5.34 (m, 1H).

The analytical sample was crystallized from aqueous ethanol; mp 118–119°, $[\alpha]^{25}D$ −76.6°.

Anal. Calcd for $C_{21}H_{32}O$ (mol wt 300.49): C, 83.94; H, 10.74. Found: C, 84.20; H, 10.83.

Pregn-4-en-20-yn-3,6-dione (V).—A solution of 3.0 g of II in 70 ml of acetone was cooled to 0° and treated dropwise with 10 ml of standard 8 *N* chromic acid oxidizing solution. The solution was stirred for 20 min, and the excess oxidizing agent was destroyed with isopropanol. Fifteen drops of 10 *N* sulfuric acid was added, the reaction mixture was refluxed for 2.5 hr, the acetone was removed, and the product was isolated with methylene chloride. The mixture was dried and treated with charcoal, and the solvent was evaporated. The crude product was recrystallized from ether–petroleum ether to afford 1.68 g of product, mp 175.5–177.5°. A further recrystallization from methylene chloride–ether afforded 1.01 g of product, mp 183–185°; uv λ_{max}^{EtOH} 250 mμ (ε 10,650); nmr δ 0.87 (s, 3H), 1.19 (s, 3H), 2.15 (s, 1H), and 6.18 (s, 1H).

The analytical sample was recrystallized from methanol chloride–ether: mp 187–189°, $[\alpha]^{25}D$ +18.0°.

Anal. Calcd for $C_{21}H_{26}O_2$ (mol wt 310.42): C, 81.25; H, 8.44. Found: C, 81.18; H, 8.64.

Pregn-4-en-20-yne-3-one (IV).—A solution of 1.63 g of II and 50 ml of cyclohexanone in 200 ml of toluene was refluxed, using a Dean–Stark water trap, until 60 ml of solvent was collected. A solution of 2.0 g of aluminum isopropoxide in 20 ml of dry toluene was added, and the mixture was refluxed for 3 hr. The mixture was cooled, ether and water were added, and the ether was washed with 2% potassium hydroxide solution and water and was then steam distilled. The resulting mixture was extracted with ether, dried, treated with charcoal, and evaporated to afford 3.6 g of yellow oil. This was chromatographed on 40 g of silica gel. Benzene–ethyl acetate (99:1 and 19:1) eluted 1.58 g of crystalline material, pure by tlc analysis. After crystallization from ether–petroleum ether, there was obtained 966 mg of product, mp 121–123°; ir ν_{max} 1670, 2120, and 3310 cm^{-1}; uv λ_{max}^{EtOH} 240 mμ (ε 16,300); nmr δ 0.85 (s, 3H), 1.20 (s, 3H), 2.14 (s, 1H), and 5.76 (s, 1H).

The analytical sample was crystallized from ether–petroleum ether: mp 143–145.5°, $[\alpha]^{25}D$ +51.0°.

Anal. Calcd for $C_{21}H_{28}O$ (mol wt 296.43): C, 85.09; H, 9.52. Found: C, 85.25; H, 9.23.

3-Methoxy-19-norpregna-1,3,5(10),16(20)-tetraen-20-one (VIII).—A solution of 20.0 g of *cis*-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene (VII)[4] and 400 mg of hematoporphyrine in 375 ml of pyridine was irradiated with 4–15-W fluorescent bulbs while a stream of oxygen was slowly bubbled through. After 16 hr, there was no starting VII detectable by tlc analysis. Acetic anhydride (100 ml) was added, and the reaction mixture, which became slightly warm, was allowed to stand at room temperature for 2 hr. After dilution with water, the reaction mixture was extracted with methylene chloride. The organic phase was washed with 5 *N* hydrochloric acid until acidic, then with water, 5% sodium bicarbonate solution, and water, and dried. After charcoal decolorization, the solvent was evaporated and the crude crystalline product was recrystallized from ethyl acetate to

(6) M. B. Rubin and B. C. Blossey, *Steroids*, **1**, 453 (1963).

(7) Compounds II–V, X, XI, and XVII–XX were tested in antigonadotropic, uterotropic, antiestrogenic, androgenic–anabolic, antiandrogenic, and progestational screens. All of the compounds were essentially inactive.

(8) All melting points are corrected. Nmr spectra were run in deuteriochloroform using tetramethylsilane as internal standard and ir spectra were run in chloroform, as were optical rotations (*c* 1), unless otherwise specified. Solutions were dried over anhydrous sodium sulfate and solvents were evaporated under reduced pressure. Silica gel for chromatography was Merck silica gel for column chromatography, 0.05–0.2 mm.

afford 13.44 g, mp 186–188°. Further recrystallization afforded material, mp 190–193°; $[\alpha]^{25}D$ +108.1° (lit.[9] mp 193–194°; $[\alpha]^{25}D$ +115°); ir ν_{max} 1670 cm^{-1}; uv λ_{max}^{EtOH} 230 mμ (ε 14,450); nmr δ 0.93 (s, 3H), 2.28 (s, 3H), and 6.6–7.4, (m, 4H).

3-Methoxy-19-norpregna-1,3,5(10)-trien-20-one (IX).—A solution of 12.9 g of VIII in 500 ml of distilled benzene was hydrogenated at room temperature and atmospheric pressure using 1.29 g of 10% Pd–C catalyst. After filtration of the catalyst and removal of the solvent, there was obtained 12.9 g of product, mp 131–132.5°.

Hydrazone of IX.—The above material (12.9 g) was converted to the hydrazone by the same method used for pregnenolone (150 ml of ethanol, 30 ml of 85% hydrazine hydrate, and 75 ml of triethylamine). The crude product weighed 13.2 g, mp 119–119.5°.

3-Methoxy-20-iodo-19-norpregna-1,3,5(10),20-tetraene.—The above hydrazone (11 g) was converted to the vinyl iodide in the same manner as for the preparation of I. The crude oily product was dissolved in benzene and filtered through 250 g of silica gel with benzene. The material eluted (12.2 g) slowly crystallized and was recrystallized from ether–methanol to afford 6.6 g, mp 86–88°; nmr δ 0.63 (s, 3H), 6.03 (d, 1H), and 6.20 (d, 1H).

This material was not very stable at room temperature, but could be stored at 0° under nitrogen.

3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yne (X).—A mixture of 3.0 g of the above iodide, 9.0 g of potassium *t*-butoxide (K & K), and 100 ml of dry *t*-butyl alcohol were heated at reflux under N_2 overnight. After cooling and dilution with water, the product (2.07 g) was isolated with ether. One recrystallization from ether–methanol afforded 1.66 g, mp 144–146°; ir ν_{max} 3310 and 2120 cm^{-1}; nmr δ 0.82 (s, 3H) and 2.06 (s, 1H).

The analytical sample was crystallized from ether–methanol: mp 148.0–148.5°, $[\alpha]^{25}D$ +115.0°.

Anal. Calcd for $C_{21}H_{26}O$ (mol wt 294.41): C, 85.66; H, 8.90. Found: C, 86.07; H, 8.96.

3-Methoxy-19-norpregna-1,3,5(10),20-tetraene (XI).—The above vinyl iodide (2.0 g) was reduced with sodium (7 g) in ethanol (100 ml), as in the preparation of III. The crude product was crystallized from ether–methanol to afford 1.22 g, mp 111–112°; ir ν_{max} 915 cm^{-1}; nmr δ 0.63 (s, 3H) and 4.7–5.9 (m, 3H).

The analytical sample was crystallized from ether–methanol: mp 112.5–113.5°, $[\alpha]^{25}D$ +49.5°.

Anal. Calcd for $C_{21}H_{28}O$ (mol wt 296.43): C, 85.09; H, 9.52. Found: C, 84.93; H, 9.40.

3-Methoxy-19-norpregna-1,3,5(10)-triene(XII). A.—A solution of 6.0 g of VII in 250 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure using 300 mg of 10% Pd–C catalyst. After filtration and removal of the solvent, there was obtained 6.0 g of material, mp 109–112°. One recrystallization afforded 5.28 g, mp 111.5–112.5°; $[\alpha]^{25}D$ +82.8°; nmr δ 0.61 (s, 3H).

Anal. Calcd for $C_{21}H_{30}O$ (mol wt 298.45): C, 84.51; H, 10.13. Found: C, 84.64; H, 10.36.

B.—A solution of 100 mg of X in a mixture of 30 ml of glacial acetic acid and 10 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure using 20 mg of prereduced platinum oxide catalyst. After the usual work-up, 97 mg of crude product, mp 112–114°, was obtained. One recrystallization from ether–methanol gave material with mp 113–114°, which was identical with that prepared in part A by tlc analysis. A mixture melting point of both samples showed no depression.

17α-Pregnenolone Acetate (XIII).—A suspension of 18.0 g of lithium aluminum hydride in 750 ml of dry tetrahydrofuran was treated dropwise with a solution of 50.0 g of 16α,17α-epoxypregnenolone acetate (G. D. Searle) in 1 l. of tetrahydrofuran. After the addition was complete, the reaction was refluxed for 2 hr. The excess hydride was destroyed by cautious addition of saturated ammonium chloride solution, and the supernatant tetrahydrofuran layer was decanted from the precipitated salts, which were thoroughly washed with ethyl acetate. The combined organic layers were dried and evaporated. The resulting crystalline material was dissolved in 875 ml of pyridine, and 275 ml of acetic anhydride was added. The mixture was allowed to stand overnight at room temperature, ice was added to hydrolyze the excess anhydride, and the mixture was poured into excess 10% phosphoric acid. After extraction (methylene chloride), the organic phase was washed with dilute phosphoric acid and water and dried, and the solvent was evaporated. The crude oily product was dissolved in 3.6 l. of distilled, dry xylene, divided in half, and each half treated separately with 550 g of purified zinc.[6] The material was stirred at reflux overnight and filtered, and the filtrates were combined and evaporated *in vacuo* to afford crystalline product, which was recrystallized from acetone–methanol to give 21.9 g of white crystals, mp 167–170°, $[\alpha]^{25}D$ −119.6° (lit.[6] mp 170–171°, $[\alpha]^{20}D$ −126°).

17α-Pregnenolone Hydrazone.—The above ketone (XIII, 21.0 g) was converted to the hydrazone with 90 ml of 100% hydrazine hydrate in 850 ml of 80% ethanol at reflux overnight under nitrogen. After the usual work-up, 19.1 g of product was obtained: mp 178–183°; nmr δ 0.81 (s, 3H) and 0.92 (s, 3H), no acetyl group.

20-Iodo-17α-pregna-5,10-dien-3β-ol (XIV).—The above hydrazone (7.0 g) was converted to the iodide as in the preparation of I, using 12.0 g of I_2 and 130 ml of triethylamine in 660 ml of dry tetrahydrofuran. After the usual work-up, there was obtained 9.0 g of brown solid, which was recrystallized from aqueous ethanol to afford 5.55 g of product, mp 193–197° (further recrystallization raised the melting point to 198.5–200.0°); nmr δ 0.83 (s, 3H), 1.00 (s, 3H), 5.34 (m, 1H), and 5.88 (m, 2H).

3β-Hydroxy-17α-pregn-5-en-20-yne (XV).—A mixture of 4.4 g of XIV, 13.2 g of potassium hydroxide, and 150 ml of ethanol was heated at reflux overnight. The solvent was removed *in vacuo*, and the residue was taken up in water, acidified, extracted with methylene chloride, and dried. After removal of the solvent, the crude crystalline product was recrystallized from aqueous ethanol to afford 2.3 g, mp 200–201°; ir ν_{max} 3620, 3310, and 2120 cm^{-1}; nmr δ 0.78 (s, 3H), 1.02 (s, 3H), and 2.12 (s, 1H).

The analytical sample was crystallized from ether–petroleum ether: mp 201.5–202.5°, $[\alpha]^{25}D$ −153.4°.

Anal. Calcd for $C_{21}H_{30}O$ (mol wt 298.49): C, 84.50; H, 10.13. Found: C, 84.66; H, 10.38.

3β-Hydroxy-17α-pregna-5,20-diene (XVI).—Compound XIV (9.9 g) was reduced (76 g of sodium, 1 l. of ethanol) in the same manner as for the preparation of III. The crude product was recrystallized from aqueous ethanol to afford 6.0 g, mp 118–121°; nmr δ 0.80 (s, 3H), 1.02 (s, 3H), and 4.6–5.9 (m, 4H).

The analytical sample was crystallized from aqueous ethanol: mp 120–121°, $[\alpha]^{25}D$ −110°.

Anal. Calcd for $C_{21}H_{32}O$ (mol wt 300.51): C, 84.01; H, 10.66. Found: C, 84.17; H, 10.65.

17α-Pregn-4-en-20-yn-3-one (XVIII).—A solution of 2.5 g of XV, 153 ml of cyclohexanone, and 460 ml of toluene was heated to reflux, and a solution of 6.02 g of aluminum isopropoxide in 60 ml of toluene was added. After refluxing overnight, the reaction was cooled, water was added, and the organic phase was washed with 2% potassium hydroxide solution. After removal of the solvent *in vacuo*, the remaining oil was steam distilled, and the residue was dissolved in methylene chloride, washed with water, dried, and evaporated. Chromatography on 100 g of silica gel afforded (after a forerun of cyclohexanone) 2.5 g of crystalline product, using ethyl acetate as eluent. The crystallization from methylene chloride–ether afforded 1.34 g, mp 213–214°; ir ν_{max} 3300, 2110, and 1670 cm^{-1}; uv λ_{max}^{EtOH} 240 mμ (ε 16,200); nmr δ 0.98 (s, 3H), 1.17 (s, 3H), and 2.33 (s, 1H).

The analytical sample was crystallized from methylene chloride–ether: mp 213–214°, $[\alpha]^{25}D$ +3.9°.

Anal. Calcd for $C_{21}H_{28}O$ (mol wt 296.43): C, 85.09; H, 9.53. Found: C, 85.12; H, 9.37.

17α-Pregna-4,20-dien-3-one (XIX).—Compound XVI (3.0 g) was subjected to the Oppenauer oxidation as in the previous example (18.5 g of cyclohexanone, 10.2 g of aluminum isopropoxide, 350 ml of toluene, reflux 3.5 hr). After work-up, the product was chromatographed on 125 g of silica gel. Benzene–ethyl acetate (19:1) eluted 2.5 g of crystalline product, which was recrystallized from petroleum ether to afford 1.33 g, mp 74–77°; ir ν_{max} 1665 and 910 cm^{-1}; uv λ_{max}^{EtOH} 240 mμ (ε 16,400); nmr δ 0.82 (s 3H), 1.18 (s, 3H), 4.7–5.2 (m, 2H), and 5.5–6.0 (m, 2H).

The analytical sample was crystallized from aqueous ethanol: mp 79.0–80.5°, $[\alpha]^{25}D$ +75.7°.

Anal. Calcd for $C_{21}H_{30}O$ (mol wt 298.49): C, 84.51; H, 10.13. Found: C, 84.45; H, 10.25.

17α-Pregn-4-en-3-one (XX).—A solution of 2.8 g of XVI in 150 ml of ethanol was hydrogenated at room temperature and atmospheric pressure using 150 mg of 10% Pd–C catalyst. The crude product weighed 2.8 g and melted at 129–133°. This material was subjected to the Oppenauer oxidation as above (17.5 g of cyclohexanone, 9.5 g of aluminum isopropoxide, 330 ml of

(9) F. Sondheimer, F. Neumann, H. J. Ringold, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **76**, 2230 (1954).

toluene, reflux 3.5 hr). The crude product was chromatographed on 125 g of silica gel to elute 2.5 g of crystalline product with benzene–ethyl acetate (19:1). After two crystallizations from aqueous ethanol, there was obtained 1.43 g of product, mp 101–102°; ir ν_{max} 1665 cm^{-1}; λ_{max}^{EtOH} 240 mμ (ε 16,400); nmr δ 0.82 (s, 3H) and 1.27 (s, 3H).

The analytical sample was crystallized from aqueous ethanol: mp 102.5–103.0°, $[\alpha]^{25}D$ +64.0°.

Anal. Calcd for $C_{21}H_{32}O$ (mol wt 300.51): C, 83.94; H, 10.73. Found: C, 83.97; H, 10.81.

Registry No.—II, 21321-87-9; III, 21321-88-0; IV, 21321-89-1; V, 21321-90-4; VIII, 21321-91-5; IX, 1624-73-3; IX (hydrazone), 21321-93-7; X, 21321-94-8; XI, 21321-95-9; XII, 21321-96-0; XIII (hydrazone), 21321-97-1; XIV, 21321-98-2; XV, 21321-99-3; XVI, 21317-79-3; XVIII, 21317-80-6; XIX, 21317-81-7; XX, 21317-82-8; 3-methyl-20-iodo-19-norpregna-1,3,5(10),20-tetraene, 21339-87-7.

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Preparation and Properties of Steroidal 17,20- and 20,21-Acetonides Epimeric at C-20. I. Derivatives of 5β-Pregnan-3α-ol[1]

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Conditions optimal for the preparation and, in some cases, the hydrolysis of steroidal 17,20- and 20,21-acetonides epimeric at C-20 have been defined. Acetonides of the latter class are formed in good yield using *p*-toluenesulfonic acid as catalyst and undergo ready hydrolysis in 60–80% acetic acid at room temperature. Acetonides of the 17,20 variety are best prepared using perchloric acid as catalyst. Among members of this class 17,20α-acetonides are relatively resistant while their C-20 epimers are very resistant to hydrolysis with aqueous acetic acid. The use of both 17,20- and 20,21-acetonides in the preparation of 3-acetates of steroidal glycols and glycerols is described. It was noted that the bromine atom in the bromacetonides **15a** and **15b** resists substitution. In an investigation of the lithium aluminum hydride reduction of **15a** and **15b**, it was observed that the 20α epimer was more resistant to attack, although both bromoacetonides afforded their respective hydrogenolysis products. The differing reactivities of **15a** and **15b** toward this reagent as well as the observations relative to the ease of hydrolysis of epimeric 17,20-acetonides are correlated with the degree of steric hindrance. Reduction of **15a** and **15b** with sodium in *n*-propyl alcohol gave in both cases about equal amounts of the *trans*-pregnenol **17** and the pregnenediol **20**. A mechanism accounting for the formation of these substances is proposed. The principal bands of 17,20- and 20,21-acetonides in the infrared region are presented and their differentiation by this means is discussed.

Steroidal acetonides of the 20,21 variety have long been used as protecting groups,[2] but we are aware of only one earlier description of a 17,20-acetonide and in that instance the configuration at C-20 was not established.[3] The paucity of published information relative to these derivatives has prompted us to undertake a systematic investigation of the preparation and properties of epimeric pairs of both 17,20- and 20,21-acetonides derived from 5β-pregnan-3α-ol. We have studied the formation and, in some cases, the hydrolysis of these derivatives and have utilized both types in the preparation of partially acetylated polyhydroxypregnanes. Also included is a description of some novel reductive eliminations undergone by 17,20-acetonido-21-bromides.

To define optimal conditions for the preparation of both types of acetonides, a small-scale experiment was performed on eight pairs of C-20-epimeric glycols and glycerols[4] (Table I). These substrates were treated with the appropriate acid catalyst in acetone solution under standard conditions and, by means of thin layer chromatography of the reaction mixtures at intervals, the time required for a greater than 90% conversion into the acetonide was estimated. In keeping with the results of others, we observed that the relatively unhindered 20,21-glycols and glycerols (pairs I and II) readily form acetonides in the presence of *p*-toluenesulfonic acid (*p*-TSA). In contrast, acetonation of 17,20-glycols unsubstituted at C-21 (pair III) proceeds at only one-thirtieth this rate. The greater resistance to cyclization involving the 17α-hydroxyl group is increased still further by the introduction of various bulky substituents at C-21 (pairs IV–VIII). However, substitution of perchloric acid for *p*-TSA provides the 17,20-acetonides of all types in 15 min or less. The relative effectiveness of the two catalysts can best be assessed by comparing the reaction times in pair IV where both were used. These results show that perchloric acid promotes acetonation of the 21-acetates at a rate approximately 5000 times as great as that provided by *p*-TSA. For all examples no appreciable differences in reaction rates of C-20 epimers were noted.

The mildest conditions for the hydrolysis (cleavage) of acetonides were sought to exploit fully their utility as intermediates. The cleavage of both 20α,21- and 20β,-21-acetonides proceeds rapidly in 60–80% acetic acid at room temperature and is complete within 2 hr. Hydrolysis of 17,20α-acetonides unsubstituted at C-21 is notably slower under these conditions, but is complete within 24 hr. In striking contrast, the 20β epimers are virtually unchanged when so treated, but can be cleaved to 17,20β-glycols in good yield by brief

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