in an ice-salt bath and the solution was stirred efficiently. A cold (0°) solution of sodium nitrite (1 g.) in water (3 ml.) was added dropwise. The resulting mixture was maintained at 0°, and stirring was continued for an additional 5 min. The solid diazonium fluoborate was filtered by suction on a sintered glass filter, washed several times with cold fluoboric acid and then with water. It was very soluble in 95% ethanol.

Then sodium nitrite (20 g.) was dissolved in water (40 ml.) and copper filings (4 g.) were added. The mixture was stirred efficiently and a suspension of the fluoborate salt in water (10 ml.) was added very slowly. Frothing occurred and a few drops of ether was added from time to time to break the foam. The reaction was complete when all of the salt was added.

The crude product was filtered by suction and washed a few times with water and dilute (10%) sodium hydroxide. The product, 3-nitro-4-phenylpyrazole, weighed 0.48 g. (0.0025 mole; 22.4% yield; m.p. 205–208°). Recrystallization of this material from chloroform gave pale yellow needles melting at 209–210°. This product caused no depression in melting point when mixed with authentic IIc.[8]

Reaction of 4-phenylpyrazole-3-diazonium chloride with ethyl mercaptan. The diazotization of I (1.8 g., 0.011 ml. was carried out as described above for the preparation of 4-phenylpyrazole. The resulting mixture was maintained at 0° and ethyl mercaptan (7.2 g., 0.0113 ml.) was added dropwise with swirling. A few drops of ethyl mercaptan was added in excess. The reaction mixture containing a yellow solid was maintained at ice-salt temperature for 24 hr. The solid was then collected, washed with water, and dried by vacuum. Crude IId (1.9 g., 72.5%, m.p. 98–100°) was recrystallized from aqueous methanol which afforded pure IId as long yellow needles (m.p. 101–101.5°).

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.89; H, 5.17; N, 24.13. Found: C, 56.47; H, 5.25, N, 24.05.

The reaction of IId *with methanol.* A solution of IId (0.56 g., 0.0024 ml.) in methanol (50 ml.) was heated at the reflux temperature for 7.5 hr. The methanol was removed, and the pale yellow solid (0.18 g., 52% yield, m.p. 222–225°) was collected and recrystallized from chloroform. The pure product (m.p. 227–228°) was identified as 4-phenylpyrazole (m.p. and mixed m.p. 227–228°).

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Practical Synthesis of 5α-Androstan-17β-ol[1]

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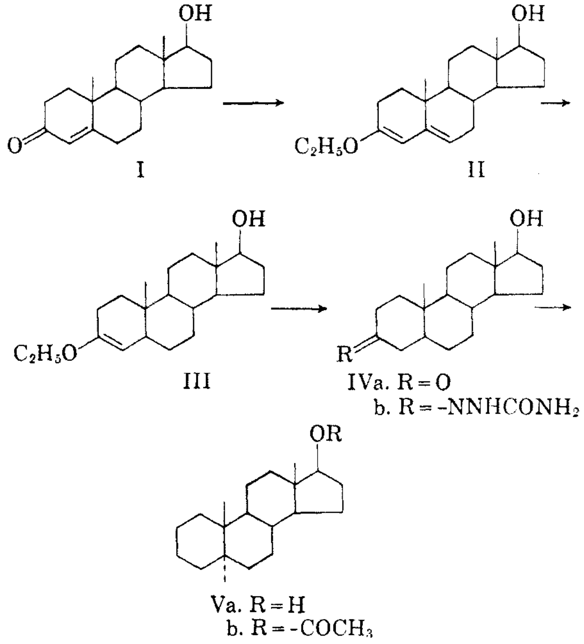
Under a contract with the Cancer Chemotherapy National Service Center, this laboratory was asked to prepare a number of steroids not available commercially. One such compound was 5α-androstan-17β-ol (Va). This latter compound has been prepared by a number of investigators from testosterone (I)[2]; however, none of the published methods appeared attractive for the preparation of V on a large scale.

In this paper a procedure is described for the preparation of V which is amenable to large scale operation. The reaction sequence is as follows:



I

II

III

IVa. R = O
b. R = -NNHCONH$_2$

Va. R = H
b. R = -COCH$_3$

Testosterone (I) was smoothly converted to 3-ethoxy-3,5-androstadien-17β-ol (II) by reaction with triethyl orthoformate in ethanolic hydrogen chloride. Reduction of the 5,6-double bond of II to give the enol ether (III) was effected catalytically with 5% palladium on charcoal in ethanol. The enol (III) was reversed to the 3-keto compound with acid and the 17β-hydroxyandrostan-3-one (IVa) was converted *in situ* to the sparingly soluble 3-semicarbazone (IVb).[3] The overall yield for the three steps was 64%. Since the completion of this work, the direct reduction of I to IVa in high yield has been reported using lithium in liquid ammonia.[4] This reduces the present scheme to a three-step synthesis. The semicarbazone (IVb) was reduced in 93% yield by the method of Wolff-Kishner as modified by Huang-Minlon.[5] Excess hydrazine hydrate was employed in the reduction to prevent the formation of the epimeric 3-ol compounds.[6]

The product obtained was identical with material obtained from IVa by the procedure of Kagi and Miescher.[2a]

EXPERIMENTAL

3-Ethoxy-3,5-Androstadien-17β-ol (II). Testosterone (100 g., 0.347 mole), 864 ml. of dry benzene, 86.4 ml. of ethyl

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[1] This work was done under Contract #SA-43-ph-1948 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

[2] (a) H. Kagi and K. Miescher, *Helv. Chim. Acta.* **22,** 683 (1939). (b) E. Muller, A. Langerbeck, and H. Neuhoff, *Ber.* **77,** 141 (1944). (c) G. Rosenkranz, St. Kaufmann, and J. Romo, *J. Am. Chem. Soc.* **71,** 3689 (1949).

[3] A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.* **68,** 2097 (1935).

[4] F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.* **81,** 1960 (1959).

[5] Huang-Minlon, *J. Am. Chem. Soc.,* **68,** 2487 (1946).

[6] J. D. Dutcher and O. Wintersteiner, *J. Am. Chem. Soc.,* **61,** 1992 (1939).

orthoformate, 172 ml. of absolute ethanol, and 8.6 ml. of 4*N* ethanolic hydrogen chloride were heated at reflux for 2 hr. The cooled solution was made slightly alkaline by the addition of a solution of sodium methoxide and then washed three times with 500 ml. of water. The dried benzene solution (potassium carbonate) was concentrated *in vacuo.* Residual benzene was removed by flushing *in vacuo* with 100 ml. of absolute ethanol. The crude residue was used without further purification for the next step.

The crude product may be purified by trituration with petroleum ether until crystalline, followed by recrystallization from methanol, m.p. 116–118° (solvated); 132–137° (desolvated). $[\alpha]_D^{23}$ −130° (ethanol).

Anal. Calcd. for $C_{21}H_{32}O_2$ (316.47); C, 79.69; H, 10.19. Found: C, 79.61; H, 9.99.

Semicarbazone of 17β-hydroxyandrostan-3-one (IVb). The crude dienol ether (II) was dissolved in 1875 ml. of absolute ethanol and hydrogenated with 8 g. of 5% palladium-charcoal catalyst under a hydrogen pressure of 40 p.s.i. The theoretical amount of hydrogen (0.347 mole) was absorbed in 10 hr. Hydrogenation was continued for a total of 19 hr., 104% of the theoretical amount of hydrogen being absorbed.

Two hundred milliliters of 2.5*N* hydrochloric acid[7] was added to the hydrogenation solution and the catalyst removed by filtration through a filter aid. The filtrate was refluxed for 20 min. A solution of 50 g. of sodium acetate in 100 ml. of water was added and the mixture stirred at 50–60° for 45 min., and to the warm (50–60°) solution of the steroid was added a warm solution of 37.5 g. (0.5 mole) of semicarbazide in 600 ml. of ethanol. The mixture was allowed to cool slowly to 20° and the filtered semicarbazone was washed with ethanol, then with ether, and dried *in vacuo,* yield 76.7 g. (64% from I), m.p. 249–251° dec., $\lambda_{max}^{CH_3OH}$ 228 mμ, ε 13,400. The melting point, mixed melting point and spectral data agreed with a sample of IVb prepared from authentic IVa.

5α-Androstan-17β-ol (V). Seventy four grams of semicarbazone, (IVb), 520 ml. of diethylene glycol, 52 ml. of 85% hydrazine hydrate, and 49 g. of powdered potassium hydroxide were heated in a round bottomed flask equipped with a thermometer, mechanical stirrer, and a vertical air condenser. The temperature was increased slowly to 200–210° and held at this temperature until the evolution of nitrogen had ceased (approximately 45 min.). The mixture was allowed to cool to 180–190° and poured into a well stirred mixture of 2 l. of water and 2 kg. of ice. The product was filtered and washed with water to neutrality. After drying at 70°, 54.8 g. (93%) of Va were obtained, m.p. 164–166.5. Recrystallization from ethanol and from heptane gave material, m.p. 165.5–166.5, $[\alpha]_D^{24}$ +12 ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{32}O$ (276.45): C, 82.54; H, 11.66. Found: C, 82.48; H, 11.48.

The infrared spectrum in carbon disulfide corresponded favorably with the published spectrum.[8]

5α-Androstan-17β-ol acetate (Vb). Forty-one grams of Va and 185 ml. of acetic anhydride were heated and stirred on the steambath for 1 hr. The hot solution was diluted slowly with water until the excess acetic anhydride was decomposed. More water (total 750 ml.) was then added to precipitate the product. After filtration and drying, the crude acetate was dissolved in ether, treated with charcoal, and the ether removed *in vacuo.* The residue was recrystallized from 110 ml. of methanol to give 43 g. (91%) of Vb, m.p. 81–82.5, $[\alpha]_D^{24}$ +5 ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{34}O_2$ (318.48): C, 79.19; H, 10.76. Found: C, 79.14; H, 10.84.

The physical properties of samples of Va and Vb made via the Clemmensen reduction of IVa[2a] were identical with those reported above.

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(7) The addition of acid before filtration coagulates the catalyst and prevents colloidal catalyst from passing into the filtrate.

(8) K. Dobriner, E. R. Katzenellenbogen, and R. N. Jones, *Infrared Absorption Spectra of Steroids*, Vol. I, Interscience Publishers, Inc., New York 1953, Spectrum No. 29.

Halochromism Studies on Prodigiosin

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Recently it was reported that prodigiosin perchlorate reacts with alcohols[1] causing spectral shifts from 536 to 542 mμ and that the solvent functioned as a Lewis base toward the pigment. During the course of experimentation in this laboratory it was observed that the pigment free base, which was yellow in nonpolar solvents or acetone, became red when shaken with water, acids, or alcohols. When red aqueous pigment solutions were extracted with water-insoluble solvents, the reaction seemed to reverse and the yellow base was extracted into the organic phase. Consequently, a determination of the acid dissociation constant was undertaken in an attempt to resolve this phenomenon. It was found that $K_a = 3.23 \times 10^{-8}$ ($pK_a = 7.51$) at 25°. This would indicate that protonated prodigiosin is about as weak an acid as hydrogen sulfide or hypochlorous acid, but still considerably stronger than water or alcohols whose pK_a values are 16 or greater. The halochromism phenomenon was finally traced to carbon dioxide in the water ($K_a = 3.5 \times 10^{-7}$ for carbonic acid) and to acid impurities in the solvents. Thus, if distilled water is boiled and cooled by passage of pure nitrogen or oxygen gas through it and an acetone solution of prodigiosin is added, there is no color change from yellow to red. If the solution is shaken or if the water is shaken or carbon dioxide passed through before addition of the pigment, the red color forms immediately because of reaction with protons derived from carbonic acid. Moreover, alcohols purified carefully in the usual fashion by drying with aluminum isopropoxide do not cause halochromism when used to dissolve the pigment.

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(1) A. J. Castro, A. H. Corwin, F. J. Waxham, and A. L. Beilby, *J. Org. Chem.*, **24**, 455 (1959).