$\Delta^{1,4}$-androstadien-17β-ol-3-one (IIa)[2e,11] was obtained in 35% yield.

Since the pyrolytic aromatization of IIa to estradiol is well known[2a,b,c] the conversion of Ia to IIa constitutes a simple two step route to this hormone from testosterone.

EXPERIMENTAL

$\Delta^{1,4}$-Androstadien-17β-ol-3-one (IIa) *by selenium dioxide dehydrogenation of testosterone* (Ia). The reaction was run under a variety of conditions and the following experiment describes those under which the best yield of IIa was obtained. Water (0.5 cc.) was added to 1 g. of selenium dioxide and a solution of 1 g. of testosterone in 30 cc. of benzene was added. The mixture was boiled under reflux for 64 hours, the supernatant liquid was decanted, and the inorganic residue was washed with benzene. The combined organic extracts were washed with water, dried, and evaporated. The residue then was chromatographed on 100 g. of neutral alumina. Crystallization of the fractions eluted with benzene-ether (4:1) from acetone-hexane furnished 0.35 g. of $\Delta^{1,4}$-androstadien-17β-ol-3-one (IIa) with m.p. 168–170°, $[\alpha]_D^{29}$ +23° (chloroform), λ_{max} 244 mμ, log ϵ 4.18 (alcohol); reported:[2c] m.p. 168.5–170°, $[\alpha]_D^{29}$ +20° (chloroform), λ_{max} 2.44 mμ, log ϵ 4.19 (alcohol). The m.p. was not depressed on admixture with an authentic sample.

(11) Inhoffen, Zühlsdorff, and Huang Minlon, *Ber.*, **73**, 451 (1940).

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Steroids. LXXVI.[1] Synthesis of Long Chain Carboxylic Acid Esters 17α-Hydroxyprogesterone

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Esters of 17α-hydroxyprogesterone (IV) have recently become of importance in view of the discovery that they possess long acting progestational activity in animals[2a] as well as in the human.[2b] In contrast, free 17α-hydroxyprogesterone shows very little, if any, progestational activity.[2] The esters may be obtained by the esterification of 17α-hydroxyprogesterone (IV),[3] a synthesis of which from Δ^5-pregnene-3β,17α-diol-20-one 3-formate (I) has been reported from this laboratory.[4] This synthesis is well suited for the direct obtention of various esters of 17α-hydroxyprogesterone, without proceeding *via* the free compound. We now describe the extension of the synthesis to the preparation of 17α-hydroxyprogesterone *n*-caproate (IIIa),[2a] enanthate (IIIb),[2a] cyclopentylpropionate (IIIc), and phenylpropionate (IIId).

The C-17 acetylation of Δ^5-pregnene-3β,17α-diol-20-one 3-formate (I) by means of acetic anhydride and *p*-toluenesulfonic acid has been described previously.[4] In the same way treatment of I with caproic anhydride and *p*-toluenesulfonic acid led to the 3-formate 17-caproate (IIa). It was found that this acylation proceeded satisfactorily when carried out with about 2 molar equivalents of the anhydride with benzene (instead of the anhydride) as solvent and in this way a saving of the anhydride was effected. Oppenauer oxidation of the diester IIa resulted in the direct formation of the Δ^4-3-keto system, as described previously,[4,5] and yielded 17α-hydroxyprogesterone caproate (IIIa).[2a] The latter was identical with a sample prepared by the treatment of 17α-hydroxyprogesterone (IV) in benzene with caproic anhydride and *p*-toluenesulfonic acid. This acylation, however, proceeded in less satisfactory yield than did the corresponding acylation of the formate I, probably due to the presence in IV of the Δ^4-3-keto function which to some extent may form the enol ester.

Δ^5-Pregnene-3β,17α-diol-20-one 3-formate (I) was converted to the 17-enanthate (IIb), cyclopentylpropionate (IIc), and phenylpropionate (IId), as described above for the 17-caproate (IIa), by use of the appropriate anhydride. Oppenauer oxidation of these diesters then produced the corresponding esters of 17α-hydroxyprogesterone (IIIb, IIIc and IIId), identified by comparison with samples prepared by the acylation of 17α-hydroxyprogesterone.

EXPERIMENTAL[6]

Δ^5-Pregnene-3β,17α-diol-20-one 3-formate 17-caproate (IIa). A mixture of 5 g. of Δ^5-pregnene-3β,17α-diol-20-one 3-formate (I),[4] 1 g. of *p*-toluenesulfonic acid hydrate, 6.5 g. of *n*-caproic anhydride, and 100 cc. of dry benzene was heated at 80° under anhydrous conditions until a homogeneous solution had resulted. The solution then was allowed to stand for 16 hours at room temperature, poured into ice and water, and the mixture was stirred to effect hydrolysis of the excess anhydride. The product was extracted with ether and the organic extract was washed with sodium hydroxide solution and water. Drying, evaporation, and crystallization of the residue from ether–hexane produced 4.90 g. (77%) of the caproate IIa with m.p. 88–91°. Further crystallization yielded the analytical specimen with m.p. 95–96°, $[\alpha]_D$ −65°.

Anal. Calc'd for $C_{28}H_{42}O_5$: C, 73.32; H, 9.23. Found: C, 73.43; H, 9.53.

17α-Hydroxyprogesterone n-caproate (IIIa) (*a*) *By Oppen-*

(1) Paper LXXV, Ringold, Rosenkranz, and Sondheimer, *J. Org. Chem.*, **21**, 239 (1956).

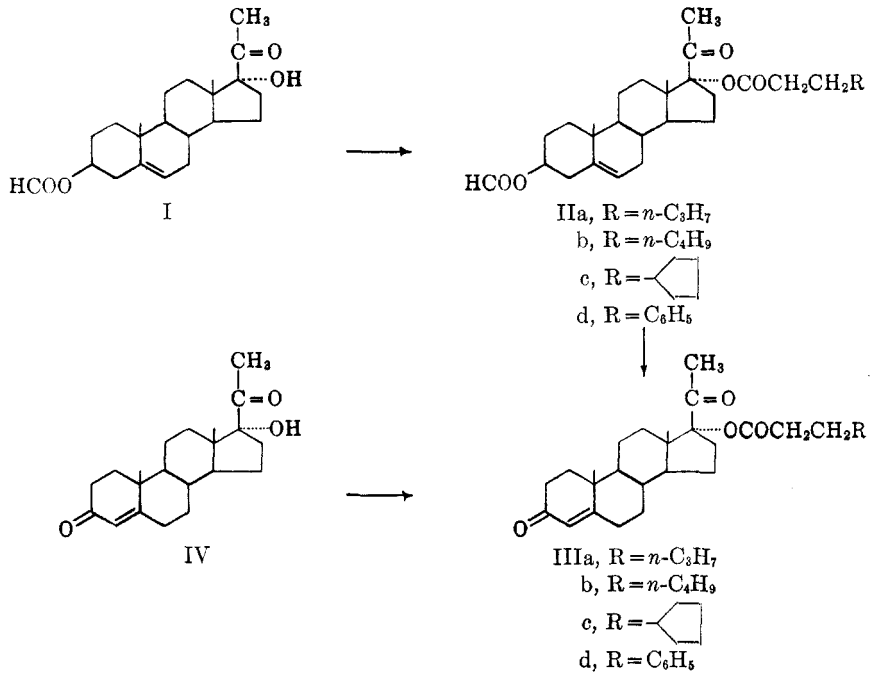
(2) (a) Junkmann, *Arch. exp. Pathol. Pharmakol.*, **223**, 244 (1954); (b) Davies and Wied, *J. Clin. Endocrinol. and Metabolism*, **15**, 923 (1955).

(3) Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953); *cf.* Huang Minlon, Wilson, Wendler, and Tishler, *J. Am. Chem. Soc.*, **74**, 5394 (1952).

(4) Ringold, Löken, Rosenkranz, and Sondheimer, *J. Am. Chem. Soc.*, **78**, 816 (1956).

(5) Ringold, Rosenkranz, and Sondheimer, *J. Am. Chem. Soc.*, **78**, 0000 (1956).

(6) Melting points are uncorrected. Ultraviolet absorption spectra were determined (Beckman D.U. spectrophotometer) in 95% ethanol and rotations in chloroform solution. We are indebted to Mrs. P. Lopez and Miss M. T. Cardenas for these measurements and Mrs. A. Gonzalez for the microanalyses.



auer oxidation of IIa. Aluminum isopropoxide (3 g.) was added to a solution of 3 g. of the caproate IIa in 80 cc. of dry xylene and 30 cc. of dry cyclohexanone and the mixture was boiled under reflux for 45 minutes. Ice and water were added to the cooled reaction mixture which then was distilled in steam to effect removal of the solvents. The resulting solid was collected on Celite and dried. The product was extracted with acetone and was most efficiently purified by chromatography on 100 g. of neutral alumina. The fractions eluted with hexane–benzene (2:3 and 1:4) on crystallization from ether–hexane furnished 1.82 g. (65%) of 17α-hydroxyprogesterone *n*-caproate with m.p. 118–121°. The analytical sample showed m.p. 122–123°, $[\alpha]_D$ +57°, λ_{max} 240 mμ, log ϵ 4.23; reported:[2a] m.p. 120–121°.

Anal. Calc'd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.72; H, 9.18.

(*b*) *By esterification of 17α-hydroxyprogesterone* (IV). A mixture of 3 g. of 17α-hydroxyprogesterone (IV), 4.5 g. of *n*-caproic anhydride, 0.6 g. of *p*-toluenesulfonic acid hydrate, and 100 cc. of dry benzene was heated at 80° until a clear solution was obtained (*ca.* 15 minutes). The solution then was allowed to stand at room temperature for 48 hours and the product was isolated as described above for the preparation of the caproate IIa. Chromatography on alumina and crystallization from ether–hexane produced 2.22 g. (57%) of the caproate IIIa with m.p. 118–120°, $[\alpha]_D$ +58°. The m.p. was undepressed on admixture with a sample prepared by method *a*.

17α-Hydroxyprogesterone enanthate (IIIb). (*a*) *From* Δ^5*-pregnene-3β,17α-diol-20-one 3-formate* (I). The formate I was converted to the 3-formate 17-enanthate IIb in 74% yield as described above for the corresponding 17-caproate IIa, enanthic anhydride being substituted for caproic anhydride. The analytical specimen of IIb exhibited m.p. 90–91°, $[\alpha]_D$ −63°.

Anal. Calc'd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.64; H, 9.29.

Oppenauer oxidation of the mixed diester IIb was carried out as with IIa and resulted in a 62% yield of 17α-hydroxyprogesterone enanthate with m.p. 113–114°, $[\alpha]_D$ +53°, λ_{max} 240 mμ, log ϵ 4.24; reported:[2a] m.p. 114–115°.

Anal. Calc'd for $C_{28}H_{42}O_4$: C, 75.97; H, 9.57. Found: C, 75.65; H, 9.69.

(*b*) *From 17α-hydroxyprogesterone* (IV). The esterification of 17α-hydroxyprogesterone with enanthic anhydride was performed as described above for caproic anhydride. The resulting enanthate IIIb (56% yield) showed m.p. 110–113°, $[\alpha]_D$ +52°. The m.p. was undepressed on admixture with a specimen prepared by method *a*.

17α-Hydroxyprogesterone cyclopentylpropionate (IIIc). This ester was prepared both from Δ^5-pregnene-3β,17α-diol-20-one 3-formate (I) and from 17α-hydroxyprogesterone (IV) as described above for the caproate IIIb and enanthate IIIc, cyclopentylpropionic anhydride being employed. 17α-Hydroxyprogesterone cyclopentylpropionate was crystallized from ether–hexane and showed m.p. 129–130°, $[\alpha]_D$ +47°, λ_{max} 240 mμ, log ϵ 4.23.

Anal. Calc'd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.91; H, 9.38.

17α-Hydroxyprogesterone phenylpropionate (IIId). This ester was prepared both from I and IV as described for the other esters, phenylpropionic anhydride being used. It was crystallized from acetone–ether and exhibited m.p. 151–152°, $[\alpha]_D$ +64°.

Anal. Calc'd for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found: C, 77.91; H, 9.26.

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Ultraviolet Absorption Spectra of Some Alkyl Disulfides and Methyl Trisulfide

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The ultraviolet absorption spectra of the normal alkyl disulfides from methyl through butyl and of methyl trisulfide have been measured in the range 220–320 mμ.

The spectra of ethyl, propyl, and butyl disulfides

(1) Thiokol Corporation Fellow, 1946–1948.