the sodium salt of phosphafluorinic acid crystallized.[9] The salt was removed by filtration and washed with 10 ml. of 10% sodium hydroxide solution. A second crop of the sodium salt could be obtained by evaporating the combined filtrate and washings to 15 ml. In order to isolate the free phosphinic acid, both crops of sodium salt were combined and dissolved in 35 ml. of water, and the solution was filtered from a trace of undissolved material; phosphafluorinic acid separated when the solution was acidified to Congo Red and cooled. The yield was 2.2 g., 41%, m.p. 239–248°. After the acid was twice recrystallized from 95% ethanol, the m.p. was 253–257° and was not changed by further recrystallization. The ultraviolet absorption of the acid was not affected by recrystallization.

Anal. Calc'd for $C_{12}H_9O_2P$: P, 14.33; Neut. equiv., 216.2. Found: P, 14.03; Neut. equiv., 215.5.

Absorption spectra measurements. The ultraviolet absorption spectra were determined in 95% ethyl alcohol by the procedure previously used [*cf.* footnote (b) of Table I].

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(9) The sodium salt of diphenylphosphinic acid does not crystallize from solution under these conditions.

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Steroids. LXXV.[1] Dehydrogenation of Testosterone to $\Delta^{1,4}$-Androstadien-17β-ol-3-one with Selenium Dioxide

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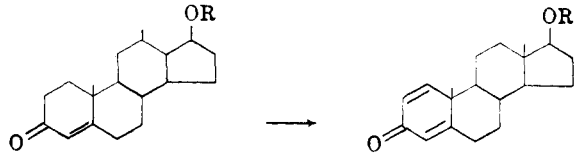
Steroidal $\Delta^{1,4}$-dien-3-ones of type II are of interest since on pyrolysis they yield 19-nor-$\Delta^{1,3,5}$-trien-3-ols of the estrone type[2,3] and they have taken on increased importance within the last year with the discovery that the $\Delta^{1,4}$-dien-3-ones corresponding to cortisone,[4a] hydrocortisone,[4a] and 9-fluoro-hydrocortisone[4b] are considerably more active than the parent hormones. The only known chemical route to such $\Delta^{1,4}$-dienones, until recently, has been one involving the 2,4-dibromination and subsequent dehydrobromination of saturated 3-ketosteroids of the 5α or 5β-configuration.[4b,5] It would be advantageous to prepare the dienones from the corresponding Δ^4-en-3-ones of type I,[6] in view of the ready availability of the latter in most series. Although it is known that the action of manganese dioxide[7] or of *N*-bromosuccinimide followed by collidine dehydrobromination[8] introduces a Δ^6-double bond into Δ^4-3-ones, it has been shown that the desired Δ^1-dehydrogenation may be effected by means of lead tetra-acetate in acetic acid;[9] in this way testosterone acetate (Ib) was converted to $\Delta^{1,4}$-androstadien-17β-ol-3-one acetate (IIb) and progesterone to $\Delta^{1,4}$-pregnadien-21-ol-3,20-dione acetate. Unfortunately the dienones were only by-products, being obtained in yields of 1.5–8%.[9,9a]



Ia, R = H
b, R = Ac

IIa, R = H
b, R = Ac

We have now investigated the action of a number of different dehydrogenating agents on steroidal Δ^4-3-ones, especially on testosterone, (Ia), with the aim of discovering a superior reagent to lead tetra-acetate. Selenium dioxide proved to be such a one and when testosterone was treated with this substance in boiling benzene containing a little water[10]

(1) Paper LXXIV, Ringold, Rosenkranz, and Sondheimer, *J. Am. Chem. Soc.*, **78**, in press (1956).

(2) *Inter al.* (a) Inhoffen and Zühlsdorff, *Ber.*, **74**, 1911 (1941); (b) Inhoffen, *Angew. Chem.*, **59**, 207 (1947); (c) Wilds and Djerassi, *J. Am. Chem. Soc.*, **68**, 2125 (1946); (d) Hershberg, Rubin, and Schwenk, *J. Org. Chem.*, **15**, 292 (1950).

(3) Such aromatic compounds are of use not only as such as estrogenic hormones but also as starting materials for the highly active 19-nor hormone analogs [Birch, *J. Chem. Soc.*, 367 (1950); Wilds and Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953); Djerassi, Rosenkranz, Sondheimer, *et al.*, *J. Am. Chem. Soc.*, **75**, 4440 (1953); **76**, 4092, 6210 (1954); **77**, 148 (1955)].

(4) Bunim, Pechet, and Bollet, *J. Am. Med. Assoc.*, **157**, 311 (1955); Herzog, Nobile, Tolksdorf, Charney, Hershberg, Perlman, and Pechet, *Science*, **121**, 176 (1955); (b) Hirshmann, Miller, Beyler, Sarett and Tishler, *J. Am. Chem. Soc.*, **77**, 3166 (1955); Fried, Florey, Sabo, Herz, Restivo, Borman, and Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(5) *Cf.* footnote 2b for leading references. See also Djerassi and Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); Djerassi and Rosenkranz, *Experientia*, **7**, 93 (1951).

(6) This type of transformation has been carried out microbiologically [Vischer and Wettstein, *Experientia*, **9**, 371 (1953); Fried, Thoma, and Klingsberg, *J. Am. Chem. Soc.*, **75**, 5764 (1953); Vischer, Meystre, and Wettstein, *Helv. Chim. Acta*, **38**, 835 (1955); Nobile, Charney, Perlman, Herzog, Payne, Tully, Jevnik, and Hershberg, *J. Am. Chem. Soc.*, **77**, 4184 (1955)].

(7) Sondheimer, Amendolla, and Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5932 (1953).

(8) Meystre and Wettstein, *Experientia*, **2**, 408 (1946); Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(9) Clarke, Dobriner, Mooradian, and Martini, *J. Am. Chem. Soc.*, **77**, 661 (1955).

(9a) Since this manuscript was prepared, another conversion of Δ^4-en-3-ones to $\Delta^{1,4}$-dien-3-ones by a three step process has been described [Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, *J. Am. Chem. Soc.*, **77**, 4438 (1955).]

(10) The fact that the presence of water was necessary indicates that the dehydrogenating agent is selenious acid rather than selenium dioxide.

$\Delta^{1,4}$-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.