The oily mother liquors (192 mg.) of the above sample were dissolved in 20 ml. of methanol and 2 ml. of dilute sulfuric acid (8.5% v./v.) and refluxed under nitrogen for 1 hr. After working up as described before and purifying chromatographically, 82 mg. of $\Delta^{3,5}$-androstadiene-3-methoxy-7,17-dione (V) was obtained. This was recrystallized from benzene–high boiling petroleum ether and methanol–water for analysis, m.p. 207–208°, $[\alpha]^{24}D$ −379° (*c* 0.94), λ_{max}^{EtOH} 311 mμ (log ε 4.37).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.55; H, 8.57.

Admixture of this compound with V, obtained from II, did not depress the melting point.

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[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH]

The Partial Degradation and Reconstitution of the "A" Ring of Estradiol[1]

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The ozonization of 19-nortestosterone-17-acetate produced the corresponding keto acid which was cyclized to the enol lactone. The latter was treated with methylmagnesium iodide and recyclized to 19-nortestosterone, purified as its 17-acetate. The aromatization into estradiol was accomplished with the use of N-bromosuccinimide, thereby providing a method for the preparation of the female sex hormone labeled at C_4.

At the present time, estrogen metabolism is not well defined. The studies using estrone-C_{16}^{14} have indicated that the "D" ring is partially destroyed. This is evidenced by the observation that of the total recovery of radiocarbon (45%), only *ca.* 4.5% was extractable with ether, the remainder being respiratory (2.4%) and water-soluble metabolites, the latter being presumably of low molecular weight.[2] Possible metabolites resulting from a complete saturation of the aromatic nucleus have been reported as being present in human non-pregnancy urine.[3] The desirability of an "A" ring labeled estrogen led to the investigation of various methods commonly used to aromatize the steroids containing the 1,4-dien-3-one structure in the "A" ring.[4] Since this approach seemed to be of little value, it was abandoned when 19-nortestosterone (IVa) became readily available by the Birch reduction of estradiol-3-ethers.[5] Methods for the incorporation of isotopic carbon into the "A" ring of the non-aromatic steroids have been well described[6,7] and it was assumed that IVa would behave in a similar manner since its stereochemistry at C_{10} is similar to that of testosterone.[5] With a new carbon at C_4, the objective could then be reached by aromatization of IV into estradiol (Ia).

The Wilds–Nelson procedure for the preparation of IVa[5] was modified slightly so that the steroid (Id) was added to the ether–ammonia–lithium mixture. Similar yields of the dihydro compound IId were obtained and an additional safety factor was introduced inasmuch as the most valuable component was added last.[8] The non-conjugated ketone IIIa and the conjugated ketone IVa were prepared and a number of derivatives of the latter examined. It has been noted that attempts to prepare the 17-propionate of IVa resulted in a mixture of mono and di(enol) acylation.[5] Direct acetylation of IVa gave a high yield of IVb; the latter was also obtained by partial saponification of the enol diacetate VIIIc. Ozonization of the 17-acetate IVb, 17-*p*-nitrobenzoate IVf and the 17-benzoate IVe gave the crystalline keto acids (Vb, f and e), respectively. Refluxing the keto acids with acetyl chloride gave the pseudo acid chlorides (VIb and e), only that of the 17-benzoate being a fairly stable solid. The infrared spectrum of the latter indicated a peak at 13.37μ which has been ascribed to structures of this type.[6] The enol lactone of the 17-benzoate VIIe was prepared by dehydrochlorination of VIe in refluxing collidine. One of the corresponding enol lactone-17-acetates VIIb was prepared by refluxing the keto acid Vb with acetic anhydride in the presence of anhydrous sodium acetate[9] to give a product which could be crystallized to a sharp melting (129–130°) solid exhibiting $[\alpha]^{25}D$ −37.9°.

Another isomer was obtained when prepared from Vb as described for testosterone.[6] This isomer was difficult to obtain in good yields and could

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(2) R. D. H. Heard, *et al.*, "Recent Progress in Hormone Research," Vol. IX, Academic Press, New York, N. Y., 1954, p. 383.

(3) R. E. Marker, E. Rohrmann, E. L. Wittle and E. J. Lawson, THIS JOURNAL, **60**, 1901 (1938).

(4) A. S. Dreiding and A. Voltman, *ibid.*, **76**, 537 (1954); and previous papers referred to therein.

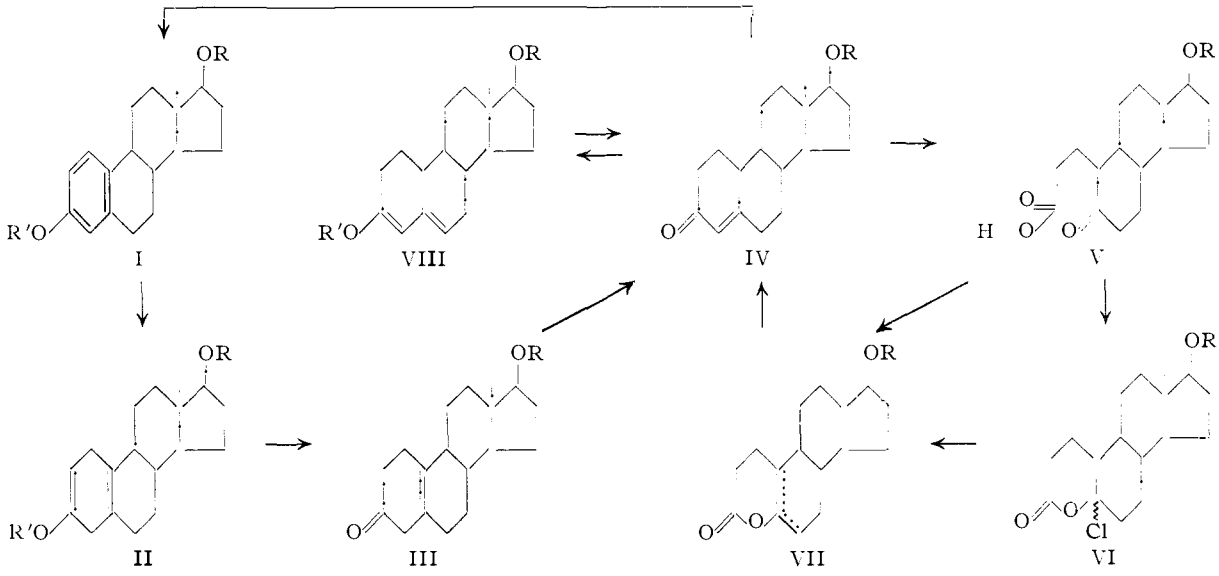
(5) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953). A superior method is described using estradiol-3-methyl ether in ether–liquid ammonia and lithium metal. The original method as described by A. J. Birch, *J. Chem. Soc.*, 2531 (1949), gives low yields.

(6) R. B. Turner, THIS JOURNAL, **72**, 579 (1950).

(7) (a) G. Fujimoto, *ibid.*, **73**, 1856 (1951); (b) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951).

(8) This modification was also used in the reduction (89% yield) of estrone-3-methyl ether-17-dioxalane.

(9) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).



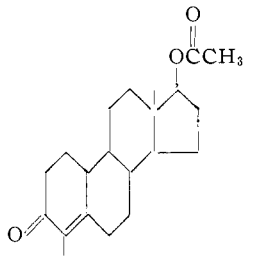
a, R′ = R = H
b, R′ = H, R = CH_3CO
c, R′ = R = CH_3CO
d, R′ = CH_3, R = H
e, R = C_6H_5CO
f, R = p-$NO_2C_6H_4CO$
g, R = H, R′ = 1-glyceryl
h, R′ = CH_3CO, R = C_6H_5CO

not be brought to a sharp melting point, 138–141°, $[\alpha]$ D +57.0°. The elemental analysis and infrared spectrum of this isomer excluded the possibility of its being the mixed anhydride suggested in similar examples.[9] The assignment of the position of the double bond in these two isomers might tentatively be assigned on the basis of M_D values. The change in M_D from the parent ketone to the corresponding enol lactone in the testosterone and cholestenone series (double bond fixed at 5,6-position) is of a large negative magnitude. In the lower melting form of VIIb, described above, the change in M_D is of a comparable value after taking into account the lower initial M_D value of IVb and hence resembles those compounds containing an angular methyl group. The higher melting form of VIIb shows only a small and positive change in M_D, indicating that the double bond may be in the 5,10-position in this isomer. Some support for this may be found in the fact that those compounds having a 5,10-double bond all exhibit a greater positive rotation than their isomers containing a double bond in the 4,5- or 5,6-position.[5,10] The enol lactone derived by dehydrochlorination of the psuedo acid chloride VIe showed a change in M_D, again in the negative direction, but only about one third that shown by comparison with the M_D values of testosterone-17-benzoate to enol lactone-17-benzoate, even after adjustment for the M_D differences of the starting ketones. Some additional supporting evidence may be found in a comparison of the infrared spectra of the two isomers of VIIb. The lower melting form of VIIb exhibits a maximum at 5.91μ (enolic double bond) and is similar to the spectrum of the enol lactone derived from testosterone. The higher melting form of VIIb does not show this peak. This is in agreement with the spectra of the corresponding model bicyclic compounds IX and X, the former containing no angular methyl group and the enolic double bond peak 5.99μ being just barely perceptible. The contribution of this chromophore to the spectrum of the steroid is perhaps too small to be visible. In X the maximum at 5.92 μ is quite pronounced and its intensity is *ca.* $^2/_3$ that of the adjacent carbonyl peak at 5.69 μ. The infrared spectrum of the enol lactone-17-benzoate VIIIe in the 5.9–6.0 μ region is overshadowed by the strong benzoyl absorption at 5.86 μ.

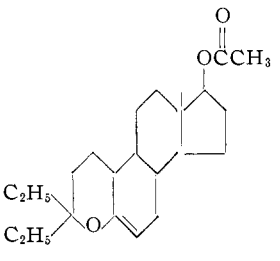
The incorporation of a new carbon atom was first approached by attempting the Claisen condensation between VIIe and phenyl acetate.[6] This proved unfruitful in our hands, only once was the 2-acetyl derivative of VIIe obtained and then in a low yield. VIIe proved to be too insoluble in benzene or benzene–ether for the introduction of a carbon atom by means of the Grignard reaction[7] to carry out the reaction. The corresponding 17-acetate VIIb (low melting isomer), when treated with one equivalent of methylmagnesium iodide, treatment with base, reacetylation and chromatography gave a 22% yield of IVb. An additional 41% was recovered as the 17-hydroxy keto acid (Va). Some insight into the nature of one other product from this reaction, commonly referred to as overreacted material,[9] was obtained when the ethyl Grignard was used. In this latter case, 4-methyl-19-nortestosterone-17-acetate (XI) was obtained as the desired product (21% yield) and an equal amount of material which, after purification, gave an elemental analysis and infrared spectrum best interpreted as fitting the structure XII, a maximum at 5.94 μ placing the double bond at the 5,6-position.

The aromatization of IVb into estradiol-17-acetate (Ib) was effected by the use of N-bromo-

(10) J. A. Hartman, THIS JOURNAL, **77**, 5151 (1955).



XI



XII

succinimide in refluxing carbon tetrachloride and catalyzed by a photoflood lamp. This is analogous to the aromatization of cyclohexenone as described earlier.[11] Since IVb contains two allylic hydrogens, some bromination at C_6 might be expected and spectroscopic evidence for some 6-dehydroestradiol was found. Catalytic hydrogenation of the reaction mixture and purification by chromatography gave Ib whose ultraviolet and infrared spectra were identical with those of an authentic sample.

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Experimental[12]

Modification of the Wilds–Nelson Procedure[5] for the Birch Reduction.—To a stirred mixture of 500 cc. of dry ethyl ether and 1 liter of liquid ammonia was added 20 g. of short pieces of lithium wire which had just been previously washed with dry benzene and then twice with dry ether. A solution containing 18.8 g. of estradiol-3-methyl ether (Id) in 200 cc. of dry ether was added dropwise, with stirring, over a period of 20 minutes. The dropping funnel and side of the flask were washed down with an additional 150 cc. of ether and after 30 minutes the mixture was decomposed by the dropwise addition of 210 cc. of absolute ethanol, requiring an additional 90 minutes. Evaporation of the ammonia followed by the careful addition of 800 cc. of water, separation, ether extraction, combination of the organic solutions, drying and concentration gave the crude dihydro product IId which was recrystallized from 150 cc. of cyclohexane to give soft plates, m.p. 99–104°; yield 17.0 g. (90%). A second crop weighed 0.42 g. (2%), m.p. 102–106° (reported[5] m.p. 105–113° in open capillary).

The *p*-nitrobenzoate crystallized from alcohol–acetone as colorless plates, m.p. 187–190°; λ_{max}^{alc} 256 mμ, ε 14,980 (isolated *p*-nitrobenzoate absorption).

Anal. Calcd. for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.79; H, 7.26; N, 3.33.

The presence of a **3-deoxy** compound was indicated as follows: the crude product from the reduction of 2 g. of Id was cleaved and isomerized with hydrochloric acid and converted into the *p*-nitrobenzoate. This derivative IVf was largely removed by crystallization and upon chromatography of the gummy residue on alumina, the benzene–petroleum ether (7:3) eluates gave 55 mg. of a new compound, m.p. 138–140°; λ_{max}^{alc} 259 mμ, ε 12,100.

Anal. Calcd. for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.06; H, 7.57; N, 3.62.

The reduction of estradiol-3-(1-glyceryl)-ether (Ig) under these conditions gave a 10–20% yield of **1,4-dihydro-17β-estradiol-3-(1-glyceryl)-ether** (IIg). It was recrystallized from absolute ethanol as short needles, m.p. 187.6–189.6°; λ_{max}^{Nujol} 5.89 μ (enol ether).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.37; H, 9.26. Found: C, 72.67; H, 9.24.

17β-Hydroxy-5(10)-estrene-3-one (IIIa).—The reported method[5] for the hydrolysis of IId with oxalic acid was found to be reproducible in our hands and the following was also found to give good results. To 0.20 g. of III in 20 cc. of methanol was added dropwise with swirling 0.20 cc. of glacial acetic acid in 3 cc. of water whereupon a transitory turbidity was produced and the mixture was then allowed to stand for 22 hr. under nitrogen. After pouring into 25 cc. of half saturated salt solution it was extracted three times with ether and the combined ethereal solutions were washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried with magnesium sulfate and on concentration with petroleum ether the ketone crystallized as fine needles, m.p. 185–194°; yield 0.124 g. A second crop of 0.020 g., m.p. 174–181°, raised the yield to 76%. The melting points of the crystalline materials are not a good indication of purity as the reported value was obtained under elaborate precautionary conditions. A more reliable criterion of purity was the rotation of a well mixed sample of the two solid crops which exhibited $[\alpha]^{27}D$ +182.7° (reported[5] m.p. 199.8–201°; $[\alpha]^{22}D$ +189.8°).

The non-crystalline residue (0.031 g., representing approx. 16%) showed only a general background absorption from 210–290 mμ, indicating that these reaction conditions were not strong enough to shift the double bond into conjugation.

The lithium aluminum hydride reduction of this ketone was reported earlier.[10]

17β-Hydroxy-4-estrene-3-one (19-Nortestosterone) (IVa).—A satisfactory method for the preparation of IVa has been described previously.[5] When 35.4 g. of IId was dissolved in 1.5 l. of dry ether and then 100 cc. of 25% hydrochloric acid, previously chilled to 0°, was added with stirring, a straw colored aqueous layer resulted. After 15 minutes of additional stirring, 250 g. of ice was added which decolorized the solution and the product was transferred back into the ether. Washing, drying and concentration with petroleum ether gave a 75% yield of crystalline IVa plus an additional 18% yield of non-crystalline material whose spectrum indicated a 36% content of IVa (part of this may be recovered as the enol diacetate or benzoate).

The crude **17-benzoate IVe** was prepared in pyridine with benzoyl chloride and was formed in a quantitative yield, m.p. 160–170°. Recrystallization from ether gave stout tan needles, m.p. 173–175.2° and not raised by further crystallization. This material is a mixture as judged by its spectrum which exhibits a pronounced inflection at 238 mμ. Chromatography of the crude benzoate on alumina gave the pure derivative as colorless stout needles, eluted and recrystallized with ether, m.p. 178.4–180.6° (reported[13] m.p. 180°); λ_{max}^{alc} 235 mμ, ε 29,450; $[\alpha]^{27}D$ +97.3°, M_D 368.7°.

The **17-*p*-nitrobenzoate** (IVf), prepared in a similar manner, was crystallized from ethanol as short stout pale yellow needles, m.p. 198.8–199.8°; λ_{max}^{alc} 244 mμ, ε 23,000.

Anal. Calcd. for $C_{25}H_{29}NO_5$: C, 70.89; H, 6.90; N, 3.31. Found: C, 71.25; H, 7.00; N, 3.70.

The **17-hexahydrobenzoate** was crystallized from aqueous methanol as needles, m.p. 90–91°.

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 78.12; H, 9.65.

The **3-oxime** was formed by dissolving IVa in a little alcohol and adding aqueous hydroxylamine, m.p. 113–123°. Recrystallization from 50% ethanol, ether–petroleum ether and then ethyl acetate–petroleum ether gave an analytical sample, as a hydrate, in the form of stout needles, m.p. 183.6° dec.; λ_{max}^{alc} 244 mμ, ε 12,100.

Anal. Calcd. for $C_{18}H_{27}NO_2.H_2O$: C, 70.31; H, 9.51; N, 4.55. Found: C, 70.48; H, 9.57; N, 4.76.

The **3,17β-diacetoxy-Δ^{3,5}-estradiene** (VIIIc) (enol diacetate of IV) was prepared by refluxing IVa with equal volumes of acetic anhydride and acetyl chloride under nitrogen overnight. Removal of the solvents *in vacuo* gave a gum which was crystallized from petroleum ether and gave colorless

(11) M. Mousseron and G. Manon, *Compt. rend.*, **227**, 533 (1948).

(12) The melting points are not corrected. Analyses by Micro-Tech Laboratories, Skokie, Ill. Optical rotations were determined in chloroform in a one decimeter tube at a concentration of 1 unless otherwise noted. Infrared spectra were run in chloroform unless otherwise noted.

(13) A. J. Birch, *Chem. and Ind.*, 616 (1951).

plates, m.p. 170–174°. Crystallization from ethanol gave needles, m.p. 170–174° not raised by further crystallizations; λ_{max}^{alc} 234 mμ, ε 21,000; $[\alpha]^{24}D$ −151.2°, M_D −541° (*c* 1.02, chf.).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 73.71; H, 8.70.

This procedure could be used to recover part of the non-crystalline IVa from the cleavage and isomerization experiments.

The sodium borohydride reduction of this material has been reported elsewhere.[10]

The **3-acetoxy-17β-benzoyloxy-Δ^{3,5}-estradiene** (VIIIh) was prepared in a similar manner from IVe in a 73% yield. Crystallization from petroleum ether and then isopropyl ether–petroleum ether gave clusters of short fine needles, m.p. 130.2–133.2°; λ_{max}^{alc} 231 mμ, ε 18,390.

Anal. Calcd. for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.29; H, 8.04.

19-Nortestosterone-17-acetate (IVb). (a).—Direct acetylation was accomplished by allowing 26.5 g. of IVa to stand overnight (room temperature) in 200 cc. each of acetic anhydride and dry pyridine. The solvents were removed at 0.1 mm. with just enough warming to keep the mixture at room temperature. The final traces of solvents were removed by slightly warming and, after seeding, the residual gum solidified. After trituration with a little petroleum ether, the material was crystallized from 525 cc. of petroleum ether and 125 cc. of dry ethyl ether by concentration to *ca.* 300 cc. and seeding. The first crop was obtained as nearly colorless needles, m.p. 90–91°; yield 25.3 g. (83%). A second crop from the mother liquors weighed 2.03 g. (7%) and melted at 89–90°. An additional 0.85 g. (2.5%) of less pure material was obtained by further concentration, m.p. 80–89°. The analytical sample was recrystallized from petroleum ether to give clusters of stout needles, m.p. 92.0–93.0°; λ_{max}^{alc} 240 mμ, ε 18,100; $[\alpha]^{24}D$ +43.8°, M_D +138.4°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.13; H, 9.14.

(b).—From the enol diacetate; a solution of 0.20 g. of VIIIc in 40 cc. of ethanol was partially saponified by the addition of 4.35 cc. of 0.12 *N* sodium hydroxide solution and after 35 minutes the solution was neutral to phenolphthalein. Concentration to *ca.* 5 cc., dilution with water and ether extraction gave a gummy residue which was taken up in petroleum ether and chromatographed on alumina. The benzene–ether and finally ether eluates gave a mixture of solids and gums which on recrystallization from petroleum ether gave IVb as clusters of plates, m.p. 92°; yield 0.073 g. A second crop of needles, m.p. 89°, raised the yield to 54% of crystalline solids.

The lithium aluminum hydride reduction products of IVb were reported earlier.[10]

The **3-oxime** of IVb was recrystallized from aqueous ethanol as short fine needles, m.p. 204.2–205.4°; λ_{max}^{alc} 240 mμ, ε 18,390.

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.52; H, 8.82; N, 4.23. Found: C, 72.21; H, 8.95; N, 4.16.

Attempts to aromatize this oxime were unsuccessful.[14]

Aromatization of 19-Nortestosterone-17-acetate (IVb) with N-Bromosuccinimide.—A 0.10-g. (1.8 equivalents) portion of recrystallized N-bromosuccinide was crushed under 25 cc. of dry carbon tetrachloride, 0.10 g. of IVb added, the system flushed with nitrogen and then refluxed for three minutes to bring all the material into solution. This refluxing mixture was exposed to the light from a photoflood lamp and after 20 seconds the mixture discolored slightly and then again became colorless. An additional 10 seconds of exposure was followed by three minutes of refluxing and then cooling. Upon opening the flask a fuming gas was evolved, acid to congo paper. The mixture was washed with saturated bicarbonate solution, filtered through magnesium sulfate and stripped by aspiration to a tan foamy solid. This product was taken up in 15 cc. of ethanol and hydrogenated at atmospheric pressure with 15 mg. of Adams catalyst. Previous experiments with these quantities of reactants showed that the crude aromatization mixture exhibited maxima at 260 and 280 mμ, the former being removed on hydrogenation and indicative of a Δ^6-dehydroestradiol structure. After separation of the catalyst, the solution was diluted with *ca.* 100 cc. of water and the product taken up in ether which on concentration gave 0.110 g. of a foamy solid. Chromatography from 4 g. of silica gel, prepared with benzene returned 0.010 g. of a gum in 75 cc. of eluate of the same solvent. The following 100 cc. of 2.5% ether in benzene returned 0.060 g. (60%) of estradiol-17-acetate (Ib) as a colorless solid whose infrared and ultraviolet spectrum were identical with an authentic sample. The melting point, 204–209°, was not depressed by admixture with an authentic sample.

Further elution with 50 cc. of 10% ether in benzene gave an additional 0.012 g. of a non-crystallizable product.

When a lesser amount of N-bromosuccinimide was employed (1.1 molar equiv.) and the crude reaction mixture concentrated, after filtration of the succinimide, it was possible to obtain direct yields of up to 47% of Ib. Under these conditions the crude product exhibited no absorption maxima in the 240 or 260 mμ region indicating the original chromophore IVb had been destroyed and that very little, if any Δ^6-dehydroestradiol-17-acetate was present. Further attempts to purify the non-crystalline residues by treatment with alkali gave solid material whose ultraviolet spectrum was identical with estradiol. However, the melting points of these products could not be brought up to that of Ia.

Ozonization of 19-Nortestosterone-17-acetate (IVb).—A solution of 5.0 g. of IVb in 125 cc. of ethyl acetate and 25 cc. of glacial acetic acid was ozonized (3 molar equivalents) at a bath temperature of −11°. After adding 5 cc. of acetic acid, 10 cc. of water and 2 cc. of 30% hydrogen peroxide, the mixture was allowed to digest overnight at room temperature. The solution was concentrated, at reduced pressure, to about 60 cc., 250 cc. of water was added and the product was extracted into ether. The combined ethereal solutions were washed with water and extracted with 70-cc. portions of ice-cold 2% sodium hydroxide followed by quick acidification in the cold with concentrated hydrochloric acid. The first two extracts gave no product due to unremoved acetic acid. The third extract yielded **17β-acetoxy-5-keto-3,5-seco-4-estrane-3-oic acid (Vb)** as a gum which, after chilling on Dry Ice and rubbing, solidified, m.p. 70–85°; yield 3.65 g. (68%). The following two extracts also afforded solid keto acid which melted at room temperature but solidified on trituration with petroleum ether to give an additional 0.49 g. (9%) of m.p. 60–80°. The analytical sample was crystallized twice from aqueous methanol to give clusters of colorless blades, m.p. 113–115°; $[\alpha]^{28}D$ −4.08°, M_D 13.7°.

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.38. Found: C, 67.58; H, 8.47.

Ozonization of 19-Nortestosterone-17-benzoate.—A solution of 0.10 g. of IVe in 10 cc. of a 1:1 mixture of ethyl acetate and acetic acid was ozonized as above. The colorless ozonide was brought to room temperature, treated with 1 cc. of 30% hydrogen peroxide, refluxed two hours and concentrated. The clear thick residual gum was desiccated overnight with potassium hydroxide and after trituration with ether gave the **17β-benzoyloxy-5-keto-3,5-seco-4-estrane-3-oic acid (Ve)** as a monohydrate, m.p. 161–163°; yield 0.042 g. (40%). Recrystallization from ether and then acetone gave the analytical sample as colorless needles, m.p. 164.8–165.4°. An unsuccessful attempt to crystallize this material has been reported.[13]

Anal. Calcd. for $C_{24}H_{30}O_5 \cdot H_2O$: C, 69.21; H, 7.75. Found: C, 69.39; H, 7.67.

On a larger scale, the crude keto acid was obtained in a 79% yield and was used as described below.

Ozonization of 19-Nortestosterone-17-*p*-nitrobenzoate.—A 0.20-g. sample of IVf was ozonized in a manner similar to that of the 17-acetate as described above. The crude keto acid was obtained as a colorless solid, m.p. 151–156°; yield 54%. After three crystallizations from ether–petroleum ether the analytical sample of **17-*p*-nitrobenzoyloxy-5-keto-3,5-seco-4-estrane-3-oic acid** was obtained as cream colored needles, m.p. 165.5–167.0°.

Anal. Calcd. for $C_{24}H_{29}NO_7$: C, 64.99; H, 6.59; N, 3.16. Found: C, 65.03; H, 6.96; N, 3.23.

17β-Acetoxy-5-chloro-3-keto-4-oxaestrane (VIb).—After refluxing 3.65 g. of the crude solid keto acid Vb with 20 cc. of acetyl chloride for 1 hour, the solvents were removed and the residual brown gum, 3.61 g., triturated with ether and petroleum ether to give 2.11 g. (62%) of VIb, m.p. 110–124°. Two crystallizations from ether and one from isopropyl ether gave VIb as light brown prisms, m.p. 131–132° dec.;

(14) F. M. Beringer and I. Ugelow, THIS JOURNAL, **75**, 2635 (1953).

$[\alpha]^{27}D$ +16.3°, M_D +57.8° (freshly prepared sample). This material slowly decomposed evolving hydrogen chloride, and consequently a satisfactory analysis could not be obtained.

17β-Benzoyloxy-5-chloro-3-keto-4-oxaestrane (VIe).—When 1.86 g. of the crude keto acid benzoate Ve was warmed with acetyl chloride, followed by chilling, the pseudo acid chloride yield was 0.70 g. (36%). Reworking the mother liquors gave an additional 0.46 g. to give a total yield of 60%. Recrystallization from acetone gave plates, m.p. 184.2–186.2° dec. This was much more stable than the corresponding 17-acetoxy derivative described above.

Anal. Calcd. for $C_{24}H_{29}ClO_4$: C, 69.13; H, 7.01. Found: C, 69.12; H, 7.32.

17β-Benzoyloxy-5-hydroxy-3,5-seco-4-nor-5(x)-estrene-3-oic Acid 3,5-Lactone (Enol Lactone Benzoate) (VIIe).—A mixture of 30 cc. of purified collidine and 1.30 g. of VIe was refluxed for 30 minutes and the resulting brown solution was diluted with ice, neutralized with hydrochloric acid, extracted into ether, washed with more acid, saturated bicarbonate solution, saturated salt solution, and dried with magnesium sulfate. Concentration gave VIIe as fine needles, m.p. 150–160°; yield 0.60 g. (51%). A second crop, m.p. 153–157°, weighed 0.16 g. to raise the yield to 64%. Recrystallization from ether gave long colorless needles, m.p. 164.8–167.0°; $[\alpha]^{27}D$ +71.2°, M_D 270°; λ^{ale}_{max} 230, 270 inf. and 278 inf. mμ, ε 15,790, 1050 and 790.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 76.07; H, 7.48.

The **2-acetyl** derivative was obtained, in a non-reproducible experiment, according to Turner[6] in a 30% crude yield, m.p. 154–174°. (Purple color with $FeCl_3$.) Recrystallization from methylene chloride–methanol and then acetone gave needles, m.p. 168–171°; λ^{ale}_{max} 230 and 280 mμ, ε 30,570 and 6,370.

Anal. Calcd. for C, 73.91; H, 7.16. Found: C, 73.72; H, 7.44.

17β-Acetoxy-5-hydroxy-3,5-seco-4-nor-5-estrene-3-oic Acid 3,5-Lactone (Enol Lactone Acetate) (VIIb).—A mixture of the crude keto acid Vb (m.p. 70–85°) and 15 cc. of redistilled acetic anhydride was refluxed under nitrogen for 90 minutes. After the addition of 0.10 g. of anhydrous sodium acetate and an additional three hours refluxing, the volatile components were removed *in vacuo* to give a yellow mixture. The steroid was taken up in ether, separated from the sodium acetate by filtration, and crystallized by concentration with petroleum ether to give VIIb as stout prisms, m.p. 126–127°; yield 0.63 g. (66.5%). A second crop, m.p. 123–125°, added an additional 18%. A third crop was evidently a mixture, m.p. 125–134°; 0.067 g. Recrystallization from ether–petroleum ether, acetone and then ether gave stout tan needles, m.p. 129.6–130.6°. Recrystallized from absolute ethanol it was obtained as colorless plates, m.p. 129–130°; $[\alpha]^{25}D$ −37.9°, M_D −120.5°; λ_{max} 5.74, 5.78 and 5.92 μ.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.70; H, 8.54.

The preparation of VIIb using a mixture of acetic anhydride and acetyl chloride[6] always gave a gummy product which was difficult to obtain crystalline and in poor yields (25–35%). This form of VIIb could not be purified to a sharp melting point. The analysis seems to exclude the possibility that this material is a mixed anhydride. Treatment of the non-crystalline portion with fresh acetic anhydride and anhydrous sodium acetate did not yield additional crystalline material.[9] The analytical sample was crystallized from ether and petroleum ether to give needles, m.p. 138.4–141.6°; $[\alpha]^{20}D$ +57.0°, M_D +180.5°; λ_{max} 5.71 and 5.77 μ (no absorption visible at 5.92 μ as above). The spectrum of the corresponding enol lactone-17-acetate from testosterone shows maxima at 5.75 and 5.90 μ.

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 72.67 and 70.66; H, 8.74 and 8.26.

Methyl Grignard Reaction on the Enol Lactone-17-acetate (VIIb).—To a solution containing 0.170 g. (0.54 mmole) of VIIb (m.p. 126–128° in 10 cc. of ether–benzene (1:1) under nitrogen and at ice-bath temperature, was added dropwise 1 cc. of an ethereal solution containing 0.53 mmole of methylmagnesium iodide. The light yellow precipitate was stirred for one hour at the same temperature and the mixture was then decomposed with hydrochloric acid (10%) and the products taken up in ether. After washing with 0.5 *N* thiosulfate, saturated sodium bicarbonate, saturated sodium chloride, drying and concentration, the residual gum (0.196 g.) containing the adduct was cyclized and saponified under nitrogen at 5° by taking up in 5 cc. of methanol and 1 cc. of 25% sodium hydroxide. After neutralization to *p*H 6 with acetic acid and dilution with 15 cc. of half saturated salt solution, the product was taken up in ether and separated into neutral and acidic fractions by washing with 10% sodium carbonate. The neutral fraction after concentration weighed 0.055 g. and its spectrum indicated a 71% content of IVa. Conversion to the acetate and chromatography gave 0.037 g. (22%) of IVb, eluted with benzene and benzene–ether; m.p. 90–91°.

Acidification of the alkaline extracts above and extraction with methylene chloride gave 0.065 g. (41%) of the **17β-hydroxyketo acid Va**. Recrystallization from acetone–petroleum ether gave very small cubes, m.p. 159.2–160.6°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 69.36; H, 8.90. Found: C, 69.45; H, 8.86.

Use of the higher melting isomer reported above gave similar results except that the yield was only *ca.* 12% on IVb.

Ethyl Grignard on Enol Lactone-17-acetate (VIIb).—In a similar manner, 0.500 g. of VIIb (m.p. 130–135°) was treated with two equivalents of ethylmagnesium iodide and carried through in a similar manner excepting that sodium ethoxide was used to cyclize the intermediate. The recovery of acidic material was 36% and the neutral fraction weighed 0.352 g. Acetylation of the neutral, as above, and chromatography from 16 g. of alumina gave two products. Elution with petroleum ether returned no material (4 × 25 cc.). Fractions 5–10, eluted with petroleum ether–benzene (1:1) gave 0.154 g. (27%) of XII as a gum whose purification is given below. Fractions 13–17, eluted with benzene–ether (1:1) gave 0.074 g. (21%) of XI which was recrystallized from ether–petroleum ether to give **4-methyl-19-nortestosterone-17-acetate (XI)** as short fine needles, m.p. 121.4–123.0°; $[\alpha]^{28}D$ +38.0°, M_D +125.5°; λ^{ale}_{max} 249 mμ, ε 15,300.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.09; H, 9.09.

Further elution with ether and finally with 10% ethyl acetate gave *ca.* 20 mg. of some uncharacterized material.

Attempts to aromatize XI with N-bromosuccinimide have been inconclusive.

The purification of XII was accomplished by combining with material obtained in a duplicate experiment, rechromatography from alumina and elution with the same solvent mixture used initially. The gummy solid was rubbed with a little acetone while chilling on a cake of Dry Ice to give **17β-acetoxy-3,3-diethyl-4-oxa-5-estrene (XII)** as a soft solid, m.p. 80–84°. Two crystallizations from methanol gave short prisms, m.p. 87.0–88.4°; λ_{max} 5.76 and 5.94 μ.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 76.61; H, 10.06. Found: C, 76.63; H, 10.03.

DETROIT 1, MICHIGAN