and crystallization of the fractions eluted with benzene–ether (1:1 and 1:3) from acetone–hexane furnished 0.58 g. (13%) of the diacetate IIIb as large shiny plates with m.p. 213–217° (Kofler, finely ground). The analytical sample was crystallized from acetone–ether or methanol and exhibited m.p. 218–220° (Kofler, finely ground), $\lambda_{max.}$ 237 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1686 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01. Found: C, 64.79; H, 7.16.

Δ⁴-Pregnene-2α,17α,21-triol-3,11,20-trione (2α-Hydroxycortisone) (IVb).—A solution of 152 mg. (2.5 equivalents) of potassium hydroxide in a few drops of water was added to a suspension of 500 mg. of the diacetate IIIb in 40 cc. of ice-cold methanol and the mixture was stirred at room temperature for 1 hour under nitrogen. The resulting solution was acidified with 1 cc. of acetic acid and evaporated to dryness under vacuum. The residual oil was diluted with saturated ammonium chloride solution, the product was extracted with chloroform and chromatographed on 25 g. of silica. The solid fractions eluted with ethyl acetate on crystallization from acetone–ether afforded 185 mg. of 2α-hydroxycortisone as small plates with m.p. 234–236° (introduced at 220°), $[\alpha]_D$ +202°, M_D +760, $\lambda_{max.}$ 237 mμ, log ε 4.21, ν_{max}^{mull} 1700 and 1670 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.42; H, 7.61.

Δ⁴-Pregnene-2α,17α,21-triol-3,11,20-trione (2α-Hydroxycortisone) Triacetate (VIb).—A solution containing 1.3 g. of cortisone 17,21-diacetate (Vb)[6] and 2.2 g. (1.5 equivalents) of lead tetraacetate (90% pure) in 50 cc. of C.P. acetic acid and 0.8 cc. of acetic anhydride was heated on the steam-bath for 5 hours. Addition of water, isolation with ether, crystallization of the product from acetone–hexane and chromatography of the mother liquors on alumina furnished a total of 0.33 g. (22%) of the triacetate VIb with m.p. 231–233°. The analytical specimen showed m.p. 243–244°, $[\alpha]_D$ +103°, M_D +517, $\lambda_{max.}$ 237 mμ, log ε 4.21, $\nu_{max}^{CHCl_3}$ 1736, 1718, 1700 and 1686 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{27}H_{34}O_9$: C, 64.53; H, 6.82. Found: C, 64.21; H, 6.68.

Δ⁴-Androsten-2α-ol-3,17-dione Acetate (VIII). (a) From 6-Bromo-Δ⁴-androstene-3,17-dione (IX).—A solution of 3 g. of 6-bromo-Δ⁴-androstene-3,17-dione[8] and 12 g. of anhydrous potassium acetate in 75 cc. of acetic acid was refluxed for 4 hours, cooled and poured into water. Isolation with ether and crystallization of the product from acetone–hexane afforded 0.58 g. (20%) of the 2α-acetoxy compound VIII with m.p. 200–203°. The analytical specimen exhibited m.p. 209–210°, $[\alpha]_D$ +146°, M_D +502, $\lambda_{max.}$ 241, log ε 4.21, $\nu_{max}^{CHCl_3}$ 1736 and 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.97; H, 8.41.

(b) **From 2-Bromo-Δ⁴-androstene-3,17-dione (VII).**—The acetolysis reaction was carried out with 1.0 g. of 2-bromo-Δ⁴-androstene-3,17-dione[7] and 4 g. of potassium acetate in 25 cc. of acetic acid (refluxing for 4 hours). Crystallization of the product from ether–pentane furnished 0.12 g. (13%) of the 2α-acetoxy compound VIII with m.p. 201–204°. A further purified sample (m.p. 208–210°) was shown to be identical with one prepared by method a as evidenced by mixture m.p. determination and infrared comparison.

Saponification of 2α-Hydroxytestosterone Diacetate.—The complete saponification[2d] of 2α-hydroxytestosterone diacetate has been repeated with potassium carbonate in boiling aqueous methanol. The carefully purified product showed m.p. 170–171.5°, $[\alpha]_D$ +120° (reported[2d] m.p. 161–162°, $[\alpha]_D$ +120°).

A partial saponification at C-2 was carried out by adding an ice-cold solution of 1.8 g. of potassium hydroxide in 2 cc. of water and 10 cc. of methanol to a suspension of 5.0 g. of 2α-hydroxytestosterone diacetate in 100 cc. of ice-cold methanol. After 15 minutes stirring a homogeneous solution resulted, but the product then began to precipitate. After being allowed to stand at room temperature for a further 1 hour, the mixture was acidified with acetic acid, concentrated nearly to dryness and diluted with water. The precipitate on crystallization from acetone furnished 1.96 g. of 2α-hydroxytestosterone 17-monoacetate with m.p. 228–230°, λ_{max} 240 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1718 and 1670 cm.$^{-1}$ and free hydroxyl band.[10]

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.52; H, 8.73.

(10) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini [*cf.* THIS JOURNAL, in press] have kindly informed us that they have obtained this compound (m.p. 221–226°) by potassium bicarbonate saponification of the diacetate.

MEXICO CITY 17, D. F.

[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO, THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. LXI.[1] Synthesis of 19-Nor-desoxycorticosterone, a Potent Mineralocorticoid Hormone[2]

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17-Nor-desoxycorticosterone (IVb), a substance exhibiting *ca.* twice the mineralcorticoid activity of desoxycorticosterone, has been synthesized by two routes.

It has recently been shown that removal of the C-19 methyl group from progesterone,[4] from 17-ethinyltestosterone[5] and from 17-methyltestosterone[5] in all cases results in increased hormonal activity. On the other hand, removal of the C-19 methyl group from testosterone considerably decreases the androgenic activity.[6,7] It was therefore of interest to make available for biological testing the C-19 nor-analogs of the adrenal cortical hormones, especially since it had been reported by Ehrenstein[8] that an amorphous 19-nor-desoxycorticosterone acetate isomer, obtained by degradation of strophanthidin, was biologically inactive. We now report upon the synthesis by two routes of 19-nor-desoxycorticosterone (IVb), which possesses the same configuration at all asymmetric centers as does desoxycorticosterone.

The first route utilized the previously described

(1) Paper LX, G. Rosenkranz, O. Mancera and F. Sondheimer, THIS JOURNAL, **77**, 145 (1955).

(2) A preliminary announcement of part of this work has been published [A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953)].

(3) (a) Universidad Nacional Autónoma de México; (b) Wayne University; (c) Syntex, S. A.

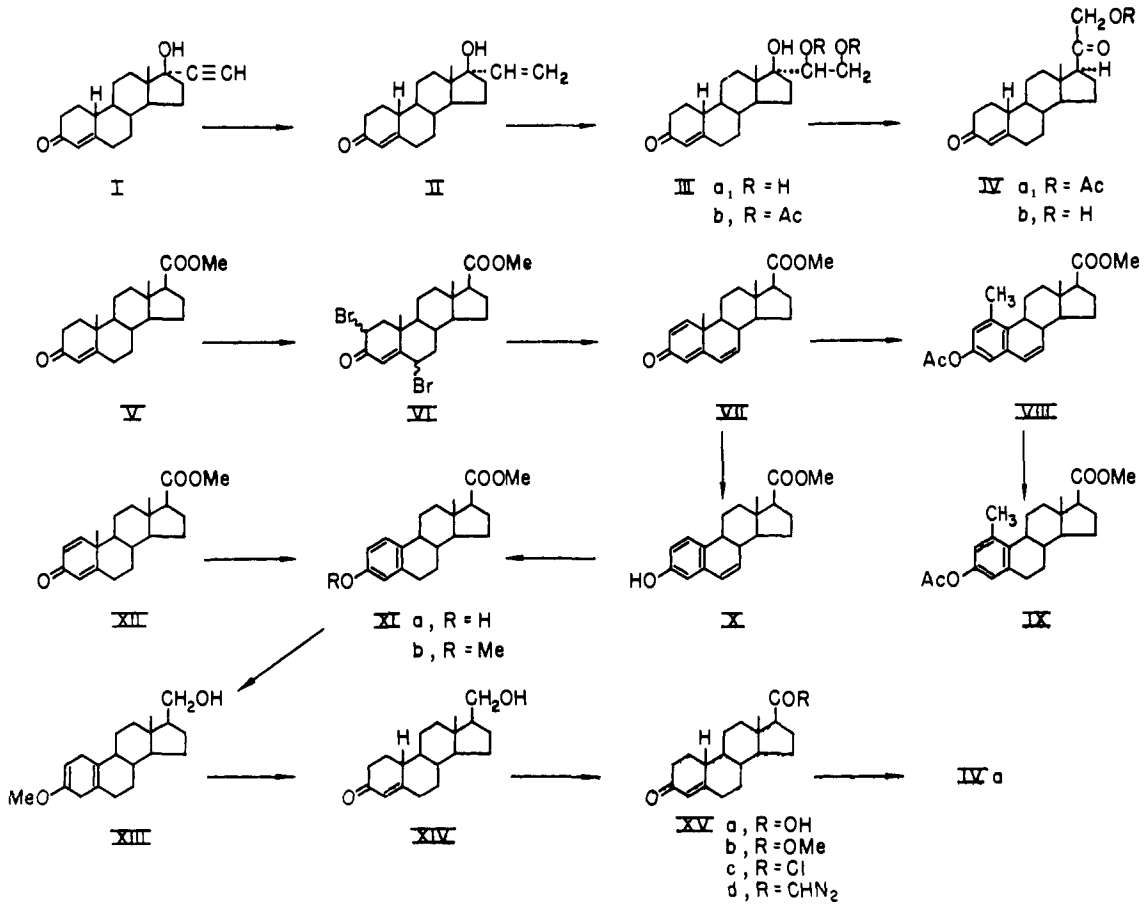
(4) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953).

(5) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(6) A. J. Birch, *Ann. Repts. Prog. Chem.* (*Chem. Soc. London*), **47**, 210 (1950).

(7) A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

(8) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944).



19-nor-17-ethinyltestosterone (I)[5] as starting material. Partial hydrogenation in pyridine solution over a palladium–calcium carbonate catalyst[9] smoothly yielded 19-nor-17-vinyltestosterone (II). The latter compound was hydroxylated with osmium tetroxide to the triol IIIa,[10] which without purification was acetylated to IIIb and then subjected to a Serini reaction with zinc dust in boiling toluene solution.[11] The crystalline product, readily isolated by chromatography on alumina, was assigned the 19-nor-desoxycorticosterone acetate structure IVa by analogy with the 19-methyl series[11a] and this assignment was confirmed by the elemental analysis, the infrared spectrum,[12] the positive reaction with triphenyltetrazolium chloride[13] and the rotation (see below). Saponification with potassium bicarbonate at room temperature produced 19-nor-desoxycorticosterone (IVb).

Since the use of osmium tetroxide was undesirable, an alternative synthesis of IVa was carried out by a route which involved construction of the side-chain from the corresponding 17β-carboxylic acid. The key intermediate in this sequence was methyl 3-hydroxy-$\Delta^{1,3,5(10)}$-estratriene-17β-carboxylate (XIa), a compound which had previously been prepared from methyl 3-keto-5α-etianate *via* methyl 3-keto-$\Delta^{1,4}$-etiadienate (XII).[11b,14] We had available a quantity of methyl 3-keto-Δ^{4}-etienate (V) and have now prepared XIa from this substance through bromination to the 2,6-dibromide VI, collidine dehydrobromination to the trienone VII, pyrolytic aromatization to the tetraene phenol X and finally catalytic hydrogenation.[15] The structure of the intermediate methyl 3-keto-$\Delta^{1,4,6}$-etiatrienate (VII) was confirmed by the typical triple maxima (at 222, 254 and 296 mμ)[15] in the ultraviolet and by carrying out the dienone–phenol rearrangement with *p*-toluenesulfonic acid in acetic anhydride to yield the 1-methyl-3-acetoxytetraene (VIII), which was hydrogenated to the 1-methyl-3-acetoxytriene (IX).[16] As expected, the last-mentioned compound differed from a substance (obtained by dienone–phenol rearrangement of the dienone XII) to which structure IX had previously been assigned,[14] but which is now known to be the corresponding 1-acetoxy-4-methyl isomer.[17]

(9) *Cf.* L. Ruzicka and P. Müller, *Helv. Chim. Acta*, **22**, 755 (1939).

(10) *Cf.* A. Serini and W. Logemann, *Ber.*, **71**, 1362 (1938).

(11) *Inter al.* (a) A. Serini, W. Logemann and W. Hildebrand, *ibid.*, **72**, 391 (1939); (b) C. Djerassi and C. R. Scholz, THIS JOURNAL, **71**, 3962 (1949).

(12) The spectrum showed bands at 1744 and 1718 cm.$^{-1}$ (in chloroform), indicative of a 21-acyloxy-20-ketone [*cf.* R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, THIS JOURNAL, **70**, 2024 (1948)].

(13) This test is specific for 21-hydroxy-20-keto and 21-acyloxy-20-keto steroids [*cf.* A. Zaffaroni, "Recent Progress in Hormone Research," Academic Press Inc., New York, N. Y., Vol. VIII, 1953, p. 77].

(14) C. Djerassi and C. R. Scholz, THIS JOURNAL, **69**, 2404 (1947).

(15) *Cf.* S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, *ibid.*, **72**, 4531 (1950); C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950).

(16) *Cf.* C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and S. Kaufmann, *ibid.*, **72**, 4540 (1950).

(17) R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950); R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. H. Menzel, *Ber.*, **86**, 594 (1953); A. S. Dreiding and A. Voltman, THIS JOURNAL, **76**, 537 (1954).

The phenol XIa was converted to the methyl ether XIb,[11b] which was then subjected to a modified Birch reduction with lithium in liquid ammonia.[7] Acid hydrolysis[7] of the resulting crude ether XIII produced 17β-hydroxymethyl-Δ⁴-estren-3-one (XIV), a Bouveault-Blanc reduction of the carboxymethyl side-chain having occurred in addition to reduction of ring A. Oxidation of the primary alcohol grouping of XIV was brought about by means of chromic acid in acetic acid and produced the required keto acid XVa, further characterized as its methyl ester XVb. Finally the 17-carboxyl group of XVa was transformed to the 21-acetoxy-20-ketone system *via* the acid chloride XVc and the diazoketone XVd, exactly as described in the 19-methyl series.[18] The resulting 19-nor-desoxycorticosterone acetate (IVa) proved to be identical in every respect with that prepared by the first method.[19]

In Table I the molecular rotations ($[M]_D$) of a number of steroidal hormones are compared with those ($[M]_D^{nor}$) of the corresponding 19-nor analogs. It can be seen that the contribution of the C-19 methyl group ($[M]_D - [M]_D^{nor}$) lies in the range +150 to +200 in all cases (*cf.* reference 7), including that of desoxycorticosterone acetate.

As reported in our preliminary communication,[2] 19-nor-desoxycorticosterone (IVb) was found to be *ca.* twice as active as desoxycorticosterone on being assayed for its mineralocorticoid activity by the method of Simpson and Tait.[20]

TABLE I

MOLECULAR ROTATION DATA OF C-19 NOR HORMONES[a]

	$[M]_D$	$[M]_D^{Nor}$	$[M]_D - [M]_D^{Nor}$
Testosterone	+314[b]	+151[7]	+163
17-Methyltestosterone	+248[c]	+ 86[b]	+162
17-Ethinyltestosterone	+122[c,d]	− 75[b]	+197
Progesterone	+640[b]	+441[e]	+199
Desoxycorticosterone acetate	+692[b]	+537[e]	+155

[a] Rotations were determined (at 20°) in chloroform solution, unless stated otherwise. [b] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, THIS JOURNAL, **75**, 4712 (1953). [c] Determined in these laboratories. [d] Determined in chloroform containing 10% of pyridine, due to insolubility in chloroform. [e] This paper.

Experimental[21]

19-Nor-17α-vinyltestosterone (II) (With L. Miramontes).—A solution of 1.82 g. of 19-nor-17α-ethinyltestosterone (I)[b] in 45 cc. of pyridine was shaken in hydrogen with 0.6 g. of a 5% palladium-on-calcium carbonate catalyst at atmospheric pressure and room temperature. After 90 minutes 1 mole of gas had been absorbed and the uptake had become slow. The catalyst was removed, the solvent was evaporated *in vacuo* and the residue was dissolved in ethyl acetate. Washing with dilute hydrochloric acid, sodium bicarbonate and water, drying, evaporation and finally crystallization from ethyl acetate furnished 1.42 g. of the partially reduced compound with m.p. 169–170°, $[\alpha]_D$ +25°, $\lambda_{max.}$ 240 mμ, log ε 4.23, $\nu_{max.}$ 1668 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.64; H, 9.27.

19-Nor-desoxycorticosterone Acetate (IVa) from II.—A solution of 1.07 g. of 19-nor-17α-vinyltestosterone (II) and 0.91 g. (1 equivalent) of osmium tetroxide in 100 cc. of dry ether containing 4 drops of pyridine was allowed to stand at room temperature for 60 hours. The solvent was evaporated and the residue was refluxed for 9 hours with 7 g. of sodium sulfite in 25 cc. of ethanol and 50 cc. of water to decompose the complex. The filtered solution was thoroughly extracted with ether and ethyl acetate and the organic extracts were dried and evaporated. The residue ($\lambda_{max.}$ 240 mμ, log ε 4.21), consisting of the crude triol IIIa, was acetylated by being heated on the steam-bath with 12 cc. of pyridine and 8 cc. of acetic anhydride for 30 minutes. The resulting crude diacetate IIIb was then refluxed with 18 g. of zinc dust in 200 cc. of dry toluene for 65 hours with stirring. The metal was removed by filtration, washed well with hot toluene and the filtrate was evaporated to dryness *in vacuo*. Chromatographic purification of the residue on 50 g. of neutral alumina and crystallization of the fractions eluted with benzene–hexane (2:3 and 1:1) from acetone–ether afforded 0.18 g. of 19-nordesoxycorticosterone acetate with m.p. 173–174°, $[\alpha]_D$ +150°, $\lambda_{max.}$ 240 mμ, log ε 4.24, $\nu_{max.}$ 1744, 1718 and 1668 cm.$^{-1}$, no free hydroxyl band. The color test with triphenyltetrazolium chloride[13] was positive.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.88; H, 8.23.

19-Nor-desoxycorticosterone (IVb) (With J. Iriarte).—A solution containing 40 mg. of the acetate IVa and 80 mg. of potassium bicarbonate in 15 cc. of distilled water and 20 cc. of methanol was allowed to stand at room temperature under nitrogen for 20 hours. Addition of water, extraction with chloroform and crystallization from ether furnished 25 mg. of 19-nor-desoxycorticosterone with m.p. 131–132°, $\lambda_{max.}$ 240 mμ (log ε 4.24). The material was shown to be homogeneous by chromatography on paper (kindly carried out under the direction of Dr. A. Zaffaroni), which showed its polarity to be very similar to that of desoxycorticosterone.

Methyl 2,6-Dibromo-3-keto-Δ⁴-etienate (VI).—A solution of 10 g. of methyl 3-keto-Δ⁴-etiocholenate (m.p. 128–130°) in 500 cc. of dry ether was cooled in ice and a few drops of 4 *N* hydrogen bromide in acetic acid were added. A solution of 10 g. of bromine in 50 cc. of acetic acid was then added dropwise at the rate at which decolorization occurred. The mixture was stirred for a further 10 minutes and the precipitated dibromo compound was removed by filtration and washed well with water. The product, when combined with a further quantity obtained from the filtrate by washing with water, drying, evaporation and trituration with ether, weighed 12.3 g. (83%) and showed m.p. 171–173°. Crystallization from acetone–ether led to the analytical sample with m.p. 179–180°, $[\alpha]_D$ +107°, $\lambda_{max.}$ 250 mμ (log ε 4.17).

Anal. Calcd. for $C_{21}H_{28}O_3Br_2$: Br, 32.73. Found: Br, 32.37.

Methyl 3-Keto-Δ¹,⁴,⁶-etiatrienate (VII).—A solution of 6.6 g. of the dibromo compound VI (m.p. 171–173°) in 35 cc. of dry, redistilled collidine was refluxed for 1 hour and was then cooled in ice. The precipitated collidine hydrobromide (4.95 g., 91%) was collected and washed well with ether. After the usual work-up, concentration of the ether extract furnished 2.75 g. (62%) of the trienone with m.p. 166–168°. Crystallization from acetone–ether yielded a sample with m.p. 176–177°, $[\alpha]_D$ +98°, $\lambda_{max.}$ 222 mμ (log ε 4.15), 254 mμ (log ε 4.08) and 296 mμ (log ε 4.20), $\nu_{max.}$ 1718 and 1656 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.16; H, 8.21.

Methyl 1-Methyl-3-acetoxy-Δ¹,³,⁵(¹⁰),⁶-estratetraene-17β-carboxylate (VIII).—A solution of 1 g. of the trienone VII and 0.2 g. of *p*-toluenesulfonic acid in 50 cc. of acetic anhy-

(18) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948).

(19) It is of interest that several transformations involving the side-chain of steroids containing the 19-nor-Δ⁴-3-ketone system (*e. g.*, II → IVa, XVa → IVa) proceeded in considerably poorer yield than the analogous transformations carried out with the corresponding 19-methyl compounds. The reduced yields in the nor series may be due to the greater reactivity of the Δ⁴-3-ketone system when it is not shielded by the 19-methyl group.

(20) S. A. Simpson and J. F. Tait, *Endocrinology*, **50**, 150 (1952). We would again like to express our thanks to these workers for carrying out this assay.

(21) Melting points are uncorrected. Rotations were measured (at 20°) in chloroform and ultraviolet absorption spectra in 95% ethanol solution. Thanks are due to Mrs. P. Lopez for these determinations, as well as for the infrared spectra which were measured in chloroform solution on a Perkin–Elmer 12C single beam spectrophotometer with sodium chloride prism. We would also like to thank Mrs. A. Gonzalez for the microanalyses and Miss N. Monroy for her skillful technical assistance.

dride was heated on the steam-bath for 4 hours. Addition of water, extraction with ether and crystallization from acetone yielded 0.64 g. of the tetraene VIII with m.p. 185–186° (Kofler block), $[\alpha]_D$ −80°, $\lambda_{max.}$ 224 mμ (log ε 4.43) and 264 mμ (log ε 3.90), $\nu_{max.}$ 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.34; H, 7.87.

Methyl 1-Methyl-3-acetoxy-$\Delta^{1,3,5(10)}$-estratriene-17β-carboxylate (IX).—The tetraene VIII (0.25 g.) dissolved in 10 cc. of ethyl acetate was hydrogenated over 0.1 g. of a 5% palladium-on-charcoal catalyst at 24° and 582 mm. Crystallization of the product from acetone furnished 0.20 g. of the triene IX with m.p. 151–152°, $[\alpha]_D$ +195°, $\lambda_{max.}$ 270 mμ (log ε 2.54), $\nu_{max.}$ 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.92; H, 8.44.

Methyl 3-Hydroxy-$\Delta^{1,3,5(10),6}$-estratetraene-17β-carboxylate (X).—A solution of 3 g. of the trienone VII in 250 cc. of mineral oil was dropped at a rate of 2 cc./sec. through a glass tube (32 × 3 cm.) filled with Pyrex helices and heated to 600°.[22] Chilling the resulting solution in ice, collecting the precipitate and washing with hexane furnished 1.47 g. of the phenol X with m.p. 201–203°. Sublimation of a sample at 180° (10^{-3} mm.), followed by crystallization from methanol, led to the analytical specimen, m.p. 206–207°, $[\alpha]_D$ −69°, $\lambda_{max.}$ 222 mμ (log ε 4.48), 264 mμ (log ε 3.95) and 302 mμ (log ε 3.42), $\nu_{max.}$ 1718 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.18; H, 7.99.

Methyl 3-Hydroxy-$\Delta^{1,3,5,(10)}$-estratriene-17β-carboxylate (XIa).—Hydrogenation of 1.5 g. of the tetraene X in 50 cc. of ethyl acetate over 0.15 g. of a 5% palladium-on-charcoal catalyst at 22° and 584 mm., followed by crystallization of the product from acetone–ether, yielded 1.29 g. of the triene XIa, m.p. 216–219°, $[\alpha]_D$ +108°, $\lambda_{max.}$ 280 mμ (log ε 3.38), $\nu_{max.}$ 1718 cm.$^{-1}$ and free hydroxyl band. Identity with an authentic specimen (m.p. 217–219°),[11b] prepared from methyl 3-keto-$\Delta^{1,4}$-etiadienate (XII), was established through mixture m.p. determination and infrared comparison.

17β-Hydroxymethyl-Δ^4-estren-3-one (XIV).—The phenolic methyl ester XIa was converted to the methyl ether XIb (m.p. 159–162°) with methyl sulfate, as described previously.[11b] To a solution of 10 g. of XIb in 800 cc. of anhydrous ether was added 1 l. of liquid ammonia, and then 15 g. of lithium wire during the course of 20 minutes. The mixture was stirred for a further 30 minutes, 200 cc. of absolute ethanol was added slowly, and the solvents were allowed to evaporate overnight at room temperature. Addition of water to the residue yielded the crude ether XIII as a solid, which after collection, washing with water and drying weighed 9.6 g. and showed m.p. 114–117°, no appreciable absorption at 280 mμ. This material, dissolved in 480 cc. of methanol and 290 cc. of 3 *N* hydrochloric acid, was heated at 60° for 30 minutes. Addition of water, isolation with ether and crystallization from acetone furnished 4.1 g. of the unsaturated ketol XIV with m.p. 129–131°, $\lambda_{max.}$ 240 mμ (log ε 4.24). Chromatographic purification of the mother liquors on neutral alumina furnished another 0.5 g. with m.p. 130–132° (total yield 52%). The analytical sample was obtained by crystallization from methanol or chloroform–ether and exhibited m.p. 138–139°, $[\alpha]_D$ +57°, λ_{max} 240 mμ (log ε 4.23), $\nu_{max.}$ 1660 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.47; H, 9.94.

In some experiments it was found difficult to crystallize the unsaturated ketol XIV directly. In those cases the product from the acid hydrolysis was subjected to a Girard separation; the ketonic fraction could then be easily crystallized and furnished XIV in yields comparable to that reported above.

Δ^4-Estren-3-one-17β-carboxylic Acid (XVa).—A solution of 0.26 g. of chromium trioxide in 5 cc. of acetic acid containing a few drops of water was added dropwise during 10 minutes to a stirred solution of 1 g. of the unsaturated ketol XIV in 40 cc. of acetic acid, kept at 20°. After being allowed to stand overnight, the solution was poured into water and the resulting precipitate was collected, washed well with water and treated with 10% potassium hydroxide solution. Neutral organic products were removed by extraction with chloroform and the aqueous layer was acidified with dilute hydrochloric acid. The precipitated keto acid XVa, after collection, washing with water and drying, weighed 0.72 g. and showed m.p. 240–245°. A sample was crystallized from chloroform and then exhibited m.p. 256–259°, $\lambda_{max.}$ 240 mμ (log ε 4.23).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.66; H, 8.77.

The methyl ester XVb, prepared by treating the acid in chloroform solution with diazomethane, was crystallized from aqueous acetone and showed m.p. 105–106°, $\lambda_{max.}$ 240 mμ (log ε 4.24), $\nu_{max.}$ 1718 and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.75; H, 8.87.

19-Nor-desoxycorticosterone Acetate (IVa) from XVa.—A solution of sodium hydroxide (14 cc., 0.109 *N*) was slowly added to a stirred suspension of 492 mg. of the keto acid XVa in 15 cc. of methanol kept at 0°. The solvent was removed *in vacuo* at room temperature and the residue was dried at 20° and 0.1 mm. for 18 hours. The resulting sodium salt was powdered under 15 cc. of dry ether, cooled in ice and then treated successively with 2 drops of pyridine and 2 cc. of freshly distilled oxalyl chloride. After 3 hours at 0°, the mixture was evaporated to dryness *in vacuo* at room temperature. Dry benzene (4 cc.) was added, the solvent was evaporated at 20° *in vacuo*, and the process was repeated twice more. The resulting acid chloride XVc was then treated with 4 cc. of dry benzene, sodium chloride was removed by filtration and the filtrate was added with stirring to an ethereal solution of diazomethane (from 5 g. of nitrosomethylurea) at −20°. The solution was kept at 0° for 1 hour, the solvent was evaporated *in vacuo* and the crude amorphous diazo ketone XVd was refluxed directly with 20 cc. of acetic acid for 3 minutes. Water was added to the cooled solution, the product was extracted with ether in the usual way and then was chromatographed on 20 g. of neutral alumina. Elution with benzene–hexane furnished crude 19-nor-desoxycorticosterone acetate [176 mg., m.p. 153–159°, $\lambda_{max.}$ 240 mμ (log ε 4.23)]. One crystallization from aqueous acetone yielded 80 mg. with m.p. 162–166°, and further crystallization led to a sample with m.p. 172–173°, identified with the above described material by mixture m.p. determination and infrared comparison.

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