VIa, crystallization from methanol, m.p. 201–202°, $[\alpha]_D$ +168° (dioxane), λ_{max} 268 and 276 mμ, log ε 2.81 and 2.81.

Anal. Calcd. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59; O, 26.14. Found: C, 67.18; H, 6.82; O, 26.07.

6β,7α-Dihydroxyestradiol 3,17-Diacetate (VIc).—Silica gel chromatography of the mother liquors from the preparation of 6α,7α-oxidoestradiol diacetate (IIc), gave a very low yield of VIc, m.p. 86–88° (ether–hexane crystallization), $(\alpha)_D$ +17° (dioxane), λ_{max} 268 and 276 mμ, log ε 2.75 and 2.71.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26; O, 24.72. Found: C, 67.52; H, 7.77; O, 25.00.

Raney Nickel Hydrogenolysis. (a) **Of 6α,7α-Oxidoestradiol (IIc).**—A solution of 200 mg. of epoxide IIc in 50 cc. of 96% ethanol was boiled for 10 hours with 2 g. of freshly prepared W-4 Raney nickel catalyst. The filtered solution was concentrated to dryness, the residue acetylated with acetic anhydride–pyridine (four hours, 25°) and the acetylated product crystallized from hexane to yield 100 mg. of estradiol diacetate (m.p. 125–126°) identical with an authentic sample.

(b) **Of 6α,7α-Dihydroxyestradiol (Vc).**—Treatment of 300 mg. of glycol Vc in 50 cc. of 96% ethanol with 3 g. of W-4 Raney nickel for 15 hours under reflux followed by evaporation of the filtered solution and crystallization of the residue from ethyl acetate–ether gave 200 mg. of estradiol (m.p. 175–176°) identical with an authentic sample.

(c) **Of 7α-Hydroxyestradiol (IIIm).**—Treatment of 300 mg. of 7α-hydroxyestradiol with Raney nickel, exactly as described in b, gave 100 mg. of estradiol, m.p. 171–173°.

Elimination Reactions of 7α-Hydroxyestrone. (a) **Treatment of 7α-Hydroxyestrone 3-Benzoate (IIIc) with Phosphorus Oxychloride.**—A solution of IIIc (220 mg.) in dry pyridine (4 cc.) and freshly distilled phosphorus oxychloride (3.5 cc.) was boiled for 1.5 hours under anhydrous conditions. The cooled mixture was poured into ice-water, the product extracted with ethyl acetate and the extract washed with dilute bicarbonate. Evaporation of solvent and crystallization of the residue from methanol gave 80 mg. of material, m.p. 170–175°, λ_{max} 230 mμ, log ε 4.41, which was then saponified with methanolic potassium hydroxide, and crystallized to give authentic 6-dehydroestrone, m.p. 259–262°. The mother liquors of the methanol crystallization were shown by chromatographic analysis to consist primarily of starting material and of 6-dehydroestrone benzoate.

(b) **Treatment of 7α-Hydroxyestrone 3-Benzoate, 7-Mesylate (IIIe) with Collidine.**—A solution of the mesylate IIIe (50 mg.) in 3 cc. of collidine was boiled for one hour and then diluted with ethyl acetate. After washing with dilute hydrochloric acid, the solvent was evaporated and the residue saponified by one hour reflux with 1% methanolic potassium hydroxide. Crystallization from methanol gave slightly impure 6-dehydroestrone of m.p. 255–257°.

(c) **Treatment of IIIe with Potassium Hydroxide.**—The mesylate IIIe (200 mg.) was heated for one hour in 30 cc. of boiling 2% methanolic potassium hydroxide. The cooled solution was acidified, diluted with water, the precipitate extracted with ethyl acetate and the residue twice recrystallized from methanol yielding 55 mg. of 6-dehydroestrone, m.p. 259–262°, $[\alpha]_D$ −100° (dioxane).

(d) **Treatment of IIIe with Potassium Acetate.**—A solution of 100 mg. of 7α-mesylate IIIe and 200 mg. of anhydrous potassium acetate in 40 cc. of absolute ethanol was boiled for one hour. Water was added, the product isolated by ethyl acetate extraction and then saponified by treatment with 1% methanolic potassium hydroxide. Chromatography of the saponified product on silica gel, gave, in the benzene–ether (9:1) fractions, 20 mg. of 6-dehydroestrone, m.p. 258–260°.

(e) **Treatment of IIIe with Potassium Benzoate.**—A solution of 300 mg. of IIIe, 1 g. of potassium benzoate and 50 cc. of absolute ethanol was boiled, under reflux, for 60 hours. After the addition of water the product was extracted, saponified and chromatographed on 30 g. of silica gel. Benzene–ether (95:5) eluted 140 mg. of crude 6-dehydroestrone which was recrystallized from ethyl acetate to yield 100 mg. of product of m.p. 258–260°, $[\alpha]_D$ −110°.

Elimination Reactions of 7β-Hydroxyestrone, (a) **Pyrolysis of 7β-Hydroxyestrone Dibenzoate (IIIk).**—In a sublimation tube, 520 mg. of IIIk was heated for four hours at 280–300° under reduced pressure (20 mm.), whereupon 115 mg. (93%) of benzoic acid sublimed. The residue was saponified in the usual manner with 1% methanolic potassium hydroxide and crystallized from methanol to yield 210 mg. of somewhat impure 6-dehydroestrone, m.p. 252–257°, $[\alpha]_D$ −61° (dioxane); λ_{max} 226, 262 and 306 mμ; log ε 4.40, 3.80 and 3.30. Chromatography of the mother liquors gave additional quantities of the same product, containing some dextrorotatory contaminant, but no equilin could be detected.

(b) **Pyrolysis of 7β-Hydroxyestrone 3-Benzoate-7-ethylcarbonate (IIIj).**—Forty mg. of IIIj was pyrolyzed at 250–260° (20 mm. pressure) for two hours. Saponification and crystallization from methanol again gave 6-dehydroestrone of m.p. 253–257°.

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[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Steroids. C.[1] Synthesis of 19-Nor-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (19-Norhydrocortisone) and Related 19-Nor-adrenal Hormones

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19-Nor-$\Delta^{1,3,5(10),16}$-pregnatetraen-3-ol-20-one (I) is converted by a seven-step sequence to 19-nor-17α-hydroxyprogesterone (VII), which on treatment first with iodine and then with potassium acetate yields 19-nor-Substance S 21-acetate (Xa). Adrenal incubation of 19-nor-17α-hydroxyprogesterone (VII) or of 19-nor-Substance S (Xb) leads to 19-norhydrocortisone (XIa) which can be oxidized to 19-norcortisone (XII). Similarly, adrenal incubation of the previously described 19-norprogesterone (XVa) or 19-nordesoxycorticosterone (XVb) yields 19-norcorticosterone (XVI). The biological activities of the various hormone analogs are reported and discussed.

It has been shown that the 19-nor analogs of progesterone,[4a] 17α-ethinyltestosterone[4b] and desoxycorticosterone[4c] are considerably more potent hormones than the corresponding 19-methyl compounds. It was therefore of interest to prepare the corresponding analogs of the 11-oxygenated adrenal hormones. This objective was achieved by use of

(1) Paper IC, J. Iriarte, H. J. Ringold and C. Djerassi, THIS JOURNAL, **80**, 6105 (1958)..

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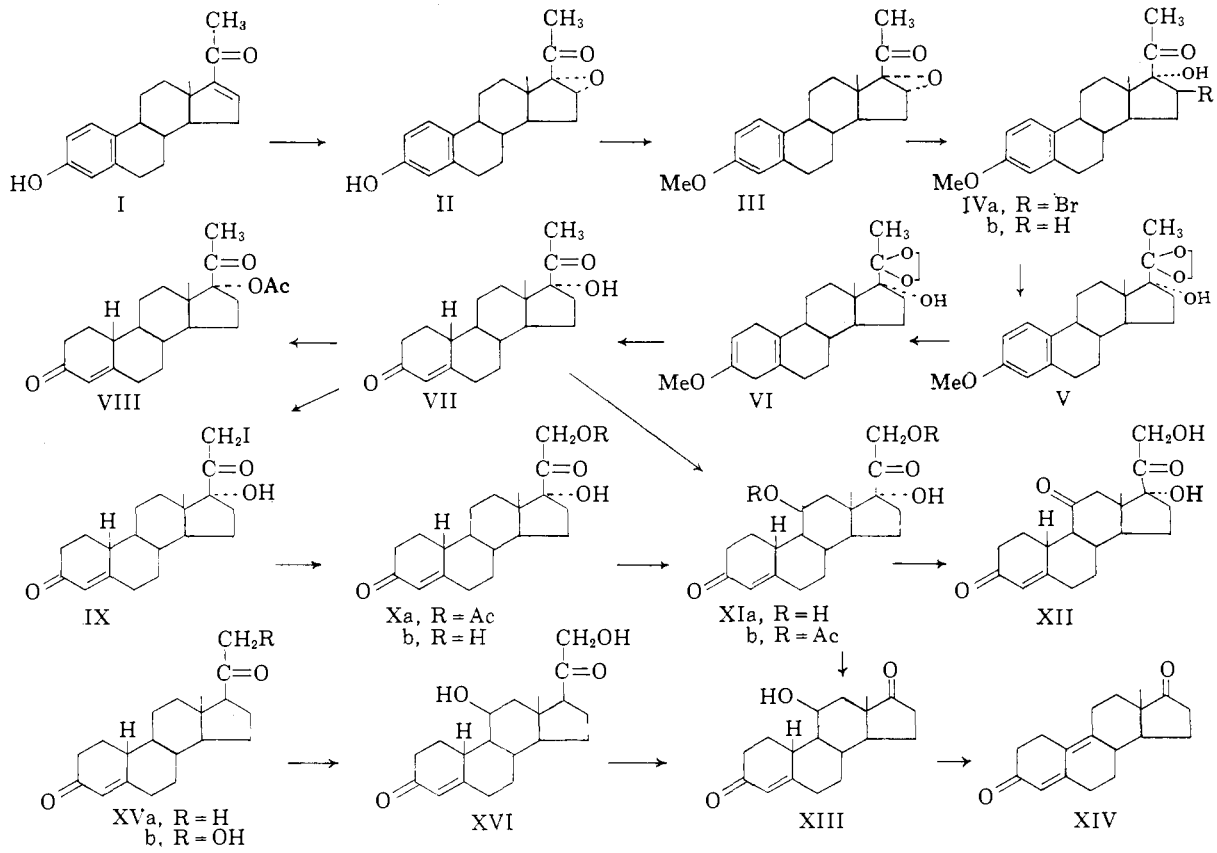
(4) (a) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953); (b) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (c) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **77**, 148 (1955).



a combined chemical–biochemical method, as has been indicated briefly by us in a preliminary communication.[5] We are now reporting on this work in full.

Our first aim was the synthesis of 19-nor-17α-hydroxyprogesterone (VII) using 19-nor-$\Delta^{1,3,5(10),16}$-pregnatetraen-3-ol-20-one (I)[6] as starting material. The 17α-hydroxy group has previously[6] been introduced into I by hydrogenation of the Δ^{16}-double bond, followed by formation of the $\Delta^{17(20)}$-enol acetate and reaction with perbenzoic acid (method of Gallagher).[7] A more convenient route employs the Kendall[8a] modification of the method of Julian.[8b] Thus, reaction of the Δ^{16}-20-ketone I with alkaline hydrogen peroxide led to the 16,17α-oxide II, the phenolic 3-hydroxy group of which was then protected by methylation. The resulting methyl ether III was converted by hydrogen bromide in acetic acid to the bromohydrin IVa, which without purification was reduced to 3-methoxy-19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-17α-ol-20-one (IVb) through hydrogenolysis over a 2% palladium–calcium carbonate catalyst.

In order to protect the side-chain, the hydroxyketone IVb was boiled with ethylene glycol and *p*-toluenesulfonic acid in benzene. The 20-cycloethylene ketal V which was smoothly formed was then subjected to the Wilds modification of the Birch reduction.[9] Treatment of the resulting dihydrobenzene derivative VI with hydrochloric acid in methanol effected both the cleavage of the enol ether grouping in ring A and the ketal at C-20 and led to the required 19-nor-17α-hydroxyprogesterone (VII). The over-all yield in the sequence I-VII was about 35%. 19-Nor-17α-acetoxyprogesterone (VIII) could be prepared by treating VII with acetic anhydride and *p*-toluenesulfonic acid, followed by saponification of the enol acetate at C-3 by means of potassium hydroxide at room temperature.

The 21-hydroxy group was introduced into 19-nor-17α-hydroxyprogesterone (VII) most efficiently by the method recently described from our laboratories.[10] This involves treatment of VII in tetrahydrofuran and methanol successively with iodine and aqueous sodium hydroxide, whereby the 21-iodo derivative IX was formed. The latter substance without purification was then boiled with potassium acetate in acetone. The resulting 19-nor-Δ^4-pregnene-17α,21-diol-3,20-dione (19-nor-Substance S) 21-acetate (Xa) showed spectral properties very similar to those of Substance S 21-acetate, the presence of the 21-acetoxy-20-keto grouping being confirmed by the red color given with triphenyltetrazolium chloride.[11] Saponification of the acetate Xa with potassium bicarbonate yielded free 19-nor-Substance S (Xb), which like

(5) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **76**, 6210 (1954).

(6) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, *ibid.*, **73**, 1526 (1951).

(7) T. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(8) (a) F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason and E. C. Kendall, *ibid.*, **194**, 235 (1952); (b) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950).

(9) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950); A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

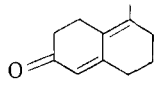
(10) H. J. Ringold and G. Stork, *ibid.*, **80**, 250 (1958).

(11) *Cf.* A. Zaffaroni, *Recent Prog. Hormone Research*, **8**, 51 (1953).

Substance S gave a cherry-red color with concentrated sulfuric acid.

Incubation of 19-nor-17α-hydroxyprogesterone (VII) with adrenal homogenates,[12] followed by dialysis,[11] yielded 19-norhydrocortisone (XIa). This substance showed color tests and spectral characteristics very similar to those of hydrocortisone. That one new oxygen function had been introduced was shown by the elemental analysis. Direct oxidation with chromium trioxide on a micro-scale led to 19-norcortisone (XII) with spectral characteristics similar to those of cortisone. Acetylation of 19-norhydrocortisone (XIa) with acetic anhydride and pyridine at room temperature yielded the 11,21-diacetate XIb.[13] The oxidation result and the formation of a diacetate on acetylation shows that the new oxygen function must be a hydroxyl group which is not tertiary. It is of interest to note that the 11β-hydroxy group in normal steroids is not acetylated with acetic anhydride and pyridine at room temperature, due to the shielding effect of the 19-methyl group not present in XIa.

Proof for the C-11 location of the new hydroxyl group in XIa was obtained through side-chain oxidation by means of sodium bismuthate.[14] This procedure yielded 19-nor-Δ^4-androsten-11β-ol-3,17-dione (XIII), which was dehydrated with *p*-toluenesulfonic acid to an oil consisting predominantly of 19-nor-$\Delta^{4,9(10)}$-androstadiene-3,17-dione (XIV). This conjugated dienone showed an ultraviolet maximum at 302 mμ, in excellent agreement with the value 302 mμ reported for 8-methyl-$\Delta^{4(10)8}$-hexal-3-one (XVII) containing the same



XVII

chromophoric system.[15] The dehydration of XIII presumably involves first the formation of the corresponding $\Delta^{4,9(11)}$-dien-3-one, the unconjugated double bond then moving into conjugation under the acidic conditions. The only location of a non-tertiary hydroxyl group compatible with the formation of XIV is at C-11. The 11β-configuration follows from the molecular rotation data (see below) and from the fact that adrenal incubation in all cases has resulted in 11β- rather than 11α-hydroxylation.[16]

Similarly, adrenal incubation of 19-norprogesterone (XVa)[4a] or of 19-nordesoxycorticosterone (XVb)[4c] yielded 19-norcorticosterone (XVI). The structure of the last-mentioned compound rests on the elemental analysis, the spectral data, molecular rotation calculations (see below) as well as on analogy with the corresponding conversion in the 19-methyl series.[12]

In Table I, the paper chromatographic movement ratios (p.m.r.'s) of various 19-nor hormones are presented. The p.m.r. is the ratio of the rate of movement of the 19-nor steroid compared with the corresponding 19-methyl compound on paper in the solvent system indicated. As expected, in view of their lower carbon content, the nor steroids in all cases are less mobile on paper than the 19-methyl compounds (p.m.r. <1). Of interest is the fact that the 11β-hydroxy-19-nor compounds are particularly strongly retarded as compared with the 19-methyl analogs (p.m.r. < 0.5) and this is undoubtedly due to the fact that the 11β-hydroxy group in the 19-nor steroids is not subject to steric hindrance from the 19-methyl group.

TABLE I

PAPER CHROMATOGRAPHIC MOVEMENT RATIOS (P.M.R.) OF 19-NOR-HORMONES[a]

Substance	P.m.r.	System
19-Nordesoxycorticosterone (XVb)[4c]	0.80	$CHCl_3$–$HCONH_2$
19-Nor-Substance S (Xb)	.72	$CHCl_3$–$HCONH_2$
19-Norcortisone (XII)	.73	$CHCl_3$–$HCONH_2$
19-Norhydrocortisone (XIa)	.40	$CHCl_3$–$HCONH_2$
19-Norcorticosterone (XVI)	.35	C_6H_6–$HCONH_2$

[a] Mobility of 19-norsteroid compared with corresponding 19-methyl analog.

In Table II the molecular rotations ($[M]_D^{nor}$) of the various 19-nor hormones described in this paper are compared with those ($[M]_D$) of the corresponding 19-methyl compounds. It can be seen that in all cases the contribution of the 19-methyl group is of the order of +200, in good agreement with the value +150 to +200 reported earlier.[4c] In particular these considerations rule out 11α-hydroxy formulations for XIa and XVI, since the $[M]_D$ values of 11α-hydroxy compounds in the pregnan-20-one series are about 150° lower than those of the corresponding 11β-hydroxy derivatives.[17]

TABLE II

MOLECULAR ROTATION DATA OF 19-NOR HORMONES[a]

Substance	$[M]_D$	$[M]_D^{nor}$	$[M]_D - [M]_D^{nor}$
17α-Hydroxyprogesterone	+314[b]	+130	+184
17α-Acetoxyprogesterone	+272[b]	+ 61	+211
Substance S 21-acetate	+554[c]	+337	+217
Hydrocortisone	+590[d,e]	+390[e]	+200
Corticosterone	+737[f,g]	+515[g]	+222

[a] Rotations were determined in chloroform unless stated otherwise. [b] H. J. Ringold, B. Löken, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 816 (1956). [c] E. Batres, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5171 (1954). [d] N. L. Wendler, R. P. Grager, R. E. Jones and M. Tishler, *ibid.*, **74**, 3630 (1952). [e] In methanol. [f] S. Bernstein and R. H. Lenhard, THIS JOURNAL, **77**, 2331 (1955). [g] In ethanol.

19-Norhydrocortisone (XIa) and 19-norcortisone (XII) were found to be considerably less active in the glycogen deposition and the pouch anti-inflammatory tests as compared to hydrocortisone.

(12) *Cf.* A. Zaffaroni, U. S. Patent 2,671,572.

(13) This was established on a micro-scale by the characteristic mobility ratios on paper (*cf.* A. Zaffaroni and R. B. Burton, *J. Biol. Chem.*, **193**, 749 (1951)).

(14) W. Rigby, *J. Chem. Soc.*, 1907 (1950); C. J. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(15) S. Julia, *Bull. soc. chim. France*, 780 (1954).

(16) Since we first reported the synthesis of 19-norhydrocortisone (footnote 5), the same substance was prepared by a different method (B. J. Magerlein and J. A. Hogg, THIS JOURNAL, **79**, 1508 (1957)). This second synthesis proceeds from authentic 11β-hydroxy compounds and confirms our assignment, in view of the excellent agreement of the physical properties of the 19-norhydrocortisone obtained by the two methods.

(17) *Cf.* R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

Consequently, in contrast to the 11-desoxy hormones, removal of the angular methyl group in this series has a deleterious effect and this may well be associated with the reduced degree of hindrance[18] at C-11 in the 19-nor series.

Acknowledgments.—We are indebted to Dr. J. Iriarte and Miss Victoria Troncoso for their valuable help in the adrenal incubation steps.

Experimental[19]

16,17α-Oxido-19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-3-ol-20-one (II).—A solution of 20 g. of 19-nor-$\Delta^{1,3,5(10),16}$-pregnatetraen 3-ol-20-one (I)[6] in 2.5 l. of methanol was cooled to 15° and 105 cc. of 35% hydrogen peroxide was added. A solution of 8.2 g. of sodium hydroxide in 52 cc. of water then was added with stirring and cooling at such a rate that the internal temperature did not exceed 25°. After being allowed to stand at room temperature (24°) for 17 hr., the mixture was poured into 8 l. of cold water, which then was acidified with dilute hydrochloric acid. The precipitated oxide II on being collected, washed with water and dried weighed 19.15 g. (91%) and showed m.p. 225–228°. The analytical sample, obtained by crystallization from chloroform–methanol, exhibited m.p. 234–236°, $[\alpha]_D$ +124°, λ_{max}^{EtOH} 280 mμ (log ε 3.49).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.72; H, 7.88.

3-Methoxy-16,17α-oxido-19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-20-one (III).—To a boiling solution of 19.1 g. of the oxide II (m.p. 225–228°) in 1.9 l. of ethanol was added a total of 320 cc. of dimethyl sulfate and a solution of 320 g. of potassium hydroxide in 320 cc. of water with continued boiling. The addition was made by adding the two liquids in 5 equal portions each alternatively during 30 minutes. The mixture was boiled for a further 45 minutes and was then cooled and poured into iced water. The resulting precipitate was collected, washed with water and dried. The methyl ether III thus obtained weighed 17.66 g. (88%) and showed m.p. 137–142°. Crystallization from chloroform–methanol led to the analytical sample with m.p. 141–144°, $[\alpha]_D$ +125°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 77.27; H, 8.03. Found: C, 77.16; H, 8.11.

3-Methoxy-19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-17α-ol-20-one (IVb).—A saturated solution of hydrogen bromide in glacial acetic acid (2.6 cc.) was added to 1.3 g. of the methyl ether III (m.p. 137–142°) in 50 cc. of acetic acid at 15°. The mixture was allowed to stand at 15–18° for 5 minutes and then was poured into iced water. The precipitated bromohydrin IVa was collected, washed with water and dried *in vacuo* at 25°. This material was shaken with hydrogen in 30 cc. of 96% ethanol (previously distilled from Raney nickel) over 4 g. of a pre-hydrogenated 2% palladium–calcium carbonate catalyst at 585 mm. and 25°. After 18 hr., the catalyst was removed and washed well with hot acetone. The combined filtrates were evaporated to small volume and then diluted with water. The resulting precipitated 17α-hydroxy compound IVb weighed 1.24 g. (95%) and showed m.p. 150–153°. Crystallization from acetone–hexane gave a sample with m.p. 151–153°, $[\alpha]_D$ +45°, $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$ and free hydroxy band.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.02; H, 8.30.

3-Methoxy-20-ethylenedioxy-19-nor-$\Delta^{1,3,5(10)}$-pregnatrien-17α-ol (V).—A mixture containing 7 g. of the 17α-hydroxy compound IVb, 0.48 g. of *p*-toluenesulfonic acid, 50 cc. of ethylene glycol and 300 cc. of benzene was boiled and stirred for 10 hr., the water being removed by means of a water separator. The mixture was then cooled and sodium bicarbonate solution was added. The benzene layer was washed with water, dried and evaporated. Crystallization of the residue from pentane furnished 6.65 g. (84%) of the ketal V with m.p. 118–122°. A further purified sample showed m.p. 124–126°, $[\alpha]_D$ +43°, hydroxyl but no carbonyl band in the infrared.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.20; H, 8.61.

3-Methoxy-20-ethylenedioxy-19-nor-$\Delta^{2,5(10)}$-pregnadien-17α-ol (VI).—To a solution of 6.5 g. of the ketal V in 750 cc. of anhydrous ether was added 900 cc. of liquid ammonia and then 7.8 g. of lithium wire during 10 minutes, with stirring. The mixture was stirred for 20 minutes more and 160 cc. of absolute ethanol then was added slowly and the ammonia was allowed to evaporate. Water was added to the residue, the ether was distilled off and the resulting solid was collected, washed with water and dried. It weighed 6.1 g. and showed m.p. 159–175°, λ_{max}^{EtOH} 272 mμ (log ε 1.52). Crystallization from acetone–hexane gave 4.52 g. (69%) of the dihydrobenzene derivative VI with m.p. 179–184°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.86; H, 9.10.

19-Nor-Δ^4-pregnen-17α-ol-3,20-dione (19-Nor-17α-hydroxyprogesterone) (VII).—A mixture containing 4.39 g. of the dihydrobenzene derivative VI, 220 cc. of methanol and 132 cc. of 3 *N* hydrochloric acid was heated at 60° for 18 minutes (a clear solution resulted after *ca.* 10 minutes). The solution was cooled, poured into iced water and the resulting precipitate (3.45 g., m.p. 196–200°) was collected, washed with water and dried. Crystallization from acetone–hexane yielded 2.94 g. (79%) of 19-nor-17α-hydroxyprogesterone with m.p. 200–203°. A further purified specimen exhibited m.p. 204–206°, $[\alpha]_D$ +41°, λ_{max}^{EtOH} 240 mμ (log ε 4.23), ν_{max}^{mull} 1704 and 1666 cm.$^{-1}$ and free hydroxy band.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.58; H, 8.98.

19-Nor-Δ^4-pregnen-17α-ol-3,20-dione Acetate (19-Nor-17α-acetoxyprogesterone) (VIII).—A mixture containing 0.5 g. of 19-nor-17α-hydroxyprogesterone (VII), 0.15 g. of *p*-toluenesulfonic acid and 10 cc. of acetic anhydride was stirred at room temperature for 18 hr. The suspension was then poured into water, the excess anhydride was allowed to hydrolyze and the precipitate was collected, washed with water and dried. The resulting material (0.55 g.), consisting mainly of the $\Delta^{3,5}$-3,17-diacetate was dissolved in 100 cc. of methanol and treated with 0.45 g. of potassium hydroxide in 2 cc. of water and 5 cc. of methanol for 7 minutes at 25°. Acetic acid (1 cc.) then was added, the solution was evaporated to small volume under reduced pressure and the residue was diluted with water. Crystallization of the resulting precipitate from acetone–hexane yielded 0.38 g. of the 17-acetoxy compound VIII with m.p. 220–224°. Further crystallization from methanol yielded the analytical sample with m.p. 225–228°, $[\alpha]_D$ +17°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.50; H, 8.50.

19-Nor-Δ^4-pregnene-17α,21-diol-3,20-dione (19-Nor-Substance S) (Xb).—Iodine (1.3 g.) was added in one batch to a solution of 1 g. of 19-nor-17α-hydroxyprogesterone (VII) in 15 cc. of tetrahydrofuran and 2.5 cc. of methanol cooled at 0°; 10% aqueous sodium hydroxide solution (4 cc.) was then added dropwise during 12 minutes with stirring and cooling. After a further 3 minutes, the color of iodine had disappeared and the mixture was poured into cold salt solution. The product was extracted into methylene chloride (4 × 50 cc.), the extract was washed with water, dried and evaporated almost to dryness in nitrogen under reduced pressure. Acetone (100 cc.) and anhydrous potassium acetate (5 g.) were added, the mixture was concentrated to *ca.* 50 cc. through distillation at atmospheric pressure and it then was boiled under reflux for 18 hr. Most of the solvent was distilled off under reduced pressure, the residue was diluted with water and the precipitate was collected, washed with water and dried. Crystallization from acetone produced 0.26 g. of 19-nor-Substance S acetate (Xa) with m.p. 234–237°. Further crystallization from acetone led to the analytical sample with m.p. 243–246°, $[\alpha]_D$ +90°, λ_{max}^{EtOH} 240 mμ (log ε 4.23); $\nu_{max}^{CHCl_3}$ 1745, 1736, 1718 and 1662 cm.$^{-1}$ and free hydroxyl band. The substance gave a red color with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.63; H, 8.35.

(18) This is shown, for instance, by the ease of acetylation at C-11 of 19-norhydrocortisone under conditions where hydrocortisone itself is not affected at that position.

(19) Melting points are uncorrected. Rotations were measured at room temperature in chloroform solution unless specified otherwise. Infrared spectra were determined on a Perkin–Elmer model 12 C single beam spectrophotometer with sodium chloride prism. Microanalyses were carried out by Mrs. A. Gonzalez and staff.

Chromatography of the mother liquors on alumina led to 0.23 g. of recovered 19-nor-17α-hydroxyprogesterone.

Free 19-nor-Substance S (Xb) was obtained by saponification of 415 mg. of the acetate Xa in 100 cc. of methanol with 500 mg. of potassium bicarbonate in 20 cc. of water for 20 hr. at room temperature under nitrogen. Addition of water, extraction with chloroform, crystallization from acetone–ether and chromatography of the mother liquors on silica yielded a total of 176 mg. of the diol Xb with m.p. 174–177°. Further crystallization yielded a constant-melting sample with m.p. 178–180°. The substance gave a bright red color with concentrated sulfuric acid.

19-Nor-Δ^4-pregnene-11β,17α,21-triol-3,20-dione (19-Norhydrocortisone) (XIa). (a) **By Adrenal Incubation of 19-Nor-17α-hydroxyprogesterone (VII).**—19-Nor-17α-hydroxyprogesterone (3.5 g.) was dissolved in 20 cc. of propylene glycol and added to 3.5 kg. of beef adrenal breis, made by finely grinding fresh beef adrenal glands in a meat grinder, suspended in 28 l. of phosphate–fumarate buffer. The latter was prepared by mixing 25.22 l. of a solution containing 0.9% sodium chloride, 0.046% potassium chloride, 0.038% magnesium sulfate and 0.815% of sodium fumarate with 2.88 l. of a 0.1 *M* phosphate buffer of *p*H 7.4 and the mixture was incubated at 30° for 3 hr. with continuous agitation in open erlenmeyer flasks. The tissue suspensions were extracted by the dialysis method,[20] the chloroform extracts were evaporated to dryness and chromatographed on paper with the system chloroform–formamide.[11] The paper chromatography was carried out using 95 17 cm.-wide paper chromatograms and the time of chromatography was adjusted to 6 hr., under which conditions a band of a compound (absorbing in the ultraviolet and giving a positive TPTZ reaction) was found occupying a position on the chromatogram from 1–4 cm. from the starting line. This area from the 95 chromatograms was cut out and eluted with methanol, using standard procedures.[11] The total eluate assayed by its ultraviolet absorption at 240 mμ gave a quantity of steroid equivalent to 365 mg. of hydrocortisone. Aliquots of this material were chromatographed alone and in mixtures with hydrocortisone with the systems chloroform–formamide and toluene–propylene glycol. In every instance the isolated substance proved to be more polar than hydrocortisone. While hydrocortisone gives a yellow color with concentrated sulfuric acid, the isolated substance gave a reddish-brown color with this reagent. The total eluate was chromatographed on silica gel to purify the steroid from impurities derived from the paper, using ether, ether–ethyl acetate (1:1) and ethyl acetate as elution solvents. After evaporation of the ether–ethyl acetate and ethyl acetate fractions and crystallization from methanol–ether, 220 mg. of 19-norhydrocortisone was obtained with m.p. 255–257°, $[\alpha]_D$ +112° (methanol), λ_{max}^{EtOH} 241 mμ (log ϵ 4.23); $\lambda_{max}^{H_2SO_4}$ 240, 282, 385 and 470 mμ; ν_{max}^{mull} 3500, 3380, 3230 cm.$^{-1}$ (multiple OH absorption), 1707 cm.$^{-1}$ (20-ketone) and 1670 cm.$^{-1}$ (Δ^4-3-ketone).[21]

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.84; H, 8.22.

(b) **By Adrenal Incubation of 19-Nor-Δ^4-pregnene-17α,21-diol-3,20-dione (Xb).**—Incubation of 250 mg. of Xb with 250 g. of beef adrenal breis suspended in 2 l. of the phosphate–fumarate buffer described above, followed by extraction by dialysis, gave rise to an extract that, when chromatographed on paper using the system chloroform–formamide for 6 hr., permitted the isolation of a substance more polar than hydrocortisone, estimated by ultraviolet to be present to the extent of 115 mg. The total eluate from the zone of the paper chromatogram containing the substance was subjected to silica gel chromatography. The fraction eluted with ether–ethyl acetate (1:1) was combined and crystallized from methanol–ether, yielding 78 mg. of 19-norhydrocortisone, m.p. 254–257°, $[\alpha]_D$ +113° (methanol).

Micro-oxidation of 19-Norhydrocortisone (XIa) to 19-Nor-Δ^4-pregnene-17α,21-diol-3,11,20-trione (19-Norcortisone) (XII).—A solution of 4 mg. of chromium trioxide in 2 cc. of acetic acid was added to 20.2 mg. of 19-norhydrocortisone (m.p. 252–254°) dissolved in 20 cc. of acetic acid. After 2 minutes, the mixture was diluted with water and the product was extracted with chloroform. Chromatography on paper of an aliquot of the resulting material indicated the presence of 30% of 19-norcortisone and 28% of unchanged 19-norhydrocortisone. The total material was therefore chromatographed on paper. The band containing XII was cut out and extracted with methanol. Evaporation of the methanol and direct crystallization from methanol–ether then yielded 19-norcortisone with m.p. 230–232°, λ_{max}^{EtOH} 238 mμ (log ϵ 4.21); $\lambda_{max}^{H_2SO_4}$ 280, 340, 415 and 490 mμ; red color with triphenyltetrazolium chloride. A further quantity was obtained by chromatography of the mother liquors on silica and elution with ethyl acetate.

19-Nor-Δ^4-androsten-11β-ol-3,17-dione (XIII) from 19-Norhydrocortisone (XIa).—A solution of 26 mg. of 19-norhydrocortisone in 5 cc. of 50% aqueous acetic acid was stirred at room temperature with 300 mg. of sodium bismuthate for 30 minutes. Water (10 cc.) then was added, followed by sufficient 3 *N* potassium hydroxide solution to neutralize 75% of the acetic acid. Benzene (15 cc.) was added, the mixture was filtered and the solid was washed with benzene. The combined benzene extracts on being washed with water, dried and evaporated yielded 22 mg. of the diketone XIII with m.p. 186–192°. Crystallization from acetone–hexane led to the analytical sample with m.p. 193–197°, $\nu_{max}^{CHCl_3}$ 1739 and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.22; H, 8.12.

Dehydration of 19-Nor-Δ^4-androsten-11β-ol-3,17-dione (XIII).—The diketone XIII (8 mg.) dissolved in 2 cc. of benzene was added to a boiling solution of 100 mg. of *p*-toluenesulfonic acid in 10 cc. of benzene, the water of crystallization of the acid previously having been removed by azeotropic distillation. The solution was boiled under reflux for 18 hr. and water and ether then were added. The organic layer was washed with sodium bicarbonate solution and water, and was then dried and evaporated. The residual crude 19-nor-$\Delta^{4,9(10)}$-androstadiene-3,17-dione (XIV) weighed 6 mg. and showed $\nu_{max}^{CHCl_3}$ 1740 and 1665 cm.$^{-1}$, λ_{max}^{EtOH} 302 mμ (log ϵ 4.01).

19-Nor-Δ^4-pregnene-11β,21-diol-3,20-dione (19-Norcorticosterone) (XVI). (a) **By Adrenal Incubation of 19-Norprogesterone (XVa).**—One gram of XVa was incubated with 1 kg. of beef adrenal breis following the same procedures for the incubation and extractions as described in the preceding experiments. The dialysis extracts were chromatographed on paper with the system chloroform–formamide, allowing the solvent to reach the front of the paper. 19-Norcorticosterone was found in the paper occupying a zone from 12 to 16 cm. from the starting line. After elution with methanol, evaporation of the solvent and chromatography of the residue on silica gel using benzene–ether mixtures for the purpose of purification, 58 mg. of 19-norcorticosterone was obtained after evaporation of the benzene–ether fraction 4:1 to 2:1 and crystallization from acetone–ether, m.p. 195–197°, $[\alpha]_D$ +155° (ethanol), λ_{max}^{EtOH} 241 mμ (log ϵ 4.21); $\lambda_{max}^{H_2SO_4}$ 285, 390 and 475 mμ.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.06; H, 8.45.

(b) **By Adrenal Incubation of 19-Nordesoxycorticosterone (XVb).**—Incubation of 60 mg. of XVb with 60 g. of beef adrenal breis, using the same procedures for incubation, extraction and chromatography described in the above experiments, gave rise to 22 mg. of 19-norcorticosterone with m.p. 194–197°, $[\alpha]_D$ +155° (ethanol); $\lambda_{max}^{H_2SO_4}$ 285, 390 and 475 mμ. The paper chromatography mobility ratio of 19-norcorticosterone to corticosterone is in agreement with the mobility ratio found for the similar pair of 19-norhydrocortisone to hydrocortisone. The sulfuric acid chromogen curve of the 19-norcorticosterone is quite similar to that of corticosterone.

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(20) L. Axelrod and A. Zaffaroni, *Arch. Biochem. & Biophys.*, **50**, 347 (1954).

(21) This spectrum was kindly determined by Dr. R. N. Jones, National Research Council, Ottawa.