The total yield was thus 59 g. (88%). The literature[4] reports a melting point of 260°.

3-(5-Nitrofurfurylideneamino)tetrahydro-2(1H)pyrimidinone (I). A solution of 59 g. (0.59 mole) of tetrahydro-2(1H)pyrimidinone in 1700 ml. of 2*N* sulfuric acid was cooled to 3°. During 8 min., 41 g. (0.59 mole) of sodium nitrite was added at a temperature of 3–5°. Stirring was continued at this temperature for 1.5 hr. Then, 85 g. (1.4 moles) of zinc dust was added in small portions during 40 min. at a temperature of 15–25°. After an additional 15 min. stirring, the excess zinc was filtered off and the clear filtrate treated with a solution of 79 g. (0.56 mole) of 5-nitrofurfural in 500 ml. of methanol. The orange precipitate which formed was filtered, washed with water, alcohol, and ether, and dried at 60°. The yield was 84 g. (63%) of I, m.p. 230–232° (copper block; uncorr.). Recrystallization from 1600 ml. of nitromethane using Darco gave an 83.5% recovery of purified product, m.p. 240–242° (copper block; uncorr.). The analytical sample melted at 242.5–244.5°, ϵ_{max} 17,600 at 286 mμ.

Anal.[12] Calcd. for $C_9H_{10}N_4O_4$: C, 45.4; H, 4.23; N, 23.5. Found: C, 45.2; H, 4.42; N, 23.35.

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(12) Microanalyses were performed by Mr. Gordon Ginther and associates of these Laboratories.

Synthesis of 17-Iso-19-nortestosterone

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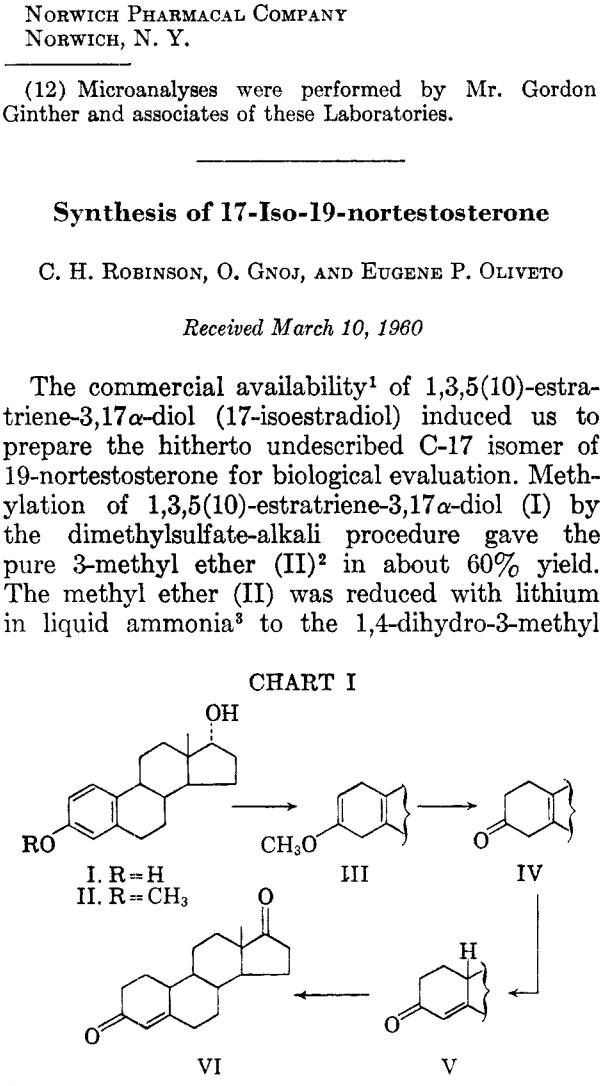
The commercial availability[1] of 1,3,5(10)-estratriene-3,17α-diol (17-isoestradiol) induced us to prepare the hitherto undescribed C-17 isomer of 19-nortestosterone for biological evaluation. Methylation of 1,3,5(10)-estratriene-3,17α-diol (I) by the dimethylsulfate-alkali procedure gave the pure 3-methyl ether (II)[2] in about 60% yield. The methyl ether (II) was reduced with lithium in liquid ammonia[3] to the 1,4-dihydro-3-methyl ether (III) which was isolated in 65% yield by direct crystallization and which showed no selective ultraviolet absorption in the 220–350 mμ region.

CHART I



The dihydromethyl ether (III) was then converted to 17-iso-19-nortestosterone (V) by refluxing methanolic hydrochloric acid. The β,γ-unsaturated ketone (IV) was obtained from III by the action of oxalic acid[8] in methanol at room temperature, and showed no selective ultraviolet absorption between 220 and 350 mμ, while exhibiting a saturated carbonyl band at 5.85 μ in the infrared spectrum. When subjected to the action of methanolic hydrochloric acid, IV was converted to the Δ⁴-3-ketone (V).

Oxidation of 17-iso-19-nortestosterone (V) with the chromium trioxide-sulfuric acid reagent[4] furnished the known[8] 19-norandrostene-3,17-dione (VI).

The molecular rotation differences between compounds II to V and the corresponding 17β-hydroxy analogs, together with figures for other pairs of 17-epimeric alcohols, are shown in the table. It is interesting to note that the Δ(17β-17α) values for the three pairs of 3-oxygenated-Δ⁴ compounds are distinctly higher (average Δ value +99°) than the Δ values for the other compounds cited (average Δ value +61°) which, with one exception (the etiocholane derivative), all share one common feature, namely a 5(10) double bond.

In view of the well known[5] biological activity of 19-nortestosterone, the properties of the 17-epimer (V) were of some interest. However V was found to be devoid of androgenic or myotrophic activity.[6]

EXPERIMENTAL[16]

1,3,5(10)-Estratriene-3,17α-diol 3-methyl ether (II). To a stirred solution of 1,3,5(10)-estratriene-3,17α-diol (3.0 g.)

(1) See British Patent No. **822,205** (1959).

(2) A. Butenandt and C. Groergens, *Z. physiol. Chem.*, **248**, 129 (1937).

(3) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(4) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

(5)(a) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953). (b) R. S. Stafford, B. J. Bowman, and K. J. Olsen, *Proc. Soc. Exptl. Biol. Med.*, **86**, 322 (1954). (c) F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956).

(6) Personal communication from Dr. M. Eisler, Biochemistry Department, Schering Corp.

(7) The $[M]_D$ values are for ethanol, dioxan, or chloroform solutions, and are marked (E), (D), or (C) respectively.

(8) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949).

(9) M. Pesez, *Bull. soc. chim. France*, 911 (1947).

(10) A. Butenandt and A. Heusner, *Ber.*, **71**, 198 (1938).

(11) H. Heusser, M. Feurer, K. Eichenberger, and V. Prelog, *Helv. Chim. Acta*, **33**, 2243 (1950).

(12) Rotation, measured in dioxan, of a purified sample prepared according to the procedure of Wilds and Nelson, ref. (3).

(13) L. Ruzicka, M. W. Goldberg, and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937).

(14) T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).

(15) L. Velluz and A. Petit, *Bull. soc. chim. France*, 1113 (1948).

TABLE I

Compound	Ref.	$[M]_D$[7]	$\Delta(17\beta-17\alpha)$
4-Androsten-17β-ol-3-one	8	+314°(E)	
4-Androsten-17α-ol-3-one	9	+221°(E)	+93°
4-Androstene-3β,17β-diol	10	+140°(E)	
4-Androstene-3β,17α-diol	11	+32°(E)	+108°
4-Estren-17β-ol-3-one	12	+122°(D)	
4-Estren-17α-ol-3-one	Exptl.	+25°(D)	+97°
Etiocholane-3α,17β-diol	13, 14	+73°(E)	
Etiocholane-3α,17α-diol	14	0°(E)	+73°
1,3,5(10)-Estratriene-3,17β-diol	15	+215°(E)	
1,3,5(10)-Estratriene-3,17α-diol	11	+146°(E)	+69°
1,3,5(10)-Estratriene-3,17β-diol 3-methyl ether	12	+215°(D)	
1,3,5(10)-Estratriene-3,17α-diol 3-methyl ether	Exptl.	+152°(D)	+63°
2,5(10)-Estradiene-3,17β-diol 3-methyl ether	3	+316°(C)	
2,5(10)-Estradiene-3,17α-diol 3-methyl ether	Exptl.	+286°(D)	+30°
5(10)-Estren-17β-ol-3-one	3	+521°(C)	
5(10)-Estren-17α-ol-3-one	Exptl.	+450°(D)	+71°

in methanol (150 ml.) and water (30 ml.) containing potassium hydroxide (18 g.) was added dimethyl sulfate (3 ml.). Three additional 3-ml. portions of dimethyl sulfate were added at 30-min. intervals to the stirred reaction mixture. Stirring was continued for 1 hr. after the last addition (total reaction time 2.5 hr.), and the reaction mixture was then concentrated *in vacuo* to about 50 ml. Water was added and the mixture was filtered. The dried residue was chromatographed on Florisil, when elution with hexane-ether (9:1) furnished the 3-methyl ether (II, 1.91 g.), m.p. 112–114° (from aqueous methanol), $[\alpha]_D$ +53°, $\lambda_{max}^{CH_3OH}$ 268 mμ (2,400) and 287 mμ (2,200), λ_{max}^{Nujol} 2.96 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.47; H, 9.25. (lit.[2] m.p. 109–110°).

2,5(10)-Estradien-3,17α-diol 3-methyl ether (III). To a stirred solution of 1,3,5(10)-estratriene-3,17α-diol 3-methyl ether (II, 1.0 g.) in ether (100 ml.) and liquid ammonia (100 ml.) was added lithium metal (1.0 g.) in small pieces. To the resulting blue solution was added ethanol (32 ml.) dropwise, with stirring, over 50 min. The decolorized solution was then allowed to evaporate, and the residue was treated with water and extracted with ether. The ethereal extract was washed with water, dried (sodium sulfate) and evaporated to a solid residue. Crystallization from acetone-hexane furnished the 1,4-dihydro compound (III, 658 mg.) m.p. 108–110°. The analytical sample was obtained by recrystallization from acetone-hexane, and exhibited m.p. 112–114°, $[\alpha]_D$ +99°. It showed no selective ultraviolet absorption between 220 and 350 mμ (ϵ_{280} 60); λ_{max}^{Nujol} 3.0, 6.18, 6.3 μ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.20; H, 10.18.

5(10)-Estren-17α-ol-3-one (IV). A solution of 2,5(10)-estradiene-3,17α-diol 3-methyl ether (III, 200 mg.) in methanol (16 ml.) and water (3.44 ml.) containing oxalic acid (264 mg.) was left at room temperature for 40 min. The reaction mixture was then poured into water and filtered. The dried residue was crystallized from ether-hexane, affording the β,γ-unsaturated ketone (IV, 95 mg.), m.p. 144–150°, $[\alpha]_D$ +164°, no selective ultraviolet absorption between 220 and 350 mμ, λ_{max}^{Nujol} 2.96, 5.88 μ.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.27; H, 9.82.

4-Estren-17α-ol-3-one (V). A solution of 2,5(10)-estradiene-3,17α-diol 3-methyl ether (III, 200 mg.) in methanol (72 ml.), water (8 ml.) and concd. hydrochloric acid (0.5 ml.) was heated to reflux for 20 min. The solution was then evaporated, *in vacuo*, to low volume, and was diluted with water. The aqueous mixture was extracted with ether and the extract was washed with water and dried (sodium sulfate). Evaporation of the ether gave an oily residue which crystallized on trituration with hexane. Crystallization from acetone-hexane gave the α,β-unsaturated ketone (V, 95 mg.), m.p. 146–149°, $[\alpha]_D$ +9°, λ_{max} 240 mμ (16,900), λ_{max}^{Nujol} 2.96, 6.00, 6.20 μ.

Anal. Calcd. $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.38; H, 9.09.

On one occasion, V was obtained in a different crystalline form,[17] m.p. 112–115°, λ_{max} 240 mμ (16,800). A mixture of this low melting material and the material of m.p. 146–149° showed m.p. 146–149°.

4-Estrene-3,17-dione (VI) *from 4-estren-17α-ol-3-one* (V). To a cooled (5°) solution of 4-estren-17α-ol-3-one (V, 50 mg.) in acetone (5 ml.) was added dropwise, with swirling, chromium trioxide–sulfuric acid reagent[4] until a permanent orange color was observed. The reaction mixture was left at room temperature for 5 min., and was then treated with methanol (0.1 ml.) and was diluted with water. The aqueous mixture was extracted with ether, and the extract was washed with water, dried (sodium sulfate) and evaporated *in vacuo* to a solid residue. Crystallization from acetone-hexane yielded 4-estrene-3,17-dione (VI, 33 mg.) m.p. 168–171°, $[\alpha]_D$ +140° ($CHCl_3$), $\lambda_{max}^{CH_3OH}$ 239 mμ (16,900), λ_{max}^{Nujol} 5.74, 5.98 μ; [lit.[3] m.p. 170–171°, $[\alpha]_D$ +137° ($CHCl_3$), λ max. 239 mμ (16,900)].

NATURAL PRODUCTS RESEARCH DEPARTMENT
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(16) Melting points were obtained on the Kofler block. Rotations were measured in dioxan solution at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infrared spectra, and of rotations. Microanalyses were carried out by Mr. E. Conner (Microanalytical Department, Schering Corp.).

(17) Wilds and Nelson (Ref. 3) observed two polymorphic forms of 19-nortestosterone.

The Preparation of Epinephrine and Norepinephrine Metabolites, 3-Methoxy-4-hydroxymandelic Acid and 3,4-Dihydroxymandelic Acid

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The preparation of 3,4-dihydroxy and 3-methoxy-4-hydroxymandelic acids, major metabolites of epinephrine and norepinephrine has been described recently by Shaw, *et al.*[1] Although this synthesis was repeated successfully in our laboratories, it was impractical for larger runs because of the

(1) K. N. F. Shaw, A. McMillan, and M. D. Armstrong, *J. Org. Chem.* **23**, 27 (1958).