ing residue was taken up in about 30 ml. of ether and treated with anhydrous hydrogen chloride to yield 0.2 g. of material which was recrystallized from ethanol–ether to yield 0.1 g. of product, m.p. 155–157°.

Anal. Calcd. for $C_9H_{13}N_3O \cdot HCl$: C, 50.11; H, 6.54; N, 19.48. Found: C, 50.30, 50.56; H, 6.52, 6.79; N, 19.88.

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COMMUNICATION TO THE EDITOR

C(19)-Substituted Steroid Hormone Analogs. I. 17β-Hydroxy-3-oxoandrost-4-ene-19-nitrile

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The intense sodium retaining activity of aldosterone as well as the favorable myotrophic/androgenic ratios of the 19-nortestosterone derivatives shows that modification of the angular methyl groups of steroids can have profound consequences relative to physiological activity. Syntheses of aldosterone[1–4] and 18-nitriloprogesterone[5] from intact steroids by use of intramolecular reactions have been described recently and the preparation of 3β-hydroxycholest-5-ene-19-nitrile[6] and various 6,19[7] and 11,19[8] ethers of saturated steroids has been disclosed.

We wish to report the preparation of 17-hydroxy-3-oxoandrost-4-ene-19-nitrile (XIII), a testosterone analog, using 5α-chloro-6β-hydroxysteroid intermediates. These intermediates are of general utility for the production of C(19) substituted steroids from the

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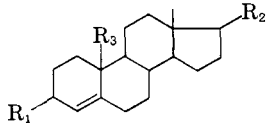
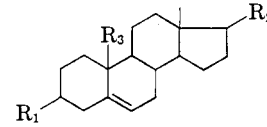
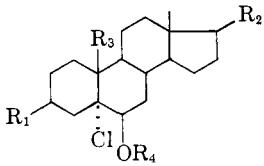


XI, R_1 = O, R_2 = O, R_3 = CN
XII, R_1 = OH, R_2 = OH, R_3 = CN
XIII, R_1 = O, R_2 = OH, R_3 = CN



I, R_1 = OAc, R_2 = OAc, R_3 = CH_3
VI, R_1 = OAc, R_2 = OAc, R_3 = CHNOH
VII, R_1 = OAc, R_2 = OAc, R_3 = CN
VIII, R_1 = OH, R_2 = OH, R_3 = CN
IX, R_1 = OH, R_2 = O, R_3 = CN
X, R_1 = O, R_2 = O, R_3 = CN
XVI, R_1 = OAc, R_2 = R_3 = CHNOH, $COCH_3$



II, R_1 = OAc, R_2 = OAc, R_3 = CH_3, R_4 = H
III, R_1 = OAc, R_2 = OAc, R_3 = CH_3, R_4 = NO
IV, R_1 = OAc, R_2 = OAc, R_3 = CH_2NO, R_4 = H
V, R_1 = OAc, R_2 = OAc, R_3 = CHNOH, R_4 = H
XIV, R_1 = OAc, R_2 = $COCH_3$, R_3 = CH_3, R_4 = H
XV, R_1 = OAc, R_2 = $COCH_3$, R_3 = CHNOH, R_4 = H

readily available Δ^5-steroids since by their use the requisite 6β-hydroxy group can be introduced and removed in two steps.

By treatment of I[9] with hypochlorous acid[10] ($Ca(OCl)_2$-HOAc-ether) there was obtained the chlorohydrin II, m.p. 200–201° (Found: C, 64.89; H, 8.24; Cl, 8.01), which was converted (NOCl-pyridine) to the unstable nitrite III, m.p. 118–120°. Photolysis[6] of III in toluene solution (Hanovia 200-watt high pressure mercury arc, borosilicate filter) furnished a precipitate of the unstable nitroso compound IV, m.p. 159–160°, as a colorless dimer. Heating IV in methanol gave the oxime V, m.p. 199–200° (Found: C, 60.44; H, 7.62; N, 3.21; Cl, 7.99) and the double bond was then readily regenerated (Zn-HOAc) to furnish VI, m.p. 147–152° (Found: C, 68.68; H, 7.97; N, 3.11). Dehydration of the oxime function produced the nitrile VII, m.p. 162–163° (Found: C, 71.50; H, 7.95; N, 3.45) and the ester groups were hydrolyzed (KOH-MeOH) to afford the diol VIII, m.p. 208–209° (Found: C, 75.39; H, 9.05; N, 4.49). Selective oxidation (CrO_3–acetone, 5 min.) of VIII formed

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the interesting hydroxy ketone IX, m.p. 193–195°, (Found: C, 76.22; H, 8.20); prolonged oxidation (CrO_3–acetone, 20 min.) of VIII gave the diketone X, m.p. 158–164° (Found: C, 76.44; H, 7.86). The double bond in X was isomerized into conjugation by passage of a solution of the compound through alumina to produce XI, m.p. 184–185°, $\lambda_{max.}^{EtOH}$ 231 mμ, log E = 4.20 (Found C, 76.94; H, 7.74), which was reduced ($LiAlH(t\text{-}BuO)_3$) to furnish the diol XII, m.p. 248–249° (Found: C, 75.68; H, 9.15). The allylic hydroxyl group in XII was selectively oxidized (MnO_2) to afford XIII, m.p. 189–190°, $\lambda_{max.}^{EtOH}$ 232 mμ, log E = 4.16 (Found: C, 75.95; H, 8.58).

As a further example of this sequence, pregnenolone acetate was subjected to the same initial reactions to furnish XIV, m.p. 201–203° (Found: C, 66.91; H, 8.54); XV, m.p. 215° (Found: C, 62.83; H, 7.91; N, 3.58); and XVI, m.p. 156–162°, (Found: C, 71.19; H, 8.79). The application of the chlorohydrin sequence to other Δ^5 steroids, as well as the conversion of intermediates like IX to 17α-alkyl testosterone analogs, is being investigated.

Biological Assay,[11]—Compounds VIII, XI, and XIII, in carboxymethocellulose (CMC) suspension, were given by subcutaneous administration, once daily for 7 days, to groups of 5 castrate male Holtzman rats 21 days of age at the start of the test. Autopsy was on the day following the last day of administration. These data were obtained:

Total Dose/Rat	Body wt. (g.) Initial	Final	Ventral prostate (mg.) (SE)	Seminal vesicles (mg.) (SE)	Levator ani (mg.) (SE)
Control (CMC)	52	86	14.5 (1.85)	11.8 (0.39)	29.7 (0.73)
Testosterone propionate (0.3 mg.)	53	89	32.2 (5.51)	17.5 (0.96)	34.3 (0.90)
VIII, 3.0 mg.	54	83	13.1 (0.62)	11.7 (0.29)	25.0 (1.46)
XI, 3.0 mg.	54	85	13.1 (0.62)	12.0 (0.22)	25.9 (1.08)
XIII, 3.0 mg.	54	90	14.2 (1.35)	15.1 (0.87)	30.8 (1.52)

These preliminary data indicate that replacement of the C(19) methyl group by a nitrile function in testosterone and related compounds abolishes both anabolic and androgenic activity. There is a suggestion that compounds VIII and XI may be catabolic, but further testing is required to substantiate this. The biological results further emphasize the importance, relative to pharmacological action, of the C(10) substituent in steroids.

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(11) The androgenic-myotrophic tests were performed at the Endocrine Laboratories, Madison, Wisconsin.