base has a half-life of only a few minutes in solution. Although III could be recrystallized from ethanol, when a dilute ethanolic solution of III was allowed to stand, gradual decomposition to several products took place, as shown by paper chromatography.

EXPERIMENTAL[8,9]

5-[Bis(2-hydroxyethyl)aminomethyl]uracil (II). A mixture of 0.96 ml. (10.0 mmoles) of diethanolamine, 1.04 g. (7.5 mmoles) of anhydrous potassium carbonate, 10 ml. of *N,N*-dimethylformamide, and 1.12 g. (7.0 mmoles) of I[5] was vigorously stirred at room temperature for 24 hr. protected from moisture. The filtered solution was evaporated to dryness *in vacuo* (bath 70°) leaving a light yellow oil which soon solidified. Trituration with cold absolute ethanol (3 × 1 ml.) at 0–5° gave 1.66 g. (97%) of crystalline product which began to decompose at about 195° but did not melt up to 300°. This material had $\lambda_{max(\mu)}^{Nujol}$ 5.80, 5.95 (C=O of uracil), 9.24, 9.58, 9.71 (C—OH), and moved as a single spot with R_f 0.26 in solvent A, R_f 0.77 in solvent B, and R_f 0.39 in solvent C.

Anal. Calcd. for $C_9H_{15}N_3O_4 \cdot 3/4H_2O$: C, 44.5; H, 6.85; N, 17.3. Found: C, 44.5; H, 6.68; N, 17.5.

5-[Bis(2-chloroethyl)aminomethyl]uracil (III). A mixture of 0.20 g. (0.82 mmole) of II in 10 ml. of thionyl chloride was stirred at room temperature for about 16 hr. protected from moisture, then refluxed for 4 hr. The solution was evaporated to dryness *in vacuo* (bath 40°) and the crystalline hydrochloride of III was triturated with petroleum ether (b.p. 30–60°); yield, 0.20 g. (76%), m.p. 224–226° dec.; $\lambda_{max(m\mu)}^{pH\ 1}$ 262 (ε 8500)[10]; $\lambda_{max(\mu)}^{Nujol}$ 3.20, 3.29 (NH), 5.80, 5.95 (C = O of uracil) and absence of C—OH absorption at 9.24–9.71. The compound moved as a single spot in solvent C and in solvent A (R_f 0.51 and R_f 0.58, respectively).

Anal. Calcd. for $C_9H_{13}Cl_2N_3O_2 \cdot HCl$: C, 35.7; H, 4.69; Cl, 35.1; N, 13.9. Found: C, 35.2; H, 5.14; Cl, 34.9; N, 14.1.

The hydrochloride of III, prepared from 0.50 g. (2.1 mmoles) of II in a similar fashion, was added to 30 ml. of saturated aqueous sodium bicarbonate cooled in an ice bath. After being stirred for 20 min., the mixture was filtered and the product washed with a little ice water; yield, 0.30 g. (54% based on II) of III, m.p. 160–161° dec. Recrystallization from 10 ml. of absolute ethanol with the aid of Norit gave 0.25 g. (45%) of white crystals, m.p. 159–160° dec.; $\lambda_{max(\mu)}^{Nujol}$ 3.20 (NH), 5.85, 6.00 (C=O of uracil) and absence of C—OH at 9.24–9.71. The compound, when dissolved in 0.1*N* hydrochloric acid, moved as a single spot (R_f 0.57) in solvent C. When the compound was dissolved in absolute ethanol, it decomposed on standing, so that several spots were observed on the chromatograms.

Anal. Calcd. for $C_9H_{13}Cl_2N_3O_2$: C, 40.6; H, 4.93; Cl, 26.6; N, 15.8. Found: C, 40.9; H, 4.65; Cl, 26.6; N, 16.0.

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(8) Melting points were determined on a Fisher-Johns block and are uncorrected.

(9) Paper chromatograms were run by the descending technique on Whatman No. 1 paper in butanol–acetic acid–water (4:1:5) (solvent A), saturated aqueous ammonium sulfate–isopropyl alcohol–water (2:28:70) (solvent B), and isopropyl alcohol-2*N* hydrochloric acid (65:35) (solvent C). Spots were detected by visual examination under ultraviolet light.

(10) Thymine has λ_{max} 264.5 mμ (ε 7,890) for the ionic specie occurring between *p*H 0–7 according to D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952).

Partial Synthesis of 19-Norandrosterone[1]

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Intramuscular administration of androsterone (3α-hydroxyandrostane-17-one) has been found to cause a significant decrease of serum cholesterol in man.[2] The synthesis of 19-norandrosterone (3α-hydroxy-19-norandrostane-17-one, IV) was undertaken to determine its hypocholesteremic effect since 19-nor analogs of other steroids have often shown enhanced biological activity. The preparation followed that of androsterone.[3] The known 19-norandrostane-3,17-dione (I) was reduced with sodium borohydride to yield 3β-hydroxy-19-norandrostane-17-one (IIa). The 3β-*p*-toluenesulfonate (IIc) of this product was epimerized to 19-norandrosterone (IV) with *N,N*-dimethylformamide according to Chang in less than 50% yield whereas, an 80% yield was realized with the parent C-10 methylated analog.[3] The discrepancy between the reaction of the two materials probably resulted from the ready access of the bulky base to the 2α-H in the case of the 19-norsteroid. The removal of the hydrogen initiated the elimination reaction affording a 35% yield of 19-nor-Δ²-androstene-17-one (V) accompanied by a trace of the Δ³-isomer. 19-Norandrosterone thus obtained was identical with a metabolite assigned this structure which was isolated from urine following administration of 19-nortestosterone to man.[4] The compound showed no hypocholesteremic effect at a dose level effective with androsterone.[5]

EXPERIMENTAL[6]

3β-Hydroxy-19-norandrostane-17-one (IIa). A solution of 3.5 g. of sodium borohydride in 1700 ml. of isopropyl alcohol and 550 ml. of water was slowly added at 20° to a solution of

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

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(5) Private communication, Dr. L. Hellman and Dr. B. Zumoff.

(6) Melting points were determined on a micro hot stage and are corrected. Optical rotations were determined in chloroform and solution unless otherwise stated. Infrared spectra were determined on a Model 21 Perkin-Elmer spectrophotometer; 4000–2750 cm.$^{-1}$ calcium fluoride prism, carbon disulfide; 1800–1600 cm.$^{-1}$ and 1500–1280 cm.$^{-1}$ calcium fluoride prism, carbon tetrachloride; 1300–650 cm.$^{-1}$ sodium chloride prism, carbon disulfide; sh = shoulder.

21.2 g. of 19-norandrostane-3,17-dione (I, m.p. 74.5–76.5°, $[\alpha]_D^{27}$ +132° (acetone)) in 1000 ml. of methanol. The mixture was allowed to stand at 20° for 30 min. and the reaction was stopped with dilute sulfuric acid. The reduction products were extracted with ethyl acetate and washed with water, dilute base, and 10% sodium chloride solution. The ethyl acetate solution was dried and the solvent evaporated to yield 18.8 g. of oily product. Chromatography on 2 kg. of silica gel with ethyl acetate–petroleum ether (b.p. 30–60°) (3:1) afforded 10.6 g. of 3β-hydroxy-19-norandrostane-17-one (IIa) contaminated with a small amount of the 3α-hydroxy epimer. Recrystallizations from acetone yielded 5.64 g. of IIa, m.p. 179–180.5°. The analytical sample of 3β-hydroxy-19-norandrostane-17-one melted at 180–180.5°; $[\alpha]_D^{26}$ +106°; reported[7] m.p. 177–179°, $[\alpha]_D^{20}$ +108°; ν_{max} 3622, 1743, and 1408 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.17; H, 9.57.

Acetylation of IIa with acetic anhydride and pyridine at room temperature yielded 3β-acetoxy-19-norandrostane-17-one (IIb). Recrystallizations from methanol yielded IIb, m.p. 182.5°; $[\alpha]_D^{26}$ +80.3°; ν_{max} 1743, 1737(sh), 1408, and 1245 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.26; H, 9.54.

Further elution of the column with ethyl acetate–petroleum ether (3:1) yielded 5.24 g. of 19-norandrostane-3,17-diols. Recrystallizations of a small portion afforded 19-norandrostane-3β,17β-diol (IIIa), m.p. 174.5–175.5°; $[\alpha]_D^{26}$ +26.3° (ethanol); reported[8] m.p. 168–170°; $[\alpha]_D$ +37°. Acetylation of IIIa with acetic anhydride and pyridine at room temperature afforded the diacetate IIIb, m.p. 144–144.5°; $[\alpha]_D^{27}$ +3.2°; reported[9] m.p. 140.2–141.8°; $[\alpha]_D^{25}$ +4.4°.

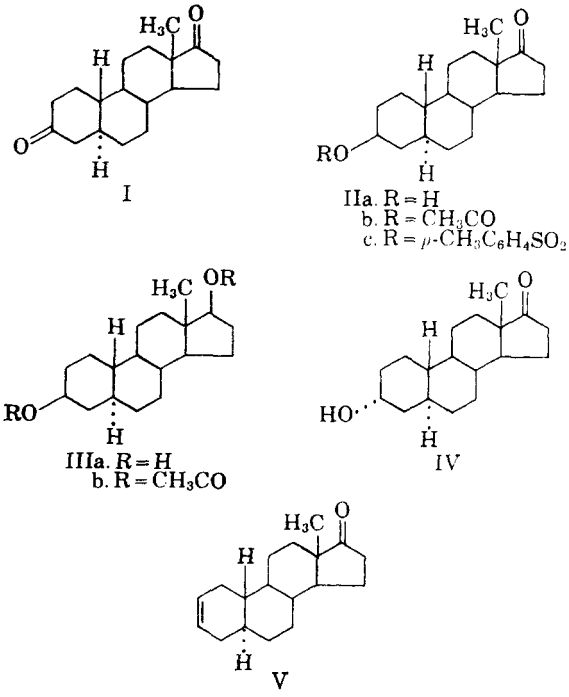
3β-p-Toluenesulfonoxy-19-norandrostane-17-one (IIc). A cold solution of 370 mg. of *p*-toluenesulfonyl chloride in 1 ml. of pyridine was added to a solution of 250 mg. of 3β-hydroxy-19-norandrostane-17-one (IIa) in 2 ml. of pyridine. The reaction mixture was allowed to stand overnight at room temperature and worked up in the usual manner. The product was recrystallized from acetone to yield 251 mg. of 3β-*p*-toluenesulfonoxy-19-norandrostane-17-one (IIc), m.p. 152–154.5° (dec.); $[\alpha]_D^{26}$ +55.9°.

Anal. Calcd. for $C_{25}H_{34}O_{11}$ S: C, 69.73; H, 7.96. Found: C, 69.78; H, 7.91.

3α-Hydroxy-19-norandrostane-17-one (IV). The crude tosylate IIc obtained from 5.28 g. of 3β-hydroxy-19-norandrostane-17-one and 7.3 g. of *p*-toluenesulfonyl chloride was dissolved in 220 ml. of *N,N*-dimethylformamide and the solution was kept at 80–85° for 68 hr. Large volumes of ice and water were added to the cooled reaction mixture. The product was extracted with ethyl acetate and washed with water. The ethyl acetate solution was dried over sodium sulfate and the solvent evaporated to yield 5.4 g. of dark brown oil. The residue was refluxed for 1 hr. with 20 g. of potassium hydroxide in 400 ml. of methanol and 45 ml. of water and the product was worked up in the usual manner to give 4.3 g. of oil. This was chromatographed on 160 g. of acid washed alumina. Elution with benzene–petroleum ether (1:3) afforded 1.87 g. of 19-nor-Δ^2-androstene-17-one (V). Recrystallizations from acetone–petroleum ether and methanol yielded V, m.p. 123.5–124.5°; $[\alpha]_D^{28}$ +170°; ν_{max} 1743, 1658, and 1408 cm.$^{-1}$ A small amount of contamination with 19-nor-Δ^2-androstene-17-one was detected by absorption at 1647 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.44; H, 9.96.

Further elution of the column with mixtures of ethyl acetate–benzene yielded 2.47 g. of 3α-hydroxy-19-norandrostane-17-one (IV). Recrystallizations from acetone–petroleum ether yielded 1.60 g. of fine needles of IV, m.p. 157.5–160° with change of crystalline form at 144°; $[\alpha]_D^{32}$ +110° Upon drying *in vacuo* at 100° for 2 hr., it melted at 164–165°. The analytical sample of 3α-hydroxy-19-norandrostane-17-one recrystallized from acetone melted at 167–168°; $[\alpha]_D^{27}$ +114°; ν_{max} 3615, 1743, and 1408 cm.$^{-1}$ The sample of 3α-hydroxy-19-norandrostane-17-one obtained from Dr. L. L. Engel melted in our laboratory at 158–161° with change in crystal form at 144°, reported m.p. 153–156°; $[\alpha]_D^{26}$ +103°. Upon heating *in vacuo* at 100° for 2 hr., it melted at 160–162°; changes in crystal form at 143°. The melting point of the synthetic sample of IV was not depressed upon admixture with the urinary steroid.[4] The infrared spectra of the two samples were identical.



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Hydrogenolysis of Thioesters

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Since the work of Nystrom and Brown,[2] the hydrogenolysis of esters by lithium aluminum hydride has been successfully applied to a wide